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Review

Progress on Regulation of NLRP3 Inflammasome by Chinese Medicine in Treatment of Ulcerative Colitis*

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ABSTRACT Ulcerative colitis (UC) is a chronic, non-specific intestinal disease that not only affects the quality of life of patients and their families but also increases the risk of colorectal cancer. The nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing protein 3 (NLRP3) inflammasome is an important component of inflammatory response system, and its activation induces an inflammatory cascade response that is involved in the development and progression of UC by releasing inflammatory cytokines, damaging intestinal epithelial cells, and disrupting the intestinal mucosal barrier. Chinese medicine (CM) plays a vital role in the prevention and treatment of UC and is able to regulate NLRP3 inflammasome. Many experimental studies on the regulation of NLRP3 inflammasome mediated by CM have been carried out, demonstrating that CM formulae with main effects of clearing heat, detoxifying toxicity, drying dampness, and activating blood circulation. Flavonoids and phenylpropanoids can effectively regulate NLRP3 inflammasome. Other active components of CM can interfere with the process of NLRP3 inflammasome assembly and activation, leading to a reduction in inflammation and UC symptoms. However, the reports are relatively scattered and lack systematic reviews. This paper reviews the latest findings regarding the NLRP3 inflammasome activation-related pathways associated with UC and the potential of CM in treating UC through modulation of NLRP3 inflammasome. The purpose of this review is to explore the possible pathological mechanisms of UC and suggest new directions for development of therapeutic tools.

KEYWORDS NLRP3 inflammasome, ulcerative colitis, Chinese medicine, mechanism of action, review

Ulcerative colitis (UC) is a common chronic inflammatory bowel disease that typically presents with symptoms of diarrhea, bloody stools, abdominal pain, and urgency. Recent data shows that the number of people affected by UC in China has increased dramatically, now totaling 11.6/100,000.[1] Chronic inflammation and ulceration can significantly reduce patients' quality of life, while the resulting increased risk of colorectal cancer can pose a serious threat to human health.[2] The pathogenesis of UC is complex and involves disruption of intestinal mucosal barrier, abnormal intestinal immune function, and alteration of intestinal microbiota, etc. The lack of a definitive understanding of pathogenesis of UC may contribute to poor treatment outcomes and recurrent disease in some patients.[3,4] The role of Chinese medicine (CM) in delaying the progression of UC disease is being more widely recognized. UC is classified as "dysentery", "diarrhea", or "large intestinal discharge" based on its symptoms according to CM theory,[5] and is considered to result from a combination of pathological factors such as "dampness, heat, deficiency, stasis, and toxicity". This combination of evils causes the disease by disrupting the balance of qi and yang, eventually damaging the intestinal ligaments.[6] CM has been shown to be an effective treatment for UC, with benefits including reducing intestinal inflammation, improving intestinal function and relieving clinical symptoms.[7,8]

The body's first barrier against external infections and endogenous influences is intrinsic immunity, and

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nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing protein 3 (NLRP3) is a key component of intrinsic immune system. NLRP3 is a multidomain protein complex that processes and handles inflammatory cytokines.[9] The NLRP3 inflammasome is the most extensively studied vesicle. When activated, it induces an inflammatory cascade response that can contribute to UC and the maintenance of a chronic inflammatory state in the gut. This is due to the release of inflammatory cytokines, damage to intestinal epithelial cells, and disruption of the intestinal mucosal barrier. It is important to explore the pathogenesis and treatment of UC from the perspective of NLRP3 inflammasome.

Several studies have suggested that NLRP3 inflammasome activation may contribute to tissue damage and cause malfunction in various organs, leading to UC.[10,11] In comparison, CM has been shown to delay the progression of UC by mediating NLRP3 inflammasome activation. However, more research is needed to confirm these findings.[12] This paper reviewed and summarized the role of NLRP3 inflammasome-related pathways in UC and current status of research on the mechanism of regulation of NLRP3 inflammasome by CM in the treatment of UC, with a view to broaden the prevention and treatment ideas of this disease and providing more clinical options.

NLRP3 Inflammasome

NLRP3 is an intracellular receptor that recognizes molecular patterns and, together with pro-cysteine aspartate-specific protease-1 (pro-Caspase-1) and apoptosis-associated speck-like protein (ASC), forms the NLRP3 inflammasome.[13] The NLRs protein contains a central domain for nucleotide binding and oligomerization (NACHT), C-terminal leucine-rich repeats (LRRs), N-terminal caspase recruitment domain (CARD), and pyrin domain (PYD). In general, the linkage of NACHT domain and LRRs is inhibited, thus blocking the formation of NLRP3 inflammasome.[14] On receipt of signals recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), LRRs change NLRP3 confirmation by regulating and exposing the NACHT-binding domain. The interaction in homotypic NACHT leads to NLRP3 oligomerization and then assembly of bound ASC and pro-Caspase-1 under the binding of PYD-PYD and CARD-CARD, respectively. Finally, the NLRP3 inflammasome, a multimeric protein complex is formed.[15] The activation of NLRP3 inflammasome has been linked to the development of UC, with studies suggesting that it plays a key role in the occurrence and progression of the disease.[16,17] The activated NLRP3 inflammasome leads to the transformation of pro-Caspase-1 into the effector protein Caspase-1. Active Caspase-1 not only induces the conversion of pro-interleukin-1β (pro-IL-1β) and pro-IL-18 to IL-1β and IL-18, but also secretes and releases them extracellularly. In addition, active Caspase-1 acts as a driver of UC, causing a cascade of inflammatory responses. This includes the cleavage of gasdermin D (GSDMD), which leads to the formation of pore structures in the cytosol. This, in turn, leads to the induction of intestinal epithelial cell death.[18] Based on this, it is relevant to prevent and treat UC by mediating the NLRP3 inflammasome.

NLRP3 Inflammasome-Related Pathways Associated with UC

Several mechanisms can lead to the activation of the NLRP3 inflammasome in UC, and the interactions in various activation pathways may control the inflammatory response. The relationship between NLRP3 inflammasome-related pathways and UC is demonstrated in Figure 1.

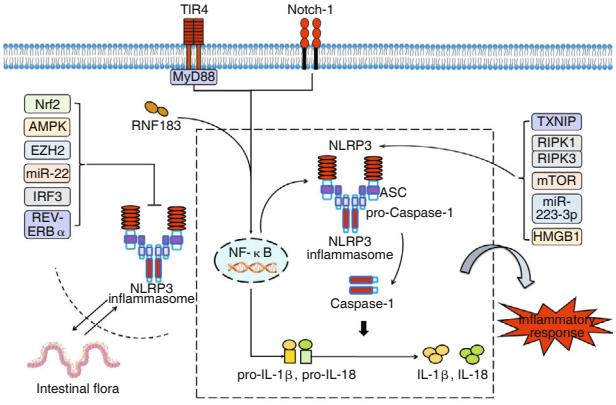

Figure 1. Association of NLRP3 Inflammasome and Related Pathways in UC

Notes: ASC: apoptosis associated speck-like protein; pro-Caspase-1: pro-cysteine aspartate-specific protease-1; NF-κB: nuclear factor-κB; IL-1β: interleukin-1β; IL-18: interleukin-18; TLR4: toll-like receptor 4; MyD88: myeloid differentiation factor 88; RNF183: ring finger protein 183; Nrf2: nuclear factor E2-related factor 2; AMPK: AMP-activated protein kinase; EZH2: enhancer of zeste homologue-2; IRF3: interferon regulator 3; TXNIP: thioredoxin interacting protein; RIPK1: receptor interacting protein kinase 1; RIPK3: receptor interacting protein kinase 3; mTOR: mammalian target of rapamycin; HMGB1: high mobility group box 1 protein

Nuclear factor-κB/NLRP3 and UC

Nuclear factor-κB (NF-κB), a nuclear

transcription factor with multifunctional capabilities, has been shown to play a role in inflammatory and immune responses in UC gut. As a key regulatory signal, NF-κB activation controls the formation and activation of NLRP3 inflammasome.[19] Experimental studies have demonstrated that the expressions of NF-κB and NLRP3 significantly increased in the colonic tissues of UC model rats. Manipulation of NF-κB/NLRP3 signaling pathway can downregulate the levels of inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, and reduce the inflammatory response.[20,21] Toll-like receptor 4 (TLR4) is activated upon receipt of stimulatory signals and induce a signaling cascade through recruitment of myeloid differentiation factor 88 (MyD88), leading to the activation of NF-κB and production of the inflammasome.[22] Notch is linked to NF-κB signaling and Notch-1 can activate NLRP3 inflammasome by coordinating NF-κB activity.[23] Ring finger protein 183 (RNF183) has been shown to promote the degradation of ubiquitinated IκBα, leading to nuclear translocation of NF-κB p65 and activation of NLRP3 transcription and inflammasome activity.[24] In summary, inflammatory response mediated by NLRP3 inflammasome appears to be an important factor in the pathogenesis of UC, with NF-κB/NLRP3 signaling pathway playing a key role.

Thioredoxin Interacting Protein/NLRP3 and UC

Thioredoxin interacting protein (TXNIP) is a member of thioredoxin (Trx) binding protein family and plays an important role in redox regulation. TXNIP is involved in the pathophysiology of UC, including inflammation and colitis-related colon carcinogenesis.[25] In response to mitochondrial dysfunction and accumulation of reactive oxygen species (ROS), the level of TXNIP is upregulated. This subsequently results in the binding of NLRP3, completing the assembly and activation of NLRP3 inflammasome.[26,27] The combination of dextran sodium sulfate (DSS) and a high-fat diet was found to induce the secretion of inflammatory cytokines and an imbalance in the homeostasis of intestinal microbiota by TXNIP/NLRP3 pathway.[28] In contrast, the expressions of TXNIP and NLRP3 were significantly upregulated in the colonic tissues of UC rats prepared by enema with 2,4,6-trinitro benzene sulfonic acid (TNBS)/anhydrous ethanol.[29] Another *in vitro* experiment demonstrated that macrophages in colonic tissue activate the NLRP3 inflammasome in a TXNIP-dependent manner under the stimulation of bacterial lipopolysaccharide (LPS), which may be involved in NF-κB pathway.[30] TXNIP is a key regulator of NLRP3 inflammasome activity, and its upregulation has been shown to induce NLRP3 expression and inflammasome activation. These findings suggest that TXNIP may be a potential therapeutic target for UC associated with NLRP3 inflammasome activity.

Nuclear Factor E2-Related Factor 2/NLRP3 and UC

Nuclear factor E2-related factor 2 (Nrf2) is a key regulator of resistance to oxidative stress and a nuclear transcription factor that protects cells from damage.[31] Under normal conditions, Nrf2 binds to Kelch-like ECH-associated protein 1 (Keap1), forming an inactive complex present in the cytoplasm. The stimulation of Nrf2 leads to its release and translocation to the nucleus, which in turn leads to the upregulation of downstream heme oxygenase-1 (HO-1) and the initiation of protective mechanisms.[32] The Nrf2 pathway has been shown to interact with NLRP3 inflammasome, and activation of Nrf2 appears to reduce the expression of genes targeted by NLRP3 and related pathways.[33] In the UC model, there was a significant reduction in Nrf2 activity in mouse colonic tissue, as well as decreased levels of endogenous antioxidants superoxide dismutase (SOD) and catalase (CAT). In contrast, levels of malondialdehyde (MDA) and ROS were increased, and NLRP3 inflammasome was activated.[34] Additionally, Nrf2/NLRP3 signaling pathway plays a role in reversing the imbalance of inflammatory cytokines and restoring the antioxidant status of the colon in DSS-induced colitis.[35] Based on the regulatory role of Nrf2 and NLRP3 in the inflammatory and oxidative stress response to UC, investigating their relationship may help to further understand the mechanisms of UC development.

Receptor Interacting Protein Kinase 1/3/NLRP3 and UC

The receptor interacting protein kinase (RIPK) family is a group of threonine/serine protein kinases with relatively conserved kinase structural domains and distinct non-kinase structural domains involved in physiological and pathological processes, including inflammation and non-specific immune responses. Members of RIPK family, such as RIPK1 and RIPK3, are particularly sensitive to cellular necrosis and inflammatory responses.[36] Of which, the defective RIPK1 gene is associated with inflammatory bowel disease (IBD), while necrostatin-1 can effectively block the interaction

between RIPK1 and RIPK3, thereby inhibiting intestinal inflammation.[37,38] In comparison to other genes, RIPK3 gene deficiency has been shown to have a more significant attenuating effect on inflammatory responses and immunodeficiency in mice.[39] The study found that mice with UC had increased levels of RIPK1 and RIPK3, as well as increased numbers of NLRP3 inflammasomes. Furthermore, the colonic mucosal tissue of these mice secreted large amounts of IL-1β and IL-18.[40] In contrast, inhibition of RIPK1/RIPK3 signaling led to decreased NLRP3 mRNA and protein expressions, limited NLRP3 inflammasome activation, and reduced colonic inflammation.[41] The key proteins RIP1K and RIP3K appear to play a role in UC by regulating the transduction of RIP1K/RIP3K/NLRP3 pathway.

Intestinal Flora/NLRP3 and UC

Changes in the gut microbiota are considered to be another important factor related to the pathogenesis of UC.[42] The intestinal microbiota can stimulate the colonic immune system, and if the diversity of the microbiota is lost and the intestinal microecological balance is disrupted, it can impair the host's intestinal immune response, leading to inflammation and pathological damage to the colonic tissues and inducing intestinal diseases such as UC.[43,44] Studies have shown that NLRP3 inflammasome can interact with various signaling pathways to regulate gut microbiota, and an imbalance of gut microbiota can also activate NLRP3 inflammasome and exacerbate intestinal inflammatory damage.[45,46] In DSS-induced model mice, the relative abundance of pathogenic species was increased and the diversity of some probiotic bacteria was lost, and activated NLRP3 inflammasome upregulated the levels of IL-1β, IL-18, etc., in colonic tissues and serum, promoting an intestinal inflammatory state.[47,48] In addition, some clinical or animal therapeutic experiments of bacterial transplantation have shown the inverse role of intestinal flora in regulating NLRP3 pathway to reduce UC inflammation.[49,50] Together, the correlation between intestinal flora, NLRP3 inflammasome, and UC is evident, but the mechanisms by which changes in intestinal microecology mediate NLRP3 and inflammasome's role in altering intestinal flora still warrant further exploration.

Other Pathways/NLRP3 and UC

AMP-activated protein kinase (AMPK) has been implicated in the control of inflammatory stress and oxidative stress. DSS-induced reduction in AMPK phosphorylation leads to activation of NLRP3 inflammasome in colonic tissue of UC mice.[51] Study has suggested that there may be crosstalk between the mammalian target of rapamycin (mTOR) and NLRP3 inflammasome signaling.[52] One study found that increased AMPK activity may reduce UC inflammation by inhibiting mTOR and NLRP3 expression.[53] Enhancer of zeste homologue-2 (EZH2) acts as a transcriptional repressor and immunomodulatory, inhibits autophagy-related protein 5 (ATG5) mRNA expression and the resulting EZH2/ATG5-mediated autophagy have an impact on NLRP3 inflammasome, which in turn affects the progression of UC.[54,55] MiRNA-mediated regulation of immune system has been well-documented.[56] The researchers found that upregulation of miR-22 level inhibited NLRP3 inflammasome activation, which in turn protected the intestinal mucosal barrier in UC rats.[57] Cellular stress induced by inflammasome can be reduced by inhibiting miR-223-3p/NLRP3 signaling.[58] Several key proteins regulate the NLRP3 inflammasome, including increased mRNA and protein levels of NLRP3 in interferon regulator 3 (IRF3) knockout UC mice, and more inflammasome production.[59] High mobility group box 1 protein (HMGB1) and NLRP3 are associated with the severity of UC. HMGB1 can activate NLRP3 inflammasome, which may contribute to the development of UC.[60] The clock protein REV-ERBα is known to interfere with inflammasome activation, and study found that it also improves UC symptoms in mice by inhibiting NLRP3 transcription in initiation phase.[61]

In conclusion, NLRP3 inflammasome and its related pathways are closely linked to UC. Multiple pathways and molecules work together to form and activate NLRP3 inflammasome in UC, resulting in the release of pro-inflammatory cytokines, colonic inflammation, and tissue damage. A more thorough understanding of pathogenic mechanisms of NLRP3 inflammasome and its related pathways in UC may provide insights into the role of inflammatory response, oxidative stress, and immune regulation UC, as well as potential targets for new therapies.

Role of CM in Regulating NLRP3 Inflammasome for UC Treatment

The current state of research on NLRP3 inflammasome and its role in the pathogenesis of UC suggests that new therapies targeting this mechanism are needed. It has been found that CM can inhibit the activation of NLRP3 inflammasome and is clinically

effective in the treatment of UC. Therefore, it is necessary to present a review of existing therapeutic effects of CM in mediating NLRP3 inflammasome activation and inhibiting intestinal inflammatory responses in the management of UC in order to provide guidance for future research on the prevention and treatment of UC.

CM Formulae

Numerous studies have found that Chinese medicinal herbs can reduce inflammation and improve UC symptoms by interfering with the expression of NLRP3 inflammasome and key genes in related pathways. According to traditional functions, CM formulae can be classified into 4 types, as shown in Appendix 1.

Clearing Heat and Detoxifying Toxicity Formula

The heat diffuses and becomes toxic over a long period of time. The herbal formulae and preparations for clearing heat and detoxifying toxicity, such as Kui jie tong (KJT, 溃结通), Qingre Jianpi Decoction (QRJPD, 清热健脾汤), Shaoyao Decoction (SYD, 芍药汤), modified Shaoyao Decoction (MSYD, 加味芍药汤), Pulsatillae Decoction (PD, 白头翁汤), Baishao Qiwu Granule (BSQWG, 白芍七物颗粒) and modified Sanhuang Decoction (MSHD, 加味三黄汤) can regulate NLRP3 inflammasome related signaling pathways, thus reducing the intestinal inflammatory response, which is consistent with the "heat and toxicity" in the pathogenesis of UC. The anti-colonic inflammatory effect of KJT was associated with the following roles, including inhibition of NIMA-related kinase 7 (NEK7) mediated classical scorch pathway as well as NLRP3 inflammasome activation, and improvement of intestinal flora.[47] QRJPD was found to inhibit activation of NLRP3 inflammasome, resulting in reduced secretion of TNF-α, IL-1β, and IL-18 in both serum and colonic mucosa.[62] Studies have shown that SYD or MSYD can inhibit NLRP3 inflammasome activation, block NF-κB pathway, downregulate the expression of TXNIP, and reduce the levels of various inflammatory cytokines to exert anti-colitis effects.[63,64] The modified PD showed potential in reducing colon tissue damage by inhibiting IL-6/STAT3 pathway, as well as lowering NLRP3 expression to a certain extent.[65] BSQWG, based on SYD, has an inhibitory effect on the expressions of pro-inflammatory cytokines in colonic tissue of NLRP3 knockout model rats through multiple targets, the main one is NLRP3 inflammasome signaling pathway.[66,67] The effect of MSHD could potentially treat UC by reducing the expression of NLRP3 inflammasome, inhibiting the activation of GSDMD and Caspase-1, and downregulating the secretion levels of IL-1β, IL-17α, and IL-6.[68]

Drying Dampness and Astringency Formula

Formulae and preparations such as Wu-Mei-Pill (WMP, 乌梅丸), Shenling Baizhu Powder (SLBZP, 参苓白术散), Huangqin Decoction (HQD, 黄芩汤) and Huangkui Lianyang Decoction (HKLYD, 黄葵敛疡汤) can inhibit the expressions of NLRP3 inflammasome and inflammatory cytokines, thus alleviating intestinal epithelial cell damage, echoing the "dampness" in the pathogenesis of UC. WMP was effective in treating UC by inhibiting the intestinal inflammatory response and promoting the repair of damaged mucosa. The mechanism may involve restricted activation of the Notch-1/NF-κB/NLRP3 pathway and reduced release of inflammatory cytokines.[23,69] SLBZP was found to inhibit proteins related to the NLRP3 inflammasome pathway, thereby mediating the expression of NF-κB mRNA and activation of downstream IL-1β and IL-18. This led to an improvement in the symptoms of colonic injury.[70,71] HQD showed an inhibitory effect on cell scorching in UC mice, and its mechanism of action was closely related to the regulation of NLRP3 inflammasome.[72] HKLYD was found to inhibit the activation of NLRP3 inflammasome and mRNA expressions of pro-inflammatory cytokines in colonic tissues.[73,74]

Cooling Blood and Activating Blood Circulation Formula

Formulae and preparations that cool blood and activate circulate blood, such as Quyu Shengxin Decoction (QYSXD, 祛瘀生新汤) and Huaijiang Recipe (HJR, 槐绛方) can mediate the activation of NLRP3 inflammasome. This ultimately has a protective effect on the intestinal mucosa, which is in line with the "stasis" in the pathogenesis of UC. QYSXD was shown to reverse mitochondrial autophagy and reduce the levels of IL-1β and IL-18 in the colonic tissues of UC animals by regulating RIP1/RIP3/NLRP3 signaling pathways, thus exerting anti-inflammatory and intestinal mucosal barrier repair functions.[40,41] HJR was found to downregulate NLRP3 expression, reduce NLRP3 inflammasome production, inhibit UC cell pyroptosis and secretion of related factors, and reduce local inflammation in model animals.[75]

Harmonizing and Regulating Qi Formula

The deficiency of yang-qi leading to the loss of harmony in the body, weak vital energy and a lack of harmonisation. The active ingredients in CM like

Banxia Xiexin Decoction (BXD, 半夏泻心汤), Kui jie kang (KJK, 溃结康), Yushi Anchang Recipe (YSR, 俞氏安肠方), and Hechang Decoction (HCD, 和肠饮) can specifically target and modulate the NLRP3 inflammasome, thereby reducing the progression of UC symptoms and manifestations, which parallels the "deficiency" theory of CM. BXD was shown to reduce the chronic inflammation associated with UC rats by inhibiting the NLRP3 inflammasome.[76] KJK, derived from Chinese medical formula Tongxieyaofang (痛泻要方), was found to regulate NLRP3, ASC, and Caspase-1 mRNA expressions and release of downstream inflammatory cytokines.[77] YSR was effective in treating UC by inhibiting the activation of NLRP3 inflammasome, protecting colonic mucosal barrier and improving histological damage.[78] The downregulation of NLRP3 and Caspase-1 mRNA and protein expressions, as well as inhibition of NLRP3 inflammasome signaling pathway, caused by HCD, led to an attenuation of colon damage caused by TNBS.[79]

In summary, CM formulae with the effects of clearing heat and detoxifying toxicity, drying dampness and astringency, cooling blood and activating blood circulation, and harmonizing and regulating qi can target the activation of NLRP3 inflammasome, significantly reducing the inflammatory response and thus preventing and treating UC, echoing its CM pathogenesis of "dampness, heat, deficiency, stasis, and toxicity". However, the active ingredients and targets of herbal compounds and their preparations are relatively complex, and their mechanisms of action need further exploration.

Active Components from CM

A large body of research demonstrated the effectiveness of components derived from CM in treating UC. The active ingredients in CM can directly influence the activation of signaling pathways related to NLRP3 inflammasome, thereby producing therapeutic effects by modulating intestinal inflammation. The study of herbal components that activate NLRP3 inflammasome is important due to the limited efficiency of inhibitors targeting NLRP3 inflammasome. We herein present a comprehensive review of 6 categories of CM that manage NLRP3 pathways to relieve UC, as shown in Appendix 2.

Flavonoid Constituents

Flavonoids, important active ingredients in CM, are commonly used to treat UC and other digestive disorders.[80] Rutin, lonicerin, 8-oxocoptisine, oroxindin, naringenin, and phloretin have been shown to target the activation of NLRP3 inflammasome, thereby reducing intestinal inflammation in UC patients. Rutin modulated the activity of NLRP3 inflammasome signaling molecules and ameliorated DSS-induced inflammation in colonic mucosa.[81] Lonicerin was found to have an inhibitory effect on the gene and protein expressions of Caspase-1, IL-1β and IL-18 by targeting EZH2-induced ATG5 expression and regulating autophagy and NLRP3 inflammasome activation.[55] 8-oxocoptisine could effectively inhibit NF-κB pathway and NLRP3 inflammasome and reduce the secretion of inflammatory mediators in UC mice.[82] Oroxindin has been shown to protect colonic tissue and ameliorate UC pathological changes by interfering with NLRP3 inflammasome formation and activation, inhibiting TXNIP and NF-κB signaling, and reducing macrophage infiltration.[30] Naringenin was found to protect UC rats with impaired intestinal epithelial barrier function by regulation of miR-22/NLRP3 signaling pathway.[57] Phloretin treatment inhibited the activation of NF-κB pathway and NLRP3 inflammasome to improve intestinal mucosal barrier function.[83]

Phenylpropanoid Constituents

Phenylpropanoids have been shown to possess both anti-inflammatory and antioxidant properties, with salidroside, schisandrin B, and sinapic acid (SA) being found to have a regulatory effect on NLRP3 inflammasome expression in UC. Salidroside demonstrated a significant ability to maintain the intestinal barrier and NLRP3 inflammasome/autophagy balance, thereby alleviating inflammation.[84] Schisandrin B could activate AMPK/Nrf2 pathway to suppress NLRP3 inflammasome signaling, reduce ROS-induced mitochondrial damage and cell death in intestine, thereby alleviating colitis.[85] SA was found to inhibit NLRP3 inflammasome activation, enhance antioxidant enzyme activity, and attenuate intestinal permeability in UC model animals.[86]

Alkaloid Constituents

Alkaloids have been shown to be effective in reducing inflammation by decreasing the levels of inflammatory cytokines. Sinomenine hydrochloride has been shown to inhibit NLRP3 inflammasome activation, modulate the composition of intestinal microbiota, and ameliorate experimental colitis in mice.[48] Evodiamine

was found to modulate NLRP3 inflammasome and NF-κB signaling, maintain the balance of intestinal microbiota, and preserve intestinal integrity.[20,87]

Phenolic Acid Constituents

Rosmarinic acid (RA) and carnosic acid (CA) are phenolic acids with anti-inflammatory effects. RA was found to reverse colonic mucosal damage by inhibiting oxidative stress and attenuating the inflammatory response. This role was contributed to modulating NLRP3 inflammasome and reconstituting Nrf2 signaling pathway.[88] CA could regulate Keap1/Nrf2 pathway, prevent NLRP3 inflammasome activation, and decrease pro-inflammatory cytokine levels to reduce colonic inflammation.[89]

Quinone Constituents

Shikonin was found to be effective in mitigating DSS-induced epithelial tight junction (TJ) damage in colon, as well as reducing inflammation and mucosal barrier damage, by inhibiting NLRP3 inflammasome and NF-κB signaling activation.[90] Rhein significantly decreased levels of pro-inflammatory cytokines in LPS-stimulated RAW264.7 cells through inhibition of NLRP3 inflammasome and NF-κB pathway, resulting in reduced migration of immune cells and amelioration of inflammation.[21]

Other Constituents

Other CM ingredients, including paeoniflorin, terpinen-4-ol (TER), tripterygium wilfordii polycoride (TWP), xinhui citrus fermentation liquor (XCFL), extracts of *Forsythia suspensa* (FS), *Ficus pandurata* Hance (FPH), and *Abelmoschus manihot* flower (AMF), may also impede UC lesion process by mediating NLRP3 inflammasome. Paeoniflorin treatment led to a reduction in the expressions of NLRP3 protein and pro-inflammatory cytokines in the colonic tissue.[91] TER has been demonstrated to ameliorate colitis through inhibition of NLRP3 inflammasome and NF-κB signaling, alteration of gut microbiota, and healing of colonic epithelial barrier.[92] TWP was found to inhibit the activity of NADPH oxidases (NOXs) and ROS production, followed by a reduction in the expressions of pro-inflammatory cytokines and an improvement in DSS-induced colitis.[93] Study has shown that XCFL could inhibit the growth of harmful bacteria, regulate intestinal flora, and enhance intestinal barrier function via Nrf2/NLRP3 pathway.[94] FS extract could significantly alleviate colonic inflammation associated with Nrf2/NLRP3 pathway-mediated cellular oxidative stress, as well as improve metabolic function.[35] The extract from FPH was found to reduce the levels of NLRP3 and IL-18 in a mouse model of DSS-induced UC, and the mechanism of action is believed to be through the inhibition of TLR4/MyD88/NF-κB pathways.[95] The anti-colonic inflammatory effect of AMF extract was associated with the inhibition of NLRP3 inflammasome and regulation of intestinal TJ proteins, leading to the protection of intestinal mucosal barrier.[96]

The current understanding of how active components from CM regulate the NLRP3 inflammasome comes primarily from research on flavonoids and phenylpropanoids, which have been shown to be effective in modulating the inflammasome. There are few studies on the effects of signaling factors in upstream and downstream of NLRP3 inflammasome, which warrants further exploration.

Summary and Outlook

As one of the important components of pattern recognition receptors, the activation of NLRP3 inflammasome is thought to play a key role in mediating the inflammatory response in UC, representing a potential therapeutic target for the prevention and treatment of UC. The latest literature reveal that CM formulae and their preparations can inhibit NLRP3 inflammasome by clearing heat and detoxifying toxicity, drying dampness and astringency, cooling blood and activating blood circulation, harmonizing and regulating qi, etc. The CM pathogenesis of UC is due to the combination of "dampness, heat, deficiency, stasis, and toxicity", resulting in an imbalance of yin and yang, disturbance of qi, lack of separation of clear and turbid, and damage of intestinal ligaments. The active components in CM, such as flavonoids, phenylpropanoids, alkaloids, phenolic acids, quinones, etc., have obvious therapeutic advantages in inhibiting the assembly and activation of NLRP3 inflammasome, reducing the inflammatory response and thus alleviating UC. Therefore, the target analysis of inhibiting the assembly and activation of NLRP3 inflammasome provides a reference for the development of a precise treatment plan for UC in CM.

CM has certain regulatory effects on NLRP3 inflammasome, but there are still many deficiencies

in the treatment of UC. Firstly, the current molecular mechanism of CM against UC is mostly focused on the study of key molecules of NLRP3 inflammasome, there is a lack of research on how CM interferes with the mechanism of NLRP3 inflammasome. In particular, there is insufficient research on the signaling factors of CM and the upstream and downstream pathways of NLRP3 inflammasome. Secondly, the active ingredients and action targets of CM formulae and their preparations are complex. It is unclear whether single or multiple ingredients, and whether they inhibit single or multiple targets, modulate NLRP3 inflammasome to play a protective role in the intestinal mucosa of UC. Thirdly, the relationship between pattern recognition receptors (PPRs) including TLR4 and UC has been researched in-depth, revealing a connection between these elements and UC. However, fewer studies have investigated the relationship between PPRs and their ligands with NLRP3 inflammasome. Consequently, it is important at this stage to explore the effects of CM on the upstream and downstream pathways related to inflammatory response and different key cytokines in the pathways. To find effective targets for CM to prevent and treat UC, it is necessary to generalize and integrate the effects of CM for treating UC on different targets related to NLRP3 inflammasome from the perspective of genomics and metabolomics. In order to elucidate the mechanisms by which active components of CM ameliorate symptoms of UC, it is important to study how those components interact with the NLRP3 inflammasome. Additionally, studying the effects of CM on synergistic/antagonistic relationships with other PPRs can provide insight into the complex interactions between different systems within the body. These findings suggest that there are new, feasible directions for contemporary CM research that can provide a more comprehensive understanding of how to clinically treat UC with CM.

Conflict of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Author Contributions

Sun HX and Zhu Y made significant contribution to the work in the conception, study design, or in all these areas; took part in drafting, revising, or reviewing the article and gave the approval of the final version of the manuscript.

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