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REVIEW

Zinc and Inflammatory Bowel Disease: From Clinical Study to Animal Experiment

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Abstract

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract (GI) with a high incidence rate globally, and IBD patients are often accompanied by zinc deficiency. This review aims to summarize the potential therapeutic value of zinc supplementation in IBD clinical patients and animal models. Zinc supplementation can relieve the severity of IBD especially in patients with zinc deficiency. The clinical severity of IBD were mainly evaluated through some scoring methods involving clinical performance, endoscopic observation, blood biochemistry, and pathologic biopsy. Through conducting animal experiments, it has been found that zinc plays an important role in alleviating clinical symptoms and improving pathological lesions. In both clinical observation and animal experiment of IBD, the therapeutic mechanisms of zinc interventions have been found to be related to immunomodulation, intestinal epithelial repair, and gut microbiota's balance. Furthermore, the antioxidant activity of zinc was clarified in animal experiment. Appropriate zinc supplementation is beneficial for IBD therapy, and the present evidence highlights that alleviating zinc-deficient status can effectively improve the severity of clinical symptoms in IBD patients and animal models.

Keywords Zinc · Inflammatory bowel disease · Clinical experiments · Animal experiment

Introduction

Inflammatory bowel disease (IBD) is a chronic and life-threatening inflammatory disease of the gastrointestinal tract [1, 2] with increasingly prevalent especially in newly industrialized countries [3, 4]. Ulcerative colitis (UC) and Crohn's disease (CD) represent the two main types of IBD [5, 6], which result from multiple factors including abnormal gut microbiota, immune response disorders, environmental disturbance, and genetic susceptibility [7, 8]. IBD, as the paradigm of auto-immune disease, is often firstly initiated by poorly understood dietary factors and then in turn presents an imbalanced internal gut environment, a first local innate, and then, chronic latent systemic immune response in patients [9]. This complex and individualized disease procedure involves variable environmental factors and damages multiple tissues [9], so the diagnosis, monitoring, and treatment of this disease has many challenges. At present, the treatment for IBD is mainly through controlling disease progression and treating specific complications by using immune-suppressants, monoclonal antibodies, and nutritional manipulation [10–13]. Considering nutritional factors, trace elements, especially zinc and selenium, have attracted much attention in IBD study [7]. As one of the most importance essential trace element, zinc participates in the formation of about 3000 proteins, which involve DNA synthesis [14], gene expression [15], anti-inflammatory, antioxidant, and wound healing [14, 15]. Due to its important biological function, zinc deficiency is associated with some clinical disorders such as dermatitis, loss of appetite, impaired wound healing, increased blood ammonia, and

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hypogonadism, and zinc excessive have toxic effects [16]. Multiple intestinal diseases are associated with zinc levels in the body, including IBD, irritable bowel syndrome (IBS), and colorectal cancer (CRC) [17].

Zinc deficiency is common in patients with CD and UC [18–20] and is associated with an increased risk of subsequent hospitalizations, surgeries, and adverse disease-specific outcomes [21, 22]. It seems that monitoring and maintaining normal levels of zinc in IBD patients are necessary [23] based on its ability to keep immune balance, redox balance, and maintain normal proliferation and structure of cell [18, 24–30]. And clinical symptoms often are relieved after zinc supplementing with different zinc sources in IBD patients. Animal experiments are suitable for studying intervention effects and related mechanisms. In this review, we describe the relationship of zinc and IBD in clinical practice and give a summary on zinc's therapeutic efficacy in animal models.

Clinical Studies Related to Zinc and IBD

According to the epidemiological analysis carried out by the affiliated hospitals or institutions, the IBD patients often suffer from zinc deficiency. The prevalence of disease and the association between zinc exposure and outcomes were evaluated in IBD populations [31]. The results indicated that IBD patients often suffer from zinc deficiency (serum zinc content < 70 μg/dL [32]) companied by the decrease of other trace elements including selenium (Se), magnesium (Mn), and copper (Cu) [19, 21, 32–35]. Exposure to plumbum (Pb), arson (As), Cu, and ferrum (Fe) in drinking water would induce the deterioration of IBD [33]. Fortunately, the zinc-deficiency-related adverse effects could be improved by zinc addition [21, 36]. Follow-up survey found that dietary zinc levels were negatively associated with the prevalence of IBD [37]. In addition, nickel (Ni) concentrations in the intestinal biopsies [33] and exposure periods to fluorine (F) [38] were also negative related to the risk of IBD. The above-mentioned studies indicate that zinc deficiency is associated with the high incidence of IBD, and zinc supplementation has a protective effect on IBD.

In some clinical trials, zinc and placebo have been used to observe the therapeutic effects on IBD. In these studies, the patients suffered from UC or CD were between 18 and 69 years old, and the zinc sources were variation, in which zinc gluconate was mainly used [39–41]; meanwhile, zinc sulfate [42], zinc acetate hydrate [43], zinc-rich foods [44], and zinc carnosine [45] were also applied (listed in Table 1). Except that zinc-carnosine chelate compound was treated by enema with a suspension, all other zinc sources were orally taken in tablets or capsules with a dose of 30–35 mg/day for 30–60 days.

The therapeutic effects of zinc supplementation on IBD could be determined through clinical examination, histopathological score, and biochemical examination [45–50]. The clinical severity of IBD were mainly evaluated through some scoring methods including the Mayo score, Ulcerative Colitis Endoscopic Severity Index (UCEIS) score, Matts endoscopic score, and the Clinical Activity Index (CAI) (listed in Table 2). The clinic performances of IBD patients include apparent bleeding, erosion, and ulcers observed under endoscopy, as well as pathological changes such as crypt expansion, mucosal layer detachment, goblet cell depletion, glandular reduction, and inflammatory cell infiltration in the biopsy intestinal tissue [45]. These situations became relived by zinc supplementation, which have been confirmed by Matts endoscopic score and Geboes histopathological score (GHS), Matts endoscopic score, and GHS et al. [40, 44, 45]. In addition, some studies showed that zinc supplementation could obviously increase the concentration of plasma and erythrocyte zinc in UC and CD patients [35, 39, 41].

The protective mechanisms of zinc on IBD have been preliminarily explored in clinical study, which mainly involve the immunomodulation, intestinal epithelial repair, and microbiota's balance. In terms of the immunomodulation, some research suggests that zinc plays an important role in maintenance of balanced intestinal mucosal immune, which mainly involved the regulation of T cells. It has been found that zinc deficiency can lead to an imbalance of T cell subsets and promote inflammatory reactions, which can then exacerbate the pathological severity of IBD [51–53]. Increased Th17 cells and decreased Tregs were observed in IBD patients [54–56], while physiological zinc

Table 1 Zinc sources and their associated therapeutic potentials

Zinc sources	Therapeutic potentials	Reference
Zinc gluconate	Increase plasma zinc; reduce cytokines and the Mayo score	[39–41]
Zinc sulfate	Resolve permeability alterations in CD patients; improve intestinal barrier function	[42]
Zinc acetate hydrate	Improve zinc deficiency and disease activity in IBD	[43]
Zinc-rich foods	Induce clinical remission in UC patients	[44]
Zinc–carnosine	Accelerate mucosal healing in UC	[45]

Table 2 Scoring methods evaluating the severity of clinical symptoms and pathological changes

Item	Scoring method	Parameters and scores	Reference
Mayo score	Mayo	Stool frequency (0–3) Rectal bleeding (0–3) Findings of flexible proctosigmoidoscopy (0–3) Physician's global assessment (0–3) Score range: 0–12 point	[46]
Endoscopic score	UCEIS	Vascular pattern (1–3) Bleeding (1–4) Erosions and ulcers (1–4) Score range: 3–10 point	[47]
	Matts	Mild granularity of the mucosa, with mild contact bleeding (1) Marked granularity and oedema of the mucosa (2) Contact bleeding, and spontaneous bleeding (3) Severe ulceration of mucosa with hemorrhage (4) Score range: 1–4 point	[48, 49]
Clinical Activity Index	CAI	No of stools weekly (0–3) Blood in stools (based on weekly average) (0–4) Investigator's global assessment of symptomatic state (0–3) Abdominal pain/cramps (0–3) Temperature due to colitis (℃) (0–3) Extraintestinal manifestations (3–9) Laboratory findings (1–4) Score range: 3–29 point	[45]
Histopathological score	GHS	Structural (architectural change) (0–3) Chronic inflammatory infiltrate (0–3) Lamina propria neutrophils and eosinophils (0–6) Neutrophils in epithelium (0–3) Crypt destruction (0–3) Erosion or ulceration (0–4) Score range: 0–22 point	[50]

supplementation could ameliorate human IBD through inhibiting Th17-induced cytokines [57] or increasing the number of Tregs [58]. Other researches focused on the changes of some frequently used immune parameters, which is not closely related to certain immune cells. Significantly elevated fecal calprotectin and serum CRP were determined in IBD patients with zinc deficiency [19, 34]. However, zinc supplementation could increase serum interleukin 10 (IL-10) [39], decrease interleukin 2 (IL-2) [40], and tumor necrosis factor-alpha (TNF-α) [39]. There are almost no clinical trials systematically studying the effects of zinc on intestinal epithelial barrier. There is only one paper which demonstrated that zinc supplementation could significantly reduce the intestinal permeability by lactulose/mannitol ratio (L/M) test [59]. The composition of gut microbiota in IBD patients is distinct from that of healthy individuals, and disruption of the microbiota's balance can lead to inflammation and intestinal damage [60]. Furtherly, gut microbiota-based therapeutic approaches might be used for the treatment of IBD [61]. However, it is a need to be explored whether zinc is involved in regulating intestinal flora in IBD patients.

Taken together, adequate zinc supplementation can help alleviate the clinical symptoms of IBD patients to some extent. However, it is worth noting that excessive zinc intake will cause obvious toxic symptoms (nausea, vomiting, epigastric pain, lethargy, and fatigue) [62] and impair immune response [63]. Although present published researches never used toxic doses to treat IBD, the toxicity of excessive zinc remains a high concern (Fig. 1).

Animal Experiments Related to Zinc and IBD

Although the relationship between appropriate zinc intake and remission of IBD severity has been determined based on clinical studies, the relevant mechanisms are still blurry. Animal experiment, as the most rigorous research method under controlled conditions, is suitable for studying intervention effects and mechanisms [64]. In the animal experiment focusing on the relationship of zinc levels and IBD, tablets, capsules, or dietary therapies are mostly used. In recent years, zinc nanoparticles (NPs) have been brought into focus due to its faster and better performance compared to traditional zinc sources [65, 66]. NPs possess higher physical activity and chemical neutrality, and their bioavailability can be enhanced because of the increased surface area of respective minerals [67]. Researchers have developed several nanomedicines to specifically treat IBD,

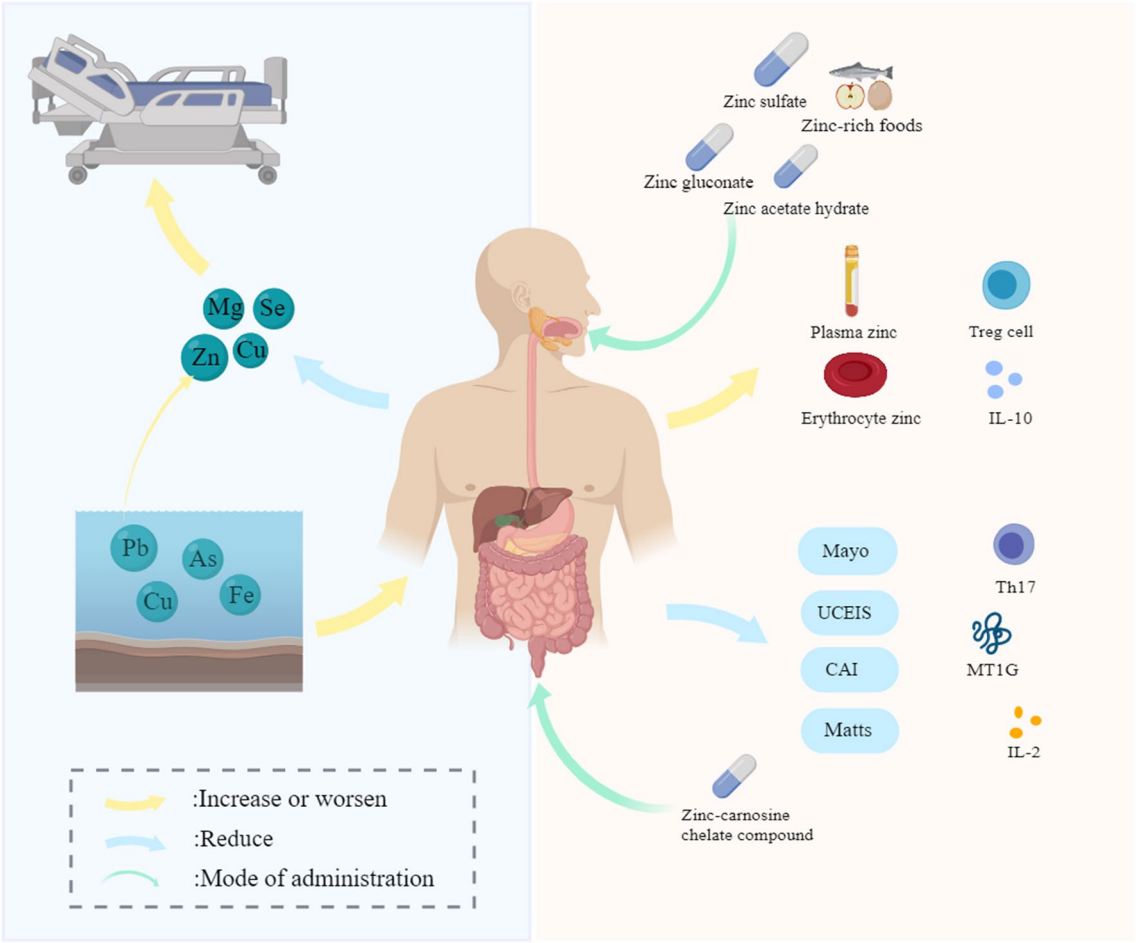

Fig. 1 The left part marked light blue shows that IBD patients suffer from deficiency of some trace elements including zinc, Mn, Se, and Cu, and exposure to Pb, As, Cu, and Fe in drinking water would induce the deterioration of IBD. IBD patients often have high hospitalization rate and surgical risk. The right part indicates that the serum zinc, erythrocyte zinc, serum IL 10, and Tregs are increased, and the scores of Mayo, UCEIS, CAI, and Matts, and the contents of Th17, MT1G, and IL-2 are decreased

and the therapeutic mechanisms of zinc NPs are similar to traditional zinc, which include eliminating reactive oxygen species (ROS), inhibiting inflammation, repairing the mucosal barrier, and eradicating pathogens [68–73]. In this review, we focus on the effects of zinc on the clinical results, inflammatory response, intestinal barrier, and gut microbiota in IBD animals, rather than the intervention differences of different zinc sources.

Clinical Evaluation and Pathological Observation

Similar to human clinical examinations, clinical detections in experimental IBD animals include clinical observation, disease activity index (DAI), colonoscopy, and serum zinc content detection. In animals suffered from colitis, food intake and body weight were obviously reduced [74–77], and DAI was significantly increased [74, 78]. Interestingly, zinc supplementation could significantly increase the average daily gain, feed intake [79–81], body weight [77, 82, 83], and serum zinc concentration [30] and markedly reduce DAI scores in IBD animals [75, 83].

Pathological examination includes gross and histopathological observation on colon. Colitis animals had shortened colon [74, 78, 84] and increased wet weight [76, 85]. The intestinal mucosa showed congestion, edema, thickening, and obvious ulcers formation [76, 86]. Intriguingly, zinc supplementation could increase the colon length [65], mitigate the colonic injury, and decrease the macroscopic colon mucosa damage index (CMDI) [75]. Microscopically, the loss of mucosal epithelia and crypts and infiltration of inflammatory cells were observed in colon [87], while zinc supplementation is able to restore the damaged histological structure [83], increase the thickness and width of intestinal mucosa [88], and increase the ratio of jejunal mucosal villus height to crypt depth [79].

These results indicate that zinc supplementation can alleviate the severity of colitis showing as improving the clinical, anatomical, and histological status of experimental animals.

Zinc and Intestinal Barrier

Intestinal barrier, which is consisted of mucous layer, epithelial tight junction, immune cells, and intestinal flora, is important for protecting body from damages caused by virus, pathogen, and toxins. Zinc plays a pivotal role in modulating the secretion of mucus, the structure of tight junction, and the balance of intestinal flora.

The mucous layer is made from lamina propria and epithelial, including differentiated cells and undifferentiated cells. Differentiated cells include absorption epithelial, goblet cells, and Pan's cell [89, 90]. Mucus secreted by goblet cells which cover overall inner surface of gut-intestine tract (GIT) is a physical barrier to protect from chemical, physical injuries and pathogens [91]. It has been reported that goblet cells became decreased in experimental colitis, while goblet cells and secreted mucus were increased with the zinc supplementation [75, 85, 92–94]. Regulation of goblet cell function may be related to Zinc Transporter (ZnT) [95]. Zinc Transporter 7(ZnT7) is responsible for the accumulation of zinc in the Golgi apparatus of cells [96, 97] and mucus secretion of goblet cells. If ZnT7 is knocked out, C57BL/6 mice become zinc deficiency [95].

Tight junction (TJ) is composed of cytoplasmic attachment proteins including occludin, claudins, and scaffold protein, which plays pivotal physiological roles in preventing abnormal immune function caused by intestine flora and active inflammation cause by bacteria and excessively infiltrated antigen in the mucous [98]. In IBD, colonic permeability is increased, which has been determined by the increasing of the flux of isothiocyanate glucan fluorescein isothiocyanate-dextran 4 kDa (FD4), the decreasing of colonic transepithelial electrical resistance (TEER), and ratio of lactose to mannitol [80, 81, 99]. The mechanisms of high colonic permeability are related to the reduced expression of tight junction proteins, including occludin and claudin-3 [100]. When dietary zinc was supplemented, increased colonic permeability was suppressed because of the increased expression of claudin-1, occludin, and tight junction protein 1(ZO-1) [80, 81, 99, 101].

It was well known that the most gut microbiota growing in the mucus layer serves as the first line of defense against harmful microbial invasion. In colitis models, the diversity and stability of gut microbiota are disturbed, showing as an increase in *actinobacteria* and decrease of *bacteroidetes* and *facultative anaerobic bacteria* [102, 103]. Zinc supplementation could increase the stability and diversity of the microbiota [88] and decrease pH values for maintaining acid–base balance of intestinal contents [93]. In addition, the internal balance of zinc affects the interaction between intestinal microbiota and mucosal immune function [18].

Zinc and Intestinal Mucosal Immunity

In terms of non-specific immunity, the functions of polymorphonuclear leukocytes, macrophages, and dendritic cells (DCs) in IBD model animals are all inhibited. In the body with zinc deficiency, the function of polymorphonuclear leucocytes (PMN) is impaired, showing decreased activity, phagocytosis, and decreased host defense [104–106]. Neutrophil infiltration is a common feature in the pathogenesis of IBD [105, 107, 108]. In IBD, mucosal myeloperoxidase (MPO) activity, mucosal prostaglandin E_2 (PGE_2), and Leukotriene B_4 (LTB_4) levels were significantly increased, all of which were improved after supplementing with zinc [109]. It has been reported that DCs in the inflamed colonic lamina propria were increased in number with colitis development [110, 111]. However, little is known about the effect of zinc levels on macrophages and DCs in IBD, which need to be further researched. It seems that researchers have overlooked the study of zinc intervention on the specific immune function of IBD animals, although many studies found that zinc deficiency or IBD decreased the production of thymulin and induced the decrease and subset-unbalance of T cells [51, 58, 86, 112, 113].

Furthermore, there are many studies about the relationship between zinc deficiency and cytokine network in IBD animal models. Zinc deficiency in IBD promotes inflammatory reactions through increasing the secretion of IL-1β and TNF-α [65, 66, 114]. After zinc supplementation, it can significantly increase the levels of Foxp3, IL-10, and TGF-1β, reduce IL-8,IL-1 β, TNF-α, prostaglandin-endoperoxide synthase 2 (Cox-2) levels in intestinal tissue [65, 66, 83, 115]. As for related mechanism, there are a few studies on signaling pathways and zinc finger proteins. Zinc enriched diet fed to piglets decreased colonic toll-like receptor 4 (TLR4) expression and reduces nuclear factor-kappa B (NF-κB) signaling and autophagy, which reduced colonic inflammation [116]. Zinc finger protein A20, induced by TNF-α, is an anti-inflammatory protein that regulates the activation of transcription factor NF-κB [117]. Mice with specific A20 deficiency will spontaneously developed lymphocytic dependent colitis and serum negative ankylosing arthritis [112], and zinc supplementation can promote upregulation of A20 mRNA and finally lead to the decreased expression of TNF-α, IL-1β, and IL-8 [118–120]. Meredith et al. found that the zinc finger transcription factor zDC (also known as Zbtb46 or Btbd4) is a negative regulatory factor that inhibits the activation of classical DCs [121], which proved a clue for further researching the relationship between zinc and DCs.

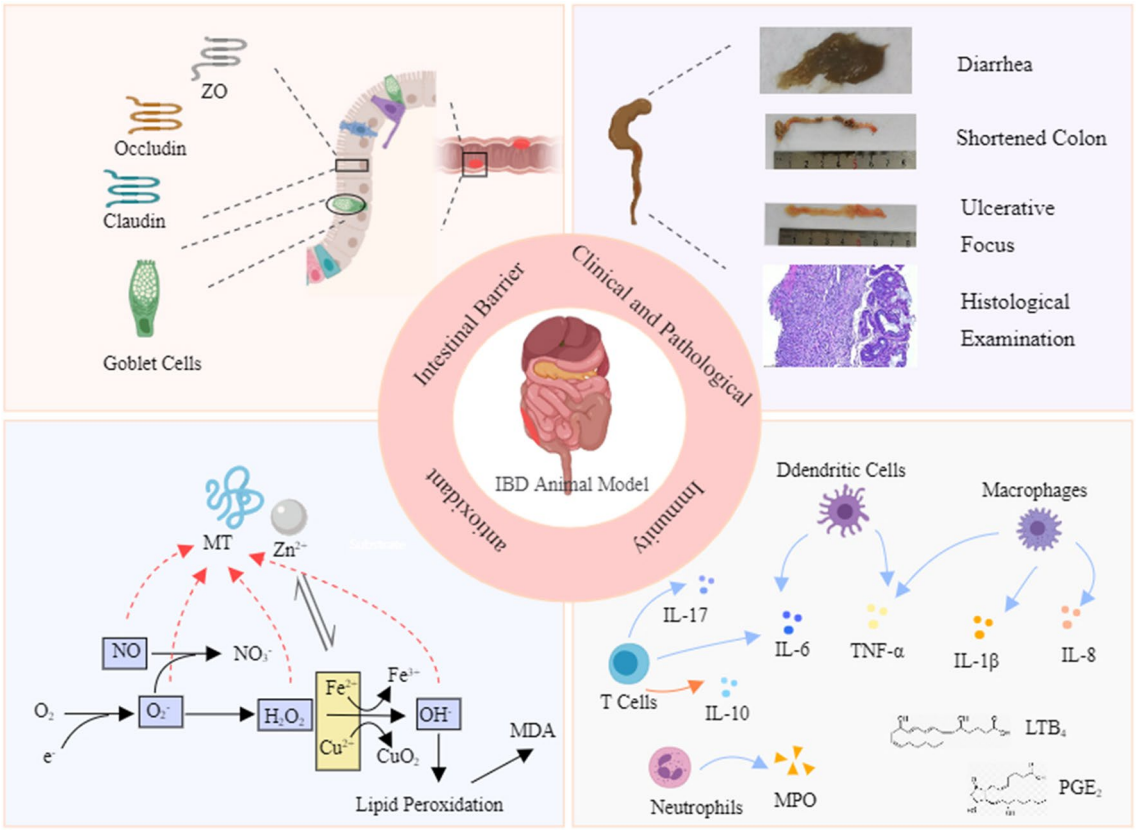

Fig. 2 Overview diagram of research on IBD animal model. The present studies involve clinical and pathological changes, and its mechanisms are about intestinal barrier, immune function, and antioxidant. Blue arrow: downregulation. Orange arrow: upregulation. Red dotted arrow: ROS combine with MT

Zinc and Antioxidant

Zinc participates in antioxidant activity by inhibiting oxidase activity, promoting antioxidant activity, inducing metallothionein (MT) gene expression, and competing with copper and iron ions.

Zinc is an inhibitor of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which acts as an electron donor and catalyzes the generation of oxygen (O_2) and generates superoxide (O_2^-). Zinc is also a cofactor of superoxide dismutase (SOD), which catalyzes the dismutation of O_2 to H_2O_2 [119, 122, 123]. During the pathogenesis of IBD, it has been found that reactive oxygen species (ROS) and malondialdehyde (MDA) levels were significantly increased, while glutathione (GSH) levels were significantly decreased [65, 66]. Interestingly, supplementary of zinc alone or in combination with other drugs can reduce MDA and nitric oxide (NO) levels and significantly increase SOD and GSH levels, indicating that zinc has antioxidant effects on experimental colitis [75, 124].

Table 3 The therapeutic mechanisms of zinc in IBD animal models

Direction	Relevant results	Reference
Intestinal barrier	Decrease the macroscopic CMDI score; restore the damaged mucosal structure; increase the thickness and width of intestinal mucosa; increase goblet cells and secreted mucus; increase expression of claudin-1, occludin, and tight junction protein 1	[75, 79, 81, 83, 88, 99]
Immunity	Reduce mucosal MPO activity, PGE2, and LTB4 levels; increase anti-inflammatory cytokines in intestinal tissue	[66, 83, 109, 115]
Antioxidant	Reduce MDA and NO levels; increase SOD and GSH levels; reduce MT gene expression; antagonize copper and iron ions	[75, 120, 124]
Microbiota	Increase the Lactobacillus and Bifidobacterium; decrease the Enterobacter, Enterococcus, and *S. aureus*	[65]

MT is a small molecule protein containing homocysteine [125], which is an effective electrophilic scavenger and anti-oxidant [126]. MT can capture various ROS, including O_2^-, H_2O_2, OH^-, and NO [127]. MT can regulate zinc homeostasis by binding with 20% intracellular zinc [125]. Under oxidative stress conditions, micronutrients are released from their complexes with MT and redistributed within cells to exert antioxidant effects [120]. The expression of endogenous MTs can be stimulated by moderate dietary zinc supplementation. By transcriptomics analysis, it was demonstrated that high-dose dietary zinc can induce the expression of MT-encoding genes in the colon of healthy mice and has a significant protective effect on colitis in mice [128]. Using wild-type (MT + / +) and MT-null (MT − / −) mice as the research object, zinc treatment suppressed DSS-induced colitis particularly in MT + / + mice [92]. In the DSS-induced mouse colitis model, MTs exert a protective effect on colonic mucosal inflammation through their anti-inflammatory effect on macrophages, while MT deficiency can exacerbate the disease [87].

In addition, Fe^{2+} and Cu^{2+} can catalyze H_2O_2 to generate OH^-, while Zn^{2+} can replace these redox active metals and reduces OH^- generation through competing with Fe^{2+} and Cu^{2+} ions and binding to cell membranes and proteins [119, 122]. It is worth noting that zinc supplementation is helpful for the recovery of IBD, but its dosage should be well controlled, as excessive zinc can lead to side effects which is related to the antagonized levels of Cu and Fe [129].

The overview of the relationship between zinc and IBD animals is shown in the Fig. 2, and the therapeutic mechanisms are listed in Table 3.

Conclusion

In this review, substantial evidence highlights the significant role of zinc interventions in mitigating the progression of IBD in clinical patients and animal models. Zinc plays an important role in maintaining intestinal homeostasis including modulating mucosal barrier integrity and immune response and maintaining the balance of redox state and gut microbiota.

Intestinal immune dysfunction is one of the important mechanisms of IBD, but there is limited research on the immune related mechanisms when studying the effect of zinc levels on IBD. In clinical study, zinc supplementation has been found to mainly regulate T cell subsets. However, in the researches of animal models, changes in polymorphonuclear leukocytes are of greater concern. Hence, the identification of disease-specific alterations in the mucosal immune function is of utmost importance to further study the immune-related mechanisms. Consequently, it is imperative to conduct further trials in order to determine appropriate zinc dosage for providing a certain positive outcome of using zinc supplementation as adjunctive therapy for IBD.

Zinc NPs are widely used as an animal feed additive because zinc NPs have higher bioavailability and can effectively improve animal growth performance compared to traditional zinc sources [130, 131]. Meanwhile, NPs have unique physicochemical properties such as targeting to the site of inflammation and altering the pharmacokinetics of other drugs [132]. Therefore, zinc NPs have the prospect of being used in clinical practice in IBD, so designing new NPs and clarifying its effects are worthy of further vigorous exploration.

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Author Contribution X. Peng determined the title and structure of this review and guided throughout the review writing process. Y. Yang and R. Zhong conducted the initial draft writing. All other authors participated in the improvement and revision of the paper and have given the final approval of the manuscript to be published.

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Data Availability No datasets were generated or analyzed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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