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Advances in Nanoparticles for Inflammatory Bowel Disease

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Abstract. Inflammatory bowel disease (IBD) is a global health concern. Existing therapies, including anti-inflammatory drugs and biologics, often suffer from limitations such as insufficient targeting and high cost. In this context, nanoformulations have shown significant potential due to their advantages in drug protection, targeted delivery, and multifunctional synergy. This article reviews the latest progress in the treatment of IBD with nanoparticles. It categorizes nanodelivery systems into two main types: drug delivery systems and plant-related delivery systems. The article also provides examples of each type, detailing their preparation methods, targeted delivery mechanisms, and experimental outcomes. The findings reveal that while studies have confirmed the effectiveness and advantages of nanoformulations for treating IBD, transformation encounters significant challenges. In the future, it is necessary to integrate new technologies to develop more intelligent nano-response systems and accelerate clinical verification, ultimately aiming for precision and universalization of IBD treatment.

Keywords: inflammatory bowel disease, drug delivery system, nanoparticles, new therapies

1. Introduction

Inflammatory bowel disease (IBD) is generally divided into ulcerative colitis and Crohn's disease. It is a systemic disease with symptoms that occur not only in the gastrointestinal tract but also in other organs. In recent years, the incidence and hospitalization rates of IBD in emerging industrialized countries have continued to rise, reflecting that IBD has gradually become an important international public health issue [1]. However, existing conventional treatments such as surgery, Mesalazine, and immunosuppressants cannot cure it, but only control inflammation and prevent complications [2-3]. In recent years, anti-TNF biologics such as subcutaneous or intravenous infliximab and their generics have been shown to be effective for moderate or severe IBD [4]. However, to achieve equality and affordability in the management of IBD worldwide, innovation in the reliance on biologics is needed [5-6]. New treatments, such as Chinese herbal medicine and intestinal flora regulation, have been shown to be effective for IBD [7-8]. Nanoparticles have the potential to protect drugs and promote targeted drug transport to improve efficacy. Previous studies have shown that delivering drugs or microorganisms through nanomaterials, or directly using plant nanoparticles, has significant effect on IBD [9-11].

This article reviews the recent progress in nano formulations for the treatment of inflammatory bowel disease and summarizes the current challenges of nanoparticles in the treatment of IBD and

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future perspectives. This study provides new ideas and suggestions for the follow-up treatment of inflammatory bowel disease.

2. Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease is divided into ulcerative colitis (UC) and Crohn's disease (CD). Two subtypes differ mainly from symptoms and affected regions. UC is a lifelong disease, usually characterized by relapses and remissions [3]. It is generally believed that the most accurate diagnostic method for UC is endoscopic biopsy [12]. Some biomarkers such as fecal leukocyte esterase and C-reactive protein-to-bilirubin are also considered to have good reference value for the diagnosis of UC [13-14]. The typical endoscopic features are the gradual disappearance of vascular structures, and the mucosa changes from erythema to blood adhesion until spontaneous bleeding and ulcers occur [3]. CD often affects the ileum and colon in a discontinuous, patchy, segmental, and transmural manner, but can also affect any part of the digestive tract [15]. Endoscopy and histopathology reveal cobblestone lesions in the colon that are only seen in CD and are therefore the best means of differentiation [16]. CD often affects the ileum and colon in a discontinuous, patchy, segmental, and transmural manner, but can also affect any part of the digestive tract [15]. Endoscopy and histopathology reveal cobblestone lesions in the colon that are only seen in CD and are therefore the best means of differentiation [16].

It is generally believed that the etiology of IBD is multifactorial [15]. In addition to common genetic susceptibility site variants that have been shown to contribute less to disease susceptibility, damage to the intestinal epithelial barrier is a key cause [15, 17]. At the same time, single nucleotide polymorphisms of genes encoding cytokines, cytokine receptors, cytokine-induced transcription factors, cytokine downstream signaling molecules, etc. have also been shown to be associated with the early onset of IBD [18]. In addition, failure of microbial recognition and phagocytosis mechanisms mediated by NOD-like cytoplasmic receptors (NLRs) and Toll-like receptors (TLRs) can cause intestinal microbial dysbiosis, leading to the invasion of bacteria such as Clostridium innocua and Escherichia coli and the further progress of IBD [19-20].

3. Some nanoparticle delivery system for IBD

3.1. Drug delivery systems

3.1.1. Cytokine and receptor-related delivery systems

IL-10 is a key cytokine in intestinal inflammation and has shown encouraging therapeutic effects in animal models of colitis [21]. Liu et al. used Escherichia coli Top10 carrying a mouse IL-10 gene plasmid to transfect human embryonic kidney 293T cells (HEK293T) and then ultracentrifuged them. The supernatant was analyzed for control to obtain IL-10-containing extracellular vesicles (IL10-EVs) with a diameter like that of normal cell extracellular vesicles [22]. Macrophage galactose C-type lectin (MGL) is a substance inducing colonic lamina propria macrophages to produce IL-10, recognizing galactose (Gal) to exert its effect [23-24]. Therefore, Liu et al. coupled Gal with 1, 2-Distearoyl-sn-glycero-3-phosphoethanolamine-Polyethyleneglycol2000-Amino (DSPE-PEG-NH2) with a targeting moiety to generate DSPE-PEG-Gal and inserted it into IL10-EVs to obtain Gal-IL10-EVs. In vitro studies showed the expression of inflammatory factors in macrophages treated with Gal-IL10-EVs was downregulated in a dose-dependent manner, reflecting the possible therapeutic effect of this delivery system on colitis [22].

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3.1.2. Metal nanoparticle-related delivery systems

Cerium dioxide is noted for its unique immunomodulatory properties and enzyme mimetic activity that protects tissues from reactive oxygen species (ROS) overproduction and inflammation [25]. Min et al. developed an oral inflamed colon-targeted nanotherapeutics (ICAN), which loaded cerium dioxide nanoparticles (CeNPs) onto mesoporous silica nanoparticles (MSNs) and coated them with negatively charged polyacrylic acid (PAA). In vitro experiments showed that it had a high ROS clearance rate in artificial gastrointestinal fluid. In vivo researches showed that it could regulate the level of oxidative stress in the lesion site, as illustrated in Figure 1 [26].

Since the antioxidant mechanism of ceria itself has energy defects, Li et al. synthesized ceria nanoparticles embedded with gold nanoparticles (Au/CeO2) and coated them with hyaluronic acid (HA) to obtain Au/CeO2@HA. The porous structure of Au/CeO2@HA increases the contact area and improves the antioxidant activity. Figure 2 shows that it can be accumulated in the inflamed colon tissue through oral administration to reduce colon damage, which to some extent makes up for the shortcomings of ceria itself [27].

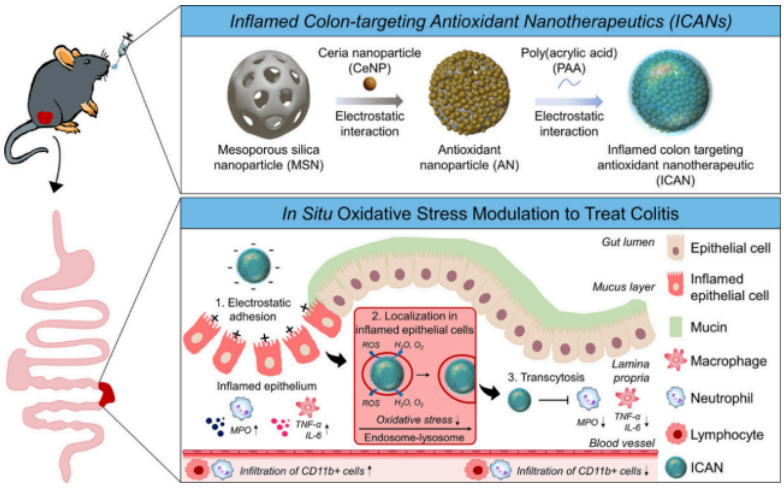

Figure 1. A schematic of ICANs and the mechanism for downstream reactions in colitis [26]

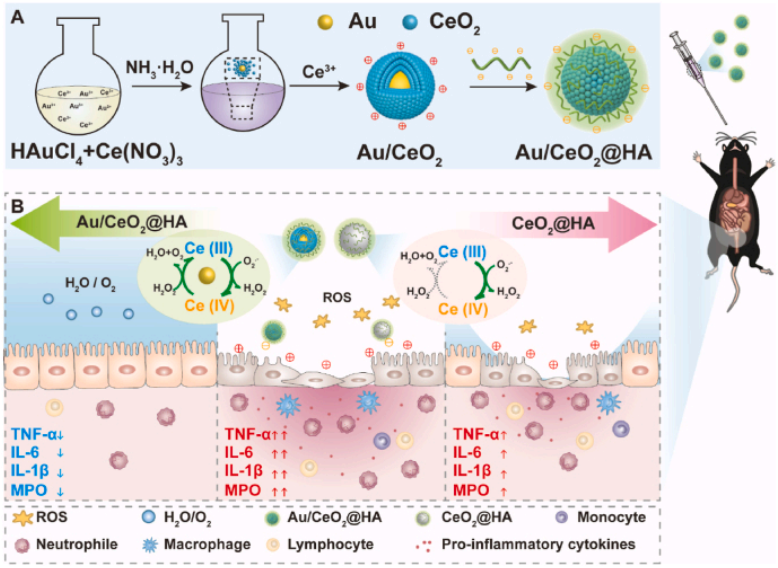

Figure 2. Schematic illustration of Au/CeO2@HA synthesis and therapeutic mechanisms [27]

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3.2. Plant related delivery systems

3.2.1. Plant exosome related delivery system

Exosomes are nanoscale lipid bilayer vesicles that accurately deliver particles of various sizes to inflammatory areas [28]. Edible plant-derived exosome-like nanoparticles (PDENs) offer benefits over animal-derived ones, such as oral therapeutic efficacy, non-toxicity, and low immunogenicity [29]. Yang et al. isolated ginseng-derived nanoparticles (GDNP) from ginseng root juice by differential centrifugation. After purification and characterization, they were gavaged into C57BL/6J male mice modeled with dextran sulfate sodium (DSS). The results of vivo distribution and stability experimental analysis showed that GDNP was significantly absorbed in the gastrointestinal tract at all time points compared with other organs, as shown in Figure 3. At the same time, GDNP can reduce inflammatory responses and damage induced by intracellular toxins and DSS by activating the p62-Nrf2-Keap1 pathway, downregulating the proinflammatory factors, and blocking the Toll-like receptor 4 (TLR4)/MAPK pathway [11]. Kim et al.'s experiments demonstrated that the GDNP treatment significantly reduced the DSS-induced disease activity index in Balb/C mice. Notably, the long-term survival rate was nearly doubled that of the group using only phosphate buffered saline (PBS), as shown in Figure 4. These findings revealed the possible therapeutic mechanism and efficacy of GDNP for human IBD [30].

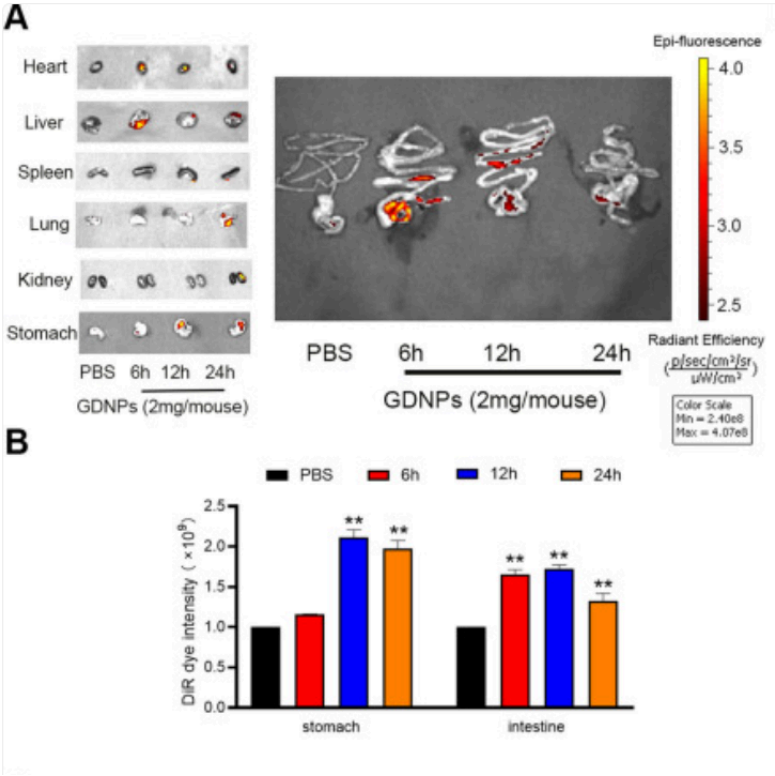

Figure 3. In vivo results. (A) Intensity of PKH-26 dye indicating high GNDP deposition in gastrointestinal tracts (B) Colocalization of intestinal macrophages and fluorescently labelled GDNPs. Scale bar: 100 m [11]

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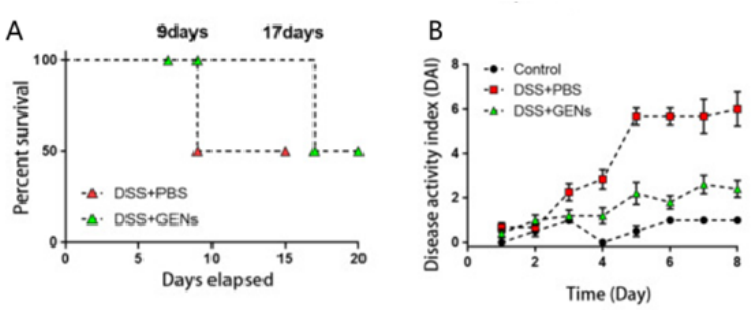

Figure 4. Effect of GENs in colitis induced by DSS (A) The Disease Activity Index (DAI) assessment. (B) Survival rate of Balb/C mice of two groups [30]

3.2.2. Plant component related delivery systems

Curcumin (CUR) is an polyphenol compound extracted from the rhizome of turmeric (Curcuma longa) with high pharmaceutical effects. As a promising candidate for the treatment of IBD, it can reduce oxidative stress damage by inhibiting NF-B activation, reducing TNF- expression levels, and improving intestinal damage by promoting the upregulation of anti-inflammatory factors such as IL-10 [31-32]. Although CUR is very beneficial, it still has problems such as low water solubility and poor metabolism [32]. To solve this problem, Lei et al. prepared nanoemulsions of curcumin and emodin (EMO), another anti-inflammatory plant ingredient with similar properties, and prepared an edible pH-sensitive colon-targeted delivery platform (CUR/EMO NE@SA) supported by a three-dimensional hydrogel network formed by sodium alginate (SA) and chitosan (CS). In vitro and in vivo experiments showed that the nanoemulsion had a high affinity for target cells and can release drug with change of microenvironment. When the concentration of CUR and EMO was 10g/mL, it significantly reduced TNF- and increased IL-10, exerting an anti-inflammatory effect. It also promoted the proliferation of caco-2 cells, indicating that it may also accelerate mucosal repair [33]. The nanoemulsion effectively improved the deficiencies of curcumin itself and revealed the feasibility of curcumin as an IBD drug.

4. Conclusion

As a global disease, inflammatory bowel disease has certain regional heterogeneity. Studies have found that the incidence of ulcerative colitis in Chinese cities is similar to that in Western countries, while the latter shown a higher rate of Crohn’s disease than the former. Some studies have also demonstrate that the higher incidence of Crohn's disease in Western countries than in Asians may be related to CD risk alleles. These studies reflect that the onset of inflammatory bowel disease is affected by multiple factors, and its causal relationship is difficult to determine. However, there are currently no nanoformulations that have been marketed and put into use for the treatment of IBD. According to theanalysis, the upcoming nanoformulations for the treatment of IBD should consider issues such as production scale, safety of long-term use, and personalized treatment strategies, and combine technologies such as microbiome regulation to develop more intelligent nanosystems while promoting clinical translation verification.

However, there are limitations in this study. For instance, the understanding of the underlying mechanisms and interactions between genetic and environmental factors remains to be explored. Future development should focus on integrating advanced technologies, such as microbiome

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modulation and personalized medicine, to create intelligent nanosystems that can better address individual patient needs and improve clinical outcomes.

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