Research Progress of *Coptis chinensis* Franch. in the Intervention of Type 2 Diabetes Mellitus: A Perspective from Chemical Constituents and Signaling Pathways

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Abstract. In recent years, the mechanism of action of *Coptis chinensis* Franch. (Huanglian) and its main active components (represented by berberine) in the prevention and treatment of type 2 diabetes mellitus (T2DM) has been extensively studied. *Coptis chinensis* Franch. regulates energy metabolism, antioxidant responses, and immunoinflammatory processes through multiple targets and pathways, thereby improving insulin sensitivity and protecting β-cell function. Emerging evidence indicates that *Coptis chinensis* Franch. exerts metabolic and anti-inflammatory effects not only via classical signalling pathways (e.g., PI3K/AKT, AMPK/Nrf2, NF-κB, mTOR) but also by intervening in various forms of regulated cell death (RCD), including autophagy, apoptosis, pyroptosis, and ferroptosis. Based on these findings, this review proposes the concept of the "Multidimensional Cell Death Network (MCDN)": under the pathological context of chronic metabolic stress induced by hyperglycaemia and hyperlipidaemia, various cell death pathways are interconnected and convertible, forming a "death network hub" centred on key molecules such as AMPK/mTOR, Nrf2, and NF-κB. *Coptis chinensis* Franch. achieves therapeutic effects from single-target inhibition to network homeostasis reconstruction through synergistic interventions at multiple nodes of this network (e.g., inhibiting the NLRP3-GSDMD proptosis axis, activating Nrf2/GPX4 to suppress ferroptosis, and promoting mitophagy via AMPK). This article systematically summarizes the chemical constituents, signalling pathways, and MCDN-related mechanisms of *Coptis chinensis* Franch. in T2DM intervention, and proposes future verification strategies based on multiomics and network pharmacology. It is expected to provide theoretical support for the clinical translation of *Coptis chinensis* Franch. and the modernization of traditional Chinese medicine (TCM).

1 Introduction

Type 2 Diabetes Mellitus (T2DM) is a metabolic disease characterized by insulin resistance (IR) and pancreatic *β*-cell dysfunction [1]. Its pathogenesis is complex, involving multiple metabolic disorders, including abnormal glucose metabolism, lipid metabolism disturbance, enhanced oxidative stress, activated inflammatory response, mitochondrial dysfunction, and endoplasmic reticulum stress [2-3]. Conventional therapeutic strategies include lifestyle interventions (diet and exercise), oral hypoglycemic agents (e.g., biguanides, sulfonylureas, GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors), and insulin therapy [1].

At the cellular level, the insulin signaling pathway (e.g., IR/PI3K/AKT pathway), AMPK regulatory pathway, and oxidative stress/antioxidant defense pathway (e.g., Nrf2/HO-1) are core pathways involved in the pathological changes of diabetes [2]. In addition, intracellular ultrastructures (such as mitochondria, endoplasmic reticulum, and organelle autophagic pathways) are damaged and closely associated with various forms of regulated cell death (RCD), including apoptosis, autophagy, inflammation, and ferroptosis [4].

As a classic heat-clearing and dampness-drying herb in traditional Chinese medicine (TCM), *Coptis chinensis* Franch. has been recorded in TCM classics for the treatment of "xiaoke" (corresponding to diabetes mellitus in modern medicine). Modern studies have demonstrated that *Coptis chinensis* Franch. and its main components (e.g., berberine, coptisine, lignans, and flavonoids) exhibit potential in regulating metabolism, suppressing inflammation, scavenging oxidative stress, improving insulin signaling transduction, and protecting *β*-cells [1,5-6]. In recent years, with the in-depth revelation of the mechanisms underlying novel types of RCD (e.g., ferroptosis, Cuproptosis, and pyroptosis), this review intends to systematically summarize the research progress of *Coptis chinensis* Franch. in T2DM intervention from the perspectives of chemical constituents, signaling pathways, inflammation, and cell death [3], and discuss future development directions.

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2 Chemical components of *Coptis chinensis* Franch.

Coptis chinensis Franch. contains a variety of bioactive components, including berberine, coptisine, jatrorrhizine, lignans, phenylpropanoic acids, flavonoids, and volatile oils [1,7].

2.1 Alkaloids

Berberine: As the most extensively studied bioactive component of Coptis rhizome Franch. , it exhibits hypoglycemic effects, regulates lipid metabolism, exerts anti-inflammatory activity, and scavenges oxidative stress [2]. Coptisine, jatrorrhizine, etc.: These alkaloids have also been reported in some studies to possess certain metabolic regulatory activities [1,5].

Coptisine is one of the major bioactive alkaloids isolated from *Coptis chinensis* Franch., which exerts synergistic pharmacological effects with berberine.

Coptisine exhibits a broad spectrum of pharmacological activities, including antibacterial and antiviral effects, anti-inflammatory and immunomodulatory properties, regulation of glucose and lipid metabolism, cardiovascular protection, neuroprotection, and antitumor activity.

As shown in Figure 1, the main alkaloid components of Coptis chinensis Franch. include berberine, coptisine, jatrorrhizine, etc.

Coptisine exerts inhibitory effects against a variety of pathogenic bacteria by disrupting the integrity of bacterial cell membranes and inhibiting bacterial DNA replication and protein synthesis, and it shows significant inhibitory efficacy against both Gram-positive and Gram-negative bacteria such as Staphylococcus aureus, Escherichia coli, and Shigella dysenteriae. Coptisine can block the process of viral adsorption to host cells and inhibit the replication of influenza virus and hepatitis B virus (HBV). Both coptisine and berberine have potential ameliorative effects on chronic inflammatory diseases such as rheumatoid arthritis and ulcerative colitis. Meanwhile, coptisine can regulate the immune function of the body by enhancing the phagocytic capacity of macrophages, promoting lymphocyte proliferation, and balancing immune responses, thus exerting a certain regulatory effect on the abnormal immune reactions of autoimmune diseases.

Coptisine can inhibit α-glucosidase activity, delay intestinal carbohydrate absorption, and reduce postprandial blood glucose peaks; it also activates the adenosine 5'-monophosphate-activated protein kinase (AMPK) signalling pathway, promotes hepatic glucose uptake and glycogen synthesis, ameliorates insulin resistance, and thus serves as an adjuvant therapeutic agent for T2DM. Both coptisine and berberine can decrease the serum levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), increase high-density lipoprotein cholesterol (HDL-C) levels, reduce lipid deposition in the vascular wall, and improve lipid metabolism disorders. Additionally, coptisine and berberine can dilate coronary arteries, increase coronary blood flow, reduce myocardial oxygen consumption, alleviate myocardial ischemia-reperfusion injury, inhibit platelet aggregation, decrease blood viscosity, and reduce the risk of thrombosis, thereby exerting protective effects on cardiovascular diseases such as coronary heart disease and atherosclerosis. Furthermore, coptisine can inhibit the expression of proteins related to cardiomyocyte hypertrophy, ameliorate myocardial remodelling, and exert a certain alleviating effect on heart failure.

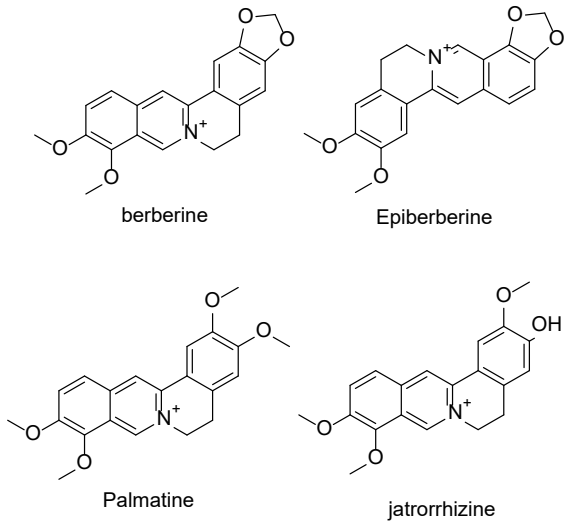

Fig. 1. Component of alkaloids

2.2 Flavonoids / lignans / phenolic acids

Coptis chinensis Franch. also contains certain flavonoids, lignans, and phenolic acid derivatives, which may be involved in auxiliary antioxidant effects, signaling pathway regulation, and synergistic actions.

Although studies on the mechanisms of these non-alkaloid components in diabetes are relatively limited [7], they may exert their effects through free radical scavenging, enzyme activity regulation, and signaling pathway modulation.As shown in Figure 2, the flavonoids in Coptis chinensis Franch. are mainly flavonols, isoflavones and flavanones.As shown in Figure 3, the main phenolic acid components include gallic acid, caffeic acid, ferulic acid and other derivatives. The flavonoids in *Coptis chinensis* Franch. are mainly flavonols, isoflavones, and flavanones (e.g., quercetin, kaempferol, baicalein, etc.), and their pharmacological activities mainly include antioxidation, anti-inflammation, hepatoprotection, cholagogic effects, immunomodulation, as well as hypoglycemic and hypolipidemic activities. Flavonoids can alleviate oxidative stress injury by scavenging reactive oxygen species (ROS) in the body and inhibiting lipid peroxidation; meanwhile, they can suppress the nuclear factor-kappa B (NF-κB) signalling pathway, reduce the release of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), thus exerting a potential ameliorative effect on chronic inflammatory diseases. Quercetin can promote hepatocyte regeneration, inhibit the expression of hepatic fibrosis-related proteins, reduce transaminase levels, and exert a protective effect against drug-induced liver injury;

it can also promote bile secretion and ameliorate cholestasis. Flavonoids can enhance the phagocytic capacity of macrophages, promote the proliferation and differentiation of lymphocytes, improve the non-specific and specific immune functions of the body, and exert a certain regulatory effect on autoimmune diseases. In addition, flavonoids can inhibit α-glucosidase activity, delay carbohydrate absorption, reduce postprandial blood glucose levels; they can also decrease the serum levels of TC and TG, increase HDL-C levels, thereby improving lipid metabolism disorders. The lignans in *Coptis chinensis* Franch. exhibit pharmacological activities including neuroprotection, antifungal and antiviral effects, and cardiovascular function improvement. The phenolic acid derivatives, such as gallic acid, caffeic acid, and ferulic acid, possess pharmacological activities including anti-inflammatory, antibacterial, anticoagulant, antithrombotic, anti-aging, antioxidative, and antitumor effects.

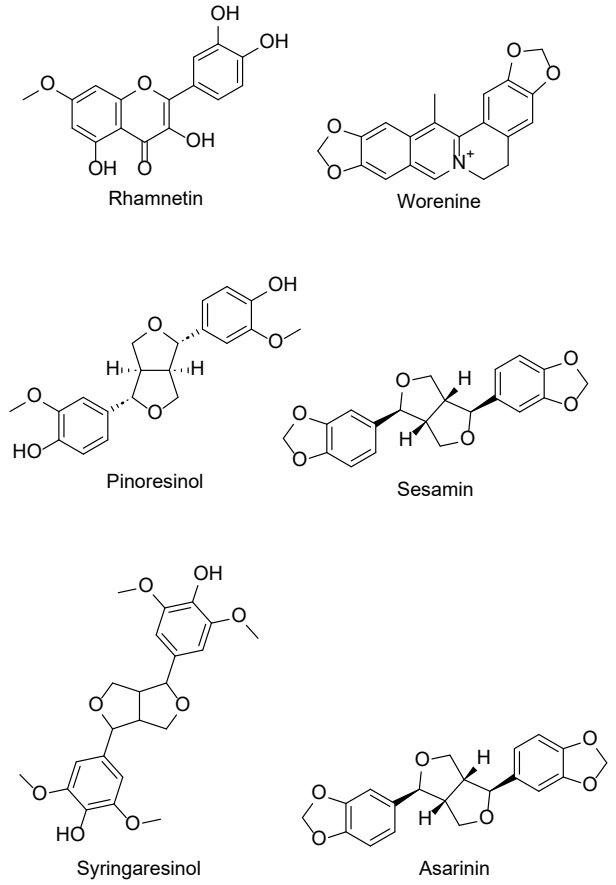

Fig. 2. Component of flavonoids and lignans

2.3 Content and dose-effect

Relationship In existing literature, researchers have explored the dose-effect relationship of different fractions of *Coptis chinensis* Franch. in hypoglycemic activity. For instance, studies have indicated that *Coptis chinensis* Franch. may regulate the PTEN/PI3K/AKT signaling pathway [7]. In practical research, attention should be paid to potential differences caused by different extracts, dosages, and component ratios.

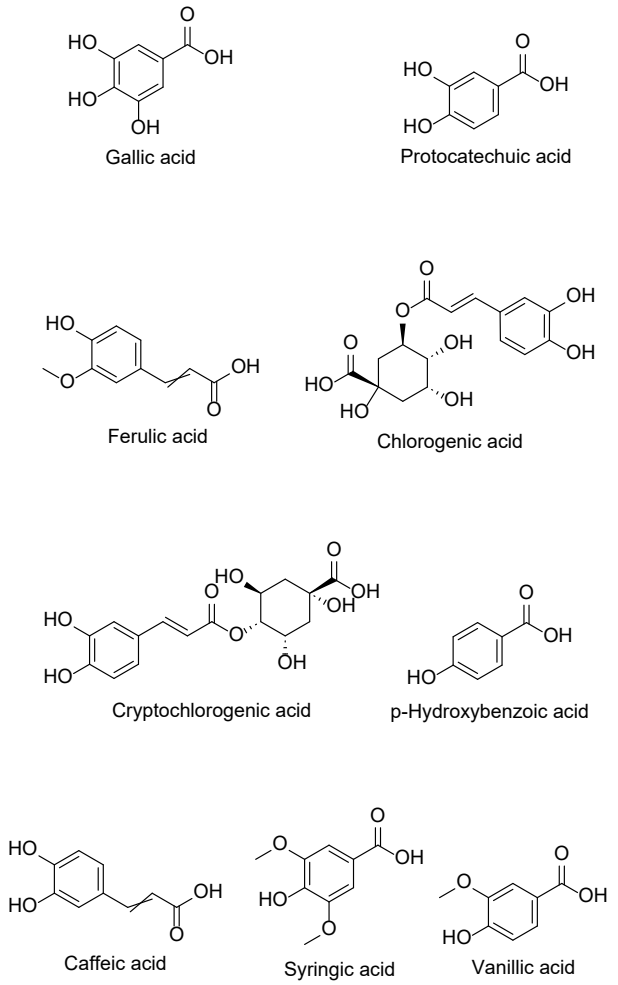

Fig. 3. Component of phenolic acids

3 Several Key signalling pathways in the occurrence and development of T2DM

During the pathological process of T2DM, several signaling pathways are generally recognized as core or frequently studied, including the PI3K/AKT pathway, AMPK pathway/antioxidant pathway, NF-κB inflammatory pathway, and mTOR/autophagy-related pathway. Each pathway is introduced below, combined with research evidence of *Coptis chinensis* Franch. berberine and other components in these pathways.

3.1 PI3K/AKT pathway

The PI3K/AKT pathway is a classic downstream pathway of the insulin signaling cascade. Upon insulin stimulation, PI3K is activated to generate PIP3, which in turn initiates AKT (protein kinase B). AKT further regulates GLUT4 translocation, GSK3, mTOR, and other molecules, thereby modulating glucose uptake and metabolism [4]. Under diabetic conditions, this pathway is often inhibited or dysregulated. As shown in Figure 4, the PI3K/AKT signaling cascade plays a key role in insulin action.Regarding the research on *Coptis chinensis* Franch. / berberine intervening in the PI3K/AKT pathway, studies

have indicated that *Coptis chinensis* Franch. may regulate the PTEN/PI3K/AKT signaling pathway [4,7]. Additionally, a review has pointed out that "regulating the insulin signaling pathway" is one of the mechanisms by which *Coptis chinensis* Franch. improves insulin resistance (IR) [5].

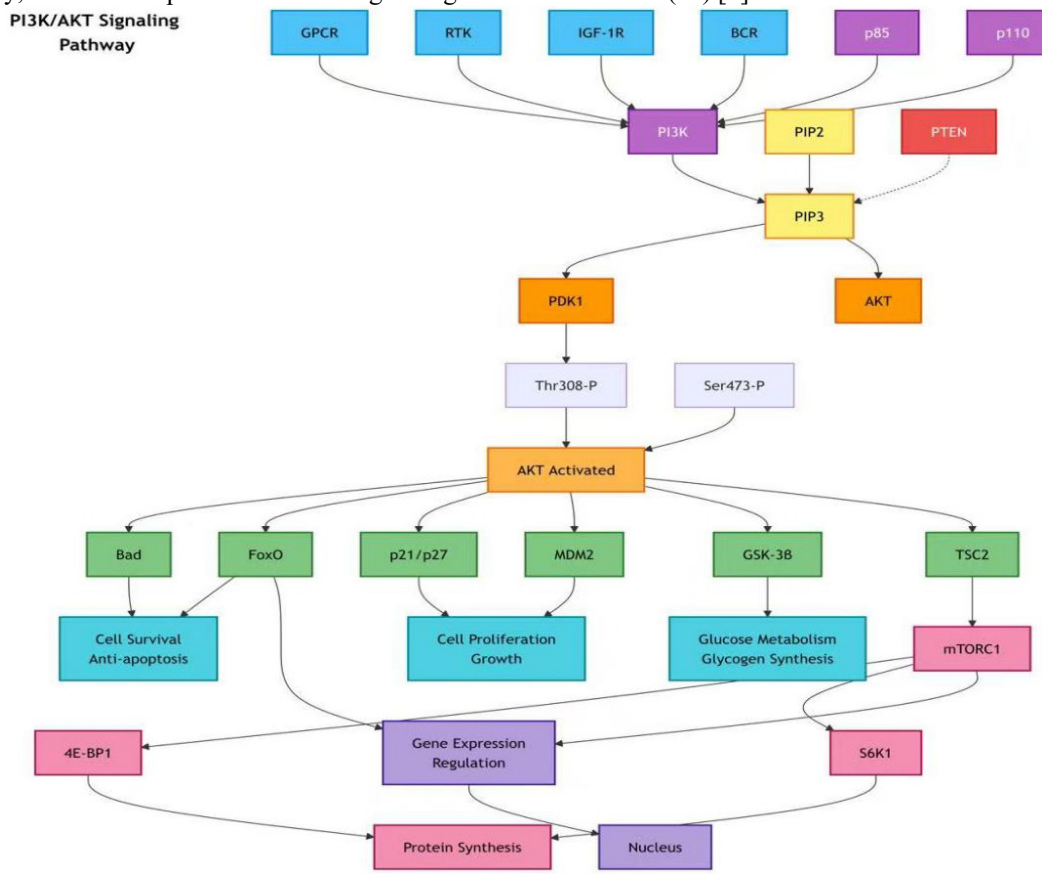

Fig. 4. PI3K / AKT Signaling Pathway

3.2 AMPK/Nrf2/anti-oxidative stress pathway

AMPK (5′-AMP-activated protein kinase) acts as a cellular energy sensor. It is activated under energy deprivation to promote energy metabolic homeostasis and regulate lipid metabolism, glucose metabolism, mitochondrial function, and oxidative stress. Nrf2 is the major antioxidant transcription factor in cells. Existing studies have demonstrated that berberine can activate the AMPK signaling pathway and downregulate the SIRT1/FoxO and Nrf2 pathways, thereby reducing reactive oxygen species (ROS) production, enhancing antioxidant enzyme activity, and alleviating mitochondrial oxidative stress damage [2,6]. Furthermore, inhibiting the mTOR/S6K pathway via AMPK is one of its potential mechanisms. Therefore, the AMPK/Nrf2 pathway is an important pathway for *Coptis chinensis* Franch. to exert antioxidant effects and maintain metabolic stability [1].

3.3 NF-κB/inflammatory pathway

Inflammatory responses play a promotional role in the pathogenesis of T2DM, especially low-grade chronic inflammation (e.g., elevated levels of TNF-α, IL-6, IL-1β) [8]. NF-κB is a classic inflammatory signal transcription factor that induces the expression of inflammatory cytokines upon activation [8]. Studies have shown that *Coptis chinensis* Franch. decoction may exert hypoglycemic effects in the liver by inhibiting the TLR4/NF-κB signaling pathway. Additionally, epiberberine has been reported to improve T2DM-related metabolic abnormalities by suppressing the IL-17RA/NF-κB signaling pathway [9]. Thus, the NF-κB pathway is of research significance for *Coptis chinensis* Franch. in regulating inflammation and inhibiting pro-inflammatory cytokines.

3.4 mTOR/autophagy-related pathway and other pathways

mTOR (mammalian target of rapamycin) is a regulator of cellular nutritional status and growth signals, and is closely associated with autophagy [6]. Excessive activation of the mTOR pathway may inhibit autophagy, while moderate autophagy is beneficial for maintaining cellular homeostasis. Studies on *Coptis chinensis* Franch. acting on the mTOR/S6K pathway have also been reported, particularly reflected in its mechanism of inhibiting mTOR signaling via AMPK. Furthermore, *Coptis chinensis* Franch. Its components may affect the HIF-1 pathway. A network pharmacology study indicated that *Coptis chinensis* Franch. Panax notoginseng acts on targets such as IL-6, EGFR, and INSR through the HIF-1 pathway [10].

4 Cellular inflammation and cell death

In the pathological process of diabetes mellitus, in addition to the activation of inflammation, cells (especially pancreatic β -cells, renal cells, cardiomyocytes, etc.) may be affected by various types of programmed cell death (including autophagy, apoptosis, pyroptosis, ferroptosis, cuproptosis, etc.). Research on the mechanism of action of Coptis chinensis Franch. is gradually expanding in these directions. Inflammation and various types of cell death are discussed in sections below.

4.1 Cellular Inflammation

As mentioned earlier, inflammation plays a key role in the development of T2DM. Hyperglycemia, lipotoxicity, oxidative stress, and other factors can induce the downstream activation of pathways such as NF- κ B, MAPK, and NLRP3 inflammasome, leading to increased secretion of pro-inflammatory cytokines (TNF- α , IL-6, IL-1 β , etc.), which further damage tissues, induce insulin resistance, and impair β -cell function[8-9]. There have been certain studies on the anti-inflammatory effects of *Coptis chinensis* Franch. / berberine. For example, *Coptis chinensis* Franch. decoction reduces the levels of IL-1 β , IL-6, and TNF- α in the liver by inhibiting the TLR4/NF- κ B pathway [9,11]. Therefore, intervention targeting inflammation is an important direction for *Coptis chinensis* Franch. in the prevention and treatment of T2DM.

4.2 Cell death

In terms of the research progress of coptisine in the five research directions of cell apoptosis, autophagy, cell-cell communication, ferroptosis, and cuproptosis, the field of cell apoptosis has formed mature preclinical research conclusions, supported by various types of evidence including cell line experiments, animal model verification, and clear molecular mechanism analysis; the direction of cell autophagy also has definite preclinical experimental data, and the relevant conclusions are mainly derived from cell line experiments and molecular mechanism detection results; the direction of ferroptosis has also obtained clear preclinical experimental evidence. Studies have confirmed that coptisine can inhibit cellular ferroptosis in sepsis models by regulating signaling pathways such as STAT1/IRF1/GPX4, and the relevant conclusions are based on cell experiments and animal model verification; however, the direction of pyroptosis is still in the stage of an unvalidated research hypothesis, which can only be indirectly deduced based on existing signaling pathway studies, and no direct experimental evidence has been obtained to confirm it yet; there is no direct experimental research support for the direction of cuproptosis, which also falls into the category of unvalidated research hypotheses. Each type is discussed below, combined with existing research evidence on *Coptis chinensis* Franch. / berberine.

4.2.1 Autophagy

Autophagy is an intracellular recycling mechanism for waste and damaged organelles, which is of great significance for maintaining cellular homeostasis. Under metabolic stress conditions, moderate autophagy can reduce intracellular damage, alleviate ROS accumulation, and maintain mitochondrial function [1,6]. The regulatory mechanism of *Coptis chinensis* Franch. / berberine on autophagy has not been fully reported in current literature, but it may indirectly affect autophagic levels by regulating the AMPK/mTOR pathway.

4.2.2 Apoptosis

Apoptosis is the earliest extensively studied form of programmed cell death. Under conditions of hyperglycemia, oxidative stress, and lipotoxicity, pancreatic *β*-cells, renal cells, and other cells are prone to apoptosis, leading to the loss of tissue function. There is certain evidence that *Coptis chinensis* Franch. /berberine can attenuate cell apoptosis. For example, it can indirectly reduce apoptotic signals by regulating inflammation, scavenging ROS, and improving mitochondrial function [1,5]. Although no studies explicitly reporting apoptotic markers (such as Caspase-3, Bcl-2/Bax ratio, etc.) of *Coptis chinensis* Franch. in T2DM models have been identified, inhibiting pancreatic β-cell apoptosis is a common research direction in most TCM hypoglycemic studies.

4.2.3 Pyroptosis

Pyroptosis is a form of cell death dependent on inflammasomes (e.g., NLRP3) and the gasdermin D (GSDMD) protein, often accompanied by the release of IL-1*β* and IL-18. In diabetes mellitus and its complications (such as diabetic nephropathy and cardiovascular injury), pyroptosis may be involved in inflammation-mediated cellular damage [11].

4.2.4 Ferroptosis

Ferroptosis is a form of programmed cell death dependent on excessive iron ions and accumulation of lipid peroxidation. In recent years, the association between ferroptosis and diabetes mellitus, especially diabetic cardiovascular and renal injury, has attracted attention. Regarding the research on *Coptis chinensis* Franch. / berberine and ferroptosis, the latest literature reports that berberine treatment can inhibit ferroptosis in NIT-1 cells (a mouse *β*-cell line) stimulated by high glucose. The specific mechanism is to reduce *O*-GlcNAc modification by downregulating OGT expression, thereby inhibiting the ferroptosis process [12].

4.2.5 Cuproptosis

Cuproptosis is a relatively novel form of programmed cell death, whose mechanism involves the specific binding of copper ions to mitochondrial lipoylated proteins, thereby

causing protein aggregation, proteotoxic stress, and mitochondrial dysfunction [13]. Currently, research on cuproptosis in the context of diabetes mellitus is still in its preliminary stage, not to mention studies on the intervention of *Coptis chinensis* Franch. / berberine in this pathway.

4.3 Multidimensional cell death network mechanism of *Coptis chinensis* Franch. in regulating T2DM

In recent years, studies have indicated that the occurrence of T2DM is not caused by a single signaling pathway or form of cellular damage, but by a complex network system intertwined with various types of Programmed Cell Death (PCD). Traditional research has mostly focused on apoptosis or autophagy, but accumulating evidence suggests that novel forms of cell death such as ferroptosis, pyroptosis, and cuproptosis are also involved in the pathological process of diabetes mellitus [14]. Based on this, this review proposes a new concept of "Multidimensional Cell Death Network (MCDN)": under the chronic hyperglycemia, hyperlipidemia, and oxidative stress environment of diabetes mellitus, multiple cell types including *β*-cells, hepatocytes, and skeletal muscle cells simultaneously trigger different forms of programmed cell death pathways, with crosstalk regulation and signal coupling existing among these pathways. Signaling nodes such as AMPK, mTOR, NF-*κ*B, and Nrf2 play hub roles in this network, forming a "Death Hub" centered on metabolic stress [15]. *Coptis chinensis* Franch. and its representative component berberine can intervene in multiple dimensions of this network through multi-target actions. For example: Inhibiting the pyroptosis pathway: Berberine can downregulate the activity of the NLRP3 inflammasome, reduce GSDMD cleavage and IL-1β release, and alleviate inflammatory cell death. Blocking the ferroptosis pathway: Berberine can activate the Nrf2/GPX4 axis, inhibit lipid peroxidation, and reduce Fe^{2+} accumulation. Promoting autophagic clearance: By activating AMPK to inhibit mTOR, berberine can enhance mitophagy and maintain cellular homeostasis. Alleviating apoptotic signals: Upregulating Bcl-2 and downregulating Bax and Caspase-3 to protect pancreatic *β*-cells. Potential regulation of cuproptosis: Preliminary studies suggest that *Coptis chinensis* Franch. can stabilize the mitochondrial TCA cycle and inhibit copper ion-induced lipoylation stress.

Through the multi-dimensional integrated regulation of these pathways, *Coptis chinensis* Franch. achieves a transformation from single-target inhibition to network homeostasis reconstruction, presenting the typical "systemic balance" regulatory characteristic of traditional Chinese medicine. This "Multidimensional Cell Death Network" model helps explain the multi-level protective effects of *Coptis chinensis* Franch. in the long-term intervention of diabetes mellitus, and provides a new theoretical framework for future research on the signaling network mechanisms of traditional Chinese medicine [14].

5 Conclusion

Current studies have demonstrated that *Coptis chinensis* Franch. and its main components (especially berberine) exert multi-targeted and multi-pathway mechanisms of action in the intervention of T2DM. It may function through activating AMPK, regulating the Nrf2 antioxidant pathway, inhibiting the NF-*κ*B inflammatory pathway, restoring PI3K/AKT signaling, modulating the mTOR/autophagy pathway, and suppressing ferroptosis (in *β*-cells). Additionally, there is certain evidence supporting the role of *Coptis chinensis* Franch. in improving gut microbiota and regulating GLP-1 secretion.

Limitations of Current Research: Studies on the intervention mechanisms of *Coptis chinensis* Franch. in novel forms of programmed cell death (such as pyroptosis and cuproptosis) are extremely limited. Most existing studies are based on cellular or animal models, lacking more high-quality clinical trials. Many studies remain at the level of signaling pathways, with insufficient systematic evaluation of dose-effect relationships, pharmacokinetics, and tissue targeting. The roles of other non-alkaloid components in *Coptis chinensis* Franch. in the prevention and treatment of diabetes have not been thoroughly explored.

Future Research Directions: Systematically detect the effects of *Coptis chinensis* Franch. / berberine on different types of cell death (e.g., pyroptosis, cuproptosis, necroptosis) in T2DM-related models. Further design dose-time dependent experiments to clarify the effective dose, toxicity threshold, and pharmacokinetic characteristics. Map the intervention network using multi-omics technologies (including metabolomics, transcriptomics, and proteomics) to systematically illustrate the network mechanism of *Coptis chinensis* Franch. in T2DM intervention. Explore the synergistic mechanisms of *Coptis chinensis* Franch. combined with other drugs or natural products.

As a classic TCM, the modern mechanistic research of *Coptis chinensis* Franch. actively serves as a bridge between TCM theory and modern biomedicine. In the context of precision medicine and metabolic disease prevention, leveraging the multi-targeted and low-toxicity advantages of TCM holds promising application prospects.

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