Acupuncture and Herbal Medicine

Puerariae Lobatae Radix: botanical traits, chemical constituents, and anti-metabolic disease effects—a review

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Abstract

Puerariae Lobatae Radix (PLR) is a traditional Chinese medicinal herb included in China's inaugural list of substances recognized as both food and medicine. PLR has a long history of use and a wide range of medicinal applications. Its use is associated with a broad range of health-promoting effects. Recent studies have shown that PLR contains abundant bioactive compounds including isoflavones and polysaccharides. These findings demonstrate significant potential for the prevention and treatment of metabolic diseases (MDs). The potential mechanisms underlying these effects involve several targets and pathways, including activation of the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and AMPK signaling pathways; regulation of key factors, such as peroxisome proliferator-activated receptors; and modulation of the gut microbiota composition. This systematic review examines the botanical characteristics and primary chemical constituents of PLR, with particular emphasis on recent research advances, mechanisms of action, and the clinical applications of its active components in MDs intervention. This review aims to provide theoretical guidance for further development, quality improvement, and application of PLR in the prevention and treatment of MDs.

Keywords: Botanical characteristics, Chemical constituents, Clinical applications, Metabolic diseases, *Puerariae Lobatae Radix*

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Introduction

Metabolic diseases (MDs), such as diabetes mellitus (DM), hyperlipidemia (HLP), obesity, and metabolic-related osteoporosis, have shown a continuous increase in global prevalence in recent years and have become a significant public health concern[1]. Moreover, MDs frequently lead to severe complications, including cardiovascular diseases and malignant tumors, which are closely associated with metabolic dysfunction. These complications place a significant burden on both the patients' families and the global healthcare system[2]. The current clinical management of MDs primarily involves the use of biguanides, statins, and glucocorticoids, which are frequently associated with adverse effects, including gastrointestinal discomfort, impaired liver and kidney function, weight gain, and cardiovascular complications[3]. Therefore, the development of safer and more effective strategies than existing medications for the prevention and treatment of MDs is a critical research priority.

Puerariae Lobatae Radix (PLR) is the dried root of the leguminous plant *Pueraria lobata* (Willd.) Ohwi., commonly known as "wild kudzu." This traditional Chinese medicinal herb has a long history and is widely used in clinical practice. According to traditional Chinese medicine theory, PLR is characterized by a cool nature and pungent, sweet flavors and is believed to enter the liver and stomach meridians. Its reported functions include resolving muscle tension, reducing fever, generating fluids to quench thirst, promoting rash eruption, elevating yang, stopping diarrhea, unblocking meridians and activating collaterals, and alleviating alcohol toxicity[4]. PLR is recognized as a quintessential "medicinal food" variety, possessing significant edible and economic value, as well as promising potential in the pharmaceutical sector. According to the Divine Farmer's Classic of

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Materia Medica, PLR elevates the clear yang qi of the spleen and stomach, alleviates lung dryness and fluid depletion, and promotes fluid generation and thirst quenching. Historically, physicians have frequently administered PLR, either alone or in combination with other substances, to treat "xiao ke," which corresponds to modern DM[5]. Formulations including Gegen-Zhuru, Gegen-Banxia, and Rougui-Gegen decoctions have demonstrated substantial efficacy in the treatment of diabetes and its associated complications[6]. Furthermore, PLR alleviates depression and irritability, enhances blood circulation, and resolves blood stasis. It is used to treat HLP associated with primary patterns, such as phlegm-damp obstruction, spleen-kidney yang deficiency, liver-kidney yin deficiency, and qi stagnation with blood stasis[7]. Given its traditional applications, PLR is now recognized as one of the most widely used Chinese herbal medicines in MDs research[8].

Recent pharmacological studies have indicated that PLR contains abundant bioactive components, such as flavonoids, polysaccharides, and saponins. These constituents exhibit diverse pharmacological activities, including hypoglycemic effects[9], lipid-regulating properties[10], and anti-osteoporotic activity[11]. PLR intervention demonstrates considerable potential to mitigate metabolic abnormalities and is associated with only minor side effects[12–13]. Despite the increasing interest in PLR, comprehensive summaries and analyses of its botanical characteristics, chemical constituents, and mechanisms of action against MDs remain insufficient. To address this gap, the present study systematically reviews the botanical features and principal chemical components of PLR and recent research progress in its application in MDs therapy. This review aims to establish a theoretical foundation and offer practical guidance for basic research, clinical translation, and product development concerning PLR-based treatments for MDs.

A comprehensive literature search was performed using PubMed, CNKI, Google Scholar, VIP, and WANFANG electronic databases for studies published between 2001 and 2025. Search terms such as PLR, Gegen, Kudzuvine root, active components of PLR, Pueraria isoflavones, Pueraria polysaccharides, MDs, DM, obesity, osteoporosis, dyslipidemia, HLP, non-alcoholic fatty liver disease, gout, clinical applications, and relevant combinations of these terms were used.

Botanical characteristics of PLR

Growth environment and distribution

PLR is widely distributed throughout China, with 242 documented records referencing this plant in local chronicles nationwide[14]. The Compendium of Materia Medica Varieties and Essentials of the Ming Dynasty identifies Jiangzhe (corresponding to the present-day Jiangxi and Zhejiang regions), Nankang (now the Ganzhou region of Jiangxi Province), and Luling (now the Ji'an region of Jiangxi Province) as the authentic regions for the production of PLR[15]. With the expansion of production, the boundaries of the authentic production regions have become increasingly indistinct. Currently, PLR is distributed across Yunnan, Guizhou, Sichuan, Tibet, Chongqing, Hubei, Hunan, Zhejiang, Anhui, Jiangsu, Gansu, Shaanxi, Shanxi, Henan, Hebei, Shandong, Beijing, Tianjin, Liaoning, and Jilin and approximately 20 other provinces, municipalities, and autonomous regions in China. This range extends from the high-altitude mountains of Southwest China to the Changbai Mountains in Northeast China, reflecting a broad geographical distribution and significant adaptability to diverse climatic conditions. PLR tolerates high temperatures and heavy rainfall typical of subtropical regions and adapts to the low-temperature and arid environments found in temperate zones. It primarily inhabits mountain forests at elevations between 0 and 1,800 m. Its presence in alpine meadows at elevations of 2,700 to 4,300 m in Zona County, Tibet further illustrates its extensive ecological adaptability.

Morphological characteristics

According to the Flora of China, the PLR is a robust vine that can reach up to 8 m in length and is entirely covered with long, stiff yellow hairs. The stem base is woody and is supported thick tuberous roots. The pinnate compound leaves comprise three leaflets. Stipules are adaxial, ovate-oblong, and linear, whereas stipulettes are linear-lanceolate and equal to or longer than the petiolules. Leaflets are typically three-lobed, although they may occasionally be entire, with the terminal leaflet being broadly or obliquely ovate. The raceme is 15 to 30 cm long and bears dense flowers above the middle. Bracts are linear-lanceolate to linear, and bracteoles are ovate. The calyx is campanulate with lanceolate lobes that taper to a point and are slightly longer than the tube. The corolla is 10 to 12 mm long and purple. The standard petal is obovate, with two auricles and a yellow scabrous appendage at the base, and it bears a short claw. The wing petal is falcate, narrower than the keel petal, and has linear downward-pointing auricles at the base. The keel petal is falcate-oblong, with minute, abruptly pointed auricles at the base. The stamen opposite the standard is free only in the upper part. The ovaries are linear and pubescent. Flowering occurs from September to October, and fruiting occurs from November to December[16]. Xie[17] surveyed PLR across multiple localities and observed considerable morphological variation in its leaves. In addition to the typical three-lobed form, variants, such as three shallowly lobed leaves, were identified, which differs slightly from the original description in the Flora of China, as shown in Figure 1A–C. In natural habitats, the root morphology of PLR is influenced by environmental conditions and is typically cylindrical, with occasional swollen forms, as depicted in Figure 1D–F. The inflorescence remains relatively consistent and is characterized by a short rachis and red flowers. The standard petals are approximately 14 to 16 mm in length. The detailed morphological features are presented in Figure 1G–I.

Harvesting and processing

PLR should be harvested when plants are 2 to 3 years old. Their leaves turn yellow to brown prior to bud break in

Figure 1. Morphological characteristics of *Puerariae Lobatae Radix* leaves, roots, and flowers[17].

the subsequent spring[18]. The optimal harvesting period occurs during the dormant season from November to December, when nutrient accumulation reaches its peak and product quality is the highest. The growth cycle comprises budding from mid-to-late March, vigorous vine growth from May to June, flowering from mid-July to early August, and pod maturation from late September to mid-October[19]. Supports and vines are removed prior to harvest, and the root tubers are carefully excavated to minimize damage. Washing is avoided to reduce the risk of rot. For processing, the root tips are cut to retain the seeds, after which the roots are washed, peeled, and sliced into chunks or diagonal pieces. The sliced roots are immediately dried in a smokeless coal fire to produce the PLR medicinal material[20]. Primary processing methods include steaming and stir-frying. Steaming techniques include

Table 1

Representative flavonoids isolated from *Puerariae Lobatae Radix*

No.	Compound name	Molecular formula	Location	Ref.
1	Puerarin	$C_{21}H_{20}O_9$	Root	[33]
2	3′-Hydroxypuerarin	$C_{21}H_{20}O_{10}$	Root	[34]
3	3′-Methoxypuerarin	$C_{22}H_{22}O_{10}$	Root	[35]
4	Daidzin	$C_{21}H_{20}O_9$	Root	[36]
5	Daidzein	$C_{15}H_{10}O_4$	Root	[37]
6	Genistein	$C_{15}H_{10}O_5$	Root	[38]
7	Formononetin	$C_{16}H_{12}O_4$	Root	[39]
8	Genistin glycoside	$C_{21}H_{20}O_{10}$	Root	[36]
9	6′-Crotonoyl-L-soybean glycoside	$C_{25}H_{24}O_{11}$	Root	[40]
10	3′-Hydroxy-daidzein	$C_{15}H_{10}O_5$	Root	[41]
11	7,2′,4′-Trihydroxyisoflavone	$C_{15}H_{10}O_5$	Root	[42]
12	Indian rosewood glycoside	$C_{22}H_{22}O_{10}$	Root	[43]
13	3-Hydroxytectorigenin-7-*O*-β-*D*-xylosyl-*(1→6)*-β-*D*-glucopyranoside	$C_{27}H_{30}O_{13}$	Flower	[44]
14	8-C-Glucosyl-chickpea flavone A	$C_{16}H_{11}O_5$	Flower	[45]
15	6″-*O*-Xylosyl-L-soybean glycoside	$C_{27}H_{30}O_{14}$	Flower	[46]
16	5,6,7,4′-Tetrahydroxyisoflavone-6,7-di-*O*-β-*D*-glucopyranoside	$C_{27}H_{30}O_{16}$	Stem	[46]
17	5,7,4′-Trihydroxy-2′,3′-dimethoxyisoflavones	$C_{17}H_{14}O_7$	Flower	[47]
18	3′-Hydroxyiriside	$C_{18}H_{14}O_9$	Flower	[48]
19	Calycosin	$C_{16}H_{12}O_5$	Root	[49]
20	Genistein-7-*O*-β-*D*-furanosyl-p-coumaric acid-(1→6)-*O*-β-*D*-glucopyranoside	$C_{27}H_{30}O_{13}$	Root	[50]

wheat bran and wet paper steaming, with wet paper being the predominant method[21]. Different processing methods and techniques alter the active components of PLR to varying degrees. For example, Liu and Yang[22] compared slicing, wheat bran steaming, and drying. The effects of temperature, processing duration, and wheat bran dosage were examined using PLR flavonoids as indicators. Their findings indicated that drying produced the highest flavonoid content, identifying it as the optimal processing method. Qiu et al.[23] utilized high-performance liquid chromatography to conduct comparative fingerprint analysis, attributing and quantifying specific characteristic peaks. Their findings demonstrated that the types of components remained unchanged before and after processing; however, post-processing resulted in varying increases in puerarin, daidzin, and daidzein aglycone levels. Zhong et al.[24] optimized the wheat bran steaming process by monitoring changes in appearance, color intensity, and puerarin content at various time points. They established correlations to assess production conditions and determined that a wheat bran dosage of 15 g per 100 g, a temperature of 160°C, and a steaming duration of 3.5 minutes produced the most favorable appearance, color intensity, and puerarin content in the processed slices.

Principal chemical constituents

PLR contains a diverse array of chemical constituents that are commonly extracted using techniques such as alcohol or water reflux extraction[25], microwave-assisted extraction[26], fermentation[27], enzymatic hydrolysis[28], and ion-pair extraction[29]. The chemical constituents of PLR include flavonoids, glycosides, terpenoids, coumarins, steroids, organic acids, and esters. Flavonoids are the primary pharmacologically active compounds[30–31]. PLR contains significant amounts of polysaccharides, essential amino acids, minerals, and trace elements[32].

Flavonoids

Isoflavones are the predominant class of flavonoids in PLR. Numerous flavonoids, such as puerarin, 3′-hydroxypuerarin, 3′-methoxypuerarin, daidzin, daidzein, genistein, formononetin, and genistin glycoside, have been isolated from PLR. Flavonoids are the characteristic constituents and primary bioactive components of PLR. Most of these compounds have been isolated from the roots, whereas smaller amounts are found in flowers, stems, and leaves. Recent studies have identified several novel flavonoid compounds in the roots. The representative flavonoid components are listed in Table 1 and Figure 2.

Polysaccharides

PLR polysaccharides (PLPs) represent a class of plant-derived polysaccharides that are primarily composed of glucose, fructose, xylose, arabinose, mannose, fucose, rhamnose, galactose, galacturonic acid, and glucuronic acid[51]. An extraction process is essential for refining PLPs. Although hot-water extraction remains the most widely used method, it is limited by a low extraction

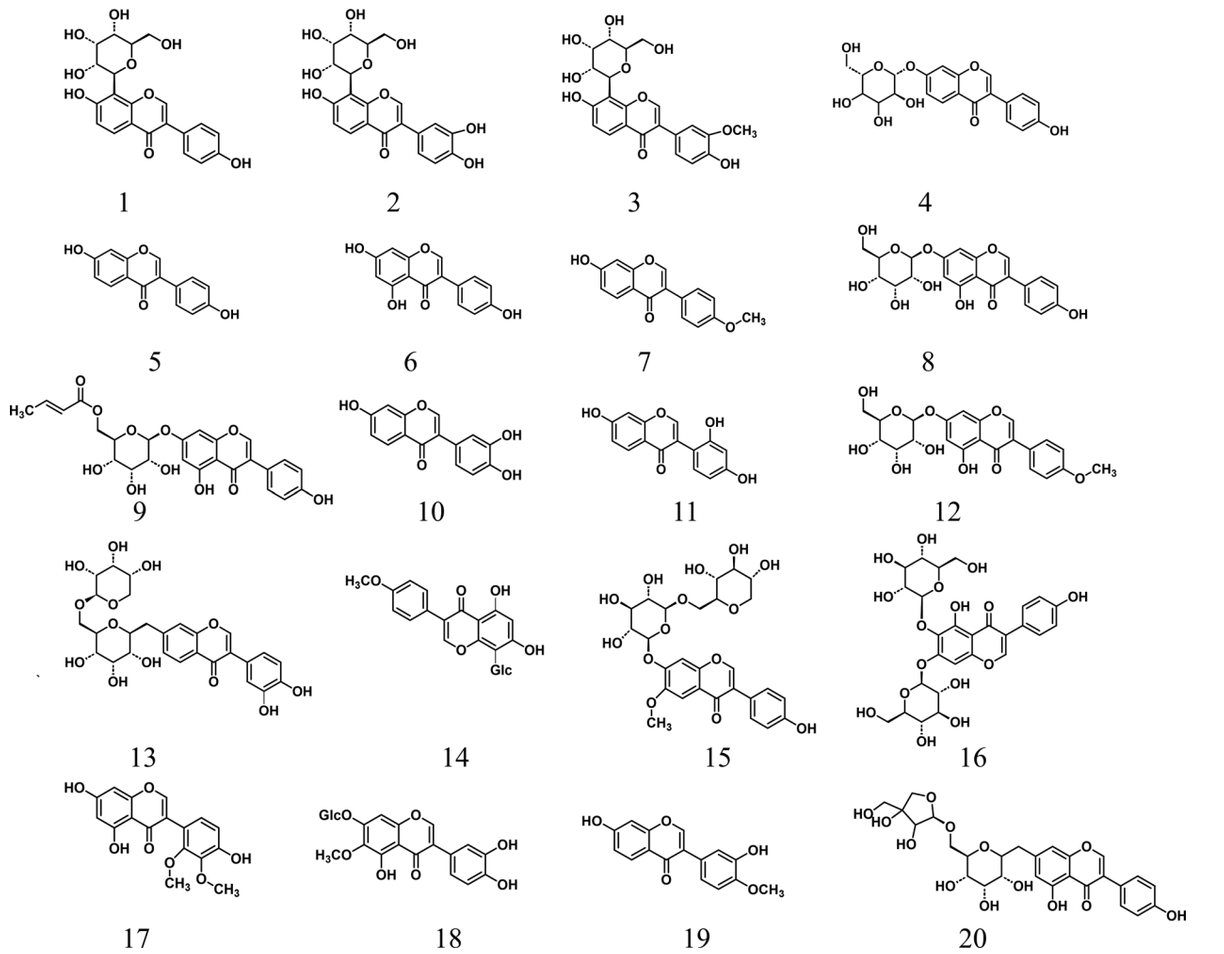


Figure 2. Representative structures of flavonoids in *Puerariae Lobatae Radix*.

rate and significant energy consumption. Emerging techniques, including ultrasonic, microwave, and enzyme-assisted extraction have demonstrated improved efficiency in the extraction of PLPs. Purification of the PLPs follows protocols similar to those used for other polysaccharides, producing pure PLPs through decolorization, protein removal, and chromatography. Recently, the primary structure of PLPs has been elucidated using nuclear magnetic resonance spectroscopy, X-ray photoelectron spectroscopy, and atomic force microscopy[52]. The polymer consists of monosaccharide units connected by α- and β-type glycosidic bonds. Figure 3 shows the representative polysaccharide components, including PLP-1(1) and PL-S2(2).

Triterpenoids

The triterpenoids present in PLR predominantly possess novel oleanane-type structures. To date, more than 30 triterpenoids have been isolated from PLR, including soyasapogenol A and soyasapogenol. They all contain a pentacyclic triterpene skeleton[53]. Furthermore, Chen et al.[54] isolated two novel oleanane-type triterpenoid saponins, pedunsaponins D and E, from PLR. Lu et al.[55] identified two additional oleanane-type triterpenoid saponins in PLR, designated as kakkasaponin II and kakkasaponin III. The representative triterpenoids are shown in Table 2 and Figure 4.

Organic acids

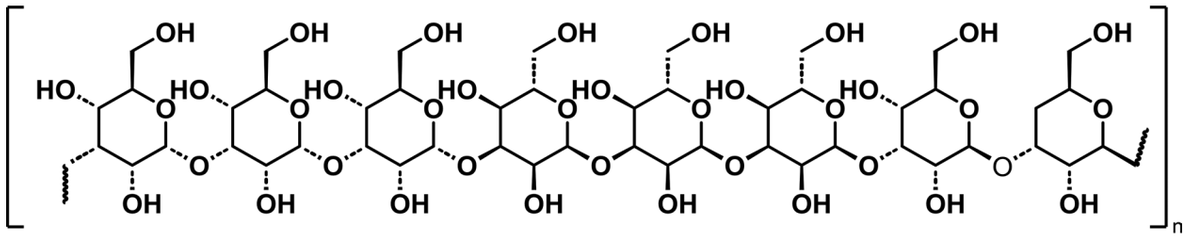
PLR contains various organic acids, such as syringic acid ester[56], and gallic acid[57]. Recent research has identified several new organic acid components in PLR. Shi [57] isolated two novel organic acid compounds from PLR produced in Yunnan Province: 4-*O*-β-*D*-glucopyranosylbenzoic acid and trans-*p*-coumaroylmalonic acid. The representative organic acids are presented in Table 3 and Figure 5.

Coumarins

The coumarin compounds present in PLR are predominantly furan-2-carboxaldehyde derivatives, including puerarol, 6,7-dimethoxycoumarin, and coumarinol. The representative coumarins are presented in Table 4 and Figure 6.

Other compounds

Recent research has led to the isolation of various phytosterols (1–3), monoterpenoids (4), alkaloids (5–6), and



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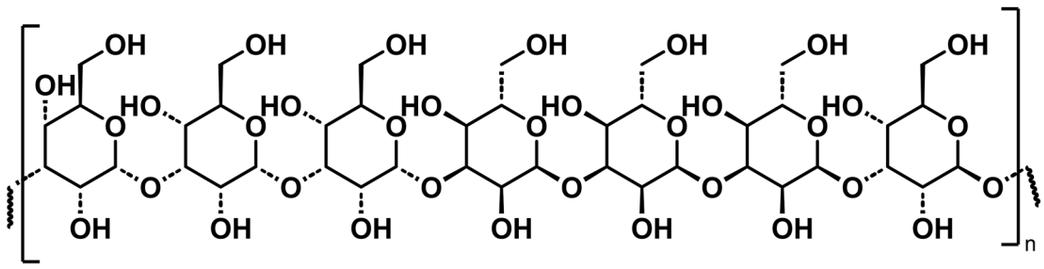

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Figure 3. Representative structures of polysaccharide compounds in *Puerariae Lobatae Radix*.

Table 2

Representative triterpenoids isolated from *Puerariae Lobatae Radix*

No.	Compound name	Molecular formula	Location	Ref.
1	Soyasapogenol A	$C_{30}H_{50}O_4$	Root	[53]
2	Soyasapogenol	$C_{29}H_{48}O_4$	Root	[53]
3	Pedunsaponin D	$C_{42}H_{64}O_{15}$	Root	[54]
4	Pedunsaponin E	$C_{55}H_{85}O_{25}$	Root	[54]
5	KakkasaponinII	$C_{42}H_{66}O_{13}$	Root	[55]
6	KakkasaponinIII	$C_{47}H_{74}O_{16}$	Root	[55]

aromatic compounds (7–8) from PLR[59]. Representative structural formulae are presented in Figure 7. Additionally, as a medicinal and edible Chinese herbal material, PLR contains abundant polysaccharides, including cellulose, starch, and pectin. The bioactive properties of these compounds have attracted considerable scientific interest[60]. Furthermore, PLR is rich in minerals and amino acids[61], especially essential amino acids. It contains 12 inorganic elements, including Fe, Zn, Ca, P, K, Mg, Li, Cu, Se, Mn, and Sr, and 18 amino acids. Notably, the trace elements Fe, Zn, Ca, Se, Mn, and Sr are present at relatively high concentrations[62].

Research on PLR and its active components in the treatment of MDs

Recent pharmacological studies have demonstrated that the active components of PLR significantly contribute to the treatment of MDs. A literature review indicated that investigations into the effects of PLR on MDs have primarily addressed three components: isoflavones, polysaccharides, and starch. Isoflavones are the principal active constituents of PLR. Compounds such as the flavonoid puerarin display pharmacological effects, including hypoglycemic activity, lipid regulation, antioxidant properties, and effects on bone density[63]. Consequently, the flavonoid components of PLR have been extensively investigated in MDs research. In addition, the polysaccharide components of PLR have hypoglycemic, hypolipidemic, and antioxidant properties, contributing to the improvement of conditions such as diabetes, HLP, and non-alcoholic fatty liver disease through distinct biological mechanisms[64–65].

Antidiabetic effects and associated mechanisms

DM is a prevalent MDs frequently associated with vascular, neurological, and retinal complications, in addition to kidney disease, all of which significantly diminish the patients' quality of life and overall health[66]. The

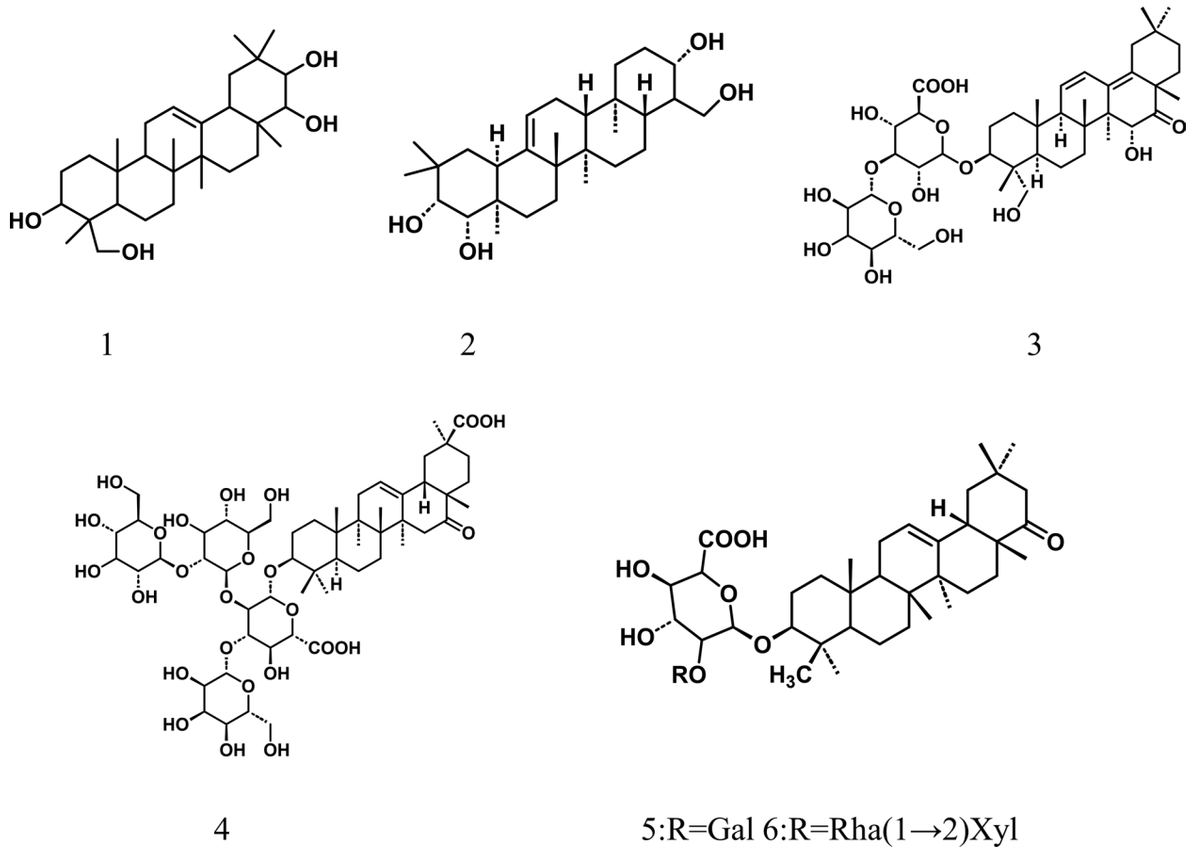

Figure 4. Representative structures of triterpenoids in *Puerariae Lobatae Radix*.

Table 3

Representative organic acid components isolated from *Puerariae Lobatae Radix*

No.	Compound name	Molecular formula	Location	Ref.
1	Syringic acid ester	$C_9H_{10}O_5$	Root	[56]
2	Gallic acid	$C_7H_6O_5$	Root	[58]
3	4-*O*-β-*D*-Glucopyranosylbenzoic acid	$C_9H_8O_5$	Root	[57]
4	Trans-p-coumaroylmalonic acid	$C_{11}H_{10}O_5$	Root	[57]

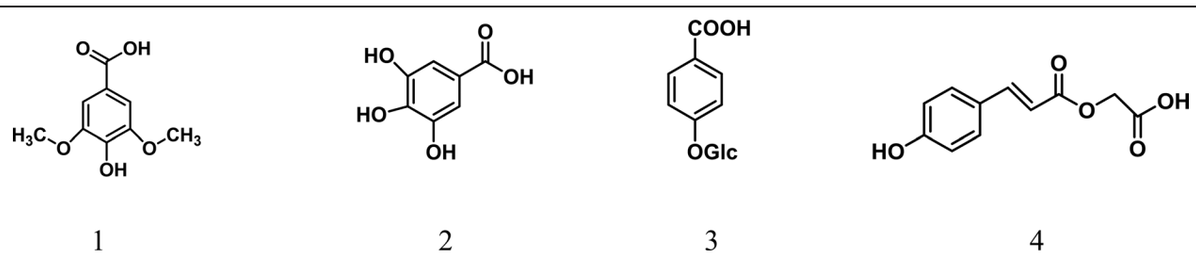

Figure 5. Representative structures of organic acid compounds in *Puerariae Lobatae Radix*.

pathogenesis of DM is multifactorial and includes insulin resistance (IR), pancreatic β-cell dysfunction, impaired glucose metabolism, and other contributing mechanisms.

Improving IR

IR is defined as a reduction in the sensitivity and responsiveness to insulin[67]. PLR and its active components, such as puerarin, primarily ameliorate IR by modulating insulin signaling pathways. *In vivo* studies have demonstrated that puerarin increases glucose transporter 4 (GLUT4) translocation by activating the insulin receptor substrate-1 (IRS-1)–associated phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt) signaling pathways in muscle cells, thereby improving IR in the muscles of diabetic rats[68]. Puerarin-mediated

Table 4

Representative coumarin compounds isolated from *Puerariae Lobatae Radix*

No.	Compound name	Molecular formula	Location	Ref.
1	Puerarol	$C_{25}H_{24}O_5$	Root/stem	[59]
2	6,7-Dimethoxycoumarin	$C_{11}H_{10}O_4$	Root/stem	[59]
3	Coumarinol	$C_{15}H_8O_5$	Root/stem	[59]

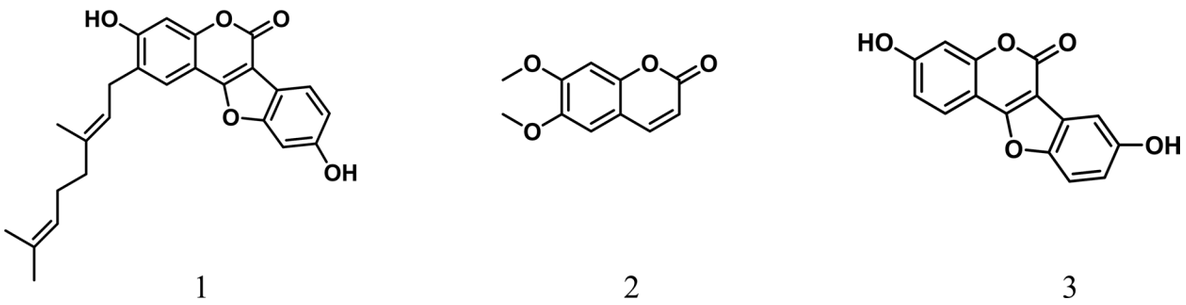

Figure 6. Representative structures of coumarin compounds in *Puerariae Lobatae Radix*.

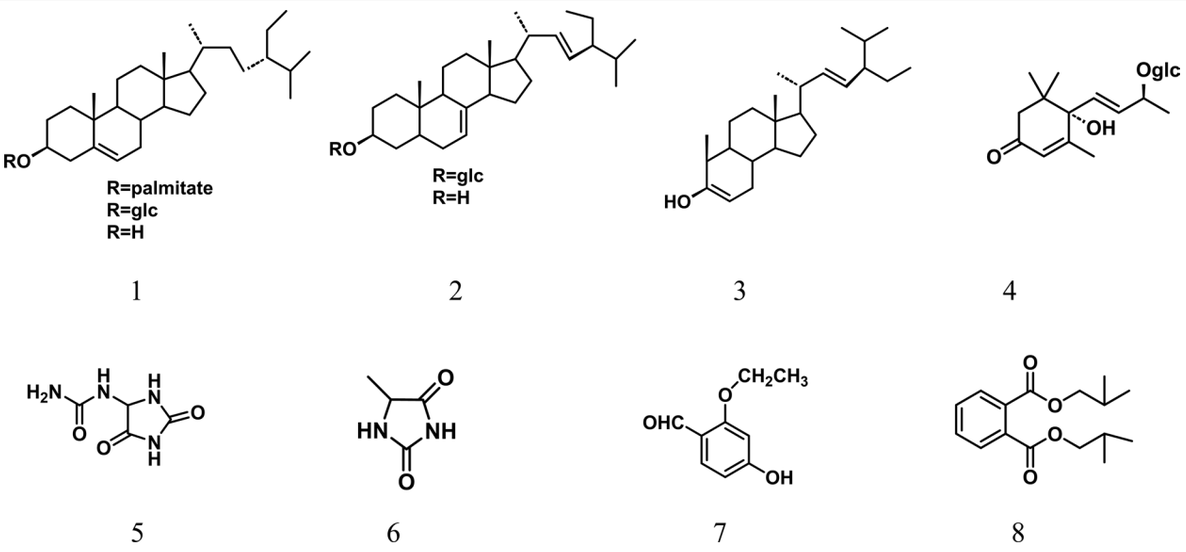

Figure 7. Representative structures of additional compounds present in *Puerariae Lobatae Radix*.

mitigation of IR is associated with increased expression levels of genes involved in muscle mitochondrial biosynthesis[68]. *In vivo* experiments have demonstrated that puerarin restores the expression of skeletal muscle mitochondrial biogenesis regulators, including Sirtuin 1, peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), and mitochondrial transcription factor A. Transmission electron microscopy confirmed that puerarin treatment restored the number of mitochondria in the muscles of diabetic rats. Peroxisome proliferator-activated receptor δ (PPARδ) primarily alleviates IR by regulating the expression of enzymes related to fatty acid oxidation[69]. Puerarin upregulates PPARδ, phosphorylated 5'-adenosine monophosphate-activated protein kinase (AMPK), phosphorylated acetyl-CoA carboxylase, and carnitine palmitoyltransferase-1b. This modulation improves mitochondrial function, enhances fatty acid oxidation, and alleviates IR in the muscles of diabetic rats[68]. Furthermore, puerarin directly activates μ-opioid receptors, improves insulin signaling, enhances insulin sensitivity in skeletal muscle, and reduces systemic IR[70]. PLPs, other key bioactive components of PLR, primarily activate the PI3K/Akt signaling pathway by upregulating the expression of PI3K and Akt in insulin-resistant cells and downregulating the expression of forkhead box protein O1 (FoxO1), phosphoenolpyruvate carboxykinase 2, and glucose-6-phosphatase. These actions exert hypoglycemic effects and thereby improve IR in diabetic patients[71–72]. Studies have demonstrated that gastric administration of PLPs to db/db mice reduces blood glucose and insulin levels and the homeostatic model assessment for IR index value, while increasing

both the mRNA and protein expression levels of PI3K, Akt2, and GLUT2 in the liver. These findings suggest that PLPs ameliorate IR in db/db mice by activating the PI3K/Akt signaling pathway[72]. Furthermore, Song et al.[73] reported immunoblotting results showing significant upregulation of key insulin signaling pathway proteins, including IRS-1, PI3K, Akt, and GLUT4, indicating that PLPs alleviate IR in mice with type 2 DM (T2DM) by modulating the expression of proteins associated with the PI3K/Akt/GLUT4 pathway.

In summary, the isoflavones and polysaccharides present in PLR are the primary active components responsible for its anti-IR effects. These components exhibit synergistic characteristics across multiple components, targets, and pathways. The potential mechanism of action involves the regulation of several signaling pathways and the enhancement of mitochondrial function, which collectively contribute to the alleviation of IR.

Protection of pancreatic β-cell

Prolonged hyperglycemia diminishes the sensitivity of pancreatic β-cell to glucose stimulation, resulting in abnormal insulin secretion and increased β-cell apoptosis. Active components in PLR, such as puerarin, inhibit β-cell apoptosis and promote β-cell regeneration by modulating pathways including the glucagon-like peptide-1 receptor (GLP-1R), caspase, and oxidative stress pathways. These mechanisms collectively provide protection for pancreatic β-cell. GLP-1R is currently the focus of diabetes research. Recent studies have indicated that puerarin restores impaired β-cell growth potential by enhancing GLP-1R and Akt/FoxO1/Pdx-1 signaling pathways[74], while facilitating β-cell neogenesis in hyperlipidemic diabetic mice *via* activation of the GLP-1R, WNT, and STAT3 signaling pathways[75]. The caspase family of proteins is involved in the initiation of apoptosis. Liang et al.[76] demonstrated that puerarin protects pancreatic β-cell in a high-fat/streptozotocin-induced T2DM mouse model by reducing cytochrome C release and decreasing the expression levels of caspase-9, caspase-3, and apoptosis-inducing factor, thereby preventing β-cell apoptosis. High-glucose-induced oxidative stress represents a primary cause of pancreatic β-cell apoptosis. Srivastava et al.[77] demonstrated that PLR extract exerts protective effects in STZ-induced T2DM rats by reducing the expression levels of biomarkers related to oxidative stress, hypoxia, apoptosis, and inflammation, thus safeguarding pancreatic β-cell through multiple pathways. Additionally, evidence suggests that puerarin regulates the endogenous non-coding RNA *miR-124a*, silent information regulator 1, and PGC-1α signaling pathways to enhance insulin secretion and mitochondrial function in palmitic acid–treated pancreatic β-cell, thereby reducing apoptosis[78].

In summary, the primary components of PLR, including puerarin, exhibit protective effects on pancreatic β-cell *via* multiple mechanisms. These potential mechanisms involve the regulation of GLP-1R signaling pathways to reverse cell growth impairment, promote cell regeneration, inhibit caspase-mediated apoptosis, and reduce high-glucose-induced oxidative stress and inflammatory responses. These findings offer valuable insights into the use of natural medicines for the prevention and treatment of diabetes.

Regulation of glucose metabolic pathways

The liver regulates glucose production and storage through gluconeogenesis and glycogen synthesis, and Akt plays a critical role in maintaining blood glucose homeostasis[79]. Liu et al.[80] established a rat model of T2DM using streptozotocin injections combined with a high-fat diet (HFD). Palmitic acid has been used to induce IR in the human hepatocellular carcinoma cell line, HepG2, cultured *in vitro*. These findings indicate that puerarin suppresses the expression of key rate-limiting enzymes involved in hepatic gluconeogenesis and reduces endogenous glucose production in the livers of diabetic animals by activating the PI3K/Akt/FoxO1 signaling pathway. These results support the conclusion that puerarin inhibits hepatic gluconeogenesis by activating the PI3K/Akt/FoxO1 signaling pathway. Qiu et al.[81] reported that formononetin enhances hepatic glycolysis by upregulating glucose kinase mRNA and protein expression in the liver, resulting in a significant increase in hepatic glycogen levels in diabetic rats. Glycogen synthase kinase-3β (GSK-3β) acts as a negative regulator of glycogen synthesis. Qian et al.[71] isolated a water-soluble neutral homopolysaccharide (PLP-1) from PLR using diethylaminoethyl (DEAE)-cellulose column chromatography and Sephadex G-200 gel chromatography. *In vitro* studies have demonstrated that PLP-1 enhances glycogen synthesis by activating the PI3K/Akt signaling pathway in pancreatic β-cell, leading to reduced GSK-3β expression levels. α-Glucosidase catalyzes the hydrolysis of dietary polysaccharides, such as starch, into monosaccharides, such as glucose, for intestinal absorption, thereby influencing blood glucose regulation. Research has shown that polysaccharide components in PLR inhibit α-glucosidase activity, decrease intestinal glucose absorption, and provide therapeutic benefits in T2DM. Xu et al.[82] isolated and purified the water-soluble polysaccharide PL70 from PLR using a DEAE-cellulose 52 anion exchange column and Sephacryl S-100 gel. *In vitro* studies indicated that PL70 exhibits significant α-glucosidase-inhibitory activity.

Active components, including puerarin and PLPs, likely modulate key pathways involved in hepatic glucose metabolism, such as gluconeogenesis, glycogen synthesis, glycolysis, and intestinal glucose absorption, thereby establishing a multidimensional hypoglycemic network.

In summary, polysaccharides and flavonoids in PLR are the principal chemical constituents responsible for its antidiabetic effects. The potential mechanisms include improving IR, protecting pancreatic β-cell, and regulating glucose metabolism by inhibiting hepatic gluconeogenesis, promoting hepatic glycolysis, and reducing intestinal glucose absorption (Figure 8). While some studies have identified key pathways involving compounds such as puerarin in the treatment of diabetes, most of the evidence is derived from animal models. Therefore, additional clinical research and comprehensive mechanistic analyses are required to substantiate the therapeutic potential of PLR as a diabetes medication or adjunct therapy.

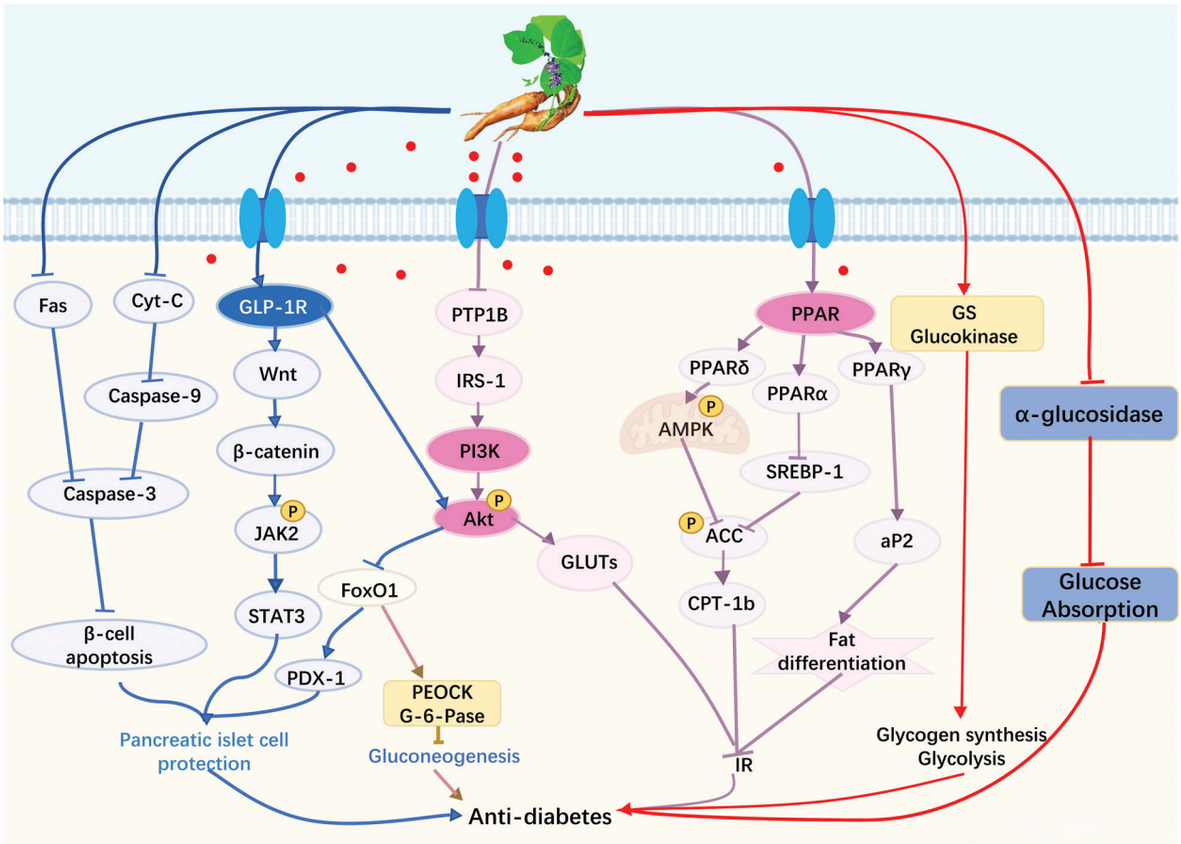

Figure 8. Mechanism of action for the treatment of diabetes with the primary active ingredients in *Puerariae Lobatae Radix*. "→": Direct stimulatory modification; "⊣": Direct inhibitory modification (created using BioRender [www.biorender.com]). ACC: Acetyl-CoA carboxylase; AMPK: adenosine monophosphate-activated protein kinase; Akt: Protein kinase B; CPT-1b: Carnitine palmitoyltransferase-1b; Cyt-C: Cytochrome C; FoxO1: Forkhead box O1; GLP-1R: Glucagon-like peptide-1 receptor; GLUTs: Glucose transporters; IR: Insulin resistance; IRS-1: Insulin receptor substrate-1; JAK2: Janus kinase 2; PDX-1: Pancreatic duodenal homology box 1; PI3K: Phosphatidylinositol 3-kinase; PPAR: Peroxisome proliferator-activated receptor; PTP1B: Protein tyrosine phosphatase 1B; SREBP-1: Sterol regulatory element-binding protein 1; STAT3: Signal transducer and activator of transcription 3.

Regulation of lipids and the associated mechanisms

Anti-HLP

HLP is an MDs characterized primarily by abnormal blood lipid levels, including elevated plasma total cholesterol, triglyceride, and low-density lipoprotein cholesterol levels, as well as reduced high-density lipoprotein cholesterol levels[83]. In China, the prevalence of HLP among adults is approximately 40%, making it a significant public health concern[84].

Lipid metabolism is regulated by polyADP-ribose polymerases (PARPs), PPARs, and additional factors, all of which contribute to lipoprotein transport and oxidation, lipogenesis, and lipolysis[85–86]. Puerarin has been shown to significantly alleviate C-C chemokine ligand 4 (CCL4)–induced lipid metabolism disorders in mice by inhibiting PARP-1 expression, reducing nuclear factor-kappa B (NF-κB) and reactive oxygen species production, and improving mitochondrial function[87]. Puerarin has been shown to ameliorate lipid accumulation and MDs by increasing the activity of AMPK, catalase, and hormone-sensitive lipase (HSL), while simultaneously downregulating PPARγ-2[10]. Bile acids (BAs) are synthesized from cholesterol and excreted through the intestines. Hepatic cholesterol 7α-hydroxylase (CYP7A1) serves as the rate-limiting enzyme in the primary biosynthetic pathway of BAs. In CCL4-treated mouse livers, puerarin enhances BAs excretion by downregulating phosphorylated JNK and upregulating CYP7A1 expression levels, which significantly inhibit HLP[88]. PL-S2, a novel homogeneous polysaccharide isolated from PLR, activates the nuclear receptor FXR for BAs. This activation upregulates hepatic CYP7A1, bile salt export pump, and multidrug resistance protein 2 in the liver of hyperlipidemic rats. As a result, PL-S2 inhibits bile acid metabolism, promotes bile acid excretion, and reduces plasma lipid levels in rats with HLP induced by an HFD[89]. Fatty acids are essential components of membrane lipids. Puerarin suppresses fatty acid synthase activity; activates AMPK, CAT, and HSL; and reduces fatty acid synthesis by enhancing leptin signaling through the janus kinase 2/signal transducer and activator of transcription 3(JAK2/STAT3) pathway, thereby improving hepatic lipid metabolism and steatosis[90]. Furthermore, genistein and genistin present in PLR inhibit lipid accumulation in 3T3-L1 cells, indicating that genistein is a promising antiadipogenic and lipid-lowering agent[91].

Anti–non-alcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is a metabolic-stress-related liver disease closely linked to IR and genetic predisposition. NAFLD encompasses non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, and cirrhosis[92]. Disruption of hepatic lipid metabolism, which leads to excessive lipid accumulation, is the primary pathogenic mechanism underlying NAFLD. Studies have shown that 70%-ethanol-extracted PLR significantly inhibits hepatic lipid accumulation, reduces oxidative damage induced by H_2O_2 in HepG2 cells, and improves liver function and histopathological features in a rat model of NAFLD[93]. Puerarin confers protective effects against NAFLD induced by a high-sugar, high-fat diet by modulating amino acid and lipid metabolism disorders. This modulation involves the upregulation of metabolites, such as L-serine, the regulation of cysteine metabolism, a reduction in oleic acid levels, and the promotion of sphingolipid degradation[94]. Li et al.[95] reported that puerarin prevented NAFLD-induced liver injury and lipid accumulation by activating flavin-containing monooxygenase (FMO). Furthermore, autophagy facilitates the clearance of intracellular lipid deposits. Puerarin alleviates hepatic lipid accumulation and NAFLD by inhibiting phosphorylation of the PI3K/Akt/rapamycin target protein (mTOR) signaling pathway, thereby activating hepatic autophagy[96].

In summary, puerarin and polysaccharides in PLR may regulate lipid metabolism by inhibiting PARPγ-1 and PPARγ-2; activating AMPK and FXR signaling pathways; modulating key enzymes, such as CYP7A1; promoting BAs excretion; suppressing fatty acid synthesis; and ameliorating lipid disorders associated with HLP. PLR may also improve NAFLD by regulating amino acid and lipid metabolism pathways, activating FMO, and promoting hepatocyte autophagy (Figure 9). PLR is a promising agent for the prevention and treatment of lipid disorders. Although Pueraria-based medications are currently used for HLP, most studies on the regulatory effects of PLR on lipids are limited to animal and cellular studies, and clinical data remain insufficient. Further clinical research on PLR is necessary in this context.

Regulation of obesity and associated mechanisms

Obesity is a significant global public health challenge. According to World Health Organization statistics, the prevalence of obesity continues to increase, with particularly sharp increases observed in developed and developing nations[97]. Obesity is associated with IR, dyslipidemia, and an elevated risk of diseases such as T2DM and cardiovascular disease[98]. Consequently, the management of obesity and related MDs has become a central focus of global medical research and public health initiatives. An imbalance between energy intake and expenditure is a key contributor to obesity. PLR extracts have been shown to reduce weight gain, hepatic fat accumulation, and adipocyte levels in mice with HFD-induced obesity. The primary mechanism involves activation of AMPK and its downstream target PGC-1α, which promotes mitochondrial biosynthesis and enhances energy metabolism in the skeletal muscle of these mice[99–100]. Recent studies have demonstrated that aqueous extracts of PLR exert significant anti-obesity effects in HFD-induced obesity models by activating brown adipocytes, enhancing energy expenditure, and improving insulin sensitivity[101]. Imbalances between fat absorption and consumption are recognized contributors to obesity. Lyu et al.[102] reported that puerarin targets the GABRA1 receptor to regulate fat absorption *via* the brain-gut axis, leading to weight loss. Puerarin inhibits the activity of neurons in the dorsal vagal motor nucleus and shortens jejunal microvilli, thereby reducing the contact area between fat and intestinal epithelial cells and decreasing fat absorption. In addition, lipid synthesis and fat accumulation are major contributors to obesity, and AMPK is a key regulator of hepatic lipogenesis. Research indicates that puerarin ameliorates hepatic steatosis in obese rats by inhibiting lipid synthesis *via* the ACC pathway[103]. OK-Hwan et al.[104–105] demonstrated that puerarin reduces body fat accumulation by activating the AMPK signaling pathway, which inhibits SREBP-1 protein expression, promotes lipolysis and fatty acid oxidation, and suppresses lipid synthesis. Anti-inflammatory and antioxidant effects are considered promising strategies for the treatment of obesity-related chronic diseases. Polyphenolic components in the PLR extract exhibit strong antioxidant capacity, significantly increasing the activity of antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase, *in vivo*. This reduces oxidative stress–induced cellular damage, and consequently, reduces the risk of obesity and related metabolic complications[106].

In summary, compounds in PLR, such as puerarin, regulate obesity through multiple pathways. Potential mechanisms include the activation of signaling pathways, such as AMPK, which promotes energy metabolism and lipolysis, thereby inhibiting fat synthesis. Additionally, PLR may regulate fat absorption *via* the brain-gut axis, thereby reducing weight gain and metabolic disorders associated with an HFD (Figure 10). These findings indicate that PLR is a promising therapeutic agent for the prevention and treatment of obesity. However, to date, most mechanistic studies have been conducted in animal models, and there is a lack of corresponding clinical data from practical application studies. Further studies are required to clarify the precise mechanisms and clinical efficacy of these drugs.

Anti-osteoporosis effects and associated mechanisms

Osteoporosis is an MDs defined by reduced bone mass and impaired bone microarchitecture. It often arises from abnormal calcium and phosphorus metabolism associated with endocrine disorders, gastrointestinal diseases, or nutritional deficiencies. The resulting low bone mass and compromised bone tissue structure increase bone fragility and fracture susceptibility[107]. The proliferation, differentiation, and mineralization of osteoblasts are critical processes in bone formation and remodeling. Puerarin has been shown to enhance osteoblast activity by promoting cell proliferation and differentiation, thereby representing a promising therapeutic strategy

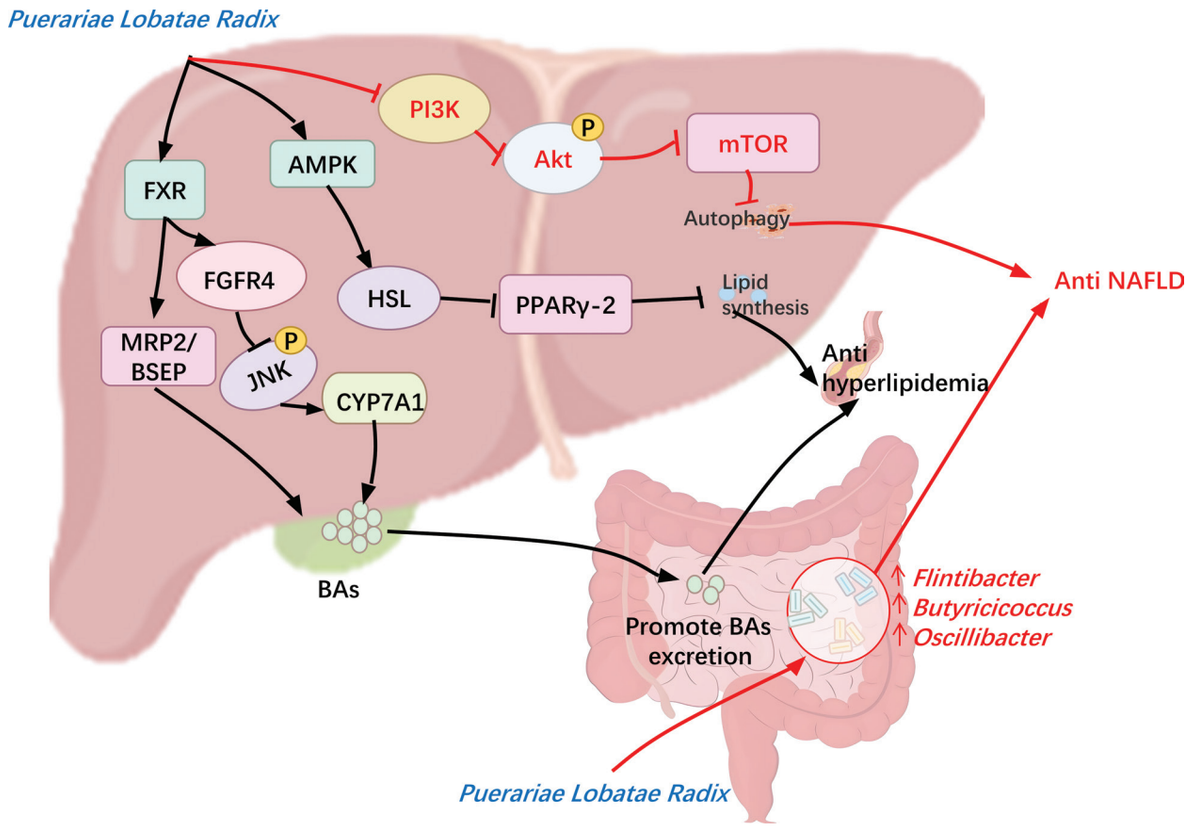

Figure 9. Mechanism of action of lipid regulation by the primary active ingredients in *Puerariae Lobatae Radix*. "→": Direct stimulatory effect; "┤": Direct inhibitory effect; Akt: Protein kinase B; AMPK: Adenosine monophosphate-activated protein kinase; BAs: Bile acids; CYP7A1: Cholesterol 7α-hydroxylase; FGFR4: Fibroblast growth factor receptor 4; FXR: Farnesoid X receptor; HSL: Hormone-sensitive lipase; JNK: c-Jun N-terminal kinase; MRP2: Multidrug resistance-associated protein; mTOR: Rapamycin target protein; PI3K: Phosphoinositide 3-kinase; PPARγ-2: Peroxisome proliferator-activated receptor γ-2.

for osteoporosis[108–109]. Feng et al.[110] reported that puerarin enhances the viability of MC3T3-E1 osteoblasts, leading to significant increases in alkaline phosphatase activity and mineralized nodule formation. Additionally, puerarin decreases *miR-204* expression levels, thereby promoting MC3T3-E1 cell viability and differentiation *via* autophagy. Yu et al.[111] demonstrated that puerarin enhances osteoblast differentiation and promotes autophagosome formation by upregulating LC3-II and Beclin-1 expression. These findings suggest that autophagy serves a critical regulatory function in puerarin-mediated osteoblast proliferation. Additionally, Zhao et al.[112] demonstrated that puerarin promotes osteoblast proliferation by modulating the JAK2/STAT3 signaling pathway, thereby mitigating osteoporosis.

Excessive activation or differentiation of osteoclasts results in increased bone resorption, decreased bone mass, compromised bone structure, and abnormal bone tissue metabolism[113]. Consequently, the inhibition of osteoclast differentiation and bone resorption represents a therapeutic strategy for osteoporosis. Studies have shown that PLR extracts significantly inhibit RANKL-induced osteoclast differentiation, formation, and activation. This effect is primarily mediated by suppression of the CREB/Pgc1β signaling pathway, which sequentially inhibits c-Fos and NFATc1 expression, ultimately reducing osteoclast production and alleviating osteoporosis[114]. Feng and Tang[115] demonstrated that puerarin mitigates bone loss in ovariectomized rats subjected to oxidative stress and increases the OPG/RANKL ratio, FoxO1 protein expression levels, and transcriptional activity, thereby inhibiting the differentiation of RAW264.7 cells into osteoclasts.

Postmenopausal women exhibit increased bone turnover because of estrogen deficiency, and the resulting imbalance between bone formation and resorption can lead to osteoporosis[116]. Puerarin exerts estrogen-like effects and alleviates osteoporosis. Yang et al.[117] demonstrated that puerarin modulates bone metabolism *in vivo* by regulating the PPARγ/Axin2/Wnt pathway, thereby alleviating osteoporosis in ovariectomized rats. Additionally, puerarin prevents postmenopausal osteoporosis in ovariectomized rats by reducing bone turnover markers, increasing plasma estradiol levels, and enhancing estrogen receptor-α protein expression[118].

In summary, an imbalance between osteoblast function and osteoclast activity, combined with postmenopausal estrogen deficiency, is a major factor in the development of osteoporosis. Animal and cellular studies have suggested that puerarin in PLR mitigates osteoporosis by modulating *miR-204*, JAK2/STAT3 pathways, and autophagy. These effects promote the proliferation, differentiation, and activity of osteoblasts. Puerarin also inhibits osteoclast differentiation through pathways such as

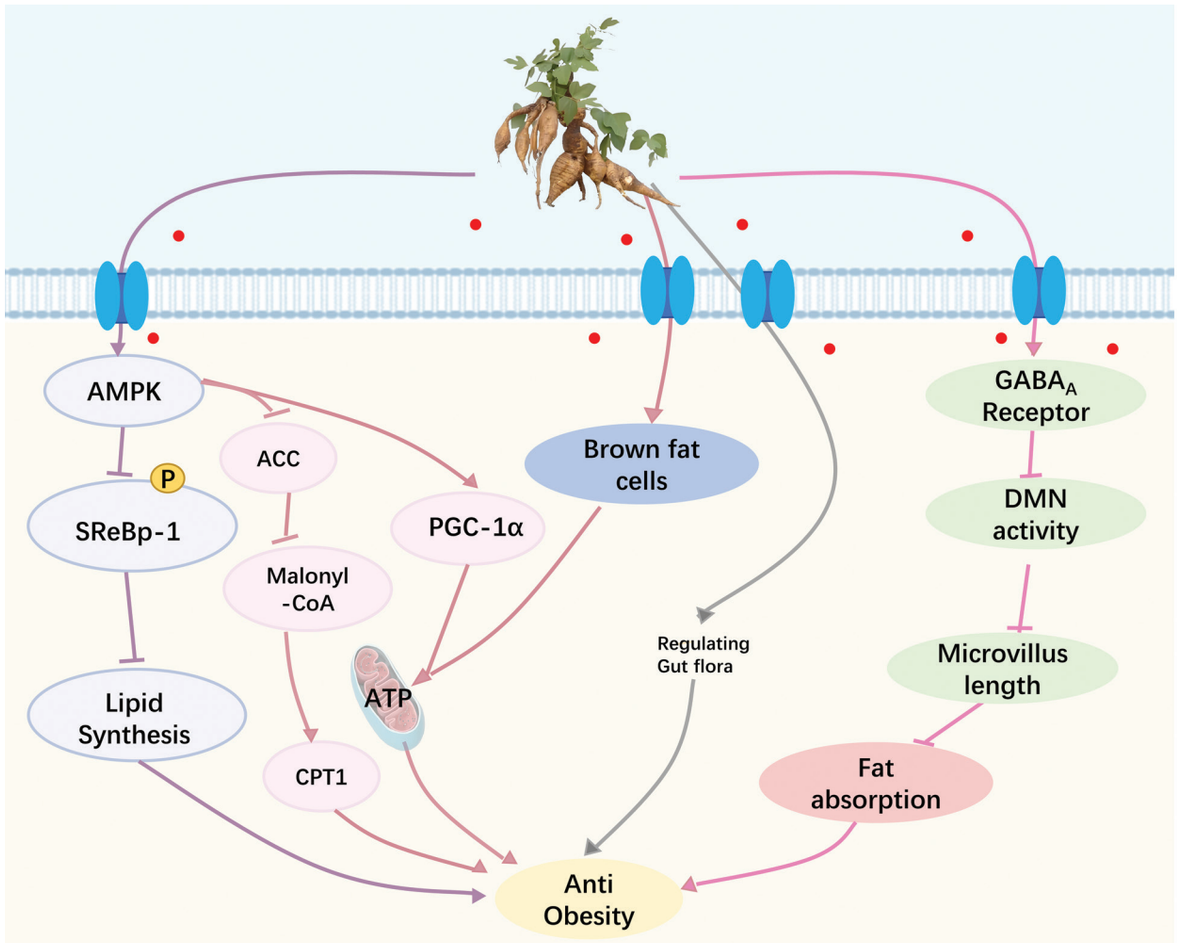

Figure 10. Mechanism of action for obesity regulation by the primary active ingredients in *Puerariae Lobatae Radix*. →: Direct stimulatory modification; ┤: Direct inhibitory modification (created using BioRender). ACC: Acetyl-CoA carboxylase; AMPK: Adenosine monophosphate-activated protein kinase; ATP: Adenosine triphosphate; CPT-1: Carnitine palmitoyl transferase 1; GABAA: Gamma-aminobutyric acid A receptor; Malonyl-CoA: Malonyl coenzyme A; PGC-1α: Peroxisome proliferator-activated receptor γ coactivator 1 α; SReBp-1: Sterol regulatory element-binding protein 1; TORC2: Transcription coactivator 2 of the TOR complex.

CREB/Pgc1β. Animal studies have shown that puerarin has estrogen-like effects that may alleviate osteoporosis. However, research on the role of puerarin in osteoporosis has been limited to animal and cellular models, and there are insufficient clinical studies to fully evaluate its therapeutic efficacy.

Anti-gout effects and associated mechanisms

Gouty arthritis (GA) is an MDs in which monosodium urate (MSU) crystals slowly accumulate in the joints and surrounding soft tissues. This is the result of the inability to properly process purines or remove sufficient acid. GA is a lifelong illness that causes joint deformities, disability, and kidney damage. It can have serious effects on both physical and mental health as well as the overall quality of life[119]. Lowering uric levels in the body is the primary way to prevent GA attacks. Zhang et al.[120] created a mouse model of GA by injecting MSU into the ankle joints. Mice treated with puerarin had significantly lower blood uric acid levels than mice in the control group. Wang[121] also studied patients with high uric levels before and after puerarin injections. They found that the serum uric acid levels decreased significantly after treatment. Xanthine oxidase (XO) is the main enzyme involved in uric acid production. It converts hypoxanthine to xanthine, and then xanthine into uric acid. Shen[122] demonstrated that both water and ethanol extracts of PLR can inhibit XO activity, which helps to lower blood uric acid levels. Shi et al.[123] used a hyperuricemic rat model and administered puerarin at 100, 300, and 500 mg/kg. Their results showed that the correct dose of puerarin reduces uric acid production by blocking XO activity. It also helps the body remove uric acid, which lowers MSU buildup and further reduces the risk of gout attacks. Zhang et al.[124] cultured human proximal tubule epithelial cells with different amounts of puerarin and found that puerarin helped remove uric acid by increasing the levels of adenosine triphosphate-binding cassette transporter G2, which lowers uric acid levels. High levels of inflammatory factors are the main cause of acute GA. Studies have shown that flavonoids in PLR have strong anti-inflammatory effects[125]. Xiong et al.[126] demonstrated that puerarin can inhibit the TLR4/

NF-κB signaling pathway, reducing the production of the inflammatory cytokines interleukin-1β (IL-1β)and tumor necrosis factor-α (TNF-α) and helping improve acute GA. Zhang et al.[127] created a mouse model of GA by injecting mice with MSU. Their experiments showed that puerarin alleviated GA by reducing inflammation, increasing arginase-1 protein levels, and decreasing NOS2 and NLRP3 protein levels.

In summary, research on PLR for the treatment of GA has primarily focused on puerarin, with few studies addressing other active components. Furthermore, most studies are limited to basic research at the animal and cellular levels. Future research should investigate additional active components in PLR and elucidate their mechanisms of action for the prevention and treatment of GA, while prioritizing large-scale, multicenter, controlled clinical trials.

The gut microbiota and MDs

In recent years, the gut microbiota has become a significant focus in the prevention and management of MDs. Through its genetic material, intermediate metabolites, and metabolic activities, the gut microbiota influences human metabolism in multiple ways and exerts both positive and negative effects on health and diseases. There is substantial evidence demonstrating that the gut microbiota and its metabolites regulate host metabolic homeostasis by modulating key pathways such as energy balance, the immune response, BAs metabolism, intestinal barrier integrity, and gut-brain axis communication[128]. The gut microbiota of patients with diabetes demonstrates varying degrees of dysbiosis, with the most significant changes occurring in the phyla Firmicutes and Bacteroidetes. Studies have shown that a water extract of PLR (PTR) significantly alleviates pancreatic tissue damage in db/db mice and decreases fasting blood glucose levels. Additionally, PTR decreases the Firmicutes/Bacteroidetes ratio and regulates the abundance of three beneficial and one harmful bacterial species. As a result, PTR ameliorates both T2DM symptoms and the gut microbiota imbalance in db/db mice, thereby affecting T2DM-related metabolic dysfunction. Zhu et al.[129] demonstrated that PLR alleviates inflammatory damage to pancreatic islet cells in db/db mice with T2DM and reduces IR. The underlying mechanism may involve an increased abundance of Actinobacteria, Bifidobacteria, and *Bacteroides* in the gut, as well as the upregulated expression of proteins related to gut microbiota metabolites. In patients with HLP, the abundance of beneficial bacteria with anti-inflammatory properties decreases, whereas the number of pathogenic microorganisms increases, suggesting a strong association between the gut microbiota composition and physiological activities in HLP patients[130]. PLR enhances intestinal barrier function, decreases the absorption of microbial metabolites and endotoxins, reduces systemic inflammation, increases the abundance of beneficial gut bacteria, inhibits the proliferation of harmful bacteria, and regulates lipid metabolism[131]. Recent studies have indicated that the gut microbiota can influence metabolic functions and the pathogenesis of NAFLD[132]. Li et al.[132–133] isolated a novel low-molecular-weight polysaccharide, RPP-2, from PLR that possesses an α-D-1,3-glucan backbone. RPP-2 modulates the abundance of *Flintibacter*, *Butyricicoccus*, and *Oscillibacter* and their metabolites, including lipopolysaccharide, BAs, and short-chain fatty acids (SCFAs). These changes subsequently influence the signaling pathways associated with inflammation, lipid metabolism, and energy metabolism, thereby ameliorating NAFLD. Dysbiosis of the gut microbiota is a key mechanism underlying obesity. Puerarin has been shown to significantly improve gut microecology. Studies have demonstrated that puerarin intervention markedly increases the α-diversity of the gut microbiota in HFD-induced obese mice and normalizes the β-diversity of the microbial community to levels comparable to those observed in the normal diet group[134]. Puerarin significantly increases the abundance of beneficial bacteria, including *Akkermansia muciniphila*, *Lactobacillus* spp., and *Clostridium celatum*. This enhanced microbial abundance contributes to the alleviation of obesity-related MDs[134–135]. Recent studies have demonstrated that the gut microbiota also influences the development of osteoporosis by inducing inflammatory responses and modulating the autoimmune system[136–137]. Puerarin enhances bone mineral density, improved intestinal mucosal integrity, and reduced systemic inflammation. Additionally, it corrects dysbiosis, elevates SCFAs levels, and enriches metabolic pathways, such as amino acid metabolism, endotoxin biosynthesis, and butyrate metabolism pathways. Collectively, these effects improve the bone microenvironment and exert anti-osteoporotic actions[138].

In summary, the gut microbiota is closely associated with MDs. Animal studies have demonstrated that components, such as PTR, puerarin, and PLPs, can ameliorate MDs, including T2DM, HLP, and osteoporosis. These effects may be mediated by the regulation of the gut microbiota, specifically by increasing the abundance of beneficial bacteria, such as Actinobacteria and Bifidobacteria, and reducing the abundance of harmful bacteria. This shift in microbial composition can influence metabolic byproducts, such as SCFAs and BAs, which are involved in glucose and lipid metabolism, ultimately contributing to improved metabolic conditions.

Clinical applications of PLR

PLR and its preparations are widely used in the clinical management of MDs. Various PLR-based medications are available, including Yufeng Ningxin Tablets for hypertension and Xinxuening Tablets for hypertension and HLP. Furthermore, health food products derived primarily from PLR, such as Danshen-Gegen capsules and Sanqi-Gegen tea, have been developed to provide auxiliary lipid-lowering effects (Table 5). These examples illustrate the broad application of PLR, ranging from therapeutic interventions to preventive measures.

Recent clinical studies have shown that PLR extract provides substantial therapeutic benefits in the treatment of osteoporotic fractures in older adult patients, with an overall cure rate of 96.0% and a low incidence of adverse reactions[139]. According to the traditional Chinese medicine theory, PLR is frequently combined with other herbal medicines to achieve beneficial outcomes in the management of metabolic disorders.

Table 5

Representative Chinese Patent Medicines and health food products containing *Puerariae Lobatae Radix*

No.	Name	Functions and indications	Dosage instructions	Specifications
Medicines				
1	Gegen-Huangqin-Huanglian Tablets	Treatment of chronic metabolic diseases	po, 3–4 tablets/dose, 3 times/day	0.3 g/tablet
2	Getong Tongluo Capsule	Treatment of atherosclerosis	po, 2 tablets/dose, 2 times/day	0.25 g/tablet
3	Yufeng Ningxin Tablets	Treatment of hypertension	po, 5 tablets/dose, 3 times/day	0.28 g/tablet
4	Xiao Ke Pills	Treatment of type 2 diabetes	po, 5–10 pills/dose, 2~3 times/day	2.5 g/10 pills
5	Jinlida Granules	Treatment of type 2 diabetes	po, 1 bag/dose, 3 times/day	9 g/bag
6	Xinxuening Tablets	Treatment of hypertension and hyperlipidemia	po, 4 tablets/dose, 3 times/day	0.21 g/tablet
Health food products				
1	Yinyanghuo-Gegen-Huangqi Granules	Increase bone density	po, 4 capsules/dose, 2 times/day	0.4 g/capsule
2	Pueraria lobata Isoflavone Extract Capsules	Increase bone density	po, 2–3 capsules/dose, 1 time/day	0.54 g/capsule
3	Taizishen-Shudihuang-Gegen Tablets	Auxiliary hypoglycemic	po, 3 tablets/dose, 3 times/day	0.5 g/tablet
4	Gegen-Huangjing-Hongshen Tablets	Auxiliary hypoglycemic	po, 3 tablets/dose, 2 times/day	1.0 g/tablet
5	Gegen-Shanyao Capsules	Auxiliary hypoglycemic	po, 3 capsules/dose, 2 times/day	0.45 g/capsule
6	Sanqi-Gegen Tea	Auxiliary blood lipid reduction	po, 1 bag/dose, 3 times/day	2.5 g/bag
7	Danshen-Gegen Capsules	Auxiliary blood lipid reduction	po, 3 capsules/dose, 2 times/day	0.35 g/capsule
8	Gegen-Mugua Pills	Auxiliary blood lipid reduction	po, 10 pills/dose, 3 times/day	0.15 g/pill
9	Ginkgo Biloba Leaf-Gegen Capsules	Auxiliary blood lipid reduction	po, 2 capsules/dose, 2 times/day	0.3 g/capsule

Clinical analyses of the efficacy and effects of Gegen Huangqin Decoction on blood glucose levels in diabetic patients suggest that this formula enhances insulin bioactivity in individuals with IR[140]. In a clinical trial, 60 patients with T2DM were randomly assigned to either a treatment group (n = 30) or a control group (n = 30). Both groups received standard saxagliptin therapy, and the treatment group received Gegen Huangqin Decoction. The treatment group exhibited significantly improved clinical indicators of glucose metabolism compared with the control group, including a lower IR index value ($P < 0.05$), decreased glycated hemoglobin levels, and decreased fasting ($P < 0.05$) and 2-hour postprandial ($P < 0.05$) blood glucose levels[141]. In accordance with the principle of treating different diseases using the same method, certain clinical settings use Ge gen qin lian Tang for the management of HLP[142]. Huangqi-Gegen Decoction, which was first documented in the Qing Dynasty's "Compendium of Diagnosis and Treatment," consists of two herbs, *Astragalus membranaceus* and PLR. Historically, this formula has been used to treat "xiao ke" (diabetes). In contemporary clinical practice, it has demonstrated significant hypoglycemic effects. Tian et al.[143] assigned 82 patients with T2DM to two groups, with the experimental group receiving adjunctive Huangqi-Gegen Decoction. After 8 weeks, both groups demonstrated reductions in fasting blood glucose, 2-hour postprandial glucose, and glycated hemoglobin levels. The experimental group achieved greater reductions in these measures than the control group. Tang[144] studied 96 patients. The experimental group in their study received a modified Huangqi-Gegen decoction in addition to conventional therapy. Lower fasting blood glucose, 2-hour postprandial glucose, and hemoglobin A1c levels were observed in the experimental group than the control group. These findings suggest that Huangqi-Gegen Decoction can effectively control blood glucose levels and alleviate symptoms during the treatment of diabetes. Furthermore, puerarin, the primary active component of PLR, demonstrates synergistic effects when used in combination with other agents. It is often administered alongside Western medications, such as metformin, angiotensin-converting enzyme inhibitors, insulin, deferiprone tablets, ferritin, and alpha-lipoic acid to manage diabetes and its complications[145]. Diabetic retinopathy is an ocular fundus disorder commonly observed in individuals with diabetes. In one clinical study, 132 patients with diabetic retinopathy were randomly assigned to either a treatment group (n = 66) or a control group (n = 66). Both groups received standard α-lipoic acid therapy, whereas the treatment group received a puerarin injection. The results indicated that puerarin injection was associated with a higher overall response rate, lower total symptom score, improved blood rheological parameters, and no increase in the incidence of adverse reactions in patients with diabetic retinopathy[146]. Selected clinical studies are summarized in Table 6.

Only a limited number of clinical trials have investigated the use of PLR, its derivatives, and puerarin in the treatment of MDs. Most of the available studies exhibited low methodological quality, frequently lacked double-blind designs, and involved participant discontinuation or withdrawal. These trials generally included fewer than 100 participants. To provide a more accurate assessment of clinical efficacy, future research should focus on well-designed, multicenter, large-scale, randomized controlled trials to evaluate the effectiveness and safety of PLR and related compounds in the management of MDs. Market research and the literature indicate that

Table 6

Partial clinical studies of *PLR* and its compound preparations in the treatment of metabolic diseases

Study design	PLR products	Other medicine	Patient numbers		Patient type	Dosage		Duration	Total clinical efficacy, %		Ref.
			Experimental group	Control group		Experimental group	Control group		Experimental group	Control group	
Randomized, controlled	Puerarin injection (Pue)	Conventional hypoglycemic drugs	86	80	Type II diabetes	Conventional hypoglycemic drugs Pue: 4 mL/day Huangqi injection: 20 mL/day	Conventional hypoglycemic drugs	10 days	94.1 ($P < 0.01$)	78.7	[147]
Randomized, controlled	Puerarin injection (Pue)	Conventional hypoglycemic drugs	26	26	Type II diabetes	Conventional hypoglycemic drugs Pue: 4 mL/day Huangqi injection: 20 mL/day	Conventional hypoglycemic drugs	10 days/course; 2 courses	92.3 ($P < 0.01$)	76.9	[148]
Randomized, controlled	Puerarin injection (Pue)	Epalrestat (Epa)	41	40	Diabetic peripheral neuropathy	Pue: 400 mg/day Epa: 50 mg/time 3 times/day	Epa: 50 mg/time 3 times/day	2 weeks	80.5 ($P < 0.05$)	60.0	[149]
Randomized, controlled	Gegen Qinlian Decoction	Metformin (Met)	25	25	Type II diabetes	Met: 0.5 g per tablet 2 times/day Gegen Qinlian Decoction: 300 mL/day	Met: 0.5 g/tablet 2 times/day	8 weeks	96 ($P < 0.05$)	80	[150]
Randomized, controlled	PLR extract	Rehabilitation therapy	50	47	Senile osteoporosis	Rehabilitation therapy PLR extract i.g	Rehabilitation therapy	60 days	96.00 ($P < 0.05$)	82.98	[139]
Randomized, controlled	Puerarin injection (Pue)	α-Lipoic acid	61	61	Diabetes and carotid atherosclerosis	Pue: 400 mg/day, 1 time/day, 5 times/week	α-Lipoic acid: 600 mg/dose iv. 1 time/day	30 days	86.89 ($P < 0.05$)	68.85	[151]

PLR: *Puerariae Lobatae Radix*.

PLR is often combined with other Chinese herbal medicines or Western pharmaceuticals for the treatment of MDs. Existing therapeutic strategies primarily target diabetes and HLP. However, clinical research data on other MDs subtypes are limited, and no approved drugs are currently available. Clinically, only puerarin and puerarin eye drops are administered. Further investigations are needed to determine whether other active components of PLR can be developed into clinical formulations. Therefore, progress in clinical research on PLR is anticipated to be a lengthy and complex process.

Conclusions and perspectives

This paper reviews the growth distribution, environmental adaptability, morphological characteristics, and harvesting and processing methods of PLR, as well as its primary bioactive components such as isoflavones, polysaccharides, and starch. The review emphasizes the pharmacological effects and clinical application prospects of PLR in the treatment of MDs. However, challenges still exist in the development and application of PLR in areas such as cultivation, species identification, constituent analysis, and clinical translation.

Currently, PLR production predominantly relies on wild-type plant resources. However, large-scale artificial cultivation has not yet been realized. Although artificial planting has started in some regions, challenges persist. However, high costs and low yields hinder sustainable utilization. Strengthening the collection of PLR germplasm resources and documenting their biological characteristics is required. Systematic analyses of phenological and morphological traits will help to establish a foundation for germplasm domestication and breeding. Priorities should include cultivating specialized medicinal varieties and selecting superior germplasm. The focus should be on stress tolerance and broad adaptability. Standardized germplasm repositories should be established to resolve the issues of confusion and inconsistent quality. Moreover,

standardized cultivation techniques should be developed to improve the stability of raw material quality and yield.

Pueraria lobata and *Puerariae thomsonii* exhibit considerable morphological similarity in medicinal materials, particularly after the aboveground parts wither during root harvesting. This similarity complicates accurate identification and can lead to clinical misapplication. Addressing these challenges requires the integration of multidisciplinary evidence, including morphological and molecular data, to revise the taxonomic system of *Pueraria*, resolve controversies regarding species delimitation, and clarify phylogenetic relationships. Advancements in identification technologies, such as DNA barcoding and quantitative fluorescent polymerase chain reaction, will support the development of precise detection methods for *Pueraria* species. Additionally, incorporating the outcomes of taxonomic classification and identification into industry standards will promote the standardized development and utilization of PLR resources.

Previous studies have primarily focused on a few components, such as puerarin. Other bioactive substances, such as polysaccharides and phenolic compounds, have received little attention. Therefore, current technologies, such as ultrasound-assisted extraction and macroporous adsorption resin separation, require optimization. It is also necessary to develop new, environmentally friendly, efficient extraction, and purification methods. These improvements should enhance extraction rates and purity, lower production costs, and enable large-scale preparation of high-purity active ingredients. This will support further product development. In addition, advanced separation and identification techniques for the chemical constituents is important. Special attention should be paid to evaluating the activity of minor bioactive components, such as polysaccharides, triterpenoids, and phenolic compounds. This approach will help to clarify the synergistic mechanisms among the different components.

The connection between basic research and the clinical application of PLR remains limited. Most of the findings are restricted to cellular and animal studies. High-quality clinical research data that constrain its clinical utilization are lacking. Future research should prioritize multicenter, large-sample, double-blind clinical trials. Integrating clinical samples with metabolomic and metagenomic studies will help clarify the relationships between components, targets, pathways, and phenotypes. This approach can also identify biomarkers of efficacy and safety, improve the quality of evidence and the clinical value, and provide scientific support for the standardized application of PLR and related compounds in MDs and other fields.

Puerarin and genistein are the key active components of PLR. They have poor solubility in both water and lipids, leading to limited oral absorption. They also undergo rapid metabolism and have short half-lives, which further reduce their bioavailability. Consequently, their therapeutic efficacies remain limited. Therefore, the development of novel drug delivery systems, such as nanomedicines and phospholipid complexes, is necessary. Exploring combination therapy strategies may also help improve the bioavailability of compounds, such as puerarin, and expand their clinical applications.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Weifeng Zhu, Jiwen Zhang, and Yongmei Guan were involved in the review and drafting of the manuscript. Xintao Chen, Jing Liu, Qiong Li, Huanhuan Dong, Xu Zhou, Xiaowei Meng, and Bo Wu were responsible for the literature searches, drafting the manuscript, and preparing the figures and tables. Ni Zhang, Wenting Wu, Zhenzhong Zang, Hui Ouyang, and Olga Maria Duarte Silva were responsible for manuscript and image editing tasks. All the authors contributed to the revision of the manuscript and approved its final version.

Ethical approval of studies and informed consent

Not applicable.

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None.

Data availability

Data sharing is not applicable to this article, as no datasets were generated or analyzed in the current study.

Declaration of generative AI in scientific writing

In the "Conclusions and perspectives" section of this paper, the content was first summarized based on the author's own work, and then AI was used for linguistic polishing. During the writing of this paper, AI was used to standardize the abbreviations of some terms.

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