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REVIEW

A Comprehensive Review of Food-Derived Compounds Targeting Pyroptosis for Colitis Therapy: From Effects to Mechanisms

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Abstract: Ulcerative colitis (UC) is a form of non-specific inflammatory bowel disease characterized by complex pathological mechanisms that remain incompletely understood, posing challenges for effective treatment. Pyroptosis, a form of inflammatory cell death mediated by the Gasdermin D protein family, occurs primarily through the classical caspase-1 pathway, the non-classical caspase-4, 5, and 11 pathways, and alternative pathways. Dysregulated activation of pyroptosis signaling has been implicated in the progression of UC, indicating that targeted inhibition of pyroptosis may serve as a therapeutic strategy. Food-derived compounds have demonstrated promise in modulating key pyroptosis-related targets, thereby providing potential therapeutic benefits for UC. This review examines the classical, non-classical, and alternative pathways of pyroptosis and their roles in UC pathogenesis and treatment. Additionally, the effects and mechanisms of action of natural compounds in targeting programmed cell death are discussed, with the aim of informing future therapeutic strategies and contributing to the development of new pharmacological interventions for UC.

Keywords: food-derived compounds, inflammation, mechanism, pyroptosis, UC

Introduction

Ulcerative colitis (UC) is a chronic, relapsing, and nonspecific inflammatory bowel disease (IBD) that primarily affects the colon and rectum.[1] It has been predominantly observed in industrialized Western countries; however, with the rapid industrialization of emerging nations such as China, India, and those in Latin America, both the incidence and hospitalization rates of UC have risen significantly in these regions.[1,2] By 2023, the global prevalence of UC is estimated to have reached approximately 5 million people worldwide.[1]

Epidemiological studies indicate substantial geographic variation in UC incidence. Figure 1 depicts the estimated incidence rates of UC (per 100,000 person-years) from 1990–2016 across different regions: North America (8.8 in the United States to 23.14 in Canada), Eastern Europe (0.97 in Romania to 11.9 in Hungary), Northern Europe (1.7 in Estonia to 57.9 in the Faroe Islands), Southern Europe (3.3 in Croatia to 11.47 in Spain), Western Europe (1.9 in France to 17.2 in the Netherlands), East Asia (0.42 in China to 4.6 in South Korea), South Asia (0.69 in Sri Lanka to 6.02 in India), West Asia (0.42 in China to 4.6 in South Korea), South America (0.19–6.76 in Brazil and 7.33–17.7 in Australia), and Oceania (3.29 in Algeria).[3]

Ulcerative colitis (UC) currently does not have a single definitive test for diagnosis; it is based on symptoms, physical examination, laboratory tests, and endoscopic evaluation. Endoscopy (such as colonoscopy) and tissue biopsy are key to diagnosing UC. Current treatment options for UC vary depending on the severity of the condition and have limited effectiveness. Patients with mild to moderate UC often use 5-aminosalicylic acid (such as mesalamine); if ineffective, they may need to use oral corticosteroids (like budesonide or prednisone). Patients with moderate to severe UC can opt

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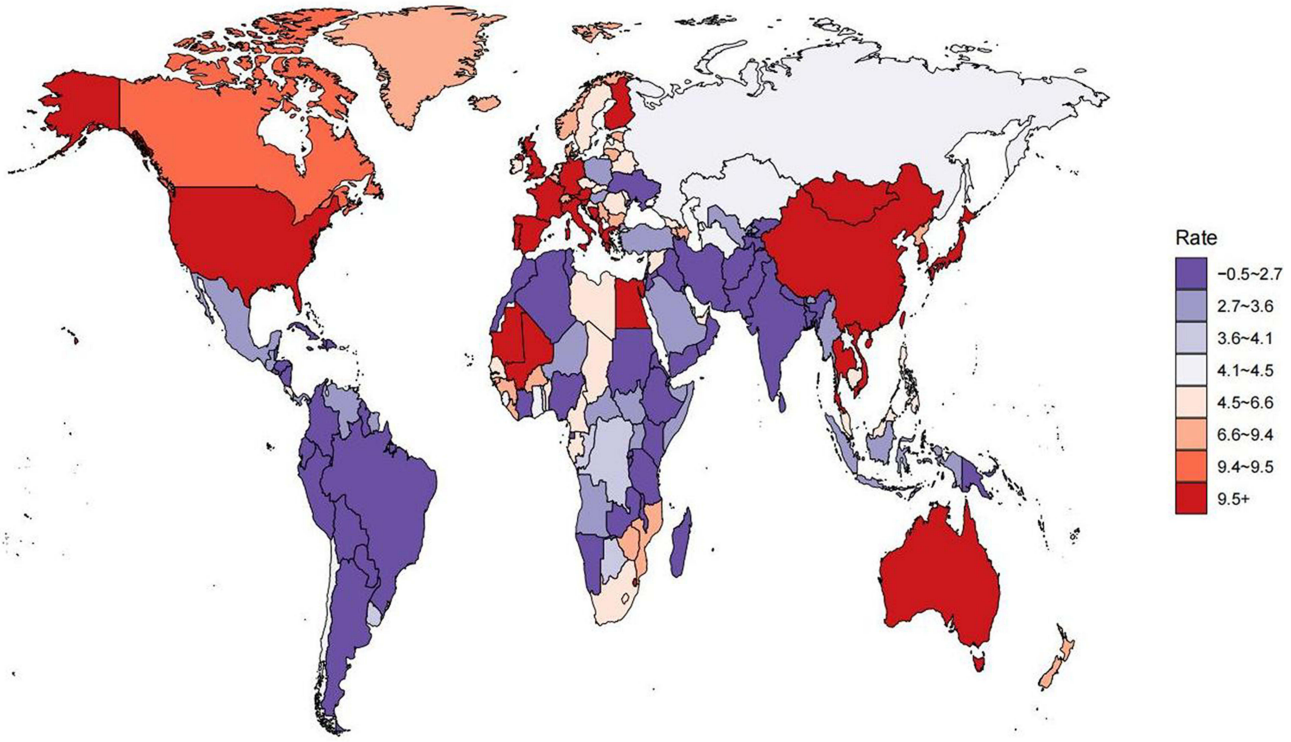

Figure 1 The global prevalence and incidence rates of ulcerative colitis.

for monoclonal antibody therapies or oral small molecule drugs. For severe UC patients whose medical treatments are ineffective or who experience complications, partial or total colectomy may be necessary.[4]

The understanding of the pathophysiology of ulcerative colitis (UC) is incomplete. Current treatments for UC remain suboptimal, with varying efficacy depending on disease severity and extent of colonic involvement. This highlights the urgent need for new therapeutic strategies.

Pyroptosis is a form of inflammatory cell death mediated by the gasdermin D (GSDMD) protein family. This process is primarily executed through the caspase-1 pathway (the classical pathway) and the caspase-4/5/11 pathways (the non-classical pathways), as well as via the caspase-3/8-mediated pyroptosis pathway and granzyme-mediated pyroptosis pathway.[5] Emerging evidence indicates that pyroptosis plays a critical role in the pathogenesis of UC. The over-expression of APOL1 activates the NLRP3/caspase-1/GSDMD pyroptosis pathway, promoting the release of chemokine CXCL1 and exacerbating UC severity.[5] Additionally, several regulatory molecules such as lncRNA MEG3, miR-141-3p, and SLC6A1 are also involved in influencing UC progression by modulating pyroptosis.[6–9]

In recent years, natural compounds have increasingly been used to treat various diseases, some demonstrating potential as therapeutic agents for UC. These compounds exert anti-inflammatory effects partly by regulating programmed cell death (PCD) pathways including pyroptosis. Thus, food-based bioactive compounds represent a promising important complementary or alternative treatment option for UC.[10,11]

Bioactive compounds found naturally in fruits, vegetables, grains, seeds, and spices have long been an important resource in drug discovery and development. Numerous studies have explored dietary components' roles in managing UC, emphasizing their potential therapeutic effects while also noting that oral bioavailability is a critical factor for applying food-derived compounds since it determines how much can be absorbed and utilized within the body. This review comprehensively summarizes recent advances concerning food-sourced compounds used in interventions against UC while particularly focusing on their inhibitory effects on pyroptosis. Furthermore, it systematically outlines food-derived compounds that inhibit pyroptosis in UC while providing deep insights into their mechanisms of action. The review also discusses challenges affecting these food-derived compounds' clinical applications—including

bioavailability, targeting precision, and stability—summarizing recent advancements in structural modification and targeted delivery strategies while exploring their potential applications in treating colitis.

The objective of this review is to serve as a valuable resource for researchers, clinicians, and the pharmaceutical industry by facilitating the identification of novel pyroptosis inhibitors for UC management. The potential of these food-derived compounds to modulate pyroptosis contribute to improved disease outcomes and enhance the development of future disease-modifying therapies, ultimately improving the quality of life for patients with UC.

Primary Pyroptosis Mechanisms and Their Role in Dextran Sulfate Sodium (DSS)-Induced Colitis

Pyroptosis and Its Primary Mechanism

The following sections provide a detailed examination of the molecular mechanisms and signaling pathways involved in pyroptosis.

Classical Pyroptosis Pathway

The classical pathway of pyroptosis (caspase-1 dependent pathway) is primarily mediated by caspase-1. Under normal circumstances, caspase-1 exists in an inactive precursor form (pro-caspase-1) in the cytoplasm, and its activation is regulated by the classical inflammasome pathway. When microbial pathogens, viruses, or endogenous danger signals are detected, intracellular pattern recognition receptors (PRRs) recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), triggering the assembly of inflammasomes that include NLRP3, AIM2, NLRP1, PYRIN, and NLRC4.[12–14]

Inflammasomes are multiprotein complexes composed of PRRs, adaptor proteins, and ASC proteins containing CARD domains to recruit caspases such as pro-caspase-1. Among them, the NLRP3 inflammasome is the most extensively studied type; it consists of Nod-like receptor protein 3 (NLRP3), apoptosis-associated speck-like protein containing a CARD domain (ASC), and effector protein caspase-1. After recruitment, pro-caspase-1 undergoes auto-catalytic cleavage to form dimers that further assemble into tetramers to ultimately produce active caspase-1.[5,12,15]

Activated caspase-1 cleaves GSDMD to generate active GSDMD-N fragments. These fragments bind to the phospholipid bilayer of cell membranes to form transmembrane pores, leading to membrane rupture and cell death while releasing pro-inflammatory cytokines such as IL-18 that further exacerbate inflammatory responses.[16,17]

Non-Classical Pyroptosis Pathway

In the non-classical pyroptosis pathway, human caspase-4/5 and mouse caspase-11 can directly bind to lipopolysaccharide (LPS) through their N-terminal CARD domains and become activated. Once activated, these caspases cleave GSDMD, releasing its N-terminal pore-forming domain (PFD), which then aggregates and translocates to the cell membrane to form pores, leading to cell membrane rupture and content release, ultimately triggering pyroptosis.[18] Moreover, the cleavage of GSDMD mediated by caspase-4/5 and caspase-11 also induces potassium ion (K^+) efflux, activating the NLRP3 inflammasome and completing its assembly while activating the classic pathway.[19] In addition, Caspase-11 activated by LPS can also activate P2X7 receptors on the cell membrane via a pannexin-1/ATP/P2X7 signaling axis, resulting in ATP-induced K^+ efflux that further activates the NLRP3 inflammasome and thus triggers the classical NLRP3/caspase-1 pathway.[20–23]

Caspase-3/8-Mediated Pyroptosis Pathway

An increasing amount of evidence suggests that apoptosis-related Caspase-3/8 is involved in pyroptotic cell death pathways.[13,24,25] In caspase-3 mediated pyroptosis, caspase-3 specifically cleaves GSDME to produce an N-terminal fragment, which forms membrane pores and leads to cell swelling and lysis. The expression level of GSDME is a key factor determining whether caspase-3 activation results in apoptosis or pyroptosis. When GSDME is abundantly expressed, cells are more likely to undergo pyroptosis rather than apoptosis under internal and external stimuli.[26] Moreover, during Yersinia infection, the effector protein YopJ can inactivate TAK1 or IκB kinase, leading to caspase-

8-mediated cleavage of GSDMD and subsequently inducing pyroptosis.[27,28] Additionally, when mouse macrophages are co-stimulated with LPS and the TAK1 inhibitor (5Z)-7-Oxozeaenol, the activation of caspase-8 also triggers pyroptosis.[28]

Granzyme-Mediated Pyroptosis Pathway

Granzyme-mediated pyroptosis involves two key enzymes: Granzyme A (GZMA) and Granzyme B (GZMB). GZMA-mediated pyroptosis is mediated through the cleavage of GSDMB and pore-forming activity.[5] GZMB induces apoptosis and pyroptosis mainly by activating caspase signaling pathways. Granzyme B released by chimeric antigen receptor T cells (CAR-T cells) activates caspase-3 in target cells, initiating the caspase-3/GSDME-mediated pyroptosis pathway.[29] Further studies have shown that GZMB can directly cleave GSDME, leading to pyroptosis.[30]

The granzyme-mediated pyroptosis pathway is a critical mechanism for cytotoxic lymphocytes to eliminate target cells, providing new insights into cytotoxic lymphocyte-mediated clearance of target cells and potentially holding significant implications for cancer immunotherapy.

The Role of Pyroptosis in DSS-Induced Colitis

The Role of NLRP3 Inflammasome Activation, IL-1β and IL-18 in Colitis

In the DSS-induced colitis model, the analysis of pyroptosis markers showed expected changes in IL-1β and caspase-1 levels. Further studies indicated that Gα12/13 expression was upregulated in mouse colon, along with increased expression of endoplasmic reticulum stress-related markers. The simultaneous activation of caspase-1 and IL-1β supports the involvement of pyroptosis, suggesting that pyroptosis in DSS-induced colitis may be mediated through the Gα12/13 signaling pathway and endoplasmic reticulum stress.[31] Additionally, research by Tak et al demonstrated that the administration of VX-765 (a caspase-1 inhibitor) effectively blocked GSDMD-mediated pyroptosis and alleviated DSS-induced ulcerative colitis in mice.[32]

Current research suggests that the NLRP3 inflammasome plays a critical role in maintaining intestinal homeostasis and promoting inflammatory responses. In NLRP3 gene knockout mice, DSS-induced colitis was reduced, alongside a decrease in pro-inflammatory cytokine production within colon tissues. These findings indicate that the NLRP3 inflammasome is an important contributor to the pathogenesis of DSS-induced colitis.[33] Pharmacological inhibition experiments using MCC950 as a specific NLRP3 inhibitor have been shown to alleviate acute colitis induced by DSS in mice, further supporting the significant role of the NLRP3 inflammasome in colorectal disease development.[33] Moreover, studies have found that IL-1β primarily facilitates inflammatory responses.[34,35] While IL-18 exhibits dual roles in DSS-induced colitis; it shows anti-inflammatory characteristics during early stages but promotes inflammation at later stages.[36,37]

The Role of GSDM Proteins in DSS-Induced Colitis

The gasdermin (GSDM) protein family is involved in DSS-induced colitis through various mechanisms, including mediating pyroptosis, regulating inflammatory responses, maintaining the integrity of the gut barrier, and potentially playing physiological roles unrelated to pyroptosis. GSDMD is the main effector molecule of pyroptosis: its pore formation leads to cell lytic death while also serving as a secretion pathway for pro-inflammatory cytokines.[38,39] These cytokines are associated with several inflammatory diseases,[40] and their contribution to disease pathogenesis revolves around promoting the release of IL-1 family members. In DSS-induced colitis models, activated GSDMD is closely related to intestinal inflammation. In macrophages, GSDMD suppresses colitis by regulating cGAS-mediated inflammation. Within macrophages, GSDMD acts as a negative regulator that controls cGAS-dependent inflammation, thereby preventing colitis. Moreover, pharmacological inhibition of cGAS has been found to reverse colon symptoms in mice lacking GSDMD.[41] Additionally, increased expression of GSDMD has been linked to structural dysfunction induced by DSS; it regulates intestinal homeostasis by promoting mucus secretion from goblet cells and facilitating mucous layer formation.[42] Furthermore, in healthy small intestine tissue, GSDM expression does not trigger significant pyroptotic or inflammatory responses, indicating that GSDM proteins may have an intrinsic physiological function in maintaining intestinal homeostasis independent of pyroptosis.[43] However, there is controversy regarding the important role of epithelial cells or immunogenic GSDMD in gut inflammation. Bulek et al used an acute DSS-induced colitis

model to demonstrate that small extracellular vesicles containing IL-1β were released from intestinal epithelial cells (IECs) through the chaperone protein GSDMD-FL,[44] while another group observed the release of IL-18, which promoted colitis development in vivo by driving standard cell loss.[39] In another mouse model, caspase 8 was found to promote inflammation in the cecum by inducing GSDMD-dependent death of intestinal epithelial cells; this study suggested a role for GSDMD-mediated pyroptosis in cecal inflammation.[45] Overall, these data strongly support the concept that activation of GSDMD in IECs mediates gut inflammation.

Although GSDMB shows some characteristics that distinguish it from other family members, recent studies indicate that GZMA derived from lymphocytes mediates the proteolytic activation of GSDMB in human intestinal epithelial cell lines.[46] It has been found that GSDMB levels are elevated in patients with IBD,[47] and polymorphisms in GSDMB are associated with several chronic inflammatory diseases, including IBD.[48]

In recent years, significant progress has been made in the role of GSDME in both tumor and non-tumor diseases. In 2023, Hu et al provided a detailed summary of GSDME's potential in early detection, diagnosis, prognosis, and treatment of tumors,[49] Remarkable advancements have also been achieved regarding non-tumor diseases, particularly inflammatory bowel disease. Xu et al found an increasing trend of the transmembrane protein CD147 in the mucosa of patients with IBD. CD147 treatment significantly enhanced the expression of GSDMD and GSDME proteins, activating pyroptosis to exacerbate intestinal inflammation. This suggests that GSDME-mediated pyroptosis may be related to the pathogenesis of IBD.[50] Recently, research by Tan et al indicated that GSDME-mediated pyroptosis accelerates intestinal inflammation and impacts the pathogenesis of Crohn's disease (CD), showing a significant presence of GSDME-N in the inflamed colonic mucosa of patients with active CD. Furthermore, due to its release of HMGB1—a pro-inflammatory factor in intestinal epithelial cells—GSDME-mediated pyroptosis promoted mucosal inflammation in mice with colitis induced by 2,4,6-trinitrobenzenesulfonic acid.[51] In this same mouse model, researchers also discovered that TNF stimulation triggers caspase-3 mediated cleavage leading to GSDME-mediated explosive cell death under IRF1 control in IECs.[52]

In summary, the pyroptosis markers NLRP3 inflammasome activation, IL-1β and IL-18, GSDMB, GSDMD, and GSDME all showed expected changes in patients with colitis and in mouse models of colitis. This suggests that pyroptosis plays a role in the pathogenesis of colitis. Monitoring pyroptosis markers during subsequent treatment of DSS-induced colitis with dietary compounds provides a theoretical basis for exploring the mechanisms of these dietary compounds in treating DSS-induced colitis.

The Effect and Mechanism of Food-Derived Compounds in Intervening DSS-Induced Colitis by Inhibiting Pyroptosis

An increasing body of experimental evidence indicates that certain food-derived compounds can mitigate DSS-induced colitis by inhibiting pyroptosis (Table 1 and Figure 2). The molecular structures of these food-derived compounds are depicted in Figure 3, while their dietary sources are depicted in Figure 4. The effects and mechanisms by which these compounds modulate DSS-induced colitis through pyroptosis inhibition are summarized in Table 1 and Figure 5, and are discussed in detail below.

1-Acetoxy-Vanillic Acid Ester

1'-Acetoxy-vanillic acid ester (ACA) is found not only in rhizomes but also in the seeds of *Alpinia galanga* and *Alpinia zerumbet*, plants traditionally used as spices and medicinal herbs in Southeast Asia. ACA has been reported to exhibit various pharmacological properties, including anticancer, anti-obesity, antidiabetic, anti-inflammatory, and neuroprotective effects.[69]

A recent study by Sok et al explored the effects of ACA in mouse bone marrow-derived macrophages and human THP-1 monocytes. The findings demonstrated that ACA inhibits the activation of the NLRP3 inflammasome and caspase-1, as well as the production of IL-1β. Additionally, ACA suppresses the effects of NLRP3 agonists, such as nigericin, monosodium urate (MSU) crystals, and ATP, by preventing the aggregation of the apoptosis-associated speck-like protein containing ASC and the caspase-1-mediated cleavage of GSDMD, a key effector of pyroptosis.

Table 1 Food-Derived Compounds Target Pyroptosis Signaling Pathway Against DSS-Induced Colitis via Anti-Pyroptosis

Food- Derived Compounds	Resource	Model	Dosage	Biological Markers	Mechanisms and Effects	References
1′-Acetoxychavicol acetate (ACA)	Tropical ginger *Alpinia* species	Mouse bmms, mouse J774 and PMA, human THP-1 macrophages; DSS-induced ulcerative colitis model in mouse	2.5 μM- 10 μM for 30 min; 100 ppm for 10 days	Ox-mtDNA↓; NLRP3↓; Caspase-1↓; ASC↓; Gasdermin D↓; IL-1β↓	Inhibit pyroptosis	Sok SPM et al[53]
Apple polyphenols extract (APE)	Apple	DSS-induced ulcerative colitis model in mouse	125, 500 mg/kg/d for 21 days	BCL-2 protein↑; NLRP3, ASC, Caspase-1/11, and GSDND proteins↓; Cox-2 mRNA↓; Psd-95 mRNA↑; ZO-1 and Occludin protein↑; MUC-2 and TTF3 protein↑	Inhibit apoptosis and pyroptosis; alleviate neuroinflammation and synaptic damage; Improve the integrity of the intestinal barrier and enhancethe function of goblet cells.	Liu et al[54]
Atranorin	Lichen family	DSS-induced ulcerative colitis model in mouse	100 μM, 50 μM and 25 μM for 30 min; 100 or 50 mg/kg/d for 7 days	NLRP3↓; Caspase-1↓; IL-1β and IL-18↓	Inhibit inflammation, improve barrier function and target ACS to inhibit pyroptosis	Wang et al[55]
Betaine	Sugar beets	DSS-induced ulcerative colitis model in mouse	600 mg/kg/d for 7 days	MDA, MPO, NOS, and COX2↓; GSH, NRF2, CAT, and SOD1↑; Occludin and zonula occluden 1 (ZO-1) protein↑; NLRP3, ASC, cleaved caspase-1 (c-Casp1), and N-terminal GSDMD↓; IL-1β and IL-18↓	Anti-oxidative stress; repair tight junction barrier injury; attenuates inflammatory pyroptosis	Chen et al[56]
Demethoxycurcumin (BUR)	Curcuma longa	DSS-induced intestinal inflammatory model in C57BL/6	200 or 400 mg/kg/d for 14 days	DAI scores↓; MPO↓; Occludin and zonula occluden 1 (ZO-1) protein↑; Bax and caspase 3 mRNA↓; Bcl2 mRNA↑; NLRP3, ASC, caspase−1, cleaved caspase 1, GSDMD and IL-1β↓; beneficial bacteria↑	Enhance intestinal barrier function; reduce apoptosis; inhibiting NLRP3 inflammasome activation and pyroptosis and regulae the gut microbiota	Zhang et al[57]
Ginsenoside Rb1	*Panax ginseng* C. A. Meyer	MODE-K and Caco-2; DSS-induced ulcerative colitis model in mouse	10, 20, and 40μM for 24 h; 10, 20, 40 mg/kg/d for 7 days	IL-6, TNF-α, IL-1β, and ROS↓; HO-1, NQO1, Nrf2 and Keap-1↓; PIP2, IP3, and DAG↓; PLCγ2↑; protein and mRNA levels of NLRP3, Caspase-1, IL-1β, pro-Caspase-1, pro-IL-1β, and ASC↓; Claudin-1 and ZO-1↑	Repair intestinal barrier integrity; anti-oxidative stress; anti-inflammation; inhibit pyroptosis	Li et al[58]
Ginsenoside Rg3 (Gin Rg3)	Ginseng	Mouse BMDMs and CECs; DSS-induced ulcerative colitis model in mouse	5 mg/mL Gin Rg3 for 1 h;10 mg/kg/day for 7 days	ASC, GSDMD-N, NLRP3 and pro-Caspase-1↓; IL-1β and IL-18↓; TUNEL staining showed cell apoptosis↓; Claudin-1, mucin-1, E-cadherin, and Occludin↑	Repair intestinal barrier integrity; inhibit apoptosis; anti-inflammation; inhibit pyroptosis	Liu et al[59]
Hydroxy safflower yellow A (HSYA)		THP-1 cells; DSS-induced ulcerative colitis model in mouse	40, 80, and 160μM for 5h; 30 and 60mg/kg/day for 7 days	NLRP3, p17 fragment of IL-1β, p20 fragment of active caspase-1, and GSDMD-N↓; IL-1β, IL-6, TNF-α, and IL-18↓; NLRP3, GSDMD-N, caspase-1 p20, IL-1β precursor, and IL-1β↓; HK1↓; occludin and claudin-1↑	Regulate dysbiosis; anti-inflammation; inhibit pyroptosis	Chen et al[60]
Narirutin	Citrus genus (such as bitter orange, Citrus aurantium L).	THP-1 macrophages and BMDMs; DSS-induced ulcerative colitis model in mouse	30–500 μM for 24 and 48 h; 300 mg/kg/d for 7 days	NLRP3 and IL-1β↓; NF-κB, MAPK, PI3K and AKT↓; ACS↓	Target NLRP3-ASC interaction to inhibit pyroptosis	Ri et al[61]

Parthenolide (PTL)	Tanacetum parthenium	BMDMs, THP-1 cells or U937 cells; DSS-induced ulcerative colitis model in mice	2.5, 5, and 10μM for 45min; 50 mg/kg/d for 7 days	mtROS and lysosomal damage↓; caspase-1 and the maturation of IL-1β↓; interaction between NLRP3 and NEK7↓; interaction between NLRP3 and ASC↓; cleavage of GSDMD↓	Anti-inflammation; inhibit NLRP3 inflammasome activation and pyroptosis	Liu et al[62]
Polysaccharides from garlic (PSG)	Garlic	DSS-induced ulcerative colitis model and liver injury in mouse	150 or 300 mg/kg/d for 7 days	MPO, DAO, iNOS, and COX2↓; ZO1, occludin and MUC2↑; LPS, IL-1β, IL-18, NLRP3, gasdermin D, caspase-1, ASC, TLR4, MyD88, NF-κB, and phosphorylated NF-κB↓; ROS, MDA, Keap-1, 8-OHDG, and phosphorylated H2AX↓; GPX4, SOD2, HO1, NQO1, and Nrf2↑	Anti-oxidative stress; anti-inflammation; inhibit pyroptosis	Zhan et al[63]
Pterostilbene (PTE) Derivatives D20	Blueberries and grapes	DSS-induced ulcerative colitis model in mouse	30 or 60 mg/kg/d for 7 days	IL-1βand NLRP3↓	Inhibit pyroptosis	Zhang et al[64]
Pterostilbene (PTE) Derivatives D22	Blueberries and grapes	DSS-induced ulcerative colitis model in mouse	30 or 60 mg/kg/d for 7 days	IL-1βand NLRP3↓	Inhibit pyroptosis	Ruan et al[65]
L. cubeba leaf extract (MLE)	Lauraceae family and the Litsea genus	DSS-induced ulcerative colitis model in mouse	20, 40 and 80 mg/kg/d for 7 days	mtROS, ACS, NLRP3, IL-1β precursor, or TNF-α↓	Inhibit pyroptosis	Wong et al[66]
β-sitosterol (SIT)	Fruits, vegetables, nuts, seeds, soybean oil, and cottonseed oil	Caco-2 cell; DSS-induced ulcerative colitis model in rat	16, 32, and 64 μg/mL for 24h; 50, 100, 200 mg/kg/d for 14 days	TNF-α, IL-1β, and IL-18↓; Caspase-1, Cleaved-Caspase-1, NLRP3, GSDMD, and GSDMD-N↓; ZO-1 and occludin↑	Repair intestinal barrier integrity; anti-inflammation; inhibit pyroptosis	Zhang et al[67]
Pelargonidin-3-galactoside (Pg3gal)	Flowers, vegetables, and fruits, such as purple sweet potatoes	DSS-induced ulcerative colitis model in mouse	10, 25 mg/kg/d for 10days	IL-6, NLRP3, ASC, cleaved-Caspase-1, TNF-a, N-GSDMS, and cleaved-IL-1b proteins↓; Proteobacteria and Deferribacteres↓ and Firmicutes, Bacteroidetes, and Verrucomicrobia↑.	Inhibit pyroptosis; Enhance the structural integrity of the gut microbiota	Chen et al[68]
Pectic polysaccharides (PPs)	Devil peppers	DSS-induced ulcerative colitis model in mouse	100 mg/kg/d for 7 days	Cleaved Caspase-1, IL-1β, and TNF-α	Inhibit pyroptosis	Cheng et al[34]

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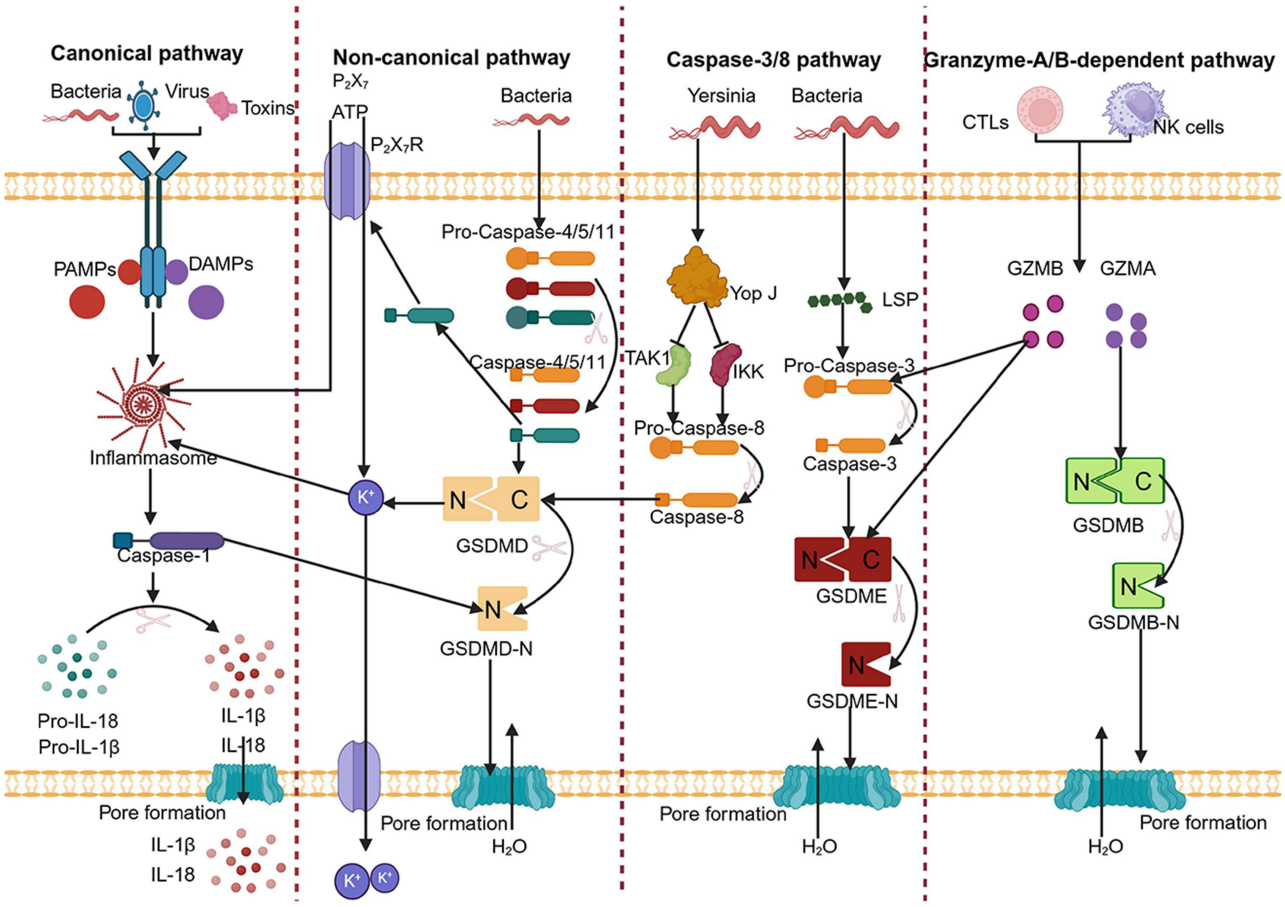

Figure 2 The molecular mechanism of pyroptosis. Created in BioRender. Jinwei, Z. (2025) https://BioRender.com/wkqlabb.

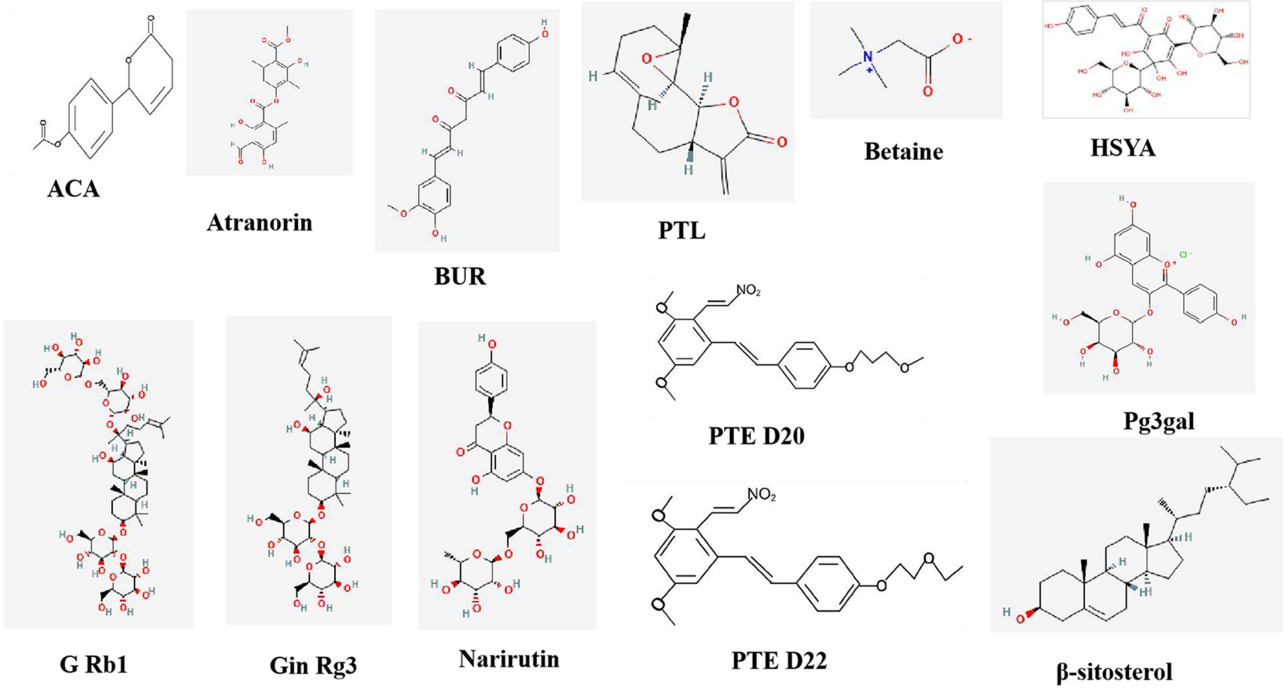

Figure 3 Chemical structure of food-derived compounds against DSS-induced colitis via anti-pyroptosis.

Figure 4 Food sources of food-derived compounds that fight dss induced colitis by anti-pyroptosis.

Further mechanistic analyses revealed that ACA prevents the generation of mitochondrial reactive oxygen species (ROS) and the release of oxidized mitochondrial DNA, both of which serve as triggers for NLRP3 inflammasome activation. Moreover, ACA suppresses NLRP3 inflammasome activation in in vivo models, as evidenced by reduced caspase-1 activation in MSU crystal-induced peritonitis and DSS-induced colitis mouse models.[53]

Apple Polyphenol Extract

Apple polyphenol extract (APE), derived from Fuji apples, has been reported to confer various health benefits, including anti-inflammatory, antioxidant, and anticancer properties.[70]

A study by Liu et al demonstrated that APE significantly ameliorated DSS-induced acute UC. The underlying mechanisms involved the inhibition of intestinal epithelial cell (IEC) apoptosis and suppression of the caspase-1/11-dependent pyroptosis pathway in IECs. This was evidenced by an increase in B-cell lymphoma 2 protein levels and a reduction in the expression of NLRP3, GSDMD, ASC, and caspase-1/11 proteins.

Additionally, APE alleviated neuroinflammation and synaptic damage associated with acute UC, as indicated by a reduction in Cox-2 mRNA expression in the hypothalamus and an increase in Psd-95 mRNA expression, while Gfap mRNA levels in the hippocampus were decreased. APE also contributed to the preservation of intestinal barrier integrity, as demonstrated by the upregulation of tight junction proteins zonula occludens-1 (ZO-1) and occludin. Furthermore, it enhanced goblet cell function, as reflected by the increased expression of mucin-2 and transcription factor 3 proteins.[54]

Atranorin

Lichens are symbiotic organisms composed of fungi and autotrophic photosynthetic species, capable of surviving in a wide range of environmental conditions, including extreme environments. Atranorin ($C_{19}H_{18}O_{8,}$ ATR) is a secondary metabolite with an ester structure derived from the Lichinaceae family. It has been demonstrated in previous studies that ATR showcases various biological activities, particularly anti-inflammatory properties.[71,72] Additionally, ATR alleviates carrageenan-induced paw edema.[73] Acute and chronic toxicity assessments in rats have further confirmed its in vivo safety.[73]

https://doi.org/10.2147/JIR.S531820

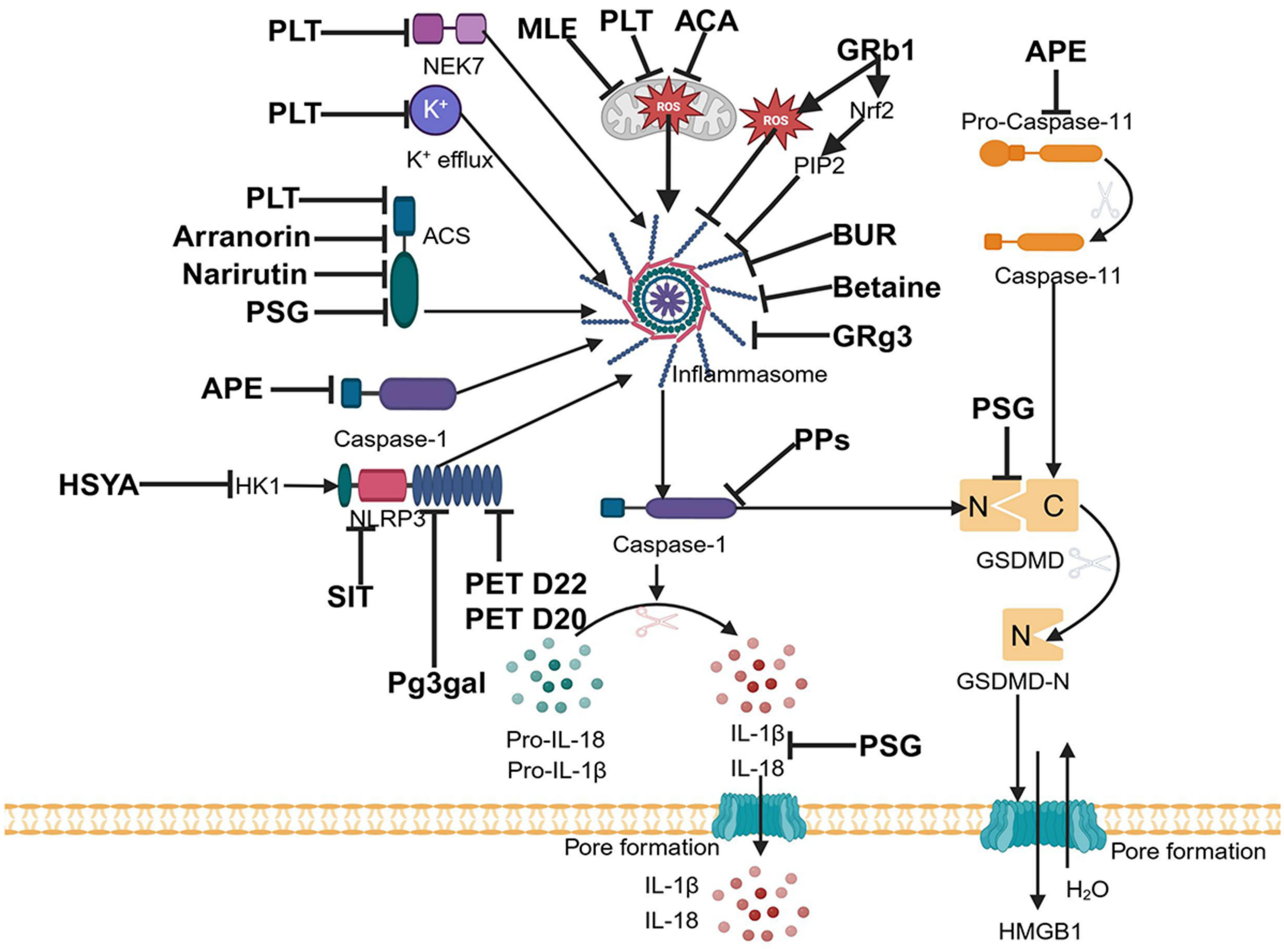

Figure 5 Molecular mechanisms of food-derived compounds against DSS-induced colitis via anti-pyroptosis. Created in BioRender. Jinwei, Z. (2025) https://BioRender.com/29in6lh.

Dysregulated activation of the NLRP3 inflammasome is closely associated with the pathogenesis of various inflammatory diseases, and to date, no small-molecule inhibitors specifically targeting the NLRP3 inflammasome have been approved for clinical use. Wang et al investigated the pharmacological effects of ATR using disease models driven by NLRP3 inflammasome activation. According to experimental findings, ATR effectively inhibits NLRP3 inflammasome activation in macrophages and dendritic cells. Mechanistically, ATR suppresses the aggregation of ASC protein by directly binding to it, thereby reducing cytokine secretion and pyroptotic cell death associated with NLRP3 activation.[55]

In LPS-induced acute inflammation model, ATR reduced serum levels of IL-1β and IL-18. Furthermore, in MSU crystal-induced gouty arthritis model, ATR lowered IL-1β levels in the ankle joint. More importantly, ATR suppressed NLRP3 inflammasome activation and improved epithelial barrier dysfunction and intestinal inflammation in a DSS-induced UC mouse model.[55]

Betaine

Betaine (BET) is a widely available nutritional supplement primarily found in beets.[74] As a key methyl donor involved in methylation processes, BET plays a key role in various physiological functions.[75,76]

Chen et al explored the effects of BET in a DSS-induced acute severe ulcerative colitis model. The findings indicated that BET administration resulted in improvements in the Disease Activity Index (DAI), mitigation of weight loss, recovery from splenomegaly, and restoration of colon length, along with the alleviation of colonic mucosal damage.[43,56]

BET demonstrated significant antioxidant properties, as evidenced by reductions in oxidative stress markers, including malondialdehyde, myeloperoxidase, nitric oxide synthase, and COX2. Concurrently, an upregulation of antioxidant

proteins such as glutathione, nuclear factor erythroid 2-related factor 2 (NRF2), catalase, and superoxide dismutase 1 was observed.[56]

Primarily, BET prevents colitis-associated pyroptosis, primarily through the inhibition of the NLRP3 inflammasome complex. This was associated with the downregulation of N-terminal GSDMD expression and a reduction in the release of pyroptosis-related inflammatory mediators.[56]

Curcumin and Demethoxycurcumin

Curcumin (CUR) is a polyphenolic compound derived from *Curcuma longa* (turmeric). Studies demonstrated that CUR mitigates DSS-induced colitis by inhibiting NLRP3 inflammasome activation and downregulating IL-1β levels.[77] In a doxorubicin-induced mouse model, CUR suppressed NLRP3-mediated pyroptosis while enhancing innate immune responses.[78] However, despite its potent anti-inflammatory properties, the clinical application of CUR is limited due to its poor absorption and low bioavailability.

Demethoxycurcumin (BUR), a CUR derivative, exhibits superior pharmacological properties and bioavailability compared to CUR.[79] Recently, BUR has garnered significant attention due to its improved absorption and enhanced therapeutic potential.[80,81]

In a DSS-induced colitis mouse model, BUR administration led to a reduction in weight loss, histopathological tissue damage, and epithelial cell apoptosis associated with DSS exposure. BUR significantly improved intestinal barrier integrity and attenuated the inflammatory response. Furthermore, BUR reinforced its role in suppressing NLRP3 inflammasome activation and pyroptosis.[57]

Additionally, BUR exerted modulatory effects on gut microbiota composition. Supplementation with BUR increased the relative abundance of beneficial bacteria, including *lactobacillus* and *bifidobacterium*, and demonstrated a significant negative correlation with pro-inflammatory biomarkers.[57]

Overall, BUR alleviates DSS-induced colitis primarily through multiple mechanisms, including enhancing intestinal barrier function, reducing epithelial apoptosis, inhibiting NLRP3 inflammasome activation, and modulating gut microbiota dysbiosis.[57]

Ginsenoside Rb1

Ginseng, an herbaceous plant of the Araliaceae family, has increasingly been recognized for its potential as a functional food and an effective adjunctive therapeutic agent. It has been seen in prior studies that various natural ginseng saponins exhibit regulatory effects on UC. Among them, ginsenoside Rb1 (GRb1) has revealed therapeutic potential in colitis through multiple signaling pathways. For instance, GRb1 has been indicated to exert protective effects by targeting the pregnane X receptor/nuclear factor-kappa B (NF-κB) signaling pathway.[82] Additionally, recent findings indicate that GRb1 activates the Hrd1 signaling pathway in intestinal epithelial cells, thereby reducing endoplasmic reticulum stress and lowering the risk of colitis in murine models.[83]

The therapeutic effects of GRb1 on UC have been further explored in both in vivo and in vitro models. Li et al examined the effects of GRb1 using a DSS-induced colitis mouse model and intestinal epithelial cell lines (MODE-K and Caco-2). The results demonstrated that GRb1 significantly reduced the levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-1β in both in vitro and in vivo models. Additionally, GRb1 exhibited antioxidant properties by decreasing ROS production and directly targeting Nrf2 to activate the Nrf2HO-1/Keap1 signaling pathway, thereby preventing NLRP3 inflammasome activation.[58]

Furthermore, GRb1 regulated the calcium-related phosphatidylinositol 4,5-bisphosphate (PIP2) signaling pathway by inhibiting inflammasome activation and calcium ion influx, thereby suppressing pyroptosis. In in vivo experiments, GRb1 administration was associated with an increase in colonic length, reduced histopathological damage, restoration of intestinal barrier integrity, and modulation of the inflammatory response.[58]

In summary, GRb1 exerts therapeutic effects on UC in both in vivo and in vitro models by regulating the Nrf2/PIP2/NLRP3 pathway. These findings indicate that targeting Nrf2 with GRb1 may represent a promising therapeutic strategy for UC management.[58]

Ginsenoside Rg3

Ginsenoside Rg3 (GRg3), a bioactive compound derived from ginseng, modulates immune function and suppresses inflammatory responses.[84,85] The key role of gut microbiota has been highlighted in the transformation and absorption of ginsenosides within the intestine in recent studies.[84] Unlike other ginsenosides such as Rd and Rk, GRg3 is a metabolic product of gut microbiota conversion and is readily absorbed, enhancing its bioavailability.[86]

The immunomodulatory effects of GRg3 in a UC model has been explored in a recent study, where its impact on NLRP3 inflammasome activation through a combination of in vitro cell-based experiments and in vivo animal studies was examined. In in vitro experiments, GRg3 counteracted the increased protein expression levels of apoptosis-associated speck-like protein containing ASC, GSDMD-N, NLRP3, and caspase-1 induced by LPS and ATP stimulation. Additionally, GRg3 downregulated IL-1β and IL-18 expression and reduced the number of caspase-1 and propidium iodide double-positive cells. Moreover, GRg3 alleviated cell swelling, membrane pore formation, nuclear condensation, and vesicle formation associated with LPS + ATP treatment while promoting apoptosis.[86]

In the DSS-induced UC mouse model, GRg3 treatment reversed the severity of colitis induced by DSS exposure. Notably, GRg3 restored the expression levels of tight junction and mucosal barrier proteins, including claudin-1, mucin-1, E-cadherin, and occludin, which were downregulated following DSS administration. Furthermore, GRg3 counteracted the DSS-induced increase in ASC, GSDMD-N, NLRP3, pro-caspase-1, and cleaved caspase-1 protein expression, as well as the elevated levels of IL-1β and IL-18. GRg3 also reduced the number of caspase-1 and PI double-positive cells.[59]

Collectively, findings from both in vitro and in vivo experiments suggest that GRg3 mitigates inflammation by inhibiting NLRP3 inflammasome activation, highlighting its potential as a therapeutic agent for ulcerative colitis.[59]

Hydroxy Safflower Yellow A

Safflower (*Carthamus tinctorius L.)* is a multipurpose crop valued for its seeds, which are rich in oleic acid and linoleic acid and serve as a source of high-quality edible oil. Additionally, its flowers are commonly used for food flavoring and as a source of orange-red dyes.[87,88] Hydroxy safflower yellow A (HSYA), a chalcone glycoside, is the primary water-soluble bioactive compound extracted from safflower. A Phase II double-blind clinical trial demonstrated that intravenous infusion of HSYA at doses of 50 or 70 mg/day was effective in treating blood stasis syndrome and acute ischemic stroke, with a favorable safety and tolerability profile.[89] Prior studies highlighted the potent anti-inflammatory and antioxidant properties of HSYA.[89,90] Additionally, HSYA inhibits NLRP3 inflammasome activation in myocardial injury, and recent findings suggest its therapeutic potential in UC through modulation of the TLR4/NF-κB pathway.[90]

Chen et al further explored the mechanisms underlying the protective effects of HSYA in UC. Their findings indicated that HSYA reduced IL-1β, TNF-α, and IL-6 levels while suppressing NLRP3/GSDMD-mediated pyroptosis in macrophages stimulated by LPS and ATP. Metabolomic analysis revealed that HSYA prevented the upregulation of hexokinase 1 (HK1) expression induced by LPS/ATP stimulation. Further validation using HK1 shRNA transfection confirmed that HSYA inhibited NLRP3/GSDMD-mediated pyroptosis by downregulating HK1 expression.[60]

In vivo experiments demonstrated that HSYA significantly alleviated DSS-induced UC symptoms and decreased the secretion of pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, and IL-18. Moreover, HSYA effectively suppressed the HK1/NLRP3/GSDMD-mediated pyroptotic response, further supporting its potential as a therapeutic agent for UC.[60]

Narirutin

Chenpi refers to the dried, mature peel of citrus fruits, particularly from Citrus aurantium L. and its cultivated varieties. It has a long history of use in traditional medicine, where it is commonly used to alleviate symptoms such as colds, indigestion, coughing, and excessive phlegm.[91] Among the bioactive compounds present in citrus peels, flavonoids—particularly narirutin—constitute a major class of phenolic compounds.[92] NR exhibits multiple biological activities, including antioxidant and anti-allergic properties.[93,94]

A study conducted by Ri et al in 2022 investigated the effects of NR on NLRP3-mediated inflammatory responses in both in vitro and in vivo models, identifying its potential mechanisms of action. The findings indicated that NR reduced

IL-1β levels and inhibited pyroptosis in macrophages stimulated with LPS and ATP. These effects were closely associated with the suppression of NF-κB, MAPK, and PI3K/AKT signaling pathways.[61]

Additionally, NR inhibited the assembly of the NLRP3 inflammasome by preventing the interaction between NLRP3 and apoptosis-associated speck-like protein containing ASC. In vivo experiments demonstrated that oral administration of NR (300 mg/kg) alleviated inflammatory symptoms in mouse models of peritonitis and colitis. These results indicate that NR exerts its anti-inflammatory effects by inhibiting NLRP3 inflammasome activation, blocking its pre-activation process, and suppressing the NLRP3-ASC interaction.[61]

Parthenolide

Parthenolide (PTL) is a natural sesquiterpene lactone originally extracted from *Tanacetum parthenium* (feverfew). According to research, PTL exhibits anti-inflammatory properties and has been traditionally used in the management of inflammatory conditions such as fever, psoriasis, and atherosclerosis.[95–97] Furthermore, PTL inhibits inflammation by suppressing NF-κB activity, a key regulator of inflammatory mediators and effector molecules.[98,99]

From research conducted by Juliana et al, it can be seen that PTL inhibits the ATPase activity of NLRP3 in mouse bone marrow cells.[98,99] Additionally, Liu et al found that PTL prevents the production of mitochondrial reactive oxygen species (mtROS) and lysosomal damage induced by Nigella sativa. PTL inhibits NLRP3 inflammasome activation through multiple mechanisms, including the suppression of potassium ion efflux, reduction of mtROS production, and prevention of NLRP3 inflammasome complex formation. The proper assembly of the NLRP3 inflammasome is essential for caspase-1 activation and the subsequent maturation of IL-1β.[62]

Moreover, PTL modulates the interaction between NLRP3 and NEK7, which plays an important role in the initial steps of NLRP3 inflammasome activation. Additionally, PTL inhibits the oligomerization of NLRP3 and prevents its interaction with apoptosis-associated speck-like protein containing ASC. Experimental results further indicated that PTL reduces caspase-1 activation induced by *nigella sativa*, thereby inhibiting GSDMD cleavage and the subsequent release of high-mobility group box 1.[62]

Polysaccharides from Garlic

Garlic (*Allium sativum L.)* is a widely consumed natural food with both culinary and medicinal properties. It has been used for thousands of years as a seasoning and in traditional Chinese medicine for the treatment of various conditions, including diabetes, obesity, hypertension, as well as kidney and liver disorders.[100] Polysaccharides, which are abundant in nature, are characterized by their multi-target biological activities and relatively low toxicity, making them promising therapeutic agents.[101]

From a recent study, it can be seen that garlic-derived polysaccharides (PSG) significantly ameliorated DSS-induced IBD in mice. PSG administration improved key indicators of disease severity, including weight loss, DAI, colon length, and histopathological changes in colonic tissue. Additionally, PSG effectively reduced colonic inflammation markers and enhanced intestinal barrier integrity in colonic epithelial cells of IBD-affected mice.[63]

Furthermore, PSG exhibited protective effects against DSS-induced secondary liver injury, as evidenced by improvements in liver morphology, liver index, liver function, and histopathological changes. Mechanistic investigations revealed that PSG attenuated systemic inflammation and pyroptosis by reducing the expression levels of LPS, IL-1β, IL-18, NLRP3, GSDMD, caspase-1, apoptosis-associated speck-like protein containing ASC, TLR4, myeloid differentiation primary response 88, NF-κB, and phosphorylated NF-κB in the liver. Simultaneously, PSG increased IL-10 levels, indicating its role in modulating inflammation and pyroptosis.[63]

These findings indicate that PSG may serve as a potential therapeutic agent for IBD, particularly in cases associated with secondary liver injury.[63]

Pterostilbene Derivatives

Pterostilbene (PTE) is a polyphenolic compound found in various plant sources, including blueberries and grapes. From studies, its diverse biological activities, including antioxidant, anti-apoptotic, and anticancer properties have become evident.[102–104]

PTE has been identified through recent research as a potential modulator of the NLRP3 inflammasome through high-throughput screening models.[105] Notably, Ruan et al designed and synthesized a series of novel para-methylstilbene derivatives (D1–D43) and systematically screened their anti-inflammatory activity by evaluating their inhibitory effects on LPS/nicotinamide-induced IL-1β production and pyroptosis. Through structure-activity relationship analysis, compound 1-((E)-4-(2-ethoxyethoxy)styrene)-3,5-dimethoxy-2-((E)-2-nitrovinyl)benzene (D22) was identified as the most potent low-toxicity compound with significant inhibitory efficacy. Preliminary mechanistic studies indicate that compound D22 may directly target the NLRP3 protein, thereby influencing the assembly and activation of the NLRP3 inflammasome. Experimental findings demonstrated that D22 exerted strong anti-inflammatory effects and had a significant therapeutic impact in a DSS-induced acute colitis mouse model.[65]

According to a study by Zhang et al the resveratrol derivative D20 may also target the NLRP3 protein and modulate the assembly and activation of the NLRP3 inflammasome. In in vivo anti-inflammatory assessments, compound D20 exhibited substantial therapeutic efficacy in the DSS-induced acute colitis mouse model.[64]

Litsea. Cubeba Leaf Extract

The bay tree (Lour)., a member of the Lauraceae family, is a traditional seasoning and medicinal plant used by the indigenous people of Taiwan. The fruit is the most commonly used part of the plant and has been reported to exhibit a range of bioactive properties. The essential oil extracted from bay tree fruit has been shown to inhibit the growth of drug-resistant *Staphylococcus aureus* and *Acinetobacter baumannii*.[106,107] Additionally, it suppresses the expression of TNF-α and IL-12 in bone marrow-derived dendritic cells stimulated by bacterial endotoxins such as LPS, and reduces contact hypersensitivity reactions in mice.[108] A novel diterpenoid compound, cubelin, isolated from the methanol extract of bay tree fruit, has demonstrated pro-apoptotic activity in HeLa cells.[109] Furthermore, citral, the primary component of bay tree essential oil, reduces kidney inflammation and improves focal segmental glomerulosclerosis and lupus nephritis in murine models.[110,111]

Wong et al further investigated the inhibitory effects of L. cubeba leaf extract (MLE) on NLRP3 inflammasome activation. Their findings demonstrated that MLE suppresses macrophage pyroptosis by reducing caspase-1 activation and IL-1β secretion in macrophages, as well as inhibiting the release of NLRP3 and apoptosis-associated speck-like protein containing ASC. Mechanistically, MLE maintained mitochondrial integrity by reducing mtROS production and preventing the release of mtDNA into the cytoplasm. However, in LPS-activated macrophages, MLE did not reduce the expression levels of NLRP3, IL-1β precursor, or TNF-α, indicating that its inhibitory effects primarily target the activation phase of the NLRP3 inflammasome rather than the initial LPS-induced priming signals.[66]

Moreover, oral administration of MLE effectively alleviated DSS-induced colitis in a mouse model. Notably, daily treatment with MLE at doses of 1 and 2 g/kg for seven consecutive days did not result in significant side effects. These findings indicate that L. cubeba leaf extract has the potential to be developed as a nutritional supplement for the prevention and management of diseases associated with NLRP3 inflammasome activation.[66]

β-Sitosterol

β-Sitosterol is a major plant sterol commonly found in fruits, vegetables, nuts, seeds, soybean oil, and cottonseed oil. In vitro and in vivo studies have provided substantial evidence of the diverse biological activities of SIT, highlighting its potential as a therapeutic agent for various diseases.[112] From experimental studies, its anti-inflammatory properties have been demonstrated, indicating that SIT serves as a safe supplementary pharmaceutical treatment for experimental colitis.[113–117] Notably, long-term use of SIT has been experimentally revealed to be non-cytotoxic.[118,119]

To further elucidate the role of SIT in UC and its potential anti-pyroptotic mechanisms, Zhang et al conducted in vivo and in vitro studies. From their findings, it was evident that SIT treatment alleviated the severity of DSS-induced UC and reduced the production of TNF-α, IL-1β, and IL-18. Mechanistically, SIT inhibited the expression of pyroptosis-related proteins in colonic tissues and Caco-2 cells by promoting the formation of autophagosomes and facilitating their fusion with lysosomes.[67]

Further analysis revealed that SIT enhanced the expression of tight junction proteins, including ZO-1 and occludin, thereby improving colon barrier integrity. These experimental findings indicate that SIT exerts protective and therapeutic

effects against DSS-induced colonic damage by inhibiting NLRP3/caspase-1/GSDMD-mediated pyroptosis and the associated inflammatory response.[67]

Pelargonidin-3-Galactoside

Anthocyanins are widely distributed among various plant species, including flowers, vegetables, and fruits. As potent antioxidants, anthocyanins effectively neutralize free radicals, thereby mitigating tissue damage. Additionally, they modulate immune responses and suppress inflammatory cascades, reducing the progression of inflammation.[120–122]

According to studies, pelargonidin-3-galactoside (Pg3gal), an anthocyanin derived from purple sweet potatoes, exerts protective effects in DSS-induced colitis in a murine model. Pg3gal treatment significantly ameliorated colonic shortening, improved colonic tissue morphology, and reduced the expression levels of interleukin IL-6, IL-1β, and TNF-α in colonic tissue.[68]

Furthermore, Pg3gal modulated DSS-induced gut microbiota dysbiosis, as indicated by a reduction in *Proteobacteria* and *Deferribacteres*, along with an increase in *Firmicutes, Bacteroidetes*, and *Verrucomicrobia*.[68]

In summary, Pg3gal alleviates DSS-induced UC by inhibiting pyroptosis in intestinal epithelial cells and enhancing gut microbiota homeostasis, thereby contributing to intestinal structural integrity.[68]

Pectic Polysaccharides

Rauvolfia spp., commonly referred to as devil peppers, are a group of evergreen shrubs and trees.[123] Pectic polysaccharides (PPs) derived from *Rauvolfia callus* (rauvolfian) have been reported to exhibit anti-inflammatory properties and have revealed potential therapeutic effects in IBD, particularly in improving UC in murine models.[124]

Studies have demonstrated that PPs extracted from Rauvolfia cultures confer protective effects against DSS-induced colitis in mice. PP treatment reduced intestinal inflammation and microvilli swelling. Additionally, it attenuated pyroptotic cell death in intestinal tissue, as evidenced by the inhibition of cleaved caspase-1, IL-1β, and TNF-α production.[43]

The above experimental research indicates that various food-derived compounds have great potential in the treatment of colitis by regulating pyroptosis, but there are still many challenges in clinical application. Among these, bioavailability is one of the most important issues, as many natural compounds exhibit poor absorption and rapid metabolism, which can significantly reduce their therapeutic effects. Furthermore, the content or clinical efficacy of natural products varies depending on the plant's origin and the processing methods used for different parts of the plant. Natural products may also lead to adverse reactions or interact with prescription medications, posing additional problems that need to be addressed for clinical translation. Current research reports show promising prospects for strategies like nanoparticle formulations and liposomal delivery regarding the bioavailability of natural compounds; thus, employing these strategies could significantly enhance the clinical development potential of natural products. Additionally, establishing strict quality control measures and standardized extraction protocols is crucial to ensuring the safety and efficacy of natural products in treating colitis.

Application of Structural Modification and Targeted Delivery Strategies of Natural Compounds in the Treatment of Colitis

Food-derived compounds are considered to have great potential in the treatment of colitis due to their rich biological activity and low toxicity. However, the bioavailability, targeting ability, and stability of these compounds often limit their clinical application. In recent years, the emergence of structural modification and targeted delivery strategies has provided new ideas for addressing these issues (as shown in Table 2).

Structural Modification Strategies

Structural modification enhances the stability and bioavailability of natural compounds by changing their chemical structure. Common methods include: ① Nanoparticle Formulation: Nanotechnology can encapsulate natural compounds in nanoparticles, improving their stability and prolonging release time. For example, in recent years, nanoliposome

Table 2 Structural Modification and Targeted Delivery Strategies of Food-Derived Compounds

Compound	Modification/Delivery Strategy	Mechanism	Effect	References
Curcumin	Chemical derivatization	Absorption and Bioavailability↑	Anti-inflammatory capability↑; intestinal barrier integrity↑	[58,82,83]
Polyphenols	Encapsulated in nanoliposomes	Bioavailability↑	Absorption rate in the intestines↑	[125]
Anthocyanin	Polymeric nanoparticle encapsulation	Drug release time↑	Anti-inflammatory effects in colitis models↑	[126]
Garlic polysaccharides	Encapsulated in liposomes	Drug concentration ↑	Efficacy of drugs in a colitis model↑	[127]

encapsulation technology has been widely used to enhance the bioavailability and intestinal absorption of polyphenolic compounds. By encapsulating polyphenolic compounds in nanoliposomes, significant improvements can be made in their solubility, stability, and absorption rate in the intestines.[128] ② Chemical Derivatization: Introducing new functional groups through chemical reactions can improve the solubility and stability of compounds. For instance, after structural modification of curcumin, its intestinal barrier integrity and anti-inflammatory capabilities are significantly enhanced.[79–81]

Targeted Delivery Strategies

Targeted delivery systems can precisely deliver drugs to inflamed areas, reducing systemic side effects. Common targeted delivery systems include: ① Liposomes: Liposomes are a widely used targeted delivery system that can encapsulate drugs within a phospholipid bilayer, thereby increasing their concentration at the inflamed site. For example, Garlic Polysaccharide (GSP) has significant anti-inflammatory and immunomodulatory effects but exhibits poor stability in the gastrointestinal tract and low bioavailability. In recent years, liposome encapsulation technology has substantially improved the stability and drug concentration of garlic polysaccharides, thereby enhancing their efficacy in colitis models.[125] ② Polymer Nanoparticles: Polymer nanoparticles can control the release rate of drugs and prolong their action time at the inflammation site. For instance, anthocyanins are a class of natural polyphenolic compounds with strong antioxidant and anti-inflammatory activities; however, they have low bioavailability in vivo and are easily degraded by gastrointestinal environments. Recently, polymer nanoparticle encapsulation technology has significantly improved the stability and bioavailability of anthocyanins while extending drug release time and enhancing their anti-inflammatory effects in colitis models.[127]

Despite the promising results of structural modification and targeted delivery strategies in animal models, several challenges remain for their translation to clinical applications. For instance, the long-term safety of nano-formulations requires further evaluation, and there needs to be more in-depth research into the toxicity and metabolic products of chemical derivatization. Additionally, issues related to the biocompatibility and immunogenicity of targeted delivery systems also need to be addressed. Future research should focus on overcoming these challenges to advance the clinical application of these strategies.

Conclusion

Pyroptosis is a recently identified form of PCD that contributes to the loss of intestinal epithelial cells through both the classical caspase-1 pathway and the non-classical caspase-4/5/11 pathways. This process plays a key role in the pathogenesis of UC, serving as one of its key pathological mechanisms. Targeting pyroptosis represents a promising therapeutic strategy for UC. In recent years, food-derived bioactive compounds have gained increasing attention due to their minimal toxicity, positioning them as potential candidates for UC management.

This review provides a comprehensive overview of the main mechanisms underlying pyroptosis, as well as the role of pyroptosis in DSS-induced colitis. Particular emphasis is placed on food-derived compounds and extracts that modulate pyroptosis in UC, detailing their mechanisms of action and molecular targets. By highlighting these findings, the

objective of this review is to offer new perspectives and directions for the therapeutic application of food-derived bioactive compounds in UC treatment.

Furthermore, the effects of various food-derived compounds and extracts in inhibiting pyroptosis and mitigating UC pathology have been discussed. Notably, these compounds not only suppress pyroptosis but also exert additional benefits, including immune regulation, maintenance of gut microbiota homeostasis, and preservation of intestinal barrier integrity through tight junction stabilization. The inhibition of pyroptosis in UC may also act synergistically with other therapeutic targets to enhance treatment efficacy.

Although food-derived compounds and extracts exhibit significant potential in UC management by inhibiting pyroptosis, further research is necessary before their clinical application. Several key challenges remain to be addressed in future studies:

Understanding the interplay between PCD pathways in UC: While pyroptosis has been recognized as a key contributor to UC progression, other forms of regulated cell death, such as apoptosis, autophagy, ferroptosis, and necroptosis, also play essential roles. However, there is limited research on how food-derived compounds or extracts modulate multiple PCD pathways simultaneously to influence UC pathogenesis.

Expanding research beyond preclinical models: Current studies on the inhibition of pyroptosis in UC by food-derived compounds are largely confined to animal and cellular models. There remains a significant gap in clinical trial data, posing a challenge for translating these findings into clinical applications.

Addressing these gaps will be crucial in advancing food-derived bioactive compounds as viable therapeutic interventions for UC. Further investigation is needed to elucidate their precise mechanisms of action and to validate their efficacy and safety in human studies.

To address these challenges, future research should integrate bioinformatics and network pharmacology to further investigate the role and mechanisms of novel food-derived compounds in UC management. A key focus should be identifying compounds capable of modulating multiple forms of programmed cell death, thereby providing a more comprehensive approach to UC intervention.

Of note, in this study, we explored the potential therapeutic effects of food-derived compounds on colitis in animal models, particularly their effectiveness in inhibiting pyroptosis. However, translating these promising preclinical findings into clinical applications still faces many challenges, especially regarding key factors such as bioavailability, toxicity, and dose-response relationships. First of all, bioavailability is one of the key factors that influence the therapeutic effects of food-derived compounds. Many bioactive compounds show good activity in in vitro experiments, but their bioavailability is often low when applied in vivo due to digestive processes in the gastrointestinal tract, degradation by metabolic enzymes, and the impact of gut microbiota.[128] Furthermore, the issue of toxicity cannot be overlooked. For instance, some glycation compounds have shown a certain level of toxicity in animal experiments, particularly at high dosages affecting kidney and liver function.[126] Therefore, a comprehensive toxicological assessment of these compounds is necessary before clinical applications. Furthermore, research on the dose-response relationship is relatively insufficient. Most current studies focus on animal models and lack dosage optimization studies specifically targeting humans. Due to physiological and metabolic differences between humans and animals, directly extrapolating animal study results to humans may introduce significant deviations. In addition, different individuals may react significantly differently to the same compound, further complicating the determination of effective dosages.[129] Finally, the lack of clinical trial data is another significant barrier to advancing these compounds into clinical application. Although many food-derived compounds have demonstrated potential therapeutic effects in vitro and in animal models, these effects are often difficult to reproduce in human clinical trials. This may result from a combination of factors such as low bioavailability, inadequate dosing, or individual differences.[129]

In summary, although food-derived compounds that regulate pyroptosis show great potential in the treatment of colitis, significant work is still needed in areas such as bioavailability enhancement, toxicity assessment, dosage optimization, and clinical trial design to successfully apply them in clinical settings. Future research should focus on these issues to ensure that these compounds can be used safely and effectively for the treatment of colitis.

Abbreviations

UC, ulcerative colitis; GSDMD, gasdermin D; PCD, programmed cell death; IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylic acid; APOL1, apolipoprotein L1; NLRP3, pyrin domain containing protein 3; chemokine CXCL1, chemokine (C-X-C motif) ligand 1; MEG3, maternally expressed gene 3; SLC6A1, solute carrier family 6 member 1; Caspase, cysteine-dependent aspartic protease family; PRRs, pattern recognition receptors; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; ASC, apoptosis-associated speck-like protein; CARD, N-terminal caspase recruitment domain; PYD, pyrin domain; LPS, lipopolysaccharide; ATP, adenosine triphosphate; Panx-1, pannexin-1; TAK1, TGF-β-activated kinase 1; IKK, IκB kinase; GZMA, granzyme A; GZMB, granzyme B; DSS, dextran sulphate sodium; Gα12/13, asgepproto-oncogenes; IRE1α, inositol-requiring enzyme 1α; ATF6, recombinant activating transcription factor 6; p-PERK, phospho-pancreatic endoplasmic reticulumkinase; ROS, reactive oxygen species; ACA, 1'-acetoxy-vanillic acid ester; MSU, monosodium urate; APE, apple polyphenol extract; IEC, intestinal epithelial cell; ZO-1, zonula occludens-; ATR, atranori; CUR, curcumin; DAI, disease activity index; MDA, malondialdehyde; MPO, myeloperoxidase; NOS, nitricoxidesynthase; COX2, cyclooxygenase-2; GSH, glutathione; NRF2, nuclear factor erythroid 2-related factor 2; CAT, catalase; SOD1, superoxide dismutase 1; BUR, demethoxycurcumin; GRb1, ginsenoside Rb; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; PIP2, phosphatidylinositol 4,5-bisphosphate; GRg3, ginsenoside Rg3; HSYA, hydroxy safflower yellow A; HK1, hexokinase 1; NR, narirutin; BMDMs, bone marrow-derived macrophages; PTL, parthenolide; mtROS, mitochondrial ROS; PSG, polysaccharides from garlic; PTE, pterostilbene; MLE, *L. cubeba* leaf extract; SIT, β-sitosterol; Pg3gal, pelargonidin-3-galactoside; PPs, pectic polysaccharides.

Data Sharing Statement

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

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