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Review Article

Applications of Metal–polyphenol Networks in the Treatment of Enteritis: A review

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Graphical Abstract

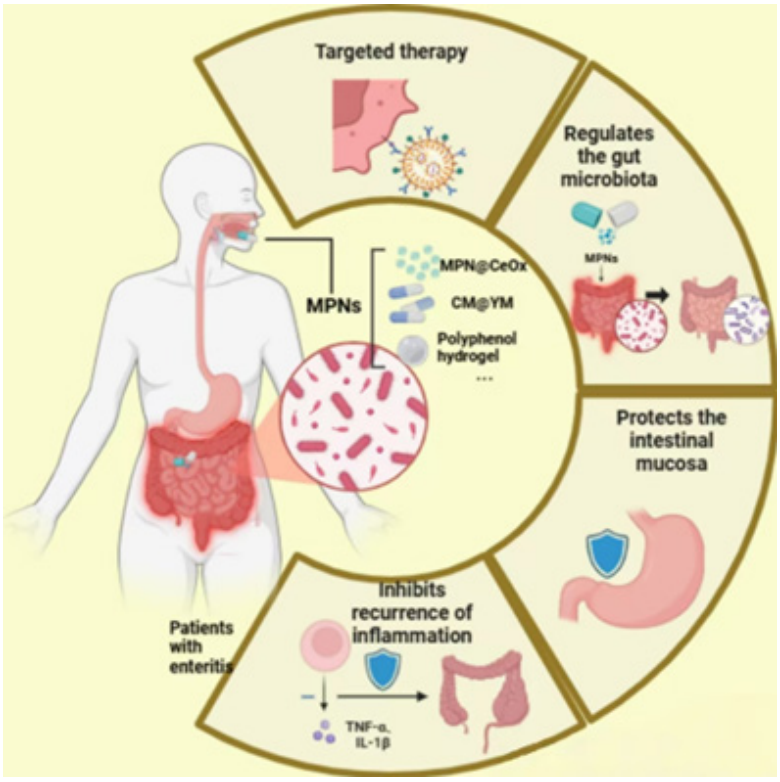

Figure 1:

Abstract

The number of patients experiencing enteritis has increased significantly worldwide. Conventional treatment methods may alleviate enteritis symptoms but often exhibit side effects or poor efficacy. Furthermore, many of the new treatment options being explored by the medical community are associated with numerous challenges. Metal–polyphenol networks (MPNs) are a new class of biomedical materials that exhibit excellent stability and biocompatibility, with strong antibacterial, antioxidant, adsorption, and pH-responsive properties. In recent years, MPNs have shown considerable application potential and unique advantages in the treatment of enteritis. This review summarizes current research progress on the use of MPNs in the prevention and treatment of enteritis and discusses their potential clinical application value. Continued advances in research and technological development are expected to position MPNs as a preferred treatment approach, providing improved therapeutic effects and quality of life for patients with enteritis.

Keywords: Metal–polyphenol networks, Enteritis, Enteritis Treatment

Abbreviations: MPNs: Metal–Polyphenol Networks; IBD: Inflammatory Bowel Disease; ROS: Reactive Oxygen Species; SPI2: Salmonella Pathogenicity Island Type 2; T3SS: Type III Secretion System; NSP1: Non-Structural Protein; IFN: Interferon; CD: Crohn's Disease; UC: Ulcerative Colitis; SCFAs: Short-Chain Fatty Acids; EGCG: Epigallocatechin Gallate; DSS: Dextran Sodium Sulfate; IL: Interleukin; TLR: Toll-Like Receptor; PI3K: Phosphatidylinositol 3 Kinase; TNF: Tumor Necrosis Factor; NF: Nuclear Factor; GA: Gallic Acid; TA: Tannic Acid; H_2O_2: hydrogen peroxide; •OH: hydroxyl radicals; ICD: Immunogenic cell death; FDEP NPs: Fe^{3+}-polyphenol-DOX-EGCG coordination nanoparticles; DOX: doxorubicin; NPs: Nanoparticles; MRSA: Methicillin-Resistant *Staphylococcus Aureus*; CA: Cellulose Acetate; HPA: An Antibacterial, Antioxidant, and Anti-inflammatory Nanocomposite; LD50: The Median Lethal Dose; PCA: Procyanidin; ALP: Alkaline Phosphatase; PGG: Pentagalloyl Glucose; HAase: Hyaluronidase; LBL: Layer-by-layer; EcN: *Escherichia coli* Nissle; BSA: Bovine Serum Albumin; TAF: The Doxorubicin (DOX)-loaded tannic acid (TA)-iron (Fe) network; MRI: Magnetic Resonance Imaging; PG@Cu–FP: Multifunctional Penta-Peptide Functionalized Polyphenol-Copper Nanoparticle Network; EcN@Fe-TA@mGN: MPN formed by Crosslinking the Fe3+–TA Network with Carboxymethylated β-glucan; uPA: Urokinase-type Plasminogen Activator; AIE: Aggregation-induced emission; FI: Fluorescence Imaging

Introduction

Enteritis is an inflammatory disease of the intestine, threatening the health of many individuals. The incidence of enteritis is rising continuously in Asia [1], imposing a heavy medical burden on society as patients must receive long-term treatment to avoid severe complications [2]. In this review, enteritis is categorized into viral enteritis, bacterial enteritis, parasitic enteritis, and Inflammatory Bowel Disease (IBD), with IBD representing a distinct subtype of enteritis characterized by chronic, immune-mediated intestinal inflammation. Sigurgeir *Olafsson et al*. sequenced 446 colon crypts from 46 patients with IBD, a cause of enteritis, and reported altered cell mutation and clonal structures compared to control crypts [3]. Furthermore, necrotic apoptosis of the intestinal stem cells induced by genomic instability can trigger intestinal inflammation [4]. The growing risk of IBD in humans is closely linked to high levels of psychological stress [5], advancing urbanization, and increasing westernization of dietary habits [6], particularly in regions experiencing rapid economic development, where the incidence of enteritis is considerable and has become an urgent clinical issue.

There are many existing treatment methods for enteritis, each with its own advantages and limitations. Drug treatments are expedient but may produce side effects, especially when using antibiotics, that can imbalance gut microbiota and lead to the development of bacterial resistance over long-term use [7]. Furthermore, nutritional therapy is slow and requires long-term adherence, surgical treatment is invasive and carries risks, and traditional Chinese medicine has a long treatment cycle using therapies that may not be supported by evidence. These limitations necessitate the development of low-side-effect drugs, reduction in antibiotic dependence, exploration of efficient non-pharmaceutical therapies, and proposal of new surgical pathways for enteritis treatment.

In recent years, Metal–Polyphenol Networks (MPNs) have emerged as an innovative organic–inorganic hybrid biomaterial. For example, a colorless antibacterial and deodorizing MPN coating made from the rapid assembly of plant polyphenols and silver ions has shown significant inhibitory effects against enveloped viruses, Gram-positive and Gram-negative bacteria, and fungi; experiments confirmed that this MPN coating provided far superior inhibition efficiency against the Phi6 virus compared to that of other metal ion coatings and maintained excellent antibacterial performance even after multiple washes [8]. Furthermore, MPNs can enhance the bioavailability of polyphenols in tumor treatment, exert immune-regulating effects, inhibit tumor growth, and serve as multifunctional nanoplatforms to improve the targeting and effectiveness of tumor therapies [9]. They can also enhance antibacterial and antifungal activities against oral infections, effectively killing *Streptococcus mutans*, *Enterococcus faecalis*, and *Candida albicans* through enzyme-like oxidation and photothermal effects [10]. Ligand MPN nano enzymes can efficiently scavenge Reactive Oxygen Species (ROS), protect cells from oxidative damage, and promote diabetic wound healing through epithelial regeneration, collagen deposition, angiogenesis, and immune regulation [11].

The use of MPNs for the treatment of enteritis is quite promising owing to their immune-regulating properties, ability to inhibit the development of inflammation by enhancing bioavailability, and applicability as multifunctional platforms to improve treatment targeting. They can also scavenge ROS, protect intestinal cells, and accelerate the healing of inflammation, and their strong antibacterial activity effectively inhibits the growth of harmful bacteria in the intestine [12], reduces inflammatory responses, providing direct relief to patients. The antioxidant capacity associated with MPNs is also noteworthy as it can eliminate excess free radicals in the body, reduce oxidative stress damage to the intestines, and protect the integrity of the intestinal mucosa [13]. Finally, the excellent bio adhesive properties of MPNs allow them to adhere closely to the surface of the intestinal mucosa where they form a robust protective layer that promotes intestinal repair and regeneration while providing patients with lasting protection [14]. As such, the application of MPNs for the treatment of enteritis is expected to rapidly cure this disease.

In summary, the prospective application of MPNs to treat enteritis are quite broad as their unique structural and functional characteristics provide ideas and solutions for addressing the many challenges associated with enteritis treatment. This review accordingly explores the characteristics of MPNs as well as their application prospects for enteritis treatment to provide a theoretical basis and practical reference for the development of new enteritis treatment methods.

Causes of Enteritis and Current Methods for Treatment

Enteritis refers to inflammatory lesions in the intestines leading to pathological changes such as damage to the intestinal mucosa, congestion, and edema; it can be caused by a variety of factors, including bacteria, viruses, parasites, and IBD.

Bacterial Enteritis

Bacterial enteritis is caused by bacteria including *Salmonella*, *Shigella*, and *Vibrio parahaemolyticus*. Upon entering the human body, Salmonella specifically attacks the epithelial cells of the ileum and colon [15] while utilizing the proteins encoded by Salmonella Pathogenicity Island Type 2 (SPI2) to form replication vacuoles within the cells, allowing for extensive proliferation and enabling the bacteria to evade host immune clearance mechanisms. Experiments conducted in mouse models have shown that *Salmonella* lacking the SPI2 type III secretion system (T3SS) exhibits a significantly reduced migratory ability. This finding confirms that SPI2 T3SS effector proteins promote the transport of *Salmonella*-containing vacuoles to facilitate their migration from the apical side to the basolateral side of intestinal epithelial cells [16]. The proteins encoded by these gene clusters disrupt the normal physiological functions of host cells, leading to cell death and tissue damage, which in turn cause neutrophilic gastroenteritis [17].

Howlader et al. observed that Shigella enters the adult zebrafish body through the intestine, where it subsequently proliferates throughout the gut and triggers an inflammatory response that causes intestinal inflammation accompanied by the infiltration of neutrophils and phagocytes [18]. Notably, Shigella is able to suppress inflammatory responses to evade host immune surveillance [19] and has developed resistance to various antibiotics, including first-line antibiotics such as ciprofloxacin [20]. These factors contribute to challenges in effectively curing Shigella-induced enteritis using existing treatments.

Finally, *Vibrio parahaemolyticus* causes enteritis through its unique virulence and intestinal colonization ability [21], which is facilitated by the direct injection of T3SS-2 effector proteins [22], such as VopY, into the intestinal epithelial cell membrane, where they interfere with normal cell functions, damaging or even killing cells and triggering an inflammatory response in the intestine. Critically, when intestinal epithelial cells are damaged, they release inflammatory factors that attract immune cells such as neutrophils to the site of inflammation, further exacerbating the inflammatory response [23]. Current treatment methods for bacterial enteritis include the use of antibiotics to control infections. However, long-term use or abuse of antibiotics can lead to bacterial resistance, and while antibiotics kill harmful bacteria, they can also harm beneficial bacteria, resulting in an imbalance in gut microbiota that necessitates the use of probiotics to improve the intestinal microenvironment [24].

Viral Enteritis

Viral enteritis is primarily caused by *Rotavirus*, *Norovirus*, and *Adenovirus* infections. Rotavirus enters cells through endocytosis by binding its VP4 and VP7 surface proteins to receptors on the surfaces of host intestinal epithelial cells. After entering a cell, the virus releases its RNA genome and utilizes the translation and replication mechanisms in the host cell to synthesize viral proteins and replicate RNA [25]. The non-structural protein (NSP1) plays a crucial role in this process by antagonizing the host Interferon (IFN) signaling pathway to promote viral replication within the cell [26]; however, the metabolic products generated by NSP1 during viral replication can also damage the intestinal epithelial cells. Critically, the replication and pathogenic effects of Rotavirus proteins in intestinal epithelial cells can impair intestinal barrier function.

Hassan et al. demonstrated that *Norovirus* infections significantly altered the composition of the intestinal microenvironment, disrupting the normal gut flora and leading to intestinal inflammation in mice [27]. Moreover, as *Norovirus* is an RNA virus [28], it is prone to mutations that have hindered efforts to develop a vaccine against it, leaving the treatment of Norovirus-induced enteritis without targeted solutions. Finally, *Hemmi et al*. studied the pathogenic mechanisms of Adenovirus in mice, reporting that it enters intestinal epithelial cells through receptor-mediated endocytosis [29]. Once viral deoxyribonucleic acid DNA

enters the cell nucleus, it utilizes the transcription and translation systems of intestinal epithelial cells to synthesize viral proteins and replicate its own DNA. After these components are assembled into new viral particles, they are released into the extracellular space via cell lysis or exocytosis [30]. No specific antiviral drugs are currently available for most cases of virus-induced enteritis.

Parasitic Enteritis

Parasitic enteritis is an infectious disease caused by an invasion of parasites into the intestinal tract. The pathogens responsible for parasitic enteritis include *Schistosoma japonicum*, *Ascaris lumbricoides*, and hookworms. The pathogenesis of schistosomiasis-induced enteritis primarily involves the deposition of eggs in the intestinal wall tissue, which leads to cellular infiltration and the formation of egg granulomas that produce tissue necrosis and inflammatory responses, triggering enteritis [31]. The pathogenesis of *Ascaris*-induced enteritis involves the activity of *Ascaris* larvae or adults in the intestinal tract, which irritates and damages the intestinal mucosa, leading to inflammatory responses and intestinal diseases [32]. Finally, the pathogenesis of hookworm-induced enteritis primarily involves the presence of hookworm larvae or adults in the intestinal tract, where they obtain nutrients by consuming the host's blood, damaging the intestinal mucosal epithelial cells, inducing inflammatory responses and forming ulcers [33].

Treatments for parasitic enteritis include drug and immunomodulatory therapies using antiparasitic drugs such as albendazole or metronidazole. These drugs can effectively kill or inhibit the growth of parasites to alleviate the symptoms caused by parasitic infections. However, the use of such drug therapies is limited by potential side effects and the possibility of targeted parasites developing drug resistance [34]. Additionally, the accurate diagnosis of parasitic infections can be difficult, leading to untimely treatment or inappropriate drug selection. Finally, parasitic infections may be accompanied by other complications, such as intestinal obstruction or intestinal perforation, that obscure the cause of the issue.

IBD

A chronic and recurrent inflammatory disease of the intestinal tract, IBD can be generally classified as resulting from either Crohn's Disease (CD) or Ulcerative Colitis (UC). The pathogenesis of IBD is extremely complex as it involves genetic, environmental, immune, and microbial factors. Genetically, patients with IBD typically possess multiple susceptibility gene mutations that can affect the intestinal immune balance, increasing abnormal immune responses to intestinal microbes. Genome-wide association studies have identified multiple gene variants associated with IBD that are involved in pathways related to immune regulation, cell signalling, and apoptosis [35]. In particular, the ATG16L1 and NOD2 genes play critical roles in the regulation of intestinal health: the former is involved in autophagy, and its mutations affect bacterial clearance and exacerbate intestinal inflammation; the latter recognizes microbes, and while its mutations increase the risk of IBD, they can alleviate inflammation owing to specific bacteria [36]. Indeed, the interaction between these two genes may be disrupted by NOD2 mutations, leading to impaired autophagy. Studies have shown that the absence of ATG16L1 enhances the inflammatory response under endoplasmic reticulum stress, particularly through the ATF6 pathway [37], thereby promoting the expression of pro-inflammatory factors. These findings reveal the complex role of gene mutations in intestinal inflammation.

Immune dysregulation forms the core of IBD pathogenesis. This occurs when immune cells in the body, such as T cells, B cells, and macrophages, respond abnormally to gut microbiota, leading to persistent inflammation of the intestinal mucosa [38]. Ileum and colon biopsies were performed on 71 patients with CD and 25 control patients to conduct single-cell RNA sequencing analyses of 720,633 cells. Significant changes in the compositions of the immune cells were observed in the inflamed areas, particularly in T and myeloid cells [39].

Finally, gut microbiota also plays a key role in IBD pathogenesis. Metabolites produced by gut microbiota, particularly Short-Chain Fatty Acids (SCFAs) and indole derivatives, are critical to maintaining intestinal homeostasis: the former protect gut health by influencing cellular energy metabolism and epithelial barrier function, whereas the latter suppress inflammation by regulating immune response [40]. Gut microbiota generates SCFAs through the fermentation of dietary fiber, which helps to maintain epithelial barrier function. Notably, an Epigallocatechin Gallate (EGCG)-rich diet promotes the proliferation of *Akkermansia* and increases SCFA production, enhancing intestinal antioxidant capacity and inhibiting pro-inflammatory factors to alleviate Dextran Sodium Sulfate (DSS)-induced colitis. Fecal microbiota transplantation experiments have shown that SCFA-rich microbiota significantly improved IBD symptoms in recipient mice by enhancing antioxidant and anti-inflammatory effects [41]. Exposure of the HCT-8 human intestinal epithelial cell line to indole strengthened the mucosal barrier and mucin-related genes expression, downregulated pro-inflammatory interleukin (IL)-8, upregulated anti-inflammatory IL-10, and enhanced transepithelial resistance and barrier function. Furthermore, indole pretreatment reduced the attachment of enterohemorrhagic *Escherichia coli* to cells, thereby decreasing pathogen colonization. Finally, indole upregulated the anti-inflammatory Toll-Like Receptor (TLR) and Phosphatidylinositol 3 Kinase (PI3K) pathway genes to regulate the TLR signaling pathway and inhibit Tumor Necrosis Factor (TNF)-α-mediated Nuclear Factor (NF)-κB activation, demonstrating significant anti-inflammatory effects [42]. Critically, the reduction of these beneficial metabolites in the intestines of patients with IBD may exacerbate disease progression by promoting inflammation and damaging epithelial barrier function. Environmental factors such

as diet, smoking, medication use, and infections may also trigger or exacerbate IBD pathology by altering the gut microenvironment. A Western lifestyle, which is characterized by a high-calorie, high-fat, low-fiber diet and lack of exercise, may increase the risk of developing IBD by adversely affecting the gut microbiota and mucosal barrier function [43].

MPNs

Definition

Generally, an MPN is a supramolecular framework material formed by the self-assembly of metal ions and polyphenolic compounds via coordination. Common polyphenolic compounds include catechins and Gallic Acid (GA) esters, which undergo spontaneous oxidation reactions to form quinone groups under aerobic and alkaline conditions. The quinone group contains two adjacent C=O bonds and at least one H atom that can be replaced by other functional groups. This unique structure enables the acquisition of other functional groups through addition or Schiff-base reactions, thereby allowing polyphenolic compounds to obtain the associated functionalities [44].

Components and Assembly Methods

Composition: The components of an MPN include metal ions and phenolic ligands [45]. When an MPN is used to treat enteritis, the metal ions generate excess ROS while the phenolic ligands—primarily polyphenolic substances that possess antioxidant capabilities—eliminate these ROS [46], thereby maintaining homeostasis in the intestinal microenvironment. Metal polyphenol network covers capsule [47], coating [48], hydrogel [49] and other forms.

***Ions*:** The metal ions present in MPNs include those of iron, copper, zinc, and silver. Iron ions (Fe^{3+}) participate in oxygen transport and energy metabolism; their homeostasis is crucial for maintaining intestinal health in terms of the microbiota composition and immune function [50]. An Fe^{3+}–Tannic Acid (TA) film is the most common MPN coating material. The addition of Fe^{3+} to an MPN can enhance its antioxidant performance and effectively eliminate free radicals. The coordination bonds between Fe^{3+} and polyphenols break under the low pH and high adenosine triphosphate conditions in the tumor environment, releasing Fe^{3+} that reacts with extant hydrogen peroxide (H_2O_2) via the Fenton reaction to generate hydroxyl radicals (•OH), thereby inducing Immunogenic Cell Death (ICD) in tumor cells and releasing tumor antigens [51]. Furthermore, the bridging role played by Fe^{3+} during coordination enhances the lignin and plant tannin-based dual polymorphonuclear neutrophils developed through pH-controlled self-assembly to achieve high uniformity and controllable synthesis of the MPN. The addition of Fe^{3+} provides this lignin-based neutrophil-derived material with efficient purification capabilities as well as magnetic responsiveness, facilitating the recovery and reuse of the MPN [52]. Furthermore, Fe^{3+} coordinates with polyphenols to enable the disintegration of FDEP NPs (Fe^{3+}-polyphenol-DOX-EGCG coordination nanoparticles), representing a multifunctional nanoplatform engineered through Fe^{3+}-mediated coordination-driven self-assembly between polyphenolic ligands, which simultaneously encapsulates chemotherapeutic agent Doxorubicin (DOX) and the bioactive polyphenol Epigallocatechin Gallate (EGCG). Nanoparticles (NPs) release drugs in the acidic tumor environment, thereby achieving targeted controlled release. They can also enhance the ability of EGCG to inhibit CBR1, improving the anticancer effect of doxorubicin while reducing cardiotoxicity [53]. Interestingly, GA has been self-assembled with Fe^{3+} to form an MPN for hair dyeing, eliminating the irritating components of traditional hair dyes while reducing hair damage owing to the use of relatively non-toxic iron. A 21-d experiment conducted on mice verified the safety of this MPN-based hair dye, reporting no adverse reactions on mouse skin; blood tests indicated that the levels of inflammatory factors were normal with no impact on hair regeneration ability [54]. This demonstrates the excellent biocompatibility of MPN technology and provides a solid foundation for future applications. Finally, the MPN formed by Fe^{3+} and TA has been shown to endow hydrogel with photothermal antibacterial activity and enhance its mechanical strength, stability, and durability, making it suitable for treating skin wounds at joints [55].

Copper ions (Cu^{2+}) are cofactors for various metabolic enzymes and participate in key biological processes such as cellular respiration and antioxidant defense [56]. They bind with polyphenol ligands (such as the phenolic group in polyethylene glycol-polyphenol-chlorine(e6)) through metal–phenolic coordination bonds to form a stable MPN structure [57]. This coordination is fundamental for the successful assembly of an MPN. Furthermore, Cu^{2+} significantly enhances the antibacterial properties of MPN NPs against bacteria such as Methicillin-Resistant *Staphylococcus Aureus* (MRSA), even at low concentrations [58]. The use of Cu^{2+}–EGCG MPN NPs was shown to accelerate wound healing by promoting cell proliferation and migration with excellent antibacterial properties and high biocompatibility; both *in vivo* and *in vitro* experiments confirmed these significant effects [59]. Notably, an MPN containing Cu^{2+} is easily degradable as the coordination bonds between the Cu^{2+} and polyphenols can be disrupted under acidic conditions. Experiments have shown that MPNs containing Cu^{2+} are more easily degraded in acidic environments or in the presence of metal chelators (such as sodium diethyl dithiocarbamate), where they can release any encapsulated substances [60]. Furthermore, the presence of Cu^{2+} can enhance the antioxidant effects of an MPN while improving its mechanical properties by forming a stable cross-linked structure that increases rigidity and strength. These ions also promote cell migration and angiogenesis and regulate the expression of the vascular endothelial growth factor and matrix metalloproteinases. Thus, they exhibit antibacterial and antioxidant properties to prevent infections, scavenge free radicals, and accelerate wound healing [61].

Zinc ions (Zn^{2+}) act as cofactors for enzymes and proteins that are crucial for processes including signal transduction and gene expression regulation and are vital for immune system function, antioxidant activity, growth and development, and neurological function [62]. They possess inherent antibacterial activity through various mechanisms, including disrupting the negative charge balance of bacterial membranes, affecting DNA replication, and reducing bacterial enzyme metabolism. These antibacterial effects can be enhanced by binding the MPN with Cellulose Acetate (CA) [63]. Shao prepared hollow nanohybrids using polyphenol-coordinated zeolitic imidazolate framework 8 to realize precise pesticide release and effective inhibition of grey mold pathogens [64]. Notably, the coordination of Zn^{2+} with polyphenols endows an MPN with ROS responsiveness; EGCG/Zn capsules have been shown to accelerate the release of Zn^{2+} in the presence of H_2O_2, exhibiting the additional ability to effectively function in oxidative stress environments such as that present in ischemia [65]. The presence of Zn^{2+} in an MPN also enhances stability coordination, regulates the corrosion rate, improves biological functions, and synergistically exerts antibacterial effects to reduce inflammatory responses and thereby improve overall MPN performance [66]. In addition, Zn^{2+} can impart antiviral capabilities to an MPN; the combination of Zn^{2+} with polyphenolic flavonoid carriers (such as EGCG, quercetin, or taxifolin) significantly elevated intracellular zinc levels and markedly enhanced the inhibition of viral replication compared to the use of zinc alone. This mechanism is effective against various RNA viruses, suggesting broad prospects for antiviral applications, and may aid in the treatment of virus-induced enteritis [67].

Silver ions (Ag^+) achieve broad-spectrum antibacterial effects by disrupting bacterial cell membrane permeability, inactivating proteins, and hindering DNA replication. However, their non-selectivity may lead to cytotoxicity [68]. A pH-responsive silver-loaded system was integrated into a hydrogel to precisely regulate the release of Ag+ in the acidic environment of acute infection wounds, realizing therapeutic effects while avoiding potential toxicity owing to sudden release [69]. The application of GA–Ag^+ NP sodium alginate hydrogels was shown to significantly accelerate the healing of MRSA-infected wounds in a rat skin defect model, achieving almost complete healing within 14 d. Indeed, Ag^+ demonstrates excellent biocompatibility and accelerates the healing process through mechanisms that include reducing bacterial counts, decreasing the expression of inflammatory factors, and promoting angiogenesis to significantly lower IL-6 and TNF-α expression [70]. Furthermore, Ag^+ plays a key role in an antibacterial, antioxidant, and anti-inflammatory nanocomposite (called HPA) nanocomposites used in the early stages of wound healing; simultaneously, Ag^+ regulates the inflammatory response by reducing the upregulation of pro-inflammatory cytokines, thereby alleviating the negative impact of excessive inflammation on tissue regeneration. This dual action mechanism provides HPA with significant therapeutic potential for use in burn wound healing [71].

Phenolic ligands: The polyphenols used in MPNs include TA, GA, dopamine, catechol, and EGCG. Simple phenolic ligands, such as TA, are commonly used to assemble MPNs [72]. When applied to treat nematode infections, the tannins in TA can reduce the degradation of rumen proteins, regulate rumen metabolism, decrease the gastrointestinal infection rate, and affect SCFA concentrations; this improvement in rumen environment can enhance the host's resistance to stress [73]. A 0.15% tannin-coated MPN improved the daily weight gain and feed intake of weaned piglets, reduced the incidence of diarrhea, increased crude protein digestibility and digestive enzyme activity, improved intestinal structure and function, optimized gut microbiota, and enhanced butyrate and tryptophan metabolism [74]. Furthermore, the presence of TA alleviates glyphosate-induced oxidative stress by inhibiting the ROS/phosphatase and tensin homolog/PI3K/protein kinase B pathways and counteracting hepatocyte apoptosis, necrosis, and immune disorders to protect the liver, reflecting considerable potential in alleviating chemical cytotoxicity [75]. Finally, tannins also reduce digestibility and fermentation in the gastrointestinal tracts of pigs, which may reduce food intake [76]. Thus, tannins may enable patients with enteritis to achieve effects that previously required a reduction in food intake.

Most of the biological activity of GA, an organic acid with phenolic and carboxylic acid groups, is attributed to the former, which react with free radicals to form stable semiquinone radicals, thereby preventing free radical chain reactions and reducing oxidative damage. The presence of GA can increase the activity of antioxidant enzymes (such as superoxide dismutase, glutathione peroxidase, and catalase) while promoting the synthesis of non-enzymatic antioxidants (such as glutathione), thereby enhancing cellular antioxidant defense [77]. Critically, the median lethal dose (LD50) of GA in mice was greater than 2000 mg/kg with no significant effects on hematological, histopathological, or behavioral parameters, confirming its safety [78]. Furthermore, GA can reduce the release of inflammatory cytokines, chemokines, and adhesion molecules while limiting cell infiltration by inhibiting the activation of the mitogen-activated protein kinase and NF-κB signaling pathways, thereby attenuating the inflammatory response. It also exerts anti-inflammatory effects by regulating the TLR4/MyD88/TRIF domain-containing adaptor-inducing IFN-β signaling pathway [79]. Finally, GA prevents oxidative DNA damage which represents an essential aspect of enteritis treatment [80].

The presence of EGCG can inhibit inflammatory responses as well as inflammation-related enzyme activity to reduce the release of inflammatory mediators, including TNF-a and IL-6, that play key roles in the inflammatory response [81]. It also inhibits the signaling of NF-κB by increasing the expression of longevity factors such as Sirtuin 1 and Forkhead box O 3a, significantly reducing oxidative damage and inflammation [82]. Finally, EGCG alters the relative abundance of specific bacteria in the gut microbiota (e.g., increasing *Bifidobacterium* and *Faecalibaculum* while decreasing

Lactobacillus), affects the production of metabolic products (e.g., increasing prostaglandin E2), and regulates the gene expression of intestinal epithelial cells (e.g., restoring purine metabolism-related genes) [83].

Therefore, optimizing the selection and design of organic ligands, regulating the types and ratios of metal ions, and introducing functional modifications represent valuable strategies for designing easily functionalized MPNs. *Yunlu et al*. evaluated the use of polyphenol derivatives with specific biological activities, reporting that they not only retained the natural antioxidant and anti-inflammatory properties associated with polyphenols but may also enhance the molecular structures of specific functional ligands through chemical modifications, introduction, or optimization of functional groups for coordination with metal ions, and adjustment of the ligand molecular weight and spatial conformation to optimize MPN nanostructure and performance. Furthermore, the composition and performance of an MPN can be optimized by adjusting the ratios and concentrations of different metal ions, and ensuring a uniform distribution of metal ions in an MPN ensures that they exert the optimal synergistic effects. For example, the synergistic action of metal ions and polyphenol derivatives in NaGdF4: Nd@NaLuF4@polyethylene glycol-polyphenol/Mn activates the stimulation of the IFN gene pathway in the tumor microenvironment, which can initiate a natural anti-tumor immune response that transforms "cold" tumors into "hot" tumors [84].

Functional modifications of MPNs: *Xie et al.* successfully applied a natural plant-derived Polyphenolic Compound Called Procyanidin (PCA) to modify the artificial surface of CA bone membranes using an innovative functional modification strategy [85]. They utilized the pre-coordination of PCA with metal ions such as Zn^{2+}, Mg^{2+}, and Cu^{2+} to form an MPN that was cleverly deposited onto the surface the membrane, endowing it with immune-regulatory functions. The modified artificial bone membrane exhibited excellent stability and free-radical scavenging ability in physiological environments. *In vitro* and *in vivo* experiments further confirmed that this artificial bone membrane significantly improved the local immune microenvironment and effectively promoted the osteogenic differentiation of stem cells as well as the biological mineralization process, significantly accelerating the regeneration and repair of bone defects. In addition, MPNs can be combined with other substances to exert specifically designed effects. For example, coating MPNs with Alkaline Phosphatase (ALP) can hydrolyze monophosphate esters, including harmful components such as lipopolysaccharides in bacterial toxins, thereby playing a detoxifying role. Notably, the ALP produced by intestinal epithelial cells plays a major local and system-wide anti-inflammatory role while maintaining intestinal homeostasis and directly participating in intestinal barrier function, which is critical for reducing harmful toxins in the gut and alleviating intestinal inflammation [86]. An MPN comprising a Ti–6Al–4V alloy coated with EGCG and Mg^{2+} significantly enhanced ALP activity in human adipose-derived stem cells cultured in vitro. In addition, the application of an MPN to the surface of polydopamine NPs forms an MPN@polydopamine composite that has exhibited enhanced anti-inflammatory effects [87]. Arginine doping further promotes the release of anti-inflammatory components and enhances the overall anti-inflammatory capacity of an MPN, providing a new strategy for inflammation treatment [88]. Finally, *Sun et al*. designed a controllable-release MPN to provide macromolecular drug delivery using Pentagalloyl Glucose (PGG), an active ingredient in traditional Chinese medicine. PGG formed an MPN NP framework with Fe^{3+} and polyvinylpyrrolidone capable of encapsulating hyaluronidase (HAase). When this MPN was exposed to desferrioxamine, its disassembly promoted the release and activation of HAase, thereby degrading the extracellular matrices of tumor cells. Indeed, the inclusion of PGG significantly influenced the structure, enzyme activity regulation, responsiveness, and drug delivery of this MPN [89].

MPN Assembly Methods

Typically, MPNs can be assembled using two methods: Layer-by-Layer (LBL) deposition or single-step co-deposition. The LBL deposition method assembles an MPN one layer at a time on a substrate surface by alternating polyphenol and metal ion solutions. The assembly of an MPN using LBL deposition requires the preparation of solutions, their placement on the substrate, and repeated deposition of metal ion and polyphenol layers, followed by post-treatment, characterization, and testing. The specific steps employed in LBL deposition must be adjusted according to the materials used and the intended application [90]. For example, an MPN based on EGCG and Mg^{2+} was generated by selecting and pre-treating an AZ31 magnesium alloy substrate, preparing polyphenol and metal ion solutions, then repeatedly depositing layers through alternating immersion, washing, and drying steps before final curing; this was followed by a series of tests conducted to characterize the coating performance [91]. A simplified LBL deposition method was used to deposit CA coating on Escherichia coli Nissle 1917(EcN,) adsorb allylated gelatin, and finally undertake allyl modification before conducting light-induced thiol-ene crosslinking of gelatin to enhance the resistance of EcN to harsh gastrointestinal environments. Studies have shown that the oral administration of this coated EcN effectively alleviated colitis, reduced inflammation, repaired the intestinal barrier, cleared ROS, and restored microbial homeostasis in mice [92]. In contrast, the single-step co-deposition method involves the direct mixing of polyphenolic compounds with metal ion solutions to rapidly form an MPN by controlling the reaction conditions (such as pH, temperature, and concentration). *Zhang et al*. used the structural characteristics of tea polyphenols (such as EGCG) to develop a universal in situ single-step self-assembly method. This method rapidly and sustainably synthesizes MPN NPs by mixing tea polyphenols, alcohol abstinence metabolites (such as diethyldithiocarbamate), and metal ions (such as Cu^{2+}) in an aqueous phase under normal temperature and pressure

conditions [58].

In-depth research conducted on MPNs in recent years has developed several innovative assembly methods, such as the use of microbubble templates to prepare hollow MPN microcapsules in a single step. *Liqin et al*. used Bovine Serum Albumin (BSA) microbubbles as templates to form stable bubbles after heating and ultrasonic treatment. Mixing TA with metal ions (such as Fe^{3+}) in the BSA bubble suspension reduced the stability of the bubbles owing to the complexation of TA with BSA and their competitive coordination with the metal ions, promoting air escape facilitated by the semi-permeability of the TA–metal ion shell layer. Notably, this process does not require the removal of the template as it directly generates hollow MPN microcapsules using a simple preparation process. This avoids the impact of template dissolution on the encapsulated substances, a common issue associated with conventional hard-template methods [93], offering superior efficiency and broader application prospects.

Critically, different assembly methods lead to significant differences in the structure and physicochemical properties of the resulting MPN, including permeability, hardness, and degradability. For example, thin-film structures were prepared from TA and Fe^{3+} using the LBL and single-step methods; although the raw materials used to prepare the MPNs were the same, significant differences were observed in their microstructures, distributions of metal ions, and physical and chemical properties. In particular, the single-step co-deposition method rapidly formed a uniform and stable network through the mixing of polyphenols and metal ions, representing a considerable improvement in efficiency over that of the LBL deposition method; however, the LBL deposition method allows for the adjustment of reaction conditions to control the thickness and morphology of the MPN to satisfy the application requirements. In addition, the network formed by the single-step co-deposition method has been shown to be highly stable and easy to functionalize [94].

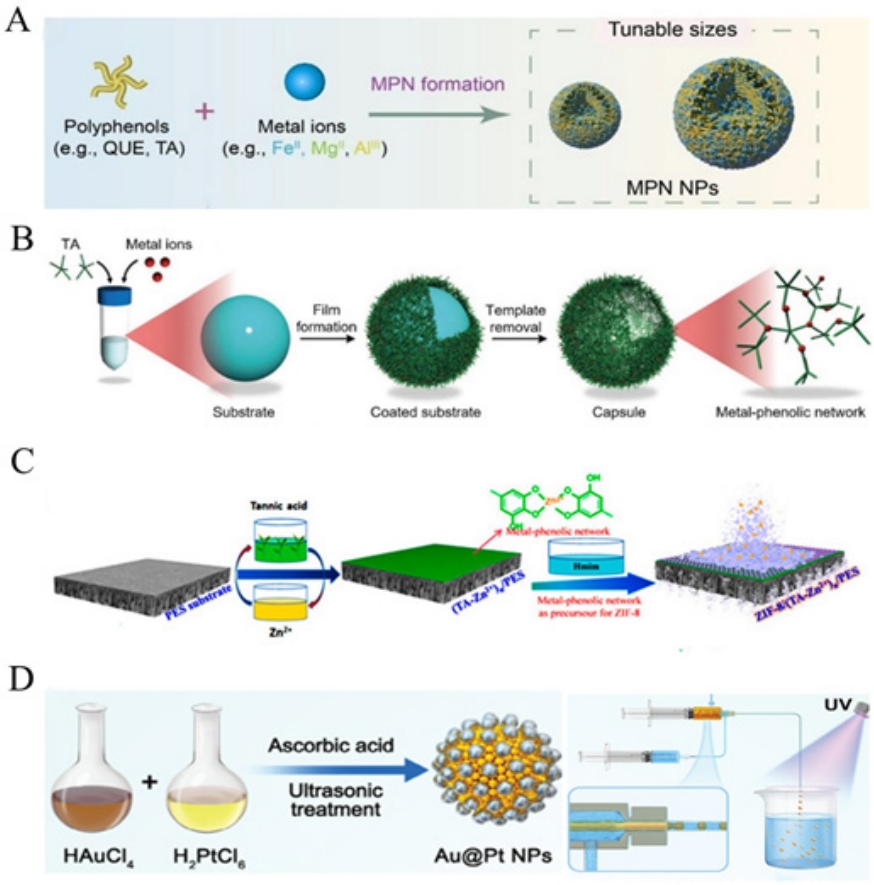

Figure 2: Diverse assembly methods for Metal-phenolic networks. A. Components of metal polyphenol network. Reprinted with permission from Ref [45] B. Schematic diagram of the composition of metal polyphenol network capsules. Reprinted with permission from Ref [47] C.Schematic diagram of metal polyphenol network coating composition. Reprinted with permission from Ref [48] D. Schematic Diagram of Metal Polyphenol Network Hydrogel Composition. Reprinted with permission from Ref [49].

The preparation of iron NPs containing tea extract using a single-step co-deposition method synchronously synthesized and removed heavy metals/metalloids from acidic mine drainage environments. The iron NPs synthesized using this method had a small particle size and large specific surface area but were prone to aggregation. Critically, the polyphenols and organic acids in the tea extract acted as complexing and reducing agents, which not only promoted the formation of iron NPs but also enhanced their surface adsorption capacity. This method is environmentally friendly, cost-effective, and easy to operate [95]. Furthermore, Fe^{3+}–TA cation films were fabricated in controlled thicknesses using LBL deposition and were shown to be extremely stable and insensitive to changes in ionic strength. These films were chemically stable at pH > 3 but dissolved rapidly upon contact with highly acidic solutions. At a pH of 5, electrostatic interactions within the films dominated over metal-coordination interactions and the TA experienced a shift in its acid dissociation constant. The film adsorption kinetics were fast and the film thickness increased linearly with the number of deposition cycles; a uniform particulate structure was consistently observed [96] (Figure 2).

Functional Characteristics of Mpns

Stability

The stability of MPNs protects *in vivo* drug activity, making these materials crucial for ensuring that delivered drugs do not lose efficacy in complex physiological environments; simultaneously, MPNs maintain the integrity of the delivery system to achieve the precise and controlled release of drugs over prolonged durations, thereby improving therapeutic safety. Notably, the presence of metal ions can affect the stability of a polyphenolic compound, and strong coordination between the two can form a more stable MPN structure. The stabilities of different MPNs have been confirmed through various multidimensional experiments. Chemical verification of the coordination effect using Fourier-transform infrared spectroscopy and ^{1}H nuclear magnetic resonance analysis indicated that TA stably binds with Pt^{2+}. Furthermore, pH-sensitive drug release experiments have shown that the MPN is stable in physiological environments and can be controllably dissociated under acidic conditions, while viscosity analyses conducted under dilution conditions, evaluations of fluorescence quenching effects, and other tests demonstrated its colloidal stability and structural integrity. Finally, co-culture experiments conducted with BSA indicated that TA modification enhanced the anti-protein adsorption capacity of an MPN; thermogravimetric analyses and dynamic light scattering/transmission electron microscopy results further validated its thermodynamic and physical stability [97]. In summary, MPNs exhibit excellent stability in circulation.

Antibacterial Activity

The antibacterial activity associated with MPNs, which stems from both the polyphenolic compounds and metal ions within, are crucial aspects of enteritis treatment. Indeed, MPNs can effectively alleviate inflammation, inhibit the growth of harmful bacteria, protect beneficial bacteria, and restore the balance of intestinal microbiota. The significant antibacterial activities of TA make it a particularly critical component of an MPN, as it disrupts the stability of bacterial cell membranes, penetrates them, and inhibits enzymatic activity within. Research has shown that ROS are generated in multicomponent metal ion-containing aqueous solutions through electron transfer by enzymes [98], while the Fenton reaction forms the primary synergistic antibacterial mechanism; this combines the advantages of biocatalysis and chemical oxidation to effectively destroy bacterial cells and inhibit their growth and reproduction [99]. Critically, the antibacterial capabilities of MPNs do not contribute to the development of microbial resistance, making them promising candidates for new antibiotics.

Antioxidant Properties

The antioxidant properties of MPNs play critical roles in the treatment of enteritis. The excessive oxidative stress often present in the intestines during enteritis can damage intestinal cells and exacerbate inflammatory symptoms. An MPN with excellent antioxidant performance can scavenge free radicals to reduce oxidative stress and thereby protect intestinal cells from damage while promoting the resolution and repair of intestinal inflammation. The antioxidant effect of an MPN is primarily generated by the phenolic hydroxyl groups in its polyphenolic compounds, which donate hydrogen or electrons to react with and eliminate free radicals from the body. Notably, the phenolic hydroxyl groups in TA only partially coordinate with the metal ions to form the MPN structure; the remaining phenolic hydroxyl groups endow the MPN with its antioxidant capabilities. Indeed, free-radical scavenging experiments indicated that an MPN membrane significantly reduced the characteristic absorption peak of 2,2-diphenyl-1-picrylhydrazyl, confirming its antioxidant ability [100]. Furthermore, the antioxidant capacity of the MPN was stronger under acidic conditions and gradually weakened as the pH increased, making it well-suited for the treatment of enteritis.

Adsorption Properties

The adsorption properties of MPNs are necessary for the treatment of enteritis, as they facilitate the adsorption and elimination of harmful substances in the intestines, such as toxins and inflammatory factors. This reduces the burden on the intestines, promotes inflammation relief and recovery, and enhances treatment effectiveness. The adsorption capacity of an MPN primarily arises from the coordination between its metal ions and polyphenol molecules, which creates a stable supramolecular framework. For example, the MPN complex formed by TA and Fe^{3+} can serve as an efficient adsorption system that effectively removes heavy metal pollutants, such as lead and cadmium. Furthermore,

Guo et al. constructed an MPN utilizing the strong adhesive properties of natural polyphenols to capture and fix bee venom peptides, which are highly cytolytic toxins, within its network structure. This innovative method successfully transformed the peptides from potentially destructive "enemies" into usable "allies" by enabling their safe *in vivo* delivery [101].

pH Responsiveness

The pH responsiveness of an MPN is particularly valuable for enteritis treatment as patients often experience local pH changes in the intestine. In acidic environments where inflammation is present, the MPN releases its encapsulated drugs or active ingredients, directly acting on inflamed areas to enhance therapeutic effects, whereas in normal physiological pH environments where no inflammation is present, the drug release rate slows down, reducing the potential impact on normal tissues. This precise pH responsiveness allows the MPN to provide efficient and safe treatment of enteritis [102]. At a pH < 2, the MPN primarily exists in a monocomplex form, which is relatively unstable; as the pH increases to within 3–6, the bimetallic complex form of the MPN gradually dominates, and once it exceeds 7, the MPN primarily exhibits a stable trimetallic complex form.

For example, the Doxorubicin (DOX)-loaded Tannic acid (TA)-iron (Fe) network (for short, TAF) nanocomposite achieves treatment through iron-enhanced ICD by dissociating in the acidic tumor microenvironment to release Fe^{3+} and trigger the Fenton reaction, which generates cytotoxic hydroxyl radicals that induce iron death in cancer cells [103]. Simultaneously, the triggering of ICD activates the body's immune response. The stability of the MPN ensures the controlled release of chemotherapeutic drugs and Fe^{3+} as well as the long-term effectiveness of the nanocomposite *in vivo*, thereby improving treatment efficiency. Thus, MPN stability ensures effective drug delivery, enhances treatment efficiency, and ensures biological safety.

Furthermore, *Jiang et al*. utilized MPNs to coat magnetic hydroxyapatite and thereby realize pH-activated Magnetic Resonance Imaging (MRI) to locate tumors or other lesions more accurately [104]. This MPN-coated magnetic hydroxyapatite can also control the delivery and release of drugs through the dissociation of the MPN and degradation of the magnetic hydroxyapatite. Critically, the magnetic responsiveness of the magnetic hydroxyapatite can also be regulated by an external magnetic field, allowing for remote control and precise localization of drug application. This functional characteristic can be exploited to clearly identify the locations of lesions and precisely treat them through external interventions (Figure 3).

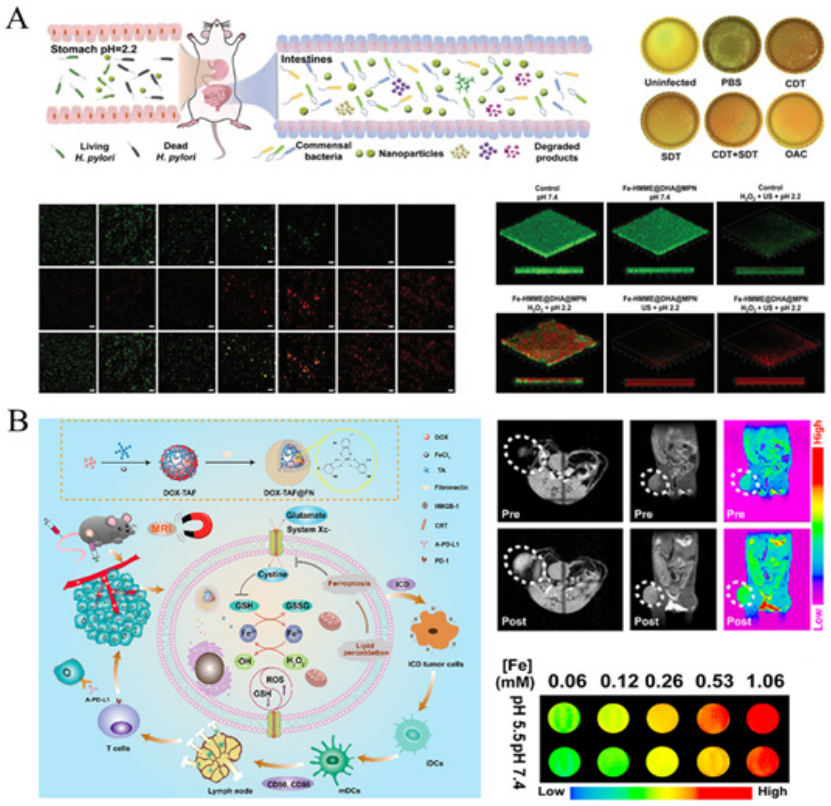

Figure 3: The pH-responsive properties of MPNs A. Schematic illustration of selective sterilization leveraging the pH-responsive properties of MPNs. Reprinted with permission from Ref [102] B. Synergistic integration of pH-responsive MPNs with MR imaging for precision-guided tumor therapy. Reprinted with permission from Ref [103].

Biocompatibility

Finally, the biocompatibility of an MPN is crucial for the successful treatment of enteritis as it ensures that the material does not cause adverse reactions in the body, such as immune or toxic responses, facilitating safe and effective interaction with biological tissues while exerting the desired therapeutic effects. A comprehensive assessment using the Cell Counting Kit-8 cell proliferation assay and Calcein acetyl methoxy methyl ester/propium iodide staining method found that EGCG and Cu^{2+}-complexed nanosheets exhibited no significant toxicity to RAW264.7 macrophages at concentrations below 100 μg/mL, with normal cell proliferation, high activity, and low mortality; in contrast, $CuCl_2$ exhibited obvious cytotoxicity [105]. This result strongly demonstrates the excellent biocompatibility of Cu-EGCG nanosheets.

In summary, the various functional characteristics of an MPN are inseparable and interrelated, collectively constituting the unique advantages of MPN use in biomedical applications (Figure 4).

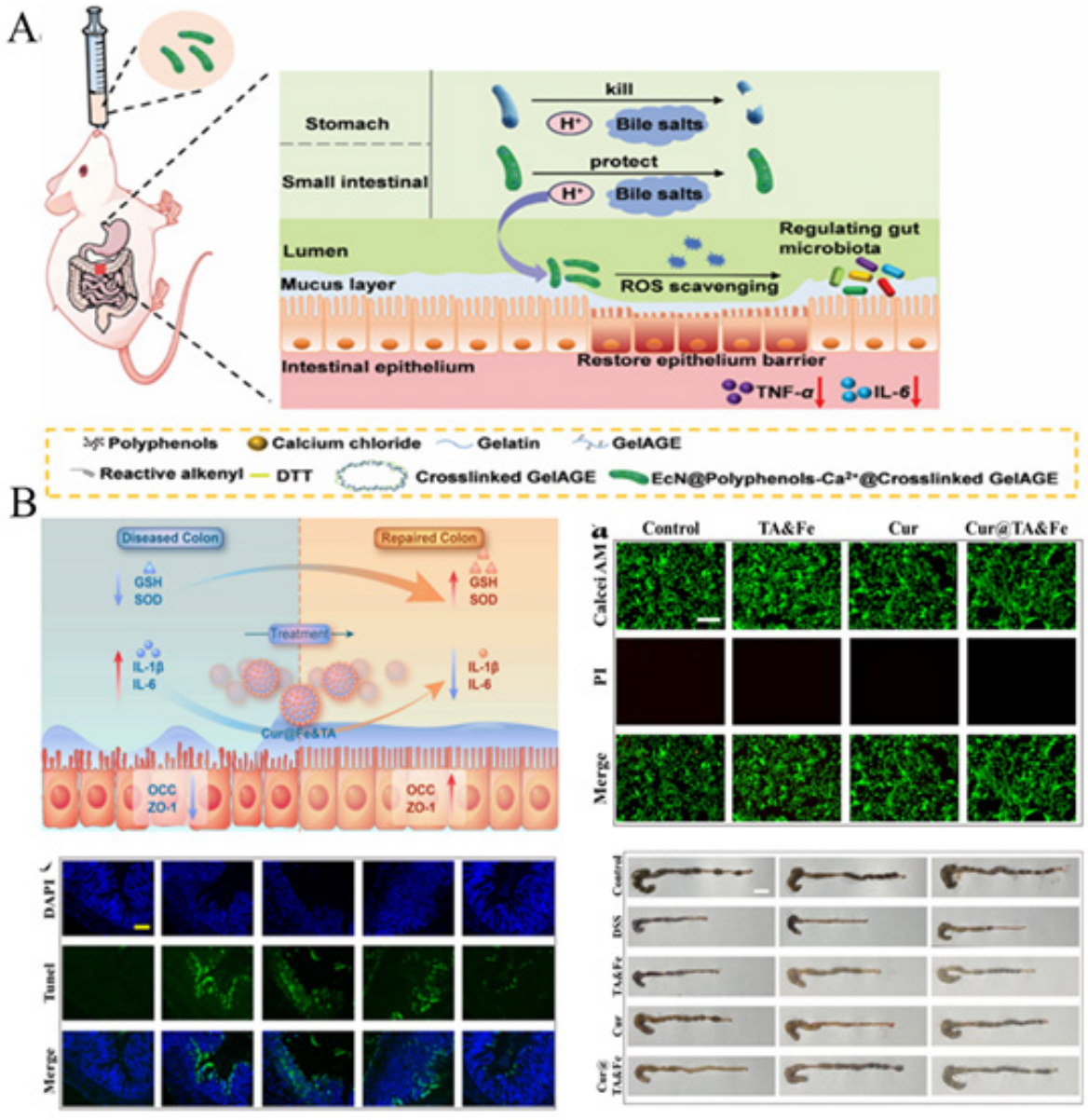

Figure 4: Evaluating the biocompatibility of MPNs A. The biocompatibility of MPNs. Reprinted with permission from Ref [92] B. The cytotoxicity and therapeutic mechanisms of MPNs in IBD treatment. Reprinted with permission from Ref [106].

Applications of MPNs in Enteritis Treatment

Advantages of MPNs

Targeted Therapy: The abilities of multifunctional Penta-Peptide Functionalized Polyphenol-Copper Nanoparticle Network with Enhanced Mitochondrial Targeting and Inhibition of Pyroptosis (PG@Cu–FP)MPN NPs have been validated in cellular and animal experiments. At the cellular level, the inherent characteristics of the FP peptide and the charge gradient of the mitochondrial membrane enable PG@Cu–FP to target mitochondria through electrostatic adsorption, and Penta-Peptide (FP) co-localization with mitochondria has a high Pearson coefficient, resulting in excellent accumulation; simultaneously, Cu^{2+} modification triggers the "proton sponge effect," facilitating the escape of particles from lysosomes and reducing co-localization [107].

Regulation Of Gut Microbiota: The MPN formed by crosslinking the Fe^{3+}–TA network with carboxymethylated β-glucan (EcN@Fe-TA@mGN) can be used to increase the abundance of beneficial gut bacteria, such as *Bacteroidetes*, while reducing the abundance of harmful bacteria, such as Proteobacteria, *Escherichia coli*, and *Shigella*. This promotes the colonization of probiotics in the gut, improves the diversity of gut microbes, and regulates the production of SCFAs, particularly butyrate, to effectively manage the gut microbiome, maintain gut health, and alleviate intestinal inflammation [108]. *Mao et.al* introduce a molecular coating made of o-nitrobenzaldehyde-modified gelatin (GelNB) that binds to intestinal -NH2 groups, forming a protective biophysical barrier. This coating adheres persistently to the intestinal surface, shielding damaged epithelium from harmful metabolites and pathogens. It promotes intestinal repair by enhancing cell migration/proliferation and reducing inflammation, outperforming the clinical drug mesalazine *in vivo*. GelNB demonstrates significant potential as a therapeutic strategy for preventing and treating IBD [109] (Figure 5).

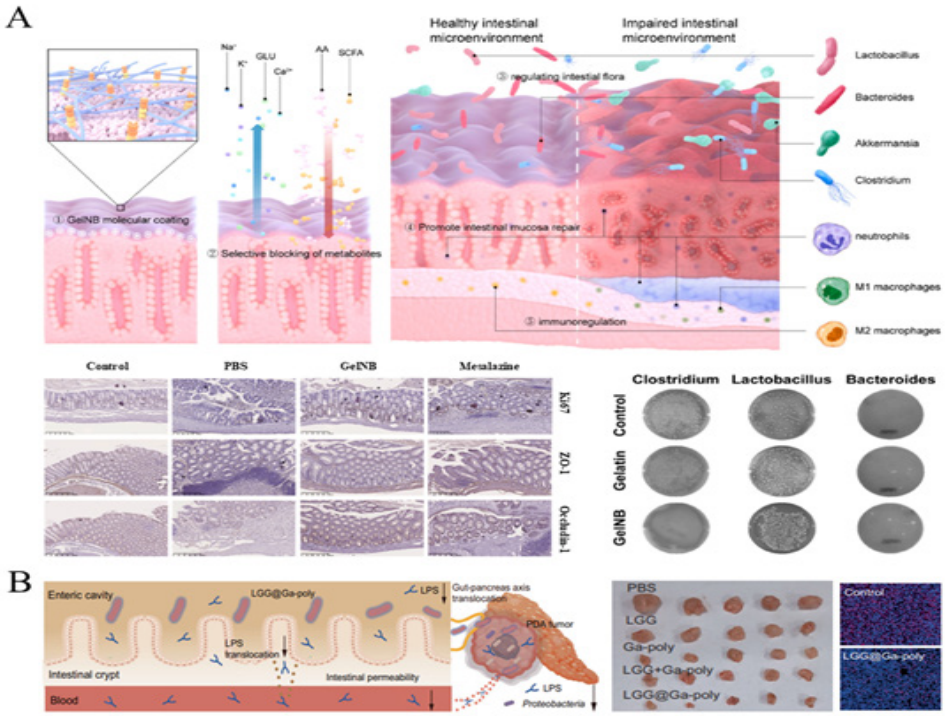

Figure 5: MPNs modulate gut microbiota A. GelNB molecular coating as a biophysical barrier to isolate intestinal irritating metabolites and regulate intestinal microbial homeostasis in the treatment of inflammatory bowel disease. Reprinted with permission from Ref [109] B. MPNs mediated modulation of the intratumoral microbiota. Reprinted with permission from Ref [110].

Protecting and Repairing the Intestinal Mucosa: The antioxidant properties of the polyphenols in an MPN can reduce oxidative stress-induced damage to the intestinal mucosa and the antibacterial properties of these polyphenols can inhibit the growth of harmful bacteria, collectively maintaining the health of the intestinal mucosa [111]. Additionally, the presence of metal ions such as Mg^{2+} and Zn^{2+} in an MPN can promote mucosal repair as they perform various critical functions in the body, including participation in cellular metabolism, promotion of cell proliferation and differentiation, and enhancement of tissue repair

and regeneration. During the mucosal repair process, these ions stimulate the expression of cell growth factors, thereby promoting the repair and regeneration of damaged cells and accelerating the healing of the mucosa. Studies have shown that high-purity magnesium has a positive effect on the expression of the tight junction proteins in intestinal epithelial cells both *in vitro* and *in vivo*, possibly enhancing intestinal barrier function [112]. Furthermore, composite zinc–rutin particles have been shown to protect the intestinal epithelial barrier through their anti-inflammatory and antioxidant effects, alleviating the symptoms of acute and chronic colitis induced by DSS [113] (Figure 6).

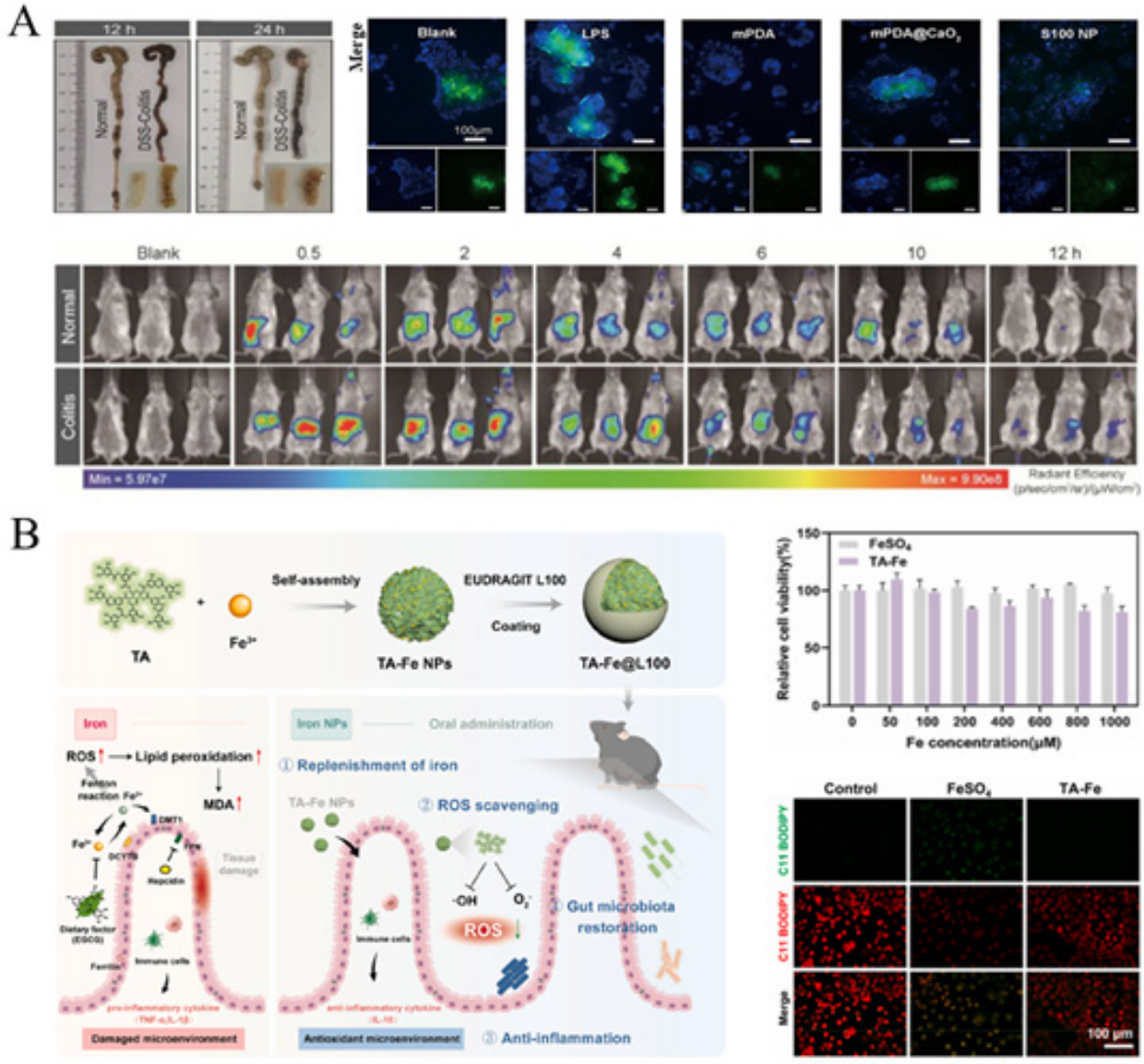

Figure 6: MPNs protect and repair intestinal mucosa A. The formation of metal-phenolic networks on the colon tissue of normal and colitis mice and there *in vivo* imaging. Reprinted with permission from Ref [114] B. Application of metal polyphenol network in colitis. Reprinted with permission from Ref [115].

Inhibiting the Release of Inflammatory Factors and Reducing Inflammation: The anti-inflammatory properties of MPNs can inhibit the production and release of inflammatory factors, thereby reducing inflammatory responses. Copper nanoenzymes induced by charge transfer from phenolic ligands to metals can scavenge ROS, suggesting potential applications in

chronic wound healing. Metal–polyphenol networks [11] were shown to utilize the synergistic effects of enzyme-like activity and photothermal properties to effectively eliminate oral polymicrobial biofilm-related infections. The NP network demonstrated a significant ability to inhibit the release of inflammatory factors, alleviating inflammation caused by infections [10] (Figure 7).

Safety: MPNs has exhibited excellent safety in thrombolytic drug delivery systems. *Tao et al*. effectively inhibited the direct contact of thrombolytic urokinase-type plasminogen activator (uPA) with the environment by coating the surfaces of lipid cubic phases with MPNs containing low-fouling peptides, thereby reducing nonspecific cell association while extending the circulation half-life and decreasing the accumulation of uPA in mouse spleens [118]. These results highlight the safety of MPNs as drug carriers (Figure 8).

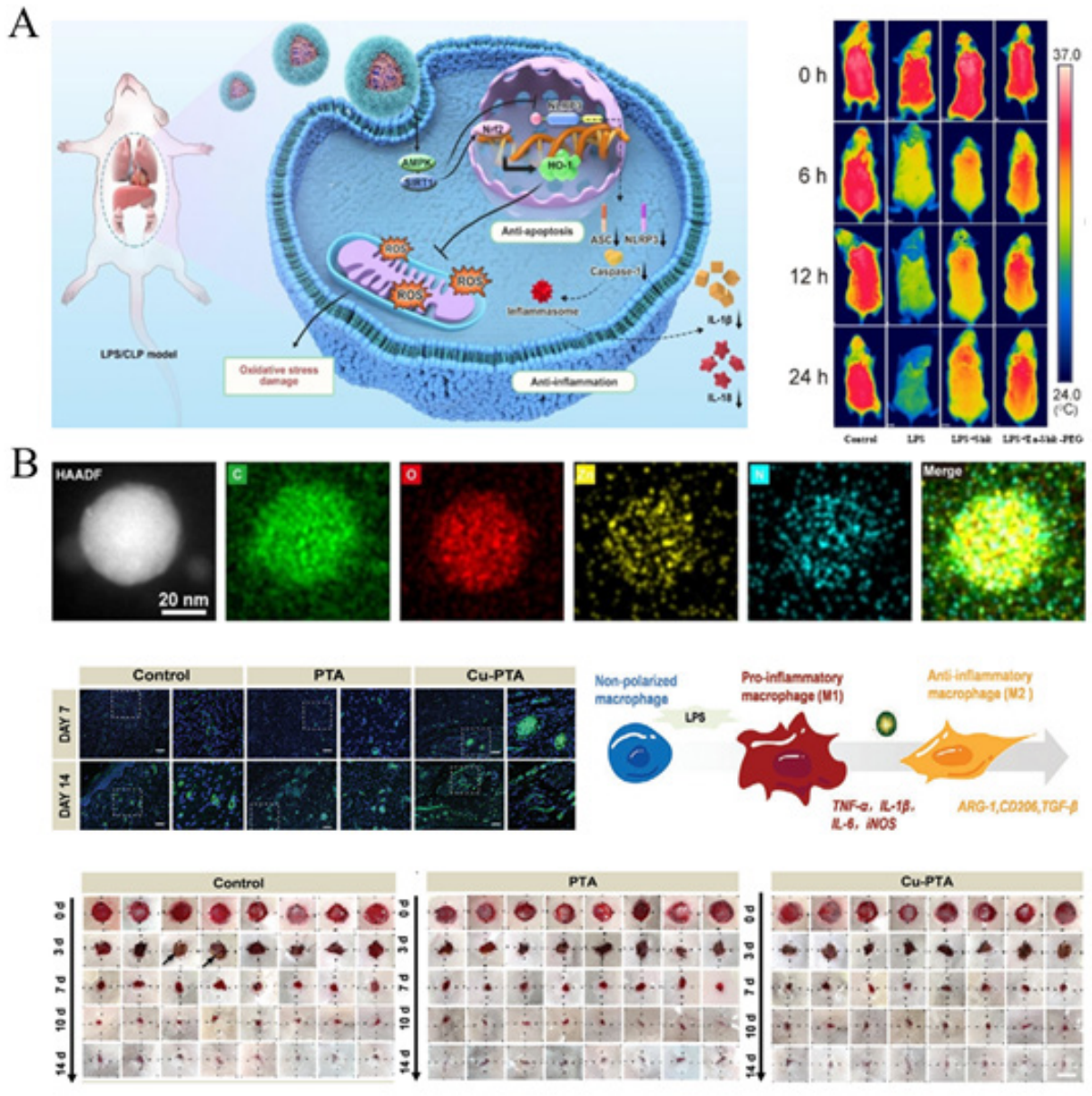

Figure 7: MPNs Inhibit the release of inflammatory factors and reducing inflammation A. Anti-inflammatory and antioxidant effects of metal polyphenol network. Reprinted with permission from Ref [116] B. The anti-inflammatory effect of metal polyphenol network and its treatment of skin wounds. Reprinted with permission from Ref [117].

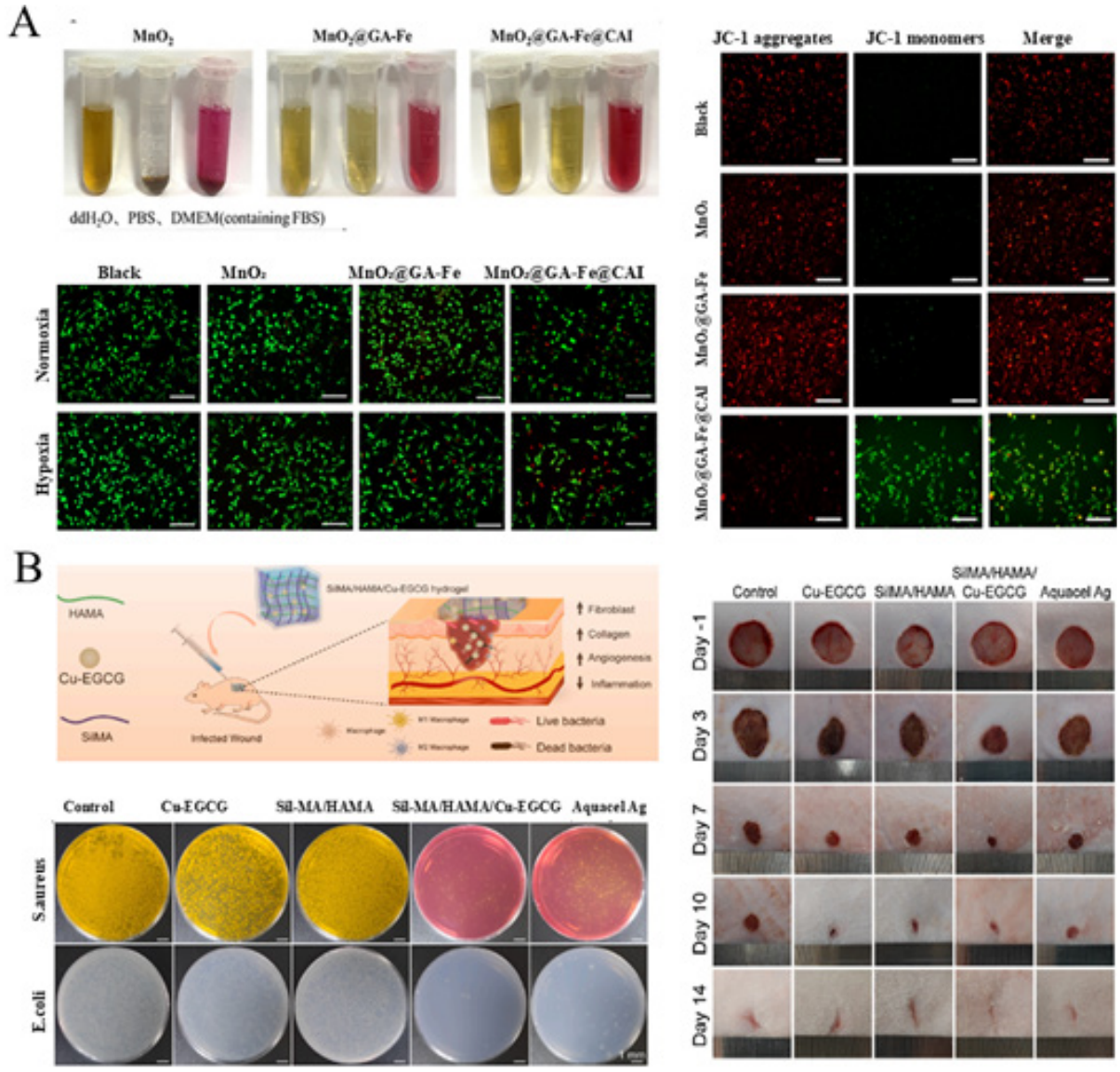

Figure 8: Safety of MPNs A. Safety of MPNs. Reprinted with permission from Ref [119] B. MPNs shows safety in wound healing. Reprinted with permission from Ref [120].

Application of MPNs for the Treatment of Enteritis

Sun et al. used Cu^{2+}, and TA to prepare phycocyanin-encapsulated Phycocyanin-Encapsulated Zeolitic Imidazolate Framework-8 with Tannic Acid Coordination Shell, Disulfide Bonds, and Hyaluronic Acid (PZTC/SS/HA) nanocapsules designed to rupture in the acidic tumor microenvironment through the action of glutathione and disulfide bonds, releasing phycocyanin and Cu^{2+}. The released Cu^{2+} reacts with hydrogen sulfide to efficiently generate CuS nanoparticles for photothermal therapy. This photothermal therapy activates chemokinetic therapy, thereby enhancing the therapeutic effects of the MPN. Both *in vitro* and *in vivo* experiments demonstrated that this nanocapsule exhibited significant toxicity against colorectal cancer cells, low toxicity to normal cells, excellent tumor suppression, and suitable biocompatibility in mouse models [121].

Lu synthesized a novel nanoparticle comprising BSA NPs encapsulating TNF-α small-interfering RNA and GA-mediated graphene quantum dots. The functionality of these NPs was enhanced by constructing a layer of polyphenol armor comprising chitosan and TA through LBL deposition. This armor not only protects the NPs as they traverse the gastrointestinal tract but also imparts bioadhesive and antioxidant properties. The NPs significantly reduced intestinal inflammation and improved anxiety, depression, and cognitive behavior in a colitis mouse

model while demonstrating excellent stability and targeting. This polyphenol armor strategy was based on the coordination effect observed between polyphenols and metal ions and can be seen as an innovative application of MPNs in the treatment of enteritis [122].

Li et al. constructed a novel and efficient MPN-based drug delivery system through the precise coordination of EGCG and Fe3+ to successfully incorporate curcumin medication. These curcumin MPNs were further encapsulated in yeast microcapsules to deliver the drug more accurately. Experimental results revealed that oral administration of the resulting microcapsules effectively eliminated ROS, reduced the levels of inflammatory factors, and regulated macrophage function [123], thereby significantly alleviating the symptoms of colitis while protecting and restoring normal intestinal function. This research provides a new approach for the treatment of enteritis and fully demonstrates the enormous potential of MPNs in the medical field, suggesting new avenues for the treatment of related diseases with far-reaching clinical significance. Similarly, *Jin et al*. utilized metal ions (such as Fe^{3+}) and polyphenols (such as TA) to construct curcumin-encapsulating MPN NPs. Experimental results indicated that these NPs not only improved the solubility and stability of the curcumin and enhanced the drug release behavior but also possessed excellent stability and biocompatibility. Furthermore, the NPs facilitated pathological improvements in the gastrointestinal tract of a colitis mouse model through their anti-inflammatory and antioxidant effects [106].

Fang combined MPN technology with light-induced thiol-ene click chemistry to coat and reinforce individual probiotic cells. This treatment protected the probiotic cells while endowing them with new functions, resulting in excellent stability and viability in simulated oral and intestinal environments. The treated probiotic cells performed exceptionally well in resisting gastric acid, bile, and other digestive fluid erosion, successfully reaching the intestines to exert the desired therapeutic effect. When used to treat enteritis these probiotic cells can regulate the balance of intestinal microbiota by inhibiting harmful bacteria while promoting beneficial bacteria and alleviating intestinal inflammation to relieve symptoms [92]. Notably, this research injected new vitality into oral probiotic therapy by providing a novel approach for the treatment of intestinal diseases, including enteritis.

The effective treatment of UC has been realized by loading MPN yeast microcapsules with nobiletin. These microcapsules were experimentally shown to precisely regulate oxidative stress responses in patients with UC by inhibiting excessive activation of the NLRP3 inflammasome and balancing immune responses. The meticulous design of the microcapsules successfully enhanced the bioavailability of the nobiletin within, allowing for stable release in the intestines to act directly on inflamed areas. The application of these microcapsules to UC animal models significantly reduced intestinal inflammation and improved the integrity of the intestinal mucosa, further validating their efficacy for UC treatment. This research offers new treatment avenues for patients with UC and demonstrates the enormous potential of MPN yeast microcapsules as a drug delivery system for the treatment of IBD [124].

Fu et al. utilized a hydrogen peroxide enzyme to catalyze the formation of a stable Fe^{3+}–TA coating and explored its potential in treating UC. *In vitro* experiments showed that the coating formed rapidly and stably on the small intestinal mucosa, and *in vivo* experiments validated its durability and protective effect on the intestinal barrier in mouse and pig models. When applied in colitis mice models, the coating significantly improved weight loss, intestinal morphology, and inflammation levels, and the results of MRI analyses confirmed its stability and imageability under pathological conditions, providing new strategies for the diagnosis and treatment of enteritis [125].

Finally, novel Zn^{2+}–TA MPN NPs have been developed for the treatment of IBD. These NPs alleviate oxidative stress and inflammation by scavenging reactive oxygen and nitrogen species to effectively promote intestinal mucosal repair; both *in vitro* and *in vivo* experiments confirmed their biocompatibility and safety. Indeed, they significantly reduced intestinal inflammation, restored colon length, and decreased weight loss and splenomegaly in DSS-induced enteritis mouse models [126], thereby suggesting a new and effective strategy for the treatment of IBD (Figure 9).

Combined Diagnosis and Treatment Using MPNs

An MPN formed by coordinating TA and metal ions was coated on the surfaces of Aggregation-Induced Emission (AIE) NPs to create an organic–inorganic composite core–shell nanostructure for *in vivo* imaging and diagnosis. This method combines the fluorescent properties of AIE molecules with the multifunctional characteristics of the MPN to achieve multimodal imaging in biological systems using technologies such as MRI [127], computed tomography, and Fluorescence Imaging (FI). Indeed, this approach was shown to facilitate dual-mode MRI and FI in A549 tumor-bearing mouse models. Notably, the various imaging modalities facilitated by the multifunctional characteristics of the shell–core structure can inform a more comprehensive diagnosis of enteritis and evaluation of its treatment. Furthermore, catalase-catalyzed oxidation polymerization of TA and chelation with Fe^{3+} to form an MPN structure significantly accelerated the oxidation polymerization rate of TA, with the addition of Fe^{3+} enhancing the formation and stability of the network. The resulting MPN formed rapidly on the intestinal mucosa, exhibiting excellent adhesion that retained it in the intestine for at least 12 h. This ability significantly reduced the required serum concentration of flourescein isiocynate-dextran and improved glucose tolerance. When applied to enteritis mice models, this MPN reduced weight loss, increased the length of the small intestine, significantly decreased intestinal permeability, and alleviated the degree of inflammation in the coated treatment group. Critically, the high longitudinal relaxation rate of Fe^{3+} was utilized to achieve real-time MRI-based monitoring of intestinal barrier damage in enteritis mice, representing a novel method for the visual monitoring of intestinal barrier damage [125].

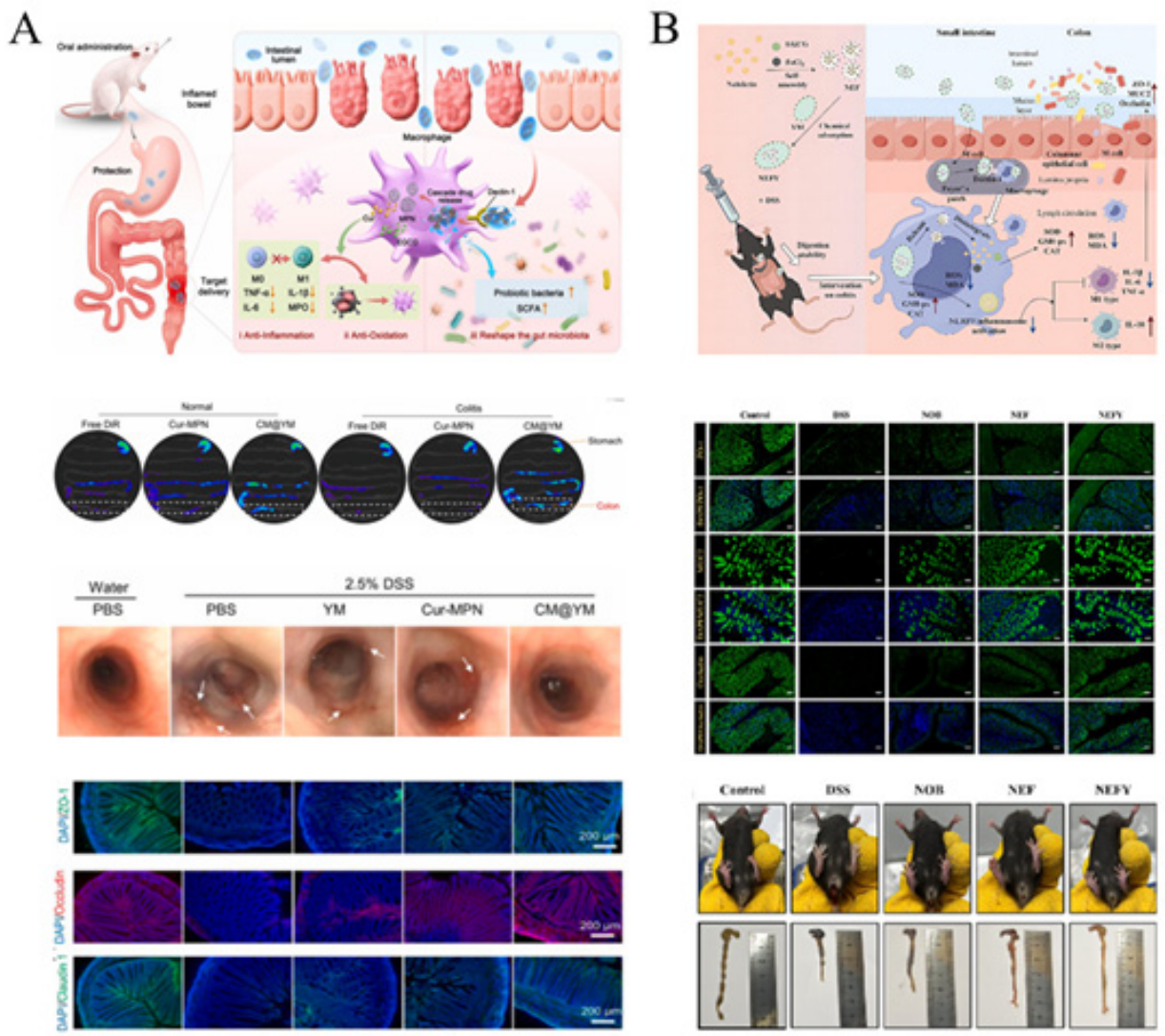

Figure 9: MPN IBD mechanisms & therapeutic outcomes A. Reprinted with permission from Ref [123] B. Reprinted with permission from Ref [124].

Summary of Prospective MPN Applications in Enteritis Treatment

The studies included in this review indicate that MPNs exhibit considerable potential for use in the treatment of enteritis. The unique pH responsiveness of the MPN facilitates precise drug release in the acidic environment of the intestine to realize targeted therapy, and the MPN positively influences host energy metabolism by protecting anaerobic bacteria and regulating the gut microbiota. The synergistic effect of the polyphenols and metal ions within an MPN protects the intestinal mucosa from oxidative stress damage while promoting mucosal repair and accelerating the healing process. The anti-inflammatory effects of polyphenols further inhibit the release of inflammatory factors, thereby fundamentally reducing inflammatory responses. Notably, MPNs demonstrate excellent safety and biocompatibility when used as drug delivery carriers, prolonging the drug circulation half-life and reducing side effects. Thus, the ability of the MPN to provide precisely targeted therapy, regulate gut microbiota, protect and repair the intestinal mucosa, and effectively reduce inflammation suggests a novel approach for the treatment of enteritis; MPNs are expected to become a focus of considerable future clinical research.

Although MPNs have demonstrated numerous advantages in the treatment of enteritis, every treatment method or material is inevitably subject to limitations. First, the process of preparing an MPN is relatively complex, requiring precise control over the ratio

of metal ions to polyphenolic compounds as well as the reaction conditions. This increases the technical difficulty and cost of production, which may limit the widespread application of MPNs for enteritis treatment, especially in economically constrained regions or patient populations. Furthermore, MPN stability is a key challenge hindering widespread application. Although an MPN can be constructed to disintegrate and release drugs under specific pH conditions, the complexity of the intestinal environment and differences among patients may harm its stability and effectiveness, adversely affecting treatment outcomes. Despite the excellent biocompatibility and safety of the MPNs reported in preliminary studies, their long-term safety and potential risks in application are not yet fully understood; further in-depth research is required to determine the degradation products of MPNs in the intestines, their interactions with the gut microbiome, and their effects on host physiological functions. Additionally, potential risks associated with the long-term use of an MPN, such as the development of drug resistance or drug accumulation effects, cannot be overlooked. Finally, the application of novel MPNs in the treatment of enteritis necessitates strict regulation and standardization of material preparation, quality control, safety assessment, and clinical application guidelines that require further research and formulation to complete.

In summary, while applications of MPNs in enteritis treatment hold considerable promise, they also face challenges related to preparation complexity, stability, differences among patients, safety, and long-term effects, and further development of regulations and standards is required. Future research should focus on addressing these issues to promote widespread application and in-depth development of MPNs for the treatment of enteritis.

Declarations

Ethics approval and Consent to Participate: Not applicable.

Consent for Publication

All authors give consent for the publication of manuscript in Journal of Nanobiotechnology.

Availability of Data and Materials

Yes.

Competing Interests

The authors declare that they have no conflict of interests.

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Author Contributions

Bingbing Deng and Weifang Liao contributed to the conceptualization, Writing-review& Editing, validation and supervision of the manuscript. Mengqi Zhang, Mengmeng Zhang and Qiuying Fan contributed to project administration.

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