**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 81687

**Manuscript Type:** REVIEW

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

Ali FE *et al*. Role of NLRP3 inflammasome in ulcerative colitis

Fares E.M Ali, Islam M. Ibrahim, Osama M Ghogar, Esraa K. Abd-alhameed, Hanan S. Althagafy, Emad H.M. Hassanein

**Fares E.M Ali, Emad H.M. Hassanein,** Pharmacology and Toxicology, Faculty of Pharmacy, Al-Azhar University, Assiut Branch, Assiut 71524, Egypt

**Islam M. Ibrahim, Osama M Ghogar,** Faculty of Pharmacy, Al-Azhar University, Assiut Branch, Assiut 71524, Egypt

**Esraa K. Abd-alhameed,** Pharmacology and Toxicology, Faculty of Pharmacy, Beni-Suef University, Beni-Suef 12345, Egypt

**Hanan S. Althagafy,** Department of Biochemistry, Faculty of Science, University of Jeddah, Jeddah 12345, Saudi Arabia

**Author contributions:** Ali FE and Hassanein EH designed and critically wrote the manuscript; Ibrahim IM, Ghogar OM, and Abd-alhameed EKcollected data, and drafted the manuscript; Althagafy HS contributed to manuscript revision and proof editing.

**Corresponding author: Fares E.M Ali, MSc, PhD, Lecturer, Research Scientist,** Pharmacology and Toxicology, Faculty of Pharmacy, Al-Azhar University, Assiut Branch, Al-Azhar Street, Assiut 71524, Egypt. faresali@azhar.edu.eg

**Received:** November 19, 2022

**Revised:** December 29, 2023

**Accepted:** January 29, 2023

**Published online:**

**Abstract**

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

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

Ali FE, Ibrahim IM, Ghogar OM, Abd-alhameed EK, Althagafy HS, Hassanein EH. Therapeutic interventions target the NLRP3 inflammasome in ulcerative colitis: Comprehensive study. *World J Gastroenterol* 2023; In press

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

**INTRODUCTION**

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

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

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

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

**NLRP3 INFLAMMASOME OVERVIEW**

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

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

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

**MECHANISMS OF NLRP3 INFLAMMASOME ACTIVATION**

It is believed that several cellular signals, including ion fluxes (K+ efflux, Cl− efflux, Ca2+ influx, and Na+ influx), mitochondrial dysfunction, and reactive oxygen species (ROS) generation, are responsible for NLRP3 inflammasome activation[55-60]. In addition, heme[61,62], particulate matter[56,63,64], pathogen-associated RNA[65-68], and bacterial and fungal toxins[69,70] are also considered NLRP3 activators.

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

Ca2+ is necessary for NLRP3 inflammasome activation by interacting with inositol 1,4,5-trisphosphate, a byproduct of phosphatidylinositol 4,5-bisphosphate hydrolysis catalyzed by phospholipase C, and the inositol 1,4,5-trisphosphate receptor on the endoplasmic reticulum, which promotes Ca2+ mobilization and NLRP3 inflammasome activation[60]. The NLRP3 inflammasome is activated by excessive ER Ca2+ release associated with mitochondrial damage and results in ROS production and an excess of Ca2+ [74-76]. Additionally, K+ efflux and a reduction in intracellular K+ are upstream events in NLRP3 activation[59,77]. The NLRP3 inflammasome also needs K+ efflux for NLRP3 formation, according to a recently discovered component called NIMA-related kinase 7 (NEK7), which may directly bind to NLRP3 protein[78,79]. Various substances can increase ROS generation and induce NLRP3 activation without requiring K+ efflux[80,81]. Na+ influx-induced NLRP3 activation also relies on K+ efflux[59]. Reducing the concentration of extracellular Cl- activates caspase-1 and the generation of IL-β1[82]. An anion channel called the intracellular chloride channel has the potential to activate the volume-regulated anion channel. It is intriguing since the K+ efflux-mitochondrial ROS axis was shown to be a downstream event of chloride intracellular channel-dependent chloride efflux. Intracellular chloride channel-mediated chloride efflux can encourage NEK7-NLRP3 association and subsequent ASC oligomerization[83].

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

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

**POST-TRANSCRIPTIONAL MODIFICATIONS OF NLRP3**

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

**THERAPEUTIC AVENUES FOR ULCERATIVE COLITIS TARGETED NLRP3 INFLAMMASOME SIGNAL**

***Phytochemicals and plant extracts***

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

**Chlorogenic acid:** Chlorogenic acid (CGA) is a phenolic acid found in foods and many plants[102,103]. Zeng *et al*[104] reported that CGA prevented DSS-induced mice colitis by down-regulating miR-155 expression and suppressing NLRP3 and NF-κB in macrophages. CGA downregulates caspase-1, pro-cleaved-IL-1β, and pro-cleaved-IL-18 in mice with colitis. In line with this study, CGA ameliorates NLRP3 inflammasome in different models, such as CCl4-induced acute liver injury[105] and lipopolysaccharide (LPS)-induced mice with acute lung injury[106].

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

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

**Phloretin:** Phloretin (PHL) is a flavonoid found in fruit, leaves, and roots of the apple tree *Malus domestica*[121,122]. Zhang *et al*[123] demonstrated that PHL suppressed DSS-induced NLRP3 inflammasome activations and regulated the NF-κB, TLR4, and PPARγ pathways. Moreover, PHL attenuated oxidative stress and regulated the expression of ZO-1 and occludin. In the same context, Wu *et al*[124] found that PHL ameliorated UC by suppressing NF-κB and NLRP3 activation. Additionally, it decreases cytokines and oxidative injury while maintaining intestinal barrier integrity.

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

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

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

**Genistein:** Genistein **(**Gen) is a significant isoflavone in soy[142]. Gen suppresses the NLRP3 inflammasome in macrophages by activating the G protein–coupled receptor 5-cAMP signal in DSS-induced UC mice. Additionally, the Gen administration boosted intracellular cAMP levels and decreased caspase-1 and IL-1β levels[143]. In agreement with this study, Gen suppressed the NLRP3 inflammasome in different models, such as cerebral ischemia in mice[144], H2O2-induced senescence of human umbilical vein endothelial cells[145], hippocampal neurons in aging rat brain tissue[146], and alloxan-induced diabetes in mice[147].

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

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

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

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

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

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

**Fumigaclavine C:** Fumigaclavine C is an indole alkaloid obtained from endophytic *Aspergillus terreus* and *Rhizophora stylosa*[175,176]. According to Guo *et al*[177], fumigaclavine C attenuates DSS-induced colitis by decreasing pro-inflammatory cytokines TNF-α, IL-1β, and IL-17A, mediated by suppressing NLRP3 inflammasome and caspase-1 activation.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**PLANT EXTRACT**

***Canna x generalis***

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

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

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

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

***Smilax china* *L.***

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

***Dendrobium officinale***

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

***Schisandra chinensis***

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

***Tripterygium wilfordii***

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

***Rubia cordifolia L.***

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

***Mulberry fruit extract***

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

**PROBIOTICS**

***Akkermansia muciniphila***

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

***Saccharomyces cerevisiae***

A facultative anaerobic fungus called *Saccharomyces cerevisiae* has been extensively employed in medicine to create modified carriers and oral vaccinations[302,303]. According to a study by Sun *et al*[304], modified *S. cerevisiae* reduced the severity of DSS-induced colitis in mice by inhibiting macrophage pyroptosis and regulating the intestinal microbiota. Lactic acid-produced *S. cerevisiae* modulated macrophage polarisation, prevented the production of pro-inflammatory cytokines *in vivo* and *in vitro*, and decreased NLRP3 inflammasome and caspase-1 levels.

***Lactobacillus acidophilus***

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

***Grape seed proanthocyanidin***

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

***Brilliant blue G***

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

***Forsythia suspensa extract***

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

***Kui jie tong***

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

***Jianpi Qingchang decoction***

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

***Bovine milk***

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

**SYNTHETIC DRUGS**

***Mirtazapine***

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

***Paeoniflorin-6’-O-benzene sulfonate***

Paeoniflorin-6*’*-O-benzene sulfonate is a new active monomer created by structurally altering paeoniflorin[334] and has anti-inflammatory and immunomodulatory characteristics[335,336]. According to Li *et al*[337], paeoniflorin-6*’*-O-benzene sulfonate has anti-colitis properties *via* suppressing TLR4-NF-κB and NLRP3 signals and G protein-coupled receptor kinase 2 translocations. Furthermore, paeoniflorin-6*’*-O-benzene sulfonate maintains intestinal barrier function in LPS-treated mice.

***Dapagliflozin***

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

***Canagliflozin***

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

***Rosuvastatin***

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

***MCC950***

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

**CONCLUSION**

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

**REFERENCES**

1 **Shouval DS**, Rufo PA. The Role of Environmental Factors in the Pathogenesis of Inflammatory Bowel Diseases: A Review. *JAMA Pediatr* 2017; **171**: 999-1005 [PMID: 28846760 DOI: 10.1001/jamapediatrics.2017.2571]

2 **Jones GR**, Lyons M, Plevris N, Jenkinson PW, Bisset C, Burgess C, Din S, Fulforth J, Henderson P, Ho GT, Kirkwood K, Noble C, Shand AG, Wilson DC, Arnott ID, Lees CW. IBD prevalence in Lothian, Scotland, derived by capture-recapture methodology. *Gut* 2019; **68**: 1953-1960 [PMID: 31300515 DOI: 10.1136/gutjnl-2019-318936]

3 **Molodecky NA**, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012; **142**: 46-54.e42; quiz e30 [PMID: 22001864 DOI: 10.1053/j.gastro.2011.10.001]

4 **Kaplan GG**. The global burden of IBD: from 2015 to 2025. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 720-727 [PMID: 26323879 DOI: 10.1038/nrgastro.2015.150]

5 **Rosenstiel P**, Sina C, Franke A, Schreiber S. Towards a molecular risk map--recent advances on the etiology of inflammatory bowel disease. *Semin Immunol* 2009; **21**: 334-345 [PMID: 19926490 DOI: 10.1016/j.smim.2009.10.001]

6 **Frolkis A**, Dieleman LA, Barkema HW, Panaccione R, Ghosh S, Fedorak RN, Madsen K, Kaplan GG; Alberta IBD Consortium. Environment and the inflammatory bowel diseases. *Can J Gastroenterol* 2013; **27**: e18-e24 [PMID: 23516681 DOI: 10.1155/2013/102859]

7 **Feuerstein JD**, Moss AC, Farraye FA. Ulcerative Colitis. *Mayo Clin Proc* 2019; **94**: 1357-1373 [PMID: 31272578 DOI: 10.1016/j.mayocp.2019.01.018]

8 **Ford AC**, Moayyedi P, Hanauer SB. Ulcerative colitis. *BMJ* 2013; **346**: f432 [PMID: 23386404 DOI: 10.1136/bmj.f432]

9 **Dignass A**, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, Mantzaris G, Reinisch W, Colombel JF, Vermeire S, Travis S, Lindsay JO, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *J Crohns Colitis* 2012; **6**: 965-990 [PMID: 23040452 DOI: 10.1016/j.crohns.2012.09.003]

10 **Cosnes J**, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011; **140**: 1785-1794 [PMID: 21530745 DOI: 10.1053/j.gastro.2011.01.055]

11 **Sýkora J**, Pomahačová R, Kreslová M, Cvalínová D, Štych P, Schwarz J. Current global trends in the incidence of pediatric-onset inflammatory bowel disease. *World J Gastroenterol* 2018; **24**: 2741-2763 [PMID: 29991879 DOI: 10.3748/wjg.v24.i25.2741]

12 **Halme L**, Paavola-Sakki P, Turunen U, Lappalainen M, Farkkila M, Kontula K. Family and twin studies in inflammatory bowel disease. *World J Gastroenterol* 2006; **12**: 3668-3672 [PMID: 16773682 DOI: 10.3748/wjg.v12.i23.3668]

13 **Moller FT**, Andersen V, Wohlfahrt J, Jess T. Familial risk of inflammatory bowel disease: a population-based cohort study 1977-2011. *Am J Gastroenterol* 2015; **110**: 564-571 [PMID: 25803400 DOI: 10.1038/ajg.2015.50]

14 **Ng SC**, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017; **390**: 2769-2778 [PMID: 29050646 DOI: 10.1016/S0140-6736(17)32448-0]

15 **Jostins L**, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, Lee JC, Schumm LP, Sharma Y, Anderson CA, Essers J, Mitrovic M, Ning K, Cleynen I, Theatre E, Spain SL, Raychaudhuri S, Goyette P, Wei Z, Abraham C, Achkar JP, Ahmad T, Amininejad L, Ananthakrishnan AN, Andersen V, Andrews JM, Baidoo L, Balschun T, Bampton PA, Bitton A, Boucher G, Brand S, Büning C, Cohain A, Cichon S, D'Amato M, De Jong D, Devaney KL, Dubinsky M, Edwards C, Ellinghaus D, Ferguson LR, Franchimont D, Fransen K, Gearry R, Georges M, Gieger C, Glas J, Haritunians T, Hart A, Hawkey C, Hedl M, Hu X, Karlsen TH, Kupcinskas L, Kugathasan S, Latiano A, Laukens D, Lawrance IC, Lees CW, Louis E, Mahy G, Mansfield J, Morgan AR, Mowat C, Newman W, Palmieri O, Ponsioen CY, Potocnik U, Prescott NJ, Regueiro M, Rotter JI, Russell RK, Sanderson JD, Sans M, Satsangi J, Schreiber S, Simms LA, Sventoraityte J, Targan SR, Taylor KD, Tremelling M, Verspaget HW, De Vos M, Wijmenga C, Wilson DC, Winkelmann J, Xavier RJ, Zeissig S, Zhang B, Zhang CK, Zhao H; International IBD Genetics Consortium (IIBDGC), Silverberg MS, Annese V, Hakonarson H, Brant SR, Radford-Smith G, Mathew CG, Rioux JD, Schadt EE, Daly MJ, Franke A, Parkes M, Vermeire S, Barrett JC, Cho JH. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 2012; **491**: 119-124 [PMID: 23128233 DOI: 10.1038/nature11582]

16 **Goyette P**, Boucher G, Mallon D, Ellinghaus E, Jostins L, Huang H, Ripke S, Gusareva ES, Annese V, Hauser SL, Oksenberg JR, Thomsen I, Leslie S; International Inflammatory Bowel Disease Genetics Consortium; Australia and New Zealand IBDGC; Belgium IBD Genetics Consortium; Italian Group for IBD Genetic Consortium; NIDDK Inflammatory Bowel Disease Genetics Consortium; United Kingdom IBDGC; Wellcome Trust Case Control Consortium; Quebec IBD Genetics Consortium, Daly MJ, Van Steen K, Duerr RH, Barrett JC, McGovern DP, Schumm LP, Traherne JA, Carrington MN, Kosmoliaptsis V, Karlsen TH, Franke A, Rioux JD. High-density mapping of the MHC identifies a shared role for HLA-DRB1\*01:03 in inflammatory bowel diseases and heterozygous advantage in ulcerative colitis. *Nat Genet* 2015; **47**: 172-179 [PMID: 25559196 DOI: 10.1038/ng.3176]

17 **Cattin AL**, Le Beyec J, Barreau F, Saint-Just S, Houllier A, Gonzalez FJ, Robine S, Pinçon-Raymond M, Cardot P, Lacasa M, Ribeiro A. Hepatocyte nuclear factor 4alpha, a key factor for homeostasis, cell architecture, and barrier function of the adult intestinal epithelium. *Mol Cell Biol* 2009; **29**: 6294-6308 [PMID: 19805521 DOI: 10.1128/MCB.00939-09]

18 **Asano K**, Matsushita T, Umeno J, Hosono N, Takahashi A, Kawaguchi T, Matsumoto T, Matsui T, Kakuta Y, Kinouchi Y, Shimosegawa T, Hosokawa M, Arimura Y, Shinomura Y, Kiyohara Y, Tsunoda T, Kamatani N, Iida M, Nakamura Y, Kubo M. A genome-wide association study identifies three new susceptibility loci for ulcerative colitis in the Japanese population. *Nat Genet* 2009; **41**: 1325-1329 [PMID: 19915573 DOI: 10.1038/ng.482]

19 **Sands BE**, Kaplan GG. The role of TNFalpha in ulcerative colitis. *J Clin Pharmacol* 2007; **47**: 930-941 [PMID: 17567930 DOI: 10.1177/0091270007301623]

20 **Van Klinken BJ**, Van der Wal JW, Einerhand AW, Büller HA, Dekker J. Sulphation and secretion of the predominant secretory human colonic mucin MUC2 in ulcerative colitis. *Gut* 1999; **44**: 387-393 [PMID: 10026326 DOI: 10.1136/gut.44.3.387]

21 **Klein A**, Eliakim R. Non Steroidal Anti-Inflammatory Drugs and Inflammatory Bowel Disease. *Pharmaceuticals (Basel)* 2010; **3**: 1084-1092 [PMID: 27713289 DOI: 10.3390/ph3041084]

22 **Chassaing B**, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE, Gewirtz AT. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature* 2015; **519**: 92-96 [PMID: 25731162 DOI: 10.1038/nature14232]

23 **Lloyd-Price J**, Arze C, Ananthakrishnan AN, Schirmer M, Avila-Pacheco J, Poon TW, Andrews E, Ajami NJ, Bonham KS, Brislawn CJ, Casero D, Courtney H, Gonzalez A, Graeber TG, Hall AB, Lake K, Landers CJ, Mallick H, Plichta DR, Prasad M, Rahnavard G, Sauk J, Shungin D, Vázquez-Baeza Y, White RA 3rd; IBDMDB Investigators, Braun J, Denson LA, Jansson JK, Knight R, Kugathasan S, McGovern DPB, Petrosino JF, Stappenbeck TS, Winter HS, Clish CB, Franzosa EA, Vlamakis H, Xavier RJ, Huttenhower C. Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. *Nature* 2019; **569**: 655-662 [PMID: 31142855 DOI: 10.1038/s41586-019-1237-9]

24 **Duvallet C**, Gibbons SM, Gurry T, Irizarry RA, Alm EJ. Meta-analysis of gut microbiome studies identifies disease-specific and shared responses. *Nat Commun* 2017; **8**: 1784 [PMID: 29209090 DOI: 10.1038/s41467-017-01973-8]

25 **Gevers D**, Kugathasan S, Denson LA, Vázquez-Baeza Y, Van Treuren W, Ren B, Schwager E, Knights D, Song SJ, Yassour M, Morgan XC, Kostic AD, Luo C, González A, McDonald D, Haberman Y, Walters T, Baker S, Rosh J, Stephens M, Heyman M, Markowitz J, Baldassano R, Griffiths A, Sylvester F, Mack D, Kim S, Crandall W, Hyams J, Huttenhower C, Knight R, Xavier RJ. The treatment-naive microbiome in new-onset Crohn's disease. *Cell Host Microbe* 2014; **15**: 382-392 [PMID: 24629344 DOI: 10.1016/j.chom.2014.02.005]

26 **Heller F**, Florian P, Bojarski C, Richter J, Christ M, Hillenbrand B, Mankertz J, Gitter AH, Bürgel N, Fromm M, Zeitz M, Fuss I, Strober W, Schulzke JD. Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. *Gastroenterology* 2005; **129**: 550-564 [PMID: 16083712 DOI: 10.1016/j.gastro.2005.05.002]

27 **Ordás I**, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet* 2012; **380**: 1606-1619 [PMID: 22914296 DOI: 10.1016/S0140-6736(12)60150-0]

28 **Kaser A**, Adolph TE, Blumberg RS. The unfolded protein response and gastrointestinal disease. *Semin Immunopathol* 2013; **35**: 307-319 [PMID: 23588234 DOI: 10.1007/s00281-013-0377-5]

29 **Tak E**, Park GC, Kim SH, Jun DY, Lee J, Hwang S, Song GW, Lee SG. Epigallocatechin-3-gallate protects against hepatic ischaemia-reperfusion injury by reducing oxidative stress and apoptotic cell death. *J Int Med Res* 2016; **44**: 1248-1262 [PMID: 27807255 DOI: 10.1177/0300060516662735]

30 **Zhang FX**, Kirschning CJ, Mancinelli R, Xu XP, Jin Y, Faure E, Mantovani A, Rothe M, Muzio M, Arditi M. Bacterial lipopolysaccharide activates nuclear factor-kappaB through interleukin-1 signaling mediators in cultured human dermal endothelial cells and mononuclear phagocytes. *J Biol Chem* 1999; **274**: 7611-7614 [PMID: 10075645 DOI: 10.1074/jbc.274.12.7611]

31 **Hart AL**, Al-Hassi HO, Rigby RJ, Bell SJ, Emmanuel AV, Knight SC, Kamm MA, Stagg AJ. Characteristics of intestinal dendritic cells in inflammatory bowel diseases. *Gastroenterology* 2005; **129**: 50-65 [PMID: 16012934 DOI: 10.1053/j.gastro.2005.05.013]

32 **Danese S**, D'Amico F, Bonovas S, Peyrin-Biroulet L. Positioning Tofacitinib in the Treatment Algorithm of Moderate to Severe Ulcerative Colitis. *Inflamm Bowel Dis* 2018; **24**: 2106-2112 [PMID: 29697791 DOI: 10.1093/ibd/izy076]

33 **Danese S**, Grisham M, Hodge J, Telliez JB. JAK inhibition using tofacitinib for inflammatory bowel disease treatment: a hub for multiple inflammatory cytokines. *Am J Physiol Gastrointest Liver Physiol* 2016; **310**: G155-G162 [PMID: 26608188 DOI: 10.1152/ajpgi.00311.2015]

34 **Próchnicki T**, Mangan MS, Latz E. Recent insights into the molecular mechanisms of the NLRP3 inflammasome activation. *F1000Res* 2016; **5** [PMID: 27508077 DOI: 10.12688/f1000research.8614.1]

35 **Mangan MSJ**, Olhava EJ, Roush WR, Seidel HM, Glick GD, Latz E. Targeting the NLRP3 inflammasome in inflammatory diseases. *Nat Rev Drug Discov* 2018; **17**: 588-606 [PMID: 30026524 DOI: 10.1038/nrd.2018.97]

36 **Gong T**, Liu L, Jiang W, Zhou R. DAMP-sensing receptors in sterile inflammation and inflammatory diseases. *Nat Rev Immunol* 2020; **20**: 95-112 [PMID: 31558839 DOI: 10.1038/s41577-019-0215-7]

37 **Cao X**. Self-regulation and cross-regulation of pattern-recognition receptor signalling in health and disease. *Nat Rev Immunol* 2016; **16**: 35-50 [PMID: 26711677 DOI: 10.1038/nri.2015.8]

38 **Allen IC**, Scull MA, Moore CB, Holl EK, McElvania-TeKippe E, Taxman DJ, Guthrie EH, Pickles RJ, Ting JP. The NLRP3 inflammasome mediates in vivo innate immunity to influenza A virus through recognition of viral RNA. *Immunity* 2009; **30**: 556-565 [PMID: 19362020 DOI: 10.1016/j.immuni.2009.02.005]

39 **Gross O**, Poeck H, Bscheider M, Dostert C, Hannesschläger N, Endres S, Hartmann G, Tardivel A, Schweighoffer E, Tybulewicz V, Mocsai A, Tschopp J, Ruland J. Syk kinase signalling couples to the Nlrp3 inflammasome for anti-fungal host defence. *Nature* 2009; **459**: 433-436 [PMID: 19339971 DOI: 10.1038/nature07965]

40 **Kanneganti TD**, Body-Malapel M, Amer A, Park JH, Whitfield J, Franchi L, Taraporewala ZF, Miller D, Patton JT, Inohara N, Núñez G. Critical role for Cryopyrin/Nalp3 in activation of caspase-1 in response to viral infection and double-stranded RNA. *J Biol Chem* 2006; **281**: 36560-36568 [PMID: 17008311 DOI: 10.1074/jbc.M607594200]

41 **Thomas PG**, Dash P, Aldridge JR Jr, Ellebedy AH, Reynolds C, Funk AJ, Martin WJ, Lamkanfi M, Webby RJ, Boyd KL, Doherty PC, Kanneganti TD. The intracellular sensor NLRP3 mediates key innate and healing responses to influenza A virus via the regulation of caspase-1. *Immunity* 2009; **30**: 566-575 [PMID: 19362023 DOI: 10.1016/j.immuni.2009.02.006]

42 **Strowig T**, Henao-Mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. *Nature* 2012; **481**: 278-286 [PMID: 22258606 DOI: 10.1038/nature10759]

43 **Rheinheimer J**, de Souza BM, Cardoso NS, Bauer AC, Crispim D. Current role of the NLRP3 inflammasome on obesity and insulin resistance: A systematic review. *Metabolism* 2017; **74**: 1-9 [PMID: 28764843 DOI: 10.1016/j.metabol.2017.06.002]

44 **Sun HJ**, Ren XS, Xiong XQ, Chen YZ, Zhao MX, Wang JJ, Zhou YB, Han Y, Chen Q, Li YH, Kang YM, Zhu GQ. NLRP3 inflammasome activation contributes to VSMC phenotypic transformation and proliferation in hypertension. *Cell Death Dis* 2017; **8**: e3074 [PMID: 28981106 DOI: 10.1038/cddis.2017.470]

45 **Guo H**, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. *Nat Med* 2015; **21**: 677-687 [PMID: 26121197 DOI: 10.1038/nm.3893]

46 **Menu P**, Vince JE. The NLRP3 inflammasome in health and disease: the good, the bad and the ugly. *Clin Exp Immunol* 2011; **166**: 1-15 [PMID: 21762124 DOI: 10.1111/j.1365-2249.2011.04440.x]

47 **Franchi L**, Warner N, Viani K, Nuñez G. Function of Nod-like receptors in microbial recognition and host defense. *Immunol Rev* 2009; **227**: 106-128 [PMID: 19120480 DOI: 10.1111/j.1600-065X.2008.00734.x]

48 **Fernandes-Alnemri T**, Wu J, Yu JW, Datta P, Miller B, Jankowski W, Rosenberg S, Zhang J, Alnemri ES. The pyroptosome: a supramolecular assembly of ASC dimers mediating inflammatory cell death via caspase-1 activation. *Cell Death Differ* 2007; **14**: 1590-1604 [PMID: 17599095 DOI: 10.1038/sj.cdd.4402194]

49 **Vajjhala PR**, Mirams RE, Hill JM. Multiple binding sites on the pyrin domain of ASC protein allow self-association and interaction with NLRP3 protein. *J Biol Chem* 2012; **287**: 41732-41743 [PMID: 23066025 DOI: 10.1074/jbc.M112.381228]

50 **De Nardo D**, Latz E. NLRP3 inflammasomes link inflammation and metabolic disease. *Trends Immunol* 2011; **32**: 373-379 [PMID: 21733753 DOI: 10.1016/j.it.2011.05.004]

51 **He WT**, Wan H, Hu L, Chen P, Wang X, Huang Z, Yang ZH, Zhong CQ, Han J. Gasdermin D is an executor of pyroptosis and required for interleukin-1β secretion. *Cell Res* 2015; **25**: 1285-1298 [PMID: 26611636 DOI: 10.1038/cr.2015.139]

52 **Ali F**, Abo-Youssef A, Messiha B, Hemeda R. Protective effects of quercetin and ursodeoxycholic acid on hepatic ischemiareperfusion injury in rats. *Clin Pharmacol Biopharm* 2015; **4**: 2

53 **Ding J**, Wang K, Liu W, She Y, Sun Q, Shi J, Sun H, Wang DC, Shao F. Pore-forming activity and structural autoinhibition of the gasdermin family. *Nature* 2016; **535**: 111-116 [PMID: 27281216 DOI: 10.1038/nature18590]

54 **Dinarello CA**. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol* 2009; **27**: 519-550 [PMID: 19302047 DOI: 10.1146/annurev.immunol.021908.132612]

55 **Yang Y**, Wang H, Kouadir M, Song H, Shi F. Recent advances in the mechanisms of NLRP3 inflammasome activation and its inhibitors. *Cell Death Dis* 2019; **10**: 128 [PMID: 30755589 DOI: 10.1038/s41419-019-1413-8]

56 **Mariathasan S**, Weiss DS, Newton K, McBride J, O'Rourke K, Roose-Girma M, Lee WP, Weinrauch Y, Monack DM, Dixit VM. Cryopyrin activates the inflammasome in response to toxins and ATP. *Nature* 2006; **440**: 228-232 [PMID: 16407890 DOI: 10.1038/nature04515]

57 **Green JP**, Yu S, Martín-Sánchez F, Pelegrin P, Lopez-Castejon G, Lawrence CB, Brough D. Chloride regulates dynamic NLRP3-dependent ASC oligomerization and inflammasome priming. *Proc Natl Acad Sci U S A* 2018; **115**: E9371-E9380 [PMID: 30232264 DOI: 10.1073/pnas.1812744115]

58 **Katsnelson M**, Dubyak G. Cytosolic K+ and extracellular Na+ as regulators of NLRP3 inflammasome activation and the IL-1β secretion response of macrophages to crystalline stimuli. 2013. Available from: https://faseb.onlinelibrary.wiley.com/doi/10.1096/fasebj.27.1\_supplement.138.8

59 **Muñoz-Planillo R**, Kuffa P, Martínez-Colón G, Smith BL, Rajendiran TM, Núñez G. K⁺ efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. *Immunity* 2013; **38**: 1142-1153 [PMID: 23809161 DOI: 10.1016/j.immuni.2013.05.016]

60 **Murakami T**, Ockinger J, Yu J, Byles V, McColl A, Hofer AM, Horng T. Critical role for calcium mobilization in activation of the NLRP3 inflammasome. *Proc Natl Acad Sci U S A* 2012; **109**: 11282-11287 [PMID: 22733741 DOI: 10.1073/pnas.1117765109]

61 **Erdei J**, Tóth A, Balogh E, Nyakundi BB, Bányai E, Ryffel B, Paragh G, Cordero MD, Jeney V. Induction of NLRP3 Inflammasome Activation by Heme in Human Endothelial Cells. *Oxid Med Cell Longev* 2018; **2018**: 4310816 [PMID: 29743981 DOI: 10.1155/2018/4310816]

62 **Silveira AA**, Cunningham C, Corr E, Ferreira Jr WA, Costa FF, Almeida CB, Conran N, Dunne A. Heme Induces NLRP3 Inflammasome Formation in Primary Human Macrophages and May Propagate Hemolytic Inflammatory Processes by Inducing S100A8 Expression. *Blood* 2016; **128**: 1256

63 **Dostert C**, Pétrilli V, Van Bruggen R, Steele C, Mossman BT, Tschopp J. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science* 2008; **320**: 674-677 [PMID: 18403674 DOI: 10.1126/science.1156995]

64 **Hornung V**, Bauernfeind F, Halle A, Samstad EO, Kono H, Rock KL, Fitzgerald KA, Latz E. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. *Nat Immunol* 2008; **9**: 847-856 [PMID: 18604214 DOI: 10.1038/ni.1631]

65 **Eigenbrod T**, Dalpke AH. Bacterial RNA: An Underestimated Stimulus for Innate Immune Responses. *J Immunol* 2015; **195**: 411-418 [PMID: 26138638 DOI: 10.4049/jimmunol.1500530]

66 **Gupta R**, Ghosh S, Monks B, DeOliveira RB, Tzeng TC, Kalantari P, Nandy A, Bhattacharjee B, Chan J, Ferreira F, Rathinam V, Sharma S, Lien E, Silverman N, Fitzgerald K, Firon A, Trieu-Cuot P, Henneke P, Golenbock DT. RNA and β-hemolysin of group B Streptococcus induce interleukin-1β (IL-1β) by activating NLRP3 inflammasomes in mouse macrophages. *J Biol Chem* 2014; **289**: 13701-13705 [PMID: 24692555 DOI: 10.1074/jbc.C114.548982]

67 **Kanneganti TD**, Ozören N, Body-Malapel M, Amer A, Park JH, Franchi L, Whitfield J, Barchet W, Colonna M, Vandenabeele P, Bertin J, Coyle A, Grant EP, Akira S, Núñez G. Bacterial RNA and small antiviral compounds activate caspase-1 through cryopyrin/Nalp3. *Nature* 2006; **440**: 233-236 [PMID: 16407888 DOI: 10.1038/nature04517]

68 **Sha W**, Mitoma H, Hanabuchi S, Bao M, Weng L, Sugimoto N, Liu Y, Zhang Z, Zhong J, Sun B, Liu YJ. Human NLRP3 inflammasome senses multiple types of bacterial RNAs. *Proc Natl Acad Sci U S A* 2014; **111**: 16059-16064 [PMID: 25355909 DOI: 10.1073/pnas.1412487111]

69 **Kasper L**, König A, Koenig PA, Gresnigt MS, Westman J, Drummond RA, Lionakis MS, Groß O, Ruland J, Naglik JR, Hube B. The fungal peptide toxin Candidalysin activates the NLRP3 inflammasome and causes cytolysis in mononuclear phagocytes. *Nat Commun* 2018; **9**: 4260 [PMID: 30323213 DOI: 10.1038/s41467-018-06607-1]

70 **Mathur A**, Feng S, Hayward JA, Ngo C, Fox D, Atmosukarto II, Price JD, Schauer K, Märtlbauer E, Robertson AAB, Burgio G, Fox EM, Leppla SH, Kaakoush NO, Man SM. A multicomponent toxin from Bacillus cereus incites inflammation and shapes host outcome via the NLRP3 inflammasome. *Nat Microbiol* 2019; **4**: 362-374 [PMID: 30531979 DOI: 10.1038/s41564-018-0318-0]

71 **Bauernfeind FG**, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, Fernandes-Alnemri T, Wu J, Monks BG, Fitzgerald KA, Hornung V, Latz E. Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. *J Immunol* 2009; **183**: 787-791 [PMID: 19570822 DOI: 10.4049/jimmunol.0901363]

72 **Franchi L**, Eigenbrod T, Núñez G. Cutting edge: TNF-alpha mediates sensitization to ATP and silica via the NLRP3 inflammasome in the absence of microbial stimulation. *J Immunol* 2009; **183**: 792-796 [PMID: 19542372 DOI: 10.4049/jimmunol.0900173]

73 **Allam R**, Lawlor KE, Yu EC, Mildenhall AL, Moujalled DM, Lewis RS, Ke F, Mason KD, White MJ, Stacey KJ, Strasser A, O'Reilly LA, Alexander W, Kile BT, Vaux DL, Vince JE. Mitochondrial apoptosis is dispensable for NLRP3 inflammasome activation but non-apoptotic caspase-8 is required for inflammasome priming. *EMBO Rep* 2014; **15**: 982-990 [PMID: 24990442 DOI: 10.15252/embr.201438463]

74 **Camello-Almaraz C**, Gomez-Pinilla PJ, Pozo MJ, Camello PJ. Mitochondrial reactive oxygen species and Ca2+ signaling. *Am J Physiol Cell Physiol* 2006; **291**: C1082-C1088 [PMID: 16760264 DOI: 10.1152/ajpcell.00217.2006]

75 **Csordás G**, Hajnóczky G. SR/ER-mitochondrial local communication: calcium and ROS. *Biochim Biophys Acta* 2009; **1787**: 1352-1362 [PMID: 19527680 DOI: 10.1016/j.bbabio.2009.06.004]

76 **Lemasters JJ**, Theruvath TP, Zhong Z, Nieminen AL. Mitochondrial calcium and the permeability transition in cell death. *Biochim Biophys Acta* 2009; **1787**: 1395-1401 [PMID: 19576166 DOI: 10.1016/j.bbabio.2009.06.009]

77 **Pétrilli V**, Papin S, Dostert C, Mayor A, Martinon F, Tschopp J. Activation of the NALP3 inflammasome is triggered by low intracellular potassium concentration. *Cell Death Differ* 2007; **14**: 1583-1589 [PMID: 17599094 DOI: 10.1038/sj.cdd.4402195]

78 **He Y**, Zeng MY, Yang D, Motro B, Núñez G. NEK7 is an essential mediator of NLRP3 activation downstream of potassium efflux. *Nature* 2016; **530**: 354-357 [PMID: 26814970 DOI: 10.1038/nature16959]

79 **Shi H**, Wang Y, Li X, Zhan X, Tang M, Fina M, Su L, Pratt D, Bu CH, Hildebrand S, Lyon S, Scott L, Quan J, Sun Q, Russell J, Arnett S, Jurek P, Chen D, Kravchenko VV, Mathison JC, Moresco EM, Monson NL, Ulevitch RJ, Beutler B. NLRP3 activation and mitosis are mutually exclusive events coordinated by NEK7, a new inflammasome component. *Nat Immunol* 2016; **17**: 250-258 [PMID: 26642356 DOI: 10.1038/ni.3333]

80 **Groß CJ**, Mishra R, Schneider KS, Médard G, Wettmarshausen J, Dittlein DC, Shi H, Gorka O, Koenig PA, Fromm S, Magnani G, Ćiković T, Hartjes L, Smollich J, Robertson AAB, Cooper MA, Schmidt-Supprian M, Schuster M, Schroder K, Broz P, Traidl-Hoffmann C, Beutler B, Kuster B, Ruland J, Schneider S, Perocchi F, Groß O. K(+) Efflux-Independent NLRP3 Inflammasome Activation by Small Molecules Targeting Mitochondria. *Immunity* 2016; **45**: 761-773 [PMID: 27692612 DOI: 10.1016/j.immuni.2016.08.010]

81 **Sanman LE**, Qian Y, Eisele NA, Ng TM, van der Linden WA, Monack DM, Weerapana E, Bogyo M. Disruption of glycolytic flux is a signal for inflammasome signaling and pyroptotic cell death. *Elife* 2016; **5**: e13663 [PMID: 27011353 DOI: 10.7554/eLife.13663]

82 **Verhoef PA**, Kertesy SB, Lundberg K, Kahlenberg JM, Dubyak GR. Inhibitory effects of chloride on the activation of caspase-1, IL-1beta secretion, and cytolysis by the P2X7 receptor. *J Immunol* 2005; **175**: 7623-7634 [PMID: 16301672 DOI: 10.4049/jimmunol.175.11.7623]

83 **Tang T**, Lang X, Xu C, Wang X, Gong T, Yang Y, Cui J, Bai L, Wang J, Jiang W, Zhou R. CLICs-dependent chloride efflux is an essential and proximal upstream event for NLRP3 inflammasome activation. *Nat Commun* 2017; **8**: 202 [PMID: 28779175 DOI: 10.1038/s41467-017-00227-x]

84 **Nakahira K**, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, Englert JA, Rabinovitch M, Cernadas M, Kim HP, Fitzgerald KA, Ryter SW, Choi AM. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. *Nat Immunol* 2011; **12**: 222-230 [PMID: 21151103 DOI: 10.1038/ni.1980]

85 **Heid ME**, Keyel PA, Kamga C, Shiva S, Watkins SC, Salter RD. Mitochondrial reactive oxygen species induces NLRP3-dependent lysosomal damage and inflammasome activation. *J Immunol* 2013; **191**: 5230-5238 [PMID: 24089192 DOI: 10.4049/jimmunol.1301490]

86 **Sorbara MT**, Girardin SE. Mitochondrial ROS fuel the inflammasome. *Cell Res* 2011; **21**: 558-560 [PMID: 21283134 DOI: 10.1038/cr.2011.20]

87 **Zhou R**, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. *Nature* 2011; **469**: 221-225 [PMID: 21124315 DOI: 10.1038/nature09663]

88 **Cruz CM**, Rinna A, Forman HJ, Ventura AL, Persechini PM, Ojcius DM. ATP activates a reactive oxygen species-dependent oxidative stress response and secretion of proinflammatory cytokines in macrophages. *J Biol Chem* 2007; **282**: 2871-2879 [PMID: 17132626 DOI: 10.1074/jbc.M608083200]

89 **Moon JS**, Nakahira K, Chung KP, DeNicola GM, Koo MJ, Pabón MA, Rooney KT, Yoon JH, Ryter SW, Stout-Delgado H, Choi AM. NOX4-dependent fatty acid oxidation promotes NLRP3 inflammasome activation in macrophages. *Nat Med* 2016; **22**: 1002-1012 [PMID: 27455510 DOI: 10.1038/nm.4153]

90 **Weber K**, Schilling JD. Lysosomes integrate metabolic-inflammatory cross-talk in primary macrophage inflammasome activation. *J Biol Chem* 2014; **289**: 9158-9171 [PMID: 24532802 DOI: 10.1074/jbc.M113.531202]

91 **Schorn C**, Frey B, Lauber K, Janko C, Strysio M, Keppeler H, Gaipl US, Voll RE, Springer E, Munoz LE, Schett G, Herrmann M. Sodium overload and water influx activate the NALP3 inflammasome. *J Biol Chem* 2011; **286**: 35-41 [PMID: 21051542 DOI: 10.1074/jbc.M110.139048]

92 **Liu J**, Qian C, Cao X. Post-Translational Modification Control of Innate Immunity. *Immunity* 2016; **45**: 15-30 [PMID: 27438764 DOI: 10.1016/j.immuni.2016.06.020]

93 **Juliana C**, Fernandes-Alnemri T, Kang S, Farias A, Qin F, Alnemri ES. Non-transcriptional priming and deubiquitination regulate NLRP3 inflammasome activation. *J Biol Chem* 2012; **287**: 36617-36622 [PMID: 22948162 DOI: 10.1074/jbc.M112.407130]

94 **Rodgers MA**, Bowman JW, Fujita H, Orazio N, Shi M, Liang Q, Amatya R, Kelly TJ, Iwai K, Ting J, Jung JU. The linear ubiquitin assembly complex (LUBAC) is essential for NLRP3 inflammasome activation. *J Exp Med* 2014; **211**: 1333-1347 [PMID: 24958845 DOI: 10.1084/jem.20132486]

95 **Song N**, Liu ZS, Xue W, Bai ZF, Wang QY, Dai J, Liu X, Huang YJ, Cai H, Zhan XY, Han QY, Wang H, Chen Y, Li HY, Li AL, Zhang XM, Zhou T, Li T. NLRP3 Phosphorylation Is an Essential Priming Event for Inflammasome Activation. *Mol Cell* 2017; **68**: 185-197.e6 [PMID: 28943315 DOI: 10.1016/j.molcel.2017.08.017]

96 **Wong KC**, Pang WY, Wang XL, Mok SK, Lai WP, Chow HK, Leung PC, Yao XS, Wong MS. Drynaria fortunei-derived total flavonoid fraction and isolated compounds exert oestrogen-like protective effects in bone. *Br J Nutr* 2013; **110**: 475-485 [PMID: 23302510 DOI: 10.1017/S0007114512005405]

97 **Manners GD**. Citrus limonoids: analysis, bioactivity, and biomedical prospects. *J Agric Food Chem* 2007; **55**: 8285-8294 [PMID: 17892257 DOI: 10.1021/jf071797h]

98 **Sui GG**, Xiao HB, Lu XY, Sun ZL. Naringin Activates AMPK Resulting in Altered Expression of SREBPs, PCSK9, and LDLR To Reduce Body Weight in Obese C57BL/6J Mice. *J Agric Food Chem* 2018; **66**: 8983-8990 [PMID: 30092639 DOI: 10.1021/acs.jafc.8b02696]

99 **Kumar VS**, Rajmane AR, Adil M, Kandhare AD, Ghosh P, Bodhankar SL. Naringin ameliorates acetic acid induced colitis through modulation of endogenous oxido-nitrosative balance and DNA damage in rats. *J Biomed Res* 2014; **28**: 132-145 [PMID: 24683411 DOI: 10.7555/JBR.27.20120082]

100 **Zhang YS**, Wang F, Cui SX, Qu XJ. Natural dietary compound naringin prevents azoxymethane/dextran sodium sulfate-induced chronic colorectal inflammation and carcinogenesis in mice. *Cancer Biol Ther* 2018; **19**: 735-744 [PMID: 29580144 DOI: 10.1080/15384047.2018.1453971]

101 **Cao H**, Liu J, Shen P, Cai J, Han Y, Zhu K, Fu Y, Zhang N, Zhang Z, Cao Y. Protective Effect of Naringin on DSS-Induced Ulcerative Colitis in Mice. *J Agric Food Chem* 2018; **66**: 13133-13140 [PMID: 30472831 DOI: 10.1021/acs.jafc.8b03942]

102 **Venditti A**, Bianco A, Frezza C, Conti F, Bini LM, Giuliani C, Bramucci M, Quassinti L, Damiano S, Lupidi GJIc, products. Essential oil composition, polar compounds, glandular trichomes and biological activity of Hyssopus officinalis subsp. aristatus (Godr.) *Nyman from central Italy* 2015; **77**: 353-363

103 **Upadhyay R**, Mohan Rao LJ. An outlook on chlorogenic acids-occurrence, chemistry, technology, and biological activities. *Crit Rev Food Sci Nutr* 2013; **53**: 968-984 [PMID: 23768188 DOI: 10.1080/10408398.2011.576319]

104 **Zeng J**, Zhang D, Wan X, Bai Y, Yuan C, Wang T, Yuan D, Zhang C, Liu C. Chlorogenic Acid Suppresses miR-155 and Ameliorates Ulcerative Colitis through the NF-κB/NLRP3 Inflammasome Pathway. *Mol Nutr Food Res* 2020: e2000452 [PMID: 33078870 DOI: 10.1002/mnfr.202000452]

105 **Shi A**, Shi H, Wang Y, Liu X, Cheng Y, Li H, Zhao H, Wang S, Dong L. Activation of Nrf2 pathway and inhibition of NLRP3 inflammasome activation contribute to the protective effect of chlorogenic acid on acute liver injury. *Int Immunopharmacol* 2018; **54**: 125-130 [PMID: 29128856 DOI: 10.1016/j.intimp.2017.11.007]

106 **Zhang L**, Fan Y, Su H, Wu L, Huang Y, Zhao L, Han B, Shu G, Xiang M, Yang JM. Chlorogenic acid methyl ester exerts strong anti-inflammatory effects via inhibiting the COX-2/NLRP3/NF-κB pathway. *Food Funct* 2018; **9**: 6155-6164 [PMID: 30379164 DOI: 10.1039/c8fo01281d]

107 **Mouli VP**, Ananthakrishnan AN. Review article: vitamin D and inflammatory bowel diseases. *Aliment Pharmacol Ther* 2014; **39**: 125-136 [PMID: 24236989 DOI: 10.1111/apt.12553]

108 **Li H**, Zhong X, Li W, Wang Q. Effects of 1,25-dihydroxyvitamin D3 on experimental periodontitis and AhR/NF-κB/NLRP3 inflammasome pathway in a mouse model. *J Appl Oral Sci* 2019; **27**: e20180713 [PMID: 31691738 DOI: 10.1590/1678-7757-2018-0713]

109 **Lu L**, Lu Q, Chen W, Li J, Li C, Zheng Z. Vitamin D(3) Protects against Diabetic Retinopathy by Inhibiting High-Glucose-Induced Activation of the ROS/TXNIP/NLRP3 Inflammasome Pathway. *J Diabetes Res* 2018; **2018**: 8193523 [PMID: 29682582 DOI: 10.1155/2018/8193523]

110 **Dong X**, He Y, Ye F, Zhao Y, Cheng J, Xiao J, Yu W, Zhao J, Sai Y, Dan G, Chen M, Zou Z. Vitamin D3 ameliorates nitrogen mustard-induced cutaneous inflammation by inactivating the NLRP3 inflammasome through the SIRT3-SOD2-mtROS signaling pathway. *Clin Transl Med* 2021; **11**: e312 [PMID: 33634989 DOI: 10.1002/ctm2.312]

111 **Dai Y**, Zhang J, Xiang J, Li Y, Wu D, Xu J. Calcitriol inhibits ROS-NLRP3-IL-1β signaling axis via activation of Nrf2-antioxidant signaling in hyperosmotic stress stimulated human corneal epithelial cells. *Redox Biol* 2019; **21**: 101093 [PMID: 30611121 DOI: 10.1016/j.redox.2018.101093]

112 **Jiang S**, Zhang H, Li X, Yi B, Huang L, Hu Z, Li A, Du J, Li Y, Zhang W. Vitamin D/VDR attenuate cisplatin-induced AKI by down-regulating NLRP3/Caspase-1/GSDMD pyroptosis pathway. *J Steroid Biochem Mol Biol* 2021; **206**: 105789 [PMID: 33259938 DOI: 10.1016/j.jsbmb.2020.105789]

113 **Huang H**, Hong JY, Wu YJ, Wang EY, Liu ZQ, Cheng BH, Mei L, Liu ZG, Yang PC, Zheng PY. Vitamin D receptor interacts with NLRP3 to restrict the allergic response. *Clin Exp Immunol* 2018; **194**: 17-26 [PMID: 30260469 DOI: 10.1111/cei.13164]

114 **Cao R**, Ma Y, Li S, Shen D, Yang S, Wang X, Cao Y, Wang Z, Wei Y, Li S, Liu G, Zhang H, Wang Y, Ma Y. 1,25(OH)(2) D(3) alleviates DSS-induced ulcerative colitis via inhibiting NLRP3 inflammasome activation. *J Leukoc Biol* 2020; **108**: 283-295 [PMID: 32237257 DOI: 10.1002/JLB.3MA0320-406RR]

115 **Kim DS**, Song M, Kim SH, Jang DS, Kim JB, Ha BK, Kim SH, Lee KJ, Kang SY, Jeong IY. The improvement of ginsenoside accumulation in Panax ginseng as a result of γ-irradiation. *J Ginseng Res* 2013; **37**: 332-340 [PMID: 24198659 DOI: 10.5142/jgr.2013.37.332]

116 **Kim HJ**, Kim P, Shin CY. A comprehensive review of the therapeutic and pharmacological effects of ginseng and ginsenosides in central nervous system. *J Ginseng Res* 2013; **37**: 8-29 [PMID: 23717153 DOI: 10.5142/jgr.2013.37.8]

117 **Lau AJ**, Seo BH, Woo SO, Koh HL. High-performance liquid chromatographic method with quantitative comparisons of whole chromatograms of raw and steamed Panax notoginseng. *J Chromatogr A* 2004; **1057**: 141-149 [PMID: 15584233 DOI: 10.1016/j.chroma.2004.09.069]

118 **Tian M**, Ma P, Zhang Y, Mi Y, Fan D. Ginsenoside Rk3 alleviated DSS-induced ulcerative colitis by protecting colon barrier and inhibiting NLRP3 inflammasome pathway. *Int Immunopharmacol* 2020; **85**: 106645 [PMID: 32521491 DOI: 10.1016/j.intimp.2020.106645]

119 **Liu H**, Yang J, Du F, Gao X, Ma X, Huang Y, Xu F, Niu W, Wang F, Mao Y, Sun Y, Lu T, Liu C, Zhang B, Li C. Absorption and disposition of ginsenosides after oral administration of Panax notoginseng extract to rats. *Drug Metab Dispos* 2009; **37**: 2290-2298 [PMID: 19786509 DOI: 10.1124/dmd.109.029819]

120 **Liu C**, Wang J, Yang Y, Liu X, Zhu Y, Zou J, Peng S, Le TH, Chen Y, Zhao S, He B, Mi Q, Zhang X, Du Q. Ginsenoside Rd ameliorates colitis by inducing p62-driven mitophagy-mediated NLRP3 inflammasome inactivation in mice. *Biochem Pharmacol* 2018; **155**: 366-379 [PMID: 30012462 DOI: 10.1016/j.bcp.2018.07.010]

121 **Lee KW**, Kim YJ, Kim DO, Lee HJ, Lee CY. Major phenolics in apple and their contribution to the total antioxidant capacity. *J Agric Food Chem* 2003; **51**: 6516-6520 [PMID: 14558772 DOI: 10.1021/jf034475w]

122 **Tsao R**, Yang R, Young JC, Zhu H. Polyphenolic profiles in eight apple cultivars using high-performance liquid chromatography (HPLC). *J Agric Food Chem* 2003; **51**: 6347-6353 [PMID: 14518966 DOI: 10.1021/jf0346298]

123 **Zhang Z**, Li S, Cao H, Shen P, Liu J, Fu Y, Cao Y, Zhang N. The protective role of phloretin against dextran sulfate sodium-induced ulcerative colitis in mice. *Food Funct* 2019; **10**: 422-431 [PMID: 30604787 DOI: 10.1039/c8fo01699b]

124 **Wu M**, Li P, An Y, Ren J, Yan D, Cui J, Li D, Li M, Wang M, Zhong G. Phloretin ameliorates dextran sulfate sodium-induced ulcerative colitis in mice by regulating the gut microbiota. *Pharmacol Res* 2019; **150**: 104489 [PMID: 31689519 DOI: 10.1016/j.phrs.2019.104489]

125 **Doyle AA**, Stephens JC. A review of cinnamaldehyde and its derivatives as antibacterial agents. *Fitoterapia* 2019; **139**: 104405 [PMID: 31707126 DOI: 10.1016/j.fitote.2019.104405]

126 **Liu P**, Wang J, Wen W, Pan T, Chen H, Fu Y, Wang F, Huang JH, Xu S. Cinnamaldehyde suppresses NLRP3 derived IL-1β via activating succinate/HIF-1 in rheumatoid arthritis rats. *Int Immunopharmacol* 2020; **84**: 106570 [PMID: 32413739 DOI: 10.1016/j.intimp.2020.106570]

127 **Xu F**, Wang F, Wen T, Sang W, Wang D, Zeng N. Inhibition of NLRP3 inflammasome: a new protective mechanism of cinnamaldehyde in endotoxin poisoning of mice. *Immunopharmacol Immunotoxicol* 2017; **39**: 296-304 [PMID: 28762847 DOI: 10.1080/08923973.2017.1355377]

128 **Luan F**, Lei Z, Peng X, Chen L, Peng L, Liu Y, Rao Z, Yang R, Zeng N. Cardioprotective effect of cinnamaldehyde pretreatment on ischemia/ reperfusion injury via inhibiting NLRP3 inflammasome activation and gasdermin D mediated cardiomyocyte pyroptosis. *Chem Biol Interact* 2022; **368**: 110245 [PMID: 36341777 DOI: 10.1016/j.cbi.2022.110245]

129 **Kang LL**, Zhang DM, Ma CH, Zhang JH, Jia KK, Liu JH, Wang R, Kong LD. Cinnamaldehyde and allopurinol reduce fructose-induced cardiac inflammation and fibrosis by attenuating CD36-mediated TLR4/6-IRAK4/1 signaling to suppress NLRP3 inflammasome activation. *Sci Rep* 2016; **6**: 27460 [PMID: 27270216 DOI: 10.1038/srep27460]

130 **Ka SM**, Kuoping Chao L, Lin JC, Chen ST, Li WT, Lin CN, Cheng JC, Jheng HL, Chen A, Hua KF. A low toxicity synthetic cinnamaldehyde derivative ameliorates renal inflammation in mice by inhibiting NLRP3 inflammasome and its related signaling pathways. *Free Radic Biol Med* 2016; **91**: 10-24 [PMID: 26675345 DOI: 10.1016/j.freeradbiomed.2015.12.003]

131 **Qu S**, Shen Y, Wang M, Wang X, Yang Y. Suppression of miR-21 and miR-155 of macrophage by cinnamaldehyde ameliorates ulcerative colitis. *Int Immunopharmacol* 2019; **67**: 22-34 [PMID: 30530166 DOI: 10.1016/j.intimp.2018.11.045]

132 **Kumar P**, Srivastava V, Chaturvedi R, Sundar D, Bisaria VJPC, Tissue, Culture O. Elicitor enhanced production of protoberberine alkaloids from in vitro cell suspension cultures of Tinospora cordifolia. *Miers ex Hook. F. Thoms* 2017; **130**: 417-426

133 **Wang YQ**, Zhang HM, Zhang GC. Studies of the interaction between palmatine hydrochloride and human serum albumin by fluorescence quenching method. *J Pharm Biomed Anal* 2006; **41**: 1041-1046 [PMID: 16549318 DOI: 10.1016/j.jpba.2006.01.028]

134 **Pustovidko AV**, Rokitskaya TI, Severina II, Simonyan RA, Trendeleva TA, Lyamzaev KG, Antonenko YN, Rogov AG, Zvyagilskaya RA, Skulachev VP, Chernyak BV. Derivatives of the cationic plant alkaloids berberine and palmatine amplify protonophorous activity of fatty acids in model membranes and mitochondria. *Mitochondrion* 2013; **13**: 520-525 [PMID: 23026390 DOI: 10.1016/j.mito.2012.09.006]

135 **Ai G**, Huang R, Xie J, Zhong L, Wu X, Qin Z, Su Z, Chen J, Yang X, Dou Y. Hypouricemic and nephroprotective effects of palmatine from Cortex Phellodendri Amurensis: A uric acid modulator targeting Keap1-Nrf2/NLRP3 axis. *J Ethnopharmacol* 2023; **301**: 115775 [PMID: 36198377 DOI: 10.1016/j.jep.2022.115775]

136 **Cheng JJ**, Ma XD, Ai GX, Yu QX, Chen XY, Yan F, Li YC, Xie JH, Su ZR, Xie QF. Palmatine Protects Against MSU-Induced Gouty Arthritis via Regulating the NF-κB/NLRP3 and Nrf2 Pathways. *Drug Des Devel Ther* 2022; **16**: 2119-2132 [PMID: 35812134 DOI: 10.2147/DDDT.S356307]

137 **Mai CT**, Wu MM, Wang CL, Su ZR, Cheng YY, Zhang XJ. Palmatine attenuated dextran sulfate sodium (DSS)-induced colitis via promoting mitophagy-mediated NLRP3 inflammasome inactivation. *Mol Immunol* 2019; **105**: 76-85 [PMID: 30496979 DOI: 10.1016/j.molimm.2018.10.015]

138 **Cheng J**, Ma X, Zhang H, Wu X, Li M, Ai G, Zhan R, Xie J, Su Z, Huang X. 8-Oxypalmatine, a novel oxidative metabolite of palmatine, exhibits superior anti-colitis effect via regulating Nrf2 and NLRP3 inflammasome. *Biomed Pharmacother* 2022; **153**: 113335 [PMID: 35779424 DOI: 10.1016/j.biopha.2022.113335]

139 **Becerra JE**, Yebra MJ, Monedero V. An L-Fucose Operon in the Probiotic Lactobacillus rhamnosus GG Is Involved in Adaptation to Gastrointestinal Conditions. *Appl Environ Microbiol* 2015; **81**: 3880-3888 [PMID: 25819967 DOI: 10.1128/AEM.00260-15]

140 **Choi SS**, Lynch BS, Baldwin N, Dakoulas EW, Roy S, Moore C, Thorsrud BA, Röhrig CH. Safety evaluation of the human-identical milk monosaccharide, l-fucose. *Regul Toxicol Pharmacol* 2015; **72**: 39-48 [PMID: 25728407 DOI: 10.1016/j.yrtph.2015.02.016]

141 **He R**, Li Y, Han C, Lin R, Qian W, Hou X. L-Fucose ameliorates DSS-induced acute colitis via inhibiting macrophage M1 polarization and inhibiting NLRP3 inflammasome and NF-kB activation. *Int Immunopharmacol* 2019; **73**: 379-388 [PMID: 31132733 DOI: 10.1016/j.intimp.2019.05.013]

142 **Walter E**. Genistin (an isoflavone glucoside) and its aglucone, genistein, from soybeans. *J Am Chem Soc* 1941; **63**: 3273-3276

143 **Chen Y**, Le TH, Du Q, Zhao Z, Liu Y, Zou J, Hua W, Liu C, Zhu Y. Genistein protects against DSS-induced colitis by inhibiting NLRP3 inflammasome via TGR5-cAMP signaling. *Int Immunopharmacol* 2019; **71**: 144-154 [PMID: 30901677 DOI: 10.1016/j.intimp.2019.01.021]

144 **Wang S**, Wang J, Wei H, Gu T, Wang J, Wu Z, Yang Q. Genistein Attenuates Acute Cerebral Ischemic Damage by Inhibiting the NLRP3 Inflammasome in Reproductively Senescent Mice. *Front Aging Neurosci* 2020; **12**: 153 [PMID: 32625078 DOI: 10.3389/fnagi.2020.00153]

145 **Wu G**, Li S, Qu G, Hua J, Zong J, Li X, Xu F. Genistein alleviates H(2)O(2)-induced senescence of human umbilical vein endothelial cells via regulating the TXNIP/NLRP3 axis. *Pharm Biol* 2021; **59**: 1388-1401 [PMID: 34663173 DOI: 10.1080/13880209.2021.1979052]

146 **Zhao K**, Li S, Chen J, Jin Q. Inhibitory Effect of Trihydroxy Isoflavone on Neuronal Apoptosis in Natural Aging Rats. *Dis Markers* 2022; **2022**: 4688203 [PMID: 36046381 DOI: 10.1155/2022/4688203]

147 **Eo H**, Lee HJ, Lim Y. Ameliorative effect of dietary genistein on diabetes induced hyper-inflammation and oxidative stress during early stage of wound healing in alloxan induced diabetic mice. *Biochem Biophys Res Commun* 2016; **478**: 1021-1027 [PMID: 27431618 DOI: 10.1016/j.bbrc.2016.07.039]

148 **Kuwahara H**, Kanazawa A, Wakamatu D, Morimura S, Kida K, Akaike T, Maeda H. Antioxidative and antimutagenic activities of 4-vinyl-2,6-dimethoxyphenol (canolol) isolated from canola oil. *J Agric Food Chem* 2004; **52**: 4380-4387 [PMID: 15237940 DOI: 10.1021/jf040045+]

149 **Moreno DA**, Pérez-Balibrea S, Ferreres F, Gil-Izquierdo Á, García-Viguera CJFC. *Acylated Anthocyanins in Broccoli Sprouts* 2010; **123**: 358-363

150 **Sawa T**, Nakao M, Akaike T, Ono K, Maeda H. Alkylperoxyl radical-scavenging activity of various flavonoids and other phenolic compounds: implications for the anti-tumor-promoter effect of vegetables. *J Agric Food Chem* 1999; **47**: 397-402 [PMID: 10563906 DOI: 10.1021/jf980765e]

151 **Lee EH**, Shin JH, Kim SS, Seo SR. Sinapic Acid Controls Inflammation by Suppressing NLRP3 Inflammasome Activation. *Cells* 2021; **10** [PMID: 34571975 DOI: 10.3390/cells10092327]

152 **Qian B**, Wang C, Zeng Z, Ren Y, Li D, Song JL. Ameliorative Effect of Sinapic Acid on Dextran Sodium Sulfate- (DSS-) Induced Ulcerative Colitis in Kunming (KM) Mice. *Oxid Med Cell Longev* 2020; **2020**: 8393504 [PMID: 33312339 DOI: 10.1155/2020/8393504]

153 **Carson CF**, Hammer KA, Riley TV. Melaleuca alternifolia (Tea Tree) oil: a review of antimicrobial and other medicinal properties. *Clin Microbiol Rev* 2006; **19**: 50-62 [PMID: 16418522 DOI: 10.1128/cmr.19.1.50-62.2006]

154 **Zhang Z**, Shen P, Lu X, Li Y, Liu J, Liu B, Fu Y, Cao Y, Zhang N. In Vivo and In Vitro Study on the Efficacy of Terpinen-4-ol in Dextran Sulfate Sodium-Induced Mice Experimental Colitis. *Front Immunol* 2017; **8**: 558 [PMID: 28553294 DOI: 10.3389/fimmu.2017.00558]

155 **Yan J**, Yu L, Xu S, Gu W, Zhu WJSH. Apigenin accumulation and expression analysis of apigenin biosynthesis relative genes in celery. *Scientia Horticulturae* 2014; **165**: 218-224

156 **Márquez-Flores YK**, Villegas I, Cárdeno A, Rosillo MÁ, Alarcón-de-la-Lastra C. Apigenin supplementation protects the development of dextran sulfate sodium-induced murine experimental colitis by inhibiting canonical and non-canonical inflammasome signaling pathways. *J Nutr Biochem* 2016; **30**: 143-152 [PMID: 27012631 DOI: 10.1016/j.jnutbio.2015.12.002]

157 **Lv Y**, Gao X, Luo Y, Fan W, Shen T, Ding C, Yao M, Song S, Yan L. Apigenin ameliorates HFD-induced NAFLD through regulation of the XO/NLRP3 pathways. *J Nutr Biochem* 2019; **71**: 110-121 [PMID: 31325892 DOI: 10.1016/j.jnutbio.2019.05.015]

158 **Meng Z**, Zhu B, Gao M, Wang G, Zhou H, Lu J, Guan S. Apigenin alleviated PA-induced pyroptosis by activating autophagy in hepatocytes. *Food Funct* 2022; **13**: 5559-5570 [PMID: 35481558 DOI: 10.1039/d1fo03771d]

159 **Yamagata K**, Hashiguchi K, Yamamoto H, Tagami M. Dietary Apigenin Reduces Induction of LOX-1 and NLRP3 Expression, Leukocyte Adhesion, and Acetylated Low-Density Lipoprotein Uptake in Human Endothelial Cells Exposed to Trimethylamine-N-Oxide. *J Cardiovasc Pharmacol* 2019; **74**: 558-565 [PMID: 31815868 DOI: 10.1097/FJC.0000000000000747]

160 **Yu J**, Jiang Q, Liu N, Fan D, Wang M, Zhao Y. Apigenin and apigenin-7, 4'-O-dioctanoate protect against acrolein-aggravated inflammation via inhibiting the activation of NLRP3 inflammasome and HMGB1/MYD88/NF-κB signaling pathway in Human umbilical vein endothelial cells (HUVEC). *Food Chem Toxicol* 2022; **168**: 113400 [PMID: 36055550 DOI: 10.1016/j.fct.2022.113400]

161 **Meng XM**, Nikolic-Paterson DJ, Lan HY. TGF-β: the master regulator of fibrosis. *Nat Rev Nephrol* 2016; **12**: 325-338 [PMID: 27108839 DOI: 10.1038/nrneph.2016.48]

162 **Wu Q**, Li W, Zhao J, Sun W, Yang Q, Chen C, Xia P, Zhu J, Zhou Y, Huang G, Yong C, Zheng M, Zhou E, Gao K. Apigenin ameliorates doxorubicin-induced renal injury via inhibition of oxidative stress and inflammation. *Biomed Pharmacother* 2021; **137**: 111308 [PMID: 33556877 DOI: 10.1016/j.biopha.2021.111308]

163 **Guan C**, Parrot D, Wiese J, Sönnichsen FD, Saha M, Tasdemir D, Weinberger F. Identification of rosmarinic acid and sulfated flavonoids as inhibitors of microfouling on the surface of eelgrass Zostera marina. *Biofouling* 2017; **33**: 867-880 [PMID: 29032711 DOI: 10.1080/08927014.2017.1383399]

164 **Wei Y**, Chen J, Hu Y, Lu W, Zhang X, Wang R, Chu K. Rosmarinic Acid Mitigates Lipopolysaccharide-Induced Neuroinflammatory Responses through the Inhibition of TLR4 and CD14 Expression and NF-κB and NLRP3 Inflammasome Activation. *Inflammation* 2018; **41**: 732-740 [PMID: 29318480 DOI: 10.1007/s10753-017-0728-9]

165 **Lv Q**, Xing Y, Liu J, Dong D, Liu Y, Qiao H, Zhang Y, Hu L. Lonicerin targets EZH2 to alleviate ulcerative colitis by autophagy-mediated NLRP3 inflammasome inactivation. *Acta Pharm Sin B* 2021; **11**: 2880-2899 [PMID: 34589402 DOI: 10.1016/j.apsb.2021.03.011]

166 **Yao Y**, Mao J, Xu S, Zhao L, Long L, Chen L, Li D, Lu S. Rosmarinic acid inhibits nicotine-induced C-reactive protein generation by inhibiting NLRP3 inflammasome activation in smooth muscle cells. *J Cell Physiol* 2019; **234**: 1758-1767 [PMID: 30146678 DOI: 10.1002/jcp.27046]

167 **Marinho S**, Illanes M, Ávila-Román J, Motilva V, Talero E. Anti-Inflammatory Effects of Rosmarinic Acid-Loaded Nanovesicles in Acute Colitis through Modulation of NLRP3 Inflammasome. *Biomolecules* 2021; **11** [PMID: 33530569 DOI: 10.3390/biom11020162]

168 **He S**, Hu Q, Yang G. Research of honeysuckle. *Yunnan Chem Technol* 2010; **37**: 72-75

169 **Shang X**, Pan H, Li M, Miao X, Ding H. Lonicera japonica Thunb.: ethnopharmacology, phytochemistry and pharmacology of an important traditional Chinese medicine. *J Ethnopharmacol* 2011; **138**: 1-21 [PMID: 21864666 DOI: 10.1016/j.jep.2011.08.016]

170 **Lee SJ**, Shin EJ, Son KH, Chang HW, Kang SS, Kim HP. Anti-inflammatory activity of the major constituents of Lonicera japonica. *Archives of Pharm Res* 1995; **18**: 133-135

171 **Bu Y**, Lee K, Jung HS, Moon SK. Therapeutic effects of traditional herbal medicine on cerebral ischemia: a perspective of vascular protection. *Chin J Integr Med* 2013; **19**: 804-814 [PMID: 24170629 DOI: 10.1007/s11655-013-1341-2]

172 **Jiang X**, Jiang Y, Sun D, Rong L. Protective effect of magnesium lithospermate B against dextran sodiumsulfate induced ulcerative colitis in mice. *Environ Toxicol Pharmacol* 2013; **36**: 97-102 [PMID: 23603461 DOI: 10.1016/j.etap.2013.03.010]

173 **Quan W**, Liu F, Zhang Y, Xie C, Wu B, Yin J, Wang L, Zhang W, Zhang X, Wu Q. Antidepressant-like effects of magnesium lithospermate B in a rat model of chronic unpredictable stress. *Pharm Biol* 2015; **53**: 1168-1175 [PMID: 25857699 DOI: 10.3109/13880209.2014.967783]

174 **Jiang X**, Zhong L, Sun D, Rong L. Magnesium lithospermate B acts against dextran sodiumsulfate-induced ulcerative colitis by inhibiting activation of the NRLP3/ASC/Caspase-1 pathway. *Environ Toxicol Pharmacol* 2016; **41**: 72-77 [PMID: 26650800 DOI: 10.1016/j.etap.2015.10.009]

175 **Fujiki H**, Mori M, Nakayasu M, Terada M, Sugimura T, Moore RE. Indole alkaloids: dihydroteleocidin B, teleocidin, and lyngbyatoxin A as members of a new class of tumor promoters. *Proc Natl Acad Sci U S A* 1981; **78**: 3872-3876 [PMID: 6791164 DOI: 10.1073/pnas.78.6.3872]

176 **Wang Y**, Zhu H, Tam NFY. Polyphenols, tannins and antioxidant activities of eight true mangrove plant species in South China. *Plant and soil* 2014; **374**: 549-563

177 **Guo W**, Hu S, Elgehama A, Shao F, Ren R, Liu W, Zhang W, Wang X, Tan R, Xu Q, Sun Y, Jiao R. Fumigaclavine C ameliorates dextran sulfate sodium-induced murine experimental colitis via NLRP3 inflammasome inhibition. *J Pharmacol Sci* 2015; **129**: 101-106 [PMID: 26320672 DOI: 10.1016/j.jphs.2015.05.003]

178 **Mohammed NK**, Meor Hussin AS, Tan CP, Abdul Manap MY, Alhelli AMJIjofp. Quality changes of microencapsulated Nigella sativa oil upon accelerated storage. *Int J Food Prop* 2017; **20**: S2395-S2408

179 **Gao XJ**, Tang B, Liang HH, Yi L, Wei ZG. The protective effect of nigeglanine on dextran sulfate sodium-induced experimental colitis in mice and Caco-2 cells. *J Cell Physiol* 2019; **234**: 23398-23408 [PMID: 31169313 DOI: 10.1002/jcp.28909]

180 Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. European Mycophenolate Mofetil Cooperative Study Group. *Lancet* 1995; **345**: 1321-1325 [PMID: 7752752]

181 **Sollinger HW**. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. U.S. Renal Transplant Mycophenolate Mofetil Study Group. *Transplantation* 1995; **60**: 225-232 [PMID: 7645033 DOI: 10.1097/00007890-199508000-00003]

182 A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. *Transplantation* 1996; **61**: 1029-1037 [PMID: 8623181]

183 **Liu Z**, Yuan X, Luo Y, He Y, Jiang Y, Chen ZK, Sun E. Evaluating the effects of immunosuppressants on human immunity using cytokine profiles of whole blood. *Cytokine* 2009; **45**: 141-147 [PMID: 19138532 DOI: 10.1016/j.cyto.2008.12.003]

184 **Serrya MS**, El-Sheakh AR, Makled MN. Evaluation of the therapeutic effects of mycophenolate mofetil targeting Nrf-2 and NLRP3 inflammasome in acetic acid induced ulcerative colitis in rats. *Life Sci* 2021; **271**: 119154 [PMID: 33539910 DOI: 10.1016/j.lfs.2021.119154]

185 **Wu WS**, Chien CC, Liu KH, Chen YC, Chiu WT. Evodiamine Prevents Glioma Growth, Induces Glioblastoma Cell Apoptosis and Cell Cycle Arrest through JNK Activation. *Am J Chin Med* 2017; **45**: 879-899 [PMID: 28514905 DOI: 10.1142/S0192415X17500471]

186 **Liao JF**, Chiou WF, Shen YC, Wang GJ, Chen CF. Anti-inflammatory and anti-infectious effects of Evodia rutaecarpa (Wuzhuyu) and its major bioactive components. *Chin Med* 2011; **6**: 6 [PMID: 21320305 DOI: 10.1186/1749-8546-6-6]

187 **Zhao Z**, Gong S, Wang S, Ma C. Effect and mechanism of evodiamine against ethanol-induced gastric ulcer in mice by suppressing Rho/NF-кB pathway. *Int Immunopharmacol* 2015; **28**: 588-595 [PMID: 26225926 DOI: 10.1016/j.intimp.2015.07.030]

188 **Ding W**, Ding Z, Wang Y, Zhu Y, Gao Q, Cao W, Du R. Evodiamine Attenuates Experimental Colitis Injury Via Activating Autophagy and Inhibiting NLRP3 Inflammasome Assembly. *Front Pharmacol* 2020; **11**: 573870 [PMID: 33240089 DOI: 10.3389/fphar.2020.573870]

189 **Li CG**, Zeng QZ, Chen MY, Xu LH, Zhang CC, Mai FY, Zeng CY, He XH, Ouyang DY. Evodiamine Augments NLRP3 Inflammasome Activation and Anti-bacterial Responses Through Inducing α-Tubulin Acetylation. *Front Pharmacol* 2019; **10**: 290 [PMID: 30971927 DOI: 10.3389/fphar.2019.00290]

190 **Shen P**, Zhang Z, Zhu K, Cao H, Liu J, Lu X, Li Y, Jing Y, Yuan X, Fu Y, Cao Y, Zhang N. Evodiamine prevents dextran sulfate sodium-induced murine experimental colitis via the regulation of NF-κB and NLRP3 inflammasome. *Biomed Pharmacother* 2019; **110**: 786-795 [PMID: 30554117 DOI: 10.1016/j.biopha.2018.12.033]

191 **Zhou J**, Tan L, Xie J, Lai Z, Huang Y, Qu C, Luo D, Lin Z, Huang P, Su Z, Xie Y. Characterization of brusatol self-microemulsifying drug delivery system and its therapeutic effect against dextran sodium sulfate-induced ulcerative colitis in mice. *Drug Deliv* 2017; **24**: 1667-1679 [PMID: 29078713 DOI: 10.1080/10717544.2017.1384521]

192 **Zhou J**, Wang T, Dou Y, Huang Y, Qu C, Gao J, Huang Z, Xie Y, Huang P, Lin Z, Su Z. Brusatol ameliorates 2, 4, 6-trinitrobenzenesulfonic acid-induced experimental colitis in rats: Involvement of NF-κB pathway and NLRP3 inflammasome. *Int Immunopharmacol* 2018; **64**: 264-274 [PMID: 30218953 DOI: 10.1016/j.intimp.2018.09.008]

193 **Bajracharya GB**. Diversity, pharmacology and synthesis of bergenin and its derivatives: potential materials for therapeutic usages. *Fitoterapia* 2015; **101**: 133-152 [PMID: 25596093 DOI: 10.1016/j.fitote.2015.01.001]

194 **Lei D**, Sun Y, Liu J, Chi J. Bergenin inhibits palmitic acid-induced pancreatic β-cell inflammatory death via regulating NLRP3 inflammasome activation. *Ann Transl Med* 2022; **10**: 1058 [PMID: 36330410 DOI: 10.21037/atm-22-3781]

195 **Lopes de Oliveira GA**, Alarcón de la Lastra C, Rosillo MÁ, Castejon Martinez ML, Sánchez-Hidalgo M, Rolim Medeiros JV, Villegas I. 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. *Chem Biol Interact* 2019; **297**: 25-33 [PMID: 30365937 DOI: 10.1016/j.cbi.2018.10.020]

196 **Yuan F**, Chen J, Sun PP, Guan S, Xu J. Wedelolactone inhibits LPS-induced pro-inflammation via NF-kappaB pathway in RAW 264.7 cells. *J Biomed Sci* 2013; **20**: 84 [PMID: 24176090 DOI: 10.1186/1423-0127-20-84]

197 **Mors WB**, do Nascimento MC, Parente JP, da Silva MH, Melo PA, Suarez-Kurtz G. Neutralization of lethal and myotoxic activities of South American rattlesnake venom by extracts and constituents of the plant Eclipta prostrata (Asteraceae). *Toxicon* 1989; **27**: 1003-1009 [PMID: 2799833 DOI: 10.1016/0041-0101(89)90151-7]

198 **Wei W**, Ding M, Zhou K, Xie H, Zhang M, Zhang C. Protective effects of wedelolactone on dextran sodium sulfate induced murine colitis partly through inhibiting the NLRP3 inflammasome activation via AMPK signaling. *Biomed Pharmacother* 2017; **94**: 27-36 [PMID: 28750357 DOI: 10.1016/j.biopha.2017.06.071]

199 **Hayes D**, Angove MJ, Tucci J, Dennis C. Walnuts (Juglans regia) Chemical Composition and Research in Human Health. *Crit Rev Food Sci Nutr* 2016; **56**: 1231-1241 [PMID: 25747270 DOI: 10.1080/10408398.2012.760516]

200 **Gao P**, Liu R, Jin Q, Wang X. Comparative study of chemical compositions and antioxidant capacities of oils obtained from two species of walnut: Juglans regia and Juglans sigillata. *Food Chem* 2019; **279**: 279-287 [PMID: 30611491 DOI: 10.1016/j.foodchem.2018.12.016]

201 **Laubertová L**, Koňariková K, Gbelcová H, Ďuračková Z, Žitňanová I. Effect of walnut oil on hyperglycemia-induced oxidative stress and pro-inflammatory cytokines production. *Eur J Nutr* 2015; **54**: 291-299 [PMID: 24817646 DOI: 10.1007/s00394-014-0710-3]

202 **Zhao H**, Li J, Zhao J, Chen Y, Ren C, Chen Y. Antioxidant effects of compound walnut oil capsule in mice aging model induced by D-galactose. *Food Nutr Res* 2018; **62** [PMID: 29720929 DOI: 10.29219/fnr.v62.1371]

203 **Miao F**, Shan C, Ma T, Geng S, Ning D. Walnut oil alleviates DSS-induced colitis in mice by inhibiting NLRP3 inflammasome activation and regulating gut microbiota. *Microb Pathog* 2021; **154**: 104866 [PMID: 33775855 DOI: 10.1016/j.micpath.2021.104866]

204 **Liu F**, Zhang Q, Lin C, Yao Y, Wang M, Liu C, Zhu C. A comparative study on pharmacokinetics and tissue distribution of 5-hydroxy-4-methoxycanthin-6-one and its metabolite in normal and dextran sodium sulfate-induced colitis rats by HPLC-MS/MS. *J Pharm Pharmacol* 2020; **72**: 1761-1770 [PMID: 32363585 DOI: 10.1111/jphp.13285]

205 **Liu F**, Yao Y, Wang Q, Zhang F, Wang M, Zhu C, Lin C. Nigakinone alleviates DSS-induced experimental colitis via regulating bile acid profile and FXR/NLRP3 signaling pathways. *Phytother Res* 2023; **37**: 15-34 [PMID: 36054406 DOI: 10.1002/ptr.7588]

206 **Yang YZ**, Tang YZ, Liu YH. Wogonoside displays anti-inflammatory effects through modulating inflammatory mediator expression using RAW264.7 cells. *J Ethnopharmacol* 2013; **148**: 271-276 [PMID: 23612420 DOI: 10.1016/j.jep.2013.04.025]

207 **Li H**, Hui H, Xu J, Yang H, Zhang X, Liu X, Zhou Y, Li Z, Guo Q, Lu N. Wogonoside induces growth inhibition and cell cycle arrest via promoting the expression and binding activity of GATA-1 in chronic myelogenous leukemia cells. *Arch Toxicol* 2016; **90**: 1507-1522 [PMID: 26104856 DOI: 10.1007/s00204-015-1552-3]

208 **Li-Weber M**. New therapeutic aspects of flavones: the anticancer properties of Scutellaria and its main active constituents Wogonin, Baicalein and Baicalin. *Cancer Treat Rev* 2009; **35**: 57-68 [PMID: 19004559 DOI: 10.1016/j.ctrv.2008.09.005]

209 **Liu Q**, Zuo R, Wang K, Nong FF, Fu YJ, Huang SW, Pan ZF, Zhang Y, Luo X, Deng XL, Zhang XX, Zhou L, Chen Y. Oroxindin inhibits macrophage NLRP3 inflammasome activation in DSS-induced ulcerative colitis in mice via suppressing TXNIP-dependent NF-κB pathway. *Acta Pharmacol Sin* 2020; **41**: 771-781 [PMID: 31937929 DOI: 10.1038/s41401-019-0335-4]

210 **Panossian A**, Wikman G. Pharmacology of Schisandra chinensis Bail.: an overview of Russian research and uses in medicine. *J Ethnopharmacol* 2008; **118**: 183-212 [PMID: 18515024 DOI: 10.1016/j.jep.2008.04.020]

211 **Chen X**, Xiao Z, Jiang Z, Jiang Y, Li W, Wang M. Schisandrin B Attenuates Airway Inflammation and Airway Remodeling in Asthma by Inhibiting NLRP3 Inflammasome Activation and Reducing Pyroptosis. *Inflammation* 2021; **44**: 2217-2231 [PMID: 34143347 DOI: 10.1007/s10753-021-01494-z]

212 **Guo M**, An F, Yu H, Wei X, Hong M, Lu Y. Comparative effects of schisandrin A, B, and C on Propionibacterium acnes-induced, NLRP3 inflammasome activation-mediated IL-1β secretion and pyroptosis. *Biomed Pharmacother* 2017; **96**: 129-136 [PMID: 28972885 DOI: 10.1016/j.biopha.2017.09.097]

213 **Zhang W**, Wang W, Shen C, Wang X, Pu Z, Yin Q. Network pharmacology for systematic understanding of Schisandrin B reduces the epithelial cells injury of colitis through regulating pyroptosis by AMPK/Nrf2/NLRP3 inflammasome. *Aging (Albany NY)* 2021; **13**: 23193-23209 [PMID: 34628369 DOI: 10.18632/aging.203611]

214 **Fujise Y**, Toda T, Itô S. Isolation of trifolirhizin from Ononis spinosa L. *Chem Pharm Bull (Tokyo)* 1965; **13**: 93-95 [PMID: 5864291 DOI: 10.1248/cpb.13.93]

215 **Zhou H**, Lutterodt H, Cheng Z, Yu LL. Anti-Inflammatory and antiproliferative activities of trifolirhizin, a flavonoid from Sophora flavescens roots. *J Agric Food Chem* 2009; **57**: 4580-4585 [PMID: 19402641 DOI: 10.1021/jf900340b]

216 **Zhang Q**, Wang S, Ji S. Trifolirhizin regulates the balance of Th17/Treg cells and inflammation in the ulcerative colitis mice through inhibiting the TXNIP-mediated activation of NLRP3 inflammasome. *Clin Exp Pharmacol Physiol* 2022; **49**: 787-796 [PMID: 35575951 DOI: 10.1111/1440-1681.13654]

217 **Reagan-Shaw S**, Breur J, Ahmad N. Enhancement of UVB radiation-mediated apoptosis by sanguinarine in HaCaT human immortalized keratinocytes. *Mol Cancer Ther* 2006; **5**: 418-429 [PMID: 16505117 DOI: 10.1158/1535-7163.MCT-05-0250]

218 **Li X**, Wu X, Wang Q, Xu W, Zhao Q, Xu N, Hu X, Ye Z, Yu S, Liu J, He X, Shi F, Zhang Q, Li W. Sanguinarine ameliorates DSS induced ulcerative colitis by inhibiting NLRP3 inflammasome activation and modulating intestinal microbiota in C57BL/6 mice. *Phytomedicine* 2022; **104**: 154321 [PMID: 35843190 DOI: 10.1016/j.phymed.2022.154321]

219 **Kim YS**, Lee CJ, Ma JY. Enhancement of active compound, genipin, from Gardeniae Fructus using immobilized glycosyl hydrolase family 3 β-glucosidase from Lactobacillus antri. *AMB Express* 2017; **7**: 64 [PMID: 28303550 DOI: 10.1186/s13568-017-0360-y]

220 **Pu Z**, Liu Y, Li C, Xu M, Xie H, Zhao J. Using Network Pharmacology for Systematic Understanding of Geniposide in Ameliorating Inflammatory Responses in Colitis Through Suppression of NLRP3 Inflammasome in Macrophage by AMPK/Sirt1 Dependent Signaling. *Am J Chin Med* 2020; **48**: 1693-1713 [PMID: 33202149 DOI: 10.1142/S0192415X20500846]

221 **Li H**, Yang DH, Zhang Y, Zheng F, Gao F, Sun J, Shi G. Geniposide suppresses NLRP3 inflammasome-mediated pyroptosis via the AMPK signaling pathway to mitigate myocardial ischemia/reperfusion injury. *Chin Med* 2022; **17**: 73 [PMID: 35715805 DOI: 10.1186/s13020-022-00616-5]

222 **Song P**, Shen DF, Meng YY, Kong CY, Zhang X, Yuan YP, Yan L, Tang QZ, Ma ZG. Geniposide protects against sepsis-induced myocardial dysfunction through AMPKα-dependent pathway. *Free Radic Biol Med* 2020; **152**: 186-196 [PMID: 32081748 DOI: 10.1016/j.freeradbiomed.2020.02.011]

223 **Song M**, Chen Z, Qiu R, Zhi T, Xie W, Zhou Y, Luo N, Fuqian Chen, Liu F, Shen C, Lin S, Zhang F, Gao Y, Liu C. Inhibition of NLRP3-mediated crosstalk between hepatocytes and liver macrophages by geniposidic acid alleviates cholestatic liver inflammatory injury. *Redox Biol* 2022; **55**: 102404 [PMID: 35868156 DOI: 10.1016/j.redox.2022.102404]

224 **Chan K**, Liu ZQ, Jiang ZH, Zhou H, Wong YF, Xu HX, Liu L. The effects of sinomenine on intestinal absorption of paeoniflorin by the everted rat gut sac model. *J Ethnopharmacol* 2006; **103**: 425-432 [PMID: 16169700 DOI: 10.1016/j.jep.2005.08.020]

225 **Zhou Y**, Chen S, Gu W, Sun X, Wang L, Tang L. Sinomenine hydrochloride ameliorates dextran sulfate sodium-induced colitis in mice by modulating the gut microbiota composition whilst suppressing the activation of the NLRP3 inflammasome. *Exp Ther Med* 2021; **22**: 1287 [PMID: 34630642 DOI: 10.3892/etm.2021.10722]

226 **Dong HC**, Li PN, Chen CJ, Xu X, Zhang H, Liu G, Zheng LJ, Li P. Sinomenine Attenuates Cartilage Degeneration by Regulating miR-223-3p/NLRP3 Inflammasome Signaling. *Inflammation* 2019; **42**: 1265-1275 [PMID: 30847744 DOI: 10.1007/s10753-019-00986-3]

227 **Kiasalari Z**, Afshin-Majd S, Baluchnejadmojarad T, Azadi-Ahmadabadi E, Fakour M, Ghasemi-Tarie R, Jalalzade-Ogvar S, Khodashenas V, Tashakori-Miyanroudi M, Roghani M. Sinomenine Alleviates Murine Experimental Autoimmune Encephalomyelitis Model of Multiple Sclerosis through Inhibiting NLRP3 Inflammasome. *J Mol Neurosci* 2021; **71**: 215-224 [PMID: 32812186 DOI: 10.1007/s12031-020-01637-1]

228 **Qiu J**, Wang M, Zhang J, Cai Q, Lu D, Li Y, Dong Y, Zhao T, Chen H. The neuroprotection of Sinomenine against ischemic stroke in mice by suppressing NLRP3 inflammasome via AMPK signaling. *Int Immunopharmacol* 2016; **40**: 492-500 [PMID: 27769021 DOI: 10.1016/j.intimp.2016.09.024]

229 **Huang Y**, Zhou M, Li C, Chen Y, Fang W, Xu G, Shi X. Picroside II protects against sepsis via suppressing inflammation in mice. *Am J Transl Res* 2016; **8**: 5519-5531 [PMID: 28078023]

230 **Gao H**, Zhou YW. Anti-lipid peroxidation and protection of liver mitochondria against injuries by picroside II. *World J Gastroenterol* 2005; **11**: 3671-3674 [PMID: 15968718 DOI: 10.3748/wjg.v11.i24.3671]

231 **Verma PC**, Basu V, Gupta V, Saxena G, Rahman LU. Pharmacology and chemistry of a potent hepatoprotective compound Picroliv isolated from the roots and rhizomes of Picrorhiza kurroa royle ex benth. (kutki). *Curr Pharm Biotechnol* 2009; **10**: 641-649 [PMID: 19619118 DOI: 10.2174/138920109789069314]

232 **Guo Y**, Xu X, Li Q, Li Z, Du F. Anti-inflammation effects of picroside 2 in cerebral ischemic injury rats. *Behav Brain Funct* 2010; **6**: 43 [PMID: 20618938 DOI: 10.1186/1744-9081-6-43]

233 **Yao H**, Yan J, Yin L, Chen W. Picroside II alleviates DSS-induced ulcerative colitis by suppressing the production of NLRP3 inflammasomes through NF-κB signaling pathway. *Immunopharmacol Immunotoxicol* 2022; **44**: 437-446 [PMID: 35293848 DOI: 10.1080/08923973.2022.2054425]

234 **Manna C**, Galletti P, Cucciolla V, Montedoro G, Zappia V. Olive oil hydroxytyrosol protects human erythrocytes against oxidative damages. *J Nutr Biochem* 1999; **10**: 159-165 [PMID: 15539284 DOI: 10.1016/s0955-2863(98)00085-0]

235 **Miao F**. Hydroxytyrosol alleviates dextran sodium sulfate-induced colitis by inhibiting NLRP3 inflammasome activation and modulating gut microbiota in vivo. *Nutrition* 2022; **97**: 111579 [PMID: 35248848 DOI: 10.1016/j.nut.2021.111579]

236 **Zheng J**, Lai W, Zhu G, Wan M, Chen J, Tai Y, Lu C. 10-Hydroxy-2-decenoic acid prevents ultraviolet A-induced damage and matrix metalloproteinases expression in human dermal fibroblasts. *J Eur Acad Dermatol Venereol* 2013; **27**: 1269-1277 [PMID: 23030720 DOI: 10.1111/j.1468-3083.2012.04707.x]

237 **Sugiyama T**, Takahashi K, Kuzumaki A, Tokoro S, Neri P, Mori H. Inhibitory mechanism of 10-hydroxy-trans-2-decenoic acid (royal jelly acid) against lipopolysaccharide- and interferon-β-induced nitric oxide production. *Inflammation* 2013; **36**: 372-378 [PMID: 23079939 DOI: 10.1007/s10753-012-9556-0]

238 **You M**, Miao Z, Tian J, Hu F. Trans-10-hydroxy-2-decenoic acid protects against LPS-induced neuroinflammation through FOXO1-mediated activation of autophagy. *Eur J Nutr* 2020; **59**: 2875-2892 [PMID: 31820078 DOI: 10.1007/s00394-019-02128-9]

239 **Huang S**, Tao R, Zhou J, Qian L, Wu J. Trans-10-Hydroxy-2-Decenoic Acid Alleviates Dextran Sulfate Sodium-Induced Colitis in Mice via Regulating the Inflammasome-Mediated Pyroptotic Pathway and Enhancing Colonic Barrier Function. *Mol Nutr Food Res* 2022; **66**: e2100821 [PMID: 35373915 DOI: 10.1002/mnfr.202100821]

240 **Khoshoo TN**, Mukherjee I. Genetic-evolutionary studies on cultivated cannas : VI. Origin and evolution of ornamental taxa. *Theor Appl Genet* 1970; **40**: 204-217 [PMID: 24435803 DOI: 10.1007/BF00285243]

241 **Doi M**, Nakamura N, Takizawa Y, Wakita M, Shimizu F, Kitamura Y, Hosokawa M. Harvest characteristics of Canna× generalis LH Bailey leaves. *Scientia Horticulturae* 2013; 150: 441-447

242 **Singh R**, Dubey AK, Sanyal I. Optimisation of adventitious shoot regeneration and agrobacterium-mediated transformation in canna× generalis (Canna Lily). *Horticult Plant J* 2019; **5**: 39-46

243 **Al-Snafi A**. Medical importance of Cichorium intybus–A review. *IOSR J Pharm* 2016; **6**: 41-56

244 **Le HL**, Nguyen TMH, Vu TT, Nguyen TTO, Ly HDT, Le NT, Nguyen TVA. Potent antiplatelet aggregation, anticoagulant and antioxidant activity of aerial Canna x generalis LH Bailey & EZ Bailey and its phytoconstituents. *South African Journal of Botany* 2022; **147**: 882-893

245 **Mahmoud TN**, El-Maadawy WH, Kandil ZA, Khalil H, El-Fiky NM, El Alfy TSMA. Canna x generalis L.H. Bailey rhizome extract ameliorates dextran sulfate sodium-induced colitis via modulating intestinal mucosal dysfunction, oxidative stress, inflammation, and TLR4/ NF-ҡB and NLRP3 inflammasome pathways. *J Ethnopharmacol* 2021; **269**: 113670 [PMID: 33301917 DOI: 10.1016/j.jep.2020.113670]

246 **Li J**, Ma XP, Yu CM, Ou WJ, Zhang MS, Liang QC, Zhao JB. [A case-control study on the duration of sleeping and cerebral infarction]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2013; **34**: 914-916 [PMID: 24331970]

247 **Li H**, Du Q, Wang WJ, Wang RJ, Wang JH, Liu SS. [Effect of kuijieling decoction on gene expression of TLR2, TLR4 in colonic mucosa of UC rats]. *Zhong Yao Cai* 2007; **30**: 56-59 [PMID: 17539306]

248 **Hossen MJ**, Chou JY, Li SM, Fu XQ, Yin C, Guo H, Amin A, Chou GX, Yu ZL. An ethanol extract of the rhizome of Atractylodes chinensis exerts anti-gastritis activities and inhibits Akt/NF-κB signaling. *J Ethnopharmacol* 2019; **228**: 18-25 [PMID: 30218812 DOI: 10.1016/j.jep.2018.09.015]

249 **Yang B**, Li H, Ruan Q, Xuan S, Chen X, Cui H, Liu Z, Jin J, Zhao Z. Effects of Gut Microbiota and Ingredient-Ingredient Interaction on the Pharmacokinetic Properties of Rotundic Acid and Pedunculoside. *Planta Med* 2019; **85**: 729-737 [PMID: 31167298 DOI: 10.1055/a-0902-5300]

250 **Long Y**, Li S, Qin J, Xie L, Gan L, Jie F, Wu Y, Li Y, Du Q. Kuijieling regulates the differentiation of Treg and Th17 cells to ameliorate experimental colitis in rats. *Biomed Pharmacother* 2018; **105**: 781-788 [PMID: 29909346 DOI: 10.1016/j.biopha.2018.06.011]

251 **Jie F**, Xiao S, Qiao Y, You Y, Feng Y, Long Y, Li S, Wu Y, Li Y, Du Q. Kuijieling decoction suppresses NLRP3-Mediated pyroptosis to alleviate inflammation and experimental colitis in vivo and in vitro. *J Ethnopharmacol* 2021; **264**: 113243 [PMID: 32781258 DOI: 10.1016/j.jep.2020.113243]

252 **Song X**, Li Y, Zhang H, Yang Q. The anticancer effect of Huaier (Review). *Oncol Rep* 2015; **34**: 12-21 [PMID: 25955759 DOI: 10.3892/or.2015.3950]

253 **Wu T**, Chen W, Liu S, Lu H, Wang H, Kong D, Huang X, Kong Q, Ning Y, Lu Z. Huaier suppresses proliferation and induces apoptosis in human pulmonary cancer cells via upregulation of miR-26b-5p. *FEBS Lett* 2014; **588**: 2107-2114 [PMID: 24815696 DOI: 10.1016/j.febslet.2014.04.044]

254 **Zhang N**, Kong X, Yan S, Yuan C, Yang Q. Huaier aqueous extract inhibits proliferation of breast cancer cells by inducing apoptosis. *Cancer Sci* 2010; **101**: 2375-2383 [PMID: 20718753 DOI: 10.1111/j.1349-7006.2010.01680.x]

255 **Wang L**, Yu Z, Wei C, Zhang L, Song H, Chen B, Yang Q. Huaier aqueous extract protects against dextran sulfate sodium-induced experimental colitis in mice by inhibiting NLRP3 inflammasome activation. *Oncotarget* 2017; **8**: 32937-32945 [PMID: 28380426 DOI: 10.18632/oncotarget.16513]

256 **Lin X**, Yi Z, Diao J, Shao M, Zhao L, Cai H, Fan Q, Yao X, Sun X. ShaoYao decoction ameliorates colitis-associated colorectal cancer by downregulating proinflammatory cytokines and promoting epithelial-mesenchymal transition. *J Transl Med* 2014; **12**: 105 [PMID: 24766737 DOI: 10.1186/1479-5876-12-105]

257 **Wang X**, Saud SM, Zhang X, Li W, Hua B. Protective effect of Shaoyao Decoction against colorectal cancer via the Keap1-Nrf2-ARE signaling pathway. *J Ethnopharmacol* 2019; **241**: 111981 [PMID: 31146002 DOI: 10.1016/j.jep.2019.111981]

258 **Chen X**. The Paeoniae decoction on the treatment of 36 cases of ulcerative colitis clinical observation. *J Pract Traditional Chin Intern Med* 2014; **28**: 39-40

259 **Wei YY**, Fan YM, Ga Y, Zhang YN, Han JC, Hao ZH. Shaoyao decoction attenuates DSS-induced ulcerative colitis, macrophage and NLRP3 inflammasome activation through the MKP1/NF-κB pathway. *Phytomedicine* 2021; **92**: 153743 [PMID: 34583225 DOI: 10.1016/j.phymed.2021.153743]

260 **Li X**, Chu L, Liu S, Zhang W, Lin L, Zheng G. Smilax china L. flavonoid alleviates HFHS-induced inflammation by regulating the gut-liver axis in mice. *Phytomedicine* 2022; **95**: 153728 [PMID: 34561124 DOI: 10.1016/j.phymed.2021.153728]

261 **Li X**, Yang L, Xu M, Qiao G, Li C, Lin L, Zheng G. Smilax china L. polyphenols alleviates obesity and inflammation by modulating gut microbiota in high fat/high sucrose diet-fed C57BL/6J mice. *J of Func Foods* 2021; **77**: 104332

262 **Tettey CO**, Yang I, Shin HM. Smilax china leaf extracts suppress pro-inflammatory adhesion response in human umbilical vein endothelial cells and proliferation of HeLa cells. *Arch Physiol Biochem* 2020; **126**: 287-291 [PMID: 30375252 DOI: 10.1080/13813455.2018.1520262]

263 **Zhang Y**, Pan X, Ran S, Wang K. Purification, structural elucidation and anti-inflammatory activity in vitro of polysaccharides from Smilax china L. *Int J Biol Macromol* 2019; **139**: 233-243 [PMID: 31376447 DOI: 10.1016/j.ijbiomac.2019.07.209]

264 **Pan X**, Wang H, Zheng Z, Huang X, Yang L, Liu J, Wang K, Zhang Y. Pectic polysaccharide from Smilax china L. ameliorated ulcerative colitis by inhibiting the galectin-3/NLRP3 inflammasome pathway. *Carbohydr Polym* 2022; **277**: 118864 [PMID: 34893269 DOI: 10.1016/j.carbpol.2021.118864]

265 **Jin XH**, Huang LQ. Investigation of original materials of Chinese medicine "Shihu" and "Tiepishihu". *Zhongguo Zhong Yao Za Zhi* 2015; **40**: 2475-2479 [PMID: 26697665]

266 **Yang S**, Gong Q, Wu Q, Li F, Lu Y, Shi J. Alkaloids enriched extract from Dendrobium nobile Lindl. attenuates tau protein hyperphosphorylation and apoptosis induced by lipopolysaccharide in rat brain. *Phytomedicine* 2014; **21**: 712-716 [PMID: 24268296 DOI: 10.1016/j.phymed.2013.10.026]

267 **Gao Y**, Zhou S, Wang F, Zhou Y, Sheng S, Qi D, Huang JH, Wu E, Lv Y, Huo X. Hepatoprotective effects of limb ischemic post-conditioning in hepatic ischemic rat model and liver cancer patients via PI3K/ERK pathways. *Int J Biol Sci* 2018; **14**: 2037-2050 [PMID: 30585267 DOI: 10.7150/ijbs.28435]

268 **Zeng YJ**, Yang HR, Ou XY, Su HH, Zong MH, Yang JG, Lou WY. Fungal polysaccharide similar with host Dendrobium officinale polysaccharide: Preparation, structure characteristics and biological activities. *Int J Biol Macromol* 2019; **141**: 460-470 [PMID: 31473318 DOI: 10.1016/j.ijbiomac.2019.08.238]

269 **Huang K**, Li Y, Tao S, Wei G, Huang Y, Chen D, Wu C. Purification, Characterization and Biological Activity of Polysaccharides from Dendrobium officinale. *Molecules* 2016; **21** [PMID: 27248989 DOI: 10.3390/molecules21060701]

270 **Liang J**, Chen S, Chen J, Lin J, Xiong Q, Yang Y, Yuan J, Zhou L, He L, Hou S, Li S, Huang S, Lai X. Therapeutic roles of polysaccharides from Dendrobium Officinaleon colitis and its underlying mechanisms. *Carbohydr Polym* 2018; **185**: 159-168 [PMID: 29421053 DOI: 10.1016/j.carbpol.2018.01.013]

271 **Liu GT**. Pharmacological actions and clinical use of fructus schizandrae. *Chin Med J (Engl)* 1989; **102**: 740-749 [PMID: 2517053]

272 **Wei H**, Sun L, Tai Z, Gao S, Xu W, Chen W. A simple and sensitive HPLC method for the simultaneous determination of eight bioactive components and fingerprint analysis of Schisandra sphenanthera. *Anal Chim Acta* 2010; **662**: 97-104 [PMID: 20152271 DOI: 10.1016/j.aca.2009.12.039]

273 **Choi YW**, Takamatsu S, Khan SI, Srinivas PV, Ferreira D, Zhao J, Khan IA. Schisandrene, a dibenzocyclooctadiene lignan from Schisandra chinensis: structure-antioxidant activity relationships of dibenzocyclooctadiene lignans. *J Nat Prod* 2006; **69**: 356-359 [PMID: 16562834 DOI: 10.1021/np0503707]

274 **Wang X**, Li Q, Sui B, Xu M, Pu Z, Qiu T. Schisandrin A from Schisandra chinensis Attenuates Ferroptosis and NLRP3 Inflammasome-Mediated Pyroptosis in Diabetic Nephropathy through Mitochondrial Damage by AdipoR1 Ubiquitination. *Oxid Med Cell Longev* 2022; **2022**: 5411462 [PMID: 35996380 DOI: 10.1155/2022/5411462]

275 **Bian Z**, Qin Y, Li L, Su L, Fei C, Li Y, Hu M, Chen X, Zhang W, Mao C, Yuan X, Lu T, Ji D. Schisandra chinensis (Turcz.) Baill. Protects against DSS-induced colitis in mice: Involvement of TLR4/NF-κB/NLRP3 inflammasome pathway and gut microbiota. *J Ethnopharmacol* 2022; **298**: 115570 [PMID: 35868549 DOI: 10.1016/j.jep.2022.115570]

276 **Li Y**, Wang J, Xiao Y, Wang Y, Chen S, Yang Y, Lu A, Zhang S. A systems pharmacology approach to investigate the mechanisms of action of Semen Strychni and Tripterygium wilfordii Hook F for treatment of rheumatoid arthritis. *J Ethnopharmacol* 2015; **175**: 301-314 [PMID: 26386382 DOI: 10.1016/j.jep.2015.09.016]

277 **Han R**, Rostami-Yazdi M, Gerdes S, Mrowietz U. Triptolide in the treatment of psoriasis and other immune-mediated inflammatory diseases. *Br J Clin Pharmacol* 2012; **74**: 424-436 [PMID: 22348323 DOI: 10.1111/j.1365-2125.2012.04221.x]

278 **Graziose R**, Lila MA, Raskin I. Merging traditional Chinese medicine with modern drug discovery technologies to find novel drugs and functional foods. *Curr Drug Discov Technol* 2010; **7**: 2-12 [PMID: 20156139 DOI: 10.2174/157016310791162767]

279 **Xue M**, Jiang ZZ, Wu T, Li J, Zhang L, Zhao Y, Li XJ, Zhang LY, Yang SY. Anti-inflammatory effects and hepatotoxicity of Tripterygium-loaded solid lipid nanoparticles on adjuvant-induced arthritis in rats. *Phytomedicine* 2012; **19**: 998-1006 [PMID: 22884304 DOI: 10.1016/j.phymed.2012.06.006]

280 **Chen YZ**, Gao Q, Zhao XZ, Chen XM, Zhang F, Chen J, Xu CG, Sun LL, Mei CL. Meta-analysis of Tripterygium wilfordii Hook F in the immunosuppressive treatment of IgA nephropathy. *Intern Med* 2010; **49**: 2049-2055 [PMID: 20930429 DOI: 10.2169/internalmedicine.49.3704]

281 **Zhu W**, Li Y, Gong J, Zuo L, Zhang W, Cao L, Gu L, Guo Z, Li N, Li J. Tripterygium wilfordii Hook. f. versus azathioprine for prevention of postoperative recurrence in patients with Crohn's disease: a randomized clinical trial. *Dig Liver Dis* 2015; **47**: 14-19 [PMID: 25445405 DOI: 10.1016/j.dld.2014.09.008]

282 **Sun YY**, Xiao L, Wang D, Ji YC, Yang YP, Ma R, Chen XH. Triptolide inhibits viability and induces apoptosis in liver cancer cells through activation of the tumor suppressor gene p53. *Int J Oncol* 2017; **50**: 847-852 [PMID: 28098861 DOI: 10.3892/ijo.2017.3850]

283 **Qin DP**, Sun PN, Zhou YJ, Chen FM, Zhang CL, Han JX, Yang XJ. [Effect of Tripterygium wilfordii polycoride upon inflammation and TLR4/MyD88 signaling pathway in ulcerative colitis rats model]. *Zhonghua Yi Xue Za Zhi* 2016; **96**: 1444-1449 [PMID: 27266354 DOI: 10.3760/cma.j.issn.0376-2491.2016.18.012]

284 **Fangxiao M**, Yifan K, Jihong Z, Yan S, Yingchao L. Effect of Tripterygium wilfordii Polycoride on the NOXs-ROS-NLRP3 Inflammasome Signaling Pathway in Mice with Ulcerative Colitis. *Evid Based Complement Alternat Med* 2019; **2019**: 9306283 [PMID: 31531121 DOI: 10.1155/2019/9306283]

285 **Gupta D**, Kumari S, Gulrajani M. Dyeing studies with hydroxyanthraquinones extracted from Indian madder. Part 1: Dyeing of nylon with purpurin. *Coloration Technology* 2001; **117**: 328-332

286 **Yusuf M**, Shahid M, Khan SA, Khan MI, Islam S-U, Mohammad F, Khan MA. Eco-dyeing of wool using aqueous extract of the roots of Indian madder (Rubia cordifolia) as natural dye. *J of Natural Fibers* 2013; **10**: 14-28

287 **López-Expósito I**, Castillo A, Yang N, Liang B, Li XM. Chinese herbal extracts of Rubia cordifolia and Dianthus superbus suppress IgE production and prevent peanut-induced anaphylaxis. *Chin Med* 2011; **6**: 35 [PMID: 21961957 DOI: 10.1186/1749-8546-6-35]

288 **Lodi S**, Sharma V, Kansal L. The protective effect of Rubia cordifolia against lead nitrate-induced immune response impairment and kidney oxidative damage. *Indian J Pharmacol* 2011; **43**: 441-444 [PMID: 21845002 DOI: 10.4103/0253-7613.83118]

289 **Shilpa PN**, Sivaramakrishnan V, Niranjali Devaraj S. Induction of apoptosis by methanolic extract of Rubia cordifolia Linn in HEp-2 cell line is mediated by reactive oxygen species. *Asian Pac J Cancer Prev* 2012; **13**: 2753-2758 [PMID: 22938454 DOI: 10.7314/apjcp.2012.13.6.2753]

290 **Qin W**, Luo H, Yang L, Hu D, Jiang SP, Peng DY, Hu JM, Liu SJ. Rubia cordifolia L. ameliorates DSS-induced ulcerative colitis in mice through dual inhibition of NLRP3 inflammasome and IL-6/JAK2/STAT3 pathways. *Heliyon* 2022; **8**: e10314 [PMID: 36082330 DOI: 10.1016/j.heliyon.2022.e10314]

291 **Nile SH**, Park SW. Edible berries: bioactive components and their effect on human health. *Nutrition* 2014; **30**: 134-144 [PMID: 24012283 DOI: 10.1016/j.nut.2013.04.007]

292 **Sánchez-Salcedo EM**, Sendra E, Carbonell-Barrachina ÁA, Martínez JJ, Hernández F. Fatty acids composition of Spanish black (Morus nigra L.) and white (Morus alba L.) mulberries. *Food Chem* 2016; **190**: 566-571 [PMID: 26213011 DOI: 10.1016/j.foodchem.2015.06.008]

293 **Salama RM**, Darwish SF, El Shaffei I, Elmongy NF, Fahmy NM, Afifi MS, Abdel-Latif GA. Morus macroura Miq. Fruit extract protects against acetic acid-induced ulcerative colitis in rats: Novel mechanistic insights on its impact on miRNA-223 and on the TNFα/NFκB/NLRP3 inflammatory axis. *Food Chem Toxicol* 2022; **165**: 113146 [PMID: 35595039 DOI: 10.1016/j.fct.2022.113146]

294 **Derrien M**, Collado MC, Ben-Amor K, Salminen S, de Vos WM. The Mucin degrader Akkermansia muciniphila is an abundant resident of the human intestinal tract. *Appl Environ Microbiol* 2008; **74**: 1646-1648 [PMID: 18083887 DOI: 10.1128/aem.01226-07]

295 **Collado MC**, Derrien M, Isolauri E, de Vos WM, Salminen S. Intestinal integrity and Akkermansia muciniphila, a mucin-degrading member of the intestinal microbiota present in infants, adults, and the elderly. *Appl Environ Microbiol* 2007; **73**: 7767-7770 [PMID: 17933936 DOI: 10.1128/aem.01477-07]

296 **Miller RS**, Hoskins LC. Mucin degradation in human colon ecosystems. Fecal population densities of mucin-degrading bacteria estimated by a "most probable number" method. *Gastroenterology* 1981; **81**: 759-765 [PMID: 7262520]

297 **Li J**, Lin S, Vanhoutte PM, Woo CW, Xu A. Akkermansia Muciniphila Protects Against Atherosclerosis by Preventing Metabolic Endotoxemia-Induced Inflammation in Apoe-/- Mice. *Circulation* 2016; **133**: 2434-2446 [PMID: 27143680 DOI: 10.1161/CIRCULATIONAHA.115.019645]

298 **Blacher E**, Bashiardes S, Shapiro H, Rothschild D, Mor U, Dori-Bachash M, Kleimeyer C, Moresi C, Harnik Y, Zur M, Zabari M, Brik RB, Kviatcovsky D, Zmora N, Cohen Y, Bar N, Levi I, Amar N, Mehlman T, Brandis A, Biton I, Kuperman Y, Tsoory M, Alfahel L, Harmelin A, Schwartz M, Israelson A, Arike L, Johansson MEV, Hansson GC, Gotkine M, Segal E, Elinav E. Potential roles of gut microbiome and metabolites in modulating ALS in mice. *Nature* 2019; **572**: 474-480 [PMID: 31330533 DOI: 10.1038/s41586-019-1443-5]

299 **Wu W**, Lv L, Shi D, Ye J, Fang D, Guo F, Li Y, He X, Li L. Protective Effect of Akkermansia muciniphila against Immune-Mediated Liver Injury in a Mouse Model. *Front Microbiol* 2017; **8**: 1804 [PMID: 29033903 DOI: 10.3389/fmicb.2017.01804]

300 **Zhai R**, Xue X, Zhang L, Yang X, Zhao L, Zhang C. Strain-Specific Anti-inflammatory Properties of Two Akkermansia muciniphila Strains on Chronic Colitis in Mice. *Front Cell Infect Microbiol* 2019; **9**: 239 [PMID: 31334133 DOI: 10.3389/fcimb.2019.00239]

301 **Qu S**, Fan L, Qi Y, Xu C, Hu Y, Chen S, Liu W, Liu W, Si J. Akkermansia muciniphila Alleviates Dextran Sulfate Sodium (DSS)-Induced Acute Colitis by NLRP3 Activation. *Microbiol Spectr* 2021; **9**: e0073021 [PMID: 34612661 DOI: 10.1128/Spectrum.00730-21]

302 **Schiller JT**, Müller M. Next generation prophylactic human papillomavirus vaccines. *Lancet Oncol* 2015; **16**: e217-e225 [PMID: 25943066 DOI: 10.1016/S1470-2045(14)71179-9]

303 **Cen Q**, Gao T, Ren Y, Lu X, Lei H. Immune evaluation of a Saccharomyces cerevisiae-based oral vaccine against Helicobacter pylori in mice. *Helicobacter* 2021; **26**: e12772 [PMID: 33219579 DOI: 10.1111/hel.12772]

304 **Sun S**, Xu X, Liang L, Wang X, Bai X, Zhu L, He Q, Liang H, Xin X, Wang L, Lou C, Cao X, Chen X, Li B, Wang B, Zhao J. Lactic Acid-Producing Probiotic Saccharomyces cerevisiae Attenuates Ulcerative Colitis via Suppressing Macrophage Pyroptosis and Modulating Gut Microbiota. *Front Immunol* 2021; **12**: 777665 [PMID: 34899735 DOI: 10.3389/fimmu.2021.777665]

305 **Anjum N**, Maqsood S, Masud T, Ahmad A, Sohail A, Momin A. Lactobacillus acidophilus: characterization of the species and application in food production. *Crit Rev Food Sci Nutr* 2014; **54**: 1241-1251 [PMID: 24499153 DOI: 10.1080/10408398.2011.621169]

306 **Foye OT**, Huang IF, Chiou CC, Walker WA, Shi HN. Early administration of probiotic Lactobacillus acidophilus and/or prebiotic inulin attenuates pathogen-mediated intestinal inflammation and Smad 7 cell signaling. *FEMS Immunol Med Microbiol* 2012; **65**: 467-480 [PMID: 22524476 DOI: 10.1111/j.1574-695X.2012.00978.x]

307 **Kumar A**, Anbazhagan AN, Coffing H, Chatterjee I, Priyamvada S, Gujral T, Saksena S, Gill RK, Alrefai WA, Borthakur A, Dudeja PK. Lactobacillus acidophilus counteracts inhibition of NHE3 and DRA expression and alleviates diarrheal phenotype in mice infected with Citrobacter rodentium. *Am J Physiol Gastrointest Liver Physiol* 2016; **311**: G817-G826 [PMID: 27634011 DOI: 10.1152/ajpgi.00173.2016]

308 **Amdekar S**, Singh V, Kumar A, Sharma P, Singh R. Lactobacillus casei and Lactobacillus acidophilus regulate inflammatory pathway and improve antioxidant status in collagen-induced arthritic rats. *J Interferon Cytokine Res* 2013; **33**: 1-8 [PMID: 23030670 DOI: 10.1089/jir.2012.0034]

309 **Al-Sadi R**, Nighot P, Nighot M, Haque M, Rawat M, Ma TY. Lactobacillus acidophilus Induces a Strain-specific and Toll-Like Receptor 2-Dependent Enhancement of Intestinal Epithelial Tight Junction Barrier and Protection Against Intestinal Inflammation. *Am J Pathol* 2021; **191**: 872-884 [PMID: 33607043 DOI: 10.1016/j.ajpath.2021.02.003]

310 **Qi H**, Li Y, Yun H, Zhang T, Huang Y, Zhou J, Yan H, Wei J, Liu Y, Zhang Z, Gao Y, Che Y, Su X, Zhu D, Zhang Y, Zhong J, Yang R. Lactobacillus maintains healthy gut mucosa by producing L-Ornithine. *Commun Biol* 2019; **2**: 171 [PMID: 31098404 DOI: 10.1038/s42003-019-0424-4]

311 **Zhang Y**, Zhao X, Zhu Y, Ma J, Ma H, Zhang H. Probiotic Mixture Protects Dextran Sulfate Sodium-Induced Colitis by Altering Tight Junction Protein Expressions and Increasing Tregs. *Mediators Inflamm* 2018; **2018**: 9416391 [PMID: 29849501 DOI: 10.1155/2018/9416391]

312 **Li P**, Chen G, Zhang J, Pei C, Chen Y, Gong J, Deng S, Cai K, Li H, Wang D, Shen B, Xie Z, Liao Q. Live Lactobacillus acidophilus alleviates ulcerative colitis via the SCFAs/mitophagy/NLRP3 inflammasome axis. *Food Funct* 2022; **13**: 2985-2997 [PMID: 35195119 DOI: 10.1039/d1fo03360c]

313 **Monagas M**, Quintanilla-López JE, Gómez-Cordovés C, Bartolomé B, Lebrón-Aguilar R. MALDI-TOF MS analysis of plant proanthocyanidins. *J Pharm Biomed Anal* 2010; **51**: 358-372 [PMID: 19410413 DOI: 10.1016/j.jpba.2009.03.035]

314 **Prasain JK**, Peng N, Dai Y, Moore R, Arabshahi A, Wilson L, Barnes S, Michael Wyss J, Kim H, Watts RL. Liquid chromatography tandem mass spectrometry identification of proanthocyanidins in rat plasma after oral administration of grape seed extract. *Phytomedicine* 2009; **16**: 233-243 [PMID: 19095430 DOI: 10.1016/j.phymed.2008.08.006]

315 **Sheng K**, Zhang G, Sun M, He S, Kong X, Wang J, Zhu F, Zha X, Wang Y. Grape seed proanthocyanidin extract ameliorates dextran sulfate sodium-induced colitis through intestinal barrier improvement, oxidative stress reduction, and inflammatory cytokines and gut microbiota modulation. *Food Funct* 2020; **11**: 7817-7829 [PMID: 32808642 DOI: 10.1039/d0fo01418d]

316 **Enaida H**, Hisatomi T, Hata Y, Ueno A, Goto Y, Yamada T, Kubota T, Ishibashi T. Brilliant blue G selectively stains the internal limiting membrane/brilliant blue G-assisted membrane peeling. *Retina* 2006; **26**: 631-636 [PMID: 16829804 DOI: 10.1097/01.iae.0000236469.71443.aa]

317 **Saber S**, Youssef ME, Sharaf H, Amin NA, El-Shedody R, Aboutouk FH, El-Galeel YA, El-Hefnawy A, Shabaka D, Khalifa A, Saleh RA, Osama D, El-Zoghby G, Gobba NA. BBG enhances OLT1177-induced NLRP3 inflammasome inactivation by targeting P2X7R/NLRP3 and MyD88/NF-κB signaling in DSS-induced colitis in rats. *Life Sci* 2021; **270**: 119123 [PMID: 33548287 DOI: 10.1016/j.lfs.2021.119123]

318 **Wang Z**, Xia Q, Liu X, Liu W, Huang W, Mei X, Luo J, Shan M, Lin R, Zou D, Ma Z. Phytochemistry, pharmacology, quality control and future research of Forsythia suspensa (Thunb.) Vahl: A review. *J Ethnopharmacol* 2018; **210**: 318-339 [PMID: 28887216 DOI: 10.1016/j.jep.2017.08.040]

319 **Chao L**, Lin J, Zhou J, Du H, Chen X, Liu M, Qu Q, Lv W, Guo S. Polyphenol Rich Forsythia suspensa Extract Alleviates DSS-Induced Ulcerative Colitis in Mice through the Nrf2-NLRP3 Pathway. *Antioxidants (Basel)* 2022; **11** [PMID: 35326124 DOI: 10.3390/antiox11030475]

320 **GU S-z,** XUE Y, ZHANG Y-l, GAO Y, DOU D-b, CAI G. Clinical Efficacy of Kuijietong Against Mild to Moderate Active Ulcerative Colitis. Chinese Journal of Experimental Traditional Medical Formulae 2021: 106-111

321 **Xue S**, Xue Y, Dou D, Wu H, Zhang P, Gao Y, Tang Y, Xia Z, Yang S, Gu S. Kui Jie Tong Ameliorates Ulcerative Colitis by Regulating Gut Microbiota and NLRP3/Caspase-1 Classical Pyroptosis Signaling Pathway. *Dis Markers* 2022; **2022**: 2782112 [PMID: 35832643 DOI: 10.1155/2022/2782112]

322 **Dai YC**, Zhang YL, Wang LJ, Guo Q, Yang K, Ye RH, Tang ZP. Clinical presentation and treatment strategies for ulcerative colitis: A retrospective study of 247 inpatients. *Chin J Integr Med* 2016; **22**: 811-816 [PMID: 26501692 DOI: 10.1007/s11655-015-2118-1]

323 **Zheng L**, Zhang YL, Dai YC, Chen X, Chen DL, Dai YT, Tang ZP. Jianpi Qingchang decoction alleviates ulcerative colitis by inhibiting nuclear factor-κB activation. *World J Gastroenterol* 2017; **23**: 1180-1188 [PMID: 28275298 DOI: 10.3748/wjg.v23.i7.1180]

324 **Zhang J**, Kang X, Sun M, Zhang S. Qingre Jianpi decoction attenuates inflammatory responses by suppressing NOD-like receptor family pyrin domain-containing 3 inflammasome activation in dextran sulfate sodium-induced colitis mice. *J Tradit Chin Med* 2021; **41**: 68-78 [PMID: 33522199 DOI: 10.19852/j.cnki.jtcm.2021.01.009]

325 **Alsaweed M**, Lai CT, Hartmann PE, Geddes DT, Kakulas F. Human milk miRNAs primarily originate from the mammary gland resulting in unique miRNA profiles of fractionated milk. *Sci Rep* 2016; **6**: 20680 [PMID: 26854194 DOI: 10.1038/srep20680]

326 **Benmoussa A**, Laugier J, Beauparlant CJ, Lambert M, Droit A, Provost P. Complexity of the microRNA transcriptome of cow milk and milk-derived extracellular vesicles isolated via differential ultracentrifugation. *J Dairy Sci* 2020; **103**: 16-29 [PMID: 31677838 DOI: 10.3168/jds.2019-16880]

327 **Gao HN**, Guo HY, Zhang H, Xie XL, Wen PC, Ren FZ. Yak-milk-derived exosomes promote proliferation of intestinal epithelial cells in an hypoxic environment. *J Dairy Sci* 2019; **102**: 985-996 [PMID: 30580945 DOI: 10.3168/jds.2018-14946]

328 **Hock A**, Miyake H, Li B, Lee C, Ermini L, Koike Y, Chen Y, Määttänen P, Zani A, Pierro A. Breast milk-derived exosomes promote intestinal epithelial cell growth. *J Pediatr Surg* 2017; **52**: 755-759 [PMID: 28188035 DOI: 10.1016/j.jpedsurg.2017.01.032]

329 **Zhou F**, Paz HA, Sadri M, Cui J, Kachman SD, Fernando SC, Zempleni J. Dietary bovine milk exosomes elicit changes in bacterial communities in C57BL/6 mice. *Am J Physiol Gastrointest Liver Physiol* 2019; **317**: G618-G624 [PMID: 31509432 DOI: 10.1152/ajpgi.00160.2019]

330 **Tong L**, Hao H, Zhang Z, Lv Y, Liang X, Liu Q, Liu T, Gong P, Zhang L, Cao F, Pastorin G, Lee CN, Chen X, Wang JW, Yi H. Milk-derived extracellular vesicles alleviate ulcerative colitis by regulating the gut immunity and reshaping the gut microbiota. *Theranostics* 2021; **11**: 8570-8586 [PMID: 34373759 DOI: 10.7150/thno.62046]

331 **Anttila SA**, Leinonen EV. A review of the pharmacological and clinical profile of mirtazapine. *CNS Drug Rev* 2001; **7**: 249-264 [PMID: 11607047 DOI: 10.1111/j.1527-3458.2001.tb00198.x]

332 **Sahin E**, Bektur E, Burukoglu Donmez D, Baycu C, Can OD, Sahinturk V. Mirtazapine suppresses sterile inflammation through NLRP3-inflammasome in diabetic rat kidney. *Acta Histochem* 2019; **121**: 289-296 [PMID: 30711241 DOI: 10.1016/j.acthis.2019.01.007]

333 **Hafez HM**, Ibrahim MA, Yehia Abdelzaher W, Gad AA, Mohammed Naguib Abdel Hafez S, Abdel-Gaber SA. Protective effect of mirtazapine against acetic acid-induced ulcerative colitis in rats: Role of NLRP3 inflammasome pathway. *Int Immunopharmacol* 2021; **101**: 108174 [PMID: 34601335 DOI: 10.1016/j.intimp.2021.108174]

334 **Chang Y**, Jia X, Wei F, Wang C, Sun X, Xu S, Yang X, Zhao Y, Chen J, Wu H, Zhang L, Wei W. CP-25, a novel compound, protects against autoimmune arthritis by modulating immune mediators of inflammation and bone damage. *Sci Rep* 2016; **6**: 26239 [PMID: 27184722 DOI: 10.1038/srep26239]

335 **Jia XY**, Chang Y, Wei F, Dai X, Wu YJ, Sun XJ, Xu S, Wu HX, Wang C, Yang XZ, Wei W. CP-25 reverses prostaglandin E4 receptor desensitization-induced fibroblast-like synoviocyte dysfunction via the G protein-coupled receptor kinase 2 in autoimmune arthritis. *Acta Pharmacol Sin* 2019; **40**: 1029-1039 [PMID: 30643209 DOI: 10.1038/s41401-018-0196-2]

336 **Wu H**, Chen X, Gu F, Zhang P, Xu S, Liu Q, Zhang Q, Wang X, Wang C, Körner H, Wei W. CP-25 alleviates antigen-induced experimental Sjögren's syndrome in mice by inhibiting JAK1-STAT1/2-CXCL13 signaling and interfering with B-cell migration. *Lab Invest* 2021; **101**: 1084-1097 [PMID: 32620868 DOI: 10.1038/s41374-020-0453-0]

337 **Li Y**, Jiang MY, Chen JY, Xu ZW, Zhang JW, Li T, Zhang LL, Wei W. CP-25 exerts therapeutic effects in mice with dextran sodium sulfate-induced colitis by inhibiting GRK2 translocation to downregulate the TLR4-NF-κB-NLRP3 inflammasome signaling pathway in macrophages. *IUBMB Life* 2021; **73**: 1406-1422 [PMID: 34590407 DOI: 10.1002/iub.2564]

338 **Cosentino F**, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020; **41**: 255-323 [PMID: 31497854 DOI: 10.1093/eurheartj/ehz486]

339 **Birnbaum Y**, Chen H, Tran D, Nylander S, Ye Y. Ticagrelor and Dapagliflozin Have Additive Effects in Ameliorating Diabetic Nephropathy in Mice with Type-2 Diabetes Mellitus. *Cardiovasc Drugs Ther* 2022; **36**: 829-840 [PMID: 34232433 DOI: 10.1007/s10557-021-07222-x]

340 **Abd El-Fattah EE**, Saber S, Mourad AAE, El-Ahwany E, Amin NA, Cavalu S, Yahya G, Saad AS, Alsharidah M, Shata A, Sami HM, Kaddah MMY, Ghanim AMH. The dynamic interplay between AMPK/NFκB signaling and NLRP3 is a new therapeutic target in inflammation: Emerging role of dapagliflozin in overcoming lipopolysaccharide-mediated lung injury. *Biomed Pharmacother* 2022; **147**: 112628 [PMID: 35032769 DOI: 10.1016/j.biopha.2022.112628]

341 **Ye Y**, Bajaj M, Yang HC, Perez-Polo JR, Birnbaum Y. SGLT-2 Inhibition with Dapagliflozin Reduces the Activation of the Nlrp3/ASC Inflammasome and Attenuates the Development of Diabetic Cardiomyopathy in Mice with Type 2 Diabetes. Further Augmentation of the Effects with Saxagliptin, a DPP4 Inhibitor. *Cardiovasc Drugs Ther* 2017; **31**: 119-132 [PMID: 28447181 DOI: 10.1007/s10557-017-6725-2]

342 **El-Rous MA**, Saber S, Raafat EM, Ahmed AAE. Dapagliflozin, an SGLT2 inhibitor, ameliorates acetic acid-induced colitis in rats by targeting NFκB/AMPK/NLRP3 axis. *Inflammopharmacology* 2021; **29**: 1169-1185 [PMID: 34002329 DOI: 10.1007/s10787-021-00818-7]

343 **Nomura S**, Sakamaki S, Hongu M, Kawanishi E, Koga Y, Sakamoto T, Yamamoto Y, Ueta K, Kimata H, Nakayama K, Tsuda-Tsukimoto M. Discovery of canagliflozin, a novel C-glucoside with thiophene ring, as sodium-dependent glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus. *J Med Chem* 2010; **53**: 6355-6360 [PMID: 20690635 DOI: 10.1021/jm100332n]

344 **Nasr M**, Cavalu S, Saber S, Youssef ME, Abdelhamid AM, Elagamy HI, Kamal I, Gaafar AGA, El-Ahwany E, Amin NA, Girgis S, El-Sandarosy R, Mahmoud F, Rizk H, Mansour M, Hasaballah A, El-Rafi AA, El-Azez RA, Essam M, Mohamed D, Essam N, Mohammed OA. Canagliflozin-loaded chitosan-hyaluronic acid microspheres modulate AMPK/NF-κB/NLRP3 axis: A new paradigm in the rectal therapy of ulcerative colitis. *Biomed Pharmacother* 2022; **153**: 113409 [PMID: 36076534 DOI: 10.1016/j.biopha.2022.113409]

345 **Zacà V**, Rastogi S, Imai M, Wang M, Sharov VG, Jiang A, Goldstein S, Sabbah HN. Chronic monotherapy with rosuvastatin prevents progressive left ventricular dysfunction and remodeling in dogs with heart failure. *J Am Coll Cardiol* 2007; **50**: 551-557 [PMID: 17678740 DOI: 10.1016/j.jacc.2007.04.050]

346 **Saber S**, Abd El-Fattah EE, Yahya G, Gobba NA, Maghmomeh AO, Khodir AE, Mourad AAE, Saad AS, Mohammed HG, Nouh NA, Shata A, Amin NA, Abou El-Rous M, Girgis S, El-Ahwany E, Khalaf EM, El-Kott AF, El-Baz AM. A Novel Combination Therapy Using Rosuvastatin and Lactobacillus Combats Dextran Sodium Sulfate-Induced Colitis in High-Fat Diet-Fed Rats by Targeting the TXNIP/NLRP3 Interaction and Influencing Gut Microbiome Composition. *Pharmaceuticals (Basel)* 2021; **14** [PMID: 33917884 DOI: 10.3390/ph14040341]

347 **Coll RC**, Robertson AA, Chae JJ, Higgins SC, Muñoz-Planillo R, Inserra MC, Vetter I, Dungan LS, Monks BG, Stutz A, Croker DE, Butler MS, Haneklaus M, Sutton CE, Núñez G, Latz E, Kastner DL, Mills KH, Masters SL, Schroder K, Cooper MA, O'Neill LA. A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. *Nat Med* 2015; **21**: 248-255 [PMID: 25686105 DOI: 10.1038/nm.3806]

348 **Van Gorp H**, Saavedra PH, de Vasconcelos NM, Van Opdenbosch N, Vande Walle L, Matusiak M, Prencipe G, Insalaco A, Van Hauwermeiren F, Demon D, Bogaert DJ, Dullaers M, De Baere E, Hochepied T, Dehoorne J, Vermaelen KY, Haerynck F, De Benedetti F, Lamkanfi M. Familial Mediterranean fever mutations lift the obligatory requirement for microtubules in Pyrin inflammasome activation. *Proc Natl Acad Sci U S A* 2016; **113**: 14384-14389 [PMID: 27911804 DOI: 10.1073/pnas.1613156113]

349 **Gaidt MM**, Ebert TS, Chauhan D, Schmidt T, Schmid-Burgk JL, Rapino F, Robertson AA, Cooper MA, Graf T, Hornung V. Human Monocytes Engage an Alternative Inflammasome Pathway. *Immunity* 2016; **44**: 833-846 [PMID: 27037191 DOI: 10.1016/j.immuni.2016.01.012]

350 **van der Heijden T**, Kritikou E, Venema W, van Duijn J, van Santbrink PJ, Slütter B, Foks AC, Bot I, Kuiper J. NLRP3 Inflammasome Inhibition by MCC950 Reduces Atherosclerotic Lesion Development in Apolipoprotein E-Deficient Mice-Brief Report. *Arterioscler Thromb Vasc Biol* 2017; **37**: 1457-1461 [PMID: 28596375 DOI: 10.1161/ATVBAHA.117.309575]

351 **Mridha AR**, Wree A, Robertson AAB, Yeh MM, Johnson CD, Van Rooyen DM, Haczeyni F, Teoh NC, Savard C, Ioannou GN, Masters SL, Schroder K, Cooper MA, Feldstein AE, Farrell GC. NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice. *J Hepatol* 2017; **66**: 1037-1046 [PMID: 28167322 DOI: 10.1016/j.jhep.2017.01.022]

352 **Qu J**, Yuan Z, Wang G, Wang X, Li K. The selective NLRP3 inflammasome inhibitor MCC950 alleviates cholestatic liver injury and fibrosis in mice. *Int Immunopharmacol* 2019; **70**: 147-155 [PMID: 30802677 DOI: 10.1016/j.intimp.2019.02.016]

353 **Wang L**, Lei W, Zhang S, Yao L. MCC950, a NLRP3 inhibitor, ameliorates lipopolysaccharide-induced lung inflammation in mice. *Bioorg Med Chem* 2021; **30**: 115954 [PMID: 33360197 DOI: 10.1016/j.bmc.2020.115954]

354 **Perera AP**, Fernando R, Shinde T, Gundamaraju R, Southam B, Sohal SS, Robertson AAB, Schroder K, Kunde D, Eri R. MCC950, a specific small molecule inhibitor of NLRP3 inflammasome attenuates colonic inflammation in spontaneous colitis mice. *Sci Rep* 2018; **8**: 8618 [PMID: 29872077 DOI: 10.1038/s41598-018-26775-w]

**Footnotes**

**Conflict-of-interest statement:** There are no conflicts of interest to report.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** November 19, 2022

**First decision:** November 30, 2022

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Egypt

**Peer-review report*’*s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

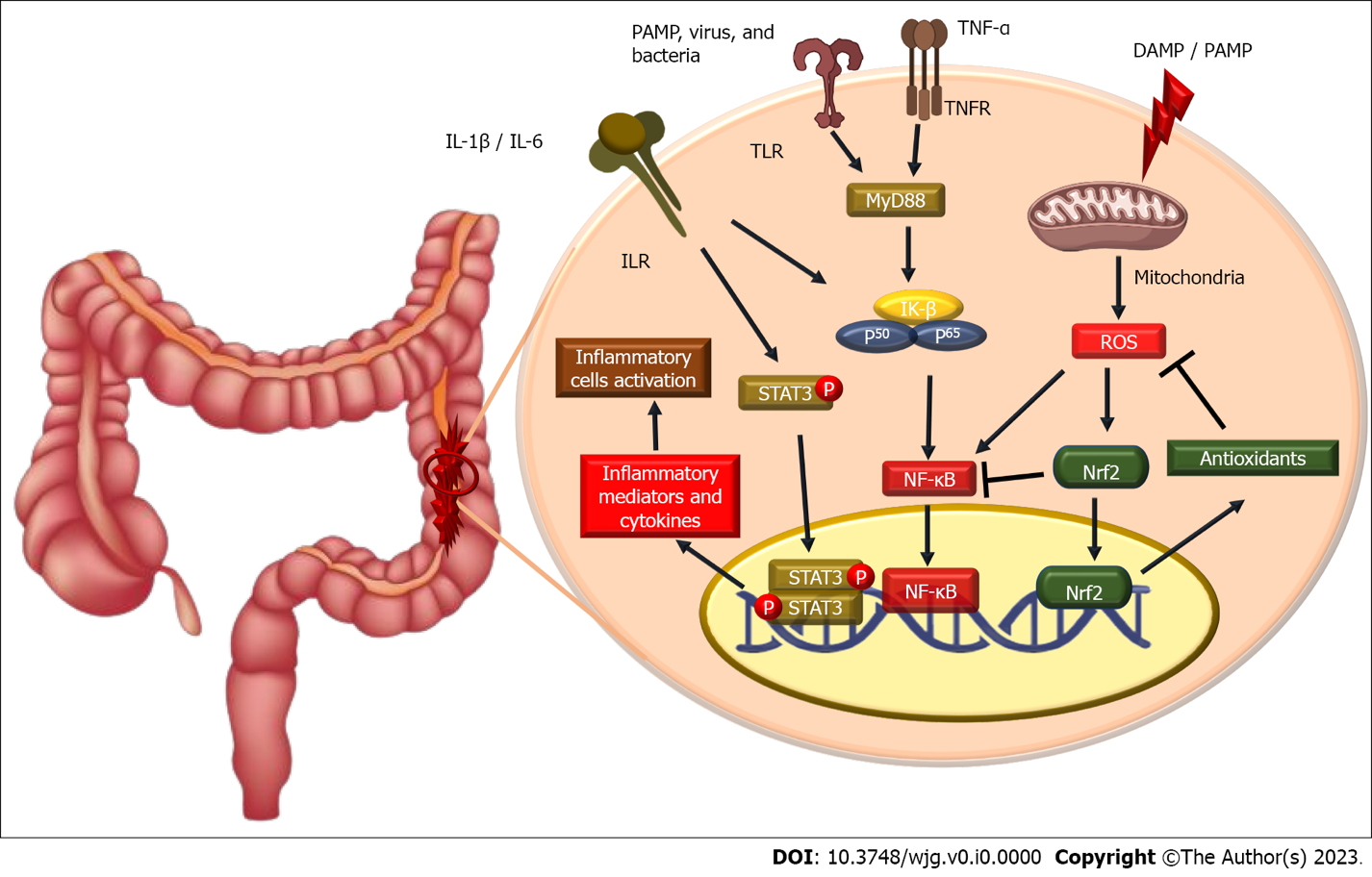
Grade C (Good): C

Grade D (Fair): 0

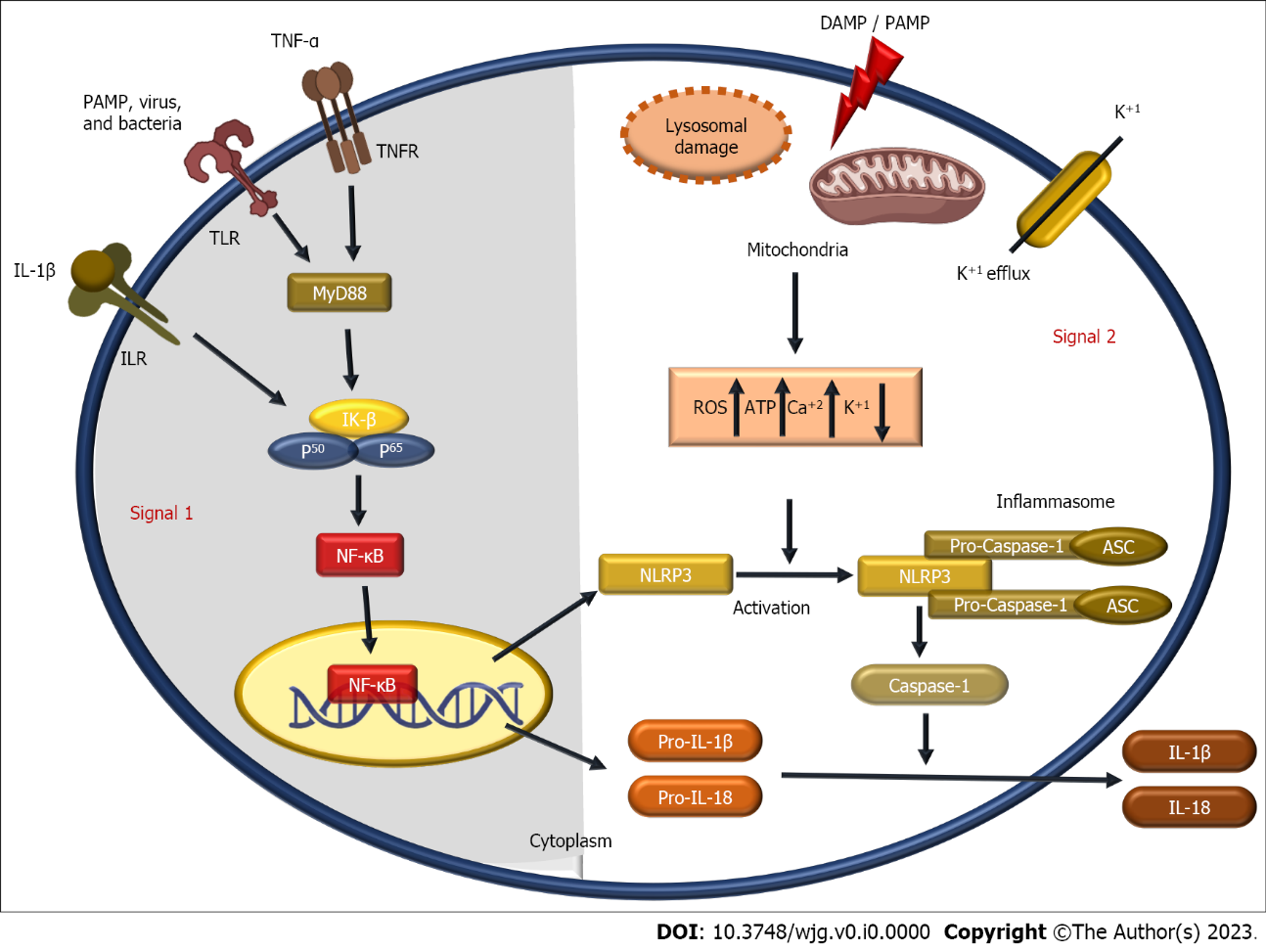
Grade E (Poor): 0

**P-Reviewer:** Arumugam VA, India; Zhao G, China **S-Editor:** Chen YL **L-Editor:** A **P-Editor:** Chen YL

**Figure Legends**



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



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