REVIEW

Targeting NLRP3 Inflammasome in Inflammatory Bowel Disease: Putting out the Fire of Inflammation

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Abstract— Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine, comprised of ulcerative colitis and Crohn's disease. Among the complicated pathogenic factors of IBD, the overaction of inflammatory and immune reaction serves as an important factor. Inflammasome is a form of innate immunity as well as inflammation. Among all kinds of inflammasomes, the NOD-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome is the most studied one, and has been revealed to be involved in the pathogenesis and progression of IBD. Here, in this review, the association between the NLRP3 inflammasome and IBD will be discussed. Furthermore, several NLRP3 inflammasome inhibitors which have been demonstrated to be effective in the alleviation of IBD will be described in this review.

KEY WORDS: inflammatory bowel disease; NLRP3 inflammasome; ulcerative colitis; Crohn's disease; inflammation; autophagy.

INTRODUCTION

The intestinal tract is the largest organ for digesting food and absorbing nutrients isolated from the intestinal contents [1, 2]. During the processes of digesting and absorbing, the intestinal mucosal barrier, composed by mucosal barrier layer, intestinal epithelial cells, and other inflammatory and immune cells, acts as important components in the intestinal defense system, preventing the invasion of external pathogens [3–5]. However, under certain conditions, the inflammatory and immune responses in the gut are over-reacted, leading to the damage of the intestinal mucosal barrier and disturbance of intestinal bacterial homeostasis [6–9]. Consequently, such abnormalities in the gut may lead to the pathogenesis and progression of inflammatory bowel disease (IBD), recognized as a group of intestinal disorders with chronic and recurrent characteristics [10, 11]. IBD is composed of two members, namely ulcerative colitis and Crohn's disease. Among multiple pathogenic factors for IBD, the over-activation of intestinal inflammatory and immune reaction has been regarded as one of the vital causes in the onset and development of IBD [12–15]. As a result, suppressing the over-activated intestinal inflammation serves as an effective and promising strategy in the treatment of IBD. Inflammasome belongs to a component of innate immunity, which is also a form of inflammation, functioning in protecting organisms from the invasion of internal and external threatening factors [16–19]. Inflammasome has been reported to be associated with inflammation- and immune-related disorders in many systems, including myocardial infarction, atherosclerosis, IBD, diabetes, and autoimmune diseases [20–23]. As a result, targeting on the suppression of the over-activated

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self-defensive mechanisms might be effective in the treatment of such diseases. Among all kinds of inflammasomes, the NOD-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome is the most studied one; the biological characteristics and connection with diseases have been widely studied [24–27]. According to previous studies, inhibiting the activation of the NLRP3 inflammasome serves as an effective and potential therapy in the treatment of IBD [28, 29]. Here, in this review, we will discuss the association between the NLRP3 inflammasome and IBD, focusing on the introduction of the NLRP3 inflammasome as well as its roles in the pathogenesis and progression of IBD. Furthermore, several therapies for the treatment of IBD taking advantage of suppressing the NLRP3 inflammasome will also be discussed.
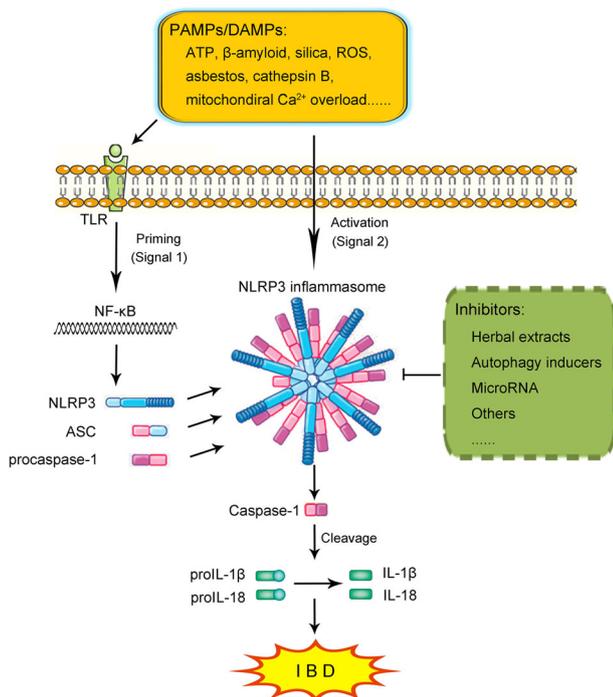
PART I: NLRP3 INFLAMMASOME

Biological Characteristics of the NLRP3 Inflammasome

Inflammasome, as a member of innate immunity, is a multi-protein oligomer responsible for the activation of inflammatory responses [30]. In the gut, inflammasome exists mainly in epithelial cells as well as subepithelial macrophages, dendritic cells, and other inflammatory and immune cells, which facilitates their recognition of pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) for the subsequent induction of adaptive immune responses [31–33]. So far, several kinds of inflammasomes have been described, including NLRP1, NLRP2, NLRP3, NLR family caspase recruitment domain-containing protein 4 (NLRC4), and double-stranded DNA sensors absent in melanoma 2 (AIM2) [34–36]. Among them, the NLRP3 inflammasome is the most characterized one, which has been considered to be important in the development of therapeutic strategies.

The NLRP3 inflammasome is a protein assembly, comprised of three components, including the NLRP3 protein, procaspase-1, and adapter protein apoptosis-associated speck-like protein (ASC) [37–39]. In normal condition, there is a connection between the NACHT domain and leucine-rich repeats (LRRs), preventing the formation of inflammasome *via* the inhibition of the interaction between the NLRP3 protein and ASC [40, 41]. Under the stimulation of PAMPs, danger-associated molecular patterns (DAMPs) as well as other exogenous invaders or environmental stress, the conformation of the NLRP3

protein is changed to facilitate the interaction between pyrin domains (PYDs) in the NLRP3 protein and ASC. After the interaction of the NLRP3 protein and ASC, another component of the NLRP3 inflammasome, procaspase-1, binds to ASC *via* CARD of procaspase-1 binding to the corresponding region of ASC, leading to the formation of the NLRP3 inflammasome. To further induce the activation of the NLRP3 inflammasome, the formation of the protein complex triggers the self-cleavage of procaspase-1, generating the active caspase-1 p10/p20 tetramer, leading to the maturation of proinflammatory cytokines including interleukin (IL)-1β and IL-18 *via* converting from their immature "pro" forms into active forms, inducing inflammatory and immune responses [42–45].

The activation of the NLRP3 inflammasome is widely regarded as a "two-step" process (illustrated in Fig. 1) [46–49]. Generally speaking, in the first step, various internal or external PAMPs or DAMPs are recognized by Toll-like receptors (TLRs), leading to the activation of the nuclear factor kappa B (NF-κB)-mediated signaling. The NF-κB-mediated signaling results in increasing transcription and production of inflammasome-related components including the NLRP3 protein, proIL-1β, and proIL-18, leading to the priming or initiation of the NLRP3 inflammasome activation. In the second step, the NLRP3 inflammasome activation is triggered by further stimuli, during which the NLRP3 protein is oligomerized, leading to the subsequent assembly of the NLRP3 protein, ASC, and procaspase-1 into a complex. The formation of the NLRP3 inflammasome induces the conversion of the mature of IL-1β and IL-18 from their "pro" forms to be secreted locally or systemically. Recently, an exciting study reported that it was the recruitment of NLRP3 to the dispersed trans-Golgi network but not the mitochondria that led to NLRP3 aggregation and activation in response to stimuli [50]. So far, several factors activating the NLRP3 inflammasome have been explored or used in study [51–55]. For the priming or initiation process of the NLRP3 inflammasome activation, lipopolysaccharide (LPS), a large molecule consisting of a lipid and a polysaccharide originally found in the outer membrane of Gram-negative bacteria, is widely regarded as a classic ligand for the activation of TLR4, thus triggering the first-step activation of the NLRP3 inflammasome [51]. For further activation of the NLRP3 inflammasome activation, various kinds of PAMPs or DAMPs have been described, including

Fig. 1. Schematic illustration of the signaling pathway of the NLRP3 inflammasome activation and association with IBD. In the challenge of P-AMPs and DAPMs, TLRs on the membrane is activated, followed by the triggering of NF-κB-mediated signaling, leading to the enhancement of the NLRP3 inflammasome components. Further stimuli including ATP, β-amyloid, silica, ROS, asbestos, cathepsin B, and overload of mitochondrial Ca^{2+} trigger the assembly of the NLRP3 inflammasome and formation of caspase-1, resulting in the cleavage of proIL-1β and proIL-18 into mature IL-1β and IL-18. The secretion of proinflammatory cytokines contributes to the pathogenesis and progression of IBD. So far, several kinds of agents have been proven to be effective in the alleviation of IBD targeting on the inhibition of the NLRP3 inflammasome activation, including herbal extracts, autophagy inducers, microRNA as well as other substances.

adenosine triphosphate (ATP), β-amyloid, silica, reactive oxygen species (ROS), asbestos, cathepsin B as well as other factors leading to the overload of mitochondrial Ca^{2+} [52–57].

Like other forms of inflammatory and immune responses, the NLRP3 inflammasome activation in a proper extent acts as a self-defensive mechanism, contributing to the prevention from the external pathogens invasion [58]. However, the over-activation of the NLRP3 inflammasome may trigger or aggravate the onset and development of various kinds of inflammation- and immune-related diseases [59–61]. Based on the previous studies related to the NLRP3 inflammasome, targeting on the inhibition of the NLRP3 inflammasome contributes greatly to the alleviation of disorders including myocardial

infarction, atherosclerosis, multiple sclerosis, stroke, and so on [62–65]. So far, many studies have focused on the study of the roles of the NLRP3 inflammasome in the pathogenesis and progression of IBD, making efforts to develop novel therapies taking advantage of targeting on inhibition of the NLRP3 inflammasome for the treatment of IBD [66–69]. In the following section of the review, the roles of the NLRP3 inflammasome in IBD, including ulcerative colitis and Crohn's disease, will be discussed in detail.

NLRP3 Inflammasome in Ulcerative Colitis

As mentioned previously, ulcerative colitis is one of the two members of IBD. Ulcerative colitis is recognized as a chronic recurrent disorder characterized with intestinal mucosa inflammation and ulceration [70–72]. The symptoms of ulcerative colitis are complicated, including bloody diarrhea, abdominal pain, anemia, fever, and weight loss, ranging from mild to severe with relatively slow progress [73–75]. Besides, ulcerative colitis may lead to several complications, including inflammation of the joints, liver, and other organs; megacolon; and most severe, colon cancer. So far, several factors have been recognized related to ulcerative colitis, including the environment, certain gene mutation, disturbance of intestinal microbiota homeostasis as well as inflammatory and immuno-modulatory factors [76, 77].

The NLRP3 inflammasome has been widely reported to be associated with the pathogenesis and progression of ulcerative colitis. A previous study conducted by Hanaei et al. [78] investigated the NLRP3 single nucleotide polymorphisms (SNPs) in blood samples from healthy subjects and ulcerative colitis patients. They showed that the NLRP3 SNP genotype of rs10754558 was significantly associated with ulcerative colitis. Another NLRP3 SNP investigation on the comparison between healthy people and ulcerative colitis patients also revealed that the SNP genotype of rs10754558 and rs10925019 were highly connected with the susceptibility of ulcerative colitis, suggesting the important role of the NLRP3 gene mutation in the onset of ulcerative colitis [79]. In addition, Yang et al. detected gene mutation of CARD8 related to the NLRP3 inflammasome [80]. They found that the stop allele of genotype re1972619 was associated with higher serum IL-1β levels in female patients with ulcerative colitis, indicating that CARD8 variants contributed to the pathogenesis of ulcerative colitis.

In dextran sulfate sodium (DSS)-induced ulcerative colitis animal models, the NLRP3 inflammasome has been

reported to be detrimental in the pathogenesis and progression of ulcerative colitis [81, 82]. Titanium dioxide (TiO_2) nanoparticles, widely used as food additives in Western lifestyle, were recently reported to damage the intestinal epithelial cells and intestinal mucosal barrier, thus leading to the aggravation of DSS-induced ulcerative colitis severity [83]. Those effects were caused by the triggering of the NLRP3-ASC-procaspase-1 assembly and the subsequent increase of IL-1β and IL-18 secretions. In addition, it was reported that excessive fecal deoxycholic acid (DCA) caused by a high-fat diet might be an endogenous DAMP for the NLRP3 inflammasome activation, thus contributing to the progression of DSS-induced colitis [67]. In addition, our previous study revealed that suppressing the NLRP3 inflammasome *via* autophagy induction contributed to the alleviation of ulcerative colitis, suggesting the detrimental role of the NLRP3 inflammasome in ulcerative colitis animal model [84].

The microenvironment of the intestinal tract forms a proper microbiota habitat, which has been revealed to affect many physiological conditions in previous studies [85–87]. An increasing number of studies have revealed the importance of gut microbiota as a target for therapeutic intervention [88]. So far, several studies have reported the detrimental effect of the NLRP3 inflammasome on the intestinal microbiota homeostasis. For instance, it was demonstrated by Zhang et al. [89] in DSS-induced ulcerative colitis mice models as well as murine macrophages that the occurrence of colitis or LPS stimulation largely disturbed the homeostasis of gut microbiota. They further demonstrated that Terpinen-4-ol functioned in re-balancing the *Escherichia coli* and *Lactobacillus* levels through the suppression of the NLRP3 inflammasome in the gut, thus alleviating the severity of colitis. Another study revealed that *Zanthoxylum bungeanum* pericarp (ZBEO) could inhibit the NLRP3 inflammasome activation, thus re-balancing the gut microbiota through increasing the levels of the commensal bacteria containing *Lactobacillus* and *Bifidobacteria* but reducing *E. coli* levels in the feces [90].

NLRP3 Inflammasome in Crohn's Disease

Crohn's disease, together with ulcerative colitis, were recognized as the two members of IBD. Under colonoscopy detection, the pathophysiology feature of Crohn's disease is a transmural pattern of inflammation, with inflammation spanning the entire depth of the intestinal wall [91]. Ulceration may be observed in the intestinal tract of patients with severe Crohn's disease, with an abrupt transition between unaffected tissue and ulcer [92]. The

symptoms of Crohn's disease often include diarrhea, abdominal pain, weight loss, and others, with bowel obstruction, anemia, and arthritis as complications [93]. Although so far, the specific mechanisms for the cause of Crohn's disease have not been clarified, yet several factors are considered to serve as pathogenic factors, including the environmental, genetic, and bacterial factors as well as abnormal activation of intestinal inflammatory and immune reaction [94–96].

So far, the NLRP3 inflammasome has been reported to be involved in the pathogenesis and progression of Crohn's disease. It has been recently demonstrated by Mao et al. [97] that the loss-of-function mutation of T60 CARD8, a negative regulator of inflammasome, significantly led to the activation of the NLRP3 inflammasome, thus increasing the secretion of IL-1β and aggravated the severity of Crohn's disease in patients. They also found out that patients with such mutation were not effectively treated with anti-tumor necrosis factor (TNF)-α therapy. Similar investigations were conducted on the study of the SNPs of CARD8 in Crohn's disease patients, suggesting the association of CARD8 mutation in the onset and severity of Crohn's disease [80, 98]. In addition, a previous study was conducted on 21 functional SNPs in 14 genes of inflammasomes using a candidate gene approach and found that some phenotypes of SNPs were associated with the activity of TLR5 and the levels of IL-12 and IL-18 among patients with Crohn's disease [99]. Furthermore, Vallani et al. [100] identified a set of NLRP3 SNPs in four sample sets from individuals of European descent, which implicated the association between NLRP3 SNPs and susceptibility of Crohn's disease. Taken together, those data indicate the roles of the NLRP3 inflammasome-related gene mutation in the pathogenesis and progression of CD. However, it is worth mentioning that a study conducted by Lewis et al. [101] failed to demonstrate a significant genetic association between NLRP3 SNPs and Crohn's disease susceptibility in a relative large cohort study through the detection of six SNPs in a regulatory region 5.3 kb downstream of NLRP3. Those findings suggest that not all NLRP3 SNPs are related to the susceptibility of Crohn's disease.

So far, intestinal microbiota detection has revealed the association between the NLRP3 inflammasome and Crohn's disease. For instance, it was recently reported by Gu et al. [102] that the fecal bacteria from patients with Crohn's disease were more effective in upregulating NOD2, the NLRP3 protein, and TLR2 and TLR4 expressions than that isolated from healthy controls, which could be repressed by IL-4. In addition, it was shown by De la

Fuente et al. [103] that one of the pathologic factors of Crohn's disease is the presence of adhere-invasive *E. coli*, which led to the activation of the NLRP3 inflammasome and the subsequent secretion of IL-1β.

The NLRP3 inflammasome has been widely reported to be detrimental in 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced Crohn's disease animal models, while suppressing the NLRP3 inflammasome plays an alleviative role in the severity of Crohn's disease [104–110]. It was demonstrated by Luo et al. [105] that the administration of Baicalein largely attenuated the NLRP3 inflammasome activation *via* declining the activation of TLR4/myeloid differentiation factor 88 (MyD88) signaling, thus alleviating the TNBS-induced colitis. In addition, the therapeutic effect of suppressing the NLRP3 inflammasome activation was revealed through the modulation of phosphorylated signal transducer and activator of transcription 3 (pSTAT3) and NF-κB signaling, thus blocking the canonical and non-canonical NLRP3/ASC inflammasome pathways [106].

PART II: PHARMACOLOGICAL INTERVENTIONS OF NLRP3 INFLAMMASOME INHIBITORS IN THE TREATMENT OF IBD

So far, various agents have been reported to be effective in the alleviation of IBD taking advantage of inhibiting the NLRP3 inflammasome activation. Among all kinds of the NLRP3 inflammasome inhibitors reported by studies, herbal extracts, agents taking advantage of autophagy induction, and microRNAs are the most studied ones and proven to be potential and effective in the development of therapies against IBD. As a result, in the following contents, herbal extracts, autophagy inducers, microRNAs as well as other well-studied NLRP3 inflammasome inhibitors will be described and discussed in detail.

Herbal Extracts

Curcumin is a kind of hyderophobic polyphenol derived from turmeric, which is a traditional Indian spice [111]. Curcumin is a diarylheptanoid, belonging to the group of curcuminoids. The value and mechanisms of curcumin in the treatment of IBD have been investigated by several studies [112–116]. It was recently reported that curcumin could inhibit the NLRP3 inflammasome activation in DSS-induced colitis animal models as well as LPS/DSS-challenged macrophages, thus ameliorating the symptoms of colitis through reducing weight loss, DAI score, and colon length [112]. Those effects were mediated *via* the inhibition of K^+ efflux, intracellular reactive oxidation species (ROS) formation, and cathepsin B release. In addition, another fundamental research revealed that the administration of the nanoparticle curcumin could inhibit the development of DSS-induced colitis through suppressing the NLRP3 inflammasome mediated by immune regulation including increasing the expansion of $CD4^+$ $Foxp3^+$ regulatory T cells and $CD103^+$ $CD8\alpha^-$ regulatory dendritic cells in the colonic mucosa [113]. Furthermore, several clinical reports and systematic reviews revealed the therapeutic effect of curcumin in the treatment of ulcerative colitis in patients through the suppression of the NLRP3 inflammasome activation [114–116].

Another well-studied herbal extract with therapeutic value of IBD is cardamonin, a kind of chalconoid isolated from several plants including *Alpinia katsumadai* and *Alpinia conchigera* [117, 118]. A previous study originally revealed an anti-inflammatory effect of cardamonin in a DSS-induced colitis animal model, thus ameliorating DSS-induced colitis in body weight loss, diarrhea, colon shortening, and histological damage [119]. This protective effect was mediated by the inhibition of the NLRP3 inflammasome activation *via* suppressing the expression of TLR4 and NF-κB. Recently, the alleviative effect of cardamonin has also been revealed by several studies in both TNBS- and DSS-induced colitis in mice. Those effects were reported to be mediated by the AhR/Nrf2 signaling-mediated suppression of the NLRP3 inflammasome activation as well as downregulation of the expression of cyclooxygenase-2 (COX-2) and caspase-3 [108, 120].

Besides those two well-studied herbal extracts discussed above, several others have been reported to be effective in the alleviation of IBD in IBD patients and/or animal models. For instance, flavonoids, a class of plant and fungus secondary metabolites, have been shown to be effective in the alleviation of IBD symptoms [68, 121–123]. In addition, polysaccharides [124] and formononetin [125] were also reported to function in IBD alleviation. Collectively, several kinds of herbal extracts might be used in the alleviation of IBD *via* NLRP3 inflammasome inhibition. However, despite the variety of herbal extracts in attenuating IBD, further researches are demanded in the exploration of novel and effective herbal extracts in the treatment of IBD taking advantage of their NLRP3 inflammasome-suppressive activity. In addition, the specific mechanisms underlying should be investigated in order to properly use in the treatment of IBD.

Autophagy Inducers

According to our previous review, autophagy is a self-protecting cellular catabolic pathway relying on lysosomes [126]. The function of autophagy is to degrade some long-lived proteins, damaged organelles, and misfolded proteins for recycling [126, 127]. Traditionally, three kinds of autophagy have been demonstrated, including macroautophagy, microautophagy, and chaperone-mediated autophagy. Since macroautophagy is the most studied one, it will be referred to as "autophagy" in the following contents. Besides those three classic forms of autophagy, several other forms of autophagy have been demonstrated, including mitophagy, lipophagy, and xenophagy according to their origins and functions [128–130]. The anti-inflammatory effect of autophagy has been revealed by various studies, via which autophagy plays an alleviative role in several inflammation- and immune-related diseases [131–133]. As a result, properly inducing autophagy might serve as an effective and potential therapy in the treatment of inflammatory or immune disorders.

So far, several NLRP3 inflammasome inhibitors have been reported to be effective on the attenuation of IBD taking advantage of autophagy induction. For example, cannabinoid receptor 2 (CB2R), a kind of seven transmembrane-spanning G protein coupled receptor, has been demonstrated to be alleviative in IBD through its roles of inflammatory suppression [134–136]. A previous study conducted by us demonstrated that activating CB2R could fight against multiple sclerosis in mice models through the suppression of the NLRP3 inflammasome via autophagy induction [137]. Recently, it was reported by us that activating CB2R could alleviate the severity of colitis in DSS-induced colitis mice models as well as inflammatory reaction in macrophages under the challenge of DSS/LPS. Those effects were mediated by the inhibition of the NLRP3 inflammasome activation through inducing adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK)-mammalian target of rapamycin (mTOR)-p70 ribosomal protein S6 kinase (p70S6K) signaling-mediated autophagy, indicating the alleviating effect of inhibiting the NLRP3 inflammasome via autophagy induction [84]. In addition, ginsenoside Rd, a component of ginseng belonging to a kind of deciduous perennial plant, has been demonstrated to suppress oxidative stress and inflammation in various kinds of disorders [138,

139]. In IBD, it was revealed by Liu et al. [140] that the administration of ginsenoside Rd could ameliorate DSS-induced colitis through the induction of p62-driven mitophagy suppression of the NLRP3 inflammasome in mice models via upregulation the AMPK/Unc-51-like kinase (ULK1) signaling pathway. Besides, kynurenic acid, an endogenous substance, was previously reported to be effective in the alleviation of DSS-induced colitis through the activation of GPR35 signaling, thus induce autophagy-dependent degradation of NLRP3 in macrophages [141]. Taken together, proper induction of autophagy might serve as a potential therapy in the treatment of IBD taking advantage of inhibiting the NLRP3 inflammasome.

MicroRNA

MicroRNAs (abbreviated as miRNAs) are a group of small non-coding RNA molecules found in plants, animals, and some virus. MiRNAs contain about 22 nucleotides, functioning in RNA silencing and post-transcriptional regulation of gene expression via binding to the 3′ untranslated regions of messenger RNAs (mRNAs) [142–144]. So far, more than 2500 miRNAs have been identified in human beings, playing a regulatory role in various kinds of diseases [145, 146].

Based on previous studies, some miRNAs have been reported to play an anti-inflammatory role in certain disorders, thus serving as a potential and effective therapeutic strategy [147, 148]. Although several miRNAs have been shown to be associated with the regulation of the NLRP3 inflammasome, so far, only one miRNA, miRNA-223, has been reported to protect against IBD taking advantage of inhibition of the NLRP3 inflammasome activation [149, 150]. According to a related study, the level of miRNA-223 in the inflamed colon tissues was increased in patients with IBD or IBD mice models [149]. The effect of miRNA-223 on IBD was revealed in a recent study conducted by Neudecker and the colleagues [150]. In the study, they demonstrated that mice with miRNA-223 deficiency showed an exacerbation in clinical and histologic signs of DSS-induced colitis as well as an enhancement of IL-1β and associated chemokines. To figure out the association of miRNA-223 and the NLRP3 inflammasome in IBD, they used nanoparticle for the overexpression of miRNA-223 and found an attenuation of experimental colitis as well as a decrease of the NLRP3 protein and the secretion of IL-1β. Collectively, those data suggest an alleviative effect of

miRNA-223 in the pathogenesis and progression of IBD *via* the inhibition of the NLRP3 inflammasome (Table 1).

Others

Besides those classifications listed above, several other well-studied agents have been reported to function in alleviating IBD targeting on the inhibition of the NLRP3 inflammasome activation. For instance, Shen et al. [151] demonstrated that vinegar and its active component, acetic acid, significantly reduced the disease activity index and histopathological scores in DSS-induced colitis mice models. This effect was mediated by the inhibition of the NLRP3 inflammasome *via* the regulation of the mitogen activated protein kinases (MAPK) signaling. In addition, levornidazole, originally used to inhibit anaerobic and protozoal infections, was revealed by Wang et al. [152] on its alleviative effect on DSS-induced colitis. They demonstrated that the pharmacological effect of levornidazole was mediated by the inhibition of the NLRP3 inflammasome through the decrease of the mitochondrial ROS generation.

In addition, it was previously reported that MCC950, a diarylsulfonylurea-containing compound, effectively alleviated IBD severity as well as other inflammation-related diseases *via* suppressing ASC oligomerization, thus inhibiting caspase-1-dependent processing of IL-1β [66, 125, 153]. MCC950 was also demonstrated to inhibit both canonical and non-canonical activation of the NLRP3 inflammasome in the absence of inhibiting NLRP1, AIM2, or NLRC4 inflammasomes [153]. Another sort of compound is caspase-1 inhibitors. Caspase-1 inhibitors, including 1-ethyl-5-methyl-2-phenyl-1H-benzo[d]imidazole and Fumigaclavine C, have been reported to effectively attenuated DSS-induced experimental colitis in mice through the inhibition of caspase-1 activation [154, 155].

CONCLUSION

Based on discussions above, the NLRP3 inflammasome serves as an important factor in the pathogenesis and progression of both ulcerative colitis and Crohn's disease. So far, numerous studies have been conducted in the exploration of specific mechanisms on IBD and several agents have been investigated which were shown to be effective in the alleviation of IBD in IBD patients or colitis animal models. However, more effective therapies against IBD are demanded to be developed. In addition, since the proper level of the NLRP3 inflammasome activation is considered to be necessary in the maintenance of intestinal homeostasis [156, 157], more efforts ought to be made in seeking of the proper application of the NLRP3 inflammasome inhibitors in the treatment of IBD. Further studies are demanded on this issue.

Table 1. Potential Mechanisms of the NLRP3 Inflammasome Inhibitors in the Treatment of IBD

Classification	Agent	Mechanism	Reference
Herbal extracts	Curcumin	Inhibition of K^+ efflux, intracellular ROS formation, and cathepsin B release; immune regulation	[55, 113–116]
	Cardamonin	Suppressing the expression of TLR4 and NF-κB; activation of AhR/Nrf2 signaling; downregulation of the expression of COX-2 and caspase-3	[108, 119, 120]
	Flavonoids	Downregulating cleaved caspase-1 and caspase-11 enzymes	[68, 121–123]
	Polysaccharides	Inhibiting the expression of β-arrestin-1	[124]
	Formononetin	Decreasing the expression of NLRP3 and ASC	[125]
Autophagy inducers	CB2R agonist	Induction of the AMPK-mTOR-p70S6K signaling-mediated autophagy	[84, 134–136]
	Ginsenoside Rd	Induction of p62-driven mitophagy	[138–140]
	Kynurenic acid	Induction of GPR35 signaling-mediated autophagy	[141]
MicroRNA	MiRNA-223	Decreasing the level of NLRP3 and secretion of IL-1β	[149, 150]
Other NLRP3 inflammasome inhibitors	Vinegar	Regulation of the MAPK signaling	[151]
	Levornidazole	Decreasing ROS generation	[152]
	MCC950	Blocking ASC oligomerization; inhibiting canonical and non-canonical NLRP3 inflammasome	[66, 125, 153]
	Caspase-1 inhibitors	Inhibiting caspase-1 activation	[154, 155]

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AUTHOR CONTRIBUTIONS

B-ZS, S-LW, and PP retrieved and analyzed concerned literatures. B-ZS and JY wrote the manuscript. S-LW and PP designed the table and figure. E-QL, YB, and Z-SL revised the manuscript. All the authors agreed to be accountable for the content of the work.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest. The authors declare that they have no conflict of interest.

REFERENCES

1. Tian, S., J. Wang, H. Yu, J. Wang, and W. Zhu. 2018. Effects of galacto-oligosaccharides on growth and gut function of newborn suckling piglets. *Journal of Animal Science and Biotechnology* 9: 75. https://doi.org/10.1186/s40104-018-0290-9.
2. Petschow, B.W., B.P. Burnett, A.L. Shaw, E.M. Weaver, and G.L. Klein. 2015. Dietary requirement for serum-derived bovine immunoglobulins in the clinical management of patients with enteropathy. *Digestive Diseases and Sciences* 60 (1): 13–23. https://doi.org/10.1007/s10620-014-3322-0.
3. Mizoguchi, A. 2017. A novel intestinal organoid-based in vitro co-culture system to dissect out the initial host defense system. *Journal of Gastroenterology* 52 (1): 123–124. https://doi.org/10.1007/s00535-016-1243-8.
4. Fornai, M., R.M. van den Wijngaard, L. Antonioli, C. Pellegrini, C. Blandizzi, and W.J. de Jonge. 2018. Neuronal regulation of intestinal immune functions in health and disease. *Neurogastroenterol Motil* 30: e13406. https://doi.org/10.1111/nmo.13406.
5. Allaire, J.M., S.M. Crowley, H.T. Law, S.Y. Chang, H.J. Ko, and B.A. Vallance. 2018. The intestinal epithelium: central coordinator of mucosal immunity. *Trends in Immunology* 39 (9): 677–696. https://doi.org/10.1016/j.it.2018.04.002.
6. Uhlig, H.H. 2013. Monogenic diseases associated with intestinal inflammation: Implications for the understanding of inflammatory bowel disease. *Gut* 62 (12): 1795–1805. https://doi.org/10.1136/gutjnl-2012-303956.
7. Mannon, P., and W. Reinisch. 2012. Interleukin 13 and its role in gut defence and inflammation. *Gut* 61 (12): 1765–1773. https://doi.org/10.1136/gutjnl-2012-303461.
8. Ullman, T.A., and S.H. Itzkowitz. 2011. Intestinal inflammation and cancer. *Gastroenterology* 140 (6): 1807–1816. https://doi.org/10.1053/j.gastro.2011.01.057.
9. Strober, W., and I.J. Fuss. 2011. Proinflammatory cytokines in the pathogenesis of inflammatory bowel diseases. *Gastroenterology* 140 (6): 1756–1767. https://doi.org/10.1053/j.gastro.2011.02.016.
10. Xu, Y.L., H.L. Tang, S.Y. Zhu, H.R. Peng, Z.T. Qi, and W. Wang. 2017. RIP3 deficiency exacerbates inflammation in dextran sodium sulfate-induced ulcerative colitis mice model. *Cell Biochemistry and Function* 35 (3): 156–163. https://doi.org/10.1002/cbf.3257.
11. Ungaro, R., S. Mehandru, P.B. Allen, L. Peyrin-Biroulet, and J.F. Colombel. 2017. Ulcerative colitis. *Lancet* 389 (10080): 1756–1770. https://doi.org/10.1016/S0140-6736(16)32126-2.
12. Ziade, F., C. Rungoe, T. Kallemose, A. Paerregaard, A.V. Wewer, and C. Jakobsen. 2018. Biochemical markers, genotype, and inflammation in pediatric inflammatory bowel disease: a Danish population-based study. *Dig Dis*: 1–7. https://doi.org/10.1159/000494215.
13. Nanini, H.F., C. Bernardazzi, F. Castro, and H.S.P. de Souza. 2018. Damage-associated molecular patterns in inflammatory bowel disease: from biomarkers to therapeutic targets. *World Journal of Gastroenterology* 24 (41): 4622–4634. https://doi.org/10.3748/wjg.v24.i41.4622.
14. Elia, G., and G. Guglielmi. 2018. CXCL9 chemokine in ulcerative colitis. *La Clinica Terapeutica* 169 (5): e235–e241. https://doi.org/10.7417/CT.2018.2085.
15. Wang, R., L. Wang, Y. Luo, D. Wang, R. Du, J. Du, and Y. Wang. 2018. Maggot protein ameliorates dextran sulfate sodium-induced ulcerative colitis in mice. *Bioscience Reports*. https://doi.org/10.1042/BSR20181799.
16. Luan, J., and D. Ju. 2018. Inflammasome: a double-edged sword in liver diseases. *Frontiers in Immunology* 9: 2201. https://doi.org/10.3389/fimmu.2018.02201.
17. Cypryk, W., T.A. Nyman, and S. Matikainen. 2018. From inflammasome to exosome-does extracellular vesicle secretion constitute an inflammasome-dependent immune response? *Frontiers in Immunology* 9: 2188. https://doi.org/10.3389/fimmu.2018.02188.
18. Kumar, S., and M. Dhiman. 2018. Inflammasome activation and regulation during Helicobacter pylori pathogenesis. *Microbial Pathogenesis* 125: 468–474. https://doi.org/10.1016/j.micpath.2018.10.012.
19. Vasconcelos, D.P., A.P. Aguas, M.A. Barbosa, P. Pelegrin, and J.N. Barbosa. 2018. The inflammasome in host response to biomaterials: bridging inflammation and tissue regeneration. *Acta Biomaterialia* 83: 1–12. https://doi.org/10.1016/j.actbio.2018.09.056.
20. Hayward, J.A., A. Mathur, C. Ngo, and S.M. Man. 2018. Cytosolic recognition of microbes and pathogens: inflammasomes in action. *Microbiology and Molecular Biology Reviews* 82 (4). https://doi.org/10.1128/MMBR.00015-18.
21. Henderson, J., S. Bhattacharyya, J. Varga, and S. O'Reilly. 2018. Targeting TLRs and the inflammasome in systemic sclerosis. *Pharmacology & Therapeutics*. https://doi.org/10.1016/j.pharmthera.2018.08.003.
22. Awad, F., E. Assrawi, C. Louvrier, C. Jumeau, S. Georgin-Lavialle, G. Grateau, S. Amselem, I. Giurgea, and S.A. Karabina. 2018. Inflammasome biology, molecular pathology and therapeutic implications. *Pharmacology & Therapeutics* 187: 133–149. https://doi.org/10.1016/j.pharmthera.2018.02.011.

23. Rathinam, V.A.K., and F.K. Chan. 2018. Inflammasome, inflammation, and tissue homeostasis. *Trends in Molecular Medicine* 24 (3): 304–318. https://doi.org/10.1016/j.molmed.2018.01.004.

24. Grebe, A., F. Hoss, and E. Latz. 2018. NLRP3 Inflammasome and the IL-1 pathway in atherosclerosis. *Circulation Research* 122 (12): 1722–1740. https://doi.org/10.1161/CIRCRESAHA.118.311362.

25. Gong, T., Y. Yang, T. Jin, W. Jiang, and R. Zhou. 2018. Orchestration of NLRP3 Inflammasome activation by ion fluxes. *Trends in Immunology* 39 (5): 393–406. https://doi.org/10.1016/j.it.2018.01.009.

26. Toldo, S., and A. Abbate. 2018. The NLRP3 inflammasome in acute myocardial infarction. *Nature Reviews. Cardiology* 15 (4): 203–214. https://doi.org/10.1038/nrcardio.2017.161.

27. Horng, T. 2014. Calcium signaling and mitochondrial destabilization in the triggering of the NLRP3 inflammasome. *Trends in Immunology* 35 (6): 253–261. https://doi.org/10.1016/j.it.2014.02.007.

28. Chung, I.C., C.N. OuYang, S.N. Yuan, H.C. Lin, K.Y. Huang, P.S. Wu, C.Y. Liu, et al. 2019. Pretreatment with a heat-killed probiotic modulates the NLRP3 inflammasome and attenuates colitis-associated colorectal cancer in mice. *Nutrients* 11 (3). https://doi.org/10.3390/nu11030516.

29. Shen, P., Z. Zhang, K. Zhu, H. Cao, J. Liu, X. Lu, Y. Li, et al. 2019. Evodiamine prevents dextran sulfate sodium-induced murine experimental colitis via the regulation of NF-kappaB and NLRP3 inflammasome. *Biomedicine & Pharmacotherapy* 110: 786–795. https://doi.org/10.1016/j.biopha.2018.12.033.

30. Mariathasan, S., K. Newton, D.M. Monack, D. Vucic, D.M. French, W.P. Lee, M. Roose-Girma, S. Erickson, and V.M. Dixit. 2004. Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf. *Nature* 430 (6996): 213–218. https://doi.org/10.1038/nature02664.

31. Alexandre, Y.O., C.D. Cocita, S. Ghilas, and M. Dalod. 2014. Deciphering the role of DC subsets in MCMV infection to better understand immune protection against viral infections. *Frontiers in Microbiology* 5: 378. https://doi.org/10.3389/fmicb.2014.00378.

32. Song, N., and T. Li. 2018. Regulation of NLRP3 Inflammasome by phosphorylation. *Frontiers in Immunology* 9: 2305. https://doi.org/10.3389/fimmu.2018.02305.

33. Lei-Leston, A.C., A.G. Murphy, and K.J. Maloy. 2017. Epithelial cell inflammasomes in intestinal immunity and inflammation. *Frontiers in Immunology* 8: 1168. https://doi.org/10.3389/fimmu.2017.01168.

34. Suarez, R., and N. Buelvas. 2015. Inflammasome: activation mechanisms. *Investigación Clínica* 56 (1): 74–99.

35. de Rivero Vaccari, J.P., W.D. Dietrich, and R.W. Keane. 2014. Activation and regulation of cellular inflammasomes: gaps in our knowledge for central nervous system injury. *Journal of Cerebral Blood Flow and Metabolism* 34 (3): 369–375. https://doi.org/10.1038/jcbfm.2013.227.

36. Petrilli, V., S. Papin, and J. Tschopp. 2005. The inflammasome. *Current Biology* 15 (15): R581. https://doi.org/10.1016/j.cub.2005.07.049.

37. Liu, Q., D. Zhang, D. Hu, X. Zhou, and Y. Zhou. 2018. The role of mitochondria in NLRP3 inflammasome activation. *Molecular Immunology* 103: 115–124. https://doi.org/10.1016/j.molimm.2018.09.010.

38. Sarvestani, S.T., and J.L. McAuley. 2017. The role of the NLRP3 inflammasome in regulation of antiviral responses to influenza A virus infection. *Antiviral Research* 148: 32–42. https://doi.org/10.1016/j.antiviral.2017.10.020.

39. Kim, J.K., H.S. Jin, H.W. Suh, and E.K. Jo. 2017. Negative regulators and their mechanisms in NLRP3 inflammasome activation and signaling. *Immunology and Cell Biology* 95 (7): 584–592. https://doi.org/10.1038/icb.2017.23.

40. Inoue, M., and M.L. Shinohara. 2013. NLRP3 Inflammasome and MS/EAE. *Autoimmune Dis* 2013: 859145–859148. https://doi.org/10.1155/2013/859145.

41. Wakabayashi, T., M. Takahashi, D. Yamamuro, T. Karasawa, A. Takei, S. Takei, H. Yamazaki, S. Nagashima, K. Ebihara, M. Takahashi, and S. Ishibashi. 2018. Inflammasome activation aggravates cutaneous Xanthomatosis and atherosclerosis in ACAT1 (acyl-CoA cholesterol acyltransferase 1) deficiency in bone marrow. *Arteriosclerosis, Thrombosis, and Vascular Biology* 38 (11): 2576–2589. https://doi.org/10.1161/ATVBAHA.118.311648.

42. Willingham, S.B., I.C. Allen, D.T. Bergstralh, W.J. Brickey, M.T. Huang, D.J. Taxman, J.A. Duncan, and J.P. Ting. 2009. NLRP3 (NALP3, Cryopyrin) facilitates in vivo caspase-1 activation, necrosis, and HMGB1 release via inflammasome-dependent and -independent pathways. *Journal of Immunology* 183 (3): 2008–2015. https://doi.org/10.4049/jimmunol.0900138.

43. Jorgensen, I., and E.A. Miao. 2015. Pyroptotic cell death defends against intracellular pathogens. *Immunological Reviews* 265 (1): 130–142. https://doi.org/10.1111/imr.12287.

44. Shirasuna, K., T. Karasawa, and M. Takahashi. 2018. Exogenous nanoparticles and endogenous crystalline molecules as danger signals for the NLRP3 inflammasomes. *Journal of Cellular Physiology.* https://doi.org/10.1002/jcp.27475.

45. Groslambert, M., and B.F. Py. 2018. Spotlight on the NLRP3 inflammasome pathway. *Journal of Inflammation Research* 11: 359–374. https://doi.org/10.2147/JIR.S141220.

46. He, Y., H. Hara, and G. Nunez. 2016. Mechanism and regulation of NLRP3 inflammasome activation. *Trends in Biochemical Sciences* 41 (12): 1012–1021. https://doi.org/10.1016/j.tibs.2016.09.002.

47. Shao, B.Z., Z.Q. Xu, B.Z. Han, D.F. Su, and C. Liu. 2015. NLRP3 inflammasome and its inhibitors: a review. *Frontiers in Pharmacology* 6: 262. https://doi.org/10.3389/fphar.2015.00262.

48. Latz, E., and P. Duewell. 2018. NLRP3 inflammasome activation in inflammaging. *Seminars in Immunology.* https://doi.org/10.1016/j.smim.2018.09.001.

49. Mangan, M.S.J., E.J. Olhava, W.R. Roush, H.M. Seidel, G.D. Glick, and E. Latz. 2018. Targeting the NLRP3 inflammasome in inflammatory diseases. *Nature Reviews. Drug Discovery* 17 (9): 688. https://doi.org/10.1038/nrd.2018.149.

50. Chen, J., and Z.J. Chen. 2018. PtdIns4P on dispersed trans-Golgi network mediates NLRP3 inflammasome activation. *Nature* 564 (7734): 71–76. https://doi.org/10.1038/s41586-018-0761-3.

51. Liao, W., X. He, Z. Yi, W. Xiang, and Y. Ding. 2018. Chelidonine suppresses LPS-induced production of inflammatory mediators through the inhibitory of the TLR4/NF-kappaB signaling pathway in RAW264.7 macrophages. *Biomedicine & Pharmacotherapy* 107: 1151–1159. https://doi.org/10.1016/j.biopha.2018.08.094.

52. Wang, R., W. Wu, W. Li, S. Huang, Z. Li, R. Liu, Z. Shan, C. Zhang, W. Li, and S. Wang. 2018. Activation of NLRP3 Inflammasome promotes foam cell formation in vascular smooth muscle cells and atherogenesis via HMGB1. *Journal of the American Heart Association* 7 (19): e008596. https://doi.org/10.1161/JAHA.118.008596.

53. Lian, D., L. Dai, Z. Xie, X. Zhou, X. Liu, Y. Zhang, Y. Huang, and Y. Chen. 2018. Periodontal ligament fibroblasts migration injury via ROS/TXNIP/Nlrp3 inflammasome pathway with Porphyromonas gingivalis lipopolysaccharide. *Molecular Immunology* 103: 209–219. https://doi.org/10.1016/j.molimm.2018.10.001.

54. Lee, G.S., N. Subramanian, A.I. Kim, I. Aksentijevich, R. Goldbach-Mansky, D.B. Sacks, R.N. Germain, D.L. Kastner, and J.J. Chae. 2012. The calcium-sensing receptor regulates the NLRP3

inflammasome through Ca2+ and cAMP. *Nature* 492 (7427): 123–127. https://doi.org/10.1038/nature11588.

55. Gutierrez-Lopez, T.Y., L.B. Orduna-Castillo, M.N. Hernandez-Vasquez, J. Vazquez-Prado, and G. Reyes-Cruz. 2018. Calcium sensing receptor activates the NLRP3 inflammasome via a chaperone-assisted degradative pathway involving Hsp70 and LC3-II. *Biochemical and Biophysical Research Communications* 505 (4): 1121–1127. https://doi.org/10.1016/j.bbrc.2018.10.028.

56. Sho, T., and J. Xu. 2018. Role and mechanism of ROS scavengers in alleviating NLRP3-mediated inflammation. *Biotechnology and Applied Biochemistry* 66: 4–13. https://doi.org/10.1002/bab.1700.

57. Bai, H., B. Yang, W. Yu, Y. Xiao, D. Yu, and Q. Zhang. 2018. Cathepsin B links oxidative stress to the activation of NLRP3 inflammasome. *Experimental Cell Research* 362 (1): 180–187. https://doi.org/10.1016/j.yexcr.2017.11.015.

58. Itani, S., T. Watanabe, Y. Nadatani, N. Sugimura, S. Shimada, S. Takeda, K. Otani, et al. 2016. NLRP3 inflammasome has a protective effect against oxazolone-induced colitis: a possible role in ulcerative colitis. *Scientific Reports* 6: 39075. https://doi.org/10.1038/srep39075.

59. Guo, C., Z. Chi, D. Jiang, T. Xu, W. Yu, Z. Wang, S. Chen, L. Zhang, Q. Liu, X. Guo, X. Zhang, W. Li, L. Lu, Y. Wu, B.L. Song, and D. Wang. 2018. Cholesterol homeostatic regulator SCAP-SREBP2 integrates NLRP3 inflammasome activation and cholesterol biosynthetic signaling in macrophages. *Immunity*. 49: 842–856.e7. https://doi.org/10.1016/j.immuni.2018.08.021.

60. Heneka, M.T., R.M. McManus, and E. Latz. 2018. Inflammasome signalling in brain function and neurodegenerative disease. *Nature Reviews. Neuroscience* 19 (10): 610–621. https://doi.org/10.1038/s41583-018-0055-7.

61. Afonina, I.S., Z. Zhong, M. Karin, and R. Beyaert. 2017. Limiting inflammation-the negative regulation of NF-kappaB and the NLRP3 inflammasome. *Nature Immunology* 18 (8): 861–869. https://doi.org/10.1038/ni.3772.

62. Baldrighi, M., Z. Mallat, and X. Li. 2017. NLRP3 inflammasome pathways in atherosclerosis. *Atherosclerosis* 267: 127–138. https://doi.org/10.1016/j.atherosclerosis.2017.10.027.

63. Du, Y., X. Gu, H. Meng, N. Aa, S. Liu, C. Peng, Y. Ge, and Z. Yang. 2018. Muscone improves cardiac function in mice after myocardial infarction by alleviating cardiac macrophage-mediated chronic inflammation through inhibition of NF-kappaB and NLRP3 inflammasome. *American Journal of Translational Research* 10 (12): 4235–4246.

64. Yu, H., M. Wu, G. Lu, T. Cao, N. Chen, Y. Zhang, Z. Jiang, H. Fan, and R. Yao. 2018. Prednisone alleviates demyelination through regulation of the NLRP3 inflammasome in a C57BL/6 mouse model of cuprizone-induced demyelination. *Brain Research* 1678: 75–84. https://doi.org/10.1016/j.brainres.2017.09.034.

65. Ward, R., W. Li, Y. Abdul, L. Jackson, G. Dong, S. Jamil, J. Filosa, S.C. Fagan, and A. Ergul. 2019. NLRP3 inflammasome inhibition with MCC950 improves diabetes-mediated cognitive impairment and vasoneuronal remodeling after ischemia. *Pharmacological Research* 142: 237–250. https://doi.org/10.1016/j.phrs.2019.01.035.

66. Perera, A.P., R. Fernando, T. Shinde, R. Gundamaraju, B. Southam, S.S. Sohal, A.A.B. Robertson, K. Schroder, D. Kunde, and R. Eri. 2018. MCC950, a specific small molecule inhibitor of NLRP3 inflammasome attenuates colonic inflammation in spontaneous colitis mice. *Scientific Reports* 8 (1): 8618. https://doi.org/10.1038/s41598-018-26775-w.

67. Zhao, S., Z. Gong, X. Du, C. Tian, L. Wang, J. Zhou, C. Xu, Y. Chen, W. Cai, and J. Wu. 2018. Deoxycholic acid-mediated sphingosine-1-phosphate receptor 2 signaling exacerbates DSS-induced colitis through promoting cathepsin B release. *Journal of*

68. He, X., Z. Wei, J. Wang, J. Kou, W. Liu, Y. Fu, and Z. Yang. 2016. Alpinetin attenuates inflammatory responses by suppressing TLR4 and NLRP3 signaling pathways in DSS-induced acute colitis. *Scientific Reports* 6: 28370. https://doi.org/10.1038/srep28370.

69. Zherebiatiev, A., and A. Kamyshnyi. 2016. Expression levels of proinflammatory cytokines and NLRP3 Inflammasome in an experimental model of Oxazolone-induced colitis. *Iranian Journal of Allergy, Asthma, and Immunology* 15 (1): 39–45.

70. Hodson, R. 2016. Inflammatory bowel disease. *Nature* 540 (7634): S97. https://doi.org/10.1038/540S97a.

71. Ford, A.C., P. Moayyedi, and S.B. Hanauer. 2013. Ulcerative colitis. *BMJ* 346: f432. https://doi.org/10.1136/bmj.f432.

72. Zhang, S.L., S.N. Wang, and C.Y. Miao. 2017. Influence of microbiota on intestinal immune system in ulcerative colitis and its intervention. *Frontiers in Immunology* 8: 1674. https://doi.org/10.3389/fimmu.2017.01674.

73. Jairath, V., J. Jeyarajah, G. Zou, C.E. Parker, A. Olson, R. Khanna, G.R. D'Haens, W.J. Sandborn, and B.G. Feagan. 2018. A composite disease activity index for early drug development in ulcerative colitis: development and validation of the UC-100 score. *The Lancet Gastroenterology & Hepatology*. https://doi.org/10.1016/S2468-1253(18)30306-6.

74. Carbonnel, F. 2018. Towards more efficient assessment of ulcerative colitis drugs. *The Lancet Gastroenterology & Hepatology*. https://doi.org/10.1016/S2468-1253(18)30342-X.

75. Laharie, D. 2017. Towards therapeutic choices in ulcerative colitis. *Lancet* 390 (10090): 98–99. https://doi.org/10.1016/S0140-6736(17)31263-1.

76. de Souza, H.S.P. 2017. Etiopathogenesis of inflammatory bowel disease: today and tomorrow. *Current Opinion in Gastroenterology* 33 (4): 222–229. https://doi.org/10.1097/MOG.0000000000000364.

77. Paramsothy, S., M.A. Kamm, N.O. Kaakoush, A.J. Walsh, J. van den Bogaerde, D. Samuel, R.W.L. Leong, et al. 2017. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet* 389 (10075): 1218–1228. https://doi.org/10.1016/S0140-6736(17)30182-4.

78. Hanaei, S., M. Sadr, A. Rezaei, S. Shahkarami, N. Ebrahimi Daryani, A.Z. Bidoki, and N. Rezaei. 2018. Association of NLRP3 single nucleotide polymorphisms with ulcerative colitis: a case-control study. *Clinics and Research in Hepatology and Gastroenterology* 42 (3): 269–275. https://doi.org/10.1016/j.clinre.2017.09.003.

79. Zhang, H.X., Z.T. Wang, X.X. Lu, Y.G. Wang, J. Zhong, and J. Liu. 2014. NLRP3 gene is associated with ulcerative colitis (UC), but not Crohn's disease (CD), in Chinese Han population. *Inflammation Research* 63 (12): 979–985. https://doi.org/10.1007/s00011-014-0774-9.

80. Yang, S.K., H. Kim, M. Hong, J. Lim, E. Choi, B.D. Ye, S.K. Park, and K. Song. 2011. Association of CARD8 with inflammatory bowel disease in Koreans. *Journal of Human Genetics* 56 (3): 217–223. https://doi.org/10.1038/jhg.2010.170.

81. Mai, C.T., M.M. Wu, C.L. Wang, Z.R. Su, Y.Y. Cheng, and X.J. Zhang. 2018. Palmatine attenuated dextran sulfate sodium (DSS)-induced colitis via promoting mitophagy-mediated NLRP3 inflammasome inactivation. *Molecular Immunology* 105: 76–85. https://doi.org/10.1016/j.molimm.2018.10.015.

82. Zhang, Z., S. Li, H. Cao, P. Shen, J. Liu, Y. Fu, Y. Cao, and N. Zhang. 2019. The protective role of phloretin against dextran sulfate sodium-induced ulcerative colitis in mice. *Food & Function*. https://doi.org/10.1039/c8fo01699b.

83. Ruiz, P.A., B. Moron, H.M. Becker, S. Lang, K. Atrott, M.R. Spalinger, M. Scharl, et al. 2017. Titanium dioxide nanoparticles exacerbate DSS-induced colitis: role of the NLRP3 inflammasome. *Gut* 66 (7): 1216–1224. https://doi.org/10.1136/gutjnl-2015-310297.

84. Ke, P., B.Z. Shao, Z.Q. Xu, W. Wei, B.Z. Han, X.W. Chen, D.F. Su, and C. Liu. 2016. Activation of cannabinoid receptor 2 ameliorates DSS-induced colitis through inhibiting NLRP3 inflammasome in macrophages. *PLoS One* 11 (9): e0155076. https://doi.org/10.1371/journal.pone.0155076.

85. Marchesi, J., and F. Shanahan. 2007. The normal intestinal microbiota. *Current Opinion in Infectious Diseases* 20 (5): 508–513. https://doi.org/10.1097/QCO.0b013e3282a56a99.

86. Hooper, L.V., D.R. Littman, and A.J. Macpherson. 2012. Interactions between the microbiota and the immune system. *Science* 336 (6086): 1268–1273. https://doi.org/10.1126/science.1223490.

87. Turnbaugh, P.J., M. Hamady, T. Yatsunenko, B.L. Cantarel, A. Duncan, R.E. Ley, M.L. Sogin, et al. 2009. A core gut microbiome in obese and lean twins. *Nature* 457 (7228): 480–484. https://doi.org/10.1038/nature07540.

88. Faith, J.J., J.L. Guruge, M. Charbonneau, S. Subramanian, H. Seedorf, A.L. Goodman, J.C. Clemente, R. Knight, A.C. Heath, R.L. Leibel, M. Rosenbaum, and J.I. Gordon. 2013. The long-term stability of the human gut microbiota. *Science* 341 (6141): 1237439. https://doi.org/10.1126/science.1237439.

89. Zhang, Z., P. Shen, X. Lu, Y. Li, J. Liu, B. Liu, Y. Fu, Y. Cao, and N. Zhang. 2017. In vivo and in vitro study on the efficacy of terpinen-4-ol in dextran sulfate sodium-induced mice experimental colitis. *Frontiers in Immunology* 8: 558. https://doi.org/10.3389/fimmu.2017.00558.

90. Zhang, Z., P. Shen, J. Liu, C. Gu, X. Lu, Y. Li, Y. Cao, B. Liu, Y. Fu, and N. Zhang. 2017. In vivo study of the efficacy of the essential oil of Zanthoxylum bungeanum pericarp in dextran sulfate sodium-induced murine experimental colitis. *Journal of Agricultural and Food Chemistry* 65 (16): 3311–3319. https://doi.org/10.1021/acs.jafc.7b01323.

91. Brooks, M. 1981. Crohn's disease, a functional deficiency of IgA? *Lancet* 1 (8212): 158.

92. Baumgart, D.C., and W.J. Sandborn. 2012. Crohn's disease. *Lancet* 380 (9853): 1590–1605. https://doi.org/10.1016/S0140-6736(12)60026-9.

93. Senussi, N.H. 2017. Exclusive and partial enteral nutrition for Crohn's disease. *Lancet* 390 (10101): 1486. https://doi.org/10.1016/S0140-6736(17)32392-9.

94. Cho, J.H., and S.R. Brant. 2011. Recent insights into the genetics of inflammatory bowel disease. *Gastroenterology* 140 (6): 1704–1712. https://doi.org/10.1053/j.gastro.2011.02.046.

95. Dessein, R., M. Chamaillard, and S. Danese. 2008. Innate immunity in Crohn's disease: the reverse side of the medal. *Journal of Clinical Gastroenterology* 42 (Suppl 3 Pt 1): S144–S147. https://doi.org/10.1097/MCG.0b013e3181662c90.

96. Stefanelli, T., A. Malesci, A. Repici, S. Vetrano, and S. Danese. 2008. New insights into inflammatory bowel disease pathophysiology: paving the way for novel therapeutic targets. *Current Drug Targets* 9 (5): 413–418.

97. Mao, L., A. Kitani, M. Similuk, A.J. Oler, L. Albenberg, J. Kelsen, A. Aktay, et al. 2018. Loss-of-function CARD8 mutation causes NLRP3 inflammasome activation and Crohn's disease. *The Journal of Clinical Investigation* 128 (5): 1793–1806. https://doi.org/10.1172/JCI98642.

98. Vasseur, F., B. Sendid, F. Broly, C. Gower-Rousseau, A. Sarazin, A. Standaert-Vitse, J.F. Colombel, D. Poulain, and T. Jouault. 2013. The CARD8 p.C10X mutation associates with a low anti-glycans antibody response in patients with Crohn's disease. *BMC Medical Genomics* 14: 35. https://doi.org/10.1186/1471-2350-14-35.

99. Bank, S., P.S. Andersen, J. Burisch, N. Pedersen, S. Roug, J. Galsgaard, S.Y. Turino, et al. 2018. Genetically determined high activity of IL-12 and IL-18 in ulcerative colitis and TLR5 in Crohns disease were associated with non-response to anti-TNF therapy. *The Pharmacogenomics Journal* 18 (1): 87–97. https://doi.org/10.1038/tpj.2016.84.

100. Villani, A.C., M. Lemire, G. Fortin, E. Louis, M.S. Silverberg, C. Collette, N. Baba, et al. 2009. Common variants in the NLRP3 region contribute to Crohn's disease susceptibility. *Nature Genetics* 41 (1): 71–76. https://doi.org/10.1038/ng.285.

101. Lewis, G.J., D.C. Massey, H. Zhang, F. Bredin, M. Tremelling, J.C. Lee, C. Berzuini, and M. Parkes. 2011. Genetic association between NLRP3 variants and Crohn's disease does not replicate in a large UK panel. *Inflammatory Bowel Diseases* 17 (6): 1387–1391. https://doi.org/10.1002/ibd.21499.

102. Gu, J., G. Liu, J. Xing, H. Song, and Z. Wang. 2018. Fecal bacteria from Crohn's disease patients more potently activated NOD-like receptors and Toll-like receptors in macrophages, in an IL-4-repressible fashion. *Microbial Pathogenesis* 121: 40–44. https://doi.org/10.1016/j.micpath.2018.05.009.

103. De la Fuente, M., L. Franchi, D. Araya, D. Diaz-Jimenez, M. Olivares, M. Alvarez-Lobos, D. Golenbock, et al. 2014. Escherichia coli isolates from inflammatory bowel diseases patients survive in macrophages and activate NLRP3 inflammasome. *International Journal of Medical Microbiology* 304 (3–4): 384–392. https://doi.org/10.1016/j.ijmm.2014.01.002.

104. Edwan, J.H., R. Goldbach-Mansky, and R.A. Colbert. 2015. Identification of interleukin-1beta-producing monocytes that are susceptible to pyronecrotic cell death in patients with neonatal-onset multisystem inflammatory disease. *Arthritis & Rheumatology* 67 (12): 3286–3297. https://doi.org/10.1002/art.39307.

105. Luo, X., Z. Yu, C. Deng, J. Zhang, G. Ren, A. Sun, S. Mani, Z. Wang, and W. Dou. 2017. Baicalein ameliorates TNBS-induced colitis by suppressing TLR4/MyD88 signaling cascade and NLRP3 inflammasome activation in mice. *Scientific Reports* 7 (1): 16374. https://doi.org/10.1038/s41598-017-12562-6.

106. Lopes de Oliveira, G.A., C. Alarcon de la Lastra, M.A. Rosillo, M.L. Castejon Martinez, M. Sanchez-Hidalgo, J.V. Rolim Medeiros, and I. Villegas. 2018. Preventive effect of bergenin against the development of TNBS-induced acute colitis in rats is associated with inflammatory mediators inhibition and NLRP3/ASC inflammasome signaling pathways. *Chemico-Biological Interactions* 297: 25–33. https://doi.org/10.1016/j.cbi.2018.10.020.

107. Yao, Y., J. Vent-Schmidt, M.D. McGeough, M. Wong, H.M. Hoffman, T.S. Steiner, and M.K. Levings. 2015. Tr1 cells, but not Foxp3+ regulatory T cells, suppress NLRP3 Inflammasome activation via an IL-10-dependent mechanism. *Journal of Immunology* 195 (2): 488–497. https://doi.org/10.4049/jimmunol.1403225.

108. Wang, K., Q. Lv, Y.M. Miao, S.M. Qiao, Y. Dai, and Z.F. Wei. 2018. Cardamonin, a natural flavone, alleviates inflammatory bowel disease by the inhibition of NLRP3 inflammasome activation via an AhR/Nrf2/NQO1 pathway. *Biochemical Pharmacology* 155: 494–509. https://doi.org/10.1016/j.bcp.2018.07.039.

109. Lv, Q., K. Wang, S.M. Qiao, Y. Dai, and Z.F. Wei. 2018. Norisoboldine, a natural aryl hydrocarbon receptor agonist, alleviates TNBS-induced colitis in mice, by inhibiting the activation of NLRP3 inflammasome. *Chinese Journal of Natural Medicines* 16 (3): 161–174. https://doi.org/10.1016/S1875-5364(18)30044-X.

110. Bauer, C., P. Duewell, H.A. Lehr, S. Endres, and M. Schnurr. 2012. Protective and aggravating effects of Nlrp3 inflammasome

activation in IBD models: Influence of genetic and environmental factors. *Digestive Diseases* 30 (Suppl 1): 82–90. https://doi.org/10.1159/000341681.

111. Nelson, K.M., J.L. Dahlin, J. Bisson, J. Graham, G.F. Pauli, and M.A. Walters. 2017. The essential medicinal chemistry of curcumin. *Journal of Medicinal Chemistry* 60 (5): 1620–1637. https://doi.org/10.1021/acs.jmedchem.6b00975.

112. Gong, Z., S. Zhao, J. Zhou, J. Yan, L. Wang, X. Du, H. Li, Y. Chen, W. Cai, and J. Wu. 2018. Curcumin alleviates DSS-induced colitis via inhibiting NLRP3 inflammsome activation and IL-1beta production. *Molecular Immunology* 104: 11–19. https://doi.org/10.1016/j.molimm.2018.09.004.

113. Ohno, M., A. Nishida, Y. Sugitani, K. Nishino, O. Inatomi, M. Sugimoto, M. Kawahara, and A. Andoh. 2017. Nanoparticle curcumin ameliorates experimental colitis via modulation of gut microbiota and induction of regulatory T cells. *PLoS One* 12 (10): e0185999. https://doi.org/10.1371/journal.pone.0185999.

114. Grammatikopoulou, M.G., K. Gkiouras, X. Theodoridis, E. Asteriou, A. Forbes, and D.P. Bogdanos. 2018. Oral adjuvant curcumin therapy for attaining clinical remission in ulcerative colitis: a systematic review and meta-analysis of randomized controlled trials. *Nutrients* 10 (11). https://doi.org/10.3390/nu10111737.

115. Iqbal, U., H. Anwar, and A.A. Quadri. 2018. Use of curcumin in achieving clinical and endoscopic remission in ulcerative colitis: a systematic review and meta-analysis. *The American Journal of the Medical Sciences* 356 (4): 350–356. https://doi.org/10.1016/j.amjms.2018.06.023.

116. Wang, Y., Q. Tang, P. Duan, and L. Yang. 2018. Curcumin as a therapeutic agent for blocking NF-kappaB activation in ulcerative colitis. *Immunopharmacology and Immunotoxicology*: 1–7. https://doi.org/10.1080/08923973.2018.1469145.

117. Kimura, Y., S. Takahashi, and I. Yoshida. 1968. Studies on the constituents of Alpinia. XII. On the constituents of the seeds of Alpinia katsumadai hayata. I. The structure of cardamomin. *Yakugaku Zasshi* 88 (2): 239–241.

118. Lee, J.H., H.S. Jung, P.M. Giang, X. Jin, S. Lee, P.T. Son, D. Lee, Y.S. Hong, K. Lee, and J.J. Lee. 2006. Blockade of nuclear factor-kappaB signaling pathway and anti-inflammatory activity of cardamomin, a chalcone analog from Alpinia conchigera. *The Journal of Pharmacology and Experimental Therapeutics* 316 (1): 271–278. https://doi.org/10.1124/jpet.105.092486.

119. Ren, G., A. Sun, C. Deng, J. Zhang, X. Wu, X. Wei, S. Mani, W. Dou, and Z. Wang. 2015. The anti-inflammatory effect and potential mechanism of cardamonin in DSS-induced colitis. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 309 (7): G517–G527. https://doi.org/10.1152/ajpgi.00133.2015.

120. Ali, A.A., E.N. Abd Al Haleem, S.A. Khaleel, and A.S. Sallam. 2017. Protective effect of cardamonin against acetic acid-induced ulcerative colitis in rats. *Pharmacological Reports* 69 (2): 268–275. https://doi.org/10.1016/j.pharep.2016.11.002.

121. Huo, X., D. Liu, L. Gao, L. Li, and L. Cao. 2016. Flavonoids extracted from licorice prevents colitis-associated carcinogenesis in AOM/DSS mouse model. *International Journal of Molecular Sciences* 17 (9). https://doi.org/10.3390/ijms17091343.

122. Sun, Y., Y. Zhao, J. Yao, L. Zhao, Z. Wu, Y. Wang, D. Pan, H. Miao, Q. Guo, and N. Lu. 2015. Wogonoside protects against dextran sulfate sodium-induced experimental colitis in mice by inhibiting NF-kappaB and NLRP3 inflammasome activation. *Biochemical Pharmacology* 94 (2): 142–154. https://doi.org/10.1016/j.bcp.2015.02.002.

123. Marquez-Flores, Y.K., I. Villegas, A. Cardeno, M.A. Rosillo, and C. Alarcon-de-la-Lastra. 2016. Apigenin supplementation protects the development of dextran sulfate sodium-induced murine experimental colitis by inhibiting canonical and non-canonical inflammasome signaling pathways. *The Journal of Nutritional Biochemistry* 30: 143–152. https://doi.org/10.1016/j.jnutbio.2015.12.002.

124. Liang, J., S. Chen, J. Chen, J. Lin, Q. Xiong, Y. Yang, J. Yuan, et al. 2018. Therapeutic roles of polysaccharides from Dendrobium Officinaleon colitis and its underlying mechanisms. *Carbohydrate Polymers* 185: 159–168. https://doi.org/10.1016/j.carbpol.2018.01.013.

125. Wu, D., K. Wu, Q. Zhu, W. Xiao, Q. Shan, Z. Yan, J. Wu, et al. 2018. Formononetin administration ameliorates dextran sulfate sodium-induced acute colitis by inhibiting NLRP3 Inflammasome signaling pathway. *Mediators of Inflammation* 2018: 3048532. https://doi.org/10.1155/2018/3048532.

126. Shao, B.Z., B.Z. Han, Y.X. Zeng, D.F. Su, and C. Liu. 2016. The roles of macrophage autophagy in atherosclerosis. *Acta Pharmacologica Sinica* 37 (2): 150–156. https://doi.org/10.1038/aps.2015.87.

127. Liao, X., J.C. Sluimer, Y. Wang, M. Subramanian, K. Brown, J.S. Pattison, J. Robbins, J. Martinez, and I. Tabas. 2012. Macrophage autophagy plays a protective role in advanced atherosclerosis. *Cell Metabolism* 15 (4): 545–553. https://doi.org/10.1016/j.cmet.2012.01.022.

128. Qian, Y.N., Y.T. Luo, H.X. Duan, L.Q. Feng, Q. Bi, Y.J. Wang, and X.Y. Yan. 2014. Adhesion molecule CD146 and its soluble form correlate well with carotid atherosclerosis and plaque instability. *CNS Neuroscience & Therapeutics* 20 (5): 438–445. https://doi.org/10.1111/cns.12234.

129. Singh, A., S.L. Kendall, and M. Campanella. 2018. Common traits spark the mitophagy/xenophagy interplay. *Frontiers in Physiology* 9: 1172. https://doi.org/10.3389/fphys.2018.01172.

130. Radomski, N., A. Rebbig, R.M. Leonhardt, and M.R. Knittler. 2017. Xenophagic pathways and their bacterial subversion in cellular self-defense - pialphanutaualpha rhoepsiloniota - everything is in flux. *International Journal of Medical Microbiology* 308: 185–196. https://doi.org/10.1016/j.ijmm.2017.10.012.

131. He, P.X., Y.S. Che, Q.J. He, Y. Chen, and J. Ding. 2014. G226, a novel epipolythiodioxopiperazine derivative, induces autophagy and caspase-dependent apoptosis in human breast cancer cells in vitro. *Acta Pharmacologica Sinica* 35 (8): 1055–1064. https://doi.org/10.1038/aps.2014.47.

132. Mizumura, K., A.M. Choi, and S.W. Ryter. 2014. Emerging role of selective autophagy in human diseases. *Frontiers in Pharmacology* 5: 244. https://doi.org/10.3389/fphar.2014.00244.

133. Mathai, B.J., A.H. Meijer, and A. Simonsen. 2017. Studying autophagy in zebrafish. *Cells* 6 (3). https://doi.org/10.3390/cells6030021.

134. Singh, U.P., N.P. Singh, B. Singh, R.L. Price, M. Nagarkatti, and P.S. Nagarkatti. 2012. Cannabinoid receptor-2 (CB2) agonist ameliorates colitis in IL-10(−/−) mice by attenuating the activation of T cells and promoting their apoptosis. *Toxicology and Applied Pharmacology* 258 (2): 256–267. https://doi.org/10.1016/j.taap.2011.11.005.

135. Tourteau, A., V. Andrzejak, M. Body-Malapel, L. Lemaire, A. Lemoine, R. Mansouri, M. Djouina, N. Renault, J. el Bakali, P. Desreumaux, G.G. Muccioli, D.M. Lambert, P. Chavatte, B. Rigo, N. Leleu-Chavain, and R. Millet. 2013. 3-Carboxamido-5-aryl-isoxazoles as new CB2 agonists for the treatment of colitis. *Bioorganic & Medicinal Chemistry* 21 (17): 5383–5394. https://doi.org/10.1016/j.bmc.2013.06.010.

136. El Bakali, J., G.G. Muccioli, M. Body-Malapel, M. Djouina, F. Klupsch, A. Ghinet, A. Barczyk, et al. 2015. Conformational restriction leading to a selective CB2 cannabinoid receptor agonist

orally active against colitis. *ACS Medicinal Chemistry Letters* 6 (2): 198–203. https://doi.org/10.1021/ml500439x.

137. Shao, B.Z., W. Wei, P. Ke, Z.Q. Xu, J.X. Zhou, and C. Liu. 2014. Activating cannabinoid receptor 2 alleviates pathogenesis of experimental autoimmune encephalomyelitis via activation of autophagy and inhibiting NLRP3 inflammasome. *CNS Neuroscience & Therapeutics* 20 (12): 1021–1028. https://doi.org/10.1111/cns.12349.

138. Li, N., L. Zhou, W. Li, Y. Liu, J. Wang, and P. He. 2015. Protective effects of ginsenosides Rg1 and Rb1 on an Alzheimer's disease mouse model: a metabolomics study. *Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences* 985: 54–61. https://doi.org/10.1016/j.jchromb.2015.01.016.

139. Fang, F., X. Chen, T. Huang, L.F. Lue, J.S. Luddy, and S.S. Yan. 2012. Multi-faced neuroprotective effects of ginsenoside Rg1 in an Alzheimer mouse model. *Biochimica et Biophysica Acta* 1822 (2): 286–292. https://doi.org/10.1016/j.bbadis.2011.10.004.

140. Liu, C., J. Wang, Y. Yang, X. Liu, Y. Zhu, J. Zou, S. Peng, et al. 2018. Ginsenoside Rd ameliorates colitis by inducing p62-driven mitophagy-mediated NLRP3 inflammasome inactivation in mice. *Biochemical Pharmacology* 155: 366–379. https://doi.org/10.1016/j.bcp.2018.07.010.

141. Zheng, X., M. Hu, X. Zang, Q. Fan, Y. Liu, Y. Che, X. Guan, Y. Hou, G. Wang, and H. Hao. 2019. Kynurenic acid/GPR35 axis restricts NLRP3 inflammasome activation and exacerbates colitis in mice with social stress. *Brain, Behavior, and Immunity.* https://doi.org/10.1016/j.bbi.2019.02.009.

142. Ambros, V. 2004. The functions of animal microRNAs. *Nature* 431 (7006): 350–355. https://doi.org/10.1038/nature02871.

143. Bartel, D.P. 2004. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 116 (2): 281–297.

144. Bartel, D.P. 2018. Metazoan microRNAs. *Cell* 173 (1): 20–51. https://doi.org/10.1016/j.cell.2018.03.006.

145. Hessam, S., M. Sand, M. Skrygan, T. Gambichler, and F.G. Bechara. 2017. Expression of miRNA-155, miRNA-223, miRNA-31, miRNA-21, miRNA-125b, and miRNA-146a in the inflammatory pathway of hidradenitis suppurativa. *Inflammation* 40 (2): 464–472. https://doi.org/10.1007/s10753-016-0492-2.

146. Bernardo, B.C., J.Y. Ooi, R.C. Lin, and J.R. McMullen. 2015. miRNA therapeutics: a new class of drugs with potential therapeutic applications in the heart. *Future Medicinal Chemistry* 7 (13): 1771–1792. https://doi.org/10.4155/fmc.15.107.

147. Brennan, E., B. Wang, A. McClelland, M. Mohan, M. Marai, O. Beuscart, S. Derouiche, et al. 2017. Protective effect of let-7 miRNA family in regulating inflammation in diabetes-associated atherosclerosis. *Diabetes* 66 (8): 2266–2277. https://doi.org/10.2337/db16-1405.

148. Improta Caria, A.C., C.K.V. Nonaka, C.S. Pereira, M.B.P. Soares, S.G. Macambira, and B.S.F. Souza. 2018. Exercise training-induced changes in microRNAs: beneficial regulatory effects in hypertension, type 2 diabetes, and obesity. *International Journal of Molecular Sciences* 19 (11). https://doi.org/10.3390/ijms19113608.

149. Kanneganti, T.D. 2017. Inflammatory bowel disease and the NLRP3 inflammasome. *The New England Journal of Medicine* 377 (7): 694–696. https://doi.org/10.1056/NEJMcibr1706536.

150. Neudecker, V., M. Haneklaus, O. Jensen, L. Khailova, J.C. Masterson, H. Tye, K. Biette, et al. 2017. Myeloid-derived miR-223 regulates intestinal inflammation via repression of the NLRP3 inflammasome. *The Journal of Experimental Medicine* 214 (6): 1737–1752. https://doi.org/10.1084/jem.20160462.

151. Shen, F., J. Feng, X. Wang, Z. Qi, X. Shi, Y. An, Q. Zhang, et al. 2016. Vinegar treatment prevents the development of murine experimental colitis via inhibition of inflammation and apoptosis. *Journal of Agricultural and Food Chemistry* 64 (5): 1111–1121. https://doi.org/10.1021/acs.jafc.5b05415.

152. Wang, X., S. Wang, C. Hu, W. Chen, Y. Shen, X. Wu, Y. Sun, and Q. Xu. 2015. A new pharmacological effect of levornidazole: inhibition of NLRP3 inflammasome activation. *Biochemical Pharmacology* 97 (2): 178–188. https://doi.org/10.1016/j.bcp.2015.06.030.

153. Coll, R.C., A.A. Robertson, J.J. Chae, S.C. Higgins, R. Munoz-Planillo, M.C. Inserra, I. Vetter, et al. 2015. A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. *Nature Medicine* 21 (3): 248–255. https://doi.org/10.1038/nm.3806.

154. Liu, W., W. Guo, J. Wu, Q. Luo, F. Tao, Y. Gu, Y. Shen, et al. 2013. A novel benzo[d]imidazole derivate prevents the development of dextran sulfate sodium-induced murine experimental colitis via inhibition of NLRP3 inflammasome. *Biochemical Pharmacology* 85 (10): 1504–1512. https://doi.org/10.1016/j.bcp.2013.03.008.

155. Guo, W., S. Hu, A. Elgehama, F. Shao, R. Ren, W. Liu, W. Zhang, et al. 2015. Fumigaclavine C ameliorates dextran sulfate sodium-induced murine experimental colitis via NLRP3 inflammasome inhibition. *Journal of Pharmacological Sciences* 129 (2): 101–106. https://doi.org/10.1016/j.jphs.2015.05.003.

156. Zaki, M.H., K.L. Boyd, P. Vogel, M.B. Kastan, M. Lamkanfi, and T.D. Kanneganti. 2010. The NLRP3 inflammasome protects against loss of epithelial integrity and mortality during experimental colitis. *Immunity* 32 (3): 379–391. https://doi.org/10.1016/j.immuni.2010.03.003.

157. Hirota, S.A., J. Ng, A. Lueng, M. Khajah, K. Parhar, Y. Li, V. Lam, M.S. Potentier, K. Ng, M. Bawa, D.M. McCafferty, K.P. Rioux, S. Ghosh, R.J. Xavier, S.P. Colgan, J. Tschopp, D. Muruve, J.A. MacDonald, and P.L. Beck. 2011. NLRP3 inflammasome plays a key role in the regulation of intestinal homeostasis. *Inflammatory Bowel Diseases* 17 (6): 1359–1372. https://doi.org/10.1002/ibd.21478.