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Research Progress on Traditional Chinese Medicine in Treating Diabetes Based on Ferroptosis Theory

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Abstract: ***Ferroptosis is an iron-dependent form of cell death driven by dysregulated iron metabolism, lipid peroxidation, and impaired antioxidant defense. Its core regulatory mechanisms involve iron accumulation (via transferrin receptors and ferritin), lipid peroxidation (dependent on polyunsaturated fatty acids and lipoxygenases), and dysfunction of the System Xc^--GSH-GPX4 antioxidant axis. Traditional Chinese Medicine (TCM) theory associates ferroptosis with pathological mechanisms such as "blood stasis," "heat-toxicity," and "yin-yang imbalance," suggesting that TCM may intervene in ferroptosis by regulating iron metabolism, scavenging free radicals, and improving metabolic homeostasis. Diabetes and its complications (e.g., pancreatic β-cell injury and vascular lesions) are closely linked to ferroptosis, as iron overload and oxidative stress exacerbate insulin resistance and organ damage. Recent studies highlight the potential of TCM in modulating ferroptosis for diabetes treatment: active components (e.g., emodin, astragalus polysaccharides, berberine) chelate iron, activate GPX4, or inhibit lipid peroxidation; compound formulas (e.g., Yi Tang Kang, Huanglian Jiedu Decoction) synergistically regulate iron metabolism and antioxidant systems through multi-target mechanisms. Future research should integrate modern molecular biology techniques to elucidate TCM's targets in ferroptosis modulation and advance drug development based on ferroptosis theory, offering novel strategies for diabetes prevention and treatment. TCM's holistic and multi-pathway regulatory approach provides unique advantages in treating ferroptosis-related diseases, but further clinical validation is needed to facilitate translational applications.***

Keywords: Ferroptosis, Diabetes, Traditional Chinese Medicine, Iron metabolism, Lipid peroxidation, Antioxidant.

1. Introduction

Diabetes and its complications have become a major global public health concern. According to the International Diabetes Federation (IDF) 2021 report, approximately 540 million adults aged 20–79 worldwide had diabetes, a number projected to rise to 640 million by 2030. Recent studies have identified ferroptosis—an iron-dependent, lipid peroxidation - driven form of programmed cell death—as critically involved in the pathogenesis of diabetes and its complications [1]. In this context, TCM, with its multi-target and holistic regulatory advantages, demonstrates remarkable potential in modulating ferroptosis, offering new insights for diabetes prevention and treatment [2, 3].

2. Overview of Ferroptosis Regulatory Mechanisms

Ferroptosis is a novel iron-dependent programmed cell death distinct from apoptosis, necrosis, and autophagy. It is primarily driven by iron-induced lipid peroxidation, leading to membrane damage and cell death. The process involves dysregulated iron metabolism, lipid peroxidation, and abnormal amino acid metabolism [4].

2.1 Iron Metabolism Pathway

Iron dyshomeostasis (e.g., intracellular iron accumulation) is central to ferroptosis. Iron, an essential trace element, participates in neurotransmitter synthesis, myelination, and DNA synthesis. Disrupted iron homeostasis impairs cellular function and triggers cell death. Iron homeostasis relies on uptake, storage, and export. Transferrin (TF) binds extracellular Fe^{3+}, which is internalized via transferrin receptor 1 (TFR1). In acidic endosomes, Fe^{3+} is reduced to Fe^{2+} and transported to the labile iron pool (LIP) or stored in ferritin (composed of FTL and FTH1). Iron export depends on ferroportin (FPN), the sole mammalian Fe^{2+} exporter, aided by ceruloplasmin (CP), which oxidizes Fe^{2+} to Fe^{3+}. FPN inhibition causes Fe^{2+} accumulation, exacerbating ferroptosis via Fenton reaction-derived reactive oxygen species (ROS) [5,6].

2.2 Lipid Peroxidation

Lipid peroxidation, catalyzed by iron, is a hallmark of ferroptosis. It occurs via non-enzymatic (iron-catalyzed free radical chain reactions) or enzymatic (lipoxygenase, LOX-driven) pathways [7,8]. Polyunsaturated fatty acids (PUFAs) are primary substrates, yielding toxic aldehydes (e.g., MDA, 4-HNE) that disrupt membrane integrity. ACSL4 and LPCAT3 esterify PUFAs into phospholipids, which are oxidized by LOXs, promoting ferroptosis. GPX4 depletion exacerbates lipid peroxidation, leading to cell death [9, 10].

2.3 Amino Acid Metabolism

Glutathione (GSH) metabolism is pivotal [11]. GSH, a tripeptide antioxidant, supports GPX4 in reducing lipid hydroperoxides. System Xc^- (composed of SLC7A11 and SLC3A2) imports cystine for GSH synthesis [12]. SLC7A11 suppression by ATF3 reduces GSH, sensitizing cells to ferroptosis [13,14].

3. TCM Theory and Ferroptosis Connections

TCM links ferroptosis to pathological mechanisms like "qi-fire imbalance" and "yin-yang disharmony":

"Latent Fire" Theory and Iron Dysmetabolism: Iron overload mirrors "latent fire," with oxidative damage reflecting "fire-heat injuring yin." Spleen dysfunction disrupts iron homeostasis, akin to "spleen failing to transport essence" [15].

"Stasis-Toxicity" and Lipid Peroxidation [16]: Lipid peroxides (MDA, 4-HNE) align with "stasis-toxicity" and ACSL4-driven lipid dysmetabolism corresponds to "phlegm-stasis intermingling" [17,18].

"Yin-Yang Imbalance" and Oxidative Stress: ROS ("yang") and iron ("yin") imbalance parallels "yin-fire" pathogenesis [16,19].

"Spleen-Kidney Deficiency" and Energy Dysmetabolism: AMPK inhibition reflects "spleen-kidney dysfunction," addressed by Qi-tonifying formulas [1,10].

TCM strategies include: "Tonifying Qi and Nourishing Yin" (e.g., Astragalus, Rehmannia) for iron homeostasis; "Clearing Heat and Detoxifying" (e.g., Coptis, Scutellaria) to suppress ROS; "Activating Blood and Resolving Stasis" (e.g., Salvia, Chuanxiong) to mitigate lipid peroxidation [2,20].

4. Association between Molecular Mechanisms of Ferroptosis and the Pathogenesis of Diabetes

The iron metabolism regulatory system involves increased iron uptake mediated by transferrin receptor 1 (TFR1) and divalent metal transporter 1 (DMT1), as well as iron release due to ferritin degradation, collectively elevating intracellular free iron levels. This excess iron catalyzes a burst of reactive oxygen species (ROS) via the Fenton reaction [1, 2].

In the lipid metabolism pathway, acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) facilitate the incorporation of polyunsaturated fatty acids (PUFAs) into membrane phospholipids, forming substrates for lipid peroxidation. Under diabetic conditions, ACSL4 expression is significantly upregulated, accelerating ferroptosis progression [1, 6].

Regarding amino acid metabolism, glutathione peroxidase 4 (GPX4) is a critical intracellular antioxidant enzyme that relies on glutathione (GSH) to detoxify lipid peroxides. The cystine/glutamate antiporter SLC7A11 (xCT) supplies cysteine for GSH synthesis. In hyperglycemic environments, decreased GPX4 activity and reduced SLC7A11 expression lead to a collapse of antioxidant defenses [1].

Additionally, ferroptosis contributes to pancreatic β-cell damage and insulin resistance. Under high-glucose conditions, β-cells exhibit GSH depletion and lipid peroxide accumulation, accelerating functional decline [20].

5. Molecular Targets of TCM in Modulating Ferroptosis

5.1 Active Components of Single Herbs

5.1.1 Antioxidant Effects

Astragalus: Polysaccharides and flavonoids enhance antioxidant enzymes, reduce ROS, and upregulate GPX4[2, 21].

Leonurus japonicus: Leonurine activates Nrf2/HO-1, mitigating ferroptosis in renal cells [22, 23].

Schisandra: Schisandrin A inhibits ferroptosis via AdipoR1/AMPK, elevating Nrf2 and GPX4 [24, 25].

Rheum palmatum: Emodin modulates NCOA4-mediated ferritinophagy and NF-κB to reduce iron overload [26].

Paeonia lactiflora: Paeoniflorin inhibits ferroptosis via Akt/Nrf2/GPX4 in gestational diabetes [27].

5.1.2 Iron Metabolism Regulation

Angelica sinensis: Promotes iron export and reduces MDA [28].

Ligusticum chuanxiong: Chuanxiongzine inhibits lipid peroxidation [28].

5.1.3 Insulin Resistance Improvement

Coptis chinensis: Berberine enhances GPX4 and β-cell function [29-31].

Pueraria lobata: Puerarin activates mitophagy and inhibits ER stress [32, 33].

Resveratrol: Attenuates ferroptosis via PERK/CHOP/PPARγ in β-cells [34].

5.1.4 Signaling Pathway Modulation

Nrf2 Activation: Gastrodin (from Gastrodia elata) and curcumin upregulate Nrf2/HO-1 [35].

p53 Inhibition: Resveratrol suppresses p53 to protect against ferroptosis [34].

5.2 Compound Formulas

Yi Tang Kang: Downregulates p53, upregulates SLC7A11/GPX4, and preserves renal structure [36].

Huanglian Jiedu Decoction: Modulates glucose-lipid metabolism via PPARγ/GSK-3 and improves β-cell function [37-42].

Qizhi Jiangtang Capsule: Alleviates diabetic kidney disease (DKD) by reducing oxidative stress and ferroptosis [43].

6. Summary and Outlook

Ferroptosis, as an emerging therapeutic target, validates TCM's multi-target approach. Future studies should integrate systems biology to elucidate TCM-ferroptosis interactions and advance precision medicine in diabetes treatment.

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