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NANOTECHNOLOGY APPLICATIONS IN ULCERATIVE COLITIS: RECENT DEVELOPMENTS AND FUTURE DIRECTIONS

APLICAÇÕES DA NANOTECNOLOGIA NA COLITE ULCERATIVA: DESENVOLVIMENTOS RECENTES E DIREÇÕES FUTURAS

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ABSTRACT

Ulcerative colitis is characterized by prolonged, lasting inflammation in the colon, leading to immune system alterations and ongoing inflammation. Despite being one of the most common intestinal diseases, its cause is still unclear and involves multiple pathophysiological factors. Common symptoms include ulcers, bleeding, diarrhea, and abdominal pain. Identifying the clinical condition involves the process of differential diagnosis, which includes conducting endoscopic examinations and biopsy. Treatment aims to manage symptoms and minimize remaining inflammation to prevent future relapses. Multiple pharmaceuticals are accessible, although their efficacy is restricted, and they may cause significant adverse reactions. Scientists have discovered that modified liposomes and co-hybridized phospholipid vesicles could be used to treat ulcerative colitis. These compounds are delivered directly to specific cells and can be released over time. Enclosing bioactive chemicals within proteins is also highly efficient. Currently, these systems are under development and face challenges. This review provides up-to-date research findings on using nanotechnology to treat ulcerative colitis.

Keywords: Inflammatory bowel disease; Ulcerative colitis; Nanotechnology.

RESUMO

A colite ulcerativa é caracterizada por uma inflamação prolongada e persistente no cólon, causando alterações no sistema imunológico e inflamação contínua. Apesar de ser uma das doenças intestinais mais comuns, sua causa ainda não está clara e envolve múltiplos fatores fisiopatológicos. Os sintomas comuns incluem úlceras, sangramento, diarreia e dor abdominal. A identificação da condição envolve o processo de diagnóstico diferencial, que inclui a realização de exames endoscópicos e biópsia. O tratamento visa gerenciar os sintomas e minimizar a inflamação remanescente para prevenir futuras recaídas. Existem múltiplos medicamentos disponíveis, embora a eficácia seja limitada e possam causar reações adversas significativas. Cientistas descobriram que lipossomos modificados e vesículas de fosfolipídios co-hibridizadas poderiam ser usados para tratar a colite ulcerativa. Esses compostos são entregues diretamente às células específicas e podem ser liberados ao longo do tempo. O processo de encapsular substâncias bioativas dentro de proteínas

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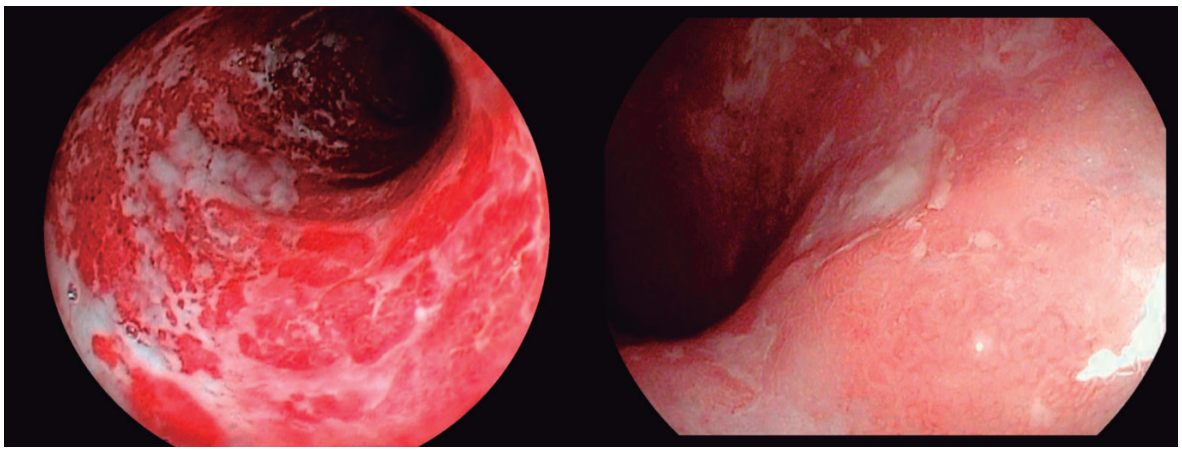
também é altamente eficiente. No entanto, atualmente, esses sistemas ainda estão em fase de desenvolvimento nas pesquisas e precisam superar desafios adicionais. Essa revisão apresenta atualizações sobre o uso da nanotecnologia no tratamento da colite ulcerativa.

Palavras-chave: *Doença inflamatória intestinal; Colite ulcerativa; Nanotecnologia.*

INTRODUCTION

Inflammatory bowel disease (IBD) is a complex disease involving chronic inflammation and mucosal immune dysregulation. It is generally classified into two subtypes: ulcerative colitis (UC) and Crohn's disease (CD), both involving chronic inflammation and characteristic rescission (Yang *et al*., 2022). UC is a recurrent inflammatory disease, classified as non-curable, that affects the colon (Figure 1). Currently, it is considered one of the most common global intestinal diseases, and its symptoms include epithelial barrier deficiency, mucosal inflammation, excessive production of reactive oxygen species (ROS), and intestinal microbial dysregulation (Ma *et al*., 2022).

Figure 1 - Typical endoscopic image of ulcerative colitis.



Source: FLORES (2021).

The initial development of the disease is generally accompanied by abnormal intestinal barrier function, thus allowing microorganisms to cross the intestinal epithelial barrier easily. This process activates macrophages and antigenic cells (APCs), which sequentially release many cytokines and consequently lead to the aggregation of neutrophils. The inflammation contributes to the chronic development of inflammatory bowel disease (Guo *et al*., 2022). The clinical manifestations are mucosal ulcers, bleeding, diarrhea, and abdominal pain (Liu *et al*., 2022).

Recent studies demonstrate a high incidence of colitis in the developed countries of North America, Northern Europe, and Australia, with approximately 100.000 cases in the United States alone. In addition, this phenomenon has increased in developing countries, possibly related to the

widespread consumption of processed foods (Guo *et al*., 2022). However, the etiology of the disease is still unclear, and there seem to be several physiopathological causes (Sung *et al*., 2022). The diagnosis is made through symptoms, endoscopy, and histology (Kobayashi *et al*., 2020). In therapy, patients need monitoring of their symptoms. Moreover, they need additional treatment for residual inflammation. Thus, one of the goals of ulcerative colitis treatment is to ensure that no residual inflammation in the colon prevents relapses (Guo *et al*., 2022).

Nanotechnology has undeniably promising results in inflammatory bowel diseases. In recent years, this technology has been emerging in the medical field, especially in therapies and treatments for chronic diseases. Therefore, it may provide surprising benefits in the treatment of ulcerative colitis (Abdelmegid *et al*., 2019).

Individuals affected by recurrent ulcerative colitis, which has a relatively high incidence, typically need to be on long-term medication to manage the progression of the disease. Various drugs, such as (*i*) salicylic acid, (*ii*) sulfasalazine, (*iii*) immunosuppressive agents, (*iv*) antibiotics, and (*v*) probiotics, are adopted to treat this colitis. However, there are limited effects and potentially serious side effects with current therapies (Zhang *et al*., 2022). There are also many problems with giving antibodies by mouth, such as the fact that they are physicochemically unstable in the stomach, easily broken down by enzymes, and have low membrane permeability. Recent studies have explored nanoparticle-containing formulations to treat colitis, aiming to overcome existing barriers (Lee *et al*., 2022). Namely, the bioactive compound curcumin, present in the roots of the *Curcuma longa* plant, was reviewed by Teixeira *et al*. (2022) for its enhanced effects when administered in nanoparticle form. This review focuses on the application of nanotechnology in treating ulcerative colitis and highlights the latest findings.

METHODOLOGY

The present study was conducted through a recent literature review regarding using nanoparticles to aid in the therapy/treatment of ulcerative colitis by consulting databases via ScienceDirect. For the query of the research, the articles framed in the keywords and their respective terms in English have been selected: “nanoparticle,” “ulcerative,” “colitis,” and “drugs,” separated by the Boolean operator AND. Given a recent review, the inclusion criteria were publications between 2020 and 2022 and journals with an impact factor greater than 5. Seventy-five articles were found in the literature; the following were discarded: articles that did not specifically address ulcerative colitis, publications that did not include nanoparticles as a therapy or treatment for UC, and literature reviews. Therefore, twenty-one experimental studies were selected for this review.

RESULTS AND DISCUSSION

Zhao *et al*. (2020) designed a lactoferrin-modified liposome (LF-lipo) to deliver *patchouli* alcohol to colonic macrophages for anti-inflammatory activity. Results demonstrated decreased disease activity index and body weight loss in mice with dextran sulfate sodium (DSS)-induced colitis. In another study, an oxime-loaded nitric oxide-releasing liposome tested in mice with DSS salt-induced ulcerative colitis significantly alleviated inflammation. Furthermore, the results also showed that the liposomes could accumulate in the inflamed colon and remain there for at least 36 hours, indicating their potential as a treatment option (Tang *et al*., 2020).

In a test with animals, it was seen that curcumin-loaded liposomes (CUR-LPs) could continuously release curcumin in a digestive tract model. These liposomes effectively reduce the clinical symptoms of ulcerative colitis and prevent DSS-induced colon tissue damage and shortening (Wang *et al*., 2021). Sequentially, the liposomes were loaded with heparin and delivered through the edema, demonstrating a dose-dependent anti-inflammatory activity *in vivo* study (Ahmad *et al*., 2021).

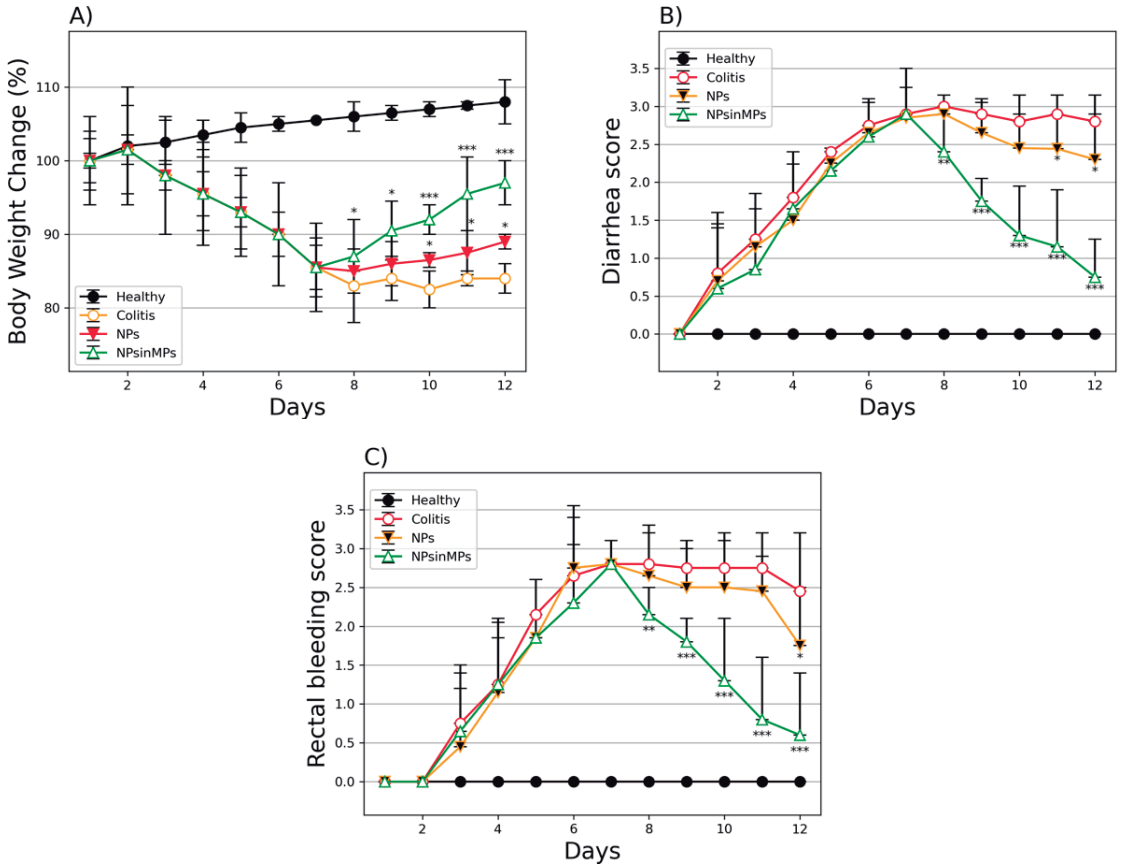
Despite the preparation challenges, hybrid drug delivery systems have enormous potential as they combine the advantages of several types of carriers in a single system. These systems use an outer compartment to protect the drugs from degradation and denaturation in the stomach's acidic environment. At the same time, the inner section is composed of nanoparticles (NPs) designed to transport the drugs (Li *et al*., 2020).

Moreover, studies have shown that encapsulation of curcumin with bovine β-lactoglobulin increases its solubility in aqueous media. When encapsulated with succinylated β-lactoglobulin, curcumin prevents its release when exposed to gastric fluids. These findings indicate that using these proteins as encapsulation systems may be an effective strategy to improve curcumin solubility and protect it from degradation in the gastric environment. They can improve the absorption and enjoyment of the benefits of curcumin in the body (Pujara *et al*., 2021).

In a study conducted by Zhang *et al.* (2020), a phospholipid vesicle co-hybridized with hyaluronic acid (HA) and ethanol (HA-ES) was developed for the transdermal delivery of eugenol (EUG) and cinnamaldehyde (CAH). The results of this experiment demonstrated that the use of HA-ES as a carrier system significantly improved the percutaneous absorption of EUG and CAH in a rat model of ulcerative colitis. Using phospholipid vesicles co-hybridized with HA-ES may be a practical approach for the transdermal administration of these compounds, improving their efficacy in treating ulcerative colitis.

Naeem *et al*. (2020) generated a polymer using poly(lactic-co-glycolic acid) (PLGA) to release medication over time. First, they produced PLGA nanoparticles, then encapsulated them in pH-sensitive Eudragit FS30DMPs (NPsinMPs) enteric microparticles to ensure complete medication protection at gastric-like pH and for targeted delivery to the colon. This approach was highly effective in reducing both diarrhea and hemorrhage scores, as demonstrated in Figure 2.

Figure 2 - Results of the article by Naeem *et al.* (2020).



(A) Changes in mouse body weight with time, normalized as a percentage of initial body weight and the mean of each group. (B) Diarrhea score; (C) Rectal bleeding score. Source: Adapted from Naeem *et al.* (2020).

Tests carried out with oral administration of trimethylchitosan nanoparticles (TMC-NPs) and alginate-coated trimethylchitosan nanoparticles (AS TMS-NPs) loaded with low molecular weight heparin (LMWH), which have been proven to improve the targeting property of this medication to the colon, indicate that LMWH-loaded NPs can accelerate mucosal healing by promoting the migration of intestinal epithelial cells. This resource is of great value in the treatment and prognosis of ulcerative colitis. It can reduce the recurrence, complications, and surgical rate of enterotomies, thus improving patients' quality of life (Yan *et al.*, 2020).

Researchers used nanoparticles loaded with dexamethasone (Dex) and modified with chitosan (CSO/Dex/LNPs) as carriers. They obtained a reduction in colonic atrophy and morphological changes in colonic tissue. At the same time, there was less damage to the mucosa, more E-cadherin, and less tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and nitric oxide (NO) in the sections of the colon that had colitis. Lipid nanoparticles were administered orally, as this is considered the preferred route due to their transmembrane solid capacity, better physical stability, greater protection of incorporated drugs against degradation, more constant plasma levels, controlled drug release and site-specific targeting, demonstrating the efficiency of these nanocarriers (Chen *et al.*, 2020).

Other studies with chitosan (CH) on nanocomposites produced by lyophilization, combining mucus-penetrating nanoemulsions (NE) and mucoadhesive chitosan sponges to prolong the intestinal administration of drugs by oral administration, were successfully designed. Mucopenetrating nanocarriers can spread through the mucosa, penetrate deep mucus regions, and reach the intestinal epithelium. The combination of different CH and NE concentrations allowed for adjusting the sponge's structural and mechanical properties and modulating the release of nanoemulsions. Because nanosystems can be released from the composite in a controlled manner and on-demand, they help to target the specific drug to the site and, ultimately, interact with the epithelial surface. Finally, oral administration of the nanocomposite in mice effectively increased intestinal permanence time (Rosso *et al*., 2021).

Finally, research states that there are relatively simple and easy-to-scale methods for preparing NPs. In addition, the principal medications used: heparin and dexamethasone; the polymers: chitosan, trimethyl chitosan, alginate, poly(lactic-co-glycolic acid) Eudragit FS30DMPs, and the natural molecules applied: lactoferrin, curcumin, hyaluronic acid, ethanol, eugenol, cinnamaldehydes, have a relatively low cost and are abundantly available. Second, most oral nanodrug delivery systems target only one site or cell type. However, some studies offer a new strategy to target two different cells based on the different mechanisms of ulcerative colitis treatment (Luo *et al*., 2021). Table 1 summarizes the major findings of each paper on review.

Table 1 - Research table which the essential features of the articles on the use of nanoparticles to aid in treating ulcerative colitis.

Reference	Test type	Major findings
Sung *et al*., 2022	*In vivo*	They suggest that reverse-engineered lipid nanoparticles (nLNPs) are excellent as a messenger ribonucleic acid (mRNA) delivery platform for treating ulcerative colitis.
Zhang *et al*., 2022	*In vivo*	Natural materials favor the combination of nanoparticles and microparticles to form edible compounds in preventing and treating ulcerative colitis.
Xu *et al*., 2022	*In vitro* *In vivo*	They related inhibition of inflammation, intestinal damage, and maintenance of intestinal flora homeostasis.
Sun *et al*., 2022	*In vivo*	The nanosystem effectively delivers the probe and drug into the colon and releases them when triggered by colonic pH. Thus, the drug released exerts high therapeutic efficiency against ulcerative colitis.
Ma *et al*., 2022	*In vivo*	It regulates the inflammatory microenvironment, repairing the epithelial barrier and regulating the microbiota.
Liu *et al*., 2022	*In vitro* *In vivo*	*In vitro*, experiments demonstrated that the nanoparticles greatly alleviated inflammatory reactions. *In vivo* studies have demonstrated that these nanoparticles associated with epigallo-catechin 3-gallate (EGCG) conjugated with cathelicidin-BF (CBF) and incorporated into the hydrogel delay the progression of ulcerative colitis and exert therapeutic effects.
Yang *et al*., 2022	*In vitro* *In vivo*	Mannose-rich oligosaccharides (MRO) used in selenium nanoparticles (SeNPs) are multifunctional, have good anti-inflammatory, and alleviate colitis symptoms.
Shrestha *et al*., 2022	*In vitro*	They obtained a good anti-inflammatory response and concluded that nanoparticle-based formulations could be adjusted to encapsulate other drugs.
Lee *et al*., 2022	*In vitro* *In vivo*	The nanocomplex successfully protected the structural integrity of the antibodies during their passage through the gastrointestinal tract and accumulation in the inflamed colon. Oral administration alleviated the symptoms of ulcerative colitis.

CONCLUSION

From reading and reflecting on the results obtained in each article, the reviewed studies indicate that modified liposomes and co-hybridized phospholipid vesicles have shown promising potential as drug delivery systems for treating ulcerative colitis. These systems can efficiently target the inflamed colon, delivering therapeutic agents directly to target cells. They also have sustained release capacity, which allows the maintenance of adequate therapeutic levels over time. Furthermore, encapsulating bioactive compounds, such as curcumin and eugenol, in proteins has also been shown to be an effective strategy for improving the solubility, protection, and absorption of these compounds in the gastrointestinal tract.

Other approaches that use nanoparticles loaded with heparin and dexamethasone have shown positive results in reducing inflammation, preserving the intestinal mucosa, and modulating inflammatory mediators. The combination of mucopenetrating and mucoadhesive nanoparticles with chitosan extended the intestinal delivery of drugs, thus increasing the residence time at the site of action.

It is important to emphasize that these drug delivery systems are still in the research and development phase, with challenges to be overcome, such as production scale and formulation optimization. However, the promising results obtained so far suggest that hybrid drug delivery systems have the potential to become effective and viable alternatives for the treatment of ulcerative colitis, providing improvements in patients' quality of life.

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