A review on curcumin colon-targeted oral drug delivery systems for the treatment of inflammatory bowel disease

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Abstract

Synthetic drugs and monoclonal antibodies are the typical treatments to combat inflammatory bowel disease (IBD). However, side effects are present when these treatments are used, and their continued application could be restricted by the high relapse rate of the disease. One potential alternative to these treatments is the use of plant-derived products. The use curcumin is one such treatment option that has seen an increase in usage in treating IBD. Curcumin is derived from a rhizome of turmeric (Curcuma longa), and the results of studies on the use of curcumin to treat IBD are promising. These studies suggest that curcumin interacts with cellular targets such as NF-κB, JAKs/STATs, MAPKs, TNF-α, IL-6, PPAR, and TRPV1 and may reduce the progression of IBD. Potentially, curcumin can be used as a therapeutic agent for patients with IBD when it reduces the incidence of clinical relapse. This review discusses the strategies utilized in designing and developing an oral colonic delivery dosage form of curcumin.

Keywords: *Curcumin, IBD, Gastrointestinal tract, Colon delivery, Microparticles, Nanoparticles,*

1. Introduction

Inflammatory bowel disease (IBD) is a chronic condition that causes inflammation of the lining of the large intestine and small intestine (Fakhoury et al., 2014). The major types of IBD are ulcerative colitis (UC) and Crohn's disease (Fakhoury et al., 2014). Crohn's disease can affect any part of the gastrointestinal tract (GIT) from the mouth to the anus, and it often affects one part of the small intestine before the large intestine (Roda et al., 2020). UC occurs in the large intestine and rectum and can progress from mild to severe disease (Nguyen et al., 2021; Sardou et al., 2022). Well-known therapies for IBD include corticosteroids and aminosalicylates, such as 5-ASA and 5-ASA, with anti-inflammatory effects is used as the oldest agent for IBD (Sardo et al., 2019; Sardou et al., 2021). Moreover, 5-ASA is also known as the first line of treatment for IBD. The anti-inflammatory effects of 5-ASA in the large intestine depend on the activity of peroxisome-activated γ-receptor (PPAR-γ), which is highly expressed in the colon epithelium and plays a role in the regulation of colonic inflammation (Fiorucci et al., 2010). Heterodimers formed by PPAR -γ and (RXR) regulate the expression of genes that control intestinal inflammation (Pekow and Bissonnette, 2014). The synergistic effect of these two receptors, PPAR-γ / RXR, has been reported to reduce colitis symptoms (Dworzanski et al., 2010). In addition, 5-ASA's ability to bind and activate PPAR-γ induces the apparent effects of this receptor (Karrout et al., 2015). Common side effects of 5-ASA include nausea, bloating, abdominal pain, diarrhea, headache, indigestion, and nasopharyngitis, which may occur in only 10% of patients taking the drug (Voskuil et al., 2019; Sardou et al., 2019; Kaffash et al., 2019). Due to the unwanted side effects of taking anti-inflammatory chemicals in treating IBD, the tendency to treat it with herbal medicines has increased (Ghasemian et al., 2016). In recent years, natural health products derived from herbs have also been widely developed as complementary treatments for many common ailments (Akkol et al., 2020; Enayati et al., 2022; Hosseini et al., 2021; Soltani et al., 2021; Zahedipour et al., 2022; Alidadi et al., 2020; Kupeli Akkol et al., 2021; Agagunduz et al., 2022; Fernandez et al., 2021). Curcumin (CUR) is an active hydrophobic polyphenol derived from the *Curcuma longa* plant, which has numerous pharmacological properties (Arora et al., 2022; Mohammed et al., 2021; Bavarsad et al., 2019; Ganjali et al., 2017; Ghasemi et al., 2019; Iranshahi et al., 2010; Panahi et al., 2017; Parsamanesh et al., 2018; Sahebkar and Henrotin, 2016), including therapeutic efficacy in IBD (H Farzaei et al., 2015). CUR's therapeutic potential includes reducing tissue damage and oxidative stress, modulation of cytokine expression, and suppression of expression of

inflammation-related genes (Razavi et al., 2021; Hassanzadeh et al., 2020; Momtazi-Borojeni et al., 2018). CUR inhibits the activation of transcription factors, multiple protein kinases, and antiapoptotic proteins and modulates various inflammatory cytokines by suppressing the inflammatory transcription factor NF-κB (Xu et al., 2022). NF-κB transcription factor plays a key role in a host of cellular functions, such as angiogenesis and apoptosis, as well as in regulating the expression of several genes involved in inflammation and the immune response (Yun Chen et al., 2019). Several molecules, such as TNF, IL-1, IL-6, IL-8, and IL-10, as well as tissue-degrading enzymes, are involved in the inflammatory response by the NF-κB pathway (Fu et al., 2019). TNF-α is the fastest cytokine released upon injury, which regulates the production of pro-inflammatory cytokines through its receptors (Lively and Schlichter, 2018). Therapies that target TNF-α significantly improve the progression of IBD. Therefore, CUR activity is essential in this context because it exerts its effects by modulating NF-κB and proinflammatory cytokines, such as IL-1β, TNF-α and IL-6 (Vecchi Brumatti et al., 2014). There are several studies on the development of site-specific delivery systems for CUR. The approaches for targeting CUR in the colon are discussed in this review.

1.1. Pharmacology of CUR

IBD is an autoimmune disease in which that CD4-positive T lymphocytes such as Th1, Th2 and Th17 are involved (Rahimi et al., 2019). Lack of immunity causes these lymphocytes to produce a large number of pro-inflammatory factors and then stimulate IBD (Rahimi et al., 2019). Studies show that CUR inhibited the expression of IL-β mediated inflammatory cytokines such as IC-1 and IL-8 in IEC-6, HT29 and Caco-2 cells (Jobin et al., 1999; Caban and Lewandowska, 2022; Lu and Zhao, 2020). The expression level of IL-1 increases significantly during the active period of IBD. This cytokine mainly activates T cells and macrophages (Abdollahi et al., 2018). CUR can inhibit the expression and secretion of inflammatory protein (MIP-2), IL-1β and cytokine (KC) by macrophages stimulated by lipopolysaccharide (LPS) and also prevents the accumulation of neutrophils at the site of intestinal inflammation and thus reduces the inflammatory response of IBD (Larmonier et al., 2011). In addition, CUR regulates the expression of ALDH1a and IL-10 in bone marrow-derived dendritic cells (DCs) (Isaacs and Hilkens, 2019). After treatment with CUR, DC cells can induce the differentiation of CD4+ T cells into T regulatory cells (Treg), thereby preventing the activation of antigen-specific T cells. Thus, it helps to restore the immune balance

(Cong et al., 2009). In the plasma and intestinal mucosa of patients with IBD, the level of IFN-γ is high and mainly produced by Th1 cells (Ju et al., 2020). CUR can inhibit IFN-γ signaling in colon epithelial cells (Walrath et al., 2020). This is a dual regulatory mechanism in colonic epithelial cells, which leads to the improvement of IBD (Midura-Kiela et al., 2012). TNF-α and IL-6 are the major inflammatory cytokine in IBD and play a key role in intestinal disorders. CUR can block the release of these inflammatory cytokines by inhibiting B lymphocytes (Maradana et al., 2013). Signal transduction pathways also play an important role in intestinal inflammation (Soendergaard et al., 2018). P38 mitogen-activated protein kinase (MAPK) leads to increased expression of inflammatory mediators, resulting in intestinal inflammatory damage (Sun et al., 2020). Studies have shown that CUR can significantly inhibit p38MAPK activation and histone acetylation, thereby reducing inflammatory responses (Epstein et al., 2010a; Khan et al., 2019; Jialuo Chen et al., 2020). CUR can also reduce the release of TNF-α and other pro-inflammatory factors by inhibiting the p38MAPK signaling pathway, thus reducing intestinal mucosal damage (Joon-Yeop Yang et al., 2013). By affecting the dendritic cells of the spleen, CUR reduces the expression of stimulated signals, thereby reducing the level of secretion of pro-inflammatory factors (Mei Yang et al., 2017). One of the main pathogenesis of IBD is the imbalance of the intestinal mucosal immune system (Guan, 2019). The JAK/STAT pathway is a pathway through which many pro-inflammatory cytokines, such as IL-1, IL-6 and INF-γ, transmit inflammatory responses (Jamilloux et al., 2019). The phosphorylation status of STAT3 in the STAT family in UC and CD patients and mice of the DSS-induced IBD model is the highest, suggesting that STAT3 may play an important role in the pathogenesis of IBD (Wang et al., 2020). The important point is that CUR can inhibit the STAT3 pathway and exert anti-inflammatory effects (Suzuki et al., 2001).

1.2. Drug delivery to the Colon

In recent years, delivering a drug to the colon has been the aim of many pharmaceutical companies (Jain, 2020). Colonic drug delivery is used not only for protein and peptide-based drugs (which are digested by intestinal enzymes) but also for low molecular weight drugs that are used to treat colon-related diseases such as UC and cancer is also beneficial (Varanko et al., 2020). The advantages of drug delivery to the colon have led to the desire to develop this system. For example, the transit time of substances in the colon is longer, which increases the duration of absorption for

drugs that have very few absorption sites (Manoj Kumar and Kaushik, 2018). The colon is the area with the least destructive impact, variety and intensity of movement compared to the stomach and small intestine (Gelberg, 2014). The colon can absorb drugs both locally and systemically, and the local release of drugs allows the local treatment of IBD. Various systems have been designed for colonic drug delivery (Amidon et al., 2015). The main mechanism of these systems is based on changes in the physiological factors of the GIT, such as pH, residence time, pharmaceutical form, and microflora in the GIT (Koziolek et al., 2015). Nano-delivery systems, osmotic control systems, pulse drug delivery systems, bioadhesive systems, and pressure-dependent systems, which are mostly research-based, are also used for colonic drug delivery (Fam et al., 2020; Nief et al., 2018; Anup Patil et al., 2018). In novel systems, it has been tried to combine different mechanisms. The advantage of these systems is that the dependence of the integrated system on changes in the physiological conditions of the GIT will be less; therefore, drug release from the system will be more predictable under different conditions (Nayak et al., 2010). For successful colonic drug delivery, the drug must be protected in the upper GIT and the drug release should be prevented in the stomach and small intestine. In other words, the formulation should be designed to release its medicinal content in the colon area (Amidon et al., 2015). To design drug delivery systems, a detailed understanding of the physiology of the GIT is needed (Amidon et al., 2015).

1.3. Anatomy and physiology of the GIT

The GIT consists of the digestive tract and its related organs. The alimentary canal is a twisted muscular tube about 7 to 9 meters long and its main function is digestion, absorption of nutrients, and elimination of waste materials (Sensoy, 2021). The GIT includes the mouth, pharynx, esophagus, stomach, small intestine, large intestine, rectum, and anus (Nguyen et al., 2021). After oral administration of food and pharmaceuticals, it is transferred through the esophagus to the stomach, aided by peristaltic contractions. In the stomach, food is digested by stomach acids and enzymes, especially peptidases (Hua, 2020; Chaudhry et al., 2021). The least drug absorption occurs in the stomach because the surface area is small (Chaudhry et al., 2021). The small intestine is the longest part of the GIT, where enzymes of the liver and pancreas complete digestion and the most absorption of nutrients takes place in this part (Sensoy, 2021). Owing to its large area, the small intestine is also the greatest absorption site of drugs (Murakami, 2017). In adults, the small intestine surface is greatly increased due to the presence of villi and microvilli that are well

supplied with blood vessels and reaches about 200 m^2 (Igam, 2019). Intestinal villi are small finger-like villi formed from the epithelial lining (Kim and Kim, 2020). There are millions of villi in the small intestine, and their type is single-layer epithelial cells, and each of these villi is about 0.5 to 1.6 mm. The villi increase the internal surface of the small intestine, which increases the absorption surface (Lim et al., 2019). Increasing the surface improves the absorption of nutrients such as monosaccharides and amino acids from the semi-permeable surface of villi. In other words, increasing the absorption level reduces the distance asked for molecules that will be absorbed (Igam, 2019). The villi are in contact with the blood vessels so that the nutrients absorbed by the blood flow can be transferred to other organs (Yanan Zhang et al., 2020). The colon is the last major part of the GIT. Its main function is to excrete waste, absorb any remaining nutrients, and return water to the system, which is important for homeostasis. In the end, the waste materials pass through the rectum and anus (Nigam et al., 2019). The colon is also used for systemic or local delivery of drugs, and anatomically it can be divided into four segments: ascending colon, transverse colon, descending colon, and sigmoid colon (Nigam et al., 2019). The colon's mucus is smooth and has no specialized villi, thus making it much smaller. However, the surface of the colonic epithelium is reinforced with pit-shaped structures. The human GIT is very complex, and many physiological barriers can be challenging in drug delivery to the colon (Hua, 2020). These challenges include poor solubility and stability, low permeability, and variation in GIT physiology (pH and residence time) (Viswanathan et al., 2017). Therefore, in formulation design, considerations should be paid to the following factors: the pH of each part of the GIT, the residence time of the pharmaceutic in each part of the GIT, and the reaction of the formulation to the enzyme activity in the colon (Hua, 2020). The pH suddenly increases from 1.2 (stomach pH) to 6.5 (duodenum pH) and suddenly reaches 7.2 in the terminal ileum (P Kumar and Mishra, 2008). It takes about two hours for the pharmaceutical dosage form to pass through the stomach, one hour through the duodenum, and two hours through the jejunum. The transit time through the ileum is one hour; on average, it takes about 10 hours to pass through the colon (Müller et al., 2018). In other words, the drug stays in the patient's GIT for about 15 hours. Depending on the type of formulation for the disease (UC or Crohn's), it must gradually and slowly release all medicinal content in the inflamed parts so that all affected areas have access to the appropriate drug concentration (Vinarov et al., 2021). Polysaccharides can also be used in colon delivery systems as a system sensitive to microbial degradation. Bacterial activity in the colon, which leads to the

production of azoreductase, nitroreductase, glucosidase, glucuronidase, and esterase enzymes, can be the breakdown and destruction of the polysaccharide in the dosage form and causes a specific release of drug in the colon area (Patel Parul et al., 2012). Therefore, all these items should be considered in the formulation design. Fig. 1. Shows the key physiological factors in the GIT that should be considered in formulation design for colon delivery.

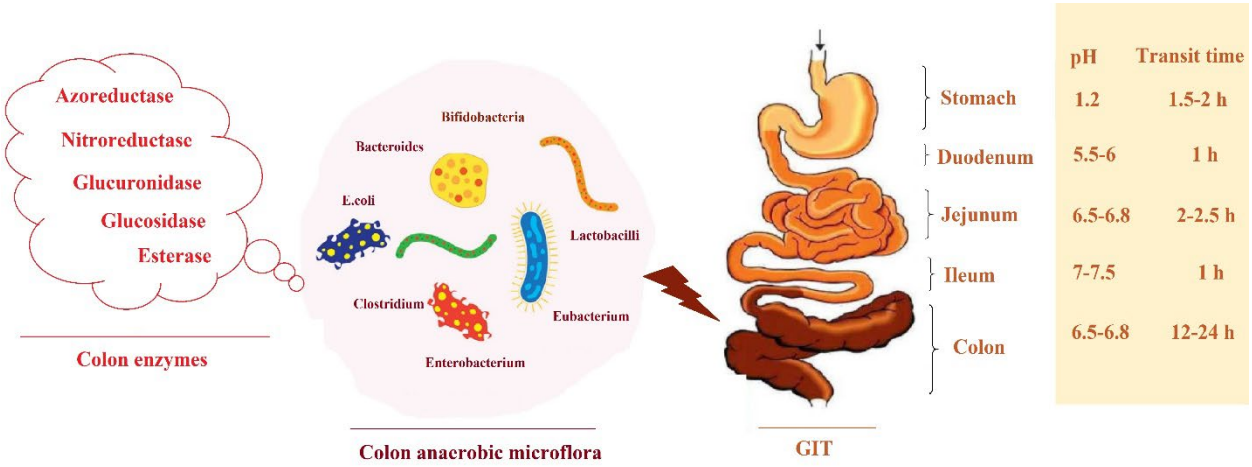

Fig. 1. Key physiological factors in the GIT that should be considered in formulation design

2. CUR colon delivery systems

2.1. CUR pellet-based systems

Pellets are spherical or semispherical particles formed by different agglomeration methods of fine powder or granules. Pellets with a size of 0.5-1.5 mm are used for oral delivery (Ahir et al., 2015). The advantages of using pellets include a fast exit from the stomach, high absorption and bioavailability, free flowing, masking, the unpleasant taste of drugs, high drug loading capacity without producing large particles, easy coating due to the smooth surface and spherical shape, the appropriate coating to adjust a controlled drug release rate, and the possibility of simultaneous use of drugs that interfere with each other (Ahir et al., 2015). Sureshkumar et al. (2009) prepared pellets containing CUR by extrusion spheronization method and coated them with hydroxypropyl methylcellulose and pectin. The dissolution test of the optimal formula of the pellets in the simulated environment of the GIT showed the minimum release of the pellets in the acidic pH and the maximum release in the buffered environment of pH 7 (Sureshkumar et al., 2009). Sha et al. (2021) constructed a self-micro emulsifying drug delivery systems (SMEDDS) formulation .This formulation led to improving CUR drug acceptability through the determination of equilibrium

solubility, the evaluation of self-emulsifier grading, and the design of ternary phase diagrams. According to the pharmacokinetic study in rabbits, $AUC_{0-\tau}$ of the CUR solid SMedds pellets and CUR suspension were 5.91 ± 0.28 μg/mL·h and 2.05 ± 0.04 μg/mL·h, respectively. Moreover, the relative bioavailability was 289.30%. Their findings suggest the industrial application of solid-SMEDDS pellets (Sha et al., 2021). In another study by Desai and Momin (2020) to treat IBD, the cores of pellets were formulated by Carbopol 940 (CP940) and hydroxypropyl cellulose (HPC-H) in a ratio 1:1 using the extrusion/spheronization process. Eudragit® S100 was a controlling agent for drug delivery to the colon. The in vitro dissolution profiles of the coated pellets indicated 12% of CUR and 14% of cyclosporine were released by the end of six hours (at pH 6.8), while 71% of CUR and 76% of cyclosporine were released by the end of 24 h (at pH 7.4). One animal study showed the effect of CUR and cyclosporine coated pellet with Eudragit® S100 coating in reducing colitis caused by acetic acid, which is associated with weight gain and improvement of clinical, macroscopic and microscopic parameters compared to free CUR and cyclosporine. Their results revealed that the combination of CUR and cyclosporine a has been shown to act as a successful targeted drug delivery system in managing IBD, with a synergistic effect compared to individual drugs at high doses (Desai and Momin, 2020). Kshirsagar and Pandit formulated sustained-release pellets of CUR using Carboxymethyl Tamarind Seed Polysaccharide (CMTSP). In vivo study of pellets revealed the presence of more drugs in plasma than in pure drug-loaded pellets (Kshirsagar and Pandit, 2018). Deng et al. made pellets from CUR-loaded PLGA and PEG (CUR-Pellets). In vitro studies showed that a high loading capacity of CUR was achieved with a diameter of about 1.0 mm of pellets. In vivo pharmacokinetics studies on Sprague-Dawley rats showed the rapid release of CUR-Pellets Gel in the body was significantly decreasing. These results exhibited that this thermosensitive pellet/gel can potentially increase the therapeutic effects of drugs with poor solubility and without rapid release in the body (Deng et al., 2020). A summary of CUR delivery systems designed for colon delivery has been presented in Table 1.

2.2. **CUR tablet-based system**

The efficacy of oral formulations is often limited by poor stability in the stomach's acidic environment and low drug solubility. Even in drugs that are coated, there is a possibility of coating destruction. In amorphous dispersions, drug crystallisation is possible; therefore, to overcome these limitations, using a polymeric prodrug hydrogel in the tablet formula can be effective (Vinod S Patil et al., 2022). In the study of Butte et al., a CUR tablet was produced using the compression

coating technique. To increase the solubility of CUR, an inclusion complex was formed with hydroxypropyl-β-cyclodextrin. The CUR inclusion complex tablet core compression was done by two layers of pectin and Eudragit® S100 polymers. The higher the coating weight and pectin ratio, the better the CUR tablet was protected in the colon. The Roentgenography method and human volunteers were used to conduct in vivo studies. Their research showed that combining pectin and Eudrgit S100 could make the system biodegradable and pH-dependent for drug targeting to the colon (Butte et al., 2014).

2.3. **CUR microparticles-based systems**

Almeida et al. (2017) used magnetic microgels made of pectin maleate, N-isopropylacrylamide, and Fe_3O_4 nanoparticles with pH and temperature-responsive properties to investigate the release of CUR. CUR was loaded into the microgels and the release assay was performed in different temperature conditions (25 or 37 °C) and simulated environments of gastric fluid (SGF) and intestinal fluid (SIF). The external magnetic field led to a slow and sustainable release of CUR. Loaded CUR showed higher stability, bioavailability, and solubility than free CUR (Almeida et al., 2017). Chen et al. (2018) reported that bowel-shaped microparticles (BMPs) could be performed as an easily scalable oral drug delivery system for the treatment of UC. They used BMP, loaded with CUR, during the fabrication process. CUR molecules were dispersed in an amorphous state inside the polymer matrix. BMPs had high hydrophilic properties due to the presence of Pluronic F127 and polyvinyl alcohol on their surface. Moreover, oral BMPs can effectively reduce UC based on a mouse model induced by sodium dextran sulfate (Qiubing Chen et al., 2018). Xiao et al. (2015) produced CUR loaded-microparticles (MPs) with pH-sensitive Eudragit® S100 and poly(lactide-co-glycolide) (PLGA) using an emulsion-solvent evaporation technique in size range from 1.52 to 1.91 μm. To prevent the rapid release of CUR from MPs at pH 1.2 and 6.8, it can be increased by PLGA content in the formulation. Eudragit® S100/PLGA MPs with a weight ratio of 1:2 were able to sustain the release of CUR and released 48% of the initial drug load at pH 7.2-7.4 during 20 hours of incubation. In vivo studies indicated a higher therapeutic efficacy of MPs compared to CUR for oral administration in reducing colitis in a mouse model. Therefore, their system could be promising as a scalable drug carrier for the effective clinical treatment of UC (Xiao et al., 2015). Hals et al. designed polymer microparticles loaded with CUR for colonic delivery. They used Eudragit® FS 30D (FS) as a pH-dependent and polycaprolactone polymer as a microbial degradation drug delivery system to optimise

294 microparticle formulation. Formulations containing a 60:40 ratio of polycaprolactone to FS
295 showed the best results in vivo studies for targeted delivery of CUR to the colon area (Hales et al.,
296 2020).

297 2.4. **CUR microspheres-based systems**

298 BLANCO-GARCÍA et al. (2017) prepared microspheres (Ms) based on zein (ZN) and
299 Gantrez® AN119 (PVMMA) by spray-drying and coated with a pH-sensitive polymer FS.
300 Although the encapsulation efficiency for ZN/PVMMA microspheres was about 89%, the coating
301 process with Eudragit® resulted in a 62% decrease in encapsulation efficiency. It was found that
302 the microsphere coating resulted in 20% retention of the drug 6 hours after release .CUR-loaded
303 microspheres significantly inhibited proinflammatory cytokines in LPS-stimulated macrophages.
304 These results suggest the beneficial properties of ZN/PVMMA microspheres as an alternative for
305 the delivery of CRM to the intestinal tract (Blanco-García et al., 2017). Zhang t et al. investigated
306 pectinate calcium microspheres coated with Eudragit® S100 as a colon delivery carrier for CUR.
307 Calcium pectinate microspheres loaded with CUR were prepared by the emulsification linkage
308 method. In vitro drug release experiments showed that the release of CUR was significantly
309 increased in the presence of 1% mouse cecum in a gastric simulation medium (Lin Zhang et al.,
310 2011). Sareen et al. (2016) used an emulsion cross-linking technique to produce CUR-loaded
311 chitosan microspheres coated by Eudragit® S-100. Their results indicated that uncoated CUR-
312 chitosan microspheres led to a rapid release of CUR in the first 4 h. In comparison, Eudragit® S-
313 100 coated microspheres prevented burst release of CUR and provided a controlled release for up
314 to 12 h. A small amount of CUR in the stomach and small intestine in an in vivo organ
315 biodistribution study confirmed the integrity of the microsphere in the upper GIT. The in vivo
316 study showed a significant reduction in the severity and extent of colon damage with CUR-loaded
317 microspheres compared to pure CUR, which was further confirmed by a histopathological study
318 (Sareen et al., 2016). In the clinical studies of Yu et al., the effect of chitosan CUR microspheres
319 on patients with UC was evaluated. The ELIZA method investigated Serum miR-224-3p, TLR4,
320 TNF-α, and NF-κB levels. In animal studies, DSS was applied to induce IBD in mouse models.
321 The expression of TNF-α, TLR4, and NF-κB increased signally in the observation group, while
322 the expression of miR-224-3p decreased. In the control group, the TNF-α, TLR4, and NF-κB
323 decreased, while the expression of miR-224-3p increased; this difference was significant ($P < 0.05$).
324 After treatment, the serum expression of TNF-α, TLR4, and NF-κB in the sulfasalazine,

CUR, and CCM groups was significantly decreased. In contrast, the expression of IFN-γ was significantly increased compared to the control group and this difference was significant ($P < 0.01$). In CCM compared to the sulfasalazine group, there was a significant difference in effectiveness ($P < 0.05$). However, in CCM compared to the CUR group, there was a significant difference in efficiency ($P < 0.05$). CCM may increase the level of IFN-γ and the protein expression levels of SDF-1, CXCR4 and miR-224-3p by inhibiting the expression of TNF-α, NF-κB and TLR4. Therefore, it reduces the inflammatory response and colon tissue damage in mice with UC through anti-inflammatory effects. (Yu et al., 2022).

2.5. **CUR Nano formulation-based systems**

Kotla et al. studied the development of anionic-charged nanocarriers (IT-NCs) loaded with an immunosuppressive model drug. Adhesion to a charge-modified surface in vitro and two murine colitis models, 2,4,6-Trinitrobenzene sulfonic acid (TNBS) and dextran sodium sulfate (DSS), was assessed. IT-NCs showed the effectiveness of treatment on colitis in both animal models compared to the free drug. Furthermore, an ex vivo study on biopsy samples from patients with colitis showed that IT-NCs preferentially adhered to inflamed biopsies compared to normal biopsies (Kotla et al., 2022). Shafiee et al. (2019) encapsulated CUR using Fe_3O_4 magnetic nanoparticles (MNPs) functionalized with 3-aminopropyltriethoxysilane (APTES) and coated by chitosan (CS) and gum kathira (TG). The release behaviour of CUR at two different pHs, 7.4 and 3.4 and temperatures of 37°C and 40°C, showed that the nanocomposite had a higher swelling ratio at pH 3.4 and temperature of 40°C with drug release profiles in temperature-sensitive conditions. The results of this study show that the presented nanocomposite has a good potential to deliver CUR to the colon area (Shafiee et al., 2019). Luo et al. (2017) encapsulated CUR using an oral food-grade edible nanocarrier composed of genipin (Gnp) cross-linked human serum albumin coated with tannic acid (TA). The TA layer and Gnp cross-linking resulted in delayed release of CUR in simulated gastric fluid, prolonged colonic adhesion, and increased uptake in Caco-2 cells. Colitis symptoms in DDS-treated mice were significantly reduced by oral administration of TA/CUR-NPs compared to the control group (Luo et al., 2020). Salah et al. (2022) used crosslinked starch nanocarrier (NPL), and the anti-inflammatory effects of NPL/Cur formulation were evaluated in the early and late stages of inflammation. NPL/Cur formulation decreased the secretion of proinflammatory cytokines IL-1β, IL-6, and IL-8 and increased the anti-inflammatory cytokine IL-10. In their ex vivo study, the

prescription NPL/Cur in mice with acute colitis delivered CUR better in the epithelium. This study emphasizes the potential of the presented formulation for ulcerative colitis treatment (Salah et al., 2022). Oshi et al. defined nanoparticles composed of CUR nanocrystals in the core and chitosan/alginate multilayers in the shell for colon delivery to treat UC. Evaluation of the release of CUR in the SGF, SIF, and colon showed that the release in the initial part of the GIT was very low, while the release in the terminal part of the GIT significantly increased. Moreover, in vivo studies in mice confirmed the in vitro studies. Hence, the biodistribution in the GIT showed that the distribution of nanoparticles is significantly higher in the colon than in the upper GIT (Oshi et al., 2020). To increase the permeability of nanoparticles to the colon mucosa, Zhou et al. functionalized CUR nanoparticles with pluronic F127. The results of in vitro studies confirmed the nontoxicity of these nanoparticles. On the other hand, in vivo study also showed that the penetration ability of CUR functionalized with pluronic F127 increased significantly compared to CUR nanoparticle alone (Zhou et al., 2019). Chen et al. designed porous and non-porous nanoparticles of CUR by emulsion solvent evaporation method. Both types of nanoparticles showed a controlled release in the simulated gastrointestinal environment. However, porous nanoparticles prevented the release of inflammatory cytokines such as TNF-a, IL-6, and IL-12 more effectively than non-porous nanoparticles. In addition, in vivo studies showed the higher therapeutic efficiency of porous nanoparticles in reducing UC induced in mice (Qiubing Chen et al., 2017). Ohno et al. investigated the effect of CUR nanoparticles called Tracurmin on UC induced in BALB/c mice. The results of their in vivo studies showed that tracurmin had a significant impact on the reduction of inflammatory symptoms such as disease activity index, body weight loss, histological colitis score and significantly improved mucosal permeability (Ohno et al., 2017).

379 Table 1

380 A summary of CUR delivery systems designed for colon delivery

-	Study type	Target drug delivery system	Type of system	Disease studied	Reference
1	In vitro - In vivo (rabbit -pharmacokinetic study)	Pellet	Pectin-hydroxypropyl methylcellulose-coated CUR pellets	IBD	(Sureshkumar et al., 2009)
2	In vitro - In vivo (rabbit - pharmacokinetic study)	Pellet	Solid self-microemulsifying pellets	IBD	(Sha et al., 2021)
3	In vitro - In vivo (rat)	Pellet	CUR pellet	IBD	(Kshirsagar and Pandit, 2018)
4	In vitro - In vivo (rat)	Pellet	Bioadhesive pellets of CUR coated with Eudragit® s	IBD	(Desai and Momin, 2020)
5	In vitro - In vivo (rat)	Pellet	CUR-Pellets-Gel (Pellets made from PLGA and PEG loaded with CUR)	IBD	(Deng et al., 2020)
6	In vitro - In vivo (human volunteers)	Tablet	CUR inclusion complex was compressed between the layers of a polymer blend of pectin and Eudragit® S100	IBD	(Butte et al., 2014)
7	In vitro	Microgels	Magnetic microgels of CUR	IBD	(Almeida et al., 2017)
8	In vitro - In vivo (mice)	Microparticles	Loading CUR on bowl-shaped microparticles	IBD	(Qiubing Chen et al., 2018)
9	In vitro - In vivo (mice)	Microparticles	Microparticles with pH-sensitive Eudragit® S100 and poly(lactide-co-glycolide) (PLGA)	IBD	(Xiao et al., 2015)
10	In vitro - In vivo (mice)	Microparticle	CUR-loaded polymeric microparticles	IBD	(Hales et al., 2020)
11	In vitro	Microspheres	CUR microspheres based on zein and Gantrez®	IBD	(Blanco-García et al., 2017)
12	In vitro - In vivo (rat)	Microspheres	Calcium pectinate microspheres of CUR	IBD	(Lin Zhang et al., 2011)
13	In vitro - In vivo (mice)	Microspheres	Eudragit® S-coated chitosan microspheres	IBD	(Sareen et al., 2016)
14	In vitro - In vivo (mice) - Clinical trial	Microsphere	CUR chitosan microsphere	IBD	(Yu et al., 2022)
15	In vitro - In vivo (mice)	Nanoparticles	nanocarriers loaded with an immunosuppressant model drug (CUR)	IBD	(Kotla et al., 2022)
16	In vitro	Nanocomposite	CUR-nanocomposite	IBD	(Shafiee et al., 2019)

17	In vitro - In vivo (mice)	Nanoparticles	Food-grade nanocarrier composed of tannic acid (TA)-coated, Genipin (Gnp)-crosslinked human serum albumin (HSA) to encapsulate CUR	IBD	(Luo et al., 2020)
18	In vitro (Cellular) - ex vivo (mice)	Nanoparticles	Starch nanocarrier + CUR	IBD	(Salah et al., 2022)
19	In vitro (Cellular) - In vivo (mice)	Nanoparticles	Nanoparticles composed of CUR nanocrystals	IBD	(Oshi et al., 2020)
20	In vitro (Cellular) - In vivo (mice)	Nanoparticles	F127-functionalized polymeric nanoparticles	IBD	(Zhou et al., 2019)
21	In vitro (Cellular) - In vivo (mice)	Nanoparticles	Porous CUR-loaded polymeric nanoparticles	IBD	(Qiubing Chen et al., 2017)
22	In vitro (Cellular) - In vivo (mice)	Nanoparticles	Nanoparticle CUR	IBD	(Ohno et al., 2017)

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3. Dose, safety and side effects

CUR's safety, tolerability, and nontoxicity at high doses are well established. Oral doses of 10-12 g/day are well tolerated in humans (Dei Cas and Ghidoni, 2019). However, due to the bulky nature of this amount of compound, it may be difficult to achieve a diet above 8 g (Epstein et al., 2010b). In clinical trials, diarrhoea has been reported as the only side effect of CUR, which is safe and well tolerated (Sasidharan et al., 2014). However, as a caveat, these trials usually examine short-term outcomes, and longer-term studies should be conducted. The safety has also been shown in vulnerable populations such as children and adolescents but further evidence is still warranted (Heidari et al., 2022).

4. Conclusion

A Delay in the remission of IBD causes relapse, which affects the patient's quality of life. And since IBD is a chronic disease and requires daily medication, the patient will incur high costs for medical treatment. Chemical drugs, including 5-ASA and budesonide, which are used as the first and second line of therapy in this disease, have a high price, and typical chemical drug-related side effects have been observed in some patients. As a natural product with a low price, CUR has received much attention from scientists in recent years. Numerous studies have demonstrated its biological activities and medicinal properties in vitro and in vivo. Over the past decades, several basic and clinical studies have shown the therapeutic potential of CUR. However, the mechanism of action of CUR is complex and includes multiple signalling pathways. Various single and numerous unit systems such as pellets, tablets, microparticles, microgels, microspheres, and nano-based systems have been adopted to modify and optimize CUR formulations for colon delivery. It should be noted that substantial clinical trials are needed to identify the safety and efficacy of CUR. Hopefully, more studies on CUR will provide new drug research directions for IBD treatment in the near future.

Conflict of interest

The authors declare no conflict of interest.

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