

# Progress in targeting the NLRP3 signaling pathway for inflammatory bowel disease (Review)

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**Abstract.** Inflammatory caspases pro-inflammatory cytokines, such as IL-1 $\beta$  IL-18, constitute a critical part in the modulation of innate immune responses by the nucleotide-binding domain leucine-rich repeat protein (NLRP)3 inflammasome. The NLRP3 inflammasome, a cytosolic complex, is composed of three distinct classes of proteins-sensor complexes, adaptor proteins, cysteine proteases. It is well-established that this pathway can powerfully influence the pathophysiology of autoimmune diseases along with an association of a plethora of inflammatory conditions. Therefore, it is of great significance to elucidate the mechanisms through which NLRP3 participates in disease development functions as a potential target for pharmacological intervention. The present review discussed the function role of the NLRP3 inflammasome in inflammatory bowel disease and described the structure assembly and activation mechanism of the NLRP3 inflammasome. Additionally, it explored novel clinical viewpoints and therapeutic advances in targeted NLRP3 inflammasome therapy. In conclusion, the present review offered a comprehensive overview of inflammatory bowel disease and the NLRP3 inflammasome. It is expected to serve as a guide for future research, potentially leading to improved patient outcomes. The present review has been submitted as a pre-print ([https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=4962722](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4962722)).

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## 1. Introduction

Inflammatory bowel disease (IBD), which encompasses two major forms, Crohn's disease (CD) and ulcerative colitis (UC), is a prevalent chronic gastrointestinal disorder. Characterized by persistent and progressive inflammation of the digestive tract, these conditions severely affect the daily lives of patients, imposing a substantial burden. Globally, the incidence of IBD has risen by ~47% since 2019 (1). Clinical histology endoscopic criteria distinguish UC from CD. In UC, inflammation is restricted to the colonic mucosa can regularly spread to other parts of the colon. Conversely, in CD, inflammation is transmural may occur in a discontinuous pattern throughout any segment of the gastrointestinal tract (2) (Figs. 1 and 2). IBD possesses a complicated and poorly understood pathophysiology. Nonetheless, research has demonstrated that a number of variables, including genetic predisposition, environmental influences and alterations in the gut microbiota, are intimately linked to its etiology. Certain individuals are more susceptible to IBD due to genetic causes. In addition, environmental factors such as smoking, a poor diet and unhealthy lifestyle choices, can trigger or exacerbate the disease. An imbalance in the gut microbiota is considered one of the crucial elements contributing to the pathophysiology of IBD.

The clinical features of IBD include common symptoms featuring various gastrointestinal issues, such as diarrhea and abdominal pain. It is even possible for stool to contain blood in more serious cases. In UC, the usual locus of inception is the rectal area, extending to nearby parts of the colon as it erodes the mucosal submucosal layers therein. CD is conspicuous for

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conflicting with the ileum, colon and perianal parts of the gut, causing foci of transmural inflammation. In terms of clinical manifestations, UC is characterized by bloody diarrhea pain that migrates to the left lower abdomen. It is also associated with an increased likelihood of developing primary sclerosing cholangitis (PSC), arthritis (peripheral) and an elevated risk of colon cancer. Endoscopically, it presents with diffuse congestion (as shown in Figs. 1 and 2), erosions and shallow ulcers. CD is the opposite, diarrhea will contain a small amount of blood, the pain is mostly in the right lower abdomen, which may lead to diseases such as oral ulcers. In severe cases, it may lead to intestinal obstruction and, abscesses. Endoscopic manifestations are aphthous ulcers, cobblestone-like changes and longitudinal ulcers; the mucous membranes are normal in the intervals between the lesions. Currently, in the treatment of UC, 5-aminosalicylic acid (5-ASA), glucocorticoids, immunosuppressants and JAK inhibitors are commonly employed. Emerging therapies such as fecal transplantation S1P receptor modulators are also being used. Substances such as 5-ASA, glucocorticoids, immunosuppressants remain widely used in the treatment of CD. In recent years, however, novel treatment modalities such as stem cell therapy anti-IL-23 have emerged are being applied.

Diagnostics of IBD have made considerable strides since the second half of the twentieth century. With careful history taking, physical examination and requisite laboratory tests, doctors can make accurate diagnoses of IBD. In terms of treatment, individualized treatment schemes have been developed based on a particular clinical picture, with the ultimate intention being long-term disease remission and well-controlled disease.

Examples of first-generation medications in the treatment of IBD are aminosalicylic acid agents, glucocorticoids and immunosuppressants (3). Second-generation drugs, namely inflammation-targeted antibody-based biological agents, have gained broad acceptance in the clinical treatment of IBD (4).

## **2. Structure of nucleotide-binding domain leucine-rich repeat protein (NLRP) 3 and the regulatory mechanism of the NLRP3 pathway**

*The structure of NLRP3.* Inflammasome systems function essentially as small regulatory molecules of inflammation, whose imperfect functioning consequently makes individuals more susceptible to a myriad of pathological conditions, such as neurodegenerative pathologies, autoinflammatory conditions and metabolic syndromes. An inflammasome comprises three essential components: A sensor, typically a pattern recognition receptor; an adapter, namely the apoptosis-associated speck-like protein containing a CARD (ASC); and a final effector, caspase-1 (5). To date, five key forms of pattern recognition receptors (PRR) that build inflammasome berths have been revealed by scientists: AIM-2, proteins with a pyrin domain and nucleotide-binding oligomerization domain-like receptors, specifically NLRP1, NLRP3 and NLRC4 (6). Among these, the NLRP3 inflammasome is of particular pathophysiological importance, as it is involved in the maturation of interleukin-1 $\beta$  pyroptotic cell death (7).

The specialized multimolecular complex is generated, triggered and assembled after having detected molecular signatures of cell injury or microbial invasion, performing

intracellular surveillance. The process is: i) NLRP3 is a tripartite cytosolic receptor. Its N-terminal features a pyrin domain, while the central C-terminal portions are NACHT domains and leucine-rich repeat regions, respectively. ii) The adapter protein ASC is dichotomous, containing a PYD a CARD. iii) caspase-1 has a CARD, along with its corresponding procaspase-1 zymogen. This ATPase activity of nucleotide-binding domain sets the stage for building the PYD-PYD interaction between NLRP3 ASC forming a brand-new formation of molecular Speck. Subsequently, procaspase-1 is associated with ASC through CARD-CARD interactions triggering oligomerization to transmute the inactive zymogen into the active form. Following that, the inflammatory cascade is amplified by activated caspase-1. It has been shown that NLRP3-associated diseases can be alleviated by modulating NLRP3 inflammasome activity (8).

The body's defense against infections and inflammatory processes relies on a coordinated interplay between the peripheral nervous system, neuroendocrine system and central nervous system, which function jointly to regulate innate immunity (9). NLRP3 was initially identified in the human brain. Its high abundance in microglia was notable, as microglia, along with astrocytes and other glial cells, serve as key immune elements within the central nervous system (10). When activated, NLRP3 triggers microglia and astrocytes to produce and release inflammatory mediators and chemokines, which drive neuroinflammatory pathways (11). Under stringent regulatory conditions, NLRP3 proteins bind to ASC and caspase-1 to assemble a multi-protein inflammasome structure. This complex is capable of converting diverse stress signals into inflammatory responses (12).

*The activation pathway of NLRP3.* The NLRP3 inflammasome has been shown to undergo two distinct activation pathways: the classical and the non-classical pathway (13) (Fig. 3). However, it should be noted that inflammasome activation is a sequential process; it first requires initiation before reaching the activation stage. The initiation step of NLRP3 is characterized by the absence of activation of macrophages (mice) by the activator because dose-responsive treatment of macrophages with the protein synthesis inhibitor actinomycin ketone results in reduced caspase-1 activation obtained through a combination of LPS and ATP, suggesting that protein synthesis from scratch in mouse macrophages is functionally limited, yet activation of the NLRP3 inflammasome was enhanced by microbial preconditioning aka microbial product activation PRR or other signals of cellular activation (via the presence of pro-inflammatory cytokines) (14). First, the inflammasome components NLRP3, caspase-1 and pro-IL-1 $\beta$  are upregulated. Recognition of specific molecular patterns, such as those associated with pathogens or damage, by PRRs such as Toll-like receptors (TLR) or nucleotide-binding oligomeric domains containing protein 2 (NOD 2), can lead to an increase in transcription. Alternatively, the process may be facilitated by cytokines such as tumor necrosis factor (TNF) and IL-1 $\beta$ , resulting in nuclear factor- $\kappa$ B (NF- $\kappa$ B) activation and subsequent gene transcription (14-16). In addition, the initiation of Toll-like receptor 4 (TLR4) ligand lipopolysaccharide (LPS) alters

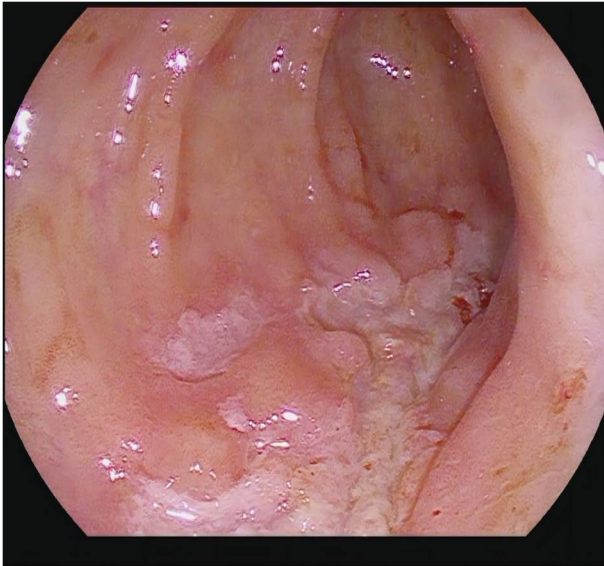


Figure 1. Representative colonoscopy image of Crohn's disease.

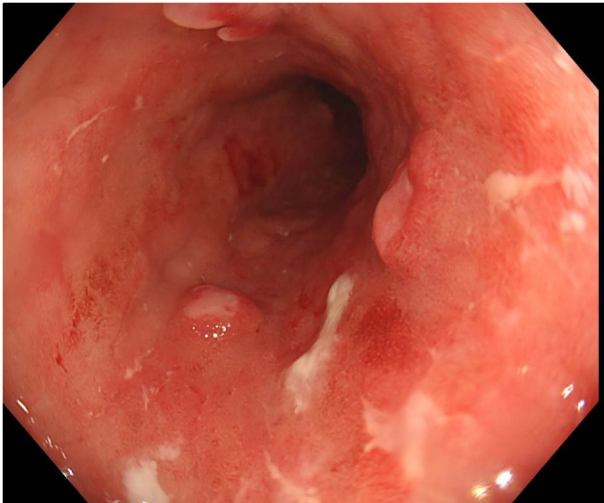


Figure 2. Representative colonoscopy image of ulcerative colitis.

macrophage metabolism from oxidative phosphorylation to glycolysis, indirectly leading to the stabilization of hypoxia-inducing factor 1 $\alpha$  (HIF-1 $\alpha$ ) and increased IL-4B gene transcription, with a second function to induce NLRP3 and stabilize NLRP3 in an autoinhibited inactive state. There are multiple PTM types, including ubiquitination, phosphorylation and SUMOylation.

The classical activation pathway unfolds as follows: The NLRP3 inflammasome serves as a key prerequisite for both activation and regulation (17). The intracellular multimeric protein complex of caspase-1 represents the primary pathway within the inflammatory activation pathway (18). Evidence shows that NLRP3 can be activated by a variety of factors, including mitochondrial channels, ion channels, lysosomal disruption channels and pathogen-associated RNA, among others. However, only a limited number of these potential activators have been experimentally validated (Fig. 4).

*Mitochondria and the reactive oxygen species (ROS) channels.* Considerable non-hematopoietic cell types, including monocytes, macrophages, dendritic cells and others, have been found to harbor the NLRP3 inflammasome (14). NLRP3 is mostly activated by mitochondria and damage to mitochondria can be a result of danger signals; this creates an upstream pathway that activates the NLRP3 (19). Notably, the majority of NLRP3 stimulants can induce ROS during treatment, thus rendering ROS a common signal for NLRP3 activation. The ROS produced by mitochondria (mtROS) is the product of oxidative phosphorylation and mtROS levels increase substantially under cellular stress conditions. Mitophagy therefore serves as a critical regulator of NLRP3 activation, as it selectively eliminates impaired as well as dysfunctional mitochondria. It has been demonstrated that ATP can generate the ROS required for NLRP3 activation (20).

Mitochondria are recognized as major contributors to ROS generation due to their respiratory activity. Research also suggests their role in inflammasome activation through ROS production or direct engagement with NLRP3 components. Mitochondrial apoptotic signals stimulate the NLRP3 inflammasome, thereby facilitating IL-1 $\beta$  synthesis. ATP and related NLRP3 activators induce mitochondrial dysfunction and cell death, causing oxidized mitochondrial DNA (mtDNA) release into the cytoplasm. There is mounting evidence that dysfunctional mitochondria release mtDNA that binds to and activates the NLRP3 inflammasome (21). Damage-associated molecular patterns (DAMPs) are discharged by damaged mitochondria, thereby activating innate immunity through pathways such as NLRP3-mediated activation. This activation affects both inflammatory responses and apoptosis in renal tubule cells (22).

Available evidence has indicated an important and unique role of mitochondrial impairment, ROS and mtDNA in triggering the activation of the NLRP3 inflammasome. Research indicates that ions also play a role in catalyzing NLRP3 activation. Initially, the dilution of potassium ions initiates the process, which subsequently triggers the influx of calcium, chloride and sodium ions (23). The release of K ions is caused by the external release of either ATP or N-arachidonylethanolamine by macrophages monocytes; K ions also represent one specific upstream requirement for NLRP3 activation, while other studies center on the decrease of K itself as one step necessary for caspase-1 activation (24).

It has been demonstrated that calcium ions (Ca<sup>2+</sup>) activate the NLRP3 bodies via DAMPs (25,26). The activation of receptor 2 + [(Ca<sup>2+</sup>)ex] through elevated levels of extracellular calcium initiates a proinflammatory reaction resulting from the assembly of the NLRP3 inflammasome the secretion of IL-1 $\beta$ . The fundamental processes involve the macropinocytosis of calponin granules (CPP), triggered in a [Ca<sup>2+</sup>]ex-CaSR-dependent way, leading to a significant release of IL-1 $\beta$  (27).

In order to activate the NLRP3 inflammasome, the chloride intracellular channel (CLIC) functions as a downstream cascade of the potassium efflux-mitochondrial ROS axis. Potassium efflux, triggered by NLRP3 agonists, results in mitochondrial damage the production of ROS. Subsequently, ROS produced by mitochondria propel CLIC to the plasma membrane, where they trigger chloride efflux, thereby reinforcing the binding of NEK7 NLRP3. The development of

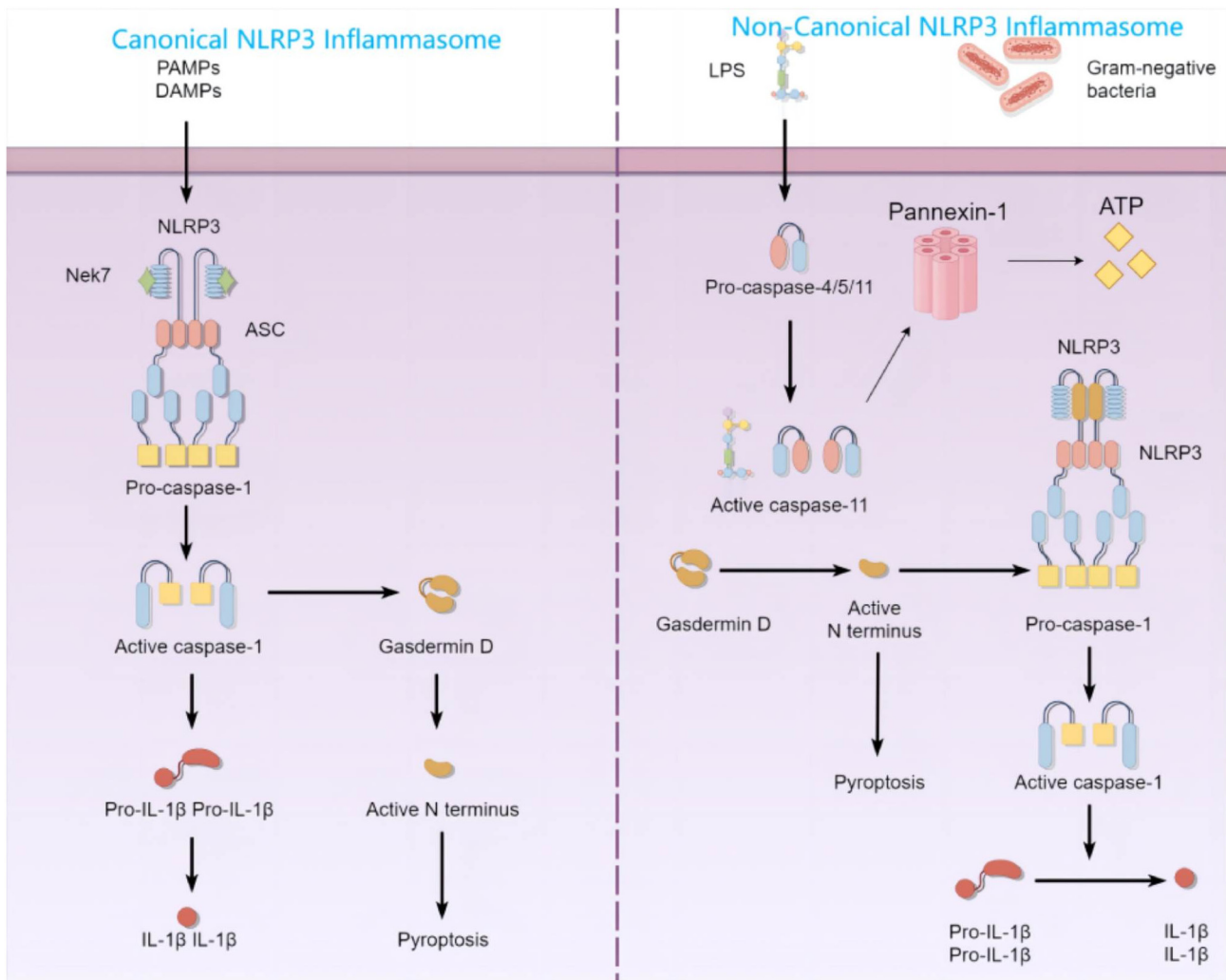


Figure 3. Non-canonical and canonical NLRP3 inflammasome. NLRP3, nucleotide-binding domain leucine-rich repeat protein 3; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; Nek7, NIMA-related kinase 7; ASC, apoptosis-associated speck-like protein containing a CARD; LPS, lipopolysaccharide; ATP, adenosine triphosphate.

inflammasomes, activation of caspase-1, release of IL-1 $\beta$  are all facilitated by this connection (28).

**Lysosomal damage.** Research shows that multiple particulate materials can activate the NLRP3 inflammasome. Substances such as uric acid, cholesterol crystals, alum, silica and asbestos are among them. These particulates induce lysosomal rupture, resulting in the release of histones into the cytoplasm (17,29,30). Hornung *et al* (28) have verified that the NLRP3 inflammasome can be activated by Leu-Leu-O-methyl ester lysosomal disruption. However, the precise relationship between NLRP3 inflammasome activation and lysosomal destabilization remains elusive. Further research is needed to gain a more comprehensive understanding of the mechanisms by which lysosomal damage connects plasma membrane dysfunction to NLRP3 inflammasome signaling pathways.

**Non-classical NLRP3 inflammasome pathway.** Pyroptosis represents a specific form of programmed cell death that is triggered when caspase-11/4/5 cleaves Gasdermin (GSDM). Simultaneously, caspase-11 activation influences pannexin-1 activity, promoting ATP release and potassium efflux. These

processes collectively drive NLRP3 inflammasome assembly, leading to IL-1 $\beta$  secretion and highlighting the complexity of these interconnected pathways (31,32). This non-canonical inflammasome mechanism specifically targets pathogens that evade TLR4 detection. In humans, it activates caspase-4 and -5, while in mice, it activates caspase-11. Markedly, this mechanism operates independently of caspase-1 activation.

**Alternative pathways.** Researchers have also identified an alternative pathway, where monocytes do not require a secondary response to activate pannexin-1 to mature and secrete IL-1 $\beta$ , only hand-interacting serine or threonine protein kinase 1 to activate and, unlike K ion efflux, does not need to induce apoptosis (33).

### 3. IBD pathogenesis

The gut is lined by a single layer of epithelial cells and contains mucus cells, including goblet cells. These components together form the first line of defense in the gut. The intestinal tract features villi structured into intricate, folded projections, with their surfaces densely lined by microvilli. This layered

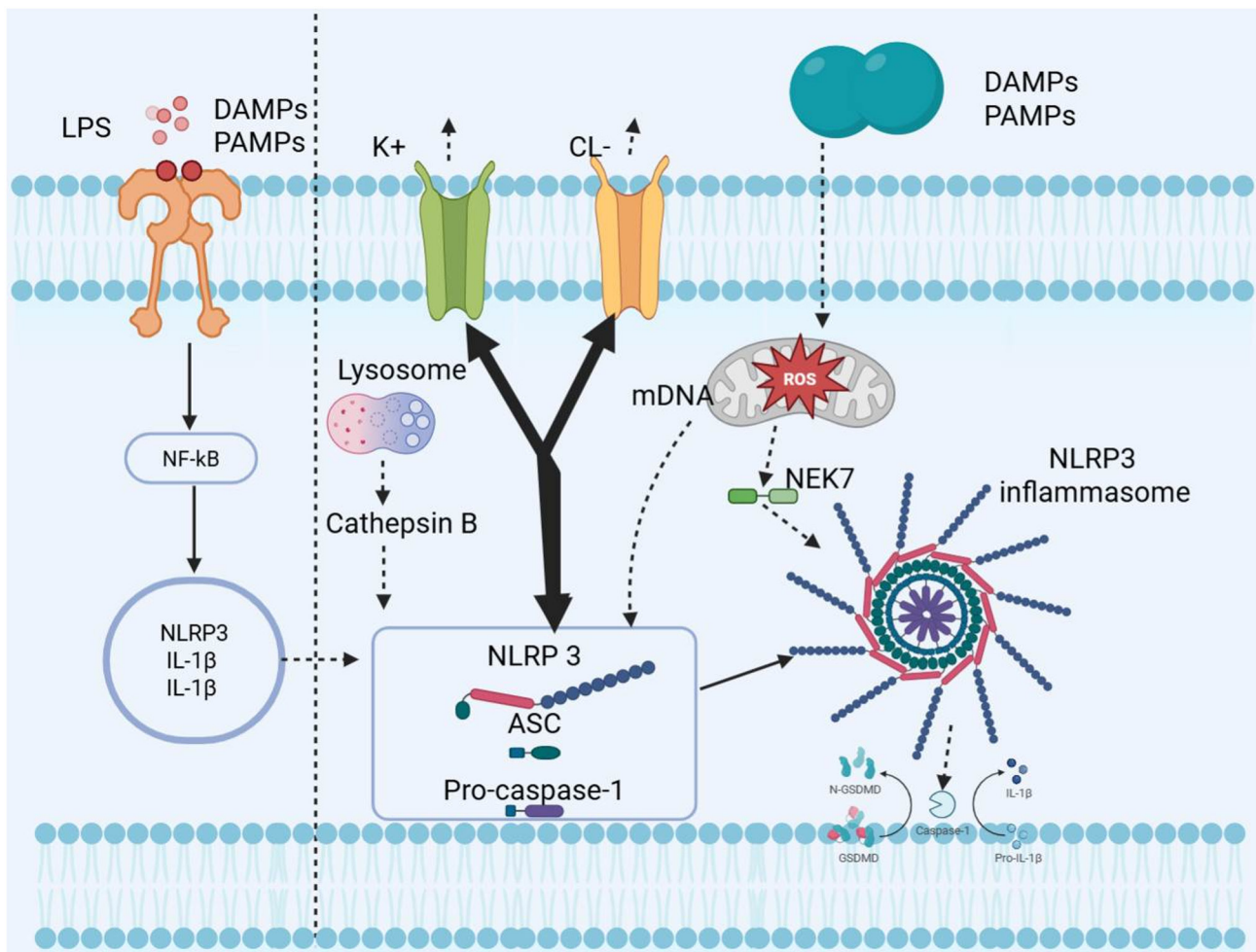


Figure 4. Alternative activation pathways. NLRP3, nucleotide-binding domain leucine-rich repeat protein 3; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; Nek7, NIMA-related kinase 7; ASC, apoptosis-associated speck-like protein containing a CARD; LPS, lipopolysaccharide; ATP, adenosine triphosphate; NF- $\kappa$ B, nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells; ROS, reactive oxygen species; N-GSDMD, N-terminal domain of GSDMD; GSDMD, Gasdermin D.

architecture markedly increases the intestinal surface area, optimizing nutrient absorption efficiency. However, this intricate structure is accompanied by an increased risk of exposure to potential threats, such as erosive digestive enzymes and harmful microorganisms. In the gut, Pan's cells and secretory epithelial cells are central to the defense mechanisms, especially within the small intestine, notably the ileal region. These cells produce antimicrobial substances, such as defensins, which serve to establish a robust chemical barrier for the gut. The health of the intestines can be maintained due to the rapid renewal of epithelial cells, the integrity of the intestinal barrier, the continuous replacement of damaged cells and the direct protective function of Pan's cells (34). IBD may be associated with the presence of pathogens and microbes in the mucosal system (35). Genetic, environmental, immunological and microbial variables are all thought to contribute to the development of IBD. However, the precise mechanisms underlying the initiation of this condition remain elusive.

**Genetic factors.** A plethora of investigations have established an association between the development of IBD and genetic susceptibility, with IBD itself emerging as a significant risk factor for the onset of celiac disease or UC. This further

underscores the intricate interplay between genetic factors and the manifestation of diseases. A genome-wide analysis of two consecutive, independent family cohorts using a nonparametric two-point sibling-pair linkage approach detected a posterior locus on chromosome 16 in families with multiple CD cases, using a transmission imbalance test and case-control study, Ogura *et al* (36) located the gene on chromosome 16 IBD 1, confirming a NOD 2 relationship to CD. The authors also demonstrated innate immune responses between bacterial components and the disease development (36). Moreover, one of the major genetic risk factors for CD is the NOD 2 polymorphism. However, it should be noted that the majority of NOD 2 gene mutations have been identified in Western populations and the major mutation site associated with IBD has not been identified in Asian populations. Nayar *et al* (37) found that loss of NOD 2 resulted in dysregulation of homeostasis in activated fibroblasts and macrophages and also predisposed to the production of tumor factors. Subsequent studies have identified 163 genetic points, with Liu *et al* (38) subsequently detecting 38 novel points and expanding them to 200. However, these variants merely account for a small proportion of the heritability of IBD (~26 vs. ~19% for UC) (39,40). IBD has been found to have a common genetic point in a number

of diseases (41,42). Indeed, the heterogeneity present within study populations, encompassing patients with varying lesion locations and disease statuses (active vs. remitting), poses challenges in elucidating the full extent of genetic influence. In order to enhance the comprehension of the impact of genetic information, researchers must conduct a more thorough investigation into the specific biological functions of genetic variants and the pathways they modulate. This necessitates incorporating rarer genetic variations epigenetic modifications, as well as focusing on larger, cell- or tissue-specific and disease-state-specific cohorts. In addition, efforts should be focused on formulating novel therapeutic approaches grounded in these understandings (43).

*Environmental factors.* Several areas, including North America, Europe and a few countries such as Israel and Australia, have witnessed significant increases in the prevalence of IBD since the beginning of the twentieth century (44). The Asia-Pacific region has seen a significant rise in UC cases and a slight decline in CD cases, according to recent statistics (45). According to the Swiss IBD cohort research, several Western nations, such as Switzerland, are experiencing an overall rise in the incidence of IBD (46). Despite the paucity of disease data in developing countries, there is an observed increase in prevalence over time. However, the occurrence of IBD coincides with the rise of other diseases, suggesting that genetic factors alone do not fully account for this increase. Conversely, environmental factors are hypothesized to exert a substantial influence on the onset of enteritis. The 'exposure group' was initially added after the genetic factor in the Christopher Paul Wild study (47), which identified the environmental factor leading to IBD. In addition to geographical and developmental disparities, numerous other factors have been identified as contributing to this phenomenon (48). Air pollution, for instance, has emerged as a pervasive environmental concern, particularly in Asian countries in recent years. Ananthakrishnan *et al* (49) identified a positive relationship between pollutant discharge and the hospitalization rate of patients with IBD. Diet holds considerable importance in the management of IBD, with studies demonstrating a correlation between linoleic acid intake and an elevated risk of UC onset (50,51). A substantial amount of research evidence indicates that insulin resistance is likely to develop in the context of high sugar intake and excessive consumption of carbohydrates. Consequently, persistent inflammation may develop. For example, research has revealed that following excessive sugar consumption, prevalence of IBD in adolescent is much higher (52). D'Souza *et al* (53) found that the risk of acquiring CD was higher in individuals whose diets were heavy in meat, fatty foods and sweets. By contrast, research revealed that the disease risk was lower in those whose diets included more grains, fruits, vegetables and fish. These results suggest that particular food choices may influence the onset of CD, with unhealthy meals posing a risk factor and healthier options providing protection (54). This may further alter the make-up of gut bacteria, thereby in turn increasing the likelihood of IBD, according to the former study. A positive correlation between antibiotic use and UC was confirmed in the study by Alperen *et al* (55). In a population-based cohort study of a foreign cohort, Kronman *et al* (56) found that exposure

to antibiotics during childhood led to an increased risk of developing IBD, with a higher risk associated with greater antibiotic usage. In a separate study, Narula *et al* (57) observed that the women using oral contraceptives had a markedly elevated risk of developing IBD compared with non-users. Cornish *et al* (58) conducted an extensive literature search that ultimately uncovered a total of 75,815 cases. Researchers identified estrogen, a component of oral contraceptives, as a potential risk factor for IBD and the authors linked the two conditions. In addition to these etiologies, lifestyle habits were considered to represent a further environmental factor. A study demonstrated that smoking increased the surgical risk of CD, with most of the risk applicable only to smokers not taking immunosuppressive drugs (59). A paradoxical relationship between smoking and IBD subtypes has been identified by various researchers. Contrary to expectations, it seems that smoking actually decreases the likelihood of developing UC, even if it has been associated with an increased risk of CD. In addition, preliminary evidence suggests that nicotine may offer certain benefits to individuals suffering from UC (60,61).

*Immune factors.* Despite the intricacies inherent to the etiology of IBD, a combination of genetic and environmental factors has been observed to contribute to its development. Furthermore, the intestinal immune system has been demonstrated to trigger responses to both microorganisms and pathogenic agents within the human body (62). The immune system is categorized into two distinct branches: Innate immunity and adaptive immunity, each fulfilling a unique role in protecting the body. Due to immune system dysfunction, the intestinal mucosa sustains damage, enabling microorganisms to penetrate the epithelial barrier (63). Generally speaking, the occurrence of IBD from innate immune system disorder extends to adaptive immune response, causing chronic inflammation (64). In such cases, the TH0 cells are activated and the immune response is initiated. TH0 cells undergo differentiation, with IL-12 and IL-18 guiding their development into Th1 cells, while IL-4 facilitates their transformation into Th2 cells. However, in the context of CD, the Th1 response interacts with the Th17 response, leading to Tc cell activation and significant release of IFN- $\gamma$  and IL-17. By contrast, during UC, the immune response is primarily driven by Th2 cells and marked by the secretion of IL-4, IL-5, IL-13 and IL-23. Of particular note are the elevated levels of IL-5 and IL-13, which are specifically augmented from IL-17 and IL-22. This is further compounded by the release of IL-17 and IL-22, thus underscoring the multifaceted nature of immune system disorders and inflammatory immune responses. As evidenced by the substantial body of literature on the subject, these responses not only trigger the recruitment of B cells and T cells but also exacerbate inflammatory responses (65).

*Microbiosis.* The human gut microbiota plays a pivotal role in human physiology and is intricately linked to numerous health conditions, notably the development of UC and CD, both exhibiting strong associations with the composition and functionality of intestinal microorganisms. Analysis of microbial communities in individuals with IBD demonstrates notable differences compared with healthy subjects. These alterations are characterized by elevated levels of Proteobacteria and

*Escherichia coli*, alongside reduced populations of Firmicutes and beneficial eubacteria (66). In a healthy state, the gut microbiota functions as a vital regulatory system, contributing to various physiological processes. These include the breakdown of complex carbohydrates through fermentation, generation of short-chain fatty acids (SCFAs), biosynthesis of essential vitamins, energy metabolism, maintenance of intestinal epithelial barrier function and protection against harmful pathogens (67). In the context of IBD, bile acids, a by-product of cholesterol decomposition, have been demonstrated to facilitate the absorption and dissolution of nutrients but also to regulate intestinal microbiota. Through these functions, they contribute to the mitigation of metabolic and inflammatory disorders.

Li *et al* (68) found that suppressing parenteral *Weillia* markedly reduced protein expression levels and the amount of damage to colon tissue. IBD issues such as UC and CD are driven by gut bacteria and this discovery added to that evidence. In the induced enteritis model employed, animals developed sterile conditions only under conventional settings (69). This was not the situation when dextran sodium sulphate (DSS) was used (70).

#### 4. Role of NLRP3 signaling in normal bowel function, IBD and IBD complications

The role of NLRP3 in the normal intestinal function. Research on numerous human diseases and cancers has centered on the NLRP3 inflammasome due to its pivotal role in the pathogenesis of these conditions. In the gut, there is a high-level antigen (LPS) that causes a low-level inflammation. Intestinal homeostasis and host defense against microbial infections depend on a delicate equilibrium between the immune system and the microbiota. According to Singh *et al* (71), inflammatory disorders bowel cancer can develop when these mechanisms are disrupted. Considering the involvement of the NLRP3 inflammasome in the progression of inflammation-related colorectal cancer, a trial of colitis showed that the medicine had a preventive effect. Comprising EGCs, IECs and immune cells, this cell group probably plays a crucial role in the intestinal mucosal inflammatory response. These cells form a complex regulatory network with NLRP3 inflammasomes, collectively contributing to intestinal barrier maintenance, immune homeostasis and neuro-immune communication (72). In microbial regulation, NLRP3 shows a unique 'two-way regulation' ability. On the one hand, it recognizes pathogen-associated molecular patterns and induces IL-1 $\beta$ /IL-18 maturation through activation of caspase-1 to effectively eliminate invading pathogenic microorganisms, such as *Salmonella*; on the other hand, moderate NLRP3 activation promotes the differentiation of regulatory T-cells and maintains immune tolerance to commensal flora. This fine balance is of utmost importance for gut flora homeostasis. Notably, NLRP3 deficiency leads to overproliferation of pathogenic Enterobacteriaceae and a decrease in the number of commensal *Lactobacillus* (73).

NLRP3 is one of the major components of intestinal homeostasis. It regulates the delicate balance of gastrointestinal ecology through a multilayered activation signal that promotes ample recruitment of immune cells to the intestines

to effectively neutralize environmental toxicants and threats from bacteria. The realization of its function mainly relies on a multi-level molecular mechanism: initially, the NLRP3-IL-18 axis works jointly to construct a solid physical-chemical barrier by enhancing the expression of intestinal epithelial cell tight junction proteins (such as ZO-1 and Occludin) and promoting the secretion of the mucin MUC2 by cuprocytes. It has been shown that NLRP3 knockout mice develop thinning of the mucus layer and increased intestinal permeability, revealing its fundamental role in barrier maintenance. Considerable research has uncovered the central role of innate immunity in providing stability among gut mucosa. Thus, clarifying the regulatory mechanism of aberrant innate immune responses to the gastrointestinal tract is important for understanding the etiology of IBD. Likewise, recent clinical investigations have demonstrated upregulation of the proinflammatory cytokine IL-1 $\beta$ , secreted by colon tissues and macrophages of IBD patients, with increased amounts of IL-1 $\beta$  correlating with disease severity, further underlining its role in the disease process (74).

Metabolic regulation constitutes another important functional dimension of NLRP3. SCFAs, especially butyrate, can regulate the activation threshold of NLRP3 through the inhibition of histone deacetylase (HDAC), resulting in a positive feedback loop of 'microbe-metabolism-immunity'. In a mouse model fed a high-fibre diet, this synergistic effect was manifested by an increase in NLRP3-mediated IL-18 secretion, which in turn promoted intestinal stem cell proliferation and tissue repair (75).

*Role of NLRP3 in IBD.* IBD is a complex chronic inflammatory disease of the intestinal tract, which features a pathogenesis closely related to the abnormal activation of the innate immune system. In recent years, the dual role of NLRP3 inflammatory vesicles in the development of IBD has received increasing attention. It has been shown that NLRP3 causes intestinal inflammation and can be reparative to the mucosa, a seemingly contradictory property that renders it an important target for IBD therapy (76).

In pathological states, hyperactivation of NLRP3 drives the inflammatory process in IBD. Pathogenic microorganisms or injury-associated molecular patterns in the gut can persistently activate NLRP3 inflammatory vesicles, leading to caspase-1-dependent cellular pyroptosis and the release of large amounts of IL-1 $\beta$  and IL-18. These inflammatory factors disrupt intestinal epithelial tight junctions, while promoting Th17 cell differentiation and amplifying the inflammatory response. Clinical observation shows that the expression of NLRP3 in the inflamed intestinal segments of IBD patients is markedly elevated and positively correlates with the disease activity (77).

However, NLRP3 plays a protective role in the physiologic state. Moderate NLRP3 activation promotes intestinal epithelial repair and maintains intestinal barrier integrity via IL-18. Experiments in NLRP3-deficient mice have shown dysregulation of their intestinal flora, with an overproliferation of pathogenic bacteria and a decrease in protective commensal bacteria. In addition, bacterial metabolites such as SCFAs can maintain intestinal immune homeostasis by modulating the NLRP3 activation threshold (78).

The pathogenesis of IBD may be related to the dysregulation or altered species of the gut microbial population composition. A colon bacteria analysis study was performed on NLRP3-/-mice and wild-type mice by Li *et al* (79). The study showed that the increased bacteria in the colon of NLRP3-/-mice belonged to *Bacillus thuringiensis*, including different *Clostridium* and rod bacteria (80). In this study, a murine model was employed to monitor the changes in the microbiome and analyze the complex crosstalk between the NLRP3 inflammasome and the gut microbiota. The results obtained demonstrated that an overactive NLRP3 inflammasome could lead to local IL-1 $\beta$ , maintain intestinal homeostasis and, by restructuring the gut microbiota, produce strong resistance to experimental colitis. The microbiota could induce regulatory T cells and enhance the anti-inflammatory ability.

Based on the dual role of NLRP3, current therapeutic strategies emphasize precise regulation over complete inhibition. Moreover, at present, there is also a small molecule inhibitor, MCC950, which can selectively block the overactivation of NLRP3 and demonstrate favorable therapeutic effects in animal models (81).

CD, as a type of IBD, is also a chronic, recurrent inflammatory disease. Apoptosis also exists in the intestinal mucosa of patients and is also dependent on caspase-1 and GSDM-mediated. During this process, the formation of pores and the swelling of cells release pro-inflammatory cytokines and immunogenic damage and the activation of the NLRP3 inflammasome contributes to the cleavage of GSDMD and participates in the occurrence of apoptosis (82). Activation of NLRP3 inflammatory vesicles is expected to contribute to the cleavage of GSDMD and participate in apoptosis. On the one hand, NLRP3 inflammatory vesicles are highly expressed in the pathological state of CD; on the other, the absence of NLRP3 tends to exacerbate the pathologic manifestations of CD (83). Concurrently, the pathogenesis of UC also involves apoptosis. The upregulation of NF- $\kappa$ B by cysteine-3 production affects the generation of NLRP3 inflammatory vesicles, promotes apoptosis and damages the intestinal mucosa. Among the diverse variety of inflammasomes currently known, NLRP3 can trigger the activation of multiple inflammatory cytokines and IBD serves as a notable example of its significance. UC has a strong relationship with CD, which closely resembles the pathogenesis of IBD (84).

## 5. NLRP3 activator used to inhibit IBD

In clinical practice, IBD management involves utilizing several synthetic medicines. Recently, the possibility of natural substances being incorporated into treatment programs of inflammatory bowel disease has seen a surge in research efforts. Multiple natural compounds and extracts have demonstrated remarkable efficacy in inhibiting the NLRP3 signaling system for IBD. Natural compounds, compared with drugs, have multi-targeted regulation, comprehensive improvement of intestinal inflammation and can regulate intestinal flora, restore micro-ecological balance, high safety, fewer side effects and the ability to have a mitigating capacity of intestinal fibrosis and the cost to patients reduces the pressure on the cost of treatment. Several natural compounds and extracts have emerged as promising candidates for acting as

inhibitors of the NLRP3 signaling pathway in the treatment of IBD. The present review critically assessed the mechanistic basis of different chemical synthesis inhibitors of NLRP3 signal transduction-inhibiting natural monomers, extracts and composite formulations, offering a comprehensive overview of this route for therapeutic exploration (Table I).

The identification of NLRP3 has presented novel possibilities for investigating treatment options for IBD, including UC and CD, as well as other inflammatory and autoimmune disorders. Ongoing studies are investigating the potential of targeting NLRP3 and its related pathways as a treatment strategy for managing these conditions. NLRP3 inhibitors represent a promising therapeutic approach by specifically targeting the NLRP3 protein, which is involved in the inflammatory response mediated by the NLRP3 inflammasome. Conversely, NLRP3 downstream inhibitors are designed to inhibit the inflammatory cascade following the occurrence of NLRP3 activation (85). Disease- or condition-specific factors dictate the selection and acceptance of these inhibitors. When the NLRP3 inflammasome is directly responsible for starting the inflammatory response, blocking its activation becomes a possible more effective treatment option. Conversely, specific downstream inhibitors can be highly effective in treating diseases that originate from a specific downstream pathway. Researchers have found a plethora of strategies and methods for treating NLRP3 inflammasome-induced IBD. Polysaccharides, saponins, terpenoids, flavonoids and polyphenols are all examples of such agents (86,87). A study conducted by Dharmapuri *et al* (88) proved the efficacy of mangiferin, a COX-2 inhibitor derived from pueraria tuber, in the management of IBD and colon cancer. The levels of several proinflammatory indicators, such as COX-2, IL-1  $\beta$ , TNF- $\alpha$ , INF- $\gamma$ , IL-6, NLRP3 and caspase-1, rose in a manner dependent on the dosage.

**Polyphenols.** When polyphenols interact with NLRP3, they trigger the activation of NF- $\kappa$ B and the transcription of both NLRP3 and Pro-IL-1 $\beta$  components. Furthermore, pineapple phenolic compounds (PLPs) can inhibit both the activation of NF- $\kappa$ B and the production of pro-inflammatory molecules. Chen *et al* (89) showed that PLPs considerably decreased inflammation by blocking NF- $\kappa$ B activation and the release of pro-inflammatory proteins in a mouse model of DSS-induced enteritis. Furthermore, PLPs have been demonstrated to prevent DSS-induced acute colitis by maintaining epithelial integrity. Marinho *et al* (90) employed DSS to induce UC in mice and observed that the administration of nutrient sugar coated with rosmarinic acid (RA) had a detrimental effect on the mice. The results of this study demonstrated that these RA nano-vesicles could reduce inflammation and oxidative stress by regulating the NLRP3 inflammasome and reconstructing the Nrf2/HO-1 signaling pathway, thus protecting the colonic mucosa from DSS-induced damage.

**Flavonoid compounds.** Zhang *et al* (91) reported that in LPS-induced enteritis animals, the administration of quercetin markedly decreased the expression levels of TLR4, NLRP3, caspase-1, GSDMD, IL-1 $\beta$ , IL-18, IL-6 and TNF $\alpha$ . The results of this study indicated that quercetin might reduce inflammation and pyroptosis caused by LPS

Table I. Novel targets agents for the NLRP3 inflammasome in inflammatory bowel disease.

| Class               | Natural products         | Experimental prototype                             | Effective dose                           | Related phenotypes                                                                                                                          | Signal channel              | (Refs.) |
|---------------------|--------------------------|----------------------------------------------------|------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|---------|
| Organic compound    | Sulforaphane             | Mice induced by DSS                                | 25/50 mg/kg                              | ROS, MLCK, IL-6, TNF- $\alpha$ , MPO, INF- $\gamma$ , iNOS, p-NF- $\kappa$ B-p65, colon length, occludin1 $\downarrow$                      | NLRP3 pathway               | (87)    |
| Alkaloid            | Penophyine sulfasalazine | Mice induced by DSS                                | 10/20/40 mg/kg                           | NO, MPO, ICAM-1, VCAM-1, NF- $\alpha$ , IL-1, IL-1 $\beta$ , IL-6, IL-10, IL-17, IL-18, PAF, COX-2, PGE 2, iNOS, NF- $\kappa$ B, HO-1, Nrf2 | HO-1/Nrf2                   | (86)    |
| Phenols             | Pineapple leaf phenol    | Mice induced by DSS                                | 200 mg/kg                                | Colon length was for IL-1 $\beta$ , p65, IL-1 $\beta$ , IL-6, TNF- $\alpha$ $\downarrow$                                                    | NF- $\kappa$ B              | (89)    |
|                     | Roseminic acid           | Mice induced by DSS                                | 20 mg/kg                                 | NLRP3, ASC, caspase-1, IL-1 $\beta$ $\downarrow$ Nrf2, HO-1 $\uparrow$                                                                      | NLRP3                       | (90)    |
| Flavonoid compounds | Meletin                  | Rat intestinal microvascular endothelial cells     | 20 $\mu$ M mistletoe                     | TLR 4, NLRP3, caspase-1, gasdermin D, IL-1 $\beta$ , IL-18, IL-6 $\downarrow$                                                               | TLR4/ NF- $\kappa$ B/ NLRP3 | (91)    |
|                     | Naringenin               | NEC mice induced by hypoxic cold stimulation + LPS | 5, 20 mg/kg                              | Relative expression levels of mRNA protein, including TNF- $\alpha$ , IL-6, IL-1 $\beta$ , IL-18 NLRP3, ASC, Caspase-1                      | NLRP3                       | (92)    |
|                     | Campherol (Kae)          | Mice induced by DSS                                | At 50 mg/kg                              | ZO-1, closed protein claudin-1, IL-1 $\beta$ , IL-6 TNF- $\alpha$ , NLRP3, caspase-1 TLR4- NF- $\kappa$ B signaling                         | LPS-TLR4- NF- $\kappa$ B    | (93)    |
|                     | Erythrocyte flavonoids   | Mice induced by DSS                                | 12.5, 25, 50 mg/kg; 12.5, 25, 50 $\mu$ M | IL-1 $\beta$ , IL-18, NLRP3, caspase-1 TXNIP                                                                                                | NF- $\kappa$ B              | (94)    |
| Saponin             | Ginsenoside Rd           | In UC mice induced by DSS                          | 10, 20, 40 mg/kg; 5, 10, 20 microns      | IL-1 $\beta$ , IL-6, NLRP3. Caspase-1, ASC; P6, TNF- $\alpha$ $\downarrow$                                                                  | AMPK- ULK1-p62              | (104)   |
| Polysaccharide      | Astragalan               | In UC mice induced by DSS                          | 100 200 mg/kg                            | NLRP3, ASC, Caspase-1; IL-1 $\beta$ , IL-18                                                                                                 | NLRP3                       | (106)   |

NLRP3, nucleotide-binding domain leucine-rich repeat protein 3; DSS, dextran sulfate sodium; UC, ulcerative colitis; ROS, reactive oxygen species; MLCK, myosin light chain kinase; MPO, myeloperoxidase; iNOS, inducible NO synthase; NO, nitric oxide; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; Nrf2, nuclear factor erythroid 2-related factor 2; ASC, apoptosis-associated speck-like protein containing a CARD; HO-1, heme oxygenase-1; TLR4, toll-like receptor 4; NEC, necrotizing enterocolitis; Kae, Kaempferol; ZO-1, zonula occludens-1; TXNIP, thioredoxin-interacting protein.

through the TLR4/NF- $\kappa$ B/NLRP3 pathway. It has also been shown that patients with necrotizing enterocolitis have a markedly increased risk of IBD and that mechanistically; both share common features such as hyperactivation of the TLR4 signaling pathway, disturbances in the intestinal flora (such as increased *Aspergillus phylum*) and SCFAs deficiency. Tian *et al* (92) established an NEC mouse model using hypoxic cold stimulation and intraperitoneal injection of LPS and the treatment group was administered different doses of naringenin for three days. The results were then compared with those of the NEC group. The NEC symptoms were found to be reduced in the mice in the H-NAR group and a significant increase in body weight and intestinal histopathological score was observed. The expression levels of the intestinal tissue inflammatory factors TNF- $\alpha$ , IL-6, IL-1 $\beta$  and IL-18 and the expression levels of mRNA and protein such as NLRP3, ASC and caspase-1 were all markedly reduced. Naringenin inhibited NLRP3 inflammasome activation while reducing the level of the inflammatory response in the intestinal tissue. In a separate study, Qu *et al* (93) treated mice with DSS solution-induced inflammatory bowel disease using kaempferol (Kae). The authors discovered that Kae attenuated DSS-induced colitis and the associated proinflammatory response. It also restored the diversity of the intestinal microbiota and suppressed the LPS-TLR4-NF- $\kappa$ B signaling pathway. *In vitro*, Kae activated LPS-induced TLR 4 to NF- $\kappa$ B. Red pigment is a substance extracted from *Scutellaria baicalensis*. Liu *et al* (94) employed DSS to establish a colitis model and intervened with red pigment. The results demonstrated that the red pigment markedly reduced the colon's length and the white harness diminished the white cell count, thereby hindering the pathological changes in colon tissue and the infiltration of macrophages (95). Sergeant *et al* (95) conducted experiments using flavonoids in an *in vitro* model of the human intestinal epithelium. In inflamed cells, the number of inflammatory factors was reduced to 50% of the control, while the corresponding mRNAs were not suppressed, confirming the possibility of down-regulating inflammation in intestinal epithelial cells.

Another flavonol, baicalein, isolated from the Chinese medicinal plant *Scutellaria baicalensis*, has also been demonstrated to reduce the activity of myeloperoxidase (MPO) and the expression of pro-inflammatory mediators, effectively alleviating the severity of colitis (96,97).

**Sosaponin.** Saponins may have a crucial function in the context of inflammation in the intestines due to their strong anti-inflammatory characteristics (98). Ginsenosides represent the primary active ingredient in ginseng (99) and can be categorized into the following classes: Ginsenoside-Rb1 (G-Rb1) (100), G-Rb2 inhibiting the production of TNF- $\alpha$  (101) and G-Rd exhibiting significant neuroprotective properties, similar to those observed in G-Rb2. The three compounds have demonstrated the capacity to suppress LPS-induced NF- $\kappa$ B activation and reduce TNF- $\alpha$  production in N9 microglial cells (102). The anti-inflammatory characteristics of G-Re are attributed to its ability to interfere with the binding of LPS to TLR4 receptors on macrophage surfaces. Research indicates that G-Re effectively prevents LPS-induced phosphorylation

and subsequent degradation of IRAK-1, consequently inhibiting IKK- $\alpha$  phosphorylation, NF- $\kappa$ B activation and the production of inflammatory mediators such as TNF- $\alpha$  and IL-1 $\beta$  (103).

Another important compound (104), ginsenoside Rg5 (G-Rg5), has been found to effectively reduce the expression of inflammatory markers including IL-1 $\beta$ , TNF- $\alpha$ , COX-2 and inducible nitric oxide synthase. Concurrently, it also suppresses the phosphorylation of key signaling molecules IRAK-1, IKK- $\alpha$  and NF- $\kappa$ B. Notably, ginsenoside Rh1 (G-Rh1), Rh2 and their metabolites produced by gut bacteria also play significant roles in these anti-inflammatory mechanisms. The anti-inflammatory effects of G-Rp1 are primarily achieved by regulating the NF- $\kappa$ B activity in both microglial cells and astrocytes, which leads to reduced inflammatory responses. In a separate study involving DSS-induced colitis models, Liu *et al* (104) demonstrated that G-Rd could alleviate intestinal inflammation in mice through NLRP3-dependent mitophagy pathways.

**Polysaccharides.** Polysaccharides are highly favorable substances. Composed of numerous monosaccharide molecules linked by glycosidic bonds, they are present in substantial amounts in the cell walls of plants, animals and microorganisms. Noted for their excellent safety profiles and low toxicity, polysaccharides can exert significant effects on the human body. Insulin resistance, blood sugar and cholesterol can be regulated by polysaccharides in the human body (105). Tian *et al* (106) found that APS further reduced the expression of NLRP3, caspase-1 and ASC in colonic tissues, thereby inhibiting NLRP3 activation. This action led to a decrease in IL-18 IL-1 $\beta$  levels, subsequently alleviating the colonic inflammation caused by DSS. In a DSS mouse experiment conducted by Dai *et al* (107), *Meconopsis polysaccharides* were employed to treat UC in mice through the PI3K/AKT signaling pathway. The results showed that compared with the control group, the Disease Activity Index (DAI) decreased markedly and the shortening of the colonic length in mice was alleviated. Additionally, the expression levels of PI3K and AKT were markedly decreased and the levels of inflammatory factors also decreased markedly. Specifically, the levels of IL-6, IL-1 $\beta$  and TNF- $\alpha$  were markedly lower than those in the model group. The levels of IL-6, IL-1 $\beta$  and TNF- $\alpha$  were markedly reduced compared with the control group. Additionally, regarding the intestinal flora results, this treatment could effectively promote the growth of beneficial bacteria and regulate the concentration of bile acids. As such, it represents a novel therapeutic method for the treatment of IBD.

**Terpenoids.** Terpenoids have the general formula (C<sub>5</sub>H<sub>8</sub>)<sub>n</sub> and are oxygen-containing compounds with different levels of saturation (108,109). These compounds can be conceived as a group of natural substances united by diverse arrangements of isoprene or isopentane units. Terpenoids are ubiquitous in nature. They occupy a prominent place in Chinese herbal medicine as crucial therapeutic agents. Traditional Chinese medicine extensively employs paeoniflorin as an anti-inflammatory agent. Peony total glucoside, or PF, has been shown in clinical trials to alleviate inflammatory diseases and inflammatory bowel symptoms (110).

**Intestinal microflora.** It has been shown that the microbiome of the intestines could be a target for treatments for IBD. Gut homeostasis stability is dependent on the mechanical, chemical, immune-related and microbial components of the gut barrier system. These interconnected components collectively contribute to intestinal health maintenance (111). Among these, the microbial component holds particular importance and warrants special attention. Extensive evidence supports the critical function of intestinal flora in modulating immune responses, metabolic processes and overall balance within the gut environment (112). In healthy individuals, the gastrointestinal tract is colonized by a diverse and abundant microbial community that exists in a state of homeostasis. Disruptions to this delicate microbial balance, however, can result in numerous pathological conditions, such as persistent diarrhea, IBD and colorectal malignancies. Such disturbances in gut flora involve alterations in both microbial population structure and metabolic activities, factors intimately connected with the initiation and progression of IBD (113). Luo *et al* (113) constructed an animal model that simulated the heat and humidity environment (DH) to delve into the effect of increased temperature and humidity on mice. Cytokines such as IFN- $\gamma$  and (IL)-4 were observed and the RNA transcriptome of intestinal tissues and the 16S rRNA gene in mouse faeces were both sequenced. According to the findings, NLRP3 was associated with IBD. Intestinal microbiota abundance data revealed that DH might enhance the inflammatory immune response by influencing the symbiotic relationship between the microflora and NLRP3 (114). Lin *et al* (78) identified *Alistipes shahii* in a study. It was considered a commensal bacterium in which strain As360 could alter cytokine release, especially the increase in IL10. It also led to a decrease in the expression of mammalian target proteins of rapamycin and Nlrp3 in mice and improved colitis in mice. In addition, Tang *et al* (115) found in an acute liver injury experiment that exercise conditioning and incorporation of betulinic acid markedly inhibited LPS plus ATP-induced release of LDH and IL-1 $\beta$ , while improving the inhibition of NLRP3 inflammatory vesicles in macrophages. In addition, betulinic acid effectively inhibited the activation of NLRP3 inflammatory vesicles in the liver of septic mice. Li *et al* (116) observed that the use of appropriate amounts of *Fusobacterium mucinophilum* could effectively inhibit NLRP3-mediated neuroinflammation in the hippocampus of mice for the treatment of cognitive impairment. Shen *et al* (117) compared DSS-induced IBD in mice with the *E. coli* group using *Peptostreptococcus anaerobius* in anaerobic *Aeromonas aeruginosa*. The authors found that colon shortening and splenomegaly were markedly greater in anaerobic *Aeromonas aeruginosa* compared with the *E. coli* group. The DAI scores were much higher than those in the *E. coli* group and the expression of inflammatory factors was promoted. This was a consequence of microbial dysbiosis. Regarding NLRP3 inflammasomes, it also demonstrated that the expression of microorganisms, which affected different types of flora within the intestinal microbiota, could have a bidirectional influence on. There is growing evidence that the gut flora can serve as a new target for the treatment of inflammatory bowel disease and various

inflammatory diseases, yet more research and exploration are needed in the future.

In China, Traditional Chinese Medicine (TCM) constitutes a long-standing medical system, rooted in distinctive theories and practices. Its holistic approach and evidence-based treatments, which are tailored to the patient's overall health status, are renowned features of this system. A significant aspect of TCM lies in its ability to address the various symptoms associated with IBD, including diarrhea, abdominal discomfort and rectal bleeding, thereby leading to substantial improvement (118,119).

Research has shown that TCM acupuncture can control oxidative stress, apoptosis, the microenvironment of tumors and microecological imbalance in the intestines, all of which are caused by inflammation. Moreover, several signal transduction pathways are involved, including NF- $\kappa$ B, STAT3, Wnt/ $\beta$ -catenin, HIF-1 $\alpha$  and Nrf2. Notably, Chinese herbal formulations hold promise as a potential approach for managing the transition from colitis to cancer. However, it is imperative to emphasize that thorough and comprehensive research remains essential to validate their effectiveness.

## 6. Conclusion

The present review focused on the potential of natural agents in treating IBD by targeting the NLRP3 signaling pathway, aiming to highlight the importance of the latter in treating IBD. The NLRP3 inflammasome markedly contributes to IBD pathogenesis due to its role in immunity. Therefore, from that perspective, the present review outlines the importance of the NLRP3 pathway in IBD treatment, emphasizing how its activation drives disease development and progression and the subsequent pathological consequences. The steadily growing number of individuals suffering from IBD poses a significant challenge as it gives rise to a heightened demand for effective treatment methodologies. The etiology of IBD is complex and ever-changing. However, it has been reported that inhibitors of the NLRP3 signaling pathways inflammatory pathway may effectively treat the disease. Thus, as awareness grows, natural compounds aimed at inhibiting the NLRP3 pathway are being increasingly employed to mitigate IBD. In addition, treatment of IBD with microorganisms regulating the NLRP3 pathway also offers significant promise. The advent of an era of natural small molecules or microorganisms acting through the NLRP3 pathway can usher in a more promising therapeutic future for IBD (118).

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## Authors' contributions

YG prepared and wrote the original manuscript and was responsible for oversight and project management. ZH, XL and SW prepared and wrote the original manuscript and were responsible for visualization. BY and XC prepared and wrote the original manuscript and were responsible for oversight, project management and access to funds. Data certification is not applicable. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

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## Competing interests

The authors declare that they have no competing interests.

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