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Research Progress on Traditional Chinese Medicine Intervention in the Nrf-2/HO-1 Pathway for the Treatment of Diabetes and Its Complications

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Abstract: Diabetes mellitus is one of the major chronic diseases posing a severe threat to global health and is regarded as the fastest-growing public health emergency of the 21st century. Its pathological characteristics are mainly manifested as absolute or relative insulin deficiency and impaired insulin utilization, resulting in hyperglycemia and various complications such as cardiovascular and cerebrovascular diseases, nephropathy, retinopathy, and diabetic foot, making it a leading cause of death, blindness, and disability. In recent years, the protective role of the Nrf-2/HO-1 signaling pathway in diabetes and its complications has received widespread attention. Intervention via this pathway is expected to offer more effective therapeutic strategies. Traditional Chinese Medicine (TCM), centered on holistic regulation and combining macro-level regulation with micro-level intervention, has shown unique advantages by improving therapeutic effects while causing fewer adverse reactions. This study reviews recent research progress on how TCM treats diabetes and its complications by modulating the Nrf-2/HO-1 signaling pathway, with the aim of providing a reference for clinical applications and future research.

Keywords: diabetes mellitus, traditional Chinese medicine, signaling pathway

1. Introduction

In the 21st century, diabetes mellitus (DM), one of the major chronic diseases affecting global health, has emerged as the fastest-growing public health emergency. Diabetes is characterized not only by hyperglycemia but also by serious complications such as cardiovascular and cerebrovascular diseases, nephropathy, retinopathy, and diabetic foot, and has become a leading cause of death, blindness, and disability [1]. In 2021, approximately 537 million adults worldwide were affected by diabetes, with 6.7 million deaths attributable to diabetes and its complications. The International Diabetes Federation (IDF) projects that by 2030, 643 million adults will have diabetes, increasing to 783 million by 2045, driven by global population growth [2]. Diabetes is a chronic disease with persistent hyperglycemia due to absolute or relative insulin deficiency or resistance. Its pathogenesis is influenced by both genetic and environmental factors, including β-cell dysfunction, insulin resistance, or both, leading to impaired blood glucose regulation. Many diabetic patients also exhibit familial clustering. Typical symptoms include the “three excesses and one loss”: excessive drinking, urination, and eating, along with weight loss. Western medicine mainly treats diabetes by controlling blood glucose, managing mental health, and alleviating pain [2]. Although hypoglycemic drugs are effective

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in controlling blood glucose, their long-term use can lead to adverse effects such as ketoacidosis, obesity, hypoglycemia, and cardiovascular disease [3]. Recently, the nuclear factor erythroid 2–related factor 2 (Nrf-2)/heme oxygenase-1 (HO-1) signaling pathway has received increasing attention for its protective role in diabetes and related complications. TCM emphasizes holistic regulation, combining traditional healing concepts with modern medical technologies. By modulating the Nrf-2/HO-1 pathway during the pathological progression of diabetes, TCM can achieve glycemic control, antioxidative, and anti-inflammatory effects with fewer side effects. This study reviews the mechanism of the Nrf-2/HO-1 pathway and explores recent research on how TCM interventions target this pathway to treat diabetes and its complications.

2. The concept of the Nrf-2/HO-1 pathway

Multiple pathways regulate the body's cellular antioxidant stress responses, among which the Nrf-2/HO-1 pathway plays a central role [4]. It regulates the expression of various antioxidant enzymes through transcriptional control, maintaining intracellular redox homeostasis [5]. This multi-organ protective mechanism is crucial under different stress conditions [6]. Nrf-2 is a key transcription factor in cellular antioxidant stress responses. Its activity modulates target protein production, affecting cell function, with HO-1 being one of its downstream antioxidant proteins. When Nrf-2 activity increases, related mRNA induces the expression of antioxidant proteins like HO-1, inhibiting reactive oxygen species (ROS) production and maintaining cellular homeostasis [7]. Besides antioxidation, Nrf-2 also plays roles in detoxification, anti-inflammation, and other cellular protective mechanisms [8]. In diabetic patients or animal models, decreased Nrf-2 activity leads to reduced HO-1 expression, elevated ROS levels, and impaired antioxidant capacity [9]. Nrf-2 has a dual role in human diseases—it can prevent disease onset but also contribute to tumor progression by enhancing cancer cells' resistance to radio- and chemotherapy, making its function complex and variable [6]. Therefore, enhancing HO-1 expression by modulating Nrf-2 activity via Chinese herbal medicine can improve antioxidant capacity, alleviate inflammation, and reduce oxidative stress damage caused by diabetes.

3. The relationship between diabetes and the Nrf-2/HO-1 signaling pathway

3.1. Traditional pattern differentiation and modern targeted therapy

According to ancient medical texts, the symptoms of Xiaoke syndrome closely resemble those of modern diabetic nephropathy. In ancient times, traditional Chinese medicine (TCM) mainly relied on the diagnostic methods of observation, listening and smelling, inquiry, and palpation. As a result, it lacked a systematic understanding of early-stage cases that only exhibited abnormalities in biochemical indicators. Traditional TCM theory holds that prolonged Xiaoke leads to the depletion of yin and qi, and ultimately damages yang, resulting in kidney essence deficiency. This theoretical framework outlines the primary pathogenesis of diabetic nephropathy. However, with the improvement in living standards and the advancement of diagnostic concepts, the clinical features of diabetes have undergone significant changes over the past 30 years. Most patients no longer exhibit weight loss, and the typical "three excesses and one deficiency" (excessive thirst, urination, and hunger, along with weight loss) have become relatively rare. Thus, the traditional theory of Xiaoke is no longer sufficient to guide clinical differentiation and treatment. In this context, obesity has been proposed as a research focus to explore its relationship with diabetes. Modern medicine classifies diabetes into two main types and further categorizes the resulting conditions into deficiency and excess syndromes. Based on this understanding, the innovative "state-target differentiation and treatment" theory has been developed. This model integrates macroscopic state regulation and microscopic target intervention [10], alongside a disease-pattern model that incorporates

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classification, staging, and pattern differentiation [11]. It enables a comprehensive understanding of disease progression while precisely identifying core pathomechanisms at different stages, thereby facilitating accurate, syndrome-specific treatment and precise targeted regulation. Through the use of "targeted prescriptions," different diseases with the same syndrome can be treated by adjusting both the disease's "state" and its "target" [12]. This has led to the concept of using Chinese medicine to "target" the Nrf-2/HO-1 signaling pathway to reduce the onset of diabetes and its complications. This theoretical framework represents a deep integration of modern precision medicine and traditional TCM holistic philosophy, offering a more comprehensive understanding of the pathogenesis of diabetes and helping to lower its incidence.

3.2. Physiological function of the Nrf-2/HO-1 pathway

Proteins are the functional executors of various physiological and pathological processes such as cellular metabolism and signal transduction. Their structural and functional complexity and variability play a critical role in the onset and progression of diseases [13].

Studies have shown that under normal conditions, the Nrf-2 factor in the cytoplasm exists at low levels in the form of a complex. When Nrf-2 is in an inactive state, it is tightly bound to Kelch-like ECH-associated protein 1 (Keap1) and undergoes ubiquitination and degradation via the ubiquitin–proteasome system. Upon stimulation by free radicals and other stressors, Nrf-2 dissociates from Keap1, becomes activated, and translocates into the nucleus. There, mediated by musculoaponeurotic fibrosarcoma (Maf) proteins, it binds to antioxidant response elements (AREs), activates the transcription of downstream target genes, and induces the expression of antioxidant enzymes such as HO-1. This process reduces the expression of reactive oxygen species (ROS), maintains the body's redox homeostasis, and thus exerts an antioxidative protective effect [14]. In addition, the Nrf-2 signaling pathway also reduces mitochondrial damage, regulates intracellular calcium homeostasis, and inhibits apoptosis, thereby enhancing the cell's intrinsic protective capacity [5].

3.3. Pathogenesis of diabetes

Oxidative stress plays a crucial role in the onset and progression of diabetes, particularly in its complications such as diabetic nephropathy and diabetic cardiomyopathy. When oxidative stress responses are impaired, they can lead to kidney cell damage and inflammatory responses [15]. Under normal physiological conditions, the Nrf-2 factor induces the synthesis of HO-1 protein, thereby maintaining oxidative homeostasis in the body. However, in the cells of diabetic patients, insulin secretion is either insufficient or the body becomes resistant to it, resulting in elevated blood glucose levels. Hyperglycemia leads to reduced expression and activity of the Nrf-2 factor, which in turn decreases the activity of its downstream targets, such as HO-1 and superoxide dismutase-1 (SOD-1), reducing the synthesis of antioxidant enzymes. As a result, reactive oxygen species (ROS) levels remain high within the cells, leading to impaired antioxidant defenses and the development of renal diseases.

In patients with diabetes, myocardial cells are damaged, showing disorganized arrangements and disrupted muscle fiber structures, accompanied by significant inflammatory cell infiltration. When pharmacological interventions increase the expression of Nrf-2/HO-1 proteins and their corresponding mRNA, antioxidant capacity is enhanced, myocardial tissue structure improves, and inflammation is reduced. Therefore, activation of the Nrf-2/HO-1 signaling pathway can mitigate pyroptosis and myocardial injury, effectively alleviating diabetes and its complications[16].

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4. TCM treatment of diabetes by mediating the Nrf-2/HO-1 pathway

4.1. Chinese herbal formulas acting on the Nrf-2/HO-1 pathway

Various traditional Chinese herbal formulas can regulate cellular oxidative stress responses through the Nrf-2/HO-1 signaling pathway, thereby improving diabetes and its associated complications. Among them, formulas such as Qizhu Tongluo Prescription, Tongluo Xifeng Decoction, and Yiqi Yangyin Formula have been confirmed to exert targeted regulatory effects on cells through this pathway.

Studies have shown that Qizhu Tongluo Prescription, which functions to tonify qi and nourish yin while promoting blood circulation and dredging the meridians, can improve states of yin deficiency. It also upregulates the expression of Nrf-2 and HO-1 proteins and mRNA via the Nrf-2/HO-1 signaling pathway, thereby enhancing cellular antioxidative capacity, inhibiting oxidative stress responses, and delaying the progression of diabetic kidney disease (DKD)[17]. Similarly, Tongluo Xifeng Decoction can reduce oxidative stress levels in myocardial cells of patients with diabetic cardiomyopathy, increase Nrf-2 expression in myocardial tissue, and promote HO-1 protein synthesis, thus protecting the cardiovascular system and reducing oxidative damage to myocardial cells[18]. Additionally, Yiqi Yangyin Formula can activate the Nrf-2/HO-1 axis to effectively alleviate oxidative stress at the cellular level and mitigate oxidative damage caused by myocardial ischemia-reperfusion injury (MIRI), thereby improving diabetes and its complications[19]. Research on these traditional herbal formulas suggests that many prescriptions not only treat the manifest symptoms of diabetes mellitus (DM) through micro-level regulation but also target the key pathogenic mechanisms of the disease itself.

4.2. Individual Chinese medicines and active compounds acting via Nrf-2/HO-1

In treating diabetes and its complications, TCM primarily uses three types of herbs: heat-clearing herbs (e.g., Scutellaria), tonic herbs (e.g., Ginseng, Astragalus, Polygonatum), and blood-activating and stasis-resolving herbs (e.g., Salvia) [20].

Research has found that Scutellaria contains a variety of compounds, including baicalein, norwogonin, wogonin, and their glycosides. Among them, baicalin can enhance the fluorescent expression of Nrf-2/HO-1 proteins in the skin wounds of mice, indicating that baicalin increases Nrf-2 activity, raises HO-1 protein levels, and inhibits oxidative processes in cells, thereby effectively preventing the onset of diabetes and its complications [21]. As an important redox regulatory pathway, the Nrf-2/HO-1 axis is also modulated by other compounds. Ginsenosides, the main active constituents in Ginseng, have been shown to regulate oxidative stress responses. Research has demonstrated that ginsenoside Rh1 can upregulate Nrf-2 and HO-1 protein expression in renal cells, reduce ROS activation levels, and alleviate oxidative damage in these cells [14]. Similarly, aqueous extracts of Polygonatum [22] and astragaloside IV from Astragalus [18] can also increase Nrf-2 expression. Under the regulation of the Nrf-2/HO-1 signaling pathway, they enhance the synthesis of antioxidant proteins, strengthen the body's antioxidative function, protect renal tissues, and improve outcomes in diabetes and its complications. Clinically, herbs like Astragalus, Polygonatum, and Scutellaria are frequently incorporated into compound formulas. This confirms that their active ingredients can modulate cellular oxidative stress mechanisms and effectively mitigate the progression of diabetes.

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5. External TCM therapies for diabetes

In addition to commonly used herbal formulas, external therapeutic methods in Traditional Chinese Medicine (TCM)—such as acupuncture, acupoint application, auricular seed pressing, and herbal fumigation—can also effectively alleviate the symptoms of diabetes and its complications.

With continuous improvements in living standards and accompanying changes in dietary habits, poor eating patterns have increasingly led to spleen and stomach dysfunction, resulting in dampness accumulation. From the holistic perspective of TCM, acupuncture is used to select points along meridians rich in qi and blood to regulate the flow of stagnant qi. This approach significantly improves nerve conduction speed, reduces the severity of diabetic peripheral neuropathy, and alleviates symptoms such as limb numbness in diabetic patients [23]. Acupoint application therapy has shown a high therapeutic efficacy. By applying herbal pastes to multiple acupoints, this method warms the meridians and disperses cold pathogens, thereby relieving sensory abnormalities in the extremities caused by qi stagnation in the meridians [24]. The combination of auricular seed pressing and moxibustion not only applies external pressure to auricular points but also uses moxibustion to restore the flow of qi and body fluids, which effectively alleviates edema caused by diabetic nephropathy and improves renal function in patients [25]. Compared to other treatment methods, external TCM therapies are relatively simple and convenient while offering symptom relief. However, the current TCM-based diagnostic and therapeutic system for the prevention and treatment of diabetes still requires improvement. Advancing multidisciplinary integration is essential to enhance the quality of basic research and elevate the standard of clinical care [26].

6. Conclusion and outlook

As one of the most serious chronic diseases, diabetes is closely associated with oxidative stress in its pathogenesis. The Nrf-2/HO-1 signaling pathway, as a crucial antioxidant defense mechanism, regulates the production of various antioxidant proteins. At the micro level, it improves insulin resistance, suppresses inflammatory responses, and mitigates myocardial cell damage, demonstrating significant potential in the treatment of diabetes and its complications. Various compound herbal formulas and active constituents can activate this signaling pathway to achieve therapeutic effects, as evidenced in animal models. However, the lack of clinical trials to confirm their efficacy and safety remains a major limitation. High-quality clinical studies are needed to further evaluate these therapeutic strategies. Although the role of the Nrf-2/HO-1 signaling pathway in the treatment of diabetes has been preliminarily established, its precise regulatory mechanisms still require deeper investigation. Moreover, there is an urgent need to develop safer Nrf-2 activators for future clinical applications.

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