DOI: 10.53469/jcmp.2024.06(10).34

Research Progress on Mechanism of Shikonin in Treatment of Colitis

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Abstract: ***Zicao, a traditional Chinese herbal medicine utilized in the clinical management of ailments such as soreness, eczema, burns from both water and fire, various forms of hemorrhage, among others. Shikonin, a naphthoquinone compound derived from the root of comfrey, exhibits properties including antioxidation, anti-inflammation, promotion of skin repair, free radical scavenging, and inhibition of lipid metabolism. Colitis is an inflammatory condition affecting the colon that can arise from diverse etiological factors including bacteria, fungi, viruses, parasites, protozoa and other organisms; its primary clinical manifestations encompass diarrhea, abdominal pain and mucus-laden stools. This condition often presents with recurrent episodes. The treatment for colitis predominantly relies on antibiotics and anti-inflammatory agents; however their long-term side effects are considerable. Therefore it is crucial to explore milder therapeutic alternatives. Recent studies have indicated that shikonin may effectively address colitis by elucidating its underlying mechanisms in this review paper aimed at providing a theoretical foundation for the treatment and recovery process associated with colitis.***

Keywords: Shikonin, Colitis, Intestinal flora, Intestinal barrier, PKM2**.**

1. Introduction

Zicao is a traditional Chinese medicine derived from the roots and stems of comfrey, which has a history of thousands of years and can treat inflammation, infection and bleeding diseases [1]. The chemical composition of comfrey is mainly naphthoquinones, its main active component is shikonin, and its chemical structural formula is C16H16O5. Shikonin is the main bioactive component of "comfrey" and has similar anti-cancer, anti-inflammatory and wound healing properties as "comfrey" [2].

Research has demonstrated that shikonin exhibits potent antioxidant properties, effectively inhibiting lipid peroxidation and scavenging free radicals. Additionally, it possesses anti-diabetic effects, promotes wound healing, reduces lipid levels, inhibits the survival of leukemia cells, induces apoptosis, suppresses angiogenesis, and enhances the inflammatory environment among other benefits. Furthermore, shikonin displays anti-inflammatory effects in conditions such as arthritis, asthma, psoriasis, mastitis, diabetic keratitis as well as diseases affecting the heart and liver [3].

Inflammatory bowel disease (IBD) impacts over 3 million individuals globally with an increasing incidence rate. Colitis represents a significant clinicopathological subtype characterized by a chronic inflammatory response within the colonic mucosa [4]. Given its high prevalence, extensive research has been conducted on its etiology; factors including genetic predisposition, immune responses, environmental influences and infectious agents are believed to contribute to its progression [5].

The primary pharmacological interventions for patients include anti-inflammatory medications and antibiotics. However, due to the chronic nature of colitis and potential long-term side effects associated with these treatments—such as disruption of intestinal homeostasis leading to cancer or infections—their use is often limited. In contrast, traditional Chinese medicine offers therapeutic approaches characterized by multiple targets and minimal adverse effects. This paper aims to review recent advancements in understanding the mechanisms through which shikonin may treat colitis in order to provide a theoretical foundation for clinical applications.

2. Targeting PKM2 for the Treatment of Colitis

Pyruvate Kinase Muscle isozyme (PKM2), recognized as the final rate-limiting enzyme in the 'Warburg effect, ' is significantly upregulated in inflammatory macrophages and plays a crucial role in mediating immune function-related inflammation [6]. Research has demonstrated that shikonin can inhibit glycolysis in tumor cells [7], downregulating phosphorylated PKM2 expression levels, while selectively targeting and inhibiting PKM2 activity without affecting PKM1 or other isoforms, thereby modulating the inflammatory response [8]. Consequently, shikonin serves as an effective inhibitor of PKM2.

In an LPS (lipopolysaccharide)-induced inflammation model, under LPS stimulation, PKM2 exists predominantly in a low-activity dimeric state which facilitates its nuclear translocation within macrophages; this low-active form of PKM2 can enhance transcriptional expression of genes associated with inflammation. The application of the PKM2 nuclear translocation inhibitor TEPP-46 (ML265) effectively prevents dimeric PKM2 from undergoing nuclear shift, leading to downregulation of pro-inflammatory gene expression and inhibition of glycolytic responses [9], thus attenuating the inflammatory response.

Inhibition of PKM2 dimerization and nuclear translocation through shikonin administration effectively mitigates intestinal injury in the colonic lamina propria of mice, while also preventing further infiltration of pro-inflammatory macrophages into the damaged intestinal tissue, thereby significantly ameliorating colitis induced by 5% dextran sulfate sodium (DSS) [10].

In addition, PKM2, as the final rater enzyme in glycolysis,

plays a key role in regulating glycolysis, and lactic acid, a metabolite of glycolysis, has also been confirmed to mediate the lactate modification of lysine residues, which can regulate the polarization of macrophages and thus regulate the inflammatory response [11]. Therefore, targeting PKM2, Inhibition of nuclear migration of PKM2 is a potential target for the treatment of colitis.

3. Mediates the Inflammatory Response to Treat Colitis

Immune cells and pro-inflammatory cytokines are important components of the body's inflammatory response. They can induce inflammation through the interaction of the body's immune regulatory response, and are closely related to the activation of the NLRP3 inflammasome.

Macrophages in immune cells are considered to be the central mediators of intestinal immune homeostasis and inflammation, and are involved in the regulation of inflammatory progression in the process of intestinal repair, which is of great significance for inflammatory intestinal diseases [12]. The continuous over-activation of NLRP3 inflammasome by colon macrophages is crucial for the occurrence and development of intestinal inflammatory response [13], and the activation of nuclear factor-κB (NF-κB) signaling pathway is an important pathway for macrophages to activate NLRP3 inflammasome [14]. Under normal conditions, the M1-proinflammatory phenotype and M2-anti-inflammatory phenotype of macrophages are in a state of mutual balance. Studies have shown that blocking the activation of NLRP3 inflammasome or knocking out NLRP3 inflammasome can mediate the polarization of M2 macrophages [15]. Entosis of macrophages on particulate matter (such as cholesterol crystals and SiO2) can lead to lysosomal rupture and histone protease destruction, thus promoting the activation of NLRP3 inflammasome [16]. Pro-inflammatory cytokines are an important part of the body's non-specific immunity [17], which can promote the expression of endothelial cell adhesion molecules, help neutrophil migration, increase the capacity of macrophages, induce the release of inflammatory mediators, further expand and activate the NLRP3 inflammatome and inflammatory signal cascade, and induce inflammation in the body to resist heterogeneous invasion. Regulating and maintaining the balance of pro-inflammatory cytokines and restoring the normal immune function of the body are crucial for the treatment of colitis [17].

The innate immune system of the gut is the primary defense against various bacterial antigens in human immunity [18]. Ulcerative colitis can cause the innate immune system to weaken, accumulate bacterial antigens, and stimulate the inflammatory response of the acquired immune system [18]. The NLRP3 inflammasome is a key component of inflammation, and its dysfunction leads to the increase of its associated pro-inflammatory cytokines. Inhibiting the activation of NLRP3 inflammasome and reducing the expression level of pro-inflammatory factors are important targets for the treatment of colitis.

Shikonin is now being studied as an anti-inflammatory agent for the treatment of ulcerative colitis. It has been found that ES100/HA/CS (SK@SAC) loaded with shikosin constructed in vivo can enter macrophages through oral administration mediated by CD44 receptor and reach the nanoparticle drug delivery system in the inflammation site of the colon, which can not only protect the colon tissue from damage, but also protect the colon tissue. Down-regulating the levels of ROS and pro-inflammatory cytokines TNF-α, IL-6, IL-1β, COX-2 and iNOS can also up-regulate the expression of anti-inflammatory cytokines IL-10 and TGF-β [19]. Shikotin also prevents colorectal shortening and ulcer formation in a dose-dependent manner, inhibits NF-κB and NLRP3 inflammasome activation, improves the pro-inflammatory environment, thereby protecting intestinal tissue and preventing bloody stools in animals [20, 21].

In addition, shikonin can not only inhibit the M1 polarization of macrophages and the production of nitric oxide, but also regulate the differentiation of helper T cell 17 (Th17)/regulatory T cell (Treg), thereby regulating the balance of Th17/Treg cells and playing an anti-inflammatory role in inflammatory animal models [22].

In conclusion, shikosin can reduce immune cell infiltration, regulate T cell differentiation, regulate macrophage polarization, and down-regulate the release of inflammatory cytokines to prevent DSS induced colitis.

4. Regulate Intestinal Flora to Treat Colitis

Intestinal flora is an important part of the intestinal microenvironment. Under normal human conditions, intestinal flora maintains the integrity and permeability of intestinal mucosa and interacts with the host immune system in various ways to maintain intestinal homeostasis [23]. Balanced and stable intestinal flora has the function of protecting intestinal mucosa and fighting inflammation, and is beneficial to human health in terms of metabolism and nutrition [24]. Studies have shown that the influence of intestinal flora on ulcerative colitis mainly includes three aspects: intestinal flora imbalance, intestinal mucosal barrier and immune system [24].

When intestinal inflammation occurs, the intestine interacts with a large number of microorganisms at the inflammation site, affecting the intestinal microecosystem [25]. Changes in gut microbiota can lead to ecological imbalance [25]. Bacterial pathogens in the gut can interact directly with host epithelium or immune cells, causing intestinal inflammation and accelerating the progression of colitis to colitis-related cancers [25].

Clinical studies have shown that the diversity of intestinal microbial population in patients with colitis and colon cancer is reduced [26], and some bacteria genera such as Clostridium and bacteroides are reduced [27], while the reduction of beneficial bacteria such as lactobacillus and paracoides can cause intestinal flora disorder and dysfunction [28]. Treatment with schistotin can regulate the reduction of intestinal bacteroides [29], Improve intestinal dysbiosis.

In addition, shikonin and acetylshikonin regulate the structure and composition of intestinal microbiota in a dose-dependent manner, improve the species richness, evenness and diversity

of intestinal microbiota, and restore the up-regulation ratio of Firmicutes and bacteroidetes, which represent the ecological imbalance of intestinal microbiota, and increase the beneficial bacteria. It can maintain the homeostasis of microflora, regulate the host immune system, resist pathogens, promote mucosal integrity, reduce bacterial translocation and other mechanisms to improve the dynamic balance of intestinal flora and ensure the health of the body [29].

In addition, shikonin can also reduce the protein expression of inflammation and cancer-related pathways, including the Wnt/β-catenin signaling pathway, regulation of pro-inflammatory factors and PKM2 [18], and effectively relieve colitis in mice.

Due to its multi-target function, Chinese medicine and its compounds can be absorbed by the small intestine by oral administration. These absorbed molecules promote the synthesis and secretion of antibacterial products by the host, such as antibacterial enzymes and antimicrobial peptides, thus affecting the intestinal flora [30]. Therefore, compared with Western medicines, Chinese medicine compounds may be more effective in regulating intestinal flora with fewer side effects. It has great potential to regulate the dysfunctional intestinal flora.

5. Repair Intestinal Barrier Damage and Treat Colitis

Intestinal barrier is an important defense line of the body's defense function. On the one hand, it can promote the absorption of nutrients and liquids; on the other hand, it can separate substances in the intestinal cavity and restrict the passage of harmful antigens and microorganisms. The maintenance of this delicate balance is strictly regulated, because it is crucial for human homeostasis [31].

Intestinal mucosal barrier plays an important role in maintaining intestinal homeostasis and is involved in the pathogenesis of ulcerative colitis. Intestinal barrier can be divided into biological barrier, immune barrier, physical barrier and chemical barrier.

The gut microbiota and its metabolites constitute the biological barrier of the gut [32], which can generate a biofilm to protect the gut and improve resistance to harmful bacteria [33].

The intestinal immune barrier is mainly composed of lymphoid tissue of intestinal mucosa lamina propria and immunoglobulin A molecules, which can specifically bind pathogenic microorganisms and toxins to prevent pathogens from passing through the intestinal mechanical barrier [34].

The intestinal mechanical barrier consists of mucus layer and intestinal epithelial cells. The mucus layer prevents inflammation by shielding the underlying epithelial cells and colon tissue, and the integrity of the intestinal epithelial barrier depends on the formation of tight junction proteins between neighboring cells [35]. Tight junctions are a multiprotein complex responsible for regulating paracellular permeability. Tight junctions of the intestinal epithelium define the paracellular permeability of the intestinal barrier [36] Tight junctions also control antigen delivery through the intestinal epithelium and play a key role in maintaining barrier integrity [36].

Studies have confirmed that the imbalance of intestinal microbiota can reduce the number of tight junction transmembrane proteins such as occludin 1, Occludin, and claudin, thus destroying the integrity of the intestinal mechanical barrier and exacerbating the development of ulcerative colitis [37].

It was found that zikonin and its derivatives can inhibit the activation of nucleotide-binding oligomeric domain-like receptor (NLRP3) inflammasome and NF-κB signaling pathway, thereby mediating the expression of epithelial tight proteins ZO-1, VCAM-1, Occludin and Claudin-1, etc. Alleviate the DSS induced breakdown of epithelial tight junctions in colon tissue [38], repair the mucosal barrier, and alleviate colitis.

6. Repair Intestinal Damage and Treat Colitis

In the external use of traditional Chinese medicine, shikonin has the effect of promoting wound healing, especially for skin repair, and is often made into paste or oil to treat burns.

Studies have shown that shikonin/shikonin dimerization isolated from bark extract can promote wound healing in the incision of albino rats [39]. Second wound healing in dogs treated with enantiomer naphthoquinanin and shikonin ointment has significantly higher mean LDF values and higher collagen and epithelial thickness scores compared to Ringer's solution treatment [40]. Shikonin also promotes wound healing in vibrio vulnificus infected mice by promoting the formation of granulation tissue, hair follicles and sebaceous glands, epithelial cell regeneration and epidermal growth factor production [41].

Shikosin analogues promote granulation tissue formation, including cell migration, angiogenesis, collagen production, and re-epithelialization. Shikonin increases the expression of basic fibroblast growth factor, thereby promoting wound healing [41]. Shikonin promotes the proliferation and migration of recombinant hepatocyte growth factor (HGF), synthesis of type I collagen and FN, and expression of vascular endothelial growth factor through the ERK 1/2 signaling pathway, thus promoting wound healing in gingival tissue [42]. There was also a novel liposome containing shikonin to enhance its action against methicillin-resistant Staphylococcus aureus and its beneficial wound-healing effect was tested. This shikosin liposome controls infection by inhibiting bacterial activity, modulates inhibitors of the NF-κB signaling pathway to reduce inflammatory infiltration and promote burn wound repair [43].

Ulcerative colitis, one of the main manifestations of inflammatory bowel disease, is an idiopathic chronic inflammatory disease of the colon mucosa.

It begins in the rectum and usually extends proximal in a continuous manner, through part or the entire colon, and is characterized by inadequate and delayed wound healing [44]. The main clinical manifestations were abdominal pain and

diarrhea, mucous pus and blood stools, posterior tenesia and so on. Shikonin, the active ingredient in the root of comfrey, has been shown to have the ability to attenuate ulcerative colitis induced by sodium dextran sulfate in mice.

Experiments have demonstrated that shikonin therapy significantly stimulates the migration of intestinal epithelial cells through a TGF-B1-dependent process, thus promoting the healing of intestinal injury. This mechanism may contribute to the improvement of DSS induced UC in mice. Although these results were obtained using an in vitro system, the observed increase in the rate of epithelial monolayer recovery suggests that shikonin can also stimulate epithelial cell migration in damaged areas in patients with ulcerative colitis [45]. Thus, shikonin may have great potential as a treatment for intestinal damage associated with intestinal inflammation.

7. Other Mechanisms to Treat Colitis

In addition to the above specific mechanisms for the treatment of colitis, the treatment of colitis still has other targeted properties. shikonin can also protect the intestinal mucosal barrier from oxidative damage by reducing the generation of lipid peroxidation products, and can clear the reactive oxygen species and other harmful free radicals in the intestine. It can also increase the number of cup cells and their ability to secrete mucus.

8. Summary and Outlook

Colitis, characterized by both acute and chronic inflammation, can recruit macrophages via glycolysis and facilitate their phenotypic differentiation to infiltrate the affected tissue. PKM2, a rate-limiting enzyme in glycolysis, plays a crucial role in lactic acid metabolism and the regulation of inflammatory responses. As an inhibitor of PKM2, shikonin disrupts PKM2 dimerization and nuclear translocation, reduces glycolytic flux, inhibits lactic acid metabolism, modulates lactate modifications, and subsequently influences immune responses such as macrophage polarization and neutrophil activation inhibition; thus presenting itself as a promising therapeutic target for colitis management.

As an active compound derived from traditional Chinese medicinal herbs, shikonin exhibits anti-inflammatory properties alongside antioxidant effects, free radical scavenging capabilities, antibacterial activity, skin repair facilitation, and maintenance of intestinal flora balance. It effectively downregulates pro-inflammatory factor expression in colitis while upregulating anti-inflammatory factors to enhance the inflammatory milieu; it also restores tight junction permeability under physiological conditions through the NK pathway. This contributes to repairing the intestinal barrier and preserving ecological balance within gut microbiota. Furthermore, shikonin ameliorates intestinal damage associated with ulcerative colitis while addressing secondary complications like intestinal tissue injury caused by this condition—significantly benefiting treatment outcomes for ulcerative colitis.

Currently, there is an increasing body of clinical evidence and experimental studies supporting the use of traditional Chinese medicine (TCM) for treating colitis. In contrast to Western medicine approaches that often focus on symptomatic relief alone, TMC emphasizes restoring ecological balance within the gastrointestinal tract by regulating gut microbiota composition—enhancing beneficial bacterial populations while inhibiting pathogenic strains. Additionally, TMC formulations—including granules containing effective active ingredients—tend to exhibit milder effects with fewer side effects compared to their Western counterparts; they offer broader selection options tailored specifically for managing complex symptoms associated with progressive forms of colitis despite currently limited clinical trial data available at present time. Nevertheless, the positive outcomes observed in animal models provide substantial optimism for future research endeavors aimed at practical applications. In conclusion, this paper reviews shikonin's potential role in treating colitis with hopes of enhancing its targeted selectivity during therapy thereby providing a theoretical foundation for further investigations into utilizing traditional Chinese active compounds against this ailment.

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