Disciplinarum Scientia. Série: Naturais e Tecnológicas, Santa Maria, v. 23, n. 3, p. 173-185, 2022.
Recebido em: 15.03.2023. Aprovado em: 11.09.2023.
ISSN 2176-462X
DOI: 10.37779/nt.v23i3.4504

ANTI-INFLAMMATORY POTENTIAL OF CURCUMIN IN THE TREATMENT OF ULCERATIVE COLITIS: A REVIEW ARTICLE

POTENCIAL ANTI-INFLAMATÓRIO DA CURCUMINA NO TRATAMENTO DA COLITE ULCERATIVA: UM ARTIGO DE REVISÃO

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ABSTRACT

Curcumin is frequently used to treat inflammatory conditions such as ulcerative colitis (UC), characterized by irritation and ulceration within the intestinal colon. Nevertheless, its limited solubility in aqueous solutions and challenges in terms of bioavailability often impact the efficacy of treatments. UC is known to have multifactorial pathogenesis, with genetic, infectious, immunological, and dietary factors contributing to its occurrence. Its manifestations include bloody diarrhea, cramps, and abdominal tenderness. The objective of this study was to conduct an exploratory and qualitative literature review concerning the utilization of curcumin for managing UC. Upon analyzing the gathered literature, it becomes evident that curcumin exhibits exceptional anti-inflammatory properties. Notably, the most favorable outcomes are observed when employing nanostructured curcumin, which enhances permeability, bioavailability, and aqueous solubility. In cases of UC, the pronounced inflammatory processes can even result in the development of neoplasms. In the reviewed studies on colitis, curcumin proves to be a therapeutic option by reducing the inflammatory process. Moreover, when combined with medications used for colitis treatment, curcumin enhances the effects of these drugs, making them more effective than when used alone to treat this disease.

Keywords: Inflammatory bowel disease, Turmeric, Nanotechnology.

RESUMO

A curcumina é frequentemente utilizada para tratar condições inflamatórias, como a colite ulcerativa (CU), caracterizada por irritação e ulceração no cólon intestinal. No entanto, a sua solubilidade limitada em soluções aquosas e os desafios em termos de biodisponibilidade frequentemente afetam a eficácia dos tratamentos. A CU é conhecida por ter uma patogênese multifatorial, com fatores genéticos, infecciosos, imunológicos e dietéticos contribuindo para a sua ocorrência. Suas manifestações incluem diarreia com sangue, cólicas e sensibilidade abdominal. O objetivo deste estudo foi realizar uma revisão exploratória e qualitativa da literatura sobre a utilização da curcumina no manejo da CU. Ao analisar a literatura coletada, torna-se evidente que a curcumina apresenta propriedades anti-inflamatórias excepcionais. Notavelmente, os resultados mais favoráveis são observados ao empregar a curcumina nanoestruturada, que melhora a permeabilidade, a biodisponibilidade e a solubilidade aquosa. Nos casos de CU, os processos inflamatórios pronunciados podem até resultar no desenvolvimento de neoplasias. Nos estudos revisados sobre colite, a curcumina demonstra ser uma opção terapêutica ao reduzir o processo

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inflamatório. Além disso, quando combinada com medicamentos usados para o tratamento da colite, a curcumina potencializa os efeitos desses fármacos, tornando-os mais eficazes do que quando usados isoladamente para tratar esta doença.

Palavras-chave: *Doença inflamatória intestinal; Cúrcuma; Nanotecnologia.*

INTRODUCTION

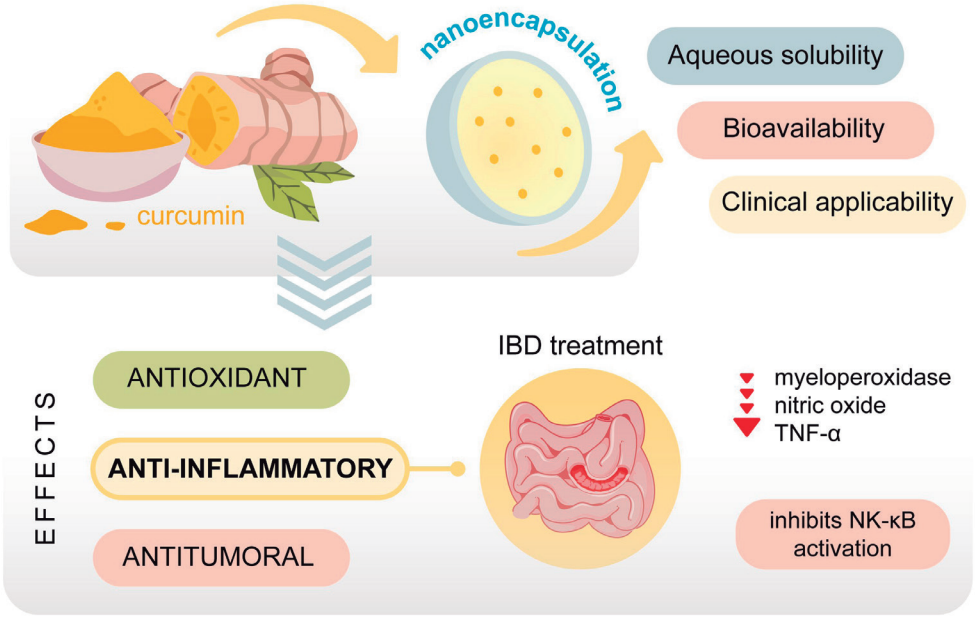
Curcumin, the primary bioactive compound found in *Curcuma longa*, has garnered substantial attention from researchers due to its multifaceted properties, including anti-inflammatory, antitumoral, antioxidant, and wound-healing capabilities (ZHANG *et al*., 2019; KARTHIKEYAN *et al*., 2021). Although curcumin was initially isolated from *Curcuma longa* rhizomes by Vogel and Pelletier in 1815, it was not until 1842 that Vogel Jr. achieved a pure curcumin preparation (KOTHA; LUTHRIA, 2019).

Ulcerative colitis (UC) is a chronic inflammatory disorder affecting the intestinal tract. Its etiology is likely multifactorial, involving intricate interactions between environmental factors, genetic susceptibility, and immune dysregulation. Although associations with these components have been established in its pathogenesis, comprehensive investigations remain necessary to unravel the underlying causes (KEDIA *et al.,* 2017).

Long-term inflammatory bowel diseases (IBD) can elevate the risk of cancer development. Research indicates that natural products endowed with anti-inflammatory attributes, such as curcumin, hold promise in mitigating inflammation associated with IBD (BURGE *et al.,* 2019). Nevertheless, curcumin's practical application is often curtailed by challenges like its low solubility in aqueous environments, limited bioavailability, and intricate pharmacokinetic profiles. These profiles, influenced by solubility and bioavailability factors, affect distribution and metabolism. Various formulations have been devised, combining curcumin with diverse components like polymers, lipids, and nanoparticles in precise ratios. This innovative approach aims to enhance solubility, cellular absorption, target specificity, retard compound degradation, and augment bioavailability (KOTHA; LUTHRIA, 2019).

The potent anti-inflammatory attributes of curcumin have positioned it as a potential treatment for colitis. Earlier studies have indicated its potential to effectively attenuate inflammation linked to experimental colitis, offering relief to individuals with UC. By alleviating intestinal inflammation through its anti-inflammatory, antioxidant, and protective effects, curcumin has demonstrated the capacity to diminish nitric oxide concentration, myeloperoxidase levels, and tumor necrosis factor (TNF-α) while inhibiting nuclear factor kappa B (NF-κB) activation (ZHANG *et al*., 2019; WEI *et al*., 2021), as illustrated in Figure 1.

Figure 1 - Anti-inflammatory potential of Curcumin for the treatment of UC.



So, UC's root causes include genetic predisposition, infectious agents, an imbalance in the gut microbiota, an immune response, and dietary influences, among others (YAN *et al*., 2009; LU e ZHAO, 2020). UC is categorized based on the severity of its symptoms, ranging from mild to moderate, severe, and even fulminant presentations ant (FEUERSTEIN; CHEIFETZ, 2014). Bloody diarrhea is the most apparent symptom of ulcerative colitis, and people with pancolitis may also experience cramps along the entire length of the colon or in the lower left quadrant. In cases of severe colitis, heightened abdominal sensitivity serves as an alert, signifying a more adverse prognosis and the potential development of fulminant colitis (KUCHARZIK *et al*., 2020).

METODOLOGY

The present study is classified as an exploratory and qualitative literature review. The search for articles was conducted using the following keywords: curcumin nanoparticles, ulcerative colitis, and curcumin, across the databases PubMed (US National Library of Medicine), Web of Science, and Scopus. Inclusion criteria were established as original articles written in English. Review articles published in languages other than English or duplicates were excluded.

The search yielded 544 articles, of which 10 met the defined inclusion criteria and were thus selected for inclusion in this review study.

RESULTS AND DISCUSSION

The incidence of recurrent IBD is rising globally, causing substantial morbidity and primarily impacting young adults (BURGE *et al*., 2019). To enhance the visualization of the outcomes from the articles identified and chosen for this bibliographic review, a table (Table 1) has been generated.

Table 1 - Use of curcumin for the treatment of ulcerative colitis.

Authors/Year	Study	Results
Singla *et al*., 2014.	45 patients - 23 received NCB-02 (standardized extract of *Curcuma longa* with a composition of 72% curcumin, 18.08% dimethoxycurcumin and 9.42% bis-dimethoxycurcumin); 22 received placebo.	NCB-02 group had a treatment response of 92.9% compared to the placebo group, which had only 50% of patients who achieved improvement; 71.4% of patients in the NCB-02 group experienced UC remission compared to the placebo group, where only 31.3% experienced UC remission ($p = 0.03$) after 8 weeks of treatment. Endoscopic analysis showed that patients in the NCB-02 group (85.7%) showed significant improvement compared to the placebo group (50%) ($p = 0.04$).
Hanai *et al*., 2006.	89 patients: 45 received 1 g of curcumin; 44 patients received placebo plus sulfasalazine or mesalamine. (sulfasalazine = 1.0-3.0 g/day; median, 2.0 g/day and mesalamine = 1.5-3.0 g/day; median, 2.25 g/day)	At 6 months, patients treated with curcumin had 4.44% recurrence, while the placebo group had 15.15% recurrence, at 12 months curcumin group had 22.2% recurrence, while the placebo group had 31.8% recurrence ($p = 0.433$). The CAI in the curcumin group improved from 1.3 ± 1.1 at baseline to 1.0 ± 2.0 at 6 months ($p = 0.038$). CAI in the placebo group showed significative increased from 1.0 ± 1.1 to 2.2 ± 2.3 ($p = 0.0003$). Patients in the curcumin group significantly improved EI (1.3 ± 0.8) compared to the placebo group (0.8 ± 0.6; $p = 0.0001$).
Lang *et al*., 2015.	50 patients: 26 patients received curcumin capsules 3 g/day and 24 patients (3 g/day for 1 month, with continued mesalamine.	14 patients (53.8%) who received curcumin achieved clinical remission at week 4, compared with the placebo group who experienced no remission (0%) ($p = 0.01$). After 1 month of treatment, 17 of 26 patients (65.3%) who received curcumin showed clinical improvement, while only 3 of 24 patients (12.5%) who received placebo ($p = 0.001$) showed clinical improvement. Endoscopic remission occurred in 8 of 22 patients in the curcumin group (38%) and none of the 16 patients in the placebo group ($p = 0.043$).
Sadegui *et al*., 2019.	70 patients: 35 patients received curcumin capsules (500 mg) three times a day (1,500 mg/day) and 35 patients received placebo capsules for eight weeks.	83.9% of the patients receiving curcumin and 43.8% of the placebo group achieved clinical remission ($p = 0.001$). Clinical improvement occurred in 93.5% of the curcumin group and 59.4% of the placebo group ($p < 0.001$).
Rachmawati *et al*., 2017.	12 Wistar rats: 6 received curcumin nanoparticles with TPGS 10 mg/kg and 6 received TPGS-curcumin 10 mg/kg	TPGS-stabilized curcumin nanoparticles demonstrated improved *in vivo* kinetic parameters. Curcumin TPGS, with the largest particle size, was absorbed slowly at a meager amount, barely detectable in plasma (maximum 0.016 ng/mL after a more extended Tmax of 1.825 h). An additional consequence is improved bioavailability, reflected by an AUC (area under the curve) value of approximately sevenfold, while the curcumin content of the physical mixture was almost undetected.
Kotla *et al*., 2022.	5-6 animals per group: Group induced by giving 2.5% (w/v) DSS in drinking water The group CsA/IT-NCs received 4 mg/kg body weight and control group received normal drinking water without DSS.	The study showed strong adhesion of curcumin nanocarriers in the inflamed colon of mice chemically induced with DSS (Dextran sodium sulfate). Adhesion results were confirmed using normal/healthy human and colitis biopsies. With the consent of patients undergoing colonoscopy, they analyzed patient biopsies (n = 6). They compared the adherence efficiency in inflamed/colitis biopsies with healthy biopsies from the same patient, obtaining a 4.6-fold increase in overall adherence compared to healthy ones.

Hales *et al*., 2022.	5 groups with 8 animals each: normal control group (C), disease control group or acetic acid group (AA), curcumin group (AA_CCS), curcumin microspheres group (AA_CCMP) and prednisolone group (AA_PLP).	Plasma catalase levels were decreased in the AA group (67.7 ± 19.1 U/mL) compared to the control group (70.9 ± 16.7 U/mL), indicating oxidative stress in AA group colon tissue. The AA_CCMP and AA_PLP groups presented similar CAT values (53.5 ± 13.5 U/mL and 44.2 ± 9.5 U/mL, respectively). The AA_CCMP group showed the highest CAT values (98.1 ± 27.7 U/mL). The AA group's antioxidant capacity (TAC) showed a significantly lower difference than that of the control group ($p = 0.02$), showing a decline in the antioxidant defense caused by the induction of colitis.
Toden *et al*., 2017.	60 mice divided into 4 groups, with 5 animals each: negative control group; DSS control group; DSS Curcumin group; DSS ETO Curcumin group. Curcumin was administered 5, 25 and 50 mg/kg.	The observed results showed that both animals treated with ETO curcumin ($p < 0.001$) and standard curcumin ($p < 0.01$) had less severe colitis from DSS treatment compared to control animals. Treatment with DSS resulted in colon shortening, whereas only curcumin ETO significantly prevented this colon shortening ($p < 0.01$). Spleen weight in mice treated with ETOcurcumin was lower than in mice treated with DSS ($p < 0.01$), reinforcing its anti-inflammatory effects.
Oshi *et al*., 2020.	Colitis was induced in mice by supplementing 2.5% (w/v) DSS. Mice were divided into five experimental groups: healthy control, colitis control, CH_1@CUNCs treated, AG_5CH_5@CUNCs-treated, and $CAP_1AG_4CH_5$@CUNCs-treated. Curcumin (15 mg/kg).	CH_1@CUNCs and AG_5CH_5@CUNCs showed an increase in DAI by approximately 18 and 16%, respectively, indicating high colitis severity, and mice treated with $CAP_1AG_4CH_5$@CUNCs achieved significantly ($p < 0.001$) lower DAI than mice treated with CH_1@CUNCs and AG_5CH_5@CUNCs untreated mice with colitis. The colon length analysis in mice from the healthy group was approximately 9 cm. In the CH_1@CUNCs and AG_5CH_5@CUNCs groups, the colon length was ~5.2 and ~5.7 cm, respectively, but the length of the colon in mice treated with $CAP_1AG_4CH_5$@CUNCs was approximately 8.4 cm, which was significantly ($p < 0.01$) more significant than in mice with untreated colitis.

Singla *et al*. (2014) analyzed curcumin to treat adult patients with mild to moderate UC in an 8-week double-blind pilot study. Forty-five patients were randomized and treated once daily for 8 weeks: 23 patients received NCB-02 enema (NCB-02: standardized *Curcuma longa* extract with a composition of 72% curcumin, 18.08% dimethoxy curcumin, and 9.42% bis-dimethoxy curcumin), each NCB-02 enema contained 140 mg of NCB-02 preparation (curcumin) dissolved in 20 mL of water. The patients took the enema preparation at night before going to sleep. Of these, 22 received placebo enemas. Of the 45 patients, only 14 patients in the NCB-02 group and 16 in the placebo group completed the study.

All patients received oral mesalamine (a medication used to treat ulcerative colitis) at 800 mg twice daily. Assessments of UC activity took place at baseline and after 4 and 8 weeks, adding the individual scores of 4 parameters: bowel frequency, rectal bleeding, endoscopic score, and medical severity rating. Rectal bleeding scores and bowel frequency were assessed by asking the patients about their symptoms over 7 days. Patients who completed 8 weeks of treatment underwent a protocol analysis. Per protocol analysis, 13 out of 14 patients in the NCB-02 group had a response to treatment (92.9%) compared with the placebo group, and 8 of 16 patients showed improvement (50%) ($p = 0.01$).

Regarding UC remission, 10 of 14 patients (71.4%) in the NCB-02 group experienced UC remission compared to the placebo group, where only 5 of 16 patients (31.3%) experienced UC remission. Remission ($p = 0.03$) after 8 weeks of treatment. Endoscopic analysis showed that patients in

the NCB-02 group showed significant improvement compared to the placebo group, as 12 out of 14 patients in the NBC-02 group (85.7%) showed improvement compared to 8 out of 16 patients (50%) of the placebo group ($p = 0.04$). The authors chose the topical curcumin preparation because curcumin has a high first-pass metabolism, so it may not reach the colonocytes in its active form. In addition, the authors cite studies showing that curcumin was effective in preventing DSS-induced colitis, and the mechanism explained was the regulation of the oxidant/antioxidant balance and the modulation of the release of TNF-alpha cytokines and nitric oxide (NO).

In 2006, Hanai *et al*. performed a randomized, double-blind study with 89 patients: 45 received 1 g of curcumin after breakfast and 1 g after dinner, plus sulfasalazine or mesalamine (sulfasalazine = 1.0-3.0 g/day; median, 2.0 g/day and mesalamine = 1.5-3.0 g/day; median, 2.25 g/day). The other 44 patients received placebo plus sulfasalazine or mesalamine for 6 months (sulfasalazine = 1.0-3.0 g/day; median, 2.0 g/day; mesalamine = 1.5-3.0 g/day; median, 2.25 g/day). From the curcumin group, 43 patients completed the experiment, and from the placebo group, 39 patients completed it. To select the participants, the authors established the following inclusion criteria: patient with a diagnosis of UC confirmed by radiological, endoscopic, or histological criteria established by the Research Committee on Inflammatory Bowel Disease; age between 13-65 years; the patient's UC had a clinical activity index (CAI) ≤ 4, stable for the previous 4 weeks; the patient achieved remission on a corticosteroid ≥ 20 mg/day of prednisolone or an alternative medication and successfully discontinued steroid therapy; patient had hemoglobin ≥ 10 g/dL. Moreover, the exclusion criteria were: the patient was receiving an immunomodulator such as azathioprine, 6-mercaptopurine, or cyclosporine; patients with severe cardiovascular disease; patients with laboratory abnormalities indicating anemia (hemoglobin < 9 g/dL), leukopenia, thrombocytopenia, or abnormal coagulation; patients with kidney or liver disease, chronic pancreatitis, diabetes mellitus or gallstones; patients with infection, sepsis or pneumonia; and finally, pregnant or breastfeeding women. Patients received either sulfasalazine (1.0-3.0 g/day; median, 2.0 g/day) or mesalamine (1.5-3.0 g/day; median, 2.25 g/day) plus 2 g of curcumin, 1 g after breakfast and 1 g after evening meal, or placebo for 6 months. The results showed a significative difference ($p = 0.049$) related to the recurrence rate at 6 months. Patients treated with curcumin had 4.44% recurrence, while the placebo group had 15.15% recurrence; at 12 months curcumin group had 22.2% recurrence, while the placebo group had 31.8% recurrence ($p = 0.433$). The authors also determined the mean values of CAI (Clinical Activity Index) and EI (Endoscopic Index) before and after treatment: CAI and EI is only indirect assessment tool of bowel inflammation and instruments for monitoring inflammatory bowel diseases. The CAI in the curcumin group improved from 1.3 ± 1.1 at baseline to 1.0 ± 2.0 at 6 months ($p = 0.038$). In contrast, the CAI in the placebo group showed significative deterioration, meaning the CAI increased from 1.0 ± 1.1 to 2.2 ± 2.3 ($p = 0.0003$). In addition, patients in the curcumin group significantly improved EI (1.3 ± 0.8) compared to the placebo group (0.8 ± 0.6; $p = 0.0001$). Thus, the authors concluded that curcumin is a promising substance to treat IBD.

In a similar study, Lang *et al*. (2015) developed a multicenter, randomized, double-blind, placebo-controlled study with 50 patients treated with mesalamine with mild to moderately active UC who did not respond to an additional 2-week period of maximum oral and topical mesalamine therapy. Patients were randomly assigned to the following groups: curcumin group (26 patients received curcumin capsules 3 g/day) and placebo group (24 patients (3 g/day) for 1 month, with continued mesalamine). The primary endpoint was the clinical remission rate at week 4. Clinical and endoscopic responses were also recorded. The results showed that in the intention-to-treat analysis, 14 patients (53.8%) who received curcumin achieved clinical remission at week 4, compared to none of the patients (0%) receiving a placebo ($p = 0.01$). After 1 month of treatment, 17 of the 26 patients (65.3%) who received curcumin showed clinical improvement, while only 3 of 24 patients (12.5%) who received placebo ($p = 0.001$) achieved clinical improvement. Endoscopic remission occurred for 8 of 22 patients in the curcumin group (38%) and none of the 16 evaluable patients in the placebo group ($p = 0.043$). The authors concluded that the curcumin-to-mesalamine therapy was superior to the combination of placebo and mesalamine in inducing clinical and endoscopic remission in patients with mild-to-moderate active UC.

In 2019, Sadegui *et al*. developed a double-blind, randomized clinical trial with 70 patients with UC classified as mild-to-moderate. Patients were distributed into two groups of 35 patients each. One group received curcumin capsules (500 mg) three times a day (1,500 mg/day); the other took placebo capsules for eight weeks. However, 31 patients in the curcumin group continued until the end of the experiment (gave up for personal reasons, allergies, and travel and did not consume capsules), and 32 patients in the placebo group worsened symptoms for personal reasons and did not consume capsules. According to the results, 83.9% of the patients receiving curcumin and 43.8% of the placebo group achieved clinical remission ($p = 0.001$). Clinical improvement occurred in 93.5% of the curcumin group and 59.4% of the placebo group ($p < 0.001$). The analysis was performed according to the intention to treat (ITT) and per protocol (PP). The analysis revealed that the mean disease activity index scores decreased in both groups ($p = 0.001$). The mean difference in changes between the two groups decreased significantly in the curcumin group, presenting a significantly decreased ESR (Blood Erythrocyte Sedimentation Value) at the end of the eighth week compared to the baseline ($p = 0.02$) and placebo group ($p = 0.01$). High-sensitivity C-reactive protein (HS-CRP) levels dropped significantly after 8 weeks of taking curcumin ($p = 0.002$ in PP analysis and $p = 0.001$ in ITT analysis). However, the placebo group did not see a significant drop. Regarding the analysis of TNFα, the results showed no significant differences between or within the two groups before or after the intervention. Thus, based on the results, the authors concluded that daily supplementation of 1,500 mg of curcumin for 8 weeks could induce clinical remission, improve response, improve quality of life, and decrease HS-CRP and ESR levels in patients with ulcerative colitis.

As previously mentioned (Kedia *et al*., 2017), nanoparticles provide better absorption and solubility in an aqueous medium, so Rachmawati *et al*. (2017) developed 200 nm curcumin nanoparticles containing D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) as a surfactant to perform multiple functions in curcumin nanoparticles, such as improving their stability. The study used 6- to 8-week-old male Wistar rats weighing 150-200 g that were pathogen-free. Animals were divided into two groups (six rats each) and received either curcumin TPGS suspension or TPGS-stabilized curcumin nanosuspension orally at the same dose of 10 mg/kg. After oral administration, blood sampling of 500 µL was performed through the tail vein at intervals of 0, 0.25, 0.5, 1, 2, 4, 8, 12, and 24 h. Data analysis followed some pre-established parameters such as stool consistency (score = 0, normal; 2, soft stools; 4, watery stools); stool bleeding (score = 0, none; 2, light bleeding; 4, bleeding coarse); and weight loss (score = 0, no weight loss; 1, 1, 5% weight loss; 2, 5, 10% weight loss; 3, 10, 15% weight loss; 4, 15 weight loss % by weight). The score ranges are 0 to 2 for normal, 3 to 5 for mild, 6 to 10 for moderate, and 11 to 12 for severe. The results showed that TPGS-stabilized curcumin nanoparticles demonstrated improved *in vivo* kinetic parameters. Curcumin TPGS, with the largest particle size, was absorbed slowly at a meager amount, barely detectable in plasma (maximum 0.016 ng/mL after a longer Tmax of 1.825 h). The reduction of particle size to approximately 200 nm, followed by the presence of TPGS, increased the rate and extent of curcumin uptake compared to the larger curcumin size mixed with TPGS. The physical mixture›s curcumin content was essentially undetectable, but improved bioavailability is another effect evident from an AUC (area under the curve) value of about sevenfold. The researchers concluded that the lowest dose of the TPGS-stabilized curcumin nanoparticle given rectally had a better local effect on the animal model of ulcerative colitis. The fact that curcumin nanolength tends to build up in the inflamed colon and that TPGS is found in the same place as the excellent antioxidant is thought to be a substantial reason for this better effect. Thus, the TPGS-stabilized curcumin nanoparticle exhibits combination effects and is a promising way to improve the therapeutic value of curcumin in the treatment of ulcerative colitis.

In 2022, Kotla *et al*. developed a study about inflammation-specific targeted carriers for local drug delivery to inflammatory bowel disease using nanotechnology. Several studies show that the size, shape, surface charge, and way ligands are made affect how nanocarriers stick to and target the inflamed intestine. The study showed strong adhesion of curcumin nanocarriers in the inflamed colon of mice chemically induced with DSS (Dextran sodium sulfate). C57BL/6 mice, 6-8 weeks old, divided into 5-6 animals per group, were used. UC was induced by administering 2.5% (w/v) DSS in drinking water for seven days and with a recovery period under normal drinking water for five days. Nanocarriers were administered at 4 mg/kg body weight orally by gavage. Mice in the control group received drinking water without DSS. At the end of the experiment (day 12), all mice were euthanized, and blood and tissue were collected for measuring colitis phenotype markers. Adhesion results were confirmed using normal/healthy human and colitis biopsies. With the consent of patients undergoing

colonoscopy, they analyzed patient biopsies (n = 6). They compared the adherence efficiency of inflamed/colitis biopsies with healthy biopsies from the same patient, obtaining a 4.6-fold increase in overall adherence compared to healthy ones. The results suggest that nanocarriers have promising therapeutic potential as delivery carriers in the treatment of colitis.

Using a different methodology, Hales *et al*. (2022) developed a study to investigate whether curcumin microspheres can specifically target the colon and attenuate oxidative stress and inflammation in an *in vivo* experimental model of the acetic acid (AA)-induced UC. The animals were divided into 5 groups with 8 animals each, normal control group (C), disease control group or acetic acid group (AA), curcumin group (AA_CCS), curcumin microspheres group (AA_CCMP) and prednisolone group (AA_PLP). Each group was treated daily by oral gavage for 7 consecutive days, groups 1 and 2 received 2% carboxymethylcellulose sodium salt (CMCNa) aqueous solution, and groups 3 and 4 received the same dose of curcumin (15 mg/kg), both suspended in a 2% aqueous CMCNa solution, while group 5 received prednisolone sodium phosphate (2 mg/kg) dissolved in a 2% aqueous CMCNa solution. After 7 days of treatment, 1.5 mL of distilled water was administered intrarectally to group 1, while the other groups received 1.5 mL of 4% AA solution for UC induction. To evaluate the effects of Col cur MPs administration in AA-induced colitis, catalase and lipid peroxidation were measured. Plasma catalase levels were decreased in the AA group (67.7 ± 19.1 U/mL) compared to the control group (70.9 ± 16.7 U/mL), indicating oxidative stress in AA group colon tissue. The AA_CCMP and AA_PLP groups presented similar CAT values (53.5 ± 13.5 U/mL and 44.2 ± 9.5 U/mL, respectively) and were lower than the values of the AA group. The ColCUR MPs group showed the highest CAT values (98.1 ± 27.7 U/mL). However, the results showed no statistically significant difference to the AA group ($p > 0.05$). The antioxidant capacity (TAC) of the AA group showed a significantly lower difference than that of the control group (p = 0.02), showing a decline in the antioxidant defense caused by the induction of colitis. Among the groups that received treatment, the highest TAC was observed in the AA_CCMP group (0.19 ± 0.03 mmol Trolox equivalent/L), which, according to the authors, indicates an antioxidant capacity provided by the Col cur MPs system. The level of MDA (lipid peroxidation) was considerably increased ($p < 0.05$) in the AA group (3.75 ± 0.7 nmol/mL) compared to the control group (2.95 ± 0.2 nmol/mL). For the AA_CCMP, Col cur MPs and AA_PLP groups, there was a slight reduction in MDA levels (3.48 ± 0.5 nmol/mL, 3.51 ± 0.5 nmol/mL and 3.52 ± 0.5 nmol/mL /mL, respectively) compared to the AA group. But the differences between the plasma levels of the AA group and the treated groups were not statistically significant.

Toden et al. (2017) tested the anti-inflammatory properties of curcumin (ETO CURCUMIN) in dextran sulfate-induced colitis using essential oils. In the study, 60 mice were divided into 4 groups with 5 animals each: the negative control group, the DSS control group, the DSS Curcumin group, and the DSS ETO Curcumin group. Curcumin was administered at 5, 25, and 50 mg/kg. First, the authors tested the efficacy of both types of curcumin (curcumin and ETO curcumin) at a low

treatment dose of 25 mg/kg body weight. Animals were pre-treated with curcumin for one week, followed by adding 3% DSS to their drinking water to induce colitis. The observed results showed that both animals treated with ETO curcumin ($p < 0.001$) and standard curcumin ($p < 0.01$) had less severe colitis from DSS treatment compared to control animals as early as day 6, indicating their ability to attenuate inflammation-mediated colitis. None of the curcumin treatments changed the consistency of the stool, but both were effective in reducing fecal bleeding compared to animals in the DSS group ($p < 0.01$). Another parameter analyzed was colon length after 7 days of DSS treatment. Treatment with DSS resulted in colon shortening, whereas only curcumin ETO significantly prevented this colon shortening ($p < 0.01$). The study also examined whether there was an enlarged spleen, another indicator of the immune response to inflammation. Spleen weight in mice treated with ETOcurcumin was lower than in mice treated with DSS ($p < 0.01$), reinforcing its anti-inflammatory effects. The results show that ETO curcumin demonstrated a dose-dependent improvement in efficacy on days 5 and 7. Significant results ($p < 0.001$) for weight change ($p < 0.001$) and fecal bleeding ($p = 0.001$) were observed when the 50 mg/kg treatment group was compared to the 5 mg/kg treatment group on days 5 and 7. A comparison of 25 mg/kg and 50 mg/kg treatments showed better results ($p < 0.05$) for ETO curcumin on days 5 and 7 compared to standard curcumin. The results indicate that ETO curcumin showed an increase in its anti-inflammatory efficacy in a dose-dependent manner. In contrast, standard curcumin showed no dose-associated improvement at the concentrations used.

Similarly, Oshi *et al*. (2020) developed oral core-shell nanoparticles composed of core curcumin nanocrystals and multilayered chitosan/alginate in the shell, targeted toward relieving inflammation caused by UC. In the preparation of core-shell nanoparticles, CUNCs (curcumin nanocrystals), CH (surrounded by chitosan), AG (sodium alginate), and CAP (cellulose acetate phthalate) multilayer shell core nanoparticles (CAP1AG4CH5@ CUNCs) were prepared by ultrasound-assisted antisolvent crystallization and layer-by-layer (LBL) coating techniques. The authors' methodology used curcumin (2 mg/mL in 60% ethanol) added to CH (2 mg/mL in 0.1 M acetic acid, pH 5) and sonicated (150 W/cm2) at 4 °C for 30 minutes. The suspension was centrifuged at 20,000 x *g* for 20 min and washed thrice with 0.05% NaCl to obtain CH1@CUNCs. This compound was resuspended in a 20 mL AG solution (2 mg/mL in water, pH 5), and the solution was gently stirred for 20 minutes to allow AG coating on the surfaces. The suspension was centrifuged at 20,000 x *g* for 20 min and washed thrice with 0.05% NaCl. The coating was then continued using CH and AG alternately until the desired number of CH/AG multilayers was obtained (AG5CH5@CUNCs). Finally, AG5CH5@ CUNCs were incubated in CAP solution (2 mg/mL, pH 6) for 20 min and washed three times with 0.05% NaCl to obtain CAP1AG4CH5@CUNCs. Regarding the animals used in the experiment, the mice were divided into five groups: healthy control, colitis control, treated with CH1@CUNCs, treated with AG5CH5@CUNCs, and treated with CAP1AG4CH5@CUNCs. Nanoparticle suspensions were prepared and orally administered to mice for 6-12 h. 2.5% (w/v) DSS supplementation in drinking

water for 7 days caused colitis in mice. After induction, water with DSS was replaced with normal water, and treatment was started. Mice from the drug-treated groups received an equal dose of curcumin (15 mg/kg) as a suspension by oral gavage for 7 days. Mice from the healthy and colitis groups did not receive curcumin. The results observed by the authors indicated that the release rate of the nanoparticle was low at a pH that mimicked the stomach and small intestine but was higher at a pH that mimicked the colon. Regarding biodistribution, studies in the gastrointestinal tract of mice showed that nanoparticle distribution was significantly higher in the colon than in the stomach and small intestine. *In vitro*, release studies showed pH-dependent curcumin release of CAP1AG4CH5@CUNCs. The DAI (disease activity index) results of mice treated with CH1@CUNCs and AG5CH5@CUNCs showed an increase in DAI by approximately 18 and 16%, respectively, indicating high colitis severity, and mice treated with CAP1AG4CH5@CUNCs achieved significantly ($p < 0.001$) lower DAI than mice treated with CH1@CUNCs and AG5CH5@CUNCs untreated mice with colitis. The colon length analysis in mice from the healthy group was approximately 9 cm, and in the CH1@CUNCs and AG5CH5@CUNCs groups, the colon length was 5.2 and 5.7 cm, respectively. However, the colon length in mice treated with CAP1AG4CH5@CUNCs was approximately 8.4 cm, significantly ($p < 0.01$) more significantly than in untreated colitis mice. The enlarged spleen can be a parameter to assess the extent of inflammation generated in ulcerative colitis. The spleen weight in healthy mice was approximately 0.083 ± 0.01 g, while for mice with untreated colitis, it was approximately 0.221 ± 0.02 g. When treated with CAP1AG4CH5@CUNCs, the spleen size was approximately 0.107 ± 0.02 g, significantly ($p < 0.001$) lower than that of mice with untreated colitis. Thus, the authors concluded that CAP1AG4CH5@CUNCs showed greater therapeutic efficacy in treating DSS chemically induced colitis in the mice used in the study.

CONCLUSION

Therefore, this review clarifies the anti-inflammatory effect of curcumin in colitis in its free, nanoparticulate form and as associated with other drugs. One of the problems in treating UC is the risk of developing neoplasms due to an intense inflammatory process.

The results of these studies suggest that curcumin combined with routine medications may be effective for treating UC and, when administered in nanoparticulate form, presents even better results in terms of permeability, solubility in aqueous medium, and increased bioavailability.

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