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Research Progress on Berberine Regulating the NLRP3 Inflammasome, Gut Microbiota and Intestinal Epithelial Barrier to Improve Inflammatory Bowel Disease

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Abstract. Berberine (BBR) is a natural alkaloid with multi-target pharmacological activity. In recent years its potential therapeutic value in inflammatory bowel disease (IBD) has received wide attention. To sort out systematically the pharmacological mechanisms by which BBR improves IBD, this study searched PubMed, Web of Science and CNKI for the literature from 2015 to 2025, focusing on basic research, systematic reviews, meta-analyses and clinical studies, and analyzed three mechanistic axes, the NLRP3 inflammasome, the gut microbiota and the intestinal epithelial barrier. The interaction among the three drew our attention. Current evidence shows that BBR can inhibit the NF-κB/NLRP3 signaling pathway and related pyroptosis, thereby reducing intestinal inflammatory response; it can also reshape gut microbiota structure, promote the recovery of beneficial bacteria and regulate microbial metabolites; in addition, BBR can upregulate tight junction protein expression, promote epithelial regeneration and mucosal repair, and thereby improve intestinal epithelial barrier function. The three axes are not independent of each other but interrelated and mutually reinforcing, forming a synergistic network centered on inflammation inhibition, microbiota recovery and barrier repair. At the clinical level, preliminary evidence from ulcerative colitis (UC) suggests that BBR combined with 5-aminosalicylic acid (5-ASA) may have some adjunctive therapeutic value, but high-quality, large-sample, multicenter randomized controlled trials (RCTs) are still insufficient. In general, BBR shows multi-target pharmacological action in IBD treatment, but its clinical efficacy and long-term safety still need further verification.

Keywords: berberine, inflammatory bowel disease, NLRP3 inflammasome, gut microbiota, intestinal epithelial barrier

1. Introduction

Inflammatory bowel disease (IBD) is a disease whose core feature is chronic relapsing intestinal inflammation, and its occurrence and development are the result of the combined action of genetic susceptibility, environmental exposure, gut microbiota dysbiosis and immune abnormality. Among them, abnormal activation of immune and inflammatory signaling, gut microbiota dysbiosis and damage to the intestinal epithelial barrier are three core pathological links, and they promote each

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other and form a vicious cycle: abnormal activation of innate immune signals such as the NLRP3 inflammasome can induce the release of large amounts of pro-inflammatory cytokines and aggravate intestinal inflammation; disordered microbiota structure and metabolic dysfunction further worsen the imbalance of immunity; barrier damage allows luminal antigens and pathogenic microorganisms to translocate and keeps activating the mucosal immune system. The three are not independent but intertwined with each other and jointly drive the chronic inflammatory process of IBD [1]. IBD mainly includes ulcerative colitis (UC) and Crohn's disease (CD) [1-4]. UC mainly involves the mucosa of the colon and rectum, whereas CD can involve different parts of the digestive tract and has deeper transmural inflammatory features, so the two differ in pathological process and clinical manifestation [2, 5].

Current IBD treatment takes the induction and maintenance of remission as its main goal, but treatment needs differ across subtypes and stages of disease, and some patients still face problems such as insufficient treatment response and relapse [5, 6]. Therefore, adjuvant treatment strategies targeting several pathological links have attracted attention [5, 6].

Berberine (BBR) is an isoquinoline alkaloid extracted from Coptis chinensis, Phellodendron and other medicinal materials. It has been used in China for more than a thousand years, traditionally for intestinal infection and diarrhea, with generally good tolerability [7]. BBR has anti-inflammatory and immunomodulatory pharmacological activities, and existing studies suggest that it can act on inflammatory signaling, gut microbiota and epithelial barrier at the same time [8-14], so it has the potential to treat IBD. Since the chemical properties of BBR have already been summarized in detail in previous literature, this paper does not expand on drug source, chemical structure and pharmacokinetics, which run parallel to the main line of this paper, but takes the pharmacological mechanism as its core, focusing on reviewing the effects of BBR on the NLRP3 inflammasome, gut microbiota and intestinal epithelial barrier, and analyzing the synergistic relationships among them and the clinical evidence [8-14].

2. Berberine improves IBD by regulating NLRP3 inflammasome-related pathways

2.1. NLRP3 inflammasome-related pathways and inflammatory response in IBD

The NLRP3 inflammasome is an important regulatory platform of innate immune responses. The classical NLRP3 inflammasome consists of three parts: the NLRP3 sensor protein, the adaptor protein apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and the effector protein Pro-Caspase-1. NLRP3 recognizes pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs); ASC interacts with NLRP3 through the PYD domain and recruits Pro-Caspase-1 through the CARD domain, which promotes inflammasome assembly; Pro-Caspase-1 then accumulates in close proximity within the complex and undergoes self-cleavage to form active Caspase-1, which promotes the maturation of IL-1β and IL-18 and cleaves GSDMD to execute pyroptosis [1].

Abnormal activation of NLRP3 promotes the maturation and release of IL-1β and IL-18, and amplifies local inflammation through GSDMD-mediated pyroptosis, so it is an important node connecting immune activation with tissue damage [1].

NLRP3 activation can be summarized as two stages, priming signal and activation signal: NF-κB participates in the expression of NLRP3 and inflammatory factor precursors, while danger signals such as reactive oxygen species, potassium efflux and mitochondrial damage can promote inflammasome activation [1]. The activated Caspase-1 promotes the maturation of IL-1β and IL-18,

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and cleaves GSDMD to induce inflammatory pyroptosis, thereby further aggravating mucosal damage [1].

Existing studies show that NLRP3-related inflammatory reactions take part in the mucosal damage process of UC, while BBR-related mechanism studies are also mainly concentrated on UC models [1, 8]. In comparison, there is less direct mechanistic evidence for BBR in CD, so the mechanisms found in UC cannot be fully extrapolated to CD without verification [15, 16].

2.2. Inhibition of NLRP3-related signaling pathways in IBD by BBR

BBR does not act only on a single step of NLRP3, but exerts anti-inflammatory effects at several levels, including inhibiting upstream NF-κB, interfering with the assembly of the inflammatory complex and reducing Caspase-1 activation, so as to build a multi-target and multi-level regulatory network.

2.2.1. BBR inhibits NLRP3 transcription via NF-κB

NF-κB is the core regulatory factor for the first signal of NLRP3, and it is also one of the most important inflammatory pathways in IBD. At rest, NF-κB binds to the inhibitory protein IκBα and stays in the cytoplasm; after stimulation by LPS and other signals, IκBα is phosphorylated and degraded, the p65 subunit enters the nucleus, and the transcription of NLRP3, IL-1β, TNF-α and others is induced. BBR blocks NF-κB by inhibiting the phosphorylation and degradation of IκBα: on the one hand it reduces the nuclear translocation of p65 and inhibits NLRP3 transcription at the stage of the first signal; on the other hand it lowers the production of TNF-α, IL-6 and IL-1β. There is positive feedback between NF-κB and NLRP3. The IL-1β released after NLRP3 activation can activate NF-κB again and promote the expression of NLRP3 and other factors, forming a continuous amplification. BBR inhibits NF-κB both by reducing the first signal and by cutting this positive feedback from upstream, so as to achieve long-term regulation of chronic inflammation. Network pharmacology studies also show that NF-κB is one of the core targets of BBR intervention in IBD, that the NF-κB pathway is significantly enriched in KEGG enrichment analysis, and that it interacts broadly with NLRP3, AMPK and barrier protection mechanisms [9].

Therefore, the pharmacological action of BBR on NLRP3 covers several links, including the initiation of inflammatory signaling, inflammasome activation and pyroptosis, and can form a continuous regulatory process of "inhibiting NF-κB, reducing NLRP3 activation, lowering the release of inflammatory factors and pyroptosis" [8, 9].

2.2.2. BBR indirectly inhibits NLRP3 by activating AMPK

AMP-activated protein kinase (AMPK) is an important signaling molecule connecting cellular energy metabolism, mitochondrial homeostasis and inflammatory response, and it is a key sensor for regulating energy metabolism and mitochondrial homeostasis, and it can negatively regulate NLRP3 activation [9]. BBR is an important natural activator of AMPK. After AMPK is activated, it both inhibits the post-translational modification and assembly of NLRP3 and improves mitochondrial function by promoting mitophagy, reducing ROS generation. ROS is the key danger signal of the second signal, so the downregulation of ROS by AMPK can further inhibit NLRP3. AMPK also maintains the energy metabolic homeostasis of the intestinal epithelium, and after activation it upregulates tight junction proteins, lowers permeability and promotes barrier repair. It can be seen that AMPK is a key negative regulator of NLRP3 and also a node connecting inflammatory

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regulation with barrier protection. BBR produces a "dual regulation" through AMPK, inhibiting NLRP3 activation and improving the barrier at the same time, which shows the advantage of its multi-target synergy [17].

In short, BBR acts against inflammation cooperatively through multiple routes such as inhibiting NF-κB, interfering with NLRP3 assembly, improving mitochondrial function, activating AMPK and inhibiting pyroptosis. It builds a complete regulatory network from the first signal and the second signal to the execution stage of pyroptosis, covers several key nodes of the IBD inflammatory process, and supports its use as a potential therapeutic drug for IBD and its translation into clinical practice.

3. Berberine improves IBD by regulating the gut microbiota

3.1. Basic features of gut microbiota dysbiosis in IBD

The gut microbiota takes part in host immune homeostasis and in maintaining the intestinal mucosal barrier, and abnormal composition of it can promote IBD inflammatory activity in turn [10, 13, 14]. IBD patients often show changes in microbiota diversity and composition, with fewer protective commensals and short-chain fatty acid-producing bacteria and more opportunistic pathogenic bacteria [10, 13, 14].

Decreases in butyrate-producing bacteria such as Faecalibacterium prausnitzii and increases in potentially pro-inflammatory groups such as the phylum Proteobacteria are the microbiota changes that have been studied more often at present [10, 13]. These changes can affect local inflammatory signaling and the state of the epithelial barrier, and take part in the chronic inflammatory process of IBD [10, 13, 14].

3.2. BBR reshapes the gut microbiota

BBR can change the composition of the gut microbiota in experimental colitis, promote the recovery of some beneficial bacteria and reduce the abundance of some potentially pathogenic bacteria [10-14]. Related studies suggest that Bifidobacterium, Lactobacillus, Akkermansia and some butyrate-producing bacteria may take part in the microbiota regulation of BBR [10, 13, 14].

3.2.1. BBR increases the abundance of beneficial bacteria

Bifidobacterium and Lactobacillus are core probiotics that maintain microecological stability, and their abundance in the gut of IBD patients is often significantly reduced [10, 13]. After BBR intervention, the relative abundance of the two can rise markedly, promoting the generation of organic acids such as acetate and lactate: on the one hand this lowers the local pH and inhibits the colonization of pathogenic bacteria, and on the other hand it supplies substrates to butyrate-producing bacteria, forming a "cross-feeding" that further promotes the synthesis of SCFAs. Bifidobacterium also promotes Treg differentiation and downregulates pro-inflammatory factors, taking part in maintaining immune homeostasis [11]. In addition, polysaccharide A secreted by Bacteroides fragilis can induce Treg differentiation and inhibit abnormal immune activation; Zheng et al. [11] found that BBR can promote the proliferation of Bacteroides fragilis and alleviate DSS-induced colitis by regulating the differentiation of dendritic cells (DCs), suggesting that it may take part in the regulation of innate immunity by BBR. Faecalibacterium prausnitzii is one of the most important butyrate-producing bacteria, its abundance change is closely related to IBD activity, and

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the butyrate it produces supplies energy and acts against inflammation by inhibiting NF-κB and promoting Treg differentiation; after BBR intervention in IBD models, the abundance of Faecalibacterium prausnitzii is partly restored, in parallel with the decrease of IL-1β and TNF-α, suggesting that it may be a key functional target bacterium for the anti-inflammatory action of BBR.

3.2.2. BBR inhibits abnormal proliferation of harmful bacteria

BBR can also inhibit the expansion of several opportunistic pathogenic bacteria and improve the pro-inflammatory microenvironment. AIEC can adhere to and invade the intestinal epithelium, survive inside macrophages and continuously induce the release of IL-1β and TNF-α; BBR can lower the adhesion and invasion of AIEC to the epithelium and further inhibit its proliferation by optimizing interspecies competition in the microbiota, reducing pathogen-related inflammatory stimulation at the source. The genus Desulfovibrio has an elevated abundance in the gut of IBD patients and produces hydrogen sulfide, which directly damages the epithelium and mitochondria; in patients with active UC the abundance of this genus is positively correlated with disease activity, and after BBR intervention its abundance declines, which both reduces the direct damage of hydrogen sulfide to the barrier and lowers ROS, indirectly inhibiting the second signal of NLRP3. The phylum Proteobacteria proliferates widely in IBD patients, and the LPS synthesized and released by its gram-negative bacteria upregulates NLRP3, Pro-IL-1β and Pro-IL-18 through TLR4/NF-κB, which is an important source of the first signal; BBR lowers the abundance of Proteobacteria, which improves the microecology and, more importantly, reduces LPS at the source and inhibits the NF-κB/NLRP3 axis, realizing indirect regulation of chronic inflammation [10, 13, 14].

3.2.3. BBR inhibits microbial metabolic pathways

The effect of BBR on the microbiota may further regulate host inflammatory responses through microbial metabolites [10, 12-14]. Among them, short-chain fatty acids, especially butyrate, can take part in immune homeostasis and barrier maintenance, and may inhibit NLRP3 inflammasome activation through related pathways such as GPR109A and AMPK [10, 13].

BBR can also affect the indole metabolites produced by tryptophan metabolism in the microbiota, activate AhR and promote IL-22-related mucosal protection [12]. One point needs emphasis: some of the mechanisms above come mainly from studies of experimental colitis, and their causal relationship in human IBD still needs further verification [12-14].

In short, BBR can promote the recovery of beneficial bacteria such as Bifidobacterium, Lactobacillus, Bacteroides fragilis and Faecalibacterium prausnitzii, inhibit potential pathogens such as AIEC and the genus Desulfovibrio, adjust the structure of the gut microbiota, and thereby act against inflammation and protect the barrier.

4. Berberine improves IBD by protecting the intestinal epithelial barrier

4.1. Physiological function of the intestinal epithelial barrier and its damage in IBD

The intestinal epithelial barrier is made up of epithelial cells, tight junctions, the mucus layer and related defense mechanisms. Its main function is to restrict luminal microorganisms and harmful substances from entering mucosal tissue, while maintaining normal material exchange and immune homeostasis [18, 19].

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In IBD, continuous stimulation by inflammatory factors can destroy epithelial junctions and the integrity of the mucus layer, raise intestinal permeability, increase the exposure of mucosal tissue to bacteria and their products, and further promote the inflammatory response [5, 18, 19].

Abnormality of tight junction proteins is an important sign of barrier damage, and abnormal expression or localization of ZO-1, Occludin and the Claudin family can lead to increased paracellular permeability [18]. UC in particular can show changes in goblet cells and in the MUC2-related mucus barrier, while NLRP3-related inflammation and pyroptosis can further aggravate epithelial damage [8, 18].

4.2. BBR upregulates tight junction proteins and improves barrier function

More and more studies confirm that BBR can act directly on the intestinal epithelium and promote tight junction repair. For example, in the Caco-2 monolayer barrier model, stimulation by TNF-α together with interferon-γ (IFN-γ) simulates the inflammatory microenvironment of IBD and induces the downregulation of tight junctions; after treatment with 1-10 μmol/L BBR, the proteins ZO-1 and Occludin rise significantly and the continuity of the membrane surface is restored, which suggests that BBR can improve intercellular junctions directly. Studies based on an intestinal organoid-macrophage co-culture model further clarify a new mechanism: in the LPS-induced inflammatory environment, BBR can restore the normal localization of ZO-1, significantly inhibit the infiltration of M1-type macrophages and the release of inflammatory factors, and protect the epithelium indirectly, which suggests that the barrier protection of BBR is not limited to promoting tight junction expression but can also regulate the interaction between immune cells and the epithelium [18-20].

Therefore, the direct pharmacological action of BBR on the intestinal epithelial barrier can be summarized as upregulating tight junction proteins, lowering abnormal permeability and improving barrier integrity [17, 18]. This process is linked with the inhibition of NLRP3 inflammation and the regulation of the gut microbiota by BBR [8, 10, 18].

4.3. BBR promotes epithelial regeneration and mucosal repair

Barrier recovery requires the reconstruction of tight junctions, the renewal of damaged epithelial cells and the restoration of the mucus layer, so "promoting epithelial regeneration" and "promoting mucosal repair" are two important aspects of barrier recovery [12, 18, 21].

4.3.1. BBR promotes intestinal stem cell proliferation and crypt-villus axis regeneration

The intestinal epithelium is one of the fastest renewing tissues in the body, and its integrity depends on the continuous proliferation and differentiation of intestinal stem cells (ISCs). The $LGR5^+$ stem cells located at the base of the crypts continuously differentiate into new epithelium, migrate upward along the crypt-villus axis and differentiate into absorptive cells, goblet cells, endocrine cells and others, and this is the core step that determines the efficiency of barrier repair. Under the chronic inflammation of IBD, the continuous release of inflammatory factors inhibits stem cell proliferation, destroys crypt structure and interferes with the normal renewal of the barrier. Luo et al. [21] found that BBR can promote the production of Wnt molecules by intestinal fibroblasts and other stromal cells and activate $LGR5^+$ stem cells, thereby promoting epithelial repair and the recovery of crypt structure in experimental colitis, which suggests that besides acting against inflammation BBR can also enhance stem cell activity and promote continuous tissue renewal. The recovery of protective

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factors such as SCFAs produced by microbial metabolism and IL-22 in turn provides a suitable regenerative microenvironment for the stem cells, so the protection of stem cells by BBR is in essence the combined effect of its reshaping of the microbiota and its improvement of the inflammatory microenvironment [21].

4.3.2. Protection of goblet cells and promotion of mucus layer reconstruction

MUC2 secreted by goblet cells is a core component of the mucus layer, and it can block the direct contact of commensal bacteria with the epithelium and maintain the integrity of the chemical barrier. IBD, especially UC, is often accompanied by a decrease in goblet cells and a downregulation of MUC2, a thinner mucus layer and a higher risk of bacterial translocation; damage to the mucus layer both aggravates dysbiosis and worsens inflammation and induces NLRP3 activation, forming positive feedback with the disorder of immune inflammation. Animal experiments show that BBR can effectively maintain MUC2 expression and promote the functional recovery of goblet cells: on the one hand it promotes the recovery of functional bacteria such as Akkermansia by regulating the microbiota and provides a favorable microenvironment for the renewal of the mucus layer; on the other hand it reduces inflammatory damage to goblet cells by inhibiting NF-κB; the AhR ligands produced by microbial metabolism can promote the secretion of IL-22, and IL-22 is what drives goblet cell differentiation and promotes the regeneration of the mucus layer. The protection of the mucus layer by BBR is the result of the synergy of multiple pathways in its regulation of the microbiota, inhibition of inflammation and promotion of barrier repair [12, 18].

4.3.3. BBR inhibits epithelial pyroptosis and maintains epithelial integrity

Pyroptosis is one of the core mechanisms mediating the irreversible damage of the IBD barrier. After NLRP3 activation, Caspase-1 cleaves GSDMD to generate GSDMD-N, which induces epithelial pyroptosis together with the release of large amounts of IL-1β and IL-18. Pyroptosis is a pro-inflammatory form of programmed cell death that reduces the number of epithelial cells and destroys tight junctions and the mucus layer, aggravating barrier damage. BBR can inhibit NLRP3-mediated pyroptosis at several levels, including NF-κB, NLRP3 assembly and AMPK: in colitis models, after BBR intervention GSDMD-N is markedly downregulated, LDH release decreases, and IL-1β and IL-18 are also markedly inhibited, which suggests that BBR both inhibits NLRP3 activation and reduces pyroptotic death of the epithelium [8]. A lower level of pyroptosis can keep the epithelial layer intact, lower permeability and reduce the leakage of bacterial products; after the barrier recovers step by step, the TLR4/NF-κB/NLRP3 axis is further suppressed, which relieves local inflammation in return. Therefore, inhibiting pyroptosis is the core mechanism of the barrier protection by BBR and also the key hub connecting NLRP3 inhibition with barrier repair.

4.4. BBR indirectly protects the barrier by regulating the inflammatory microenvironment

Apart from promoting regeneration directly, BBR can also protect the barrier indirectly by regulating the local inflammatory microenvironment. In IBD there are abnormal macrophage polarization, an imbalance among helper T cell subsets and sustained activation of pro-inflammatory signals, all of which can destroy tight junctions, induce epithelial death and aggravate barrier damage; reshaping the local immune microenvironment is an important direction for promoting barrier recovery. Abnormal macrophage polarization is a key inducer of the prolongation of chronic inflammation: M1-type macrophages secrete large amounts of TNF-α, IL-1β and IL-6, which can

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directly downregulate ZO-1 and Occludin and raise permeability; studies based on the organoid-macrophage co-culture model confirm that BBR can significantly inhibit M1-type infiltration and the release of pro-inflammatory factors, relieve the damage to the epithelium and promote the return of ZO-1 to its normal localization [20], and this immunomodulatory effect is related to the regulation of macrophage polarization through the PI3K/AKT pathway [22], suggesting that the barrier protection by BBR comes from direct regulation of the epithelium and, indirectly, from the regulation of innate immunity. Imbalance among helper T cell subsets also takes part in barrier damage: under physiological conditions Tregs and Th17 maintain a dynamic balance, while in IBD patients Th17 is abnormally activated and IL-17 is secreted in large amounts, and IL-17 keeps the inflammation activated and directly downregulates the expression of the Claudin family and raises permeability; BBR can promote Treg differentiation, inhibit Th17 activation and restore the Treg/Th17 balance, while the recovery of SCFAs also helps promote Treg differentiation, which suggests that microbiota regulation and immune regulation interact closely here [10]. In addition, the oncostatin M (OSM)-OSM receptor (OSMR) axis is a key pro-inflammatory pathway of IBD found in recent years, its sustained activation is related to resistance to anti-TNF treatment, and it takes part in intestinal fibrosis and abnormal stromal activation; OSM in the intestinal tissue of patients with chronic UC is elevated and positively correlated with severity. Li et al [8]. found that BBR can inhibit the activation of the OSM-OSMR axis, reduce infiltration, improve the stromal microenvironment and promote barrier recovery under chronic inflammation; this finding suggests that BBR has the potential value of regulating the chronic inflammatory microenvironment and of anti-fibrotic action, but the specific mechanism in IBD still needs to be studied further.

In summary, the protection of the barrier by BBR is not limited to promoting tight junction protein expression, but is achieved through multi-level mechanisms, promoting stem cell regeneration, protecting the mucus layer, inhibiting pyroptosis and reshaping the inflammatory microenvironment, which intervene on IBD together; NLRP3 inhibition, microbiota reshaping and the recovery of local immune homeostasis together form the core basis of barrier repair, and barrier repair in turn can reduce the translocation of bacterial products and inhibit abnormal immune activation, so that a positive regulatory network of "BBR, microbiota, NLRP3 and barrier" is finally formed and the rebuilding of intestinal homeostasis is promoted.

5. Synergistic mechanism of the NLRP3-microbiota-barrier three axes

5.1. Interactions among the three mechanistic axes

The NLRP3 inflammasome, the gut microbiota and the intestinal epithelial barrier all take part in the maintenance of inflammation in IBD [1, 10, 17]. NLRP3 activation can aggravate epithelial damage through IL-1β, IL-18 and pyroptosis, while barrier damage in turn increases the exposure of luminal microorganisms and their products, further stimulating innate immunity [1, 8, 18].

Dysbiosis can increase inflammatory stimuli such as LPS and weaken the action of protective metabolites, thereby promoting the activation of NF-κB/NLRP3 signaling; the reshaping of the microbiota by BBR may in turn lower inflammatory stimuli and improve the environment for barrier repair [10, 13, 14].

As shown in Table 1, the three main mechanistic axes of BBR influence each other, so the action of BBR is more likely a dynamic synergistic process of "inhibiting inflammation, restoring the microbiota, repairing the barrier and further lowering inflammatory stimuli" rather than three mutually independent pathways [8, 10, 12-14, 18, 20].

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Table 1. The three main pharmacological mechanism axes of BBR in improving IBD

Mechanism axis	Main targets and links	Main pharmacological effects
NLRP3 inflammasome axis	NF-κB, NLRP3, ASC, Caspase-1, GSDMD, AMPK	Inhibit inflammasome activation, reduce IL-1β/IL-18 release and pyroptosis
Gut microbiota axis	Bifidobacterium, Lactobacillus, Akkermansia, butyrate-producing bacteria and some pro-inflammatory groups	Reshape microbiota composition, improve the metabolic environment, indirectly inhibit inflammation
Intestinal epithelial barrier axis	ZO-1, Occludin, Claudin, MUC2, $LGR5^{+}$ stem cells	Restore tight junctions, promote epithelial regeneration and mucosal repair

5.2. Pharmacological significance of the three-axis synergy

The potential advantage of BBR lies in its ability to act on several pathological links at the same time, including inflammation, the microecology and the barrier [8-14]. NLRP3 inhibition can reduce inflammation and pyroptosis, reshaping of the microbiota can cut pro-inflammatory stimuli and improve the metabolic environment, and barrier repair can lower the chance for luminal antigens and microbial products to enter the mucosa further [1, 10, 18].

But at present the evidence for the "three-axis synergy" comes mainly from in vitro and animal studies, so this concept should be taken as a mechanistic model explaining the multi-target pharmacological action of BBR, and not as a clinical mechanism that has already been sufficiently verified in human IBD patients [8-14].

6. Clinical translation evidence and research limitations

6.1. Clinical evidence

At present human studies of BBR in IBD are concentrated mainly on UC, and the clinical evidence is clearly less than the basic research [15, 23]. The phase I randomized placebo-controlled trial carried out by Xu et al. suggests that BBR combined with mesalazine is well tolerated in the short term and may improve histological inflammation, but the sample size was small and the main purpose was the evaluation of safety, so the long-term efficacy of BBR cannot be established on this basis [15].

A 2024 systematic review and meta-analysis included 10 randomized controlled trials (RCTs) and 952 UC patients. The results suggest that BBR combined with 5-aminosalicylic acid (5-ASA) can improve some clinical and inflammatory indicators compared with 5-ASA alone, but the included studies commonly have problems such as small sample sizes, limited study quality and limited follow-up time, and the overall quality of the evidence is still insufficient to support adding BBR to the standard treatment regimen for IBD [23].

Systematic reviews and meta-analyses of animal experiments show that BBR has relatively stable anti-inflammatory and tissue-protective effects in experimental UC models, but animal results cannot replace efficacy evidence in humans [16]. Therefore, the more rigorous conclusion at the

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present stage is that BBR has potential value as an adjuvant treatment, but its clinical efficacy still needs to be verified by higher-quality RCTs [15, 16, 23, 24].

6.2. Research limitations

The existing mechanistic evidence still rests mainly on in vitro and animal studies, and the causal relationships among the three axes of NLRP3, the microbiota and the barrier have not yet been fully clarified [8-14, 18-21]. The existing studies also lean clearly towards UC, while direct mechanistic and clinical studies on CD are insufficient, so whether different IBD subtypes show the same pharmacological response still needs further study [15, 16].

In addition, the BBR concentrations used in some basic studies differ from the actual exposure levels in humans, so whether the pharmacological effects observed in experiments can be realized stably under actual clinical dosing conditions still needs verification [15]. The existing clinical studies are small in scale and have limited follow-up time, and their evaluation of long-term efficacy and safety is still not sufficient [15, 23].

7. Future prospects

Future research should first strengthen the causal verification of the three-axis mechanism, with the key point of making clear whether the microbiota changes induced by BBR are the direct cause of the efficacy or a concomitant result after the inflammation improves [10, 13, 14]. Studies such as fecal microbiota transplantation, intervention with specific strains and mechanism blocking can further verify the causal chain of "BBR, microbiota, NLRP3 and barrier" [10, 14].

Second, the delivery mode should be optimized for the local intestinal action of BBR, raising the effective exposure in the colon while controlling systemic exposure, so as to improve the feasibility of translating basic research into clinical practice [15, 24].

Third, RCTs with larger samples, at multiple centers and guided by mechanism should be carried out, and inflammatory markers, microbiota characteristics and barrier function indicators should be included in the evaluation of efficacy, to judge whether BBR can achieve synchronized regulation of the three axes in the human body [15, 23].

In addition, the pharmacological characteristics of UC and CD should be further distinguished and the potentially suitable populations for different subtypes and different disease stages should be made clear [15, 16]. Combination strategies of BBR with mesalazine, biological agents or other targeted therapies can serve as directions for later research, but the relevant clinical evidence is limited at present, so no excessive inference should be made in the conclusions [15, 23].

8. Conclusion

BBR can improve IBD through three main pharmacological pathways: inhibiting the NF-κB/NLRP3 inflammasome and the related pyroptosis, reshaping the gut microbiota and improving the related metabolic environment, and upregulating tight junction proteins and promoting epithelial regeneration and mucosal repair [8-14, 17-20]. The three pathways are not independent of each other but form a synergistic network through the two-way regulation among inflammation, the microbiota and the barrier [8, 10, 12, 17].

At present the basic research evidence for BBR is relatively sufficient, but high-quality, large-sample, multicenter clinical RCTs are still scarce, especially the clinical evidence for CD [15, 16, 23]. Therefore, at this stage BBR is more suitable as a candidate drug with potential adjuvant value,

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and its clinical positioning still needs to be further defined through mechanism-guided clinical research [15, 23].

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