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REVIEW

Therapeutic interventions target the NLRP3 inflammasome in ulcerative colitis: Comprehensive study

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Abstract

One of the significant health issues in the world is the prevalence of ulcerative colitis (UC). UC is a chronic disorder that mainly affects the colon, beginning with the rectum, and can progress from asymptomatic mild inflammation to extensive inflammation of the entire colon. Understanding the underlying molecular mechanisms of UC pathogenesis emphasizes the need for innovative therapeutic approaches based on identifying molecular targets. Interestingly, in response to cellular injury, the NLR family pyrin domain containing 3 (NLRP3) inflammasome is a crucial part of the inflammation and immunological reaction by promoting caspase-1 activation and the release of interleukin-1β. This review discusses the mechanisms of NLRP3 inflammasome activation by various signals and its regulation and impact on UC.

Key Words: Ulcerative colitis; NLR family pyrin domain containing 3 inflammasome; Therapeutic strategies; Phytochemicals; Probiotics

Core Tip: Ulcerative colitis (UC) is a common chronic type of inflammatory bowel disease that affects a significant number of populations. Needing to counteract the UC prevalence, attract scientists to study its pathological mechanism deeply. NLR family pyrin domain containing 3 (NLRP3) inflammasome has been observed to have a crucial role in the pathological features of UC. Targeting NLRP3 inflammasome signals with phytochemicals, plants, probiotics, and chemical agents could be promising candidates for fixing the UC problem.

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INTRODUCTION

Inflammatory bowel diseases (IBD), most referred to as Crohn's disease and ulcerative colitis (UC), are chronic, idiopathic disorders characterized by intestinal inflammation that have increased incidence and prevalence over time and in various countries worldwide[1-3]. The global prevalence is expected to impact up to 30 million by 2025[4]. Several factors are known to play a considerable role in disease pathogenesis. IBD has been linked to genetic etiology and other variables such as pathogens, appendectomy, stress, and air pollution[5,6]. UC is a chronic disorder that mainly affects the colon, beginning with the rectum and perhaps progressing to inflammation of the entire large intestine[7]. UC can begin with severe illnesses such as melena, diarrhea, and mucus production[8,9], and often between the ages of 50 years and 80 years [3,10,11].

A family history of IBD elevates the potential risk of UC, and first-degree relatives are four times more likely to acquire the disease, suggesting that genetic factors are likely related to UC[12,13]. Also, environmental factors play a crucial role in its development[14]. About 110 of the 163 susceptibility loci (67%) encode innate and adaptive immunity pathways, cytokine signaling, and immunological sensing. Several other autoimmune diseases, including psoriasis and ankylosing spondylitis, share many of these genes[15,16]. Additionally, many UC-specific genes have a role in controlling epithelial barrier function[17,18].

The gastrointestinal mucosa is susceptible to many antigens from food, the environment, and the microbiome[19]. The mucin layer that covers the epithelium, the mucosa's outer layer, serves as the gut immune system's first line of defense since it physically separates antigens from gut immune cells and has antimicrobial capabilities. Patients with active UC have been demonstrated to have a thinner mucin-containing mucosal layer in the colon, primarily due to a reduction in mucin 2 production[20]. In addition, exposure to potentially harmful stimuli such as nonsteroidal anti-inflammatory drugs and food components such as emulsifiers may prompt colitis[21,22]. Moreover, dysbiosis reduces short-chain fatty acid synthesis, which is required for epithelial energy supply and mucus formation[23]. On the same approach, UC has been attributed to a decrease in short-chain fatty acid-producing *Ruminococcaceae* and *Lachnospiraceae* and an increase in pro-inflammatory microorganisms such as Enterobacteriaceae[24,25].

When the epithelium is damaged, the mucosa becomes more permeable to luminal pathogens, increasing the absorption of these antigens and possibly activating gastrointestinal tract immunity[26,27]. Since it is the link between the host immune response repertoire and the intestinal microbiota, the intestinal epithelium plays a crucial role in the innate immune system[28]. Antigens activate the innate immune response *via* antigen-presenting cells and T cells, which evoke an inflammatory response that activates the adaptive immune system[27,29]. Mechanistically, mature dendritic cells express a lot of Toll-like receptors (TLR), which activate multiple transcription factors like nuclear factor-κB (NF-κB), which in turn causes an inflammatory response in UC[30,31]. These inflammatory cascades result in the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins (IL)[26,27,29]. These pro-inflammatory cytokines have critical roles in signaling through intracellular proteins, including Janus kinase (Jak), which enhances lymphocyte activation and proliferation[32,33]. Interestingly, innate immune signaling *via* cytokine receptors, TNF receptors, and TLR-adaptor myeloid differentiation as a primary response promotes NLRP3 transcription and oligomerization through NF-kB activation[34,35]. Figure 1 outlines this inflammatory response inside the colon in IBDs, including UC.

NLRP3 INFLAMMASOME OVERVIEW

The innate immune system is the primary mechanism by which most organisms respond quickly to diseases or injury. Pattern-recognition receptors (PRRs) are activated by the host and identify chemicals released by infections or damaged cells. Pathogen-associated molecular patterns and damage-associated molecular patterns are the names of these molecular signals[36]. Numerous intracellular DNA sensors, TLRs, nucleotide-binding and oligomerization domain (NOD)-like receptors, C-type lectin receptors, RLRs, and NOD-inducible gene-I-like receptors are among the numerous members of the PRR family[37].

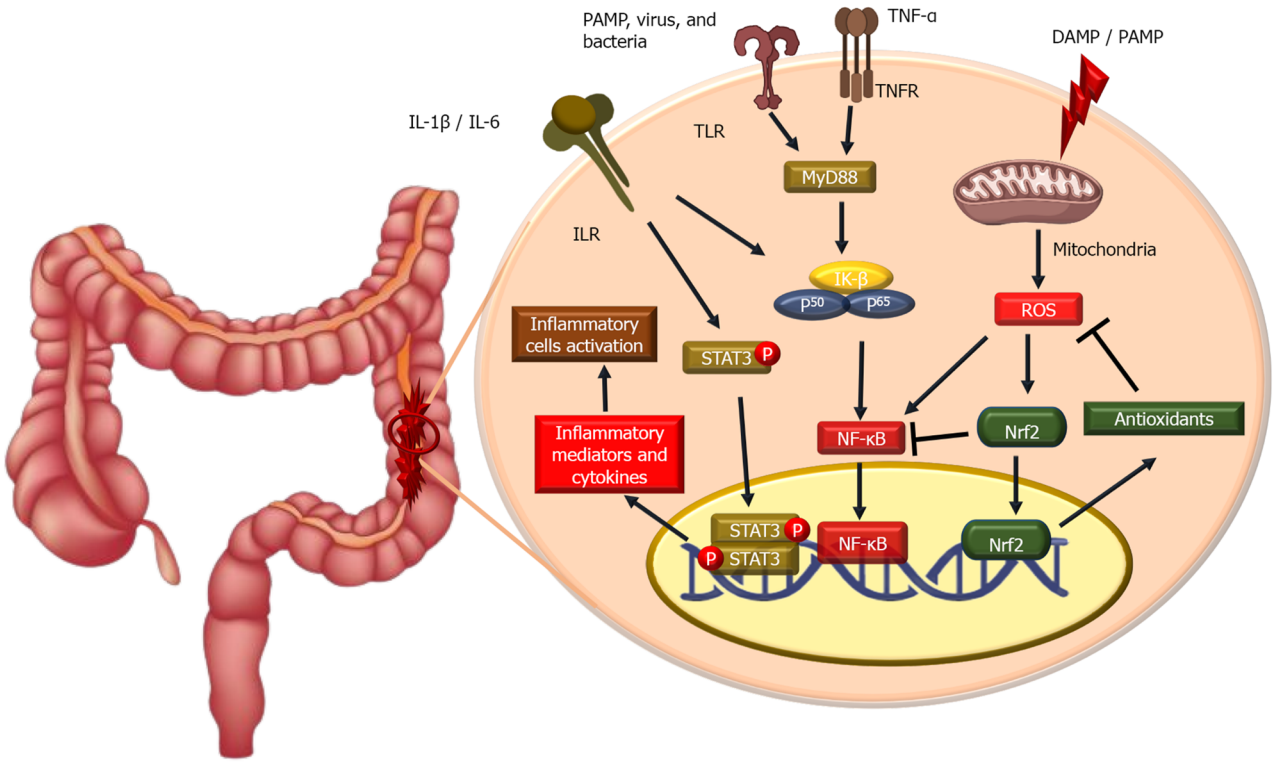

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Figure 1 Inflammatory response inside the colon in inflammatory bowel diseases including ulcerative colitis. Several inflammatory pathways are involved in ulcerative colitis (UC), which result in increased inflammatory mediators and cytokines and subsequent activation of inflammatory cells. First, activation of Toll-like receptors (TLR) by pathogen associated molecular pattern (PAMP), bacteria and viruses as well as tumor necrosis factor-alpha receptor (TNFR) stimulation by TNF-α, induce nuclear factor-κB (NF-κB) translocation through upregulation of MyD88 and IK-β, P50, and P65 complex. Second, along with NF-κB upregulation, interleukin receptor stimulation by interleukin (IL)-1β and/or IL-6 activates signal transducer and activator of transcription 3 signalling activation. Third, damage associated molecular pattern and/or PAMP are stimulates mitochondria to generates reactive oxygen species (ROS) which enhances inflammatory response through NF-κB activation whereas activating nuclear factor erythroid 2-related factor 2 signalling by ROS suppresses the inflammatory response by blocking NF-κB signalling and inducing antioxidants that downregulates ROS. IBDs: Inflammatory bowel diseases; UC: Ulcerative colitis; IL-(1β): Interleukin-1 beta; DAMP: Damage associated molecular pattern; PAMP: Pathogen associated molecular pattern; TNF-α: Tumour necrosis factor-alpha; ILR: Interleukin receptor; TLR: Toll-like receptor; TNFR: Tumour necrosis factor receptor; MyD88: Myeloid differentiation primary response 88; IK-β: Inhibitor *kappa*-beta; P50: Nuclear factor-kappa B P50 subunit; P65: Nuclear factor-kappa B P65 subunit; ROS: Reactive oxygen species; STAT3: Signal transducer and activator of transcription 3; NF-κB: Nuclear factor-kappa B; Nrf2: Nuclear factor erythroid 2-related factor.

A multi-protein complex NLRP3 inflammasome is a type of PRR essential for the host's innate defenses against bacterial, fungal, and viral infections[38-41]. However, when it is dysregulated, it has been connected to the pathogenesis of many inflammatory-associated diseases, including cancer, neuroinflammation, retinopathy, stroke, diabetes, atherosclerosis, and autoinflammatory diseases[42-46]. The three protein components that make up NLRP3 are an amino-terminal pyrin domain (PYD), a NOD, and a leucine-rich repeat domain at the protein's C-terminus[47]. Apoptosis-associated speck-like protein (ASC) is composed of two proteins, pyrin and a caspase-recruitment domain (CARD), but their interaction to initiate inflammasome assembly facilitates it to recruit pro-caspase-1 to the inflammasome complex[48, 49].

The activation of the NLRP3 inflammasome is essentially caspase-1 autocatalysis. Once turned on, NLRP3 functions as a sensor molecule that self-oligomerizes and recruits ASC through homotypic PYD-PYD interaction, causing ASC to assemble into sizable speck-like formations. Caspase-1 is then autocatalytically activated as aggregated ASC recruits pro-caspase-1 through CARD-CARD interaction. Proteolytic activation of the pro-inflammatory cytokines IL-1β and IL-18 and the soluble cytosolic protein gasdermin D (GSDMD) is the function of activated caspase-1 heterotetramers. Following proteolysis, the oligomerized gasdermin N can bind membrane lipids and create membrane pores to mediate the release of IL-1β and IL-18 outside the normal secretory pathway. In parallel, cells go through pyroptosis, a pro-inflammatory cell death[50-53]. IL-1β stimulates endothelial cell response by allowing immune cell infiltration into infected or injured tissues *via* the activation of genes that regulate temperature, pain threshold, vasodilation, and hypotension[54]. IL-18 is a co-stimulatory cytokine necessary for mediating adaptive immunity through the influence of interferon-gamma production[54].

MECHANISMS OF NLRP3 INFLAMMASOME ACTIVATION

It is believed that several cellular signals, including ion fluxes (K^+ efflux, Cl^- efflux, Ca^{2+} influx, and Na^+ influx), mitochondrial dysfunction, and reactive oxygen species (ROS) generation, are responsible for NLRP3 inflammasome activation[55-60]. In addition, heme[61,62], particulate matter[56,63,64], pathogen-associated RNA[65-68], and bacterial and fungal toxins[69,70] are also considered NLRP3 activators.

NLRP3 activators require a priming signal (signal 1) to be activated[71]. TLRs, NOD-like receptors (*e.g.*, NOD1 and NOD2), or cytokine receptors such as TNF-α and IL-1β, bind to stimuli in the priming signal, which is crucial for macrophage stimulation. Pro-IL-1β, which is not constitutively produced in inactive macrophages, is upregulated by NF-κB. In addition, NF-κB also upregulates the expression of NLRP3, which is assumed to exist in quantities insufficient for starting inflammasome activation during rest[71,72]. In contrast, priming signals are not crucial for ASC, pro-caspase-1, and pro-IL-18 production levels[71]. Inflammasome activation and NLRP3 self-association are regulated by the priming signal's induction of Jun N-terminal 1-mediated phosphorylation of NLRP3[73].

Ca^{2+} is necessary for NLRP3 inflammasome activation by interacting with inositol 1,4,5-trisphosphate, a byproduct of phosphatidylinositol 4,5-bisphosphate hydrolysis catalyzed by phospholipase C, and the inositol 1,4,5-trisphosphate receptor on the endoplasmic reticulum, which promotes Ca^{2+} mobilization and NLRP3 inflammasome activation[60]. The NLRP3 inflammasome is activated by excessive ER Ca^{2+} release associated with mitochondrial damage and results in ROS production and an excess of Ca^{2+}[74-76]. Additionally, K^+ efflux and a reduction in intracellular K^+ are upstream events in NLRP3 activation[59,77]. The NLRP3 inflammasome also needs K^+ efflux for NLRP3 formation, according to a recently discovered component called NIMA-related kinase 7 (NEK7), which may directly bind to NLRP3 protein[78,79]. Various substances can increase ROS generation and induce NLRP3 activation without requiring K^+ efflux[80,81]. Na^+ influx-induced NLRP3 activation also relies on K^+ efflux[59]. Reducing the concentration of extracellular Cl^- activates caspase-1 and the generation of IL-β1[82]. An anion channel called the intracellular chloride channel has the potential to activate the volume-regulated anion channel. It is intriguing since the K^+ efflux-mitochondrial ROS axis was shown to be a downstream event of chloride intracellular channel-dependent chloride efflux. Intracellular chloride channel-mediated chloride efflux can encourage NEK7-NLRP3 association and subsequent ASC oligomerization[83].

ROS are one of the earliest identified triggers to engage the NLRP3 inflammasome. Lysosomal NADPH oxidase was once believed to be the source of ROS formation, even though mitochondria are the primary site of ROS production[59,84]. According to several studies, most NLRP3 inflammasome agonists have been shown to produce mitochondrial ROS in various cell types[63,85-88]. NADPH oxidase 4 (NOX4) has also been shown to influence carnitine palmitoyl transferase 1A and promote fatty acid oxidation, which aids NLRP3 activation[89].

Lysosomal destabilization contributes to NLRP3 activation in both phases (signal 2) and the priming step (signal 1); in palmitate-induced NLRP3 activation. By controlling the stability of the IL-1 mRNA, lysosomal calcium signaling controls the production of pro-IL-1β (signal 1), whereas cathepsin B, a lysosomal protease, contributes to the NLRP3 activation [90]. It has been hypothesized that acidic conditions are necessary for monosodium urate crystals to activate the inflammasome within lysosomes as the significant Na^+ release raises the cellular osmolality and water influx and lowers intracellular K^+ concentration[91].

POST-TRANSCRIPTIONAL MODIFICATIONS OF NLRP3

Protein folding, localization, and functional activity are all controlled by post-translational modifications. Numerous post-translational modifications have been shown to affect innate immunity by affecting immune cells' activation, survival, differentiation, and migration[92]. NLRP3 is ubiquitylated in dormant macrophages and deubiquitylated following activation and priming[93]. For the NLRP3 inflammasome to activate, the linear ubiquitin assembly complex must selectively ubiquitylate NLRP3 and ASC[94]. TLR priming enhances NLRP3 self-association and activation by causing Jun N-terminal kinase 1 to phosphorylate NLRP3[95]. The mechanism of NLRP3 inflammasome activation is outlined in Figure 2.

THERAPEUTIC AVENUES FOR ULCERATIVE COLITIS TARGETED NLRP3 INFLAMMASOME SIGNAL

Phytochemicals and plant extracts

Naringin: Naringin is a flavonoid glycoside, rich in citrus fruits such as grapefruit and orange[96,97]. Naringin protects mice from obesity, azoxymethane/dextran sodium sulfate (DSS)-induced carcinogenesis, and acetic acid (AA)-induced colitis[98-100]. In 2018, Cao *et al*[101] revealed that naringin protects mice from DSS-induced UC owing to its NLRP3 inflammasome and mitogen-activated protein kinase (MAPK) inhibitory effects. Furthermore, it upregulated peroxisome proliferator-activated receptor γ (PPARγ) while suppressing NF-κB activation.

Chlorogenic acid: Chlorogenic acid (CGA) is a phenolic acid found in foods and many plants[102,103]. Zeng *et al*[104] reported that CGA prevented DSS-induced mice colitis by down-regulating miR-155 expression and suppressing NLRP3 and NF-κB in macrophages. CGA downregulates caspase-1, pro-cleaved-IL-1β, and pro-cleaved-IL-18 in mice with colitis. In line with this study, CGA ameliorates NLRP3 inflammasome in different models, such as CCl_4-induced acute liver

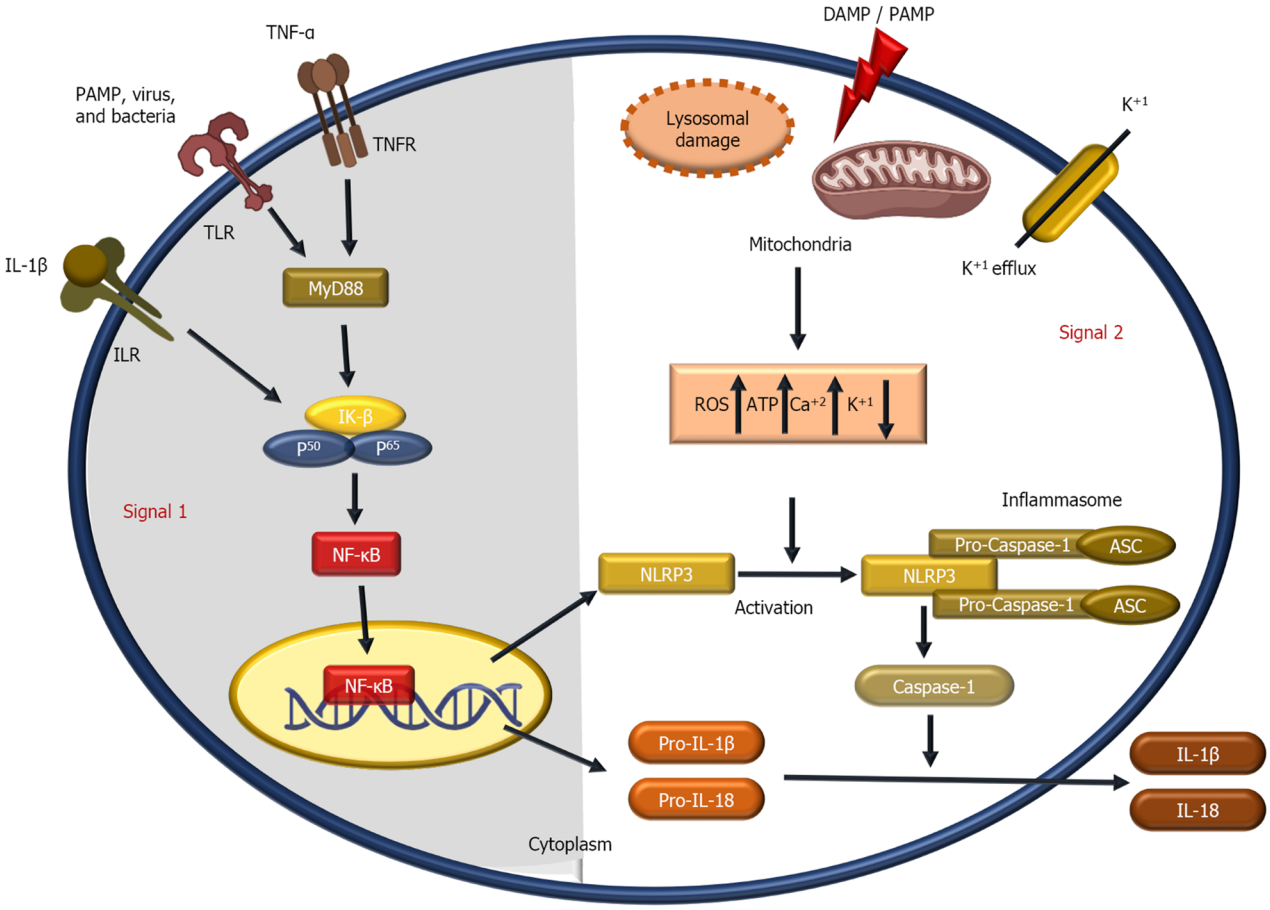

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Figure 2 The mechanism of nod-like receptor protein-3 inflammasome activation. Nod-like receptor protein-3 (NLRP3) inflammasome activation occurs through two signals, (signal 1) toll-like receptor stimulation by pathogen associated molecular pattern (PAMP), bacteria and viruses, tumour necrosis factor receptor stimulation by TNF-α, and interleukin receptor (ILR) stimulation by IL-1β leads to activation of nuclear factor-kappa B (NF-Kb) *via* upregulation of MyD88, and Iκ-β, P50, and P65 complex. Pro-IL-1β, pro-IL-18, and inactive NLRP3 expression were all increased by the translocation of activated NF-κB into the nucleus. (Signal 2) Increased intracellular reactive oxygen species, adenosine triphosphate, and Ca^{+} levels are caused by damage associated molecular pattern and PAMP-induced lysosomal damage, and mitochondrial dysfunction, while K^{+} efflux lowered intracellular K^{+} level. The previous intracellular events lead to activates NLRP3 to inflammasome that promotes caspase-1 which begin to convert pro-IL-1β and pro-IL-18 into IL-1β and IL-18. IL-(1β): Interleukin-1 beta; DAMP: Damage associated molecular pattern; PAMP: Pathogen associated molecular pattern; TNF-α: Tumour necrosis factor-alpha; ILR: Interleukin receptor; TLR: Toll-like receptor; TNFR: Tumour necrosis factor receptor; MyD88: Myeloid differentiation primary response 88; IK-β: Inhibitor *kappa*-beta; P50: Nuclear factor-kappa B P50 subunit; P65: Nuclear factor-kappa B P65 subunit; ROS: Reactive oxygen species; ATP: Adenosine triphosphate; Ca+: Calcium ion; K+: Potassium ion; NF-Kb: Nuclear factor-kappa B; NLRP3: Nod-like receptor protein-3; ASC: Apoptosis-associated speck-like protein.

injury[105] and lipopolysaccharide (LPS)-induced mice with acute lung injury[106].

1, 25-dihydroxy vitamin D3: Vitamin D (Vit D3) is a fat-soluble vitamin that maintains calcium and phosphorus homeostasis[107]. Significantly, Vit D3 ameliorates the NLRP3 inflammasome in variant mouse models like periodontitis [108], diabetes-induced retinal vascular damage[109], nitrogen mustard-induced cutaneous inflammation[110], hyperosmotic stress-induced injury[111], cisplatin-induced acute renal injury[112], and allergy inhibition[113]. Cao *et al* [114] reported that it suppresses NLRP3 inflammasome activation, NLRP3-mediated ASC oligomerization, caspase-1 activation, and IL-1β production. Also, NLRP3 binding to NEK7 was inhibited in DSS-induced UC.

Ginsenosides: Ginsenosides are the most significant phytochemical of ginseng obtained from the *Panax* species family *Araliaceae*[115,116]. Ginsenoside Rk3 (Rk3) is a tetracyclic triterpenoid reportedly found in Radix notoginseng herbs[117]. Tian *et al*[118] revealed that Rk3 protects against DSS-induced UC by suppressing NLRP3 expression. Rk3 administration significantly attenuated myeloperoxidase (MPO), inducible nitric oxide synthase activities, and downregulated NLRP3, ASC, and caspase-1 expression. Ginsenoside Rd (Rd) is another ginsenoside that inhibits NLRP3 in UC[119]. Rd suppresses NLRP3 activation and decreases caspase-1 production and IL-1β levels in DSS-induced UC. Also, Rd inhibits MPO and inducible nitric oxide synthase activities while increasing antioxidant glutathione content[120].

Phloretin: Phloretin (PHL) is a flavonoid found in fruit, leaves, and roots of the apple tree *Malus domestica*[121,122]. Zhang *et al*[123] demonstrated that PHL suppressed DSS-induced NLRP3 inflammasome activations and regulated the NF-κB, TLR4, and PPARγ pathways. Moreover, PHL attenuated oxidative stress and regulated the expression of ZO-1

and occludin. In the same context, Wu *et al*[124] found that PHL ameliorated UC by suppressing NF-κB and NLRP3 activation. Additionally, it decreases cytokines and oxidative injury while maintaining intestinal barrier integrity.

Cinnamaldehyde: Cinnamaldehyde (CA) is the principal constituent of the bark of *Cinnamomum cassia* and *C. verum* [125]. CA suppresses NLRP3 in several models like rheumatoid arthritis[126], endotoxin-poisoned mice[127], cardiac ischemia-reperfusion[128], fructose-induced cardiac inflammation and fibrosis[129], and LPS-induced renal inflammation [130]. CA mitigates DSS-induced colitis by suppressing NLRP3 activation and miR-21, miR-155, IL-1β, and IL-6 levels. Furthermore, the suppression of NLRP3, miR-21, and miR-155 was observed in CA-treated, LPS-stimulated RAW264.7 cells. The production ROS and protein kinase B/mammalian target of rapamycin phosphorylation was also reduced[131].

Palmatine: Palmatine is an isoquinoline alkaloid found in traditional Chinese medicine (TCM), including *Fibraurea spp*., *Corydalis spp*., *Berberis spp*., and *Phellodendron spp*[132-134]. Palmatine suppresses NLRP3 inflammasomes in different models, like hyperuricemia-induced kidney injury[135] and monosodium uric acid-induced gouty arthritis[136]. Mai *et al* [137] revealed that palmatine attenuates DSS-induced colitis in mice by suppressing NLRP3 inflammasomes and decreasing the colonic levels of MPO, IL-1β, and TNF-α. In 2022, Cheng and co-workers recently suggested that 8-oxypalmatine exerted an appreciable protective effect on DSS-induced colitis, suppressing the NLRP3 inflammasome and activating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway[138].

L-fucose: L-fucose, a naturally safe monosaccharide found in animals, is often utilized as a food ingredient[139,140]. L-fucose attenuates colitis by suppressing NLRP3 inflammasome and NF-κB activation, decreasing pro-inflammatory cytokines, and reducing neutrophil and macrophage infiltration[141].

Genistein: Genistein (Gen) is a significant isoflavone in soy[142]. Gen suppresses the NLRP3 inflammasome in macrophages by activating the G protein–coupled receptor 5-cAMP signal in DSS-induced UC mice. Additionally, the Gen administration boosted intracellular cAMP levels and decreased caspase-1 and IL-1β levels[143]. In agreement with this study, Gen suppressed the NLRP3 inflammasome in different models, such as cerebral ischemia in mice[144], H_2O_2-induced senescence of human umbilical vein endothelial cells[145], hippocampal neurons in aging rat brain tissue[146], and alloxan-induced diabetes in mice[147].

Sinapic acid: Sinapic acid (SA) is a phytochemical abundant in various food plants, including spices, citrus and berry fruits, cereals, and others[148-150]. SA was shown to have potential therapeutic efficacy in inhibiting NLRP3-associated inflammatory disorders[151]. In conjunction with that, SA upregulated tight junction protein-1 (ZO-1) and claudin-1 in DSS-induced UC, suppressing the NLRP3 activation and attenuating intestinal permeability. Additionally, SA attenuates oxidative injury by boosting antioxidants superoxide dismutase, glutathione peroxidase, and catalase activity while lowering MPO and pro-inflammatory cytokine mRNA levels in circulation and colonic tissue[152].

Terpinen-4-ol: Terpinen-4-ol (TER) is a primary ingredient in *Zanthoxylum bungeanum* Maxim's essential oil[153]. Zhang *et al*[154] investigated whether the protective effect of TER may be substantially related to its suppression of NLRP3 activation in DSS-induced colitis. TER balanced the amounts of *Lactobacillus* and *Escherichia coli* while lowering the plasmatic LPS content. Additionally, TER inhibited the breakdown of the colon epithelial barrier by controlling the expression of ZO-1 and occluding and decreasing IL-1β production.

Apigenin: Apigenin (API) is a flavone found in many vascular plants' leaves, vegetables, stems, and fruits[155]. According to Márquez-Flores *et al*[156], API anti-inflammatory activity was attributed to a suppression of the NLRP3 inflammasome by lowering levels of pro-inflammatory cytokines and oxidative stress as a result of controlling the activity of cleaved caspase-1 and caspase-11 enzymes. In agreement with this study, API suppresses NLRP3 inflammasome activation in high-fat diet-induced non-alcoholic fatty liver disease[157], palmitic acid-induced liver injury[158], arteriosclerosis[159], human umbilical vein endothelial cells inflammation[160], depression in chronic unpredictable mild stress rats[161], and doxorubicin-induced renal injury[162].

Rosmarinic acid: Rosmarinic acid (RA) is a natural polyphenol found in plants from the *Labiatae* family[163]. RA downregulates the NRLP3-inflammasome in neuroinflammation[164], acetaminophen-induced liver injury[165], and nicotine-induced atherosclerosis[166]. In 2021, Marinho *et al*[167] demonstrated that RA-loaded nanovesicles enhanced Nrf2 and heme oxygenase-1 expression while decreasing NLRP3 inflammasome, ASC, and caspase-1 protein expression and IL-1β levels. RA also reduces TNF-α and MPO activity.

Lonicerin: A flavonoid glycoside, lonicerin, is extracted from the plant *Lonicera japonica* Thunb. It treats infectious and inflammatory diseases[168,169]. Numerous investigations have shown that lonicerin is among the main ingredients with anti-inflammatory and immunomodulatory properties[170]. Lv *et al*[165] suggested that lonicerin reduces colitis through NLRP3-ASC-pro-caspase-1 complex assembly. Lonicerin has a therapeutic impact on intestinal inflammation by directly binding to the histone methyltransferase enhancer of zeste homolog 2, which promotes autophagy and speeds up the destruction of NLRP3 by autolysosomes.

Magnesium lithospermate B: Magnesium lithospermate B (MLB) is the primary ingredient of *Salviae miltiorrhizae*[171]. It has been reported that MLB treats acute colitis[172,173]. Jiang *et al*[174] found that MLB might treat acute and chronic colitis by downregulating NLRP3, ASC, and caspase-1 levels.

Fumigaclavine C: Fumigaclavine C is an indole alkaloid obtained from endophytic *Aspergillus terreus* and *Rhizophora*

stylosa[175,176]. According to Guo *et al*[177], fumigaclavine C attenuates DSS-induced colitis by decreasing pro-inflammatory cytokines TNF-α, IL-1β, and IL-17A, mediated by suppressing NLRP3 inflammasome and caspase-1 activation.

Nigeglanine: Nigeglanine is a phytochemical obtained from *Nigella sativa* oil[178]. According to a study conducted in 2019 by Gao *et al*[179], nigeglanine inhibits colon epithelial cell pyroptosis by suppressing the NLRP3 inflammasome, NF-κB, and MAPK in DSS-induced colitis in mice. Surprisingly, nigeglanine supplementation enhanced ZO-1 and occludin protein levels, indicating that nigeglanine protects barrier integrity.

Mycophenolate mofetil: Mycophenolate mofetil (MMF) is a fermentation byproduct of *Penicillium stoloniferum*[180-182]. MMF is an immunosuppressant commonly used to treat systemic lupus erythematosus, lupus nephritis, and other autoimmune disorders[183]. Serrya *et al*[184] observed that MMF had coloprotective effects against AA-induced UC by suppressing the NLRP3 inflammasome and consequent release of IL-1β, IL-18, and INF-γ. In colon tissues, MMF considerably reduced oxidative stress and boosted antioxidants glutathione, catalase, and superoxide dismutase levels as well as total antioxidant capacity mediated by upregulating Nrf-2.

Evodiamine: Evodiamine (EVO), a significant alkaloidal substance discovered from *Evodia rutaecarpa*, has long been used in TCM to treat various infection-related diseases, such as diarrhea, beriberi, and oral ulcers[185,186]. Additionally, EVO effectively treats nausea and abdominal discomfort[187]. Furthermore, EVO inhibits NLRP3 inflammasome activation, indicating the application of EVO in treating IBD[188] and enhancing innate immunity against bacterial infection[189]. In DSS-induced UC mice, EVO reduced inflammation by controlling the NF-κB signal and NLRP3 inflammasome, which reduced the production of TNF-α, IL-1β, and IL-6 and altered the expression of ZO-1 and occludin[190]. Similarly, Ding *et al*[188] showed that EVO inhibits NLRP3 inflammasome activation by enhancing autophagosome degradation and inhibiting the NF-κB pathway.

Brusatol: Brusatol is a major quassinoid of *Brucea javanica* used in treating inflammatory disorders, particularly intestinal inflammation, such as colitis and dysentery[191]. Zhou *et al*[192] revealed that the anti-UC activity of brusatol is closely related to the suppression of NF-κB and NLRP3 signals and the activation of Nrf2 expression-mediated anti-oxidative effects. The TNF-α, pro- IL-1β, IL-18, prostaglandin E2, and nitric oxide levels were significantly reduced by brusatol in LPS-stimulated macrophages.

Bergenin: Bergenin, a C-glycoside produced from 4-O-methyl gallic acid, is one of the primary active components of plants in the genus *Peltophorum*[193]. Bergenin reduces palmitic acid-induced pancreatic injury by suppressing NLRP3 activation[194]. Likewise, Lopes de Oliveira *et al*[195] showed that bergenin attenuates 2,4,6-trinitrobenzene sulfonic acid-induced acute colitis in rats. Bergenin decreased inflammatory cytokines levels mediated by suppressing phosphorated signal transducer and activator of transcription 3 (STAT3), NF-κB, and NLRP3/ASC inflammasome signals.

Wedelolactone: Wedelolactone is a coumarin obtained from plants found in *Wedelia chinensis*[196,197]. Wei *et al*[198] revealed that wedelolactone administration significantly suppressed NLRP3 and caspase-1 activation to reduce IL-1β production in DSS-induced UC. Wedelolactone also successfully maintains intestinal barrier function by activating AMP-activated protein kinase (AMPK).

Walnut oil: Walnut oil is commonly recommended as a nutritious, premium food oil and is used extensively in TCM [199]. Walnut oil has anti-inflammatory and antioxidant effects[200-202]. Miao *et al*[203] explored how walnut oil inhibits the NLRP3 inflammasome activation and modifies gut microbiota in DSS-induced colitis in mice. Walnut oil enhanced the levels of short-chain fatty acids and blocked apoptosis while reducing ROS generation and pro-inflammatory cytokines release by sup-pressing NLRP3, ASC, and caspase-1 activation.

Nigakinone: Nigakinone is the principal active ingredient of *Ramulus et Folium Picrasmae*, and it is one of the TCM substances frequently used to treat diarrhea, colitis, and dysentery[204]. In DSS-induced colitis, nigakinone alleviated symptoms by regulating the farnesoid X receptor/NLRP3 pathway[205].

Oroxindin: Oroxindin is a natural bioflavonoid that was identified in Huang Qin. Oroxindin has been shown in several studies to have a variety of bioactivities, including anti-inflammatory, antioxidant, and anticancer effects[206-208]. According to Liu *et al*[209], oroxindin reduces inflammatory responses by suppressing NLRP3 inflammasome activation and reducing colonic IL-1β and IL-18 Levels. Oroxindin modulated the production of thioredoxin interacting protein (TXNIP), reducing LPS-induced NLRP3 inflammasome and caspase-1 activation in cultured macrophages, hence decreasing TXNIP-dependent NF-κB activation.

Schisandrin B: Schisandrin B is the most significant component in *Schisandra chinensis*[210]. Schisandrin B suppresses NLRP3 inflammasome activation in LPS-induced airway inflammation and airway remodeling[211] and propionibacterium acnes-induced pyroptosis[212]. In 2021, Zhang *et al*[213] demonstrated schisandrin B reduces NLRP3 inflammasome activation mediated by IL-1β release in intestinal epithelial cells of a colitis model.

Trifolirhizin: Trifolirhizin is a pterocarpan identified from *Trifolium pratense* and *Sophora flavescens*[214,215]. Trifolirhizin treatment successfully controlled the balance of T helper/T regulatory (Th17/Treg) cells and inflammation in DSS-induced UC mice by suppressing NLRP3 activation by TXNIP. Trifolirhizin has also been shown to control the AMPK-TXNIP pathway[216].

Sanguinarine: Sanguinarine, benzylisoquinoline alkaloids, is obtained from *Sanguinaria canadensis* and *Fumaria*[217]. According to Li *et al*[218], sanguinarine showed a potential therapeutic impact on DSS-induced UC mice by suppressing NLRP3-(Caspase-1)/IL-1β pathway and enhancing gut microbial dysbiosis. Additionally, sanguinarine decreased the expression of NLRP3 and the activation of caspase-1 and IL-1β in THP-1 cells induced by LPS[218].

Geniposide: The primary active ingredient of *Gardenia jasminoides* is geniposide, an iridoid glycoside extracted from the *Gardenia* used in TCM[219]. Geniposide was shown by Pu *et al*[220] to reduce macrophage differentiation in mice with acute colitis induced by DSS by inhibiting the NLRP3. In addition, geniposide augmented AMPK/Sirt1 signal and inhibited the NLRP3 inflammasome in LPS-induced BMDM cell or RAW264.7 cell cultures. In line with this study, geniposide suppressed the activation of the NLRP3 inflammasome in different *in vivo* and *in vitro* models, such as myocardial ischemia/reperfusion injury[221], sepsis-induced myocardial dysfunction[222], and cholestatic liver inflammatory injury[223].

Sinomenine hydrochloride: Sinomenine is a pure alkaloid derived from the plant *Sinomenium acutum* of the *Menispermaceae* family[224]. According to Zhou *et al*[225], sinomenine may reduce the symptoms of experimental colitis by altering the production of the gut microbiota and reducing the activity of the NLRP3 inflammasome and pro-inflammatory mediators levels in mice. In line with this study, sinomenine inhibits the NLRP3 inflammasome, which has a favorable effect on cartilage degradation[226], autoimmune encephalomyelitis[227], ischemic stroke[228], and others.

Picroside II: Picroside II is a kind of iridoid chemical that is used in TMC. There are now three known iridoids in *Picrorhiza scrophulariі* flora *pennell*[229]. Picroside II possesses hepatoprotective, immune-regulating, anti-inflammatory, and antioxidant properties[230-232]. Yao *et al*[233] demonstrated that picroside II alleviated DDS-induced UC by significantly suppressing NLRP3 inflammasomes and inflammatory components *in vivo* induced by DDS.

Hydroxytyrosol: Hydroxytyrosol is a prominent and typical phenolic component in olive oil and leaves[234]. Miao[235] demonstrated that hydroxytyrosol supplementation has a coloprotective effect on DSS-induced UC by suppressing NLRP3, caspase-1, and ASC expression levels and downregulating IL-18 and IL-1β levels. Additionally, hydroxytyrosol modifies the *in vivo* gut microbiota while boosting colonic antioxidant functionality.

Trans-10-hydroxy-2-decenoic acid: The most prevalent fatty acid and main lipid in royal jelly is 10-hydroxy-2-decenoic acid, which also has antibacterial[236], antioxidant[236], immunomodulatory[237], anti-inflammatory[238] properties, and others. According to Huang *et al*[239], trans-10-hydroxy-2-decenoic acid improves colonic barrier function, decreases colonic TXNIP, ASC, caspase-1, GSDMD, IL-1β, and IL-18 Levels, and regulates the NLRP3 inflammasome-mediated pyroptosis to treat DSS-induced colitis.

PLANT EXTRACT

Canna x generalis

Canna x generalis (CG) LH Bailey is a hybrid of two closely related species that belongs to the *Canna* genus[240]. With its enormous leaves and gorgeous blooms, CG may grow without special care and can adapt to various soil conditions[241, 242]. CG exhibits anti-inflammatory[243] and antioxidant[244] activities. CG extract exhibits a protective effect against DSS-induced UC mice by suppressing colonic activation of NLRP3 and NF-κB/TLR4 signals. CG extract reduces pro-inflammatory mediators, oxidative stress, and the inflammatory cascade in colonic tissues. Additionally, CG extract downregulates caspase-1, ASC, TLR4, and caspase-3 expressions[245].

Kuijieling decoction: An empirical formula known as Kuijieling decoction (KJL) has been introduced in clinical conditions for several years and is effective in treating UC[246,247]. KJL showed anti-inflammatory and antioxidant bioactivities[248,249]. KJL effectively attenuates UC symptoms in the UC rat model[250]. Jie *et al*[251] revealed that KJL suspension attenuates UC by decreasing NLRP3, caspase 1, and pro-inflammatory cytokines levels. They also showed that in DSS-induced UC mice, KJL downregulates NLRP3, caspase-1, GSDMD-N, IL-1β, and IL-18. Also, the expression levels of ASC, caspase-1, IL-1β, IL-18, and Mir-223 were downregulated in colon tissue.

Huaier: For more than 1600 years, *Trametes robiniophila Murr* (Huaier), a sandy beige fungus that grows on tree trunks, has been extensively employed in TCM[252-254]. Wang *et al*[255] showed that Huaier has anti-inflammatory activity in DSS-induced murine colitis in mice by downregulating NLRP3 expression and preventing NLRP3 inflammasome activation-induced IL-1β production and caspase-1 cleavage.

Shaoyao decoction: Shaoyao decoction (SYD) is a TCM that has demonstrated that it has anti-inflammatory[256] and anticancer[257] effects, among others. In addition, a recent study revealed that SYD had been successfully utilized to treat IBD and other disorders linked to the damp-heat syndrome in the intestines[258]. Wei *et al*[259] reported the protective effects of SYD on DSS-induced UC and pyroptosis by suppressing the NLRP3 and NF-κB/P38 signals. Moreover, SYD supplementation decreases caspase-1 activity and the release of ASC and GSDMD, preventing the formation of NLRP3 and protecting the intestinal barrier integrity.

Smilax china L.

Smilax china L. is one of the TCM that is effective in reducing inflammation[260], nociception[261], and cancer[262]. *S. china L.* polysaccharide (also known as SCLP) was isolated from the rhizome of *S. china* L. and is a TCM used to treat inflammatory disorders[263]. SCLP treats UC, according to Pan *et al*[264], by inhibiting the galectin-3 expression and its connection with NLRP3 activation and IL-1β production, which in turn decreases the release of inflammatory mediators in the DSS mice model.

Dendrobium officinale

Dendrobium officinale Kimura et Migo is the second-biggest genus of *Orchidaceae*[265,266]. Polysaccharides, the main active constituents in *D. officinale*, have received much interest due to their numerous biological activities[267-269]. Moreover, a prior investigation showed that *D. officinale* polysaccharides (DOPS) could successfully alleviate DSS-induced colitis in mice[270]. In 2018, Liang *et al*[270] found that DOPS has a notable therapeutic effect in treating DSS-induced acute UC mice. They also examined whether DOPS administration might significantly reduce the activation of the NLRP3 inflammasome and the β-arrestin1 signaling pathways. DOPS significantly decreases colonic pathological damage, relieves clinical signs and symptoms, and restores the pro- and anti-inflammatory cytokines balances.

Schisandra chinensis

As a result of its various pharmacological properties, the fruit of *Schisandra chinensis*, a member of the *Magnoliaceae* family, has long been utilized as an herbal remedy in TCM[271,272]. These fruits were often utilized as wholesome meals and pharmaceuticals for several chronic diseases, such as cancer, liver injuries, and gastrointestinal disorders[210,273]. *S. chinensis* mitigates ferroptosis and NLRP3 inflammasome-mediated pyroptosis in diabetic nephrosis[274]. Recently, Bian *et al*[275] found that *S. chinensis* extract can reduce the symptoms of DSS-induced colitis by TLR4/NF-κB and NLRP3 inflammasome suppression. Additionally, *S. chinensis* extract might correct the gut microbiota imbalance brought on by UC while maintaining gut barrier function by raising ZO-1 and occludin levels.

Tripterygium wilfordii

Tripterygium wilfordii Hook. f., commonly referred to as Lei Gong Teng, is a TCM herb frequently used to treat autoimmune and inflammatory diseases[276-278]. The root bark of *T. wilfordii* demonstrated pharmacological actions against inflammation[279], autoimmune disorders[280], Crohn's disease[281], liver cancer[282], and others. *T. wilfordii* polycoride is the primary active ingredient of *T. wilfordii*[283]. Fangxiao *et al*[284] reported the anti-inflammatory effects of *T. wilfordii* polycoride on 2,4,6-trinitrobenzenesulfonic acid-induced colitis by downregulating the NOXs-ROS-NLRP3 signal. *T. wilfordii* polycoride decreased ROS production, and NOXs' activity was mediated by downregulating colonic NLRP3, ASC, and caspase-1.

Rubia cordifolia L.

Rubia cordifolia L. is a perennial climbing vine from the Rubiaceae family[285,286]. Its aerial portion possesses a range of bioactivities, including anti-inflammatory[287], antioxidant[288,289], and others. Recent findings by Qin *et al*[290] showed that using *R. cordifolia* extract inhibits the NLRP3 inflammasome and IL-6/Jak-2/STAT3 signal activation in DSS-induced UC. *R. cordifolia* extract improves the symptoms, diminishes colonic mucosal injury and macrophage infiltration, inhibits the production of inflammatory cytokines, and lowers mortality.

Mulberry fruit extract

Mulberry fruit extract (MFE) is obtained from the fully ripened fruits of *Morus macroura*[291,292]. Salama *et al*[293] recently reported the involvement of NLRP3, miRNA-223, and the TNF-α/NF-κB pathway in the coloprotective effects of MFE against AA-induced UC in rats. MFE also reduces levels of TNFR1, NLRP3, NF-κB p65, TNF-α, IL-1β, IL-18, and caspase-1, while increases miRNA-223 expression.

PROBIOTICS

Akkermansia muciniphila

Akkermansia muciniphila, a Gram-negative and anaerobes bacterium, is a member of the *Verrucomicrobia phylum*, which has been discovered to be common in the human gut[294-296]. According to investigations, *A. muciniphila* may protect against major diseases like atherosclerosis[297], amyotrophic lateral sclerosis[298], and immune-mediated liver damage[299]. Additionally, it was reported that *A. muciniphila* improves chronic colitis[300]. Recently, Qu *et al*[301] revealed that oral treatment of *A. muciniphila* strain BAA-835 effectively reduces the signs and symptoms of DSS-induced acute colitis dependent on NLRP3 activation. The expression of NLRP3, caspase-1, and IL-1β was elevated in mouse macrophage cells in *A. muciniphila*-treated animals, as well as pro-inflammatory cytokines such as TNF-α, IL-6, and monocyte chemoattractant protein 1 (MCP-1).

Saccharomyces cerevisiae

A facultative anaerobic fungus called *Saccharomyces cerevisiae* has been extensively employed in medicine to create modified carriers and oral vaccinations[302,303]. According to a study by Sun *et al*[304], modified *S. cerevisiae* reduced the severity of DSS-induced colitis in mice by inhibiting macrophage pyroptosis and regulating the intestinal microbiota.

Lactic acid-produced *S. cerevisiae* modulated macrophage polarisation, prevented the production of pro-inflammatory cytokines *in vivo* and *in vitro*, and decreased NLRP3 inflammasome and caspase-1 levels.

Lactobacillus acidophilus

Lactobacillus acidophilus is one of the most common commercial species of lactic acid bacteria, found in various dairy products and nutritional supplements with probiotic indications[305]. According to studies, *L. acidophilus* may have immunomodulatory, anti-inflammatory, and antioxidant[306-308] activities. Furthermore, it improves the intestinal epithelial barrier function[309,310]. Additionally, it was demonstrated to be efficient in preventing colitis caused by *Citrobacter rodentium*[309] and relieving DSS-induced colitis[311]. According to Li *et al*[312], *L. acidophilus* attenuates UC in rats by inhibiting the NLRP3 inflammasome pathway, increasing the short-chain fatty acids level, and promoting autophagy.

Grape seed proanthocyanidin

Grape seed proanthocyanidin extract (GSPE) is a grape seed extract that contains catechin, epicatechin gallate, and epigallocatechin[313,314]. According to Sheng *et al*[315], GSPE supplementation reduces inflammatory cytokines and oxidative stress, maintains the intestinal barrier, and enhances the microbiome in DSS-induced colitis. GSPE decreases the NLRP3 inflammasome and increases ZO-1, occludin, and claudin-1 levels. Furthermore, GSPE treatment of colon tissues resulted in a considerable decrease in TNF-α and IL-1β levels.

Brilliant blue G

Brilliant blue G (BBG) is a triarylmethane dye with a modest hydrophilicity that has been proven to stain the inner limiting membrane selectively[316]. In 2021, Saber *et al*[317] revealed that the BBG/OLT1177 combination produced complementary effects and significantly alleviated DSS-induced UC by downregulating NLRP3, caspase-1, IL-1β, and IL-18 levels. In addition to reducing purinergic receptor (P2X7R) and oxidative stress levels, BBG treatment downregulated myeloid differentiation primary response 88, NF-κB, IL-6, TNF-α, the recruitment of the NLRP3 inflammasome, and the consequent activation of caspase-1, IL-1β, and IL-18.

Forsythia suspensa extract

Forsythia suspensa (Thunb.) Vahl is well-known in TCM[318]. Chao *et al*[319] showed that *Forsythia suspensa* extract effectively reduces metabolic dysfunction and DSS-induced UC damage by suppressing the NLRP3 pathway and activating Nrf2.

Kui jie tong

Kui jie tong is a herbal extract that effectively treats UC[320]. Xue *et al*[321] reported that Kui jie tong mitigates UC by downregulating NLRP3 and caspase-1 as well as serum IL-1β, IL-18, and IL-33 and enhancing intestinal microbiota.

Jianpi Qingchang decoction

Jianpi Qingchang decoction, a TCM prescription, is composed of nine Chinese herbs and effectively attenuates moderate or beginning cases of UC[322,323]. Zhang *et al*[324] stated that Jianpi Qingchang decoction has a protective function by preventing DSS-induced NLRP3 inflammasome activation. Jianpi Qingchang decoction decreases inflammatory cytokine release.

Bovine milk

Bioactive extracellular vesicles are present in the milk of all mammalian species[325,326]. Bovine milk exosomes have been shown to support intestinal cell proliferation, boost the number of goblet cells and mucin synthesis, inhibit bacterial growth, and support the intestinal microbiota[327-329]. According to the Tong *et al*[330] study, milk-derived extracellular vesicles regulate intestinal immunological homeostasis by suppressing TLR4- NF-κB and NLRP3 signaling pathways, re-establishing the balance of Treg/Th17 cells, and altering the gut microbiota. In a mouse UC model, milk-derived extracellular vesicles were proven to have a role in the control of immunological and inflammatory pathways, which decreased intestinal epithelium disruption, blocked the infiltration of inflammatory cells, and reduced tissue fibrosis[330].

SYNTHETIC DRUGS

Mirtazapine

Mirtazapine is a well-known antidepressant medication used to treat depression, anxiety, and sleep disorders[331]. In addition, mirtazapine reduces inflammation in diabetic rat kidneys by inhibiting the NLRP3 inflammasome[332]. The same results showed that mirtazapine has a coloprotective effect against UC, which was mediated by suppressing NLRP3 and caspase-1 activation and restoring the antioxidant/oxidant balance in AA-induced UC in rats. Additionally, mirtazapine reduces the levels of NF-κB, TNF-α, IL-1β, and IL-18[333].

Paeoniflorin-6'-O-benzene sulfonate

Paeoniflorin-6′-O-benzene sulfonate is a new active monomer created by structurally altering paeoniflorin[334] and has

anti-inflammatory and immunomodulatory characteristics[335,336]. According to Li *et al*[337], paeoniflorin-6′-O-benzene sulfonate has anti-colitis properties *via* suppressing TLR4-NF-κB and NLRP3 signals and G protein-coupled receptor kinase 2 translocations. Furthermore, paeoniflorin-6′-O-benzene sulfonate maintains intestinal barrier function in LPS-treated mice.

Dapagliflozin

Dapagliflozin (DPZ), a sodium-glucose cotransporter-2 inhibitor, is recommended in addition to routine medical treatment for managing type 2 diabetes mellitus that has not been effectively controlled[338]. Interestingly, DPZ modulates the NLRP3 inflammasome in different models, such as diabetic nephropathy[339], LPS-induced lung damage [340], and type 2 diabetes mellitus- induced cardiomyopathy[341]. El-Rous and colleagues reported that DPZ suppressed the activation stage (signal 2) of NLRP3 inflammasome activation and prevented the priming step (signal 1) of that activation in AA-induced UC through altering NF-κB/AMPK interaction and halting NLRP3/caspase-1 communication. Furthermore, DPZ increases the anti-inflammatory cytokine IL-10 and remarkably suppresses caspase-1 activity and IL-1β and IL-18 production[342].

Canagliflozin

Canagliflozin is a small-molecule hypoglycemic medication that lowers blood glucose levels by blocking the type 2 sodium-glucose cotransporter, which prevents the kidneys from reabsorbing glucose[343]. Nasr *et al*[344] reported that canagliflozin-loaded chitosan-hyaluronic acid microspheres significantly suppressed NF-κB and NLRP3 activation, resulting in a decrease in caspase-1 cleavage and the inhibition of several inflammatory cytokines, including IL-1β and IL-18, in AA-induced colitis.

Rosuvastatin

Rosuvastatin, an HMG-CoA inhibitor that is relatively new, has a safety and tolerability profile that is comparable to or better than the regularly prescribed dosages of other statins[345]. Rosuvastatin and *Lactobacillus* inhibit the NLRP3 inflammasome assembly, pro- IL-1β, pro-IL-18, and NF-κB, decreasing caspase-1 activity and IL-1β-driven pyroptotic activity in DSS in high-fat diet-induced colitis in rats[346].

MCC950

MCC950 is an IL-1β inhibitor and is known to be a potent inhibitor of the NLRP3 inflammasome[347]. MCC950 inhibits NLRP3 among inflammasomes[347,348] and blocks canonical, non-canonical, and alternative NLRP3 activation[80,347,349]. MCC950 showed promising therapeutic potential for inhibiting NLRP3 inflammasome in the atherosclerotic lesion [350], cholestatic liver, non-alcoholic steatohepatitis-induced liver fibrosis[351,352], LPS-induced lung inflammation[353], and others. In 2018, Perera *et al*[354] revealed that MCC950 effectively treats murine UC. MCC950 significantly suppresses NLRP3 inflammasome activation and decreases colonic cytokines, chemokines, and nitric oxide levels. Moreover, MCC950 suppresses caspase-1 activation in the colon and macrophage cells.

CONCLUSION

The incidence and prevalence of UC, a recurrent and remitting condition, are rising. The goal of treatment is to increase a patient's quality of life while achieving quick symptom alleviation and mucosal healing. There are still a lot of unsolved concerns despite the abundance of evidence pointing to genetic and host-related variables in UC. Numerous opportunities exist for further inquiry to improve our understanding of the pathogenesis of UC and uncover possible predictors of disease severity, responsiveness to medication, and novel therapeutic targets as the incidence and prevalence of UC around the world increase. The NLRP3 inflammasome plays a crucial role in the inflammation and immunological reaction by promoting caspase-1 activation and the release of IL-1β. Interestingly, phytochemicals, plant extracts, and synthetic drugs exhibit promising colon protective effects mediated by NLRP3 and caspase-1 activation suppression and, subsequently, the release of the pro-inflammatory cytokine IL-1β, which has a key role in UC-associated inflammation. However, future clinical studies are required to comprehend how NLRP3 inflammasome activation inhibition significantly treats and controls UC.

FOOTNOTES

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