# Dysregulated programmed cell death of intestinal epithelial cells in ulcerative colitis: Molecular mechanisms and novel therapeutic interventions (Review)

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**Abstract.** Ulcerative colitis (UC), a chronic idiopathic inflammatory bowel disease affecting the colonic mucosa, has seen a rising global incidence and poses a growing public health challenge. The clinical presentation typically includes recurrent abdominal pain, hematochezia, weight loss and structural damage to the colonic epithelium, substantially impacting patients' quality of life. Recent research has underscored the role of intestinal barrier dysfunction as a fundamental driver of persistent inflammation and disease progression in UC. Intestinal epithelial cells (IECs) form a monolayer through tight intercellular junctions and constitute the primary defense against luminal pathogens. Dysregulation of programmed cell death pathways in IECs such as apoptosis, necroptosis, pyroptosis, ferroptosis and autophagy-related cell death compromises epithelial integrity and exacerbates inflammation. The present review systematically examines how these death pathways contribute to UC pathogenesis, highlighting the molecular mechanisms through which natural bioactive compounds and nanoparticle-based drug delivery systems modulate them. Key signaling targets include the NF-κB pathway, MAPK cascade, NLR family pyrin domain containing 3 inflammasome and autophagy-related networks. By integrating advances in target identification, structure-activity relationship optimization and mechanistic insights, the present review provides a comprehensive framework for understanding UC and facilitates the development of innovative therapeutic approaches aimed at restoring barrier function and regulating epithelial cell death.

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**Contents**



## 1. Introduction

Ulcerative colitis (UC), a prototypical clinical subtype of inflammatory bowel disease (IBD), is characterized by chronic and recurrent non-specific inflammation primarily localized within the mucosal and submucosal layers of the rectum and colon. Surveillance data have highlighted a concerning rise in the global incidence of UC (1,2), a trend that not only severely compromises the quality of life of patients but also significantly elevates the risk of colorectal carcinogenesis (3,4). At present, conventional therapeutic agents such as 5-aminosalicylic acid, glucocorticoids and biologics (such as anti-TNF and anti-integrin agents) are commonly employed. Nevertheless, these pharmacotherapeutic interventions are hampered by notable limitations in terms of efficacy, adverse effects, individual responsiveness and a high relapse rate (5). Moreover, the economic burden and psychological impact of long-term treatment further exacerbate patient stress, underscoring the necessity for more effective and individualized therapeutic approaches. Despite extensive research efforts, the precise etiological determinants and comprehensive pathophysiological mechanisms underlying UC remain incompletely elucidated. Growing evidence accentuates the pivotal role of intestinal barrier integrity (6,7), a sophisticated, multi-layered defense system encompassing the mucus layer, epithelial cells and intercellular junction complexes (8), in both the initiation and progression of UC. Mechanistic investigations have demonstrated that UC pathogenesis involves intricate interactions among immune dysregulation, disruption of intestinal epithelial homeostasis, dysbiosis-driven bacterial colonization and compromised epithelial barrier function (9).

Pathological alterations in tight junction (TJ) proteins, such as ZO-1 and occludin, result in abnormal intestinal permeability, facilitating the translocation of luminal bacteria, endotoxins and undigested dietary antigens into the lamina propria (10). These microbial components and metabolites directly activate lamina propria immune cells, triggering

the robust release of pro-inflammatory cytokines (11). This chemotactic signaling recruits additional leukocytes to the inflammatory sites, initiating a cascade that results in characteristic pathological manifestations, including tissue erythema, exudation and mucosal erosion. Notably, this self-perpetuating inflammatory milieu exacerbates the degradation of TJ proteins (12,13), establishing a detrimental cycle that perpetuates mucosal injury.

Intestinal epithelial cells (IECs) constitute the primary defense of the intestinal mucosal barrier, playing a pivotal role in maintaining mucosal homeostasis through dynamic cell turnover and selective permeability regulation. Recent investigations have identified dysregulated IEC death as a key factor contributing to the perpetuation of colonic inflammation and the resistance to therapy in UC pathogenesis (14-16). Under physiological conditions, apoptosis maintains intestinal epithelial homeostasis through programmed cell turnover. However, an excess of apoptotic activity exceeding regenerative capacity can lead to extensive depletion of IECs, causing structural denudation and compromising barrier integrity (17). In addition to apoptosis, other cell death mechanisms, including necroptosis, PANoptosis, pyroptosis, ferroptosis and autophagy, have been implicated in the pathogenesis of UC (18-22).

Therefore, elucidating the role of IEC death in UC pathogenesis and systematically consolidating current research achievements on modulating excessive IEC death through natural compounds and nanoparticle-mediated drug delivery systems to alleviate UC progression (particularly by integrating recent advances in mechanistic pathways, bioactive constituents and molecular targets) may offer novel perspectives for unraveling UC etiology. This strategy could facilitate the precise identification of potential therapeutic targets, thereby paving the way for innovative methods for clinical UC management. Future research endeavors should concentrate on developing targeted therapies that address the multifaceted nature of IEC death and its downstream inflammatory repercussions, ultimately disrupting the cycle of mucosal damage and the inflammation characteristic of UC.

## 2. Major forms of IEC death

*IEC apoptosis*. IECs are characterized by rapid and continuous cellular renewal. Apoptosis, a key programmed cell death mechanism, serves as an essential pathway for the physiological elimination of aged IECs at the end of their life cycle and plays a critical role in sustaining intestinal homeostasis (23). However, excessive activation of apoptosis during UC progression may amplify inflammatory responses via enhanced cytokine signaling (24). Upon exposure to stress stimuli, such as the inflammatory microenvironment of UC, pro-apoptotic proteins Bax and Bak undergo oligomerization and translocate to the mitochondrial outer membrane, forming transmembrane pores (25). This event triggers mitochondrial swelling and facilitates the efflux of cytochrome c from the intermembrane space into the cytosol (26). Released cytochrome c subsequently binds to apoptotic protease-activating factor-1, assembling the apoptosome complex that activates caspase-9 through proteolytic cleavage (27). This initiates a downstream caspase cascade culminating in the execution phase of apoptosis via caspase-3 activation and eventual cellular dismantling (28).

In the dextran sulfate sodium (DSS)-induced mouse model of UC, intestinal tissues display a pronounced state of oxidative stress, accompanied by upregulated Bax protein expression, decreased mitochondrial membrane potential, increased cytochrome c release, markedly elevated apoptosis of IECs and impaired intestinal barrier function, which manifests as increased intestinal permeability and frequent bacterial translocation (29,30). Clinical investigations have demonstrated that patients with UC exhibit significantly elevated expression levels of Fas and Fas ligand (FasL) in intestinal mucosal tissues compared with healthy controls, with these levels positively correlating with clinical severity indices (31,32). These findings collectively suggest that the Fas/FasL-mediated extrinsic apoptosis pathway is aberrantly activated during UC pathogenesis, driving excessive IEC apoptosis and thereby compromising barrier integrity. Within the colonic tissues of patients with UC, the tumor suppressor p53 functions as a pivotal transcriptional regulator orchestrating multiple apoptosis-related genes (33). Notably, enhanced phosphorylation of p53 has been shown to be positively correlated with disease severity (34). Under inflammatory conditions, interleukin (IL)-1β released from activated immune cells potentiates p53-mediated apoptotic signaling, thereby exacerbating epithelial apoptosis and amplifying mucosal inflammation (35). An experimental study employing TNF-α-induced murine models revealed augmented IEC apoptosis in both acute and chronic inflammation settings (36). This apoptotic imbalance disrupts epithelial homeostasis, thereby facilitating UC progression. Moreover, the upregulated expression of METTL3 and long non-coding RNAs such as MALAT1 under inflammatory conditions has been mechanistically linked to suppressed cellular viability and enhanced IEC apoptosis, unveiling novel molecular pathways in UC pathogenesis (37,38).

Following IEC apoptosis, multiple chemokines are released to recruit immune cells to intestinal inflammatory sites, including monocyte chemoattractant protein-1 and IL-8, a process that plays a central role in the pathogenesis of UC. During disease progression, persistent inflammatory stimuli and sustained cell death signaling maintain macrophage activation, thereby establishing a self-amplifying pathological loop (39,40). In DSS-induced murine UC models, a rapid elevation of IL-8 levels has been observed in intestinal tissues post-induction, concomitant with robust neutrophil infiltration. This pathological progression exhibits temporal synchronization with IEC apoptosis and necrosis, and these three pathological events mutually reinforce one another through feed-forward mechanisms. Collectively, this triad drives the chronicity and perpetuation of intestinal inflammation (41).

Conventional therapies have been predominantly aimed at suppressing excessive immune responses but have largely neglected emerging pathological aspects such as the restoration of intestinal mucosal barrier integrity and the correction of dysregulated IEC apoptosis, resulting in suboptimal efficacy and frequent relapses in certain patient populations (42). These limitations have catalyzed the exploration of natural compounds and novel targeted therapeutic. Ginkgetin (GK), a natural compound derived from *Ginkgo biloba* with multi-protective properties, has been shown to ameliorate DSS-induced

experimental colitis in murine models. Mechanistic investigations reveal that GK administration attenuates IEC apoptosis through inhibition of the EGFR/PI3K/AKT signaling pathway, accompanied by upregulation of the anti-apoptotic protein Bcl-2 and downregulation of pro-apoptotic proteins Bax and caspase-3, thereby restoring intestinal barrier integrity (43). Similarly, in acetic acid-induced rat models of UC, *Centella asiatica* treatment effectively normalizes dysregulated apoptosis markers, including elevated Bcl-2 alongside reduced Bax and caspase-3, while mitigating oxidative stress and attenuating inflammatory responses (44). Despite consistent modulation of key biomarkers, studies on *Centella asiatica* often lack rigorous dose-response evaluation and thorough long-term toxicity assessments, which are essential for translational applicability. Daphnetin exerts protective effects against IEC apoptosis by inhibiting the regenerating islet-derived protein 3α-dependent Janus kinase 2 (JAK2)/STAT3 signaling pathway, resulting in reduced expression of pro-apoptotic proteins and decreased levels of pro-inflammatory cytokines (45). Both lipopolysaccharide (LPS)-treated human colon adenocarcinoma Caco-2 cell inflammatory models and DSS-induced UC rat models have demonstrated that the natural bioactive compound paeoniflorin alleviates UC by modulating serum metabolites and suppressing the CDC42/JNK signaling pathway, thereby inhibiting IEC apoptosis (46).

Nonetheless, current investigations primarily emphasize acute therapeutic efficacy, with limited assessment of remission durability or relapse prevention in chronic UC contexts. Emerging as a promising therapeutic approach, exosome-based interventions have gained attention due to their low immunogenicity and superior circulatory stability. In murine UC models, caprine milk-derived exosomes have been shown to attenuate oxidative stress, suppress apoptosis, restore intestinal barrier integrity and modulate gut microbiota composition (47). Mechanistically, oxidative stress acts as a key driver of IEC apoptosis and recent evidence indicates that mesenchymal stem cell-derived exosomes confer protective effects by mitigating ROS accumulation in IECs, thereby alleviating UC-associated tissue damage (48). While exosome therapies offer multi-modal benefits, current preclinical studies face challenges including heterogeneity in exosome isolation techniques, lack of standardized dosing regimens and limited investigation of potential off-target effects. Furthermore, the precise mechanisms underlying exosome-mediated immunomodulation, barrier restoration and concurrent suppression of inflammatory signaling and apoptotic pathways remain to be fully elucidated.

While active exploration into natural compounds and biological vectors such as exosomes continues, advances in pharmaceutical engineering and drug repurposing have concurrently unveiled innovative avenues for UC therapy. Prior investigations have substantiated that berberine (BBR), a bioactive constituent of traditional Chinese medicine, effectively mitigates DSS-induced colonic inflammation; however, its clinical translation has been hampered by inherent limitations including poor aqueous solubility and short half-life (49,50). In recent years, the advent of nanotechnology-engineered poly (lactic-co-glycolic acid) nanoparticles encapsulating BBR has markedly enhanced drug encapsulation efficiency, aqueous solubility and bioactivity, thereby conferring superior therapeutic outcomes in UC experimental models (51). Donepezil, originally developed for Alzheimer's disease management, is renowned for its neuroprotective, anti-inflammatory and antioxidant attributes (52,53). Evidence has further elucidated its capacity to upregulate low-density lipoprotein receptor-related protein 1 expression, activate AMPK signaling and suppress the NF-κB inflammatory cascade, thereby attenuating intestinal inflammation and epithelial apoptosis (54). Analogously, the small-molecule inhibitor ruxolitinib ameliorates UC pathological progression by targeting the JAK/STAT3 pathway, effectively suppressing NF-κB activation, curtailing apoptosis and fostering barrier repair, thus presenting a promising targeted therapeutic strategy (55). Notwithstanding these advancements, emerging modalities continue to confront key challenges, including unresolved optimal dosing regimens, tissue-specific targeting and sustained long-term efficacy within the intestinal milieu.

*IEC necroptosis*. Necroptosis, a distinct form of programmed necrotic cell death, exerts a pivotal influence on intestinal inflammation. The core molecular machinery involves sequential activation and signaling transduction of receptor-interacting protein kinase (RIPK) 1, RIPK3 and mixed lineage kinase domain-like protein (MLKL) (56). Under homeostatic conditions, RIPK1 serves as a central signaling hub that coordinates cellular stress responses and preserves epithelial integrity (57). During intestinal inflammation triggered by pathogenic stimuli or excessive TNF-α release, TNF-α engagement with tumor necrosis factor receptor 1 initiates RIPK1 oligomerization via death domain interactions, culminating in kinase activation (58). RIPK1 is subsequently incorporated into a complex containing Fas-associated death domain (FADD) and caspase-8 (complex IIa), in which caspase-8 acts as a critical molecular switch. Upon activation, caspase-8 cleaves RIPK1 and RIPK3, thereby promoting apoptotic cell death while concurrently suppressing necroptosis initiation (59). By contrast, when caspase-8 activity is compromised (for example, by genetic deletion or pharmacological inhibition) RIPK1 interacts with RIPK3 to facilitate formation of the RIPK1-RIPK3 complex, known as the necrosome (60-62). Activated RIPK3 phosphorylates MLKL, converting it from an inactive monomer to a functional oligomeric state (63). The phosphorylated MLKL oligomers acquire membrane-targeting capability through conformational changes and subsequently translocate to the plasma membrane, ultimately leading to cellular swelling, membrane rupture and necroptosis. The resultant released of damage-associated molecular patterns (DAMPs), including bioactive molecules such as high mobility group box 1 (HMGB1) and ATP, have been demonstrated to exert immunomodulatory effects (64). Studies have demonstrated that selective deficiency or functional impairment of caspase-8 in the intestinal epithelium markedly increases susceptibility to necroptosis, exacerbates experimental colitis and further underscores its protective role in the pathogenesis of UC (65,66).

Studies encompassing patients with UC and animal models have substantiated that hyperactivation of the necroptosis pathway represents a pivotal pathogenic determinant, contributing to both intestinal barrier disruption and aberrant inflammatory cascades (67,68). Histopathological analyses

have revealed markedly elevated expression levels of RIPK1, RIPK3 and MLKL in IECs, accompanied by enhanced phosphorylation status, within the inflammatory lesions of patients with UC and experimental models (22). Accumulating evidence indicates that additional regulatory molecules, including purinergic receptor P2Y14 (P2Y14), retinoic acid-inducible gene I (RIG-I) and macrophage migration inhibitory factor (MIF), may participate in the fine-tuned regulation of this process. For instance, the purinergic receptor P2Y14 is upregulated in the inflamed colonic mucosa of patients with UC, where it facilitates RIPK1 transcription via the cAMP/protein kinase A/cAMP response element-binding protein signaling pathway, thereby aggravating IEC necroptosis and amplifying intestinal inflammation (69). Furthermore, upon ligand engagement, the cytosolic RNA sensor RIG-I upregulates MLKL expression via interferon signaling, directly facilitating pore formation (70). Alternatively, RIG-I may indirectly amplify RIPK3-dependent necroptosis by eliciting cytokine production, including type I interferons and TNF (71). Under pathological stress conditions such as ischemia and inflammation, MIF actively fosters RIPK1-mediated necroptosis, thereby intensifying tissue injury (72,73). Collectively, these findings underscore that necroptosis in UC is governed by a sophisticated, multifaceted regulatory network. Furthermore, investigations using the DSS-induced murine colitis model have demonstrated significantly upregulated expression of A20-binding inhibitor of NF-κB activation 1, RIPK1, RIPK3 and MLKL in colonic tissues. Notably, pharmacological blockade with Nec-1s potently inhibits RIPK1 kinase activity, markedly suppressing IEC necroptosis and mitigating colonic inflammatory responses (74). Subsequent analyses of clinical specimens have corroborated a statistically significant positive correlation between RIPK3 expression in the colonic tissues of patients with UC and disease severity indices. Concurrently, genetic ablation of the RIPK3 gene in mice confers notable protection against IEC apoptosis through blockade of the Toll-like receptor 4 (TLR4)/myeloid differentiation primary response protein 88 (MyD88)/NF-κB pathway, effectively alleviating experimental colitis (75).

Contemporary research endeavors are centered on the development of targeted inhibitors against pivotal necroptosis regulators, such as RIPK1, RIPK3 and MLKL, with accumulating evidence demonstrating that pharmacologically modulating these targets in IEC can effectively ameliorate UC. For instance, the citrus flavonoid naringenin and curcumin have been shown to suppress IEC necroptosis by downregulating the mRNA expression of RIPK3 and MLKL, thereby preserving intestinal barrier integrity and markedly ameliorating colitis pathology (76,77). A natural chalcone derivative, ermanin from the genus *Leptinella*, has exhibited dual inhibition of RIPK1/3 kinases in the DSS-induced colitis model. Mechanistic elucidation revealed that it attenuates intestinal barrier impairment via blockade of MLKL phosphorylation, demonstrating promising therapeutic potential for UC (78). Further investigations demonstrated that polysaccharides from pine pollen and their sulfated derivatives markedly attenuate the inflammatory index in the colitis model, diminish IEC necroptosis incidence and enhance mucosal barrier function through augmented mucin 2 secretion, thereby furnishing robust experimental substantiation for clinical translation (79). The traditional Chinese herbal remedy *Sargentodoxa cuneata* ameliorates disease manifestations in murine colitis models by curtailing IEC necroptosis (80).

In addition to the aforementioned natural products, chemically modified compounds and targeted chemical agents have likewise unveiled therapeutic utility. For instance, the myricetin-3-*O*-β-D-lactose sodium salt derivative M10, engineered via incorporation of a hydrophilic glycosyl moiety, displays full aqueous solubility and high stability. A study has established that oral administration of M10 inhibits necroptosis in inflamed colonic epithelium by suppressing TNF-α signaling, exhibiting superior efficacy relative to mesalazine in averting chronic colitis (81). Indole-3-carbinol, a naturally occurring dietary agonist of the aryl hydrocarbon receptor, upon receptor engagement, impedes RIPK1 activation and necrosome assembly in a temporally regulated manner, thereby reducing IEC apoptosis and ameliorating intestinal inflammation (82). As a linchpin modulator of necroptosis and inflammatory cascades, RIPK1 inhibitors potently disrupt inflammatory signaling, attenuate IEC injury and curtail leukocyte infiltration. Multiple studies have corroborated that RIPK1 inhibitors such as SZ-15, HtrA2 and LY3009120 markedly attenuate colonic inflammation, foster tissue regeneration and ameliorate UC progression, thereby illuminating the compelling therapeutic prospects of RIPK1-targeted interventions in UC management (83-85).

Dynamic regulatory nodes orchestrate the delicate equilibrium between necroptosis and apoptosis, ensuring adaptive responses to inflammatory stimuli. In the nascent phases of inflammation, where cellular insult remains modest, the organism preferentially engages programmed apoptotic pathways. This non-inflammatory clearance modality safeguards tissue homeostasis and mitigates excessive immune activation (86). This phase is characterized by selective engagement of apoptotic cascades, where the extrinsic apoptotic pathway mediated by the Fas/FasL pathway and the mitochondrial-dependent intrinsic apoptotic pathway are preferentially activated to facilitate the orderly clearance of damaged cells (87). As inflammatory escalation ensues, perturbations in intracellular homeostasis, such as caspase inhibition or aberrant upregulation of anti-apoptotic effectors, precipitate a phenotypic shift in cell death modality toward necroptosis (88). Notably, DAMPs released during necroptosis engage pattern recognition receptors on adjacent cells via paracrine signaling, thereby upregulating death receptor expression and fostering an apoptosis-prone milieu (89). This ultimately leads to a positive feedback loop of cell death and inflammation, significantly exacerbating intestinal epithelial barrier dysfunction and the spread of inflammation (90). Precise modulation of apoptosis-associated gene expression is expected to fundamentally restore the homeostasis of cell death and promote the repair of intestinal epithelial barrier function. This paradigm unveils a novel molecular intervention strategy for personalized UC management, holding notable clinical translational promise. Nonetheless, effectively implementing these conceptual advances into practical therapeutics mandates surmounting critical challenges, including target specificity, efficacious delivery platforms and inter-individual heterogeneity in gene expression signatures.

*IEC pyroptosis*. Pyroptosis, a distinct programmed inflammatory cell death modality, has a molecular foundation based on inflammasome-dependent activation of select caspase family members, notably caspase-1 and the caspase-4/5/11 isoforms (91,92). In the pathological evolution of UC, the NLR family pyrin domain containing 3 (NLRP3) inflammasome has emerged as a pivotal regulatory hub mediating inflammatory cascades within the intestinal mucosa. As an intracellular multiprotein complex, the canonical NLRP3 inflammasome incorporates three foundational constituents: The pattern recognition receptor NLRP3, the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC) and the procaspase-1 precursor (93). Under homeostatic conditions, NLRP3 adopts an auto-inhibited conformation with its activation meticulously governed by an array of modulatory factors, thereby safeguarding equilibrium in IECs. Upon perturbation of the intestinal milieu by pathological cues, pathological stimuli including pathogen-associated molecular patterns (PAMPs), DAMPs or metabolic stress, the NLRP3 inflammasome initiates its assembly process (94). In patients with UC, intestinal dysbiosis results in a marked elevation of LPS derived from Gram-negative bacteria. Functioning as a canonical PAMP, LPS initiates nuclear translocation of NF-κB through engagement with TLR4. Activated NF-κB upregulates NLRP3 gene expression and fosters synthesis of pro-inflammatory cytokines (95,96). Consequent to secondary signal stimulation, intracellular potassium efflux, ROS accumulation or lysosomal destabilization, the nascent NLRP3 undergoes NACHT domain-mediated oligomerization, recruiting the adaptor protein ASC to form multiprotein inflammasome complexes. ASC, through PYD-CARD domain interplay, facilitates autoproteolytic maturation of procaspase-1, yielding enzymatically proficient caspase-1 heterotetramers (97). Activated caspase-1 exerts dichotomous biological effects: i) Orchestrates extracellular release of mature IL-1β and IL-18 through cleavage of their pro-forms; and ii) specifically cleaves gasdermin D (GSDMD) to generate the pore-forming N-terminal domain (GSDMD-N). GSDMD-N subsequently oligomerizes to form transmembrane pores on the plasma membrane, triggering cellular osmotic lysis (98). This lytic event facilitates a large release of DAMPs and HMGB1, thereby engendering a self-amplifying feedback loop that intensifies intestinal inflammatory amplification (99).

Pyroptosis in IECs triggers a cascade of immune responses that disrupt the intestinal immune perturbations that destabilize the intestinal immune milieu, a phenomenon intimately linked to UC pathogenesis. In DSS-induced colitis models, transgenic overexpression of lipocalin-2 in wild-type mice markedly exacerbates colonic inflammation and epithelial injury, concomitant with elevated pyroptosis biomarkers specifically localized to the IECs of colonic mucosa derived from patients with UC (100). Type III interferons (IFN-λ) have been demonstrated to augment IEC pyroptosis, thereby undermining mucosal wound repair and curtailing regenerative potential (101). Danger signals released during pyroptosis foster dendritic cell maturation and enhance their antigen-presenting capacity, driving naïve T cell differentiation toward pro-inflammatory Th1 and Th17 subsets (102). Concurrently, these signals attenuate regulatory T cell functionality, engendering an immunosuppressive imbalance that perpetuates uncontrolled inflammatory responses (103). Collectively, these observations delineate IEC pyroptosis as a perpetuator of intestinal inflammation in UC via a self-sustaining inflammatory circuit, which fundamentally underpins the therapeutic refractoriness encountered in clinical practice.

While pyroptosis predominantly exerts pro-inflammatory and tissue-damaging effects in the pathogenesis of UC, elucidation of its molecular underpinnings furnishes a foundational rationale for devising targeted therapeutic interventions. Phytosterols, a class of plant-derived bioactive sterols, exhibit therapeutic potential through their prototypical constituent sitosterol (SIT). Mechanistically, SIT modulates the NLRP3/caspase-1/GSDMD signaling axis to significantly attenuate IEC pyroptosis and pro-inflammatory cytokine release, while concurrently augmenting TJ protein expression to bolster mucosal barrier integrity (104). However, most evidence remains preclinical, and the pharmacokinetics, bioavailability and safety of SIT in chronic UC contexts remain inadequately characterized. The extract from *Astragalus membranaceus* Bunge has been shown to ameliorate UC by curtailing IEC pyroptosis via upregulation of phospholipase C-β2 (105). The pathological characteristics of refractory UC progression primarily encompass a self-perpetuating cycle linking mucosal barrier disruption and unrelenting inflammatory amplification. Recent evidence substantiates that nanocarrier-mediated targeted delivery of 4-octyl itaconate to IECs potently suppresses GSDME-mediated pyroptosis (14). Further investigation has revealed that the artemisinin derivative SM934 exhibits dual modulatory effects in experimental colitis models; it concurrently inhibits programmed cell death modalities and abrogates caspase-1-dependent pyroptotic cascades, thereby markedly ameliorating epithelial barrier impairment (106). Nevertheless, the long-term efficacy, toxicity and dosing regimens for SM934 in chronic models warrant comprehensive evaluation to surmount translational hurdles. Schisandrin B attenuates NLRP3 inflammasome activation-mediated IL-1β secretion and IEC pyroptosis in colitis models by activating AMPK/Nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent signaling to mitigate ROS-induced mitochondrial damage, suggesting its potential as a therapeutic strategy for acute colitis (107). In LPS/ATP-induced *in vitro* models of IEC pyroptosis and inflammation utilizing HT29 human colonic carcinoma cells, resveratrol forestalls pyroptosis onset by impeding NF-κB pathway activation (108). Beyond phytogenic agents, mesenchymal stem cells (MSCs) and their secreted exosomes have recently garnered notable attention for therapeutic applications. Hair follicle-derived MSC exosomes convey differentially expressed microRNAs (miRNAs) that concurrently suppress both tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) signaling and IFN-γ inflammatory pathways, thereby effectively inhibiting IEC pyroptosis (109). Notably, bone marrow-derived MSC exosomes selectively suppress NLRP3/caspase-1 pathway activation via miR-539-5p shuttling, thereby modulating the pyroptosis-associated molecular network and ultimately attenuating UC progression (110).

In recent years, contemporary drug discovery paradigms targeting pyroptosis have diversified, with numerous chemical and nucleic acid therapeutics evincing robust efficacy. For

instance, miR-141-3p effectively inhibits LPS-induced IEC pyroptosis by targeting the HSP90 molecular chaperone, while concurrently alleviating inflammation in DSS-induced murine colitis, highlighting its promise as a nucleic acid-based therapeutic approach for UC (111). The broad-spectrum antiviral nucleotide remdesivir likewise ameliorates IEC pyroptosis and gut inflammatory cascades by inhibiting the NLRP3 inflammasome and downstream caspase-1/GSDMD signaling (112). Meanwhile, ruscogenin, a steroidal sapogenin from *Ophiopogon japonicus*, has demonstrated potential in mitigating inflammatory processes by suppressing NLRP3 inflammasome activation and caspase-1-dependent canonical pyroptosis (113). Moreover, in acute severe UC, the methyl-donor betaine effectively inhibits oxidative stress-induced inflammatory pyroptosis, thereby expanding the therapeutic repertoire for UC (114). These findings suggest that precision regulation strategies targeting aberrant pyroptosis in IECs may disrupt the 'pyroptosis-inflammation-barrier disruption' positive feedback loop, thereby establishing an innovative therapeutic paradigm for UC pathological intervention.

*IEC ferroptosis.* Ferroptosis, a unique modality of programmed cell death, was initially characterized and designated in 2012 by Dixon *et al* (115) through systematic investigation. Distinct from other forms of regulated cell death, ferroptosis is pathologically defined by the intricate interplay between iron ion homeostasis dysregulation and lipid peroxidation accumulation (116). IECs predominantly internalize iron via transferrin receptor 1-dependent endocytosis (117). Upon endocytosis, $Fe^{3+}$ is enzymatically reduced to biologically active $Fe^{2+}$ species via metalloreductases such as Six-transmembrane epithelial antigen of prostate 3 (118,119). During the pathogenesis of UC, IECs are subjected to a sustained inflammatory milieu, which elicits dysregulated mobilization of excess $Fe^{2+}$ from the labile iron pool and thereby instigates ROS generation through Fenton reaction cascades (19). The Fenton reaction employs $Fe^{2+}$-mediated catalytic cycles to decompose hydrogen peroxide into highly reactive hydroxyl radicals. These radicals preferentially attack membrane phospholipids containing polyunsaturated fatty acids (120), thereby initiating a self-amplifying chain reaction of lipid peroxidation. Glutathione peroxidase 4 (GPX4), a pivotal regulator of lipid redox balance, forms the cornerstone of ferroptosis suppression. Under homeostatic conditions, GPX4 utilizes reduced glutathione (GSH) to transmute deleterious lipid hydroperoxides into innocuous lipid alcohols, effectively suppressing the cascade amplification of lipid peroxidation (121). Notably, in UC progression, multiple pathogenic factors synergistically inhibit GPX4 enzymatic activity, thereby impairing its detoxification of peroxidation intermediates. Upon decompensation of the antioxidant defense system, lipid peroxidation products surpass cellular homeostatic thresholds, ultimately triggering ferroptosis in IECs through the disruption of membrane structural integrity (122,123).

As the principal mucosal interface organ, the intestinal tract exhibits a characteristic oxidative stress microenvironment due to persistent exposure to exogenous stimuli including microbiota, metabolites and food-derived antigens (124). Investigations have revealed a reciprocal pathophysiological interplay between ferroptosis in IECs and gut oxidative stress status. In murine colitis models, inflammation-orchestrated oxidative perturbations markedly elevate ferroptosis effectors [cyclooxygenase-2 and acyl-CoA synthetase long-chain family member 4 (ACSL4)] in parallel with diminished protein abundance of GPX4 and ferritin heavy chain 1. These molecular signatures demonstrate positive correlation with the extent of IEC injury (125). Pharmacological preconditioning with ferroptosis inhibitors has been demonstrated to markedly attenuate above-mentioned histopathological manifestations in DSS-induced colitis. Integrative multi-omics profiling has unveiled signature expression patterns of ferroptosis-linked genes in tissues derived from patients with UC (126,127). Mechanistic investigations have demonstrated that ACSL4, a master regulator of ferroptosis, accelerates IEC ferroptosis by activating the NF-κB signaling pathway, thereby contributing to UC pathogenesis (128).

There have been notable advancements in therapeutic modalities targeting ferroptosis regulation in IECs, with innovative interventions conferring antioxidant cytoprotection and inflammatory attenuation via selective ferroptosis pathway blockade. Astragalus polysaccharide (APS), the predominant bioactive polysaccharide from the traditional Chinese herb *A. membranaceus*, has demonstrated anti-ferroptotic efficacy across multiple experimental models. Experimental evidence demonstrated that APS significantly suppresses ferroptosis progression and sustains cellular homeostasis in DSS-induced murine colitis models and as well as RSL3-treated human IECs *in vitro* (129). Multi-omics analyses has unveiled that vanillic acid (VA) modulates the ferroptosis axis through targeted ligation to carbonic anhydrase IX and stromal interaction molecule 1, effectively restoring intestinal epithelial barrier integrity and emerging as a novel therapeutic candidate for UC (130). Nevertheless, the target fidelity and off-target liabilities of VA within intricate human milieus necessitate rigorous delineation. Emerging data implicate that disrupted iron homeostasis exacerbates colitis progression via dual mechanisms involving ferroptosis activation and gut microbiota dysbiosis (131,132). Pharmacological investigations confirm that palmatine, a natural isoquinoline alkaloid, markedly diminishes colonic iron deposition and ameliorates experimental UC pathology via multi-target modulation, concurrently suppressing NF-κB inflammatory signaling, ROS generation and ferroptosis signal cascades (133). Notably, the oral iron chelator deferasirox represses IEC ferroptosis, reprograms gut microbiota architecture and augments short-chain fatty acid (SCFA) biosynthesis, thereby ameliorating DSS-induced UC inflammation through multifaceted mechanisms and evincing clinical promise (134). However, the use of iron chelators still requires cautious monitoring of dosage and safety to avoid potential adverse effects (135,136).

Beyond directly targeting the ferroptosis pathway, certain nutritional factors and metabolites also demonstrate therapeutic value. Butyrate is a microbiota-derived SCFA depleted in colitis-afflicted murine cohorts. A study has revealed that sodium butyrate treatment activates the Nrf2/GPX4 signaling pathway, thereby inhibiting ferroptosis, alleviating oxidative stress and inflammatory responses and restoring intestinal barrier function (137). Furthermore, vitamin D has been demonstrated to attenuate ferroptosis in DSS-induced murine models and LPS-stimulated HCT116 cells through

ACSL4 repression, consequently tempering UC severity (138). Additionally, supplementation with the essential trace element selenium, particularly in the form of sodium selenite, effectively reduces IEC mortality, intracellular iron content, lipid ROS and mitochondrial membrane damage, ultimately attenuating DSS-induced colitis (139). Nevertheless, these benefits, optimal dosing paradigms, delivery modalities and protracted efficacy demand validation via robust clinical trials.

Oxymatrine (OY), the primary bioactive compound derived from *Sophora flavescens*, is routinely employed in Chinese integrative UC management. Through integrated approaches combining bioinformatics, molecular biology and animal experimentation, OY has been demonstrated to alleviate UC symptoms via mechanisms involving the regulation of $Fe^{2+}$ and GSH levels, as well as anti-inflammatory pathways (140). Lizhong decoction (LZD) potently represses IEC ferroptosis by reducing iron overload and elevating recombinant solute carrier family 7 member 11 and GPX4 expression in colonic mucosa (141). However, the polypharmacology of multi-herbal decoctions such as LZD complicates mechanistic attribution, underscoring the imperative for active constituent isolation to facilitate clinical advancement.

While breakthrough advances have been achieved in natural compound research, exosomes (critical mediators of intercellular communication) have emerged as possessing unique biomedical potential in the therapeutics of UC. Human umbilical cord MSC-derived exosomes can deliver miR-129-5p to specifically suppress the expression of ACSL4, dually regulating the progression of lipid peroxidation and the function of the GSH-GPX4 antioxidant axis (142). A recent study has demonstrated that endometrial regenerative cell-derived exosomes enhance GSH biosynthesis and GPX4 enzymatic activity while coordinately attenuating tissue iron accumulation, malondialdehyde levels and ACSL4 protein expression, demonstrating marked efficacy in ameliorating both histopathological damage and clinical manifestations of colitis (143). An in-depth analysis of the molecular regulatory network underlying abnormal ferroptosis in IECs would not only yield precise therapeutic targets for UC but also promises the advent of innovative pharmacotherapeutics through targeted modulation of key ferroptosis pathways, thereby improving intestinal barrier function.

*IEC autophagy.* Autophagy, an evolutionarily conserved intracellular degradation system, orchestrates cellular homeostasis and stress adaptation via regulated material recycling. Based on substrate transport mechanisms, autophagy is categorized into three subtypes: Macroautophagy, microautophagy and chaperone-mediated autophagy (144). Among these, macroautophagy predominates as the primary regulatory mechanism, forming the cornerstone of autophagy research. Upon microenvironmental stimuli such as nutrient deprivation or oxidative stress (145,146), endoplasmic reticulum-resident unfolded protein response sensors synergize with other stress detectors to trigger a transcriptional cascade of autophagy-related genes via regulators including transcription factor EB (147). This process initiates with the formation of a double-membrane structure termed the phagophore in the cytoplasm (148), which achieves quality control by selectively enveloping targeted substrates including damaged organelles and misfolded proteins. Following subsequent membrane extension and closure, the phagophore matures into an autophagosome that fuses with lysosomal membranes to form an autolysosome (149). Within the autolysosomal lumen, acid hydrolases degrade the enclosed cargo into recyclable metabolites, such as amino acids and free fatty acids (150), that are effluxed into the cytoplasm through lysosomal transporters. These metabolites are released into the cytoplasm via lysosomal membrane transporters, where they re-enter biosynthetic pathways or fuel the tricarboxylic acid cycle, thereby completing the closed-loop regulation of intracellular material recycling (151).

In recent years, the regulatory role of autophagy in UC pathogenesis has garnered substantial attention in gastroenterology research, with its dual regulatory properties exhibiting complex biological effects during disease progression. Pathologically, UC is characterized by dysregulated dynamic equilibrium of pro-/anti-inflammatory cytokine networks, coupled with unrelenting inflammatory cascades, aberrant intestinal barrier permeability and perturbed expression of TJ proteins, collectively driving disease chronicity (152). Mechanistic investigations have elucidated that TNF-α-driven inflammatory microenvironments impair intestinal epithelial barrier integrity via impaired autophagic flux, manifesting as aberrant claudin-2 expression and TJ disruption, a process mechanistically linked to autolysosomal system dysfunction (153). Analyses of clinical specimens from patients with active UC reveal notable downregulation of autophagy regulator activating transcription factor 4 in intestinal mucosa, implicating diminished autophagic capacity in disease exacerbation (154). Pharmacological autophagy activation in LPS-stimulated Caco-2 cell models and experimental colitis animals significantly reduces pro-inflammatory cytokines and ameliorates oxidative stress indices, underscoring the therapeutic potential of autophagy modulation in IBD (155,156). In DSS-induced colitis models, autophagy impairment intensifies intestinal inflammation through hyperactivation of the NLRP3 inflammasome, thereby promoting caspase-1 cleavage and maturation of IL-1β/IL-18 (157,158). Crucially, excessive autophagy activation may induce type II programmed cell death, underscoring the importance of precise autophagic activity regulation given this dual-edged effect. In Erbin knockout murine models, autophagy inhibitor chloroquine mitigates DSS-induced hyperinflammation by blocking autophagosome-lysosome fusion, with mechanisms involving downregulation of cell death-associated proteins, thereby illustrating the context-specific utility of autophagy suppression (159). Collectively, current evidence establishes autophagy as a homeostatic modulator in UC, with its pro-survival and pro-death duality being precisely controlled by microenvironmental signaling networks.

Pharmacological investigations on the classical formula Baitouweng decoction have demonstrated that it augments autophagic flux via AMPKα phosphorylation activation and mTORC1 complex inhibition, thereby restoring intestinal epithelial barrier integrity and attenuating disease activity index scores in DSS-induced murine colitis models (160). Mechanistic investigations reveal that procyanidin A1 augments autophagic activity through the AMPK/mTOR/p70S6K signaling axis in LPS-stimulated IEC inflammation models, markedly suppressing pro-inflammatory cytokine secretion (161).

Notably, the probiotic strain *Lactobacillus plantarum* OLL2712 activates protective autophagy in IECs via the MyD88-dependent pathway, thereby reorganizing TJ proteins to fortify intestinal barrier mechanics (162). Although probiotic-mediated autophagy modulation represents a burgeoning therapeutic avenue, elucidation of strain specificity, dosage regimens and host microbiome interplay remains imperative. Compound sophora decoction significantly alleviates DSS-induced intestinal inflammation by fostering autophagy through suppression of PI3K/AKT pathway activation (163). Moreover, the Jianpi Qingchang (JPQC) decoction, composed of nine traditional Chinese medicinal herbs, alleviates colitis progression by suppressing endoplasmic reticulum stress-associated excessive autophagy in IECs within a DSS-induced model (164) Notably, JPQC underscores the contextual therapeutic merits of both autophagy activation and inhibition, albeit the dose-dependent dichotomous effects warrant deeper scrutiny.

Accumulating evidence indicates that disrupting autophagic homeostasis is a pivotal node in UC pathogenesis, with pharmacological restoration of autophagic dynamic equilibrium emerging as a novel therapeutic target. Beyond the aforementioned Chinese herbal and natural products, diverse active compounds and biomacromolecules have shown therapeutic promise in UC management via autophagy modulation. For instance, epimedium polysaccharide (EPS), a bioactive compound, has been shown to engender autophagy augmentation via the AMPK/mTOR pathway amid colonic inflammation, exerting a protective effect in DSS-induced UC models, which suggests EPS as a potential therapeutic target (165). Upregulation of circular RNA HECTD1 has been shown to orchestrate HuR-dependent autophagy in IECs via miR-182-5p sequestration, consequently ameliorating UC histopathology (166) The Slit family of glycoproteins (Slit1-3), canonically expressed in neural and immune compartments, exert regulatory oversight on inflammatory cascades (167,168). Overexpression of Slit2 has been shown to sustain intestinal stem cell proliferation and normal autophagic flux in mice following DSS challenge, thereby mitigating colonic inflammation and curtailing pro-inflammatory cytokine secretion (169). These emerging strategies provide innovative perspectives for UC intervention through the modulation of autophagy; however, the majority of current studies remain focused on mechanistic exploration and are still considerably distant from clinical application. Future research should focus on enhancing target specificity, optimizing delivery systems and clarifying the pharmacodynamic-to-toxicological equilibrium, thereby facilitating their translation into clinical practice.

## 3. Discussion

Disruption of intestinal barrier integrity is firmly established as a central pathological feature of UC, driven by intricate molecular mechanisms involving a dynamic interplay between IEC homeostatic imbalance and dysregulation of the immune microenvironment. The present review summarizes the major programmed cell death modalities in IECs in UC: Autophagy, ferroptosis, pyroptosis, apoptosis and necroptosis (Fig. 1). As the principal components of the intestinal mechanical barrier, dysregulated IEC death directly impairs TJ complexes, leading to epithelial barrier breakdown and subsequent hyperactivation of pattern recognition receptor-mediated innate immune responses. This series of events leads to a self-sustaining cycle of persistent inflammation and mucosal injury. Recent progress in single-cell RNA sequencing and intestinal organoid technologies has yielded unprecedented insights into the spatiotemporal dynamics of IEC death modalities and their association with UC pathological phenotypes, providing a molecular framework for understanding disease heterogeneity and patient-specific variations (14,17,100,170-172).

Recent studies have unveiled a novel programmed cell death pathway known as PANoptosis, which merges key molecular characteristics of pyroptosis, apoptosis and necroptosis to form a multifaceted death complex (173,174). The regulatory framework of PANoptosis entails the integration and interplay of multiple signaling pathways. Research has highlighted the crucial roles of key regulatory molecules such as Z-DNA binding protein 1 (ZBP1), RIPK1 and RIPK3 in the PANoptosis pathway (175). The nucleic acid sensor ZBP1, activated during pathogen infection or cellular stress by recognizing viral nucleic acids or endogenous DAMPs, undergoes conformational changes to recruit and phosphorylate RIPK3 (176). Notably, upon activation by death receptor ligands or PAMPs, RIPK1 initiates PANoptosis signaling transduction by engaging downstream molecules through its death domain. Additionally, RIPK1 forms a functional complex with RIPK3, jointly driving the phosphorylation cascade of MLKL and ultimately inducing cells to enter the PANoptosis program (177,178). Within IECs, a complex molecular interplay exists among apoptosis, necroptosis, pyroptosis and the resulting PANoptosis, all of which play critical roles in the pathogenesis of IBD. Caspase-8 and its adaptor protein FADD serve as central molecules interconnecting these three programmed cell death pathways (59). Upon excessive stimulation by TNF or TLR signaling, caspase-8 is activated and regulates cell fate by initiating apoptosis through the cleavage of downstream caspase-3/7, while also modulating RIPK1 and RIPK3 to inhibit necroptosis (179). Concurrently, caspase-8 can interact with ASC to activate caspase-1 and cleave GSDMD, thereby triggering pyroptosis (180). When caspase-8 function is compromised or inhibited by pathogens, both apoptotic and pyroptotic pathways are impaired, leading cells to undergo RIPK3-mediated necroptosis, which exacerbates intestinal barrier disruption and inflammatory responses. Furthermore, in the absence of caspase-1 in IECs, inflammasome sensors such as NLRP1b and NLRC4 can still initiate apoptosis through ASC-dependent caspase-8 activation (181). The necroptosis effector MLKL can also promote ASC oligomerization and caspase-1 activation, thereby linking necroptosis with pyroptosis (182). These intricate molecular interactions illustrate that apoptosis, necroptosis and pyroptosis are interconnected through shared molecular components, collectively driving epithelial cell death, barrier dysfunction and exacerbated intestinal inflammation in UC. Emerging evidence has demonstrated that PANoptosis plays a crucial regulatory role in the pathogenesis of IBD, particularly UC. In the DSS-induced murine colitis model, IECs exhibited concurrent phenotypes of Dynamin related protein 1 mediated mitochondrial fission and ZBP1-dependent PANoptosis. Notably, analysis of clinical specimens revealed

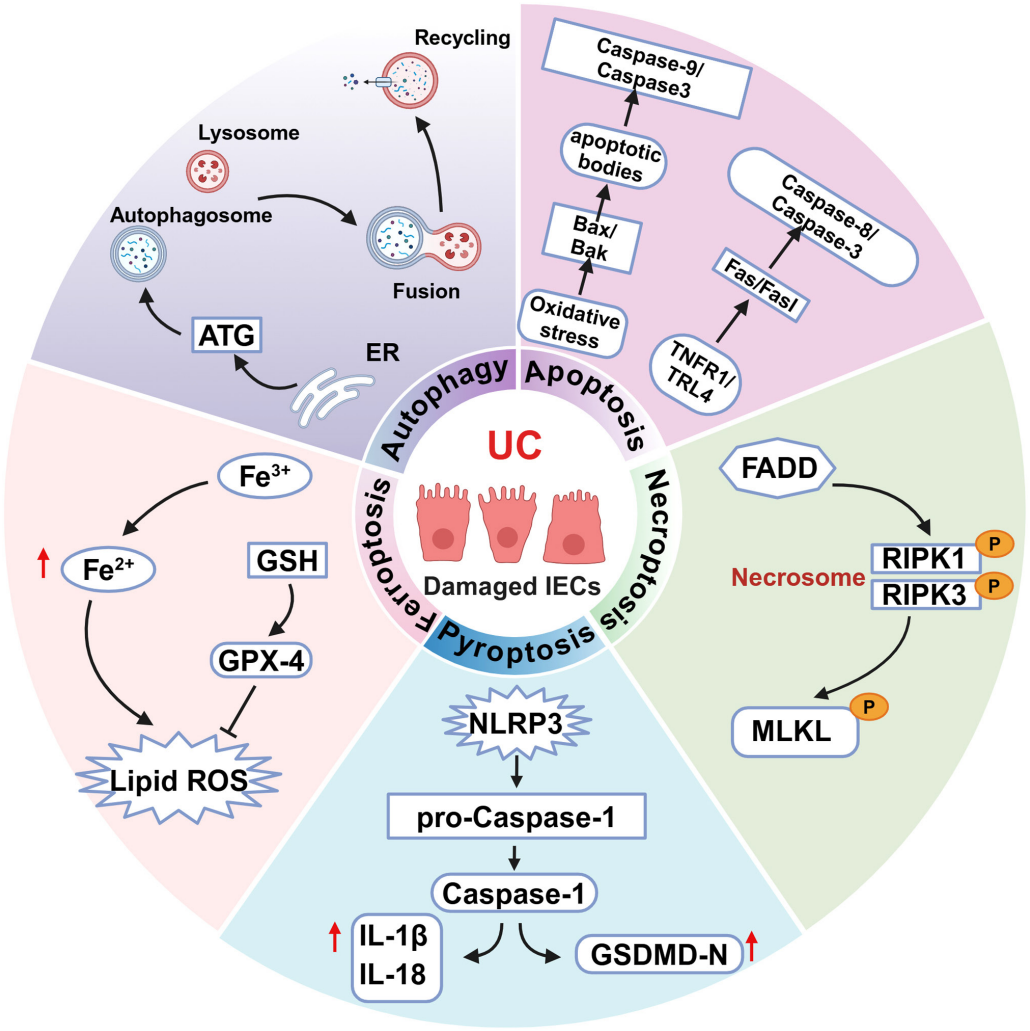


Figure 1. Mechanism of programmed cell death in IECs. During the development of UC, various forms of programmed cell death mechanisms occur in IECs, including apoptosis, necroptosis, pyroptosis, ferroptosis and autophagy. IECs, intestinal epithelial cells; UC, ulcerative colitis; Bak, Bcl-2 homologous antagonist/killer; FasL, Fas ligand; TNFR1, tumor necrosis factor receptor 1; TLR4, Toll-like receptor 4; FADD, Fas-associated protein with death domain; RIPK1/3, receptor-interacting serine/threonine-protein kinase 1/3; MLKL, mixed lineage kinase domain-like protein; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; IL, interleukin; GSDMD-N, N-terminal domain of Gasdermin D; GSH, glutathione; GPX-4, glutathione peroxidase 4; ROS, reactive oxygen species; ER, endoplasmic reticulum; ATG, autophagy-related gene.

a significant positive correlation between the activation levels of PANoptosis in IECs and the clinical activity index of patients with UC (21,183).

Despite notable advancements in recent years in elucidating the mechanisms of IEC programmed death in UC, several crucial issues remain unresolved. For instance, the intricate interplay between various programmed death pathways, including apoptosis, necroptosis, pyroptosis and ferroptosis, requires further elucidation. For instance, the novel multimodal cell death pathway PANoptosis, which integrates key molecular features of apoptosis, necroptosis and pyroptosis, necessitates in-depth exploration of its specific regulatory mechanisms in UC and its synergistic or antagonistic interactions with other death pathways. Additionally, the dynamic interactions between programmed death pathways and the intestinal microenvironment, such as dysbiosis and metabolic products, demand thorough investigation to unravel the complex networks in the pathological progression of UC. Given the intricate interconnections and mutual regulation among these programmed cell death pathways, combination therapies that target multiple key nodes of apoptosis, necroptosis and pyroptosis concurrently may enable precise modulation of the cell death network, leading to more comprehensive intestinal protection and inflammation control. Furthermore, emerging strategies such as the utilization of gene-editing technologies (such as CRISPR/Cas9) to regulate the expression of critical genes including caspase-8 and RIPK3, or the application of stem cell and genetically engineered cell-based therapies to restore compromised epithelial function, offer promising avenues for future therapeutics. Collectively, interventions that target programmed cell death in IECs at multiple levels and from various angles hold significant promise for mitigating epithelial damage and inflammation in UC, thereby advancing therapeutic strategies for this disease.

Natural bioactive compounds and nanoparticle-mediated drug delivery systems have gained significant attention in biomedical research due to their notable translational potential, especially in the management of metabolic disorders and tumor immunomodulation. Their therapeutic efficacy stems from their unique ability to simultaneously modulate multiple

molecular targets, while maintaining favorable biosafety profiles, offering innovative and multifaceted strategies for UC treatment. Notably, an increasing body of evidence highlights the distinct potential of natural bioactive compounds and nanoparticle-mediated drug delivery systems in UC therapy, particularly in their capability to preserve colonic epithelial barrier integrity and mitigate pro-inflammatory cytokine cascades by precisely regulating programmed cell death pathways. These compounds and nanoparticles exert their protective effects by targeting key molecular mechanisms underlying epithelial dysfunction and immune dysregulation, thereby addressing the dual pathological axes of UC.

The present review provides a comprehensive analysis of the central role of IEC death in the pathogenesis of UC-associated chronic inflammation and mucosal injury. Furthermore, it consolidates recent progress in the utilization of natural small-molecule compounds and nanoparticle-mediated drug delivery systems that selectively target abnormal IEC death to mitigate barrier dysfunction, as summarized in Table SI. These compounds, sourced from a variety of natural origins, have exhibited effectiveness in modulating crucial signaling pathways, presenting promising therapeutic opportunities for UC management. In terms of clinical translation, while natural compounds and nanomedicines have demonstrated significant potential in modulating programmed death pathways, their targeting and bioavailability encounter challenges. For instance, the delivery efficiency of nanomedicines is constrained by the intricate intestinal milieu, and enhancing their targeting, such as through surface ligand modification or utilization of intestinal-specific receptors, represents a current research priority. Additionally, despite the advantages of the multi-target properties of natural compounds in treating UC, their potential for unforeseen side effects necessitates further structural refinement and pharmacological assessment. Future research should integrate single-cell omics, organoid models and systems pharmacology techniques to precisely decipher the molecular mechanisms of programmed death pathways and develop more efficient and safer targeted therapeutic strategies to surmount existing treatment bottlenecks and improve the clinical prognosis of patients with UC.

Looking forward, transformative breakthroughs in UC therapy will necessitate the development of integrated therapeutic strategies that concurrently target IEC death pathways and their downstream hyperinflammatory responses. These strategies aim to disrupt the self-sustaining cycle of 'barrier damage-inflammation amplification' that underlies the core of UC pathogenesis. One approach involves the development of therapeutic agents capable of synergistically modulating multiple targets within the regulated cell death network. Given the intricate molecular crosstalk among different forms of programmed cell death, involving key molecules such as caspase-8, RIPK3 and GSDMD, inhibitors targeting a single pathway may be insufficient to fully prevent the dysregulated death of IECs. The design of small molecules or biologics that concurrently regulate multiple critical nodes holds potential for more effectively restoring IEC homeostasis, thereby achieving comprehensive protection of the intestinal barrier and improved control of inflammation. Additionally, enhancing targeting specificity while minimizing systemic side effects is crucial for successful clinical translation. Employing nanotechnology, antibody-drug conjugates or oral targeted delivery systems to selectively accumulate therapeutics within inflamed intestinal tissues or IECs can enhance local drug concentrations and markedly reduce off-target effects in other organs. Novel therapeutic approaches involving gene editing and cell therapy also warrant exploration. While still in the early stages of investigation, *in vivo* or *ex vivo* editing of dysregulated genes in IEC (such as caspase-8 or RIPK3) using technologies such as CRISPR/Cas9, or the administration of genetically engineered stem cells or organoids to repair damaged epithelium, presents a highly promising next-generation treatment strategy. These interventions may provide novel options for patients with refractory UC who are intolerant to conventional pharmacological or biological therapies. In summary, future drug development for UC should transcend the traditional 'single target, single disease' paradigm and adopt integrated, multi-targeted, multimodal and precision-focused strategies with an emphasis on local intestinal targeting. By addressing these unresolved mechanisms and clinical translation challenges, the present review not only establishes a new theoretical framework for understanding the pathomechanism of UC but also establishes a robust basis for the advancement of innovative therapeutic strategies, offering significant scientific and clinical implications.

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**Authors' contributions**

BW drafted and revised the manuscript. BW and SS conceptualized the review and contributed to the writing. YL participated in literature collation and manuscript editing. LG reviewed and revised the manuscript. All authors contributed to the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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**Competing interests**

The authors declare that they have no competing interests.

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