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Research Progress of Berberine in the Prevention and Treatment of Atherosclerosis

Peng Zhang[1]*, Jili Xu[1], Xiao Jiang[1], Wei Zheng[2], Jing Zhang[3], Hongmei Wang[4], Yutao Wang[5], Guangbo Shi[6], Lizhen Wang[7], Daijie Wang[7]

1.College of Traditional Chinese Medicine, Binzhou Medical University, Yantai, 264003, China

2.Shandong Qingdao Hospital of Integrated Traditional Chinese and Western Medicine, Qingdao, 266000, China

3.Shandong Mental Health Center, Jinan, 250014, China

4.Zibo Occupational Disease Prevention and Treatment Hospital, Zibo, 255000, China

5.Jinan Hospital of Traditional Chinese Medicine, Jinan, 250012, China

6.Shandong Academy of Traditional Chinese Medicine, Jinan, 250014, China

7.Qilu University of Technology (Shandong Academy of Sciences), Jinan 250014, China

Corresponding author: Peng Zhang, bzyxyzp@bzmc.edu.cn

Abstract: Atherosclerosis (AS) is the core pathological basis of Cardiovascular Disease (CVD) worldwide. Its occurrence and development involve endothelial dysfunction, lipid deposition, chronic inflammation and abnormal proliferation of smooth muscle cells. Berberine (BBR), also known as berberine, is an isoquinoline alkaloid extracted from traditional Chinese medicine such as Coptis coptidis and Phelloberia angustifolia. It has traditionally been used for antibacterial and anti-inflammatory treatment. In recent years, it has been found that it has multi-target metabolic regulation and anti-inflammatory properties, showing significant potential in the prevention and treatment of AS. This article systematically reviews the research progress of berberine in the treatment of AS by improving endothelial function, regulating lipid metabolism, inhibiting inflammatory response, regulating smooth muscle cell phenotypic transformation, and anti-oxidative stress, and discusses the current status and challenges of its clinical application.

Keywords: Berberine; Atherosclerosis; Research Progress

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1.Introduction

Arteriosclerosis is a chronic progressive disease characterized by lipid deposition, plaque formation, and luminal stenosis in the arterial intima, which is the main cause[1] of CVD such as myocardial infarction and stroke. Studies have shown that CVD causes about 18 million deaths in the world every year, accounting for 32%[2] of the total deaths. Statins play a positive role in reducing low-density lipoprotein cholesterol and stabilizing plaque, but their important side effects, such as elevated liver enzymes and muscle toxicity,[3] greatly limit their clinical promotion and use. Therefore, it is of great clinical significance to find safe and effective adjuvant therapy drugs.

Berberine (molecular form $C_{20}H_{17}NO_4$, molecular weight 336.36), $_7NO_4$, is a natural component in plants such as

Ranunculaceae and Berberidaceae, which is mainly used to treat intestinal infection and diarrhea[4]. Later studies have confirmed that berberine has hypoglycemic and lipid-regulating effects[5], and with the deepening of research, the mechanism of berberine in metabolic diseases has gradually become clear[6]. In recent years, with the recognition of the complex pathological network of AS, the research on the intervention of berberine through multiple targets has become a hot topic. This article focuses on the pathological mechanism of AS, systematically summarizes the anti-AS effect and mechanism of berberine.

2.The main pathological mechanisms of atherosclerosis

The occurrence of atherosclerosis (AS) is a complex process involving multiple factors and interrelated pathological links. The core process of AS is endothelial dysfunction, which is manifested as endothelial cell (ECs) injury leading to reduced nitric oxide (NO) bioavailability and impaired vasodilation function, and at the same time, the expression of adhesion molecules (such as VCAM-1 and ICAM-1) is up-regulated, which promotes the adhesion and infiltration of circulating monocytes into the vascular intima. These macrophages, together with the damaged ECs themselves, take up oxidized low-density lipoprotein (ox-LDL) through scavenger receptors (such as SR-A and CD36) on their surface, leading to intracellular lipid accumulation and transformation into foam cells, forming lipid striations, which are the hallmark of early lesions. This lipid deposition environment continuously stimulates and drives the chronic inflammatory response: activated macrophages secrete large amounts of proinflammatory factors (such as TNF-α and IL-6), which further recruit more inflammatory cells and maintain the inflammatory state, while inducing increased expression of metalloproteinases (MMPs) and destroying the stable structure of the plaque. In the process, membrane in vascular smooth muscle cells (SMCs) key phenotypic transformation, by deflating, into synthetic migrated to vascular intima. It is worth noting that oxidative stress runs through the process. The excessive production of reactive oxygen species (ROS) not only directly aggravates ECs injury, promotes the oxidation of lipids (especially LDL) to ox-LDL, but also amplicates inflammatory signaling transduction[7], forming a self-reinforcing vicious cycle that jointly promotes the initiation, progression, and finally formation of unstable plaques in AS.

3.Multiple target mechanisms of berberine intervention on atherosclerosis

3.1 Introduction to Berberine

Berberine is a naturally occurring alkaloid compound found in the roots, rhizomes, and stem bark of several plants, including Coptis chinensis (Goldthread) and Berberis species (such as Barberry). It has a long history of use in traditional Chinese and Ayurvedic medicine, primarily for treating bacterial diarrhea and gastrointestinal infections. Modern research has revealed that berberine possesses a wide range of pharmacological activities. It is now widely recognized as a multi-functional agent with demonstrated effects on cardiovascular health, metabolic regulation (including diabetes and high cholesterol), anti-inflammatory responses, and anti-cancer properties. Its ability to interact with multiple molecular pathways makes it a promising therapeutic compound for complex diseases like atherosclerosis.

3.2 Improve endothelial function and protect vascular barrier

Endothelial dysfunction is the key initiating link of atherosclerosis (AS). Studies have shown that berberine can effectively improve endothelial function through multiple pathways. On the one hand, berberine significantly enhanced the bioavailability of nitric oxide (NO), which has vasodilator and protective effects. The main mechanism is that berberine promotes the phosphorylation of eNOS at the key site (serine 1177) through the PI3K/Akt signaling pathway, thereby enhancing the enzyme activity and increasing the synthesis and release of NO. At the same time, berberine can also inhibit the uncoupling process of eNOS, reduce the production of harmful superoxide anion, and further ensure the availability[8] of NO. Li et[9] al. found that pretreatment of human umbilical vein endothelial cells (HUVECs) with berberine (10 μmol/L) effectively reversed the downregulation of eNOS mRNA expression induced by oxidized low-density lipoprotein (ox-LDL) and significantly increased NO level by 32%. On the other hand, berberine could effectively inhibit the expression of inflammation-related vascular endothelial adhesion molecules. Under inflammatory stimulation, IκB kinase (IKK) is usually activated, leading to the phosphorylation and degradation of the inhibitory protein IκB, which allows NF-κB to translocate into the nucleus to initiate the transcription[10] of adhesion molecule genes such as VCAM-1 and ICAM-1. Berberine can inhibit IKK activity, reducing I

kappa B predominate phosphorylation and degradation, preventing the nf-kappa B of nuclear transfer and downstream target gene expression. Animal model experiment proved that, in the high fat diet of apolipoprotein E knockout mice (ApoE $^{-}$ / $^{-}$), giving berberine (100 mg/kg/d) intervention after 8 weeks, the aorta tissue VCAM 1 protein expression of less intervention model group significantly reduced the amount of 45%[11].

3.3 Regulation of lipid metabolism and reduction of ox-LDL deposition

Disorders of lipid metabolism, especially hypercholesterolemia, are the core risk factors that promote the development of atherosclerosis (AS). Studies have confirmed that berberine can play a regulatory role by intervening multiple key links of lipid metabolism. In terms of source regulation, berberine can effectively inhibit the synthesis[12] of fatty acid and triglyceride (TG) in the liver. Berberine inhibited the activity of its downstream target acetyl-coa carboxylase (ACC) through enhancing the phosphorylation of AMPKα at ser108 in A dose-dependent manner. This cascade of activation leads to A decrease in malonyl-coa production, which ultimately inhibits fatty acid synthase (FASN) expression and reduces lipid deposition[13] in the liver.

Berberine can significantly up-regulate the expression levels of ABCA1 and ABCG1 in macrophages, effectively promote the efflux of intracellular cholesterol to HDL particles, thereby reducing the formation[14] of foam cells. Zhang et[14] al. observed that treatment of RAW264.7 macrophages with 20 μmol/L berberine resulted in a 2.1-fold increase in ABCA1 mRNA expression and a significant 38% reduction in intracellular total cholesterol content.

Berberine can selectively inhibit the activity of some strains of intestinal flora involved in bile acid unconjugation, reduce the production of secondary bile acids, and promote the reabsorption of primary bile acids in the hepato-intestinal circulation. This activates the farnesoid X receptor (FXR) signaling pathway in the liver, which in turn inhibits the liver's own cholesterol synthesis[16]. Notably, the abundance of beneficial mucoid Akkermansia muciniphila in the gut was significantly increased[17] after berberine intervention. The enrichment of Akkermansia muciniphila can strengthen the intestinal mucosal barrier function (in part due to the short-chain fatty acid SCFAs produced by it) and reduce the release of harmful substances such AS endotoxin into the blood circulation, which can induce the production of inflammatory factors in the liver and indirectly promote the process of AS.

3.4 Inhibit chronic inflammation and block the inflammatory cascade

Chronic inflammation is the core pathological process that drives the initiation, progression and even plaque instability of atherosclerosis (AS). Studies have shown that berberine can effectively inhibit the synthesis and release of key pro-inflammatory factors. In macrophages and vascular smooth muscle cells, berberine can significantly reduce the mRNA transcription level and protein expression of TNF-α, IL-6, IL-1β and other inflammatory mediators. On the one hand, berberine can inhibit the activation of nuclear factor-κB (NF-κB) pathway (such as reducing the phosphorylation of IκBα inhibitor protein, thereby hindering the nuclear translocation and transcriptional activation of NF-κB dimer), and on the other hand, it can reduce the phosphorylation level[18] of mitogen-activated protein kinase (MAPK) pathway members (such as p38 and ERK1/2). It was found that in the ApoE$^{-/-}$ mice model of atherosclerosis, berberine intervention significantly reduced the serum TNF-α concentration by 52% and the aortic IL-6 mRNA expression level by 40%[19].

Berberine can inhibit the maturation and differentiation of dendritic cells (DCs) and weaken their antigen presentation ability, thereby reducing excessive immune activation. At the same time, berberine can also promote the differentiation and expansion of regulatory T cells (Tregs) with anti-inflammatory function and enhance the immune tolerance[20] of the body. In addition, berberine can also inhibit the formation of neutrophil extracellular traps (NETs), an important link in the inflammatory cascade of neutrophils, which helps to reduce NETS-mediated vascular endothelial injury and local inflammation amplification[21].

Berberine significantly down-regulated the mRNA and protein expression of matrix metalloproteinases, especially MMP-2 and MMP-9, induced by inflammation, mainly by inhibiting the NF-κB pathway as described above, while upregulating the expression of its endogenous inhibitor, tissue inhibitors of metalloproteinases. The regulation of MMP/TIMP balance is beneficial to protect the integrity of collagen and other components in the fibrous cap of plaque and enhance the stability[22] of plaque. In support of this mechanism, human aortic smooth muscle cells (HASMCs) treated with 50 μmol/L berberine

showed that the up-regulation of MMP-9 mRNA induced by tumor necrosis factor-α (TNF-α) stimulation was effectively inhibited by 60%[23].

3.5 Regulation of phenotypic transformation of smooth muscle cells and inhibition of plaque progression

The transformation of smooth muscle cells (SMCs) from a contractile type that maintains vascular tone to a synthetic type with high proliferation and migration ability is a key pathological step that drives the enlargement of atherosclerotic plaques. Platelet-derived growth factor (PDGF) plays an important role in the phenotypic transformation, proliferation and migration of SMCs through the activation of the downstream PI3K/Akt and MAPK/ERK1/2 signaling pathways. Berberine can directly inhibit the tyrosine phosphorylation of PDGF receptor (PDGFR), thus significantly interfere with the activation of the receptor, and finally block the transmission of its downstream signaling cascade, which creates conditions[24] for SMCs to maintain a relatively quiescent phenotype. Berberine can significantly increase the expression levels of key cyclin-dependent kinase inhibitors such as p21 and p27, effectively arrest the cell cycle progression (especially the transition from G0/G1 phase to S phase), arrest the cell cycle progression in the less active phase, and finally inhibit the pathological expansion[25] of SMCs. In the rabbit model of atherosclerosis, treatment with berberine (50 mg/kg/ day for 4 weeks) resulted in a 48%[26] reduction in proliferating cell nuclear antigen (PCNA) positive SMCs proliferation index in the aortic intima.

3.6 Anti-oxidative stress and reduction of oxidative damage

Excessive oxidative stress directly damages vascular endothelial cells (ECs), accelerates the oxidation of low-density lipoprotein (LDL) and amplifies the inflammatory cascade, which plays a complex role in the process of atherosclerosis (AS). Studies have shown that berberine significantly activates the antioxidant defense pathway of nuclear factor erythroid 2-related factor 2 (Nrf2) in cells. The results showed that berberine (20 μmol/L) significantly increased the mRNA expression level of HO-1 and effectively reduced the intracellular ROS load[27,28] by 50%. At the same time, the isoquinoline ring conjugated system and quaternary ammonium group in the molecular structure of berberine can effectively provide electrons, quickly neutralize reactive oxygen species such as superoxide anion and hydroxyl radicals, and play an immediate antioxidant protection role[29] in the cellular microenvironment.

4.Clinical study of berberine in the prevention and treatment of atherosclerosis

4.1 Efficacy of intervention alone or combined with statins

A number of randomized controlled trials have confirmed that berberine monotherapy or combination therapy can significantly improve the pathological indicators related to AS. A clinical trial in patients with hyperlipidemia and carotid plaque showed that oral berberine 1500 mg (500 mg thrice daily) for 12 months significantly reduced serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels, as well as carotid intima-media thickness (IMT). It is worth noting that the curative effect with atorvastatin (20 mg/day) standard treatment group effect, prompt berberine has with statins is quite stable[30] plaques.

Further study in type 2 diabetic patients with AS showed that after 16 weeks of treatment with berberine combined with metformin, serum oxidized low-density lipoprotein (ox-LDL) levels were significantly reduced, and endothelial function was significantly improved as measured by brachial flow-mediated vasodilation (FMD). This finding confirmed the synergistic intervention value[31] of berberine and metformin on the progression of diabetes-related AS.

4.2 Safety and tolerability

Berberine has good clinical safety, and the common adverse reactions are mild gastrointestinal discomfort (such as diarrhea and nausea), with an incidence of about 5%-10%, and most of them are transient[32]. No serious adverse events[33] caused by significant interactions were found when berberine was used in combination with existing AS treatment drugs (such as statins and antiplatelet drugs). However, it should be noted that berberine may affect the metabolism of some drugs, and relevant indicators[34] need to be monitored when combined with AS in clinical practice.

5.Challenges and prospects

Although berberine has shown unique multi-target intervention advantages in the prevention and treatment of atherosclerosis

(AS), its clinical translation still faces key challenges. The primary constraint is its inherent low bioavailability. After oral administration, berberine is susceptible to the metabolism of the intestinal first-pass effect, resulting in a systemic bioavailability of only about 1%-3%[35], significantly restricting its therapeutic potential. In order to break through this bottleneck, researchers are actively exploring new delivery strategies, including the use of nanoparticles such as liposomes or polymer micelles, the design of prodrug molecules such as berberine-oleate complex, and the combination of probiotics to improve the intestinal absorption environment[36]. Among them, the relative bioavailability of berberine-oleic acid nanoparticles in the mouse model has been increased by 4.2-fold[37] compared with the free drug, showing significant technical prospects. Secondly, the dose optimization for clinical application needs to be clarified urgently. However, long-term high doses (>1000 mg/d) may increase the risk[38] of gastrointestinal adverse reactions. Therefore, it is urgent to establish an accurate dose-response relationship and safety boundary through large-scale and long-term studies. Thirdly, the extensive effects of berberine on multiple cell populations, such as vascular endothelial cells, macrophages, and smooth muscle cells, constitute the basis of the therapeutic effect, but also increase the difficulty of mechanism analysis. In the future, it is necessary to integrate cutting-edge technologies such as single-cell transcriptomics and spatial metabolomics to fine characterize the cell type-specific signaling network and provide a theoretical foundation for the development of intervention strategies based on precise regulation of pathways.

6.Conclusions

Berberine has shown significant clinical application potential by improving endothelial function, regulating lipid metabolism, inhibiting inflammatory response, regulating SMCs phenotypic transformation and anti-oxidative stress. Although the problems of bioavailability and dosage optimization still need to be solved, with the progress of preparation technology and the in-depth study of mechanism, berberine is expected to become an important adjuvant drug for the prevention and treatment of AS and provide a new strategy for the comprehensive management of CVD.

7.Contributions

Zhang P: Responsible for literature retrieval, data extraction, full-text writing. Xu JL and J X: Participated in literature screening and verification of key data, and assisted in analyzing controversial points. Z W : Guided the selection of topics and framework design, reviewed and validated the scientific rigor and logic of the full text, and assumed ultimate responsibility for the paper.

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Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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