Mechanisms and Research Progress of Type 2 Diabetes Mellitus and Its Hepatic Complications

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Abstract: Type 2 diabetes (T2DM) is the most common form of diabetes and is a heterogeneous disease that is typically associated with compensatory insulin secretion impairment and insulin resistance. Insulin resistance (IR) is a common pathological feature of metabolic diseases, including obesity, non-alcoholic fatty liver disease (NAFLD), and T2DM, which can reduce the metabolic response of target cells to insulin, leading to impaired ability of circulating or injected insulin to lower blood glucose levels at the whole-body level. This review summarizes the common pathogenic mechanism of T2DM and NAFLD, IR and its concomitant factors, and the current status of traditional Chinese medicine compound therapy, providing a theoretical basis for clinical medicine treatment.

1. The relationship between type 2 diabetes and non-alcoholic fatty liver disease

Diabetes is a disease characterized by high blood glucose levels due to inadequate insulin secretion and/or insulin resistance (IR)[1], type 2 diabetes (T2DM) is characterized by high blood sugar, IR, and relative insulin deficiency, Its main risk factors are related to lifestyle behaviors such as lack of exercise, unhealthy diet habits, smoking, and alcohol consumption, with approximately 89% of T2DM cases related to overweight and obesity[2]. Additionally, IR is directly related to obesity, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD), which is a broad-spectrum disease that can manifest as fatty degeneration, NASH, fibrosis, and cirrhosis.

The main pathological and physiological connection between T2DM and NAFLD is IR[3]. Liver steatosis and fibrosis are associated with the development of IR, which, in turn, increases the risk of subsequent T2DM. On the one hand, high blood glucose is a harmful factor in the development of liver steatosis and fibrosis. HepG2 cells induce fatty degeneration through intracellular lipid accumulation under high blood glucose conditions; high blood glucose-induced inflammation was found to accelerate the progression of NAFLD. In addition, upregulation of the tricarboxylic acid cycle and the expression of ChREBP and LXR-α can promote free fatty acid (FFA) accumulation in cells, stimulate liver lipid synthesis, and increase glucose substrates in liver cells. This cascade reaction activates downstream fibrosis pathways, such as activating the inflammasome through activating inflammatory cytokines IL-1β, IL-6, or TNF-α, leading to cell apoptosis, and ultimately

causing inflammation, liver cell damage, and liver fibrosis. On the other hand, excessive synthesis of triglycerides (TG) is another pathological and physiological marker of NAFLD. Studies on high insulin-positive glucose clamp and HOMA-IR index confirmed that IR is the cause of increased liver cell obesity, which leads to an increase in the glycogenolysis cascade reaction, elevated FFA levels, and impaired liver glycogen synthesis[4], FFA accumulation and IR can activate multiple inflammatory pathways, producing a pro-inflammatory environment and releasing hepatotoxic free radicals, leading to liver cell damage and fibrosis.

In addition, FFA accumulation in liver cells is caused by impaired synthesis and secretion of very low-density lipoprotein (VLDL) and excessive input of FFA from adipose tissue[5], The activation of these cascade reactions ultimately leads to impaired liver antioxidant capacity, increased oxidative stress, and mitochondrial dysfunction or defects, ultimately causing liver fibrosis and IR[6].

1.1. Overnutrition and Insulin Resistance

Obesity and high-calorie diets contribute to the development of insulin resistance (IR), promoting hepatic fat accumulation, fat toxicity, liver damage, and inflammation[7]. Hepatic lipid accumulation is associated with IR in liver, adipose, and muscle tissues, as well as an increased risk of type 2 diabetes mellitus. Nutrient excess in susceptible individuals leads to peripheral tissue IR, which raises blood glucose levels, stimulates insulin secretion by pancreatic beta cells, and hyperinsulinemia contributes to insulin resistance in obese patients.

High-fat diets (HFDs) and overeating directly or indirectly activate liver cell glycemic regulation factors (such as FoxO1), leading to increased hepatic glucose output and the stimulation of glucose transporter GLUT4 in muscle, which reduces glucose uptake and exacerbates insulin resistance in the setting of reduced responsiveness of adipose to insulin[8]. Additionally, patients with insulin resistance caused by a single genetic mutation in insulin signaling components have similarly high circulating insulin levels, indicating that both monogenic and common forms of obesity initially lead to IR, followed by hyperinsulinemia, promoting fatty liver and hypertriglyceridemia.

Under conditions of nutrient excess, primary hyperinsulinemia is the initial cause of IR in target organs such as the liver, and the mechanism of this association may include the downregulation of AKT in the insulin signaling pathway. Activation of AKT by insulin signal in the liver increases the synthesis of free fatty acids (FFAs) from glucose and amino acids, which are eventually packaged into VLDL for output and uptake by peripheral tissues[9]. However, hyperinsulinemia during nutrient excess may amplify the stimulation of fatty acid synthesis pathways that occur under normal feeding conditions, leading to sustained obesity and excessive lipid production. Although AKT can inactivate FOXO1 and control glycogen synthesis, the AKT-activated mTORC1 complex and transcription factor SREBP1C can promote lipogenesis[10]. Under HFD conditions, AKT, which is inactivated by insulin, cannot inhibit liver FOXO1 and adipocyte lipolysis, but it is still capable of activating mTORC1 and the lipogenesis pathway. Additional substrates used in TG synthesis in the liver, accompanied by overnutrition and amino acids, may further activate mTORC1, leading to active fat generation and VLDL synthesis and output in obesity[9].

Additionally, in obesity, the ability of adipocytes to store and retain TG decreases, and fat tissue overloads due to excessive lipid energy storage, causing ectopic fat accumulation and "lipotoxicity" in the liver and muscles, which is a potential cause of IR，Primary IR caused by this condition can also lead to increased blood glucose levels, stimulate insulin secretion, and thus contribute to hyperinsulinemia.

1.2. Type 2 diabetes and Insulin Resistance

Insulin is a metabolic hormone that mediates the liquid-state, ion transport, and storage of TG in adipose tissue and promotes esterification and storage of fatty acids in lipid droplets while suppressing lipolysis. Under normal conditions, pancreatic β-cells secrete insulin after a meal or release of hormones such as catecholamines and glucagon to promote glucose uptake in adipose and liver tissue while inhibiting hepatic glucose production, mediating glucose metabolism. Hormones such as glucagon-like peptide-1 (GLP-1) stimulate gluconeogenesis, glycogenolysis, and hepatic glucose production[11]. Insulin resistance (IR) refers to impaired biological responses to insulin stimulation in target tissues (muscle, liver, and adipose tissue) that usually results in compensatory increases in endogenous insulin secretion. The metabolic consequences can lead to hyperglycemia, hypertension, dyslipidemia, visceral fat, hyperuricemia, elevated inflammation markers, endothelial dysfunction, and a prothrombotic state.

The main consequence of IR is type 2 diabetes mellitus (T2DM). Elevated endogenous insulin levels associated with IR can lead to weight gain, exacerbating IR. This vicious cycle continues until the activity of pancreatic β-cells is unable to fully meet the demands of insulin production, resulting in a sustained imbalance between insulin demand and production, leading to hyperglycemia and T2DM[12]. Insulin acts on all cells by binding to specific receptors and activating cascaded signal transduction pathways. IRS1 and IRS2 are the main mediators of insulin signaling in the liver, controlling insulin sensitivity[13], The typical IRS signaling pathways include IRS1/IRS2-dependent PI3K-PDK-AKT and RAS-ERK pathways, where the PI3K-PDK-AKT pathway mediates gluconeogenesis and glycogen synthesis and the RAS-ERK pathway mediates cell proliferation and survival.

After a meal, high blood glucose is sensed by pancreatic β-cells, stimulating insulin secretion. Insulin binds to and activates insulin receptor tyrosine kinase (IRTK), promoting phosphorylation of insulin receptor substrate 1/2 (IRS1/2), The phosphorylation of IRS2 induces a conformational change, producing a binding site for phosphatidylinositol-3-kinase (PI3K), which converts phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-trisphosphate (PIP3), leading to phosphorylation and activation of PIP3-dependent kinase 1 (PDK1) and subsequent activation of protein kinase B (AKT). Glucose transporter GLUT4 mediates insulin-stimulated glucose uptake in skeletal muscle, liver, and adipose tissue. After AKT activation, GLUT4 translocates to the plasma membrane by inhibiting the action of AS160 protein[14].

Gluconeogenesis and glycogenolysis are two major pathways for endogenous glucose production. Phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) are downstream regulatory factors of FoxO1 in the gluconeogenesis pathway, playing irreversible roles. Reducing their transcription can decrease excessive endogenous glucose production in T2DM patients.[15]. GP, GS, and GK respectively regulate hepatic glycogenolysis, synthesis, and metabolism, among them, GS and GK are downstream negative feedback regulatory factors of glycogen synthase kinase 3β (GSK3β). Activated AKT can initiate hepatic glycogen synthesis by inhibiting GSK3β, promoting the activity of GS and GK[16], reducing the phosphorylation and nuclear exclusion of FoxO1, and inhibiting the activity of PEPCK and G6Pase to suppress gluconeogenesis[15].

1.3. Insulin Resistance and inflammation

Inflammation is one of the main driving factors for simple fatty liver to develop into non-alcoholic steatohepatitis (NASH), and it is also one of the main potential molecular mechanisms of pathological and physiological mechanisms of insulin resistance, diabetes, and related complications, Chronic activation of pro-inflammatory pathways in insulin target cells can lead to

obesity-related insulin resistance, which in turn stimulates the release of cytokines and chemokines such as CCL2, interleukin (IL)-6, IL-1β, and TNFα from fat and macrophage cells[17]. In the state of obesity, macrophages infiltrate target organs and are activated to M1 polarization state, producing abundant inflammatory factors that negatively affect insulin signal transmission, increase the occurrence of chronic inflammation, and thus increase insulin resistance.

Activation of pathways such as IKKβ/NF-κB, JNK, and JAK/STAT may be involved in the connection between inflammation and insulin resistance. Excessive stimulation can activate these inflammatory signaling pathways, and conversely, increased insulin resistance can also stimulate the expression of inflammatory factors .

TNF-α is a pro-inflammatory cytokine derived from adipose tissue that participates in obesity-induced insulin resistance [18]. In the case of insulin resistance and obesity, TNF-α expression in adipose tissue is increased and, with the help of TNFR-1, TNF-α plays an important role in activating and recruiting immune cells to spread inflammation. TNF-α can induce the dual kinase system, including JNK kinase and IKK complex [19]. JNK has JNK-1 and JNK-2 subgroups, in the case of insulin resistance, JNK-1 and IKK signals are upregulated in adipose tissue, skeletal muscle and liver, and JNK can also be activated by TNF-α, IL-1β, and UV light, Activated JNK can cause serine phosphorylation of insulin receptor substrate 1 (IRS-1), thus reducing the tyrosine phosphorylation of IRS-1 and reducing the PI3K and AKT signaling pathways, which are involved in insulin signal impairment.

In addition to the JNK signaling pathway, insulin resistance is also closely related to the activation of NF-κB induced by TNF-α, IL-1β, and IL-6. NF-κB is a transcription factor of Rel family proteins that participates in inflammation and immune responses. IκB retains NF-κB in a stable inhibitory cytoplasmic complex, IKK phosphorylation can phosphorylate IκBα under inflammatory conditions to dissociate IκBα from NF-κB and degrade it [20], releasing free NF-κB to transport to the nucleus and interact with relevant DNA response elements to induce the transactivation of inflammatory genes such as TNF-α, IL-1β, and IL-6, further promoting insulin resistance. IL-1β can disrupt insulin signals in peripheral tissues, reduce the insulin sensitivity and secretion of β-cells. Gao et al. found that the absence of IL-1β completely altered the inhibitory effect of macrophage regulation (MC) medium on insulin signal molecules such as IRS-1 and PI3K, indicating that IL-1β is a key mediator of macrophage-induced insulin resistance . High-fat diet (HFD) feeding increases the activation of NF-κB in mice, which leads to an elevation in the level of IKKε in liver and fat cells. Knocking out IKKε in mice prevents them from being affected by HFD-induced obesity and chronic inflammation.

1.4. Insulin Resistance and oxidative stress

The imbalance between the generation of reactive oxygen species (ROS) and antioxidant defense, as well as oxidative stress caused by chronic inflammation in non-adipose tissue, is a major regulator of insulin sensitivity. Oxidative stress plays a key role in the pathological physiology of various complications of diabetes, including lipid peroxidation, DNA damage, and mitochondrial dysfunction, and can impair insulin signal transduction, increasing the risk of insulin resistance[21]. In addition, oxidative stress is an upstream event of inflammation that induces the activation of monocytes and macrophages, promoting both insulin resistance and inflammatory reactions in diabetes. Elevated pro-inflammatory stimuli may be further amplified by excess ROS, directly damaging insulin signaling in target tissues.

The impairment of pancreatic beta cell number and function is the main cause of diabetes, oxidative stress can also damage β-cell function[22]; induce cell apoptosis in the pancreas resulting in the death and loss of β-cells; and reduce the proliferation and differentiation of β-cells by

complex interactions with various factors such as PDX1, NKX6.1, NGN3, FOXO1, and MAFA, thereby exacerbating insulin resistance. Moreover, the mitochondrial respiratory chain (MRC) and NADPH (nicotinamide adenine dinucleotide phosphate) oxidase or NOX enzyme activity are the main sources of free radicals in pancreatic β-cells，which may negatively affect metabolic pathways in β-cells, damage K+ ATP channels, and lead to a decrease in insulin secretion; furthermore, free radicals can activate TLRs (toll-like receptors) and impair β-cell function; high levels of free radicals also inhibit the expression of insulin gene transcription factors PDX1 and MAFA, thereby reducing insulin production at the DNA level. Nf-κB, JNK/SAPK, p38 MAPK, and the hexosamine pathway were also induced by oxidative stress.

GLUT4 regulates glucose entry into insulin-independent cells such as adipocytes, myocytes, and hepatocytes. Therefore, normal expression and localization of GLUT4 in these tissues is necessary to maintain insulin sensitivity[23]. Oxidative stress significantly inhibits GLUT4 transport. Prolonged oxidative stress can also inhibit transcription factors responsible for GLUT4 expression, such as PPAR-γ (peroxisome proliferator-activated receptor γ), CEB/Ps (CCAAT-enhancer-binding proteins), NF-1 (nuclear factor-1), p85, HIF-1α (hypoxia-inducible factor α), MEF2 (myocyte enhancer factor 2), and Nf-κB; as well as microRNAs that participate in GLUT4 expression, such as miR-21a-5p, miR-222-3p, miR-133b-3p, miR-10b, miR-106b-5p, miR-29c-3p, and miR-133a-3p. In addition, various oxidative stress-inducing factors and products such as p38 MAPK, JNK/SAPK, PKC, sorbitol, and hexosamine can be activated by oxidative damage and inhibit GLUT4 expression. Therefore, the reduction of GLUT4 expression/localization is one of the main molecular mechanisms by which oxidative stress induces insulin resistance and promotes the occurrence of DM.

Any defects in the insulin signaling pathway can lead to insulin resistance and the development of diabetes. Oxidative stress can impair normal insulin signaling transduction (IST) at different levels, including IRs, IRS-1, and IRS2; PI3K enzyme; AKT signaling pathway[24]. Oxidative stress induces serine phosphorylation of IRS1 and IRS2, leading to IST disorder; free radicals can induce serine phosphorylation (Ser 307) of IRS1 by activating the JNK/SAPK signaling pathway, inhibiting normal IST; and can also inhibit normal IST through a molecular mechanism dependent on p38 MAPK inhibition, suppressing the molecular pathway can restore normal IST in vitro and in diabetes animal models. High glucose-induced oxidative stress can activate different stress-sensitive serine/threonine kinases, such as IKK-β, phosphorylating multiple targets such as IRs, IRS1, and IRS2, and having adverse effects on downstream, including reduced PI3K activation and insulin resistance. The inhibitor of IKK-β, salicylates, can restore normal IST under oxidative stress. Other types of serine/threonine kinases, such as AKT, GSK-3, AMPK, and mTOR, are also highly sensitive to oxidative stress and may damage IST. Oxidative stress can also down-regulate proteins involved in normal IST, leading to IST impairment. The main components of IST such as AKT, IRS, IRS1, and GSK-3 are affected by free radicals, which are down-regulated by oxidative stress, leading to impaired insulin sensitivity and insulin resistance and diabetes[25].

In addition, lipid excess can lead to liver fat storage accumulation, abnormal lipid peroxides, pro-inflammatory cytokines, release of high reactive oxygen species (ROS), and reactive nitrogen species (RNS). Lipid peroxidation promotes proliferation of hepatic stellate cells, exacerbating the formation of liver fibrosis; the NRF2/ARE pathway that regulates the antioxidant effects of ROS and RNS is defective in obese and IR patients[26]; ROS induces the release of cytokines from liver cells, triggering TLR4 synthesis and promoting the activation of inflammatory hepatic macrophages[23].

1.5. Insulin Resistance and liver fibrosis

NAFLD is a broad-spectrum disease characterized by the accumulation of liver triglycerides (TG) and insulin resistance, it is the liver manifestation of metabolic syndrome and a disease ranging from benign liver steatosis to non-alcoholic fatty liver disease (NASH), fibrosis, and cirrhosis. Insulin resistance is the core pathophysiology that leads to fatty degeneration, NASH, fibrosis, and cirrhosis[27]. Hyperglycemia and insulin resistance (IR) are fundamental metabolic disorders that trigger the fibrotic cascade in diabetic patients. Their pro-fibrotic effects are mediated by direct actions on fibroblasts, as well as through immune cells, microvascular cells, and epithelial cells, and are mediated indirectly through mechanisms involving damage to organ-specific parenchymal cells (such as hepatocytes or cardiomyocytes), which are perceived by reparative fibroblasts and stimulate matrix deposition. In addition, poor lifestyle habits, such as high-calorie diets, inflammation activation caused by genetic factors, oxidative stress, and lipotoxicity, are potential mechanisms underlying NAFLD and progressive fibrosis.

Liver fibrosis is characterized by excessive extracellular matrix protein (ECMs) deposition, primarily secreted by hepatic stellate cells (HSCs)[28]. When liver injury or chronic inflammation occurs, HSC cells located in the Disse space (also the primary site of vitamin A storage) are activated and differentiate into myofibroblast-like cells with contractile, pro-inflammatory, and fibrotic properties. Activated HSCs migrate and accumulate at sites of reparative tissue, secreting large amounts of ECM, including collagen (I, III, and IV), fibronectin, elastin, laminin, and proteoglycans, and expressing alpha-smooth muscle actin (α-SMA, a myofibroblast cell protein marker). Moreover, an increase in ECM synthesis or a decrease in degradation can lead to ECM accumulation, matrix metalloproteinases (MMPs) can degrade ECM, while tissue inhibitors of metalloproteinases (TIMPs) can inhibit ECM production.

TGF-βs play a key role in the pathogenesis of tissue fibrosis in various diseases and experimental models[29]. The three isoforms of TGF-β (TGF-β1, -β2, and -β3) are induced, secreted, and activated after injury, promoting myofibroblast transformation, activating matrix synthesis, and stimulating the secretion of antiproteases that inhibit matrix degradation (such as TIMP1 and PAI-1)[30]. The fibrotic role of TGFβs includes activation of a cascade of intracellular effectors called Smads or Smad-independent pathways. In diabetic experimental models, TGF-βs and downstream cascades dependent on Smad3 play a role in the pathogenesis of liver, kidney, and heart fibrosis [30].

Although the isoform expression profile and cellular source of TGF-βs in diabetic tissue remain unclear, several cell types, including fibroblasts, macrophages, epithelial cells, vascular cells, platelets, and organ-specific thin-walled cells, may be stimulated to produce and secrete TGF-βs when exposed to high levels of glucose. The high glucose-mediated TGF-β signaling cascade involved in induction and activation in diabetic tissue involves several distinct pathways. First, RAAS stimulation can trigger TGF-β synthesis and promote its activation from potential stores. Second, high glucose induces oxidative stress, leading to TGF-β expression and activation. Third, glucose-induced pro-inflammatory cytokines may stimulate the re-synthesis of TGF-β and the induction of protease activation from potential stores. Fourth, high glucose may generate a TGF-β activation environment in the pericellular area by promoting the secretion of specialized matrix proteins (such as thrombospondin-1 and ED-A fibronectin), upregulating integrins involved in TGF-β activation, which involves releasing active dimers from latent TGF-β stores. Fifth, glucose can rapidly induce the externalization of TGF-β receptors (TβRs) on the cell surface, enhancing the TGF-β/TβR1/Smad3 signaling pathway[31].

2. Effect of traditional Chinese medicine on Type II diabetes mellitus complicated with nonalcoholic fatty liver

Currently, the mainstream treatment methods for Type 2 Diabetes (T2DM) mainly include dietary control, exercise, and oral blood sugar medications, with limited efficacy of subcutaneous insulin injection. Its therapeutic mechanism focuses on a single component, which can effectively control patients' blood sugar levels but has no preventive effect on complications. Diabetes belongs to the category of "Xiao Ke" in Traditional Chinese Medicine (TCM), roughly divided into three types: Yin deficiency with dryness, Qi and Yin deficiency, and Yin-Yang deficiency types. Bitter Chinese herbal medicines are mainly used to treat Yin deficiency and heat type diabetes[32]. Ancient TCM theory believes that the pathogenesis of T2DM lies in Qi stagnation, blood stasis, and phlegm stagnation, leading to damp-heat accumulation in the stomach. Many clinical studies have shown that the Chinese herbal formula has a therapeutic effect on T2DM. Therefore, based on the advantages of TCM's multi-component and multi-target effects, gradually searching for multi-target hypoglycemic drugs from Chinese herbal resources has become a new research hotspot.

2.1. Yinchen-Gongying Decoction

Yinchen-Gongying Decoction, first recorded in 《Jing Yan Fang》, is a traditional small formula composed of Yin Chen and Pu Gong Ying in a ratio of 2:1, which is a medicinal diet with the same source. Yin Chen promotes bile secretion, clears damp-heat, and eliminates jaundice, acting as the sovereign; Pu Gong Ying clears heat and detoxifies, clears the liver, and brightens the eyes, acting as the minister. This formula is suitable for feverish patients with acute jaundice-type hepatitis. Modern pharmacological studies have shown that the combination of the two has effects such as regulating blood lipids, anti-oxidation, anti-inflammation, anti-apoptosis, anti-fibrosis, reducing blood glucose, and improving insulin resistance.

The Chinese herbal medicine Yin Chen is the dried above-ground part of the Chrysanthemum family plants Inula britannica or Inula japonica, with the effects of clearing heat and dampness, promoting bile secretion, and eliminating jaundice. Its main active ingredients are coumarin, flavonoids, organic acids, volatile oils, and other components, which regulate signal pathways and affect the expression of related genes, proteins, or cytokines. When used in combination with Pu Gong Ying, it can reduce swelling, eliminate nodules, promote urination, and clear dampness. Yin Chen has a variety of biological activities, including (1) choleretic effects: Yin Chen can promote the excretion of bile by inducing the expression of the constitutive androstane receptor (CAR) and UDP-glucuronosyltransferase 1A1 (UGT1A1). (2) Hepatoprotective effects: Yin Chen can reduce liver TG and lipid synthesis and improve non-alcoholic fatty liver disease and obesity by activating the PI3K-AKT signaling pathway and promoting SREBP-1c expression . (3) Anti-inflammatory effects: 6,7-dimethoxycoumarin is its main active ingredient, which can enhance mitosis and inhibit the activation of NLRP3 inflammasomes mediated by mitochondrial autophagy, reducing the expression of IL-6, IL-1β, IL-18, and TNF-α. (4) Anti-fibrotic effects: Yin Chen can significantly inhibit the expression of α-SMA, type I collagen, NOX isoforms, and ROS production by suppressing the TGF-β/Smad signaling pathway, thereby weakening TGF-β1-induced HSC-T6 cell activation and preventing hepatic fibrosis. (5) Chlorogenic acid not only reduces the expression of PPARγ1, PPARγ2, and downstream genes CD36, FABP4, and MGAT1 to inhibit hepatic lipid accumulation, but also enhances the expression of PPARα and its target genes FGF21 and acyl-CoA oxidase 1 (Acox1), thereby protecting the stable state of liver lipid metabolism. (6) Water extract of Herba Artemisiae Scopariae regulates the ROS/MAPK axis to affect factors such as caspase-3, Bcl-2, Bax, and SOD-1, exhibiting anti-apoptotic and anti-oxidative effects. (7) Yinchenhao (Herba

Artemisiae Scopariae) can lower the blood glucose of mice with diabetes mellitus, and its mechanism is similar to metformin, and it achieves its lipid-lowering effect by reducing serum TC, TG, and HDL-C levels[33]..

Dandelion is a plant that belongs to the Asteraceae family. Dandelion contains various chemical substances such as sesquiterpene lactones, triterpenoids (such as taraxasterol, taraxerol, and taraxacin), phenolic acids, and flavonoids. Dandelion has various specific bioactivities, and its component, dandelion sterol, has various pharmacological activities: (1) Anti-inflammatory effect: Dandelion can exert its anti-inflammatory effect by inhibiting the TLR2-NF-κB/MAPK signaling pathway; and dandelion sterol can inhibit mTOR signal overactivation induced by LPS, alleviating mitochondrial damage after NLRP3 inflammasome stimulation. (2) Antioxidant effect: The flavonoids in Dandelion have activities to scavenge free radicals, indicating its good antioxidant activity. (3) Hypoglycemic effect: Dandelion can lower blood glucose levels in T2DM rats by improving insulin resistance[34, 35].

2.2. Huanglian Jiedu Tang

Huanglian Jiedu Tang is a classic traditional Chinese medicine prescription that originates from the "Handbook of Emergency Prescriptions" (which is the first clinical emergency manual in China). It consists of four herbs, namely Huanglian (Coptidis Rhizoma), Huangqin (Scutellariae Radix), Huangbai (Phellodendri Chinensis Cortex), and Zhizi (Gardeniae Fructus) in a ratio of 3:2:2:3. It is a heat-clearing agent with detoxifying properties. Quercetin, naringenin, baicalin, and berberine have been identified as potential active ingredients in Huanglian Jiedu Tang. Its mechanism of action is similar to metformin, and it can lower blood glucose levels, improve glucose transporter 4 (GLUT4) and AMP-activated protein kinase (AMPK) expression in skeletal muscle and adipose tissue, thereby enhancing insulin sensitivity and improving pancreatic β-cell mass[36].

Shan nai phenol can improve Akt and hexokinase activity in the liver, reduce pyruvate carboxylase and glucose-6-phosphatase activity, and exert an anti-diabetic effect by inhibiting hepatic gluconeogenesis. It can also alleviate myocardial ischemia-reperfusion injury/MAPK-induced oxidative stress and inflammatory reactions in diabetic rats by reducing AGE-RAGE. Eun et al. found that baicalein selectively activates PPARα and AMPK to regulate blood glucose levels, reduce hepatic lipid droplets and glycogen deposits, and improve insulin sensitivity and lipid metabolism in db/db mice. Hao et al. discovered that quercetin can alleviate liver swelling in db/db mice, lower liver enzyme activity, liver high blood glucose, and lipid accumulation, and improve lipid metabolism induced by type 2 diabetes by its antioxidative, anti-inflammatory, and FXR1/TGR5 signaling pathway activation effects. Yang et al. found that baicalin (10-6 and 10-5 mol/L) may promote glucose uptake and glycolysis of liver cells through the InsR/IRS1/PI3K/AKT pathway, inhibit gluconeogenesis, and possess a strong activity against insulin resistance in liver cells.

2.3. Gegen Qinlian Tang

Gegen Qinlian Tang is a famous traditional Chinese herbal medicine that originated from the book "Shang Han Lun". It is composed of four medicinal ingredients: Ge Gen (Pueraria lobata), Huang Qin (Scutellaria baicalensis), Huang Lian (Coptis chinensis), and Zhi Gan Cao (Glycyrrhiza uralensis), with a ratio of 5:3:3:2. It is used to treat chronic diarrhea and damp-heat syndrome[37]. Modern clinical studies have shown that Ge Gen Qin Lian Tang can normalize high blood sugar and hyperlipidemia in patients with type 2 diabetes. GO/KEGG analysis showed that Gegen Qinlian Tang regulates binding kinases in plasma or cell membranes through the PI3K-AKT and TNF

signaling pathways, thereby regulating inflammation, oxidative stress and glucose metabolism.

Bioactive isoflavones extracted from Ge Gen, such as puerarin and daidzein, have been shown to have anti-diabetic effects in animal models. Puerarin can improve insulin resistance and pancreatic damage by inhibiting inflammation and oxidative stress in diabetes and diabetic complications, while daidzein can regulate glucose and lipid metabolism and reduce inflammation through the TNF-α/JNK signaling pathway in T2DM macrophages.

Active ingredients in Huang Qin, such as baicalein, wogonin, baicalin, and wogonoside, are potential antioxidants and anti-inflammatory agents that can treat obesity, insulin resistance, and inflammatory diseases. Baicalein can increase glucose cell absorption through the AKT and GLUT4 pathways, thus lowering high blood sugar, and also play an anti-inflammatory and anti-fibrotic role through the NF-κB signaling pathway and the TGF-β1/Smad3 signaling pathway. Wogonin can improve insulin resistance by inhibiting free fatty acid and inflammation factor (IL-1β, IL-6, etc.) production in T2DM. Wogonoside can reduce the level of leptin factor regulated by SOCS3 in HepG2 cells, promote expression of insulin pathway-related genes OB-R, IRS2, PI3K, p-Akt/Akt, and GLUT1/2/4 proteins, promote glycogen synthesis, alleviate insulin resistance, and thus improve the body's sensitivity to insulin and glucose transport capacity. Baicalin can inhibit the expression of p-P38-MAPK, PGC-1α, and p-CREB in the P38-MAPK/PGC-1 pathway, thereby improving hepatic insulin resistance.

Huang Lian mainly exerts its therapeutic effects through berberine and coptisine, which can have a beneficial effect on diabetes and diabetic complications by regulating the AKT/AMPK/NF-κB/MAPK/PI3K and oxidative stress signaling pathways. Berberine, as an anti-hyperglycemic agent, can improve insulin resistance through activation of AMPK by increasing the phosphorylation level of AKT during T2DM treatment. Coptisine can improve oxidative damage in diabetic nephropathy by regulating the Nrf2 signaling pathway.

Glycyrrhetinic acid and isoliquiritigenin are effective components of Zhi Gan Cao. Glycyrrhetinic acid can inhibit diabetes-induced mesangial matrix accumulation in diabetic nephropathy by reducing NF-κB and NLRP3 inflammasome. Isoliquiritigenin can alleviate inflammation and oxidative stress in diabetic kidney injury through a SIRT1-dependent mechanism.

2.4. Huanglian Decoction

Huanglian Decoction is composed of huanglian, dried ginger, ginseng, banxia, guizhi, licorice, and jujube. In recent years, some clinical trials based on the intervention of Huanglian decoction have shown that it has good hypoglycemic effects on patients with type 2 diabetes mellitus (T2DM)[38]. Modern pharmacological research has shown that many active ingredients in Huanglian decoction, such as polysaccharides, flavonoids, alkaloids, and trace elements, have the effect of regulating glucose metabolism.

Huanglian can increase insulin resistance index and insulin sensitivity; licorice can improve renal filtration function, reduce urinary protein excretion, and inhibit renal fibrosis; ginseng extract can increase insulin sensitivity, IRS, AKT, FoxO1, reduce blood glucose, ALT, AST, inhibit inflammation and oxidative stress, enhance antioxidant capacity, and alleviate diabetic complications; banxia can promote insulin sensitivity, improve liver insulin resistance, and regulate glucose and lipid metabolism.

3. Conclusions

In summary, the pathogenesis of type 2 diabetes mellitus (T2DM) and its hepatic complications is complex, involving multiple factors, targets, and genes. Single herb and compound traditional Chinese medicine (TCM) formulations can be used as natural medicines for clinical treatment. The

therapeutic effects of TCM, which involve multiple components, targets, and pathways, have been fully verified based on the holistic concept and the principle of dialectical treatment of TCM theory. Moreover, TCM has advantages such as low toxicity, minimal side effects, and even the possibility of being used as a food therapy.

Acknowledgements

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