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Mechanisms Underlying the Intervention of Coptis Chinensis Franch. and Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey. in Type 2 Diabetes Mellitus

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Abstract. This study explores the mechanisms underlying the intervention of Coptis Chinensis Franch. and Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey. in type 2 diabetes mellitus (T2DM). Modern research has confirmed that Coptis chinensis Franch. contains chemical components such as berberine, jatrorrhizine, and palmatine. Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey. is rich in catalpol, Rehmannia glutinosa polysaccharides, and acteoside. These components can improve insulin resistance, regulate glucose metabolism pathways, alleviate oxidative stress and inflammation, protect pancreatic β-cells, modulate gut microbiota, and synergistically regulate blood glucose, thereby effectively alleviating the progression of T2DM and the occurrence of complications. This article systematically summarizes their mechanisms of action, providing a basis for the compatibility application of Coptis Chinensis Franch. and Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey. and the optimization of traditional Chinese medicine compound prescriptions.

Keywords: Coptis chinensis Franch., Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey., Type 2 Diabetes Mellitus, Mechanism of Action

1. Introduction

Type 2 diabetes mellitus (T2DM), a prevalent chronic metabolic disorder, witnesses a rising incidence rate year after year. Data from the International Diabetes Federation (IDF) show that the number of adults diagnosed with diabetes worldwide reached 536.6 million in 2021 and is projected to rise to 783.7 million by 2045 [1]. China has the largest number of patients globally, imposing a significant economic burden on individuals, families, and society. The pathological basis of T2DM mainly lies in pancreatic β-cell dysfunction and insulin resistance, which disrupt the dynamic balance maintained by pancreatic β and α cells. Specifically, pancreatic β-cell dysfunction is characterized by deficient insulin secretion and a decreased number of cells, while glucagon secreted by pancreatic α cells promotes an increase in blood glucose. In traditional Chinese medicine (TCM), T2DM falls into the category of "Xiaoke" (wasting-thirst). Its basic pathogenesis is characterized by yin fluid deficiency and excessive dryness-heat, with "heat toxin" being one of the key etiological factors [2]. Based on TCM theories such as "fragile spleen prone to Xiaodan (emaciation-thirst)" and

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"spleen deficiency leading to Xiaoke", the therapeutic principle mainly focuses on invigorating spleen qi and clearing heat. Coptis chinensis Franch. (Huanglian) is the dried rhizome of plants belonging to the genus Coptis (Ranunculaceae). It tastes bitter and is cold in nature, entering the liver, gallbladder, heart, spleen, stomach, and large intestine meridians, and exhibits the effects of "clearing heat and drying dampness, purging fire and detoxifying" [3]. Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey. (Shengdihuang) is a perennial herb of the genus Rehmannia, with a sweet and bitter taste and cold nature. It enters the liver, heart, and kidney meridians, and possesses the effects of "clearing heat and cooling the blood to stop bleeding, nourishing yin and enhancing fluid production" [4]. Huanglian contains a variety of active components, such as berberine, coptisine, and palmatine, which exert functions including anti-oxidative stress, regulating inflammatory responses, enhancing pancreatic islet function, and modulating gut microbiota, thereby demonstrating significant efficacy in the treatment of T2DM [5]. Meanwhile, Shengdihuang extracts and its active ingredients (e.g., catalpol, Rehmannia glutinosa polycarbohydrates, and acteoside) exert hypoglycemic effects by regulating glucose-lipid metabolism disorders, insulin resistance, and related signaling pathways [6]. Currently, research on the intervention of Shengdihuang in T2DM has attracted increasing attention. Experiments on T2DM rats intervened with the "Astragalus membranaceus-Huanglian." herb pair at different compatibility ratios have shown that this combination exhibits a favorable hypoglycemic effect. It can effectively restore the number and arrangement of pancreatic β-cells as well as the β/α cell ratio in pancreatic islets, with the 3∶1 compatibility ratio of "Astragalus membranaceus-Huanglian." showing the optimal intervention effect [7]. Huanglian and Shengdihuang have demonstrated potential application value in the treatment of T2DM. This review aims to summarize the research progress on the mechanisms underlying the intervention of Huanglian and Shengdihuang in T2DM, providing a reference for clinical application and further studies. According to data analysis, Rehmannia glutinosa and Coptis chinensis rank first and sixth among the high-frequency medicinal herbs in prescriptions for diabetes mellitus, respectively. They are not only frequently used alone but also form the most common core compatibility pair, with an occurrence frequency as high as 138 times [8]. These data indicate that Huanglian and Shengdihuang are widely applied and closely combined in TCM prescriptions for T2DM. Therefore, this study aims to thoroughly investigate their significant role in the treatment of T2DM.

2. Chemical components of coptis Chinensis Franch. and Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey

The chemical constituents of Huanglian and Shengdihuang exhibit significant differences: Coptis chinensis primarily contains alkaloids, whereas Rehmannia glutinosa is predominantly composed of iridoid glycosides.

2.1. Component of coptis Chinensis Franch

Modern studies have identified numerous chemical components in Huanglian, including 8-oxo-berberine, gentisic acid, palmatine, epi-berberine, wogonin, jatrorrhizine, indole-3-carboxaldehyde, berberine, cyclo-(phenylalanine-leucine) dipeptide, secoisolariciresinol, cyclo-(phenylalanine-valine) dipeptide, coptisine, columbamine, magnoflorine, 13-methylberberine, and tetrahydroepiberberine [9]. Among these, berberine exhibits the highest content, accounting for more than 50% of the total alkaloids, and acts as the core pharmacologically active ingredients of Huanglian Coptisine, a characteristic marker component of Huanglian, can serve as an identification

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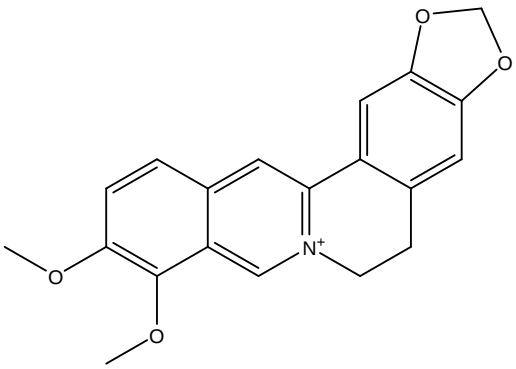
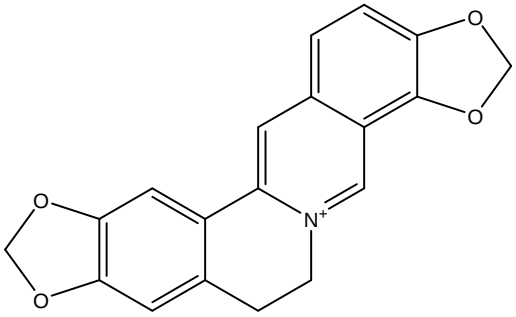
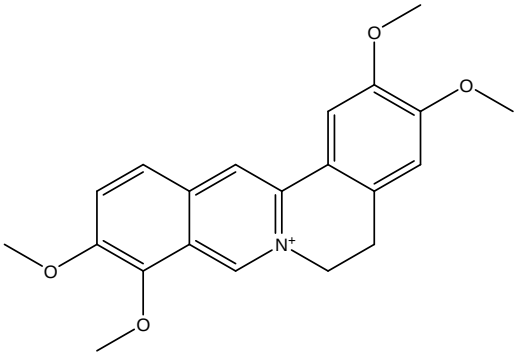
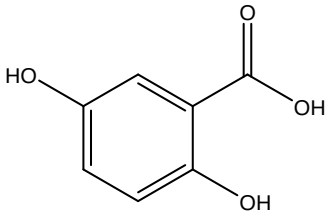
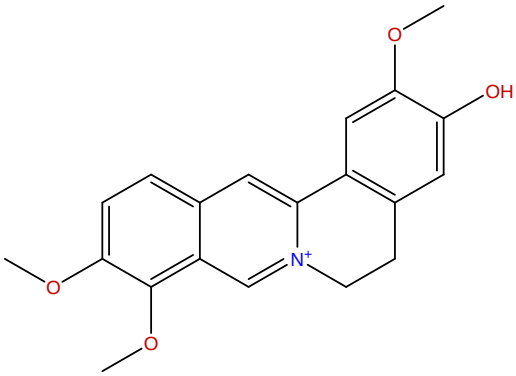
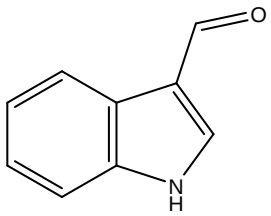
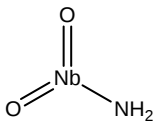
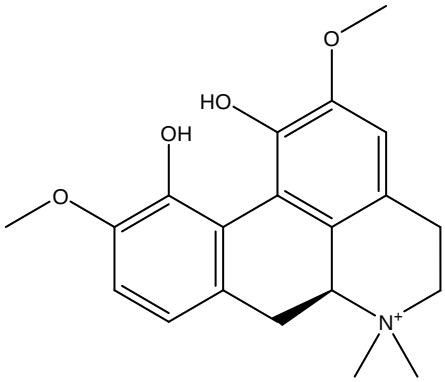
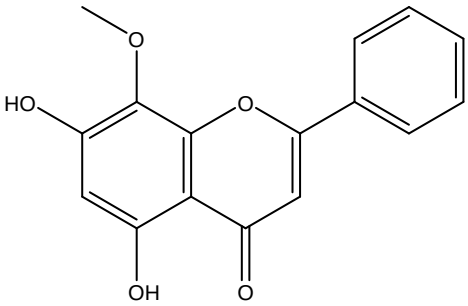
index to distinguish it from other berberine-containing medicinal herbs (e.g., Phellodendri Chinensis Cortex, Berberidis Radix). Additionally, Huanglian contains small amounts of non-alkaloid components for example ferulic acid, chlorogenic acid, and quercetin; however, its primary biological activities are predominantly attributed to alkaloid substances [10].

Table 1. List of component of coptis Chinensis Franch. and Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey

No.	Chemical Name	Structure Description	References
1	Berberine		[9]
2	Coptisine		[9]
3	Palmatine		[9]
4	Gentisic acid		[9]

DOI: 10.54254/2753-8818/2026.PJ30984

Table 1. (continued)

5	Jatrorrhizine		[9]
6	Indole-3-carboxaldehyde		[9]
7	Columbamine		[9]
8	Magnoflorine		[9]
9	Wogonin		[9]

DOI: 10.54254/2753-8818/2026.PJ30984

Table 1. (continued)

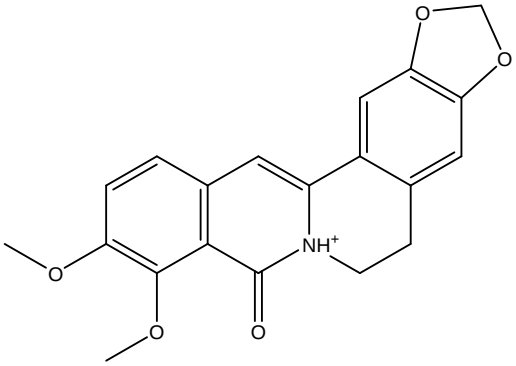
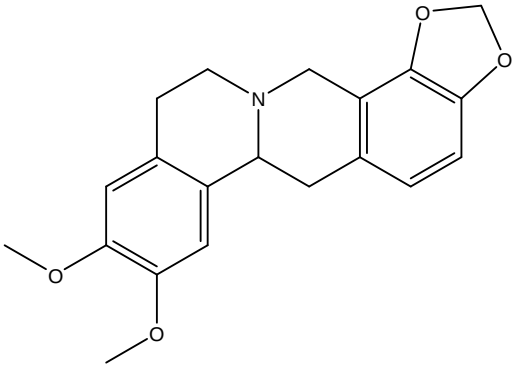
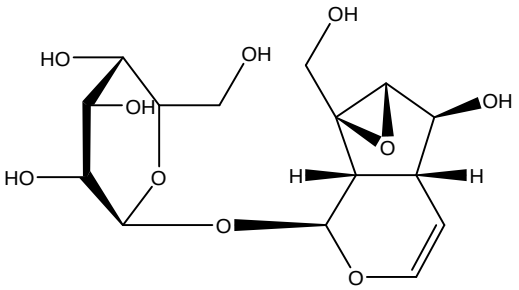
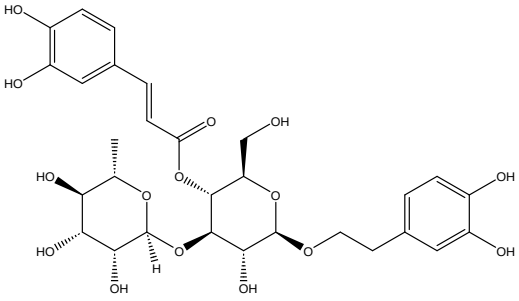
10	8-oxo-berberine		[9]
11	Tetrahydroepiberberine		[9]
12	Catalpol		[13]
13	Acteoside		[13]

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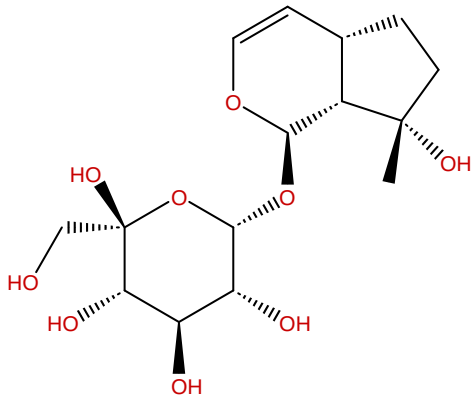
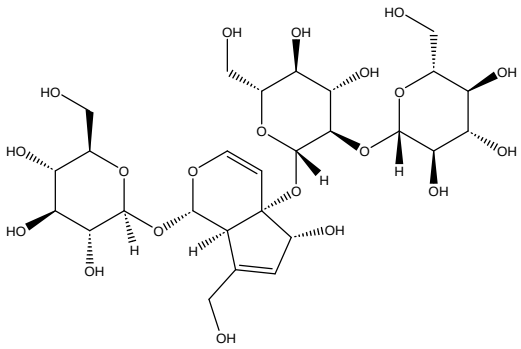
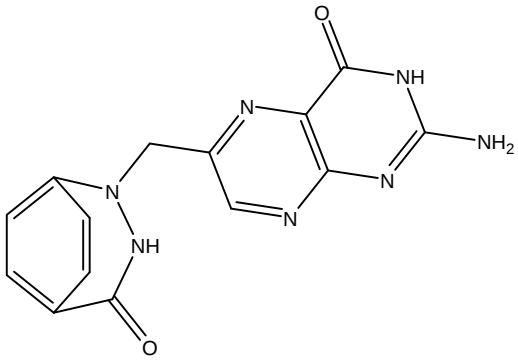
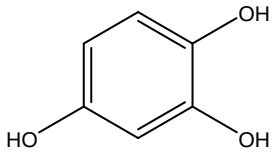
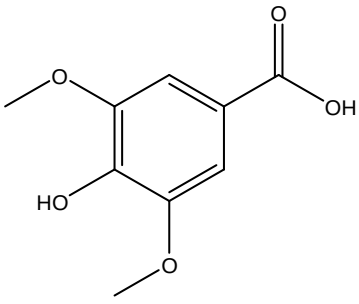
Table 1. (continued)

14	Ajugol		[13]
15	Rehmannioside D		[13]
16	pterolactam		[13]
17	1,2,4-Benzenetriol		[13]
18	Syringic acid		[13]

DOI: 10.54254/2753-8818/2026.PJ30984

2.2. Component of Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey

Modern studies have shown that the chemical constituents of Shengdihuang include iridoids and iridoid glycosides, ionones, phenylethanoid glycosides, and carbohydrates, among others. Specifically. Iridoids: Including ajugol, rehmannioside D, catalpol, 10-deoxyeucommiol, and Rehmannia glutinosa neoterpene H. Ionones: Including rehmionoside C, rehmapicrogenin, 2rehmapicrogenin A, Rehmannia glutinosa neoterpene G, rehmannioside D, and rehmionoside A. Phenylethanoid glycosides: Including leonoside F, echinoside, rehmannioside, acteoside, and isoacteoside. Lignans: Including Rehmannia glutinosa neolignan A, Rehmannia glutinosa neolignan B, and trans-liovil [11-12]. Phenylpropanoids: Including guaiacylglycerol, 7-O-ethyl guaiacylglycerol, coniferin, and methyl ferulate. Other components: Including pterolactam, 1,2,4-benzenetriol, syringic acid, p-hydroxy phenylacetic acid, indole-3-carboxylic acid, and glutinosalactone A [13]. Among these constituents, catalpol is the most abundant small-molecule iridoid, exhibiting significant hypoglycemic, anti-inflammatory, and neuroprotective effects [14]. Rehmannia glutinosa polysaccharide, composed of glucose, galactose, mannose, and other monosaccharides, is a key bioactive substance for regulating immunity and improving insulin resistance [15]. These two components can exert the therapeutic effect of "nourishing yin and promoting fluid production, clearing heat and cooling blood" in the treatment of diabetes mellitus (xiao ke) by activating the AMPK/PI3K/AKT pathway, promoting hepatic glycogen synthesis, inhibiting hepatic gluconeogenesis, and regulating the gut microbiota-enteric neuron homeostasis[14,15].

3. Pharmacological effects of coptis Chinensis Franch. and Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey

Both Huanglian and Shengdihuang exhibit hypoglycemic, anti-inflammatory, and other pharmacological activities. Their compatibility exerts a synergistic effect, improving insulin resistance through multi-target and multi-pathway mechanisms, thereby enhancing the therapeutic efficacy in T2DM.

3.1. Pharmacological effects of coptis Chinensis Franch

Huanglian and its bioactive components (e.g., berberine, coptisine, palmatine) exert significant anti-diabetic effects through multi-target regulation. Berberine, as the core active ingredient, can reduce fasting blood glucose (FBG) by 23.5%–38.2% and glycated hemoglobin (HbA1c) by 19.8%–27.4% in type 2 diabetic animal models (e.g., db/db mice, high-fat diet-induced diabetic rats) [7]. By activating the PI3K/AKT signaling pathway, it upregulates the phosphorylation levels of PI3K (p - PI3K) and AKT (p - AKT) (by 1.8–2.5 folds and 2.1–3.0 folds, respectively). This promotes glucose uptake in skeletal muscle and adipose tissues, and as a result, improves insulin sensitivity [7]. Meanwhile, Huanglian modulates glucose metabolic pathways: it reduces serum glucagon levels by 31.6%–42.3%, downregulates the expression of gluconeogenic enzymes (PEPCK, G6Pase) by 40.1%–55.7%, and inhibits hepatic gluconeogenesis [7]. Additionally, berberine and coptisine synergistically inhibit α-glucosidase activity with an IC_{50} value of 12.3 μmol/L (lower than that of berberine alone, 28.7 μmol/L), slowing down the digestion and absorption of carbohydrates in the small intestine and decreasing the post - prandial blood glucose peak by 28.9%–36.5% [16].In terms of anti-inflammatory and pancreatic islet protection, Huanglian significantly downregulates the mRNA and protein expression of pro-inflammatory cytokines TNF-α (by 45.2%–61.8%) and IL-6

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(by 38.7%–54.3%) in pancreatic islet tissues [7]. This alleviates local inflammation in the pancreatic islet microenvironment, reduces immune cell infiltration, and improves pancreatic β-cell viability (by 29.6%–41.3%) and insulin secretion capacity (by 33.5%–47.2%) [7]. Moreover, palmatine and berberine jointly inhibit the activation of the NF-κB signaling pathway: they reduce the phosphorylation of IκBα (by 52.8%–67.4%) and the nuclear translocation of p65 (by 48.3%–62.1%), thereby reducing the production of reactive oxygen species (ROS) in pancreatic islet cells and protecting them from oxidative damage [16].

3.2. Pharmacological effects of Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey

Shengdihuang exerts multi-target and multi-pathway pharmacological effects in the treatment of T2DM. It can markedly improve insulin resistance and lower the levels of inflammatory markers such as serum free fatty acids (FFA), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), thereby alleviating chronic inflammation and enhancing insulin sensitivity [16]. Shengdihuang regulates glucose metabolic disorders by modulating signaling pathways such as IRS-1/PI3K/Akt, which promotes glucose transport and glycogen synthesis [15]. Its bioactive components, including catalpol and polysaccharides, exhibit significant antioxidant activities: they mitigate oxidative stress-induced damage, protect the structure and function of pancreatic β-cells, and reduce cell apoptosis [17]. Additionally, Shengdihuang modulates the composition of gut microbiota, thereby effectively regulating glucose homeostasis [15].

3.3. Clinical compatibility application of coptis Chinensis Franch. and Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey

The compatibility of Huanglian and Shengdihuang exerts significant pharmacological effects in the treatment of T2DM. A study conducted by Yang et al. demonstrated that both single administration of each herb and their combination could reduce hyperglycemia, hypertriglyceridemia, and hypercholesterolemia in type 2 diabetic rats, with the combined group showing superior efficacy, suggesting a synergistic effect [16]. Compared with the model group, All treatment groups showed a significant decrease in blood glucose levels at every time point, a notable increase in the area under the insulin curve (AUC insulin), and a significant rise in the insulin sensitivity index (ISI).. Additionally, serum triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) were significantly decreased, while high-density lipoprotein cholesterol (HDL-C) was significantly increased [16]. Notably, the improvement in these indicators in the single-herb groups (Huanglian or Shengdihuang alone) was less pronounced than that in the combined group [16]. From a metabolomic perspective, the compatibility of the two herbs could regulate 12 differential metabolites associated with T2DM [18]. Among them, the metabolic profile of the Huanglian single group was closest to that of the normal group, indicating that Huanglian plays a dominant role in different compatibility ratios—serving as the Jun Yao in traditional Chinese medicine theory. Shengdihuang acts as the Chen Yao, assisting Huanglian to enhance its therapeutic effects [18].

4. Mechanisms of action of coptis Chinensis Franch. and Rehmannia glutinosa (Gaetn.) Libosch. ex Fisch. et Mey. in intervening T2DM

Huanglian and Shengdihuang exert a significant effect in intervening T2DM. They can improve insulin resistance, regulate glucose metabolic pathways, and alleviate oxidative stress as well as

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inflammation. Additionally, they protect pancreatic β-cells, modulate gut microbiota, and synergistically regulate blood glucose, thereby effectively alleviating the progression of T2DM and reducing the incidence of complications.

4.1. Improvement of insulin resistance

Berberine, the main bioactive component of Huanglian, can improve insulin resistance by activating the activity of relevant receptors or inhibiting the activity of negatively correlated receptors and cells. It can activate α7 nicotinic acetylcholine receptor (α7nAChR) to enhance glucose uptake in HepG2 cells, and also act on the IKK/NF-κB signaling pathway to reduce hepatic inflammatory responses, thereby improving insulin resistance [19]. Studies have shown that the aqueous extract of Shengdihuang regulates cellular glucose homeostasis, but its hypoglycemic effect in rats was not significant in in vivo studies. However, it can reduce relevant indicators in rats with diabetic nephropathy and alleviate tissue damage. Additionally, it can upregulate the expression of proinsulin gene, inhibit resistin gene, reduce insulin resistance, and attenuate renal fibrosis in T2DM rats [6]. A study by Yang et al. showed that both Huanglian and Shengdihuang have certain effects in improving insulin resistance [16]. Compared with the model group, the Huanglian group, Shengdihuang group, and Huanglian and Shengdihuang combination group showed a significant reduction in blood glucose levels at all time points, a marked increase in the area under the insulin curve (INS AUC), and a significant elevation in the insulin sensitivity index (ISI) [16]. Notably, compared with the single-herb groups, the combination group exhibited superior efficacy, with lower blood glucose levels, larger INS AUC, and higher ISI [16]. Furthermore, all treatment groups exhibited a significant reduction in serum triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), along with a significant increase in high-density lipoprotein cholesterol (HDL-C). The combination group also showed superior improvements in lipid profiles compared to the single-herb groups, indicating a synergistic effect of the two herbs [16].

4.2. Regulation of glucose metabolic pathways

Berberine, the main bioactive component of Huanglian, coordinates hepatic glucose metabolism by regulating the BMAL1: CLOCK circadian clock complex. It can promote the nuclear translocation of Nrf2, upregulate the expression of HO-1 and NQO1, alleviate reactive oxygen species (ROS) accumulation and Ca^{2+} overload, thereby improving mitochondrial function. Meanwhile, it enhances FGF21 expression, activates the AMPK pathway, upregulates UCP1/UCP2, promotes energy expenditure, and improves insulin resistance. Additionally, berberine modulates the expression of proteins related to glycolysis (PFKL), glucose oxidation (PDHA1), and gluconeogenesis (G6Pase, FoxO1, PGC1α), balancing glucose metabolism. This effect depends on the clock-controlled gene network regulated by BMAL1: CLOCK and exhibits circadian rhythmicity. The CLK8 inhibitor can attenuate berberine's regulatory effects on the aforementioned pathways, verifying that its mechanism is dependent on the circadian clock pathway. These findings indicate that berberine synergistically improves hepatic glucose metabolism disorders through the circadian clock-antioxidant-energy metabolism network, providing a new perspective for the treatment of diabetes mellitus [20]. Catalpol and Rehmannia glutinosa polysaccharides, the bioactive components of Shengdihuang, can significantly regulate glucose metabolism in type 2 diabetes mellitus. Catalpol reduces fasting blood glucose and insulin resistance, and improves lipid metabolism, with mechanisms related to activating the AMPK/NOX4/PI3K/AKT pathway, inhibiting hepatic

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gluconeogenesis, and promoting hepatic glycogen synthesis. Rehmannia glutinosa polysaccharides decrease blood glucose, total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), increase insulin levels, enhance basal and glucose-stimulated insulin secretion, reverse the abnormal expression of PEPCK mRNA, and promote glycogen synthesis. Furthermore, the aqueous extract of Shengdihuang improves glucose tolerance, activates the Nrf2 pathway, enhances PKB phosphorylation, inhibits PTEN, improves muscle insulin signaling, alleviates insulin resistance, and comprehensively regulates glucose and lipid metabolism disorders [14].

4.3. Antioxidant and anti-inflammatory effects

Huanglian exerts significant antioxidant and anti-inflammatory effects. Regarding antioxidant stress, T2DM is positively correlated with oxidative stress levels, which constitutes a major pathological mechanism underlying hyperglycemia and its complications. Berberine from Coptis chinensis can exert antioxidant effects by regulating the expression of glutathione peroxidase (GSH-Px) and CuZn-superoxide dismutase (CuZn-SOD), and it also reduces fasting blood glucose in diabetic mice. Modified Dahuang Huanglian Xiexin Decoction (a TCM compound containing Coptis chinensis) can alleviate hepatic oxidative stress-induced damage in T2DM rats. In terms of anti-inflammatory activity, Coptis chinensis can inhibit the endoplasmic reticulum stress signaling pathway to reduce blood glucose and alleviate inflammation; berberine specifically upregulates regulatory T cells (Tregs) and downregulates inflammatory factors, thereby mitigating the inflammatory state [5]. Shengdihuang also exhibits remarkable anti-inflammatory effects, with its main bioactive components—Rehmannia glutinosa polysaccharides and catalpol—playing key roles. Rehmannia glutinosa polysaccharides can inhibit the production of inflammatory factors interleukin-6 (IL-6) and transforming growth factor-β (TGF-β) in lipopolysaccharide (LPS)-induced macrophages, through a mechanism involving the downregulation of AKT/ERK phosphorylation and inhibition of the AKT/ERK/JNK signaling pathway. Catalpol exerts anti-inflammatory effects through multiple pathways: it reduces the levels of various inflammatory factors in the supernatant of RAW264.7 cells, inhibits the NF-κB and MAPK signaling pathways, and reduces blood glucose as well as serum levels of IL-6, tumor necrosis factor-α (TNF-α), and high-sensitivity C-reactive protein (hs-CRP) in diabetic rats, thereby ameliorating the diabetic microinflammatory state [14].

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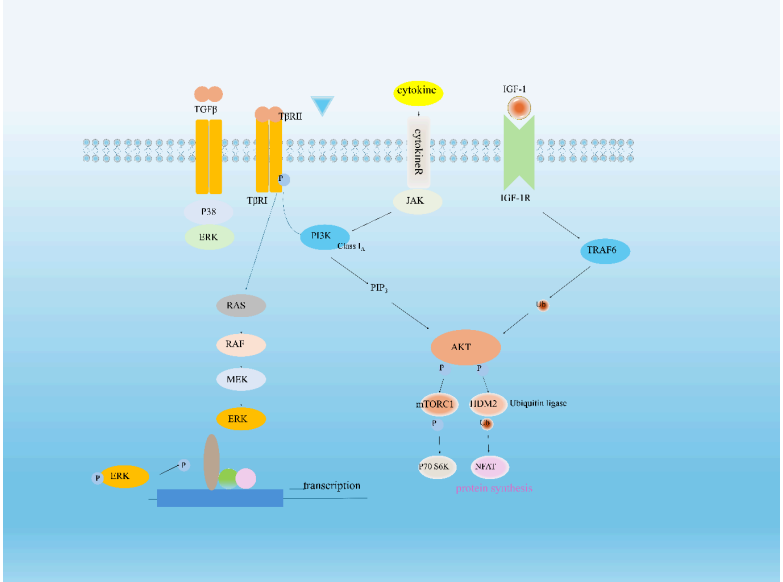

Figure 1. Key signaling pathways

4.4. Protection of pancreatic β-cells

Berberine, the main bioactive component of Huanglian, exhibits a significant hypoglycemic effect. It can promote the repair and regeneration of pancreatic β-cells, improve their insulin secretion function, and enhance insulin sensitivity. Berberine inhibits gluconeogenesis, promotes glucose glycolysis in peripheral tissues, and reduces insulin resistance. Additionally, it lowers postprandial blood glucose by inhibiting intestinal disaccharidase activity, exerting a similar effect to α-glucosidase inhibitors, while simultaneously increasing glucose transport and consumption in adipocytes. Furthermore, its antioxidant activity can reduce the levels of malondialdehyde (MDA) and lactate dehydrogenase (LDH), boost the activity of superoxide dismutase (SOD), and mitigate free radical-induced damage, thereby protecting pancreatic β-cells, slow down the progression of diabetes mellitus, and preventing complications [12]. Shengdihuang exerts a positive effect on protecting pancreatic β-cells in the treatment of T2DM. The aqueous extract of Rehmannia glutinosa can upregulate the mRNA and protein expression of the proinsulin gene in 2-DM rats, improve pancreatic β-cell function, inhibit the expression of the resistin gene in adipose tissue, and reduce insulin resistance. Rehmannia glutinosa oligosaccharides can increase serum insulin levels in diabetic rats, possibly improving insulin resistance by regulating the body's microecological balance and activating related signaling pathways. Rehmannia glutinosa polysaccharides can lower blood glucose and increase hepatic glycogen in alloxan-induced diabetic rats. Catalpol exerts a dose-dependent hypoglycemic effect and comprehensively regulates glucose and lipid metabolism in diabetic mice all of which contribute to the protection of pancreatic β-cells [6].

4.5. Regulation of gut microbiota

The gastrointestinal damp-heat syndrome in TCM is prone to inducing chronic inflammation and impairing gastrointestinal function. Hyperglycemic conditions disrupt the immune system, damage pancreatic β-cells, and may also lead to gastroparesis and constipation. Modern studies have revealed that gut microbiota plays a vital role in the onset and development of Type 2 Diabetes Mellitus (T2DM). Berberine, derived from Huanglian, has antibacterial and anti - inflammatory

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properties and can be utilized to treat diseases related to gut microbiota dysbiosis. Research suggests that berberine can regulate the composition of gut microbiota, safeguard the intestinal barrier, enhance glucagon - like peptide - 1 (GLP - 1) to modulate gut microbiota, boost the activity of Bifidobacterium to improve glucose metabolism, regulate fasting ghrelin to stimulate gastrointestinal peristalsis, and increase the abundance of Lactobacillus acidophilus in the intestines of diabetic mice, bringing it back to normal levels [5]. Oligosaccharides such as stachyose and raffinose in Shengdihuang can regulate gut microbiota and improve T2DM. Due to its α-(1→2) glycosidic bond, stachyose is difficult to be digested in the small intestine; after entering the colon, it is fermented by microorganisms, which can enhance β-amylase activity, increase the abundance of short-chain fatty acids (SCFAs) and beneficial bacteria, activate the PPAR-γ pathway, strengthen the intestinal barrier, and improve the function of the microbiota-metabolism-immune axis. Raffinose is partially hydrolyzed via α-(1→6) glycosidic bonds and can also promote the proliferation of probiotics, inhibit the TLR4-MyD88-NF-κB pathway, and alleviate inflammation. These two oligosaccharides synergistically optimize the intestinal microecology, but their effects are species-specific. Different extraction methods influence the bioactivity of oligosaccharides. Collectively, these effects help improve insulin resistance, regulate glucose and lipid metabolism, and contribute to the management of diabetes mellitus [21].

5. Conclusion

The combination of Huanglian and Shengdihuang exerts a synergistic therapeutic effect against T2DM through multi-component, multi-target, and multi-pathway regulation. Huanglian , with berberine as its core bioactive component, regulates glucose and lipid metabolic pathways, improves insulin resistance, protects pancreatic β-cell function, and exerts significant antioxidant and anti-inflammatory effects. Specifically, it activates pathways such as AMPK and Nrf2/HO-1, modulates the BMAL1: CLOCK circadian clock gene network, enhances mitochondrial function, promotes glucose utilization, and inhibits hepatic gluconeogenesis. In contrast, Shengdihuang relies on its main active components—catalpol, Rehmannia glutinosa polysaccharides, and oligosaccharides—to ameliorate glucose metabolism disorders. It achieves this by upregulating proinsulin gene expression, promoting hepatic glycogen synthesis, and modulating the IRS-1/PI3K/Akt signaling pathway; additionally, it inhibits resistin expression to enhance insulin sensitivity. Both herbs alleviate oxidative stress and chronic inflammation, thereby protecting pancreatic β-cells from damage. Furthermore, Huanglian and Shengdihuang can modulate the composition of gut microbiota, increase the abundance of beneficial bacteria, and strengthen intestinal barrier function, ultimately improving systemic metabolic homeostasis via the "microbiota-metabolism-immunity" axis. Notably, clinical compatibility studies have demonstrated that the combined use of Huanglian and Shengdihuang significantly reduces blood glucose levels and improves dyslipidemia, with superior efficacy compared to the single use of either herb—confirming a synergistic enhancement effect. In summary, the Huanglian- Shengdihuang compatibility provides a solid theoretical basis and application prospect for the optimization of TCM compound prescriptions and precision treatment of T2DM.

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