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Advances in the Treatment of Diabetic Retinal Inflammatory Factors with Curcumin

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Abstract: ***Retinal vein occlusion (RVO) is one of the common retinal vascular diseases characterized by vascular obstruction leading to intraretinal RVO is one of the common retinal vascular diseases characterized by vascular obstruction leading to intraretinal hemorrhage, fluid exudation, and varying degrees of retinal ischemia, and its secondary macular edema (ME) is the main cause of visual impairment in patients. Retinal vein occlusion secondary to macular edema is a pathophysiological process involving multiple factors, with a complex pathogenesis and many cytokines involved, and a high degree of visual impairment in patients. and many cytokines involved, resulting in an imbalance of fluid into and out of the retina, which leads to the formation of ME. In recent years, with the development of molecular biology techniques, inflammatory factors associated with RVO-ME have become an important aspect in the study of RVO-ME. this article, we review the inflammatory factors associated with retinal vein occlusion secondary to macular edema and the pathogenesis of RVO-ME.***

Keywords: Curcumin, Diabetic retina, Inflammatory factors, Traditional Chinese medicine treatment, Mechanisms.

1. Introduction

Diabetic retinopathy (DR) is one of the serious complications of diabetes mellitus and an important blinding eye disease. According to Chinese medicine, the cause of diabetic retinopathy is "deficiency of the root cause", and the treatment process is based on the deficiency of qi and yin as the root cause, blood stasis as the surface, and qi and yin as the main disease mechanism [1].

In Western medicine, diabetes mellitus (DM) is considered to be a chronic disease that encompasses a variety of metabolic disorders, i.e., uncontrolled elevation of blood glucose levels. According to the International Diabetes Federation, 415 million adults had diabetes in 2015, and this number is expected to rise to 642 million by 2040, a rise that will undoubtedly exacerbate the impact of this public health burden [2]. Diabetes can lead to a chronic hyperglycemic state that damages multiple organ systems and causes life-threatening and disabling health complications. Chronic microvascular complications include diabetic retinopathy (DR), neuropathy and nephropathy, while macrovascular complications include coronary heart disease, peripheral vascular disease and stroke. These diabetic complications are the main cause of diabetes-related burden. At this stage, the main clinical treatments for DR include retinal photocoagulation and vitrectomy, but most of the above treatments can only slow down the progression of the disease, but not improve the visual function of the patients, and there are many limitations and the risk of medical complications should not be ignored [3]. Vitreous injection of anti-vascular endothelial growth factor (VEGF) drugs has been an emerging treatment in recent years, and numerous studies have confirmed its effectiveness in controlling the progression of DR and diabetic macular edema (DME) in the short term.2 However, such treatments need to be repeated over a long period of time, and their long-term safety and efficacy have yet to be further confirmed. Therefore, the search for and development of drugs that can target the development mechanism of DR is currently a hot and difficult issue in the treatment of this disease. Since ancient times, Chinese medicine has accumulated rich experience in the use of traditional Chinese herbs to prevent and treat diseases, thus forming a relatively unique and complete theoretical system. Combined with the theories of TCM evidence-based treatment and holistic view, traditional Chinese medicine has unique advantages in the treatment of DR, and many TCM monomers, extracts and TCM compounds have been found to work through the regulation of inflammatory factors, and these drugs may become novel agents for the treatment of DR [4]. The progress of the research on curcumin in the treatment of inflammatory factors in DR is summarized as follows [5].

2. Physiological Properties of Curcumin

2.1 Structure and Chemical Properties of Curcumin

Curcuminoids are curcumin-like compounds extracted from turmeric (Curcuma longa), which belongs to the turmeric family. They belong to the group of phytocompounds, which are biologically active molecules obtained from plants that have a positive impact on health, E100 (European food additive code) or natural yellow 3. it has two o-o metho cyphenol groups in an aromatic ring system, and these groups are connected to a seven-carbon linker consisting of α, β-unsaturated β-diketone portions [4]. It also exists in two interconjugated isomeric forms, ketoenol and diketo interconjugated isomer. It exists in polar organic solvents in the form of ketoenol, which is the predominant form of the interconjugated isomer. Curcumin is hydrophobic and insoluble in water, but soluble in methanol, ethanol, chloroform, dimethyl sulfoxide, ethyl acetate and acetonitrile. The antioxidant effects of curcumin are mediated by inhibition of stress-induced elevated levels of 8-hydroxydeoxyguanosine and 8-nitroguanine, modulation of mitochondrial respiratory complex activity, and induction of up-regulation of Nrf2 (Nuclear Factor Red Lineage Derived 2-related Factor 2) of Heme Oxygen Synthesis Synthesizing Enzyme-1 (HO-1) The antioxidant activity of curcumin is mainly due to the hydroxyl group [6]. Rats pretreated with a daily dose of intragastric curcumin (200 mg/kg for 7 days) prior to induction of ischemia and reperfusion showed

attenuated mitochondrial lipid peroxidation and altered oxygen consumption while preventing the reduction of GSH, SOD and GR (glutathione reductase) activities [17]. Curcumin stimulated Nrf2 expression in a concentration- and time-dependent manner, which in turn increased HO-1 expression and HO-1 activity, a redox-sensitive inducible protein that protects cultured rat renal epithelial cells from various forms of stress. It stimulates ARE (antioxidant response element) binding activity in rat kidney NRK cells. Scree et al. showed that curcumin at a dose of 25 μm reduced the production of nitrite from sodium nitroprusside incubation solutions in phosphate buffered saline. The scavenging of nitric oxide (NO) by curcumin was concentration-dependent (50% at 20.4 and 100% at 50 μM). Curcumin was shown not to interact with the nitrite detection assay or to interact directly with nitrite. All forms of curcumin - demethox ycurcumin, bisdeme thoxycurcumin, and diacetylcurcumin - whether methoxy or phenolic, had no scavenging properties [15].

2.2 Targeting Vascular Endothelial Growth Factor

VEGF is one of the important inflammatory factors that stimulate neovascularization and cause vascular leakage in PDR. Under normal conditions, VEGF is expressed at low levels in human retinal cells, and when the body is stimulated to over express VEGF, VEGF binds to its corresponding receptors, such as VEGFR-3, VEGFR-2, and VEGFR-1, which triggers a series of biological effects. The level of VEGF in patients with DR is significantly higher than that in normal controls, and VEGF increases to a certain extent with the progression of DR. VEGF levels in DR patients were significantly higher than those in normal controls, and with the progression of DR, VEGF increased to a certain extent, and because of its high specificity, it can be used as one of the important indicators for the early diagnosis of DR[4]. As capillary obstruction increases, retinal ischemia becomes more severe, leading to an increase in VEGF levels, which in turn promotes the formation of pathologic neovascularization. Pathologic neovascularization often leads to rupture and hemorrhage due to its fragile structure. The resulting progressive hemorrhage can further increase VEGF expression and exacerbate the chronic inflammatory response. Signal transducer and activator of transcription 3 (STAT3) is a cytoplasmic transcription factor involved in angiogenesis [7]. In DR, the pro-inflammatory factor IL-6 upregulates STAT3 levels, and STAT3 activation also induces VEGF production. The number of pathological neovascularization of retinal endothelial cells increases under the combined effect of STAT3 and VEGF. DR can also affect the retinal neurovascular system consisting of optic neurons, Müller cells, endothelial cells (ECs), and pericytes (PCs), which are cellular structures that play an important role in constituting the retinal barrier [8]. Among them, the loss of retinal pericytes has been recognized as one of the earliest signs of DR. When pericytes are lost, capillary dilation, microaneurysm formation, thickening of the vascular basement membrane, and finally neovascularization, resulting in vascular leakage and macular edema, severely affect vision. Curcumin also reduces the expression of VEGF, inducible nitric oxide synthase (INOS), and ICAM-1 by inhibiting the activation of CaMKII/NF signaling in the retina of diabetic rats and in high-glucose cultured Müller cells.

3. Role for Each Signaling Pathway

3.1 JNK Signaling Pathway

The JNK signaling pathway plays an important role in the development of diabetes [10]. JNK can contribute to insulin resistance and β-cell dysfunction, and therefore could be a potential target for diabetes treatment. This role has also been demonstrated in diabetic mice, where down-regulation of JNK expression significantly reduced blood glucose levels and increased insulin sensitivity5. The JNK signaling pathway has been found to be extensively involved in the regulation of autophagic activity in cells and tissues. Studies have shown that with the activation of JNK phosphorylation in hepatocellular carcinoma, the expression of autophagy-associated protein LC3 was up-regulated, and the autophagy level was enhanced, which played an inhibitory role in the activity of hepatocellular carcinoma cells [11]. The expression level of autophagy-related protein Beclin-1 was also down-regulated with the application of JNK inhibitors. Sheng et al. demonstrated that LncRNANBR2 could inhibit Beclin-1-dependent autophagy through the JNK pathway. JNK expression can be regulated by curcumin and analogs, which play a role in diabetes mellitus and other complications [12]. Wang et al. showed that that curcumin analogs can protect against diabetes-induced nephropathy by inhibiting the phosphorylated expression of JNK to attenuate the degree of fibrosis in diabetic kidneys. In STZ-induced diabetic mice, curcumin significantly reduced diabetes-induced JNK phosphorylation in myocardial tissues and exerted a protective effect by controlling fibrosis and oxidative stress damage [13]. Quantitative studies have shown that retinal neuronal apoptosis is increased in diabetic animal models, suggesting that neuronal apoptosis may play a crucial role in DR, providing an idea for this experiment. The occurrence of apoptosis is closely related to the regulation of a variety of apoptosis-related genes, especially bax and bcl-26. The Bc1-2 protein family is distributed in the outer membrane of the mitochondria, the nuclear membrane, and the endoplasmic reticulum membrane, and it can be divided into two groups according to its function. One group of proteins inhibits apoptosis as Bcl-2 does, such as mammalian Bcl-XL, Bcl-W. Mcl-1, A1, Bcl-W, Mcl-1, A1, Mcl-1, A1, Bcl-W, and Mcl-1, A1, A1, and Mcl-1, A1, Mcl-1, A1, nematode Ced-9, and cowpox virus E1B119kD, while the other family is pro-apoptotic, such as Bax, Bcl-Xs, Bax, Bak, Bik/Nbk, Bid, and Harakiri. The Bcl-2 family is involved in the regulation of neuronal survival or apoptosis, and Bax can regulate cell death, and has been found to be involved in the regulation of cell death in retinal specimens from diabetic donors. Bax regulates cell death and has been found to be increased in retinal specimens from diabetic donors, which may contribute to the progression of vascular complications in diabetic retinopathy. Some reports suggest that the protein Bax plays an important role in retinal neuronal apoptosis and is one of the target proteins for gene therapy strategies to protect damaged neuronal cells. Bcl-2 is an apoptosis suppressor gene that inhibits the release of cytochrome C and the activation of proapoptotic components. The intracellular protein Bcl-2 prolongs cell survival and can specifically block apoptotic cell death through many signaling pathways [10].

3.2 PI3K/Akt Signaling Pathway

The PI3K/Akt pathway is widely present in biological organisms and plays an important role in a series of physiological and pathological activities of cells. The PI3K/Akt pathway has a regulatory role in a series of life science activities such as cell growth, proliferation and differentiation. When activated, the PI3K/Akt pathway prolongs the survival cycle of endothelial cells and synergistically interacts with VEGF to regulate cell survival, migration, and ultimately neovascularization. PI3K is a family of enzymes that affects cellular function through the involvement of a series of related intracellular signaling enzymes, and when activated, its second messenger PIP3 further activates molecules downstream of the pathway (mainly Akt). After activation, its second messenger PIP3 is able to further activate molecules located downstream of PI3K (mainly Akt), thereby contributing to the stimulation of a variety of physiopathological processes such as cell migration, proliferation, and angiogenesis. Akt is an antimortality signal that has a regulatory function on serine kinases, and its biological activity is mainly to regulate the hydrolysis of D1, an important mediator in the transition of cells from the G1 to the S phases of the cell cycle and its localization inside the cell, and thus to play a role in the inhibition of the transition from G1 to S phases. In addition, it can play a role in cell survival, autophagy, and angiogenesis through a variety of pathways. mTOR is a member of the PI3K-related kinase family, and the mTOR pathway is a central regulator of mammalian metabolism and physiology, which is dysregulated in a variety of diseases, such as diabetes, obesity, and some tumors. Numerous studies have now demonstrated that the PI3K/Akt signaling pathway is associated with some of the complications of diabetes, such as diabetic nephropathy, glomerular hypertrophy, and myocardial ischemia.

3.3 SphK1-S1P Signaling Pathway

Curcumin is a yellow pigment extracted from the rhizomes of turmeric and other plants in the ginger family, and is one of the main active ingredients of turmeric. The main pharmacological effects of curcumin include anti-aging, elimination of free radical oxidation, anti-inflammatory, anticoagulant, hypolipidemic, anti-atherosclerotic and tumor growth inhibition. Its wide range of pharmacological effects such as hypoglycemic, hypolipidemic, antiproliferative, antioxidant, anti-inflammatory and immunomodulatory effects have been found in both laboratory studies and clinical trials8, which are all beneficial in improving the course of renal fibrosis in DKD. Curcumin was found to significantly alter the expression of MAPKp38, histone H3 and heat shock protein-27 in STZ-induced diabetic rats, which in turn improved renal function in type I DKD. Hao Jie et al. confirmed through experimental studies that curcumin has a significant ameliorative effect on STZ-induced renal injury in diabetic rats, and antagonizes the process of diabetic renal fibrosis by inhibiting the SphK1-S1P signaling pathway16.

4. Conclusions and Outlook

Recent findings suggest that curcumin has the potential to treat a wide range of diseases and has many signaling molecular targets. These preclinical studies provide a solid foundation for evaluating the efficacy of curcumin in clinical trials. In clinical trials, curcumin and its preparations, alone or in combination with other drugs, exerted anti-inflammatory effects in ulcerative colitis, osteoarthritis, metabolic diseases, periodontitis, and other diseases. For example, nutritional intervention with curcumin - galactomannan complex has a significant hepatoprotective effect in attenuating alcohol-induced alterations in liver function markers; curcumin significantly reduces serum pro-inflammatory cytokine concentrations in Mets patients. Curcumin is very promising in the treatment and prevention of various chronic inflammatory diseases, but its hydrophobic nature leads to pharmacokinetic limitations, such as low absorption and bioavailability by the oral routeand rapid metabolism and elimination. However, the dose at which curcumin produces its drug effect is very high, thus severely limiting its use in clinical practice. In response to these problems, a variety of new dosage forms of curcumin have been developed in recent years, thereby improving the bioavailability of curcumin, such as liposomes, solid dispersions, polymeric micelles, cyclodextrin inclusion complexes, microspheres, and nanoformulations. Curcumin is able to inhibit inflammation-related molecular and cellular pathways, targeting a variety of inflammation-related cell signaling networks, such as JAKs/STATs, PI3K/AKT/mTOR, Wnt/β-cate-nin, NF-κB, and MAPK/ERK pathways, which have the potential to prevent and treat chronic inflammatory diseases, which will lay the foundation for further design and clinical application of drugs with potential therapeutic significance. However, most of the current studies on curcumin are based on cell culture and animal experiments, which is due to its poor water solubility, low permeability, and belonging to the BCS IV class of compounds, which limits its application in the clinic. With the deepening of curcumin dosage form research in recent years, the problems of its absorption, distribution, metabolism and excretion have been gradually solved, and the understanding of the mechanism of curcumin's anti-inflammatory factors will have a great role in the future development of the use of curcumin for the prevention and treatment of chronic inflammatory diseases, and has a very good prospect for research.

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