BIOCELL
2022 46(9): 2015-2047

Tech Science Press

Efficacy of oral consumption of curcumin/*Curcuma longa* for symptom improvement in inflammatory bowel disease: A systematic review of animal models and a meta-analysis of randomized clinical trials

Marla de Cerqueira ALVES[1]; Monise Oliveira SANTOS[1]; Nassib Bezerra BUENO[1]; Orlando Roberto Pimentel de ARAÚJO[2]; Marília Oliveira Fonseca GOULART[2,3,4]; Fabiana Andréa MOURA[1,5,*]

[1] Programa de Pós-Graduação em Nutrição (PPGNUT), Universidade Federal de Alagoas (UFAL), Maceió, AL 57072-970, Brazil
[2] Instituto de Química e Biotecnologia (IQB), Universidade Federal de Alagoas (UFAL), Maceió, AL 57072-970, Brazil
[3] Programa de Pós-Graduação em Ciências da Saúde (PPGCS), Universidade Federal de Alagoas (UFAL), Maceió, AL 57072-970, Brazil
[4] Programa de Pós-Graduação da Rede Nordeste de Biotecnologia (RENORBIO), Universidade Federal de Alagoas (UFAL), Maceió, AL 57072-970, Brazil
[5] Programa de Pós-Graduação em Ciências Médicas (PPGCM), Universidade Federal de Alagoas (UFAL), Maceió, AL 57072-970, Brazil

Key words: Ulcerative colitis, Crohn's disease, Oxidative stress, Curcuma, Turmeric

Abstract: The roots of the vegetal Curcuma due to its high content of polyphenols, has been used successfully in several clinical situations. This review assessed the effect of curcumin/*Curcuma longa* on symptoms and metabolic changes in inflammatory bowel disease (IBD). A systematic review of animal models and randomized clinical trials (RCTs) was conducted by searching the following electronic databases: PubMed, CENTRAL, LILACS, Science Direct, and ClinicalTrials.gov. From 997 found records, 62 were included. More than 90% of the animal studies reported an improvement in macroscopic, histologic and/or functional activity; 80% identified decreased oxidative and/or inflammatory biomarkers in animals treated with curcumin. Among the RCTs, intention-to-treat analysis showed that oral curcumin was effective in inducing clinical remission (n = 281, RR: 3.15 CI 95% [1.22–8.10] p = 0.0017; i^2 = 72.2%, p = 0.006) and clinical response (n = 259, RR: 1.60 CI 95% [1.09–2.35] p = 0.0017; i^2 = 59.7%, p = 0.042) but not endoscopic remission (n = 161, RR: 2.91 CI 95% [0.58–14.58] p = 0.195; i^2 = 72.7%, p = 0.026). These results confirm that oral supplementation with curcumin/*Curcuma longa* has beneficial actions in animal colitis and, when associated with drug therapy, is effective in the treatment of patients with IBD.

Introduction

Curcuma or turmeric is a yellowish powder, known as a constituent of the curry condiment, extracted from *Curcuma longa* rhizome, and used as a religious item and as a medicine in both condiment and natural dye forms (Kotha and Luthria, 2019). For medicinal purposes, it has been used for at least 2500 years in traditional Chinese and Indian medicine in a range of clinical conditions. Its beneficial action on health is due to the presence of active polyphenols, called curcuminoids - demethoxycurcumin, bisdemethoxycurcumin, and especially curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], which has high antioxidant and anti-inflammatory power (Sueth-Santiago *et al.*, 2015). Other properties are also attributed to curcumin, such as antimicrobial, antifungal, hypoglycemic, antiproliferative, anticarcinogenic, and with healing properties, through interaction with various gene transcription factors, enzymes, inflammatory cytokines, proteins, growth factors, and receptors (Jurenka, 2009; Stanić, 2017).

The antioxidant mechanism attributed to curcumin depends directly on the presence of two structural subunits, the phenolic hydroxyls, and the central methylene group. It may involve one or more of the following mechanisms: elimination or neutralization of reactive species (Lucas *et al.*, 2021); inhibition of oxidative enzymes; interaction with oxygen-reduced species, making them less available for oxidative reactions; interaction with the oxidative cascade, and inhibition of its propagation; chelation, or deactivation

*Address correspondence to: Fabiana Andréa Moura, fabiana.moura@fanut.ufal.br
Received: 22 November 2021; Accepted: 11 February 2022

Doi: 10.32604/biocell.2022.020407

of oxidative properties of metal ions, such as iron (Sueth-Santiago *et al.*, 2015; Kumar *et al.*, 2016).

Additionally, curcumin and other curcuminoids (to a lesser extent) present anti-inflammatory activity, regulating the expression of genes that encode proinflammatory interleukins, cytokines, and growth factors; reducing the levels of several reactive oxygen and nitrogen species (RONS); and inhibiting enzymes that produce RONS, such as nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and xanthine oxidase (XO), thus suppressing nuclear factor B (NF-kB) activation (Kumar *et al.*, 2016).

In general, oral consumption of curcumin is safe because no toxicity was observed in humans or animal models (Soleimani *et al.*, 2018). However, in some animal models, the consumption of high doses can induce liver injury (Qiu *et al.*, 2016). In a study conducted by Qiu *et al.* (2016), the overdose of oral curcumin in rats, (100 mg/90 days), each day, resulted in imbalance in animals by increased overexpression of interleukin (IL)-6 and reduction of superoxide dismutase (SOD) in liver tissues. Another study, that tested curcumin-loaded nanocomplexes, demonstrated changes in the liver function markers aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in high doses in chronic toxicity test (0,8 g/kg/day in mice - equivalent to 0.225 g/kg b.w. of curcumin-and 1,61 g/Kg/day in hamsters-0.45 g/kg b. w. of curcumin-for six months) (Jantawong *et al.*, 2021).

Curcumin has a low bioavailability due to its poor aqueous solubility, instability at intestinal pH, and low intestinal permeability (Esatbeyoglu *et al.*, 2012), which makes the clinical use of curcumin a challenge. Despite its low bioavailability (approximately 1%), curcumin and its metabolites appears to be pharmacologically effective, since it has shown effects, in several clinical conditions, such as cancer (Martínez *et al.*, 2019), neurological disorders (Yavarpour-Bali *et al.*, 2019), cardiovascular diseases (Oliver *et al.*, 2016), metabolic disorders (Mohammadi *et al.*, 2018; Panahi *et al.*, 2018), autoimmune diseases (Momtazi-Borojeni *et al.*, 2018), and inflammatory bowel disease (IBD) (Cunha Neto *et al.*, 2019).

The IBD is a complex and multifactorial disease mediated by immunological components of the gastrointestinal tract and characterized by recurrent inflammation, with ulcerative colitis (UC) and Crohn's disease (CD) being its main forms (Actis *et al.*, 2019; Martins *et al.*, 2021). IBD symptoms include pain, vomiting, diarrhea, weight loss, and fever and greatly impact the quality of life of the patients. Chronically, UC and CD increase the risk of surgical procedures, toxic megacolon, and colorectal cancer (CRC) (Moura *et al.*, 2015). Several drug classes, such as aminosalicylates, corticosteroids, immunomodulators, and biological therapy are utilized to minimize these effects. However, adverse effects resulting from a prolonged use of these medications, disease recurrence, and medicine dependency are observed in many patients (Sairenji *et al.*, 2017).

Due to the crosslink between redox imbalance, inflammatory activity, and immune deficiency in IBD, research suggests that the use of therapeutic strategies with antioxidant and anti-inflammatory substances may be a promising unconventional treatment alternative. Among these, the use of *Curcuma longa* and/or its curcuminoids, especially curcumin, is highlighted. In this context, the aim of this systematic review is to identify the effects of *Curcuma longa*, curcumin, or other curcuminoids on symptoms and metabolic changes in patients and animal models of IBD.

Materials and Methods

Registration

This systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) platform, with registration numbers CRD42020164513 and CRD42020168827 for the review with human studies and studies with animal models, respectively.

Search strategy and selection of studies

The search was conducted until January 2021 in the following databases: MEDLINE (via PubMed), Cochrane Controlled Register of Trials (CENTRAL), Literatura Latino-Americano e do Caribe em Ciências da Saúde (LILACS), Science Direct, and Clinical Trials. The following keywords were used: "inflammatory bowel disease", "ulcerative colitis", "colitis", "Crohn's disease", "curcumin", "curcuma", "turmeric", and "Indian saffron". Boolean operators "OR" and "AND" were used. The full search strategy for all the databases is reported in the Supplementary Material. All records retrieved had their titles and abstracts evaluated. In addition, no year of publication filter was used. Then, we evaluated titles for the removal of duplicate records. A complete search strategy is shown in Suppl. Box 1.

Eligibility of animal models' research

Studies with experimental models (rats or mice) of UC or CD were included, without restriction for the inducing agent or the inflammation model (acute or chronic) and in which *Curcuma longa*/curcuminoids were administered orally (diet or gavage) for treatment. The results of the research should include at least one of the following aspects: macroscopic, anatomical and/or histological evaluation of the colon; body weight; disease activity index; and serological and/or tissue analysis of biomarkers of nitroxidative stress and inflammation. Studies carried out exclusively *in vitro*, with the use a mixture of turmeric, and/or curcuminoids with other substances as an intervention, were excluded.

Studies were divided according to *Curcuma longa*/curcumin and/or other curcuminoids supplementation doses: ≤0.005 mg/kg day/0.01 mmol/kg day; 5–50 mg/kg day/0.01–0.15 mmol/kg day; 60–200 mg/kg day/0.25–0.50 mmol/kg day; >200 mg/kg day/0.54 mmol/kg day; ≤2% (w/w) of the diet; and >2% (w/w) of the diet. In studies that have tested more than one dose we chose to categorize it in the subgroup of higher dosages.

Eligibility of clinical research

Randomized clinical trials with participants of both sexes, aged 18 years or older, diagnosed with UC or DC, and treated with oral *Curcuma longa*/curcuminoids isolated or combined with drugs, were included. There was no restriction on the severity of the disease (mild, moderate, or severe) or the intestinal lesion location (proximal or distal). Studies were excluded if they evaluated pregnant or lactating

women or participants with other associated comorbidities, such as diabetes and hepatic, kidney, and autoimmune diseases. Finally, records in languages other than English, Portuguese and Spanish were excluded.

Data extraction

The following data were extracted from the studies:

- Animal model research: sex, species, age (week), and/or body weight (b.w.); experimental model of IBD; supplement presentation; doses, time of supplementation; administration via; groups of treatment; nitroxidative stress and inflammation effects; other results. The studies with multiple doses of supplementation were allocated, according to the highest dose.
- RCT: IBD clinical situation; number of randomized individuals (n)/age (years)/and sex; supplement presentation/ doses, and time of supplementation; treatment association; clinical, histological, and image parameters, nitroxidative stress/inflammation/serum and fecal biomarkers effects.
- Meta-analysis: RCTs included in the meta-analysis needed to present data on clinical remission (primary outcome) and endoscopic remission (secondary outcome). Outcomes that assessed disease activity based on one or more of the following parameters: clinical manifestations, histological patterns of intestinal lesions, inflammation/ nitroxidative stress biomarkers, and serological or fecal markers were also included. The percentage of patients in the intervention and control groups who achieved remission and/ or clinical response at the end of the experiment were statistically analyzed, using tools that assign scores based on the intensity and frequency of symptomatic manifestations. Other analyzed outcomes included the percentage of patients in the intervention and control groups who achieved remission as assessed by endoscopic examinations at the end of the test period. Trials were classified as ITT (intention-to-treat) or PP (per protocol). Missing data were requested to the authors of the studies by e-mail, when applicable.

Assessment of the risk of bias and quality of evidence

For animal model research, the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) was applied. This tool assesses the risk of bias, according to ten domains: bias in sequence generation, bias due to baseline characteristics, bias according to allocation concealment, bias due to random housing, bias in blinding of trial caregivers and researchers, bias in random outcome assessment, bias in blinding of outcome assessors, bias due to incomplete outcome data, bias in selective outcome reporting, and overall bias. Each category was assessed as having low, high, or uncertain risk of bias. Then, each study received an overall rating of risk of bias.

For RCTs, the risk of bias was assessed using the Cochrane Collaboration tool, which uses six domains: sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessors, missing data, and selective outcome report. Each category was defined as low, high risk or uncertain risk of bias, and introduced, in each study. The evidence quality was also assessed by the method proposed by the Grading of Recommendations Assessment, Developing and Evaluation (GRADE). This method classifies the evidence of each outcome in the meta-analysis into four categories: high, moderate, low, or very low. Five criteria were evaluated: study limitations (risk of bias), inconsistency of the results (heterogeneity), indirect evidence, inaccuracy, and publication of bias, which generated a score to allow the final classification.

Statistical analysis

As all the meta-analyzed variables were categorized, the relative risk (RR) between groups for each variable was calculated for each study. Studies weights were assigned, according to the inverse variance method, and calculations were based on a random-effects model. An alpha value of 0.05 was adopted.

Statistical heterogeneity among the studies was tested using the Cochran Q test, and inconsistency was assessed using I^2 statistics. Whenever a result showed heterogeneity, it was explored by repeating the analysis with the removal of one study at a time to assess whether a particular study explained the heterogeneity. All analysis were conducted using the RevMan 5.3 program (The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark).

Results

Search results

From the nine hundred and ninety-seven unique screened records, sixty-two were included in the qualitative synthesis. Of these, fifty-four (87.1%) studies were in animal models, and eight (12.9%) were randomized controlled trials (RCTs). Five (62.5%) RCTs were included in the meta-analysis for the following outcomes: clinical remission and clinical response, and three RCTs (37,5%) were included for endoscopic remission. Fig. 1 shows the flow diagram of study selection.

Animal model research: study characteristics

Among the fifty-four studies (Table 1) that evaluated oral *Curcuma longa* or curcumin (extract or modified formulations) in experimental colitis, twenty-seven used as inducing agent, the dextran sulfate sodium (DSS) (50%), thirteen used 2,4,6-trinitrobenzenesulfonic acid (TNBS) (24.1%), seven used acetic acid (13%), four used genetic modification (7.4%), and three used dinitrobenzene sulfonic acid (DNB) (5.6%). Curcumin was the main form of supplementation used in the studies (n = 52; 96.3%). Same studies used modified curcumin to improve its bioavailability (n = 20; 37%): nanoparticles/nanocarriers in seven (35%), microparticles/microspheres in six (30%), polymers complexed with other substances in two (10%), and other forms in three (15%). In the studies in which these modified forms were compared to curcumin (n = 12; 60%), all showed more beneficial results in oxidative stress/inflammation markers, general and histological parameters, or in both.

However, even in cases where pure curcumin was used, the majority of studies confirmed its antioxidant and anti-inflammatory roles as well as its effectiveness in improving clinical, metabolic, macroscopic, and histological parameters. Only two studies showed no beneficial effects or negative action of curcumin. In this latter study, a worsening of all biochemical parameters of anemia was observed, in addition to the worsening of clinical and histological signs of IBD.

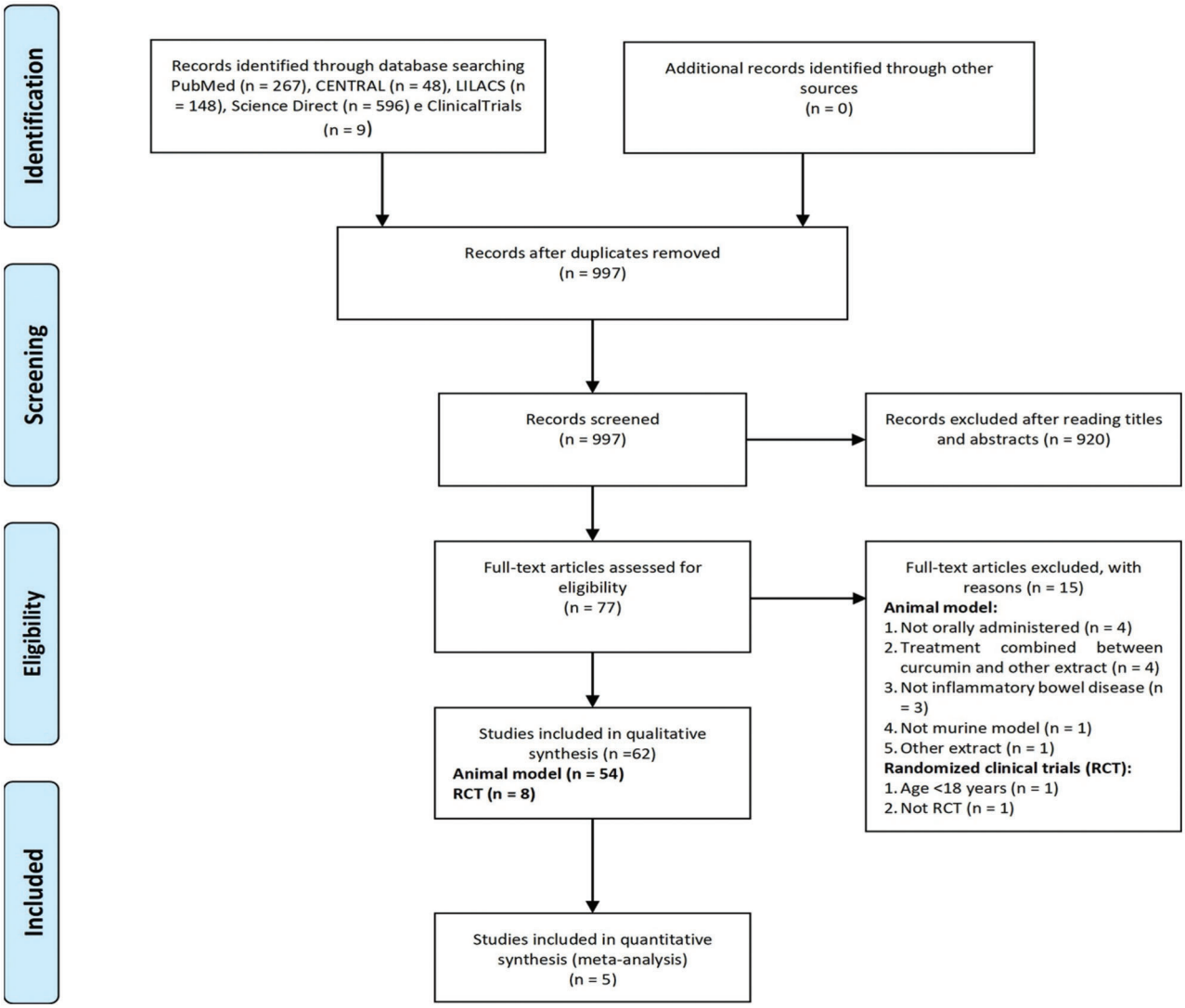

FIGURE 1. Flow diagram of study selection.

There was a great variability in the included studies of the curcumin doses (0.005 mg/kg day to 500 mg/kg day), supplementation period (three days until eighteen weeks), and the moment when supplementation was performed (before, during or after colitis induction, or in two different moments of the disease).

The most used doses of curcumin (modified or not)/ *Curcuma longa* were 100 mg/kg day, followed by 50 mg/kg day, and 15 mg/kg day. Among those who were supplemented in the diet (w/w), six had ≤0.3% (w/w) and five ≥2%. Multiple doses were used in twelve (22.2%) studies. In these cases, only one reported better results at the lowest dose (2 mg/kg day *vs.* 15 mg/kg day), using curcumin nanocarriers; in most of them, the highest dose led to better results. These results indicate that the action of curcumin may be dose-dependent, which would be related to its low toxicity and bioavailability.

The effect of oral curcumin/*Curcuma longa* supplementation on inflammatory and nitroxidative stress biomarkers was not evaluated in eight (14.8%) studies. Among those who analyzed these parameters (n = 46; 85.2%), forty-five (45, 97.8%) observed some beneficial effects. The main inflammatory biomarkers studied were the enzyme myeloperoxidase (MPO); the cytokines tumor necrosis factor alpha (TNF-α), the IL-6, IL-10, IL-1β and interferon gamma (INF-γ); the nuclear factors, NF-κB and signal transducer and activator of transcription 3 (STAT3); and the membrane receptor toll-like receptor 4 (TLR-4).

Concerning redox imbalance biomarkers, the reactive species-producing enzymes iNOS and COX-2; the enzymatic and nonenzymatic defense biomarkers catalase (CAT), SOD, glutathione peroxidase (GPx), and reduced glutathione (GSH); the cell membrane damage biomarkers thiobarbituric acid reactive substances (TBARS)/malondialdehyde (MDA); and the reactive species nitric oxide (•NO)/nitrite are highlighted.

The risk of bias assessment, according to SYRCLE, is shown in Suppl. Table 1. In general, there was a high risk of bias in the domains of "random sequence generation", "allocation concealment", "blinding", and "incomplete outcome data". Another consideration refers to the high number of studies whose main objective was to produce and test formulations containing curcumin. In such publications, the manuscript, specifically, on animal experimentation tends to be less detailed, which can result in the assessment of risks as "high" or "unclear" bias in several domains.

TABLE 1

Effect of oral *Curcuma longa*/curcumin supplementation in inflammatory bowel disease in animal models

Author, year	Sex/species/age and/or body weight (b.w.)	Experimental model of IBD	Supplement presentation	Doses/time of supplementation/oral administration via	Groups of treatments	Nitroxidative stress and inflammation effects	Clinical, metabolic, macroscopic, and histological effects
≤5 mg/kg day/0.01 mmol/kg day							
(Chen *et al.*, 2019)	Female Kunming mice; 8 weeks old	DSS	**Curcumin:** • Porous nanoparticle (a); • PF127-Nonporous nanoparticle (b); • PF127-porous nanoparticle # (c)	• 5 mg/kg day • 11 days in total – during colitis induction Oral route uninformed	• Colitis + porous nanoparticle; • Colitis + PF127-Nonporous nanoparticle; • Colitis + PF127-porous nanoparticle	• ↓ MPO activity in the colon (c); • ↓ TNF-α and IL-6 serum levels (a,b,c); • ↑ IL-10 serum levels (b,c)	• Attenuated the increase in the splenic weight (c); • ↓ Shortening of the colon (c).
(Zhou *et al.*, 2019)	Female Kunming mice; 8 weeks old	DSS	**Curcumin:** • Porous microparticle #(a); • Nonporous microparticle (b)	• 5 mg/kg day • 11 days in total – during colitis induction Gavage	• Colitis + porous microparticle; • Colitis + nonporous microparticle	• Normalized MPO activity in the colon (a)	• Attenuated the increase in the splenic weight (a); • ↓ Shortening of the colon (a); • ↓ Histological damage in the colon
(Chen *et al.*, 2018)	Female Kunming mice; 8 weeks old	DSS	**Curcumin:** • Bowl-shaped microparticles	• 5 mg/kg day • 11 days in total – during colitis induction Oral route uninformed	Colitis + Bowl-shaped microparticles	• Normalized MPO activity in the colon	• Normalized splenic weight and shortening of the colon; • ↓ Histological damage in the colon
(Sareen *et al.*, 2016)	Male Swiss mice; 18–22 g (b.w.)	Acetic acid	**Curcumin:** • *Sigma* standard (a); • Microspheres[1] # (b)	• 1% (w/v) in 0.5 mL/d = 0.005 mg/kg day • 3 days in total – after colitis induction Oral route uninformed	• Colitis + curcumin *Sigma* standard; Colitis + curcumin microspheres	**UNEVALUATED PARAMETERS**	• ↓ Macroscopic and histological damage score in the colon (b > a); • ↓ Weight/length ratio in the colon (a,b)
>5–50 mg/kg day/0.01–0.15 mmol/kg day							
(Altinel *et al.*, 2020)	Female Wistar Hannover rats; 300–500 g (b.w.)	TNBS	**Curcumin:** • *Sigma* Standard	• 20 mg/kg day • 7 days in total – during colitis induction Gavage	• Sham group (no colitis induction, only rectal insertion of feeding tube; • Colitis + Curcumin *Sigma* standard + corn oil (a); • Colitis + corn oil (b);	***Versus* Control Group:** • ↑ NF-kB serum levels. **Versus *Sham Group:*** • ↓ NF-kB, PDGF, IL-6, TNF-α, MPO, MDA, NO levels in the colon	**Versus *Sham Group:*** • ↓ Macroscopic and microscope damage score; cell accumulation, and ulceration; and colonic granuloma formation
(Oshi *et al.*, 2020)	Male ICR mice; 30–35 g (b.w.)	DSS	**Core–Shell Curcumin Nanoparticles** • CH1@CUNCs[2] (a); • AG5CH5@CUNCs[3] (b); • CAP1AG4CH5@CUNCs[4] # (c)	15 mg/kg day; • 7 days in total – after colitis induction; Gavage	• Colitis + CH1@CUNCs; • Colitis + AG5CH5@CUNCs; • Colitis + CAP1AG4CH5@CUNCs	• ↓ MPO activity in the colon (c); • ↓ TNF-α and IL-6 levels in the colon (c)	• ↓ DAI (c); • ↓ Shortening of the colon (c); • Attenuated the ↑ in splenic weight (c);

(Continued)

Table 1 (continued).

Author, year	Sex/species/age and/or body weight (b.w.)	Experimental model of IBD	Supplement presentation	Doses/time of supplementation/oral administration via	Groups of treatments	Nitroxidative stress and inflammation effects	Clinical, metabolic, macroscopic, and histological effects
							• ↓ Histological damage in the colon (c)
(Luo *et al.*, 2020)	Male BALB/c mice; 22–25 g (b.w.)	DSS	**Curcumin:** • Pure (unspecified purity) (a); • Nanoparticle (CUR-NP)[5] (b); • Tannic acid nanoparticle (TA/CUR-NPs)[6] # (c)	• 50 mg/kg day; • 8 days in total – 5 days during, and 3 days after colitis induction; Oral route uninformed	• Colitis + curcumin; • Colite + CUR-NPs; • Colitis + TA/CUR-NPs	• ↓ MPO activity; and IL-6, TNF-α, IL-1β, and iNOS levels in the colon (c); • ↓ TLR4, MyD88, p65 expression in the colon (c)	• Reversed colon shortening (b,c), and body weight loss (a,b,c); • ↓ Histological damage in the colon (b,c)
(Zhang *et al.*, 2019)	Male BALB/c mice; 7–8 weeks old, 20–22 g (b.w.)	DSS	**Curcumin:** • Unspecified purity	• 50 mg/kg day; • 14 days in total – 7 days during, and 7 days after colitis induction; Diet	• Colitis + curcumin;	• ↓ IL6 expression in the colon	• Reversed body weight loss; • ↓ DAI, shortening, and histological damage in the colon; • ↓ Atg12, Beclin1, and LC3-II proteins in the colon; • ↑ p-mTOR and SIRT1 protein expression in the colon
(Kesharwani *et al.*, 2018)	Male C57BL/6 mice; 8–10 weeks old	DSS	**Curcumin:** • Curcumin-Eudragit® S100 Polymer (Ora-Curcumin-S)	• 15 mg/kg day; • 9 days in total – 2 days before, and 7 days during colitis induction; Gavage	• Colitis + Ora-Curcumin-S	• ↓ TNFα and IL6 expression in the colon; • ↑ IL-10 expression in the colon; • ↓ p65 nucleus concentration	• ↓ Body weight loss; • ↓ DAI; macroscopic and histological damage score in the colon; shortening and edema of the colon; • Attenuated the ↑ in splenic weight; • ↑ Mucin-2 production in the colon
(Chen *et al.*, 2017)	Female Kunming mice; 8 weeks old	DSS	**Curcumin:** • Porous nanoparticle # (a); • Nonporous nanoparticle (b)	• 50 mg/kg day; • 9 days in total – during colitis induction; Oral route uninformed	• Colitis + porous nanoparticle; • Colitis + nonporous nanoparticle	• ↓ MPO activity in the colon (a)	• Attenuated the ↑ in splenic weight (a,b); • ↓ Shortening of the colon (a,b); • ↓ Histological damage in the (a,b)
(Qiao *et al.*, 2017)	Female C57BL/6 mice; 8 weeks old, 18–20 g (b.w.)	DSS	**Curcumin:** • Unspecified purity (a); Amphiphilic curcumin polymer (PCur)[7] # (b)	• 50 mg/kg day; • 7 days in total – during colitis induction; Gavage	• Colitis + curcumin; • Colitis + PCur; Colitis + sulfasalazine (SSZ)	• ↓: MPO activity (a); and MDA (b), IL-6 (a,b), and TNF-α (a,b) levels in the colon (a,b)	• Attenuated body weight loss (b,c); • ↓ DAI and shortening of the colon (b,c); • ↓ Histological damage in the colon (b)

(Continued)

Table 1 (continued).

Author, year	Sex/species/age and/or body weight (b.w.)	Experimental model of IBD	Supplement presentation	Doses/time of supplementation/oral administration via	Groups of treatments	Nitroxidative stress and inflammation effects	Clinical, metabolic, macroscopic, and histological effects
(Beloqui *et al.*, 2016)	Female C57BL/6 mice; 8 weeks old,18–20 g (b.w.)	DSS	**Curcumin:** ● *Sigma* standard (a); ● Nanocarriers ● self-nanoemulsifying drug delivery systems (SNEEDS) (b); ● nanostructured lipid carriers (NLC) (c); ● lipid core-shell protamine nanocapsules (NC) # (d)	● 15 mg/kg day: ● *Sigma* standard; ● Curcumin SNEEDS; ● Curcumin NLC; ● 2 mg/kg day curcumin NC (d) ● 5 days during colitis induction Gavage	● Colitis + curcumin *Sigma* standard; ● Colitis + curcumin SNEEDS; ● Colitis + curcumin NLC; ● Colitis + curcumin NC	● ↓ MPO activity, and TNF-α expression in the colon (d)	● ↓ Histological damage; submucosal edema; and the increased leukocyte infiltration
(Gopu *et al.*, 2015)	Male Wistar rats; 300 ± 10 g (b.w.)	Acetic acid	**Curcumin:** ● Unspecified purity (a)	● 50 mg/kg day; ● 14 after in total – after colitis induction; ● Gavage.	● Colitis + curcumin (a); ● Colitis + flunixin (b) (2.5 mg/kg day subcutaneous)	● ↑ SOD, CAT, and GPx activity; and GSH and IL-10 levels in the colon (a,b); ● ↓ MPO activity; and TBARS, protein carbonyl, IL-1β, TNF-α, PGE_2 levels in the colon (a,b)	● Attenuated body weight loss (a,b); ● ↓ Shortening of the colon (a,b); ● Attenuated increased of colon relative weight [colon weight (mg)/body weight (mg)] (a,b); ● ↓ DAI; and macroscopic and histological score damage in the colon; ● ↓ ALP and LDH serum levels (a,b)
(Xiao *et al.*, 2015)	Male FVB mice; 8 weeks old	DSS	**Curcumin:** ● *Sigma* standard (a); ● Microparticles with a weight ratio of 1:2 (MPs-4)[8] # (b)	● 50 mg/kg day; ● 5 days in total – during colitis induction; ● Gavage	● Colitis + curcumin *Sigma* standard; ● Colitis + MPs-4	● ↓ MPO activity in the colon (b)	● Reversed body weight loss (b); ● Attenuated the ↑ in splenic and colon weight (a,b); ● ↓ Histological damage in the colon
(Beloqui *et al.*, 2014)	Female C57BL/6 mice; 8 weeks old, 18–20 g (b.w.)	DSS	**Curcumin:** ● 80% pure (a); ● Nanoparticle # (b)	● 15 mg/kg day; ● 5 days in total – during colitis induction; ● Gavage	● Colitis + empty nanoparticle; ● Colitis + curcumin 80% pure; ● Colitis + curcumin nanoparticle	● ↓ MPO activity in the colon (b); ● ↓ TNF-α expression in the colon (b)	● ↓ Histological damage in the colon (b)
(Sareen *et al.*, 2014)	Male Albino Wistar rats; 160–200 g (b.w.)	Acetic acid	**Curcumin:** ● Unspecified purity (a); ● Microesponjes[9] # (b)	● 20 mg/kg day; ● 3 days in total – after colitis induction; ● Gavage	● Colitis + curcumin; ● Colitis + microesponjes	**UNEVALUATED PARAMETERS**	● ↓ macroscopic and histological damage in the colon (a,b)

(Continued)

Table 1 (continued).

Author, year	Sex/species/age and/or body weight (b.w.)	Experimental model of IBD	Supplement presentation	Doses/time of supplementation/oral administration via	Groups of treatments	Nitroxidative stress and inflammation effects	Clinical, metabolic, macroscopic, and histological effects
(Liu *et al.*, 2013)	Male BALB/c mice; 6–8 weeks old, 12–23 g (b.w.)	DSS	**Curcumin:** • *Sigma* standard	• 50 mg/kg day; • 8 days in total – 1 day during, and 7 days after colitis induction; • Gavage	• Colitis + *Sigma* standard	• ↓ phospho-STAT3 activity, DNA-binding activity of STAT3 dimers, MPO activity, IL-1β, and TNF-α expression in the colon	• ↓ DAI and histological score in colon
(Martelli *et al.*, 2007)	Male BALB/c mice; 6–8 weeks old, 21–23 g (b.w.)	DNB	**Curcumin:** • Unspecified purity	• 45 mg/kg day; • 7 days in total – 2 days before and 5 days after colitis induction; • Gavage	• Colitis + curcumin (a); • Colitis + curcumin and capsazepine (30 mg/kg day (b) (intraperitoneally)	• ↓ MPO activity in colon (a)	• Attenuated body weight loss; • ↓ macroscopic and histological damage score in the colon (a)
60–200 mg/kg day/0.25–0.50 mmol/kg day							
(Wei *et al.*, 2021)	Male BALB/c SPF mice; 6–7 weeks old, 22–26 g (b.w.)	DSS	**Curcumin:** • Pure (98.5% ≥ 98.5%)	• 100 mg/kg day; • 7 days in total – after colitis induction; • Gavage.	• Colitis + Pure curcumin	• ↑ Treg/Th17 splenic; • ↑ IL-6, IL-17A, IL-23 levels in the colon; • ↑IL-10 levels in the colon	• ↓ spleen index [spleen weight (mg)/body weight (mg)]; • ↓ histological damage in the colon; • ↓ HIF-1α expression in the colon
(Yang *et al.*, 2018)	Male ICR mice; 5 weeks old	DSS	**Curcumin:** • Unspecified purity (a) #; • Tetrahydrocurcumin (THC)	• (a), 0.25 # (b) mmol/kg day of curcumin; • 0.1 (c), 0.25 (d) mmol/kg day of THC; • 14 days in total – 7 days before, and 7 days during colitis induction; • Oral route unspecified	• Colitis + 0.1 mmol.kg.d^{-1} curcumin; • Colitis + 0.25 mmol.kg.d^{-1} curcumin; • Colitis + 0.1 mmol.kg.d^{-1} THC; • Colitis + 0.25 mmol.kg.d^{-1} THC	• ↓ activation of NF-κB and STAT3 pathway in the colon (b); • ↓ expression of COX-2 and iNOS in the colon (b)	• Reversed body weight loss and shortening of the colon (b); • ↓ DAI and histological damage
(Zhao *et al.*, 2017)	Male C57BL/6 mice; 9–12 weeks old, 20–4 g	TNBS	**Curcumin:** • Pure (≥ 98.5%)	• 100 mg/kg day; • 7 days in total – after colitis induction; • Gavage.	• Colitis + curcumin (a); • Colitis + mesalazine (300 mg/kg day intragastric) (b)	• Normalized $CD8^+CD11c^+$ cells in the spleen and Peyer's patches (a,b); Normalized TGF-β1 (a,b), IFN-γ (a) and IL-10 (a,b) levels in the colon; • Normalized IFN-γ and IL-10 levels in the spleen (a,b); • ↑ TGF-β1 expression in the spleen (a,b); • Normalized CD40, CD40 L, CD54, CD205, and MHC II cells expression in the spleen and Peyer's patches	• Improve histological damage score; • Restored body weight and colon length (a,b); • Attenuated: the increased of colon weight; and the decreased of colon length (a,b); • ↓ DAI and histological damage in the colon; • ↓ colon weight and colon index [colon weight (mg)/body weight (mg)] of the colon;

(Continued)

Table 1 (continued).

Author, year	Sex/species/age and/or body weight (b.w.)	Experimental model of IBD	Supplement presentation	Doses/time of supplementation/oral administration via	Groups of treatments	Nitroxidative stress and inflammation effects	Clinical, metabolic, macroscopic, and histological effects
(Toden *et al.*, 2017)	Male C57BL/6 mice; 5 weeks old	DSS	**Curcumin:** ● Unspecified purity (a); ● Essential turmeric oils (ETO-Curcumin)[10] #	● 5 (a), 25 (b), 50 (c) mg/kg day of standard curcumin; ● 5 (d), 25 (e) or 50 # (f) mg/kg day of ETO; ● 14 days in total - 7 days before, and 7 days during colitis induction; ● Gavage	● Colitis + 5 mg/kg day curcumin; ● Colitis + 25 mg/kg day curcumin; ● Colitis + 50 mg/kg day curcumin; ● Colitis + 5 mg/kg day ETO-Curcumin; ● Colitis + 25 mg/kg day ETO-Curcumin; ● Colitis + 50 mg/kg day ETO-Curcumin	● ↑ IL-10 (f), IL-11(f), and FOXP3 (f) expression in the colon; ● ↓ CCL17 (f) and CXCL5 (c) expression in the colon	● ↓ colon shortening (b,c,e,f); ● ↓ increased of spleen weight (e,f); ● ↓ histological damage score (b,c,e, f); ● Attenuated weight loss (c, e, f); ● ↓ DAI (b,c,e,f); ● ↓ fecal bleeding (b,c,e,f)
(Yang *et al.*, 2017)	Mile Sprague–Dawley rats; 190–210 g (b.w.)	DSS	**Curcumin:** ● *Sigma* standard	● 20 (a), 60 # (b) mg/kg day; ● 10 days in total – starting 3 days in total – after the end of colitis induction; ● Gavage	● Colitis + 20 mg/kg day *Sigma* standard ● Colitis + 60 mg/kg day *Sigma* standard	**UNEVALUATED PARAMETERS**	● ↓ Visceral hiperalgesia[11] (b); ● Attenuated the increase of TRPV1 and pTRPV1 in the colon (b); ● Attenuated the increased of TRPV1 expression in L6-S1 dorsal root ganglion (b)
(Bastaki *et al.*, 2016)[12]	Male Wistar rats; 225–240 g (b.w.)	Acetic acid	***Curcuma longa*:** ● Powder	● 1 (a), 10 (b), 100 (c) mg/kg day for 7 days in total – before colitis induction; ● 1 (d), 10 (e), 100 (f) mg/kg day for 7 days in total – after colitis induction; ● Gavage	**Pre-treatment/Pos-treatment** ● Colitis + 1 mg/kg day curcumin powder; ● Colitis + 10 mg/kg day curcumin powder; ● Colitis + 100 mg/kg day curcumin powder	● ↑ GSH serum levels (e); ● ↓ GSH serum levels (c,f); ● Normalized GSH serum levels (b,f); ● ↓ colonic MPO activity	● Did not alter body weight; ● Mean macroscopic ulcer score in the colon (c,d); ● Mean microscopic ulcer score in the colon (c)
(Zhao *et al.*, 2016b)	Male C57BL/6 mice; 9–12 weeks old	TNBS	**Curcumin:** ● Pure (>95%)	● 200 mg/kg day; ● 7 days in total – after colitis induction; ● Gavage	● Colitis + curcumin (a); ● Colite + mesalazine (100 mg/kg day) (b)	● ↓ $CD4^+$ T cells in the GALT (a,b); ● ↑ Treg cells in the GALT (a,b); ● ↓ TNF-α, IL-2, IL-6, IL-12 p40, IL-17, and IL-21 levels in the colon (a,b); ● ↓ CD205, CD54, TLR4, CD252, CD256, and CD254 expression in the GALT (a, b)	● ↓ Colon weight and colon weight index [colonic weight (g)/body weight (g) × 100%]. of the colon (a,b); ● ↓ Shortening of the colon (a,b); ● ↓ Histological damage score in the colon (a,b)
(Kao *et al.*, 2016)	Male BALB/c mice; 6–8 weeks old	DSS	**Curcumin:** ● Pure (98%)	● 100 mg/kg day; ● 6 days in total – after colitis induction; ● Gavage.	● Colitis + curcumin dissolved in olive oil (0.2 mL); ● Colitis + olive oil (0.2 mL);	● ↓ iNOS, TNF-α, IL-1β, and IL-6 expression in the colon; ● ↓ nitrite in the colon; ● ↓ S-nitrosylation on IKKβ (day 2) in the colon	● Attenuated body weight loss; ● Restored colon length and body weight; ● ↓ DAI

(Continued)

Table 1 (continued).

Author, year	Sex/species/age and/or body weight (b.w.)	Experimental model of IBD	Supplement presentation	Doses/time of supplementation/oral administration via	Groups of treatments	Nitroxidative stress and inflammation effects	Clinical, metabolic, macroscopic, and histological effects
(Yildirim *et al.*, 2016)	Female BALB/c mice; 6–7 weeks old	DSS	**Curcumin:** • Unspecified purity	• 100 mg/kg day; 7 days in total – during colitis induction (a); • 100 mg/kg day; 7 days in total – before colitis induction (b); • Gavage	**Pre-treatment /treatment** • Colitis + olive oil; • Colitis + curcumin dissolved in olive oil; • Colitis + sulfasalazine (100 mg/kg day) dissolved in olive oil	• ↓ MPO activity in the colon (a,b); • Restored paraoxonase activity in serum and liver	• Did not improve body weight and colon length; • Histological changes were not evaluated in the treatment groups
(Zhao *et al.*, 2016a)	Female C57BL/6 mice; 9–12 weeks old	TNBS	**Curcumin:** • Pure (>95%)	• 100 mg/kg day; • 7 days in total – after colitis induction; • Gavage	• Colitis + curcumin (a); • Colitis + mesalazine (300 mg/kg day orally) (b)	• ↓ Total number of Dendritic cells in Peyer's patches (a,b); • ↓CD40 L, CD83, MHC-II, CD28, CD273, CD40, and CD282 expression in Peyer's patches (a,b); • ↓GM-CSF, IL-12p70, IL-15, IL-23, TGF-β, p-JAK2, p-JAK2/JAK2 levels in the colon (a,b); • ↑ IL-4, IL-10, and IFN-γ levels in the colon (a,b); • ↑pias3, SOCS1, and SOCS3 proteins in the colon (a,b)	• Attenuated body weight loss; colonic weight, and colon weight index [colonic weight (g)/body weight (g) × 100%] (a,b); • ↓ Shortening of the colon and histological injury score (a,b)
(Topcu-Tarladacalisir *et al.*, 2013)	Male Albino Wistar rats; 4 months old, 300–350 g (b.w.)	Acetic acid	**Curcumin:** • *Sigma* standard	• 100 mg/kg day; • 12 days in total – 10 days before, and 2 days after colitis induction; • Gavage	• Colitis + *Sigma* standard	• ↓ MPO activity in the colon; • ↓ Cellular apoptosis and p-p38 immunoreactivity in the colon; • ↑ p-JNK immunoreactivity in the colon; • ↓ MDA and normalized CAT levels in the colon	• Attenuated body weight loss; • ↓ macroscopic and histological damage score in the colon; • Attenuated the increased of wet weight of colon
(Yang *et al.*, 2013)	Male ICR mice, 5 weeks old	DSS	**Curcumin:** • Unspecified purity	• 0.1 (a), and 0.25 (b) nmol/kg day; • 14 days in total – 7 days before, and 7 days after colitis induction; • Gavage	• Colitis + 0.1 nmol.kg.d^{-1} curcumin; • Colitis + 0.25 nmol.kg.d^{-1} curcumin;	• Inhibited DNA binding of STAT3 (a,b); • Expression of p53 and p21 (a,b)	• ↓ Cyclin D1 and CDK4 expression in the colon (a,b)
(Zeng *et al.*, 2013)	Male Sprague Dawley rats; 200–250 g (b.w.)	TNBS	**Curcumin:** • Pure (>90%)	• 100 mg/kg day; • 7 days in total – after colitis induction; • Gavage	• Colitis + curcumin; • Colitis + sulfasalazine (100 mg/kg day)	• ↓ MPO, NF-κB, IL-27, TLR4, NF-κB p65, and p28 expression in colon	• ↓ DAI and histological damage score

(Continued)

Table 1 (continued).

Author, year	Sex/species/age and/or body weight (b.w.)	Experimental model of IBD	Supplement presentation	Doses/time of supplementation/oral administration via	Groups of treatments	Nitroxidative stress and inflammation effects	Clinical, metabolic, macroscopic, and histological effects
(Aldini *et al.*, 2012)	Male BALB/c mice; 8 weeks old, 25–30 g (b.w.)	DSS	***Curcuma longa*:** ● Extract[13]	● 200 mg/kg day for 7, 14 or 21 days after chronic colitis (a). ● 200 mg/kg day for 7 days after acute colitis (b). ● Diet	● Chronic colitis + *Curcuma Longa* extract; ● Acute colitis + Curcuma Longa extract	**UNEVALUATED PARAMETERS**	● ↓ Histological damage score in the colon (a,b); ● Partial normalization of spontaneous motility in ileo (b); ● Inhibited spontaneous basal motility in ileum and colon (a)
(Lubbad *et al.*, 2009)	Male Sprague Dawley rats; 150 and 250 g	TNBS	**Curcumin:** ● Unspecified purity	● 100 mg/kg day; ● 5 days in total – starting 2 hours before, and for 5 days during colitis induction; ● Oral route uninformed	● Colitis + curcumin	● ↓: MPO activity; MDA levels; TLR4, MyD88, and NF-κB expression in the colon	● ↓ Body weight loss; ● Reversed histological damage score in the colon
(Yadav *et al.*, 2009a)	Male Sprague Dawley rats; 6–7 weeks old, 175–205 g (b.w.)	DSS	**Curcumin:** ● Unspecified purity (a); ● Curcumin-cyclodextrin complex # (b)	● 100 mg/kg day; ● 81 days in total – after colitis induction; ● Pulsatile capsule – oral route unspecified	● Colitis + curcumin; ● Colitis + curcumin-cyclodextrin complex	**UNEVALUATED PARAMETERS**	● ↓ DAI and histological damage score in the colon (a,b); ● Reversed body weight loss (a,b); ● ↓ weight/length ratio of the colon (a,b)
(Yadav *et al.*, 2009b)	Male Sprague Dawley rats; 6–7 weeks old, 175–205 g (b.w.)	DSS	**Curcumin:** ● Unspecified purity (a); Solid lipid microparticles (SLM) # (b)	● 100 mg/kg day; ● 81 days in total – after colitis induction ● Pulsatile capsule – oral route unspecified	● Colitis + curcumin; ● Colitis + SLM	**UNEVALUATED PARAMETERS**	● ↓ DAI and histological damage score in the colon (a,b); ● Reversed body weight loss (a,b);
(Ung *et al.*, 2010)	Male Il-10 homozygous mice −/−; 12 - 13 weeks old	Genetic modification	**Curcumin:** ● Pure (>75%)	● 200 mg/kg day; ● 14 days in total; ● Gavage	● Colitis + curcumin	**UNEVALUATED PARAMETERS**	● Did not improve disease activity index and histology
(Venkataranganna *et al.*, 2007)	Male Wistar rats; 220–250 g (b.w.)	DNB	**Curcumin:** ● Standardized preparation (NCB-02)[14]	● 25 (a), 50 (b), 100[#] (c) mg/kg day; ● 10 days in total – after colitis induction; ● Oral route unspecified	● Colitis + 25 mg/kg day curcumin NCB-02; ● Colitis + 50 mg/kg day curcumin NCB-02; ● Colitis + 100 mg/kg day curcumin NCB-02; ● Colitis + sulfasalazine (100 mg/kg day orally) (d)	● ↓LPO (b,c,d) and MPO (c,d) activity in the colon; ● ↓ NFκ-B and iNOS expression in the colon (c,d)	● Attenuated the increased of weight of the total and distal colon (c,d); ● ↓ Macroscopic damage in the colon (b,c,d); ● ↓ ALP activity in the colon (c)

(Continued)

Table 1 (continued).

Author, year	Sex/species/age and/or body weight (b.w.)	Experimental model of IBD	Supplement presentation	Doses/time of supplementation/oral administration via	Groups of treatments	Nitroxidative stress and inflammation effects	Clinical, metabolic, macroscopic, and histological effects
(Camacho-Barquero *et al.*, 2007)	Male and Female Wistar rats; 180–220 g (b.w.)	TNBS	**Curcumin:** ● *Sigma* standard	● 50 (a), 100 (b) mg/kg day; ● 14 days in total – starting 24 hours after colitis induction; ● Gavage	● Colitis + 50 mg/kg day *Sigma* standard; ● Colitis + 100 mg/kg day *Sigma* standard	● ↓: MPO activity; and $^{\bullet}$NO, COX-2 and iNOS levels in the colon (a,b); ● ↓ TNF-α levels in the colon (a,b); ● ↑ IL-10 levels in the colon (a,b); ● ↓ COX-2 expression and p38 MAPK activation in the colon (a)	● ↓ Macroscopic damage score in the colon (b); ● ↓ Adherence to adjacent organs (a,b); ● ↓ Diarrhea (a,b); ● ↓ Histological changes (a); ● Reversed body weight loss (a,b)
(Ukil *et al.*, 2003)	Female BALB/c mice; 25–30 g (b.w.)	TNBS	**Curcumin:** ● *Sigma* standard	● 25 (a), 50 (b), 100 (c) or 300 (d) mg/kg day ● 18 days in total – 10 days before, and 8 days after colitis induction; ● Gavage	● Colitis + 25 mg/kg day *Sigma* standard; ● Colitis + 50 mg/kg day *Sigma* standard; ● Colitis + 100 mg/kg day *Sigma* standard ● Colitis + 300 mg/kg day *Sigma* standard	● ↓ $^{\bullet}$NO and $O_2^{\bullet-}$ in the colon (b,c,d); ● ↓ MPO activity and MDA levels in the colon (b,c,d); ● ↓ IFN-γ, IL-12, iNOS expression in the colon (b); ● ↑ IL-4 expression in the colon (b); ● ↓ NF-κB activation (b,d)	● ↓ Macroscopic and histological damage score in the colon (b,c,d); ● Attenuated body weight loss and the increased in the splenic weight (b,c,d); ● ↓ Serine protease activity in the colon (b)
≥200 mg/kg day/0.54 mmol.kg.d^{-1}							
(Sheethal *et al.*, 2020)	Male Wistar rats; 150 ± 10 g (b.w.)	Acetic acid	**Curcumin:** ● Pure (≥ 90%) (a); ● Galactomannoside Complex (CGM)[15] # (b)	● 250 mg/kg day; ● 21 days in total – after colitis induction; ● Gavage	● Colitis + curcumin; ● Colitis + CGM; ● Colitis + Sulfasalazine (100 mg/kg day orally) (c)	● ↑: SOD, CAT, and GPx activity; and GSH levels in the colon (a,b,c); ● ↓ MPO and total COX activity in the colon (a,b,c); ● ↓ TBARS, nitrite, PGE-2 levels in the colon (a,b); ● ↓ iNOS, COX 2, TLR 4, TNF-α, and IL-6 expression in the colon (a,b,c); ● ↓ CRP and CTL plasmatic levels (a,b,c)	● ↓ Macroscopic and histological damage score in the colon (b,c)
(Rotrekl *et al.*, 2021)	Male Wistar rats; 180–220 g (b.w.)	DSS	**Curcumin:** ● Pure (≥ 99.9%); ● Composite Glucan Particle (GPs+C); ● Physical mixture with GPs # (Mix. GPs+C)	● 100 mg/kg day of pure curcumin (a); ● 500 mg/kg day of Comp. GPs+C (20% w/w) (b); ● 500 mg/kg day Mix. GPs+C (20% w/w) (c); ● 5 days in total – starting 24 hours before, and maintain for 5 days during colitis induction; ● Gavage	● Colitis + pure curcumin; ● Colite - Comp. GPs-C; ● Colite - Mix. GPs-C; ● Colitis + tioguanine (d)	● ↓ TNF-α (b), TGF-β1 (b), and MMP-9 (a) production in the colon; ● ↓ IL-1β (b) and IL-6 (b,c) levels in the colon; ● ↓ MPO (c) and CAT (b) activity in the colon	● ↓ DAI (b)

(Continued)

Table 1 (continued).

Author, year	Sex/species/age and/or body weight (b.w.)	Experimental model of IBD	Supplement presentation	Doses/time of supplementation/oral administration via	Groups of treatments	Nitroxidative stress and inflammation effects	Clinical, metabolic, macroscopic, and histological effects
<2.0% (w/w) of diet							
(Ohno *et al.*, 2017)	Female BALB/c mice; 6–8 weeks old	DSS	**Curcumin:** ● Nanoparticle (Theracurmin)	● 0.2%; ● 18 days in total – 7 days before, and 11 days during colitis induction	● Colitis + Theracurmin	● Suppressed activation of NF-κB in the colon; ● ↓ TNF-α, IL-1β, IL-6, CXCL1 and CXCL2 expression in the colon; ● ↓ neutrophilic infiltration in the colon; ● ↑proportion of Treg $CD4^+$ $Foxp3^+$, and $CD103^+$ $CD8\alpha^-$ cells in the colon	● Reversed body weight loss; ● ↓ DAI; ● ↓ Histological damage score; ● Reversed shortening in the colon and colon weight (mg)/colon length (cm) ratio of the colon; ● Regulated mucosal permeability; ● Altered the composition of the microbiota; ● ↑Fecal butyrate
(Cooney *et al.*, 2016)	Male Mdr1a−/− and FVB/NTac mice; 4–5 weeks old	Genetic modification	**Curcumin:** ● ≥94% curcuminoids and ≥80% curcumin	● 0.2%; ● 18 weeks	● Colitis + curcumin	● Downregulated genes associated with immunity and inflammation[16]; ● ↓ NF-κB, PI3K, and MAPK pathways[16]	● ↓ Histological damage score in the colon; ● ↑ Remodeling and repair at barrier[16]; ● ↑α-catenin; ● ↑Xenobiotic metabolism[16]; ● ↓ Stress response of endoplasmic reticulum
(Zhang *et al.*, 2016)	Male Sprague Dawley; 180–200 g (b.w.)	TNBS	**Curcumin:** ● Pure (> 95%)	● 0.25%; ● 5 days in total – before colitis induction	● Colitis + curcumin	● ↓ MPO activity in the colon; ● ↓ TNF-α and IFN-γ levels in the colon; ● ↑ IL-13, TGF-β, and IL-10 levels in the colon; ● ↓ CD11c and CD163 cells in the colon; ● ↑ SOCS-1 and STAT1 expression and level in the colon; ● ↓ cellular apoptosis; ● ↓ cytochrome C in the colon	● Attenuated body weight loss and the increased of colon weight; ● ↓ Macroscopic and histological damage score in the colon
(Shigeshiro *et al.*, 2013)	Male BALB/c mice; 6 weeks old	DSS	**Curcumin:** ● Unspecified purity	● 0.3%; ● 12 days in total - starting 3 days before, and continuous for 9 days during colitis induction	● Colitis + curcumin	**UNEVALUATED PARAMETERS**	● ↓ DAI; ● Attenuated body weight loss; ● ↓ colonic permeability to FD-4
(Nones *et al.*, 2009)	Mile Mdr1a−/− male; 5–6 weeks old, 23.6 ± 0.6 g (b.w.)	Genetic modification	**Curcumin:** ● ≥94% curcuminoids and ≥80% curcumin	● 0.2%; ● 17 weeks	● Colitis + curcumin	● Differentiated expression of genes generating pro-inflammatory pathways	● ↓ Histological damage score in the colon; ● Upregulation of xenobiotic metabolism and a downregulation of pro-inflammatory pathways

(Continued)

Table 1 (continued).

Author, year	Sex/species/age and/or body weight (b.w.)	Experimental model of IBD	Supplement presentation	Doses/time of supplementation/oral administration via	Groups of treatments	Nitroxidative stress and inflammation effects	Clinical, metabolic, macroscopic, and histological effects
(Larmonier *et al.*, 2008)	Mile SPF WT 129/SvEv e IL-10 −/− "germ-free" mice	Genetic modification + Fecal bacterial colonization in germ-free species	**Curcumin:** ● Pure (98.05%)	● 0.1% (a), 0.5% (b), 1% (c); ● 16 days in total – 2 days before, and 14 days after colonization	● Colitis + 0.1% pure curcumin; ● Colitis + 0.5% pure curcumin; ● Colitis + 1% pure curcumin;	● ↓ IL-12/23p40 expression in proximal colon (a); ● ↓ IL-12/23p40 secretion in the colon (b, c); ● ↓ secretion of IL-12/23p40 (b,c) and IFN-γ (c) in mesenteric lymph node; ● ↓ NF-κB activation in proximal colon (a); ● ↓ phospho-Ser276p65-positive cells in the epithelium of the proximal colon (a)	● ↓ Histological damage score in the proximal (a) and distal (a,b,c) colon
(Salh *et al.*, 2003)	Mile C3H mice; 7 weeks old	DNB	**Curcumin:** ● Unspecified purity	● 0.25%; ● 10 days in total – 5 days before, and 5 days after colitis induction.	● Colitis + curcumin	● ↓ IL-1β expression in the colon; ● ↓ MPO activity in the colon; ● ↓ NF-κB activation in the colon; ● ↓ MAPK p38 activation and activity in the colon	● ↓ Macroscopic and histological damage score in the colon; ● Attenuated body weight loss
≥2.0% (w/w) of diet							
(Samba-Mondonga *et al.*, 2019)	Female BALB/c and C57BL/6; 8 weeks old	DSS	**Curcumin:** ● Unspecified purity	● 2.0%; ● 15 days in total – before colitis induction	● Colitis + curcumin;	● ↑ Lipocalin 2 expression in the colon in BALB/c and C57BL/6; ● ↓ MyD88 expression in the colon in C57BL/6	● ↓ Iron concentration in the spleen and liver; ● ↓ Red blood cells, hemoglobin, mean corpuscular volume, and hematocrit values; ● ↓ Serum iron levels *vs*. Control +Curcumin group; ● ↓ Hepcidin expression; ● ↑ Body weight loss, DAI, and histological damage score in the colon; ● ↑ Diarrhea in mice C57BL/6
(Motawi *et al.*, 2012)	Male Albino Wistar rats; 150 ± 10 g (b.w.)	TNBS	**Curcumin:** ● *Sigma* standard	● 2.0%; ● 8 days in total – 3 days before, and 5 days after colitis induction	● Colitis + *Sigma* standard;	● ↓ TNF-α and •NO serum levels; ● ↓ MPO activity and •NO levels in the colon; ● ↓ MMP-1, MMP-3, and TIMP-1 expression in the colon	● ↓ Histological damage score in the colon; ● ↓ Hydroxyproline in the colon; ● ↓ Ceruloplasmin serum levels
		TNBS	**Curcumin:**				

(Continued)

Table 1 (continued).

Author, year	Sex/species/age and/or body weight (b.w.)	Experimental model of IBD	Supplement presentation	Doses/time of supplementation/oral administration via	Groups of treatments	Nitroxidative stress and inflammation effects	Clinical, metabolic, macroscopic, and histological effects
(Billerey-Larmonier *et al.*, 2008)	Mile BALB/c and SJL/J mice; 6 weeks old, 18–21 g (b.w.)		• Pure (97%)	• 2.0%; • 9 days in total – 2 days before, and 7 days after colitis induction	• Colitis + curcumin	• Normalized the expression of colonic genes associated with the inflammatory process[17]; • ↓ TNF-α expression in the colon	• ↑ Survival rates; • ↓ Histological damage score; • Attenuated body weight loss
(Deguchi *et al.*, 2007)	Mile BALB/c mice; 6–8 weeks old	DSS	**Curcumin:** • Unspecified purity	• 2.0%; • 14 days in total – during colitis induction	• Colitis + curcumin	• ↓ MPO activity in the colon; • ↓ CD4 and CD8 T cells in the colon; • ↓ Nf-κB p65 activation in the colon; • ↑IκB activation in the colon	• Reversed body weight loss; • ↓ DAI and histological damage score; • Reversed shortening of the colon and colon weight (mg)/colon length (mm)
(Jian *et al.*, 2005)	Male Wistar SPF rats; 10–12 weeks old, 200–250 g (b.w.)	TNBS	**Curcumin:** • Pure (95%)	• 2.0% • 3 days before (a) or immediately after (b) colitis induction	• Colitis + 2.0% curcumin before colitis induction; • Colitis + 2.0% curcumin after colitis induction; • Colitis + sulfasalazine (0.5% in diet)	• ↓ NF-κB activity in the colon (a,b,c); • ↓ IκB degradation in the colon (a,b,c); • ↓ IL-1β expression in the colon (a,b,c); • ↑ β0 expression in the colon (a,b,c)	• ↑ Survival rate (a,c); • ↓ Histological damage score in the colon (a,b,c)
(Sugimoto *et al.*, 2002)	Male C57BL/6 and BALB/c mice; 7–8 weeks old, 21–23 g (b.w.)	TNBS	**Curcumin:** • Pure (99.9%)	• 0.5% (a); 2.0% # (b) or 5.0% (c); for 7 days in total – starting immediately after colitis induction and maintained for 7 days; • 2% (d) – 3 days in total - before colitis induction; • 2% (e) - 2 days in total – after colitis induction	• Colitis + 0.5% after colitis induction; • Colitis + 2.0% after colitis induction; • Colitis + 5.0% after colitis induction; • Colitis + 2.0% for 3 days before colitis induction; • Colitis + 2.0% for 2 days after colitis induction	• ↓ NF-κB and p65 activation in the colon (b); • ↑ IκB activation in the colon (b); • ↓ IL-6, IFN-γ, TNF-α, and IL-12 expression in the colon (b); • ↓ Mac-1-positive cells in the colon (b); • ↑ IκB cells– positive in the colon (b)	**In C57BL/6 mice:** • ↓ Mortality (d); • ↓ Histological damage score (b,c, d); • Attenuated body weight loss (b); **In mice BALB/c:** • Attenuated body weight loss (b,c, d)

Note: [1]Eudragit-coated chitosan microspheres containing curcumin; [2]Curcumin nanocrystals coated with chitosan; [3]Multilayer-shell core nanoparticles; [4]Multilayer nucleus-shell nanoparticles incubated in cellulose phthalate acetate solution; [5]Nanoparticles containing curcumin; [6]Oral food-grade nanocarriers composed of coated tannic acid, human serum albumin with genipin cross-linking to encapsulate curcumin; [7]Polycurcumin amphiphilic, resulting from the conjugation of polyethylene glycol and curcumin with disulfide bonds; [8]Eudragit S100/poly microparticle formulation (lactide-coglycolide) (with a weight ratio of 1:2) containing curcumin; [9]Microsponges loaded with curcumin using Eudragit and water-soluble porogen; [10]Curcumin formulation + turmeric essential oil; [11]According to a WRA score (abdominal withdrawal reflex) with Al-Chaer criteria; Kawasaki and Water-soluble porogen; [12]Given the high number of results, in this study, we chose to use data from the 7th day of intervention; [13]Patented formula containing curcumin (free Curcumin; Curcuminglucuronide; Curcuminsulfate) with soy lecithin; [14]Standardized extract of *Curcuma longa* containing 78% curcuminoids, 72% of which is curcumin, 18.08% demethoxycurcumin, and 9.42% bisdemethoxycurcumin; [15]Preparation of soluble fenugreek fiber microgranules impregnated with curcumin; [16]Results obtained by transcriptomic and proteomic analysis of the colon; [17]Results obtained by transcriptomic analysis of the colon; [#]doses or formulas that obtained better results in the study; ↑, increase; ↓, decrease; (a)(b)(c)(d)(e)(f), different treatments; ALP, alkaline phosphatase; Atg12, autophagy related 12; CAT, catalase; CCL17, C-C Motif Chemokine Ligand 17; CDK, cyclin-dependent kinase; COX, cyclooxygenase; CRP, C-reactive protein; CXCL5, C-X-C Motif Chemokine Ligand 5; DAÍ, disease activity index; DCNB, dinitrochlorobenzene; DNA, deoxyribonucleic acid; DNB, dinitrobenzene; DSS, dextran sulfate sodium; FD-4, FITC-labeled dextran with a molecular weight of 4,000 Da; FOXP3, fork head box P3; GALT, gut-associated lymphoid tissue; GPx, glutathione peroxidase; GSH, glutathione; GM-CSF, granulocyte-macrophage colony-stimulating factor; IKKβ, inhibitory kappa B kinase beta; IBD, inflammatory bowel disease; IFN-γ, interferon-gamma; IL, interleukin; iNOS, induced nitric oxide synthase; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LC3-II, light chain 3 - II; LDH, lactate dehydrogenase; LPO, lipid peroxidation; Mac-1, membrane attack complex 1; MAPK, mitogen-activated protein kinase; MDA, malonaldehyde; MHC II, major histocompatibility complex II; MMP, metalloproteinase; MPO, myeloperoxidase; mTOR, mechanistic target of rapamycin; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor kappa B; NO, nitric oxide; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; PI3K, phosphatidylinositide 3-kinase; PIASSS, protein inhibitors of activated STAT; SIRT1, sirtuin 1; SOCS, suppressor of cytokine signaling proteins; SOD, superoxide dismutase; SPF, specific pathogen free ; STAT, signal transducer and activator of transcription; TBARS, thiobarbituric acid reactive substances; TGF-β, transforming growth factor beta; Th, T helper cells; TIMP, tissue inhibitor of metalloproteinase; TLR, toll-like receptor; TNBS, trinitrobenzene sulfonic acid; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cells; TRPV1, transient receptor potential vanilloid 1; *vs*., *versus*; WBC, white blood count; WT, wild type.

Randomized controlled trials: study characteristics

In the systematic review, eight RCTs (Table 2) were identified. Six (75%) included, in its supplementation protocol, only individuals with UC and two (25%), only patients with CD. Most of them (n = 6; 75%) chose to study mild or moderate IBD, while Bommelaer *et al.* (2020) analyzed CD surgical cases, and Kumar *et al.* (2020) comprised UC active forms. In all RCTs, individuals of both sexes were included.

In three RCTs (3, 37.5%), modified curcumin/curcuminoids were utilized to increase its bioavailability; in other three RCTs (37.5%), pure curcumin was used; and in two RCTs (25%), *Curcuma longa* extract was evaluated. Doses and supplementation period showed a high variation between RCTs. The doses used ranged from 100 mg/day to 10 g/day, while the supplementation period varied from one month to six months. All included RCTs used an association of oral supplementation with drug therapy, especially mesalamine, either in the oral or oral + rectal route.

Finally, positive results in clinical, histological, and imaging parameters in the curcumin/*Curcuma longa* oral supplementation group *versus* the placebo group were observed in five (5, 62.5%) RCTs. The better effects were observed in the clinical remission rate, clinical response rate, endoscopic remission rate, and quality of life. Bommelaer *et al.* (2020), that tested 3 g/day, were the only to observe negative effects related to an increase in the severe endoscopic postoperative recurrence rate (54,8% *vs.* 25,5%; p = 0,034), while Kumar *et al.* (2020)–who used *Curcuma longa* (10 g/day for 8 weeks)–and Kedia *et al.* (2017)–who tested curcumin at a dose of 240 mg/day for 4 weeks–both in patients with UC– did not find any effect caused by oral supplementation.

Unlike the animal models included in this study, no nitroxidative stress/cytokines/nuclear factors were analyzed in the RCTs included in the present systematic review. In fact, half of them studied the effect of curcumin/*Curcuma longa* on serological or fecal parameters, and only two (25%) found positive results: decreased fecal calprotectin, C-reactive protein (CRP), erythrocyte sedimentation, and monocytes.

The risk of bias at the primary outcome level was assessed using the Cochrane collaboration tool. It is included in the Supplementary information. In general, all studies assessed risks were classified as “low” or “unclear” bias (Suppl. Table 2).

Meta-analysis

According to Fig. 2, oral supplementation with *Curcuma longa* extract or curcumin (modified or not) led to higher rates of clinical remission than placebo in both intention-to-treat (ITT) analysis (n = 281, RR: 3.15; CI 95% [1.22–8.10] p = 0.0017; i^2 = 72.2%, p = 0.006, Fig. 2A), and per-protocol (PP) analysis (n = 239, RR: 3.35; CI 95% [1.39–8.06] p = 0.007; i^2 = 71.7%, p = 0.006, Fig. 2B). High heterogeneity was observed in the analysis performed. When we removed the studies by Banerjee *et al.* (2020) and Lang *et al.* (2015), the heterogeneity of clinical remission in the ITT category was reversed (n = 162, RR: 1.70 ic95% [1.16–2.49] p = 0.006; i^2 = 0.0%, p = 0.38.

For clinical response, PP analysis (n = 259, RR: 1.60 CI 95% [1.09–2.35] p = 0.0017; i^2 = 59.7%, p = 0.042, Fig. 3A), but not ITT analysis (n = 304, RR: 1.51 CI95% [0.94–2.41] p = 0.086; i^2 = 67.7%, p = 0.015, Fig. 3B), indicates a protective effect of the *Curcuma longa* extract and curcumin.

For endoscopic remission, both ITT (n = 161, RR: 2.91 CI 95% [0.58–14.58] p = 0.195; i^2 = 72.7%, p = 0.026, Fig. 4A), and PP analysis (n = 129, RR: 3.34 CI 95% [0.76–14.68] p = 0.11; i^2 = 69.7%, p = 0.033, Fig. 4B) did not demonstrate any superior efficacy of curcumin/*Curcuma longa* extract compared to placebo.

GRADE assessment

A summary of the findings according to the GRADE assessment is shown in Table 3. In general, the quality of evidence ranged from low to very low, especially due to inconsistency and/or imprecision.

Discussion

The results found in this systematic review with meta-analysis generally indicate that the therapeutic supplementation of curcumin/*Curcuma longa* has essential effects on animal-induced colitis and IBD in humans. These effects were evidenced by the improvement of clinical markers–animal and human models–and biological features–animal models–and given these results, together with the safety in consumption, the discussion presented should stimulate the interest of professionals who deal with this disease daily clinical practices.

Animal model research

According to the present systematic review, animal studies consistently explore the effects of turmeric, attenuating nitroxidative and inflammatory responses on the characteristics of IBD. Studies also show that the antioxidant action of supplementation occurs at the molecular level by inhibiting the formation of ERONs, increasing the endogenous antioxidant response, and reducing cell damage (Esatbeyoglu *et al.*, 2012; Maiti and Dunbar, 2018).

Chronic intestinal inflammation is notably mediated by proinflammatory immune responses stimulated by antigens of different nature (Jian *et al.*, 2005). In this context, immune cells such as macrophages and lymphocytes act as important agents of the expression of proinflammatory cytokines (Duque and Descoteaux, 2014). Cytokines lead to the main proinflammatory signals, characteristic of colitis. The IL-1, IL-1β, and IL-18 families can be synthesized by intestinal epithelial cells or phagocytes (Duque and Descoteaux, 2014). In response to pathogens, IL-1β can stimulate T-cell differentiation in Th17 cells and the production of the cytokine IFN-γ (Friedrich *et al.*, 2019). In experimental models, the absence of IL-1β and IL-18, either due to genetic deficiency or signaling inhibition, is associated with colitis improvement (Dinarello *et al.*, 2013).

TNF-α, produced by phagocytes, participates in intestinal inflammation, exerting multiple intestinal cell effects (Sands and Kaplan, 2007). This cytokine’s high levels may alter the intestinal barrier’s functionality and integrity since stimulation of apoptosis occurs in epithelial cells. IL-6 is produced by phagocytes, epithelial cells, and mesenchymal cells. In the latter two, it influences the

TABLE 2

Effect of oral *Curcuma longa*/curcumin supplementation alone/combined on inflammatory bowel disease in randomized clinical trials

Author, year/country	Clinical situation	n/age/sex	Supplementation/ dose/duration	Treatment association	Control	Clinical, histological, and imaging parameters effects	Nitroxidative stress/inflammation biomarkers, serum, and fecal biomarkers effect
(Banerjee *et al.*, 2020) India	Mild to moderate ulcerative colitis in active form, in treatment with maximum dose of mesalamine[1] for at least 4 weeks	• 69 patients; • 18–70 years; • 26 M/43F	• Bioenhanced form of curcumin (BEC) (self-micro emulsifying drug delivery system); • 50 mg, twice a day; • 3 months.	• Rectal (1.0 g) + oral (4.8 g) mesalamine	• Unspecified Placebo + mesalamine	• ↑ Clinical remission rate (partial Mayo score ≤ 1) [55.9% *vs.* 5.7%, Δ%:50.2%, 95% CI: 29.3–65.9; $p < 0.01$]; • ↑ Clinical response rate (reduction ≥2 in partial Mayo score from the baseline) [58.8% *vs.* 28.6%, Δ% = 30%, 95% CI: 6.8–49.5; $p = 0.013$]; • ↑ Endoscopic remission rate (partial Mayo endoscopic score ≤ 1) [44% *vs.* 5.7%, Δ% = 38.4%, 95% CI: 18.5–55; $p < 0.001$]	**UNEVALUATED PARAMETERS**
(Kumar *et al.*, 2020) India	Ulcerative colitis in active form	• 53 patients; • 18–60 years; • 28 M/25 F	• *Curcuma longa* powder[2]; • 10 g/day; 8 weeks	• Mesalamine (2.4 g/day)	• Placebo (starch from maize, cocoa, and dextrose powder) + mesalamine	• **NO SIGNIFICANT DIFERENCE** for clinical improvement rate	• ↑ Rate of patients with decrease in fecal calprotectin by at least 25 points [83,3% *vs.* 50%; $p = 0.034$]
(Sugimoto *et al.*, 2020) Japan	Mild to moderate active Crohn's disease with manifestation in small and/or large intestine	• 30 patients; • 20–60 years; • 21 M/9F	• Theracurmin® (highly (absorbable curcumin nanoparticles); • 360 mg/day; • 12 weeks	• Current drug treatment	• Unspecified Placebo + medications	• ↑ Clinical remission rate (CDAI < 150) [40% *vs* 0%; $p = 0,02$]; • ↓ CDAI score [149 *vs.* 203; $p = 0,035$]; • ↑ Anal lesion improvement rates at week 8 [63,3% *vs.* 0%; $p = 0,017$]; • For rate at which the CDAI score decreased by 70 points or more (CR-70), SESCD score, and endoscopic remission rate (SESCD ≤ 4), there were no significant differences between groups	• C-reactive protein and hemoglobin: no significant differences between groups
(Bommelaer *et al.*, 2020) France	Crohn's disease with recent surgical resection in ileum and/or colon with anastomosis visible at ileocolonoscopy	• 62 patients; • ≥18 years; • 22 M/40F	• Curcumin, • (95%-pure curcumin preparation); • 3 g/day; • 6 months	• Azathioprine • (2–2,5 mg/kg day)	• Unspecified placebo + azathioprine	• ↑ Severe endoscopic postoperative recurrence rate (Rutgeerts index ≥ i3) [54,8% *vs.* 25,5%; $p = 0,034$]; • **NO SIGNIFICANT DIFERENCE** for endoscopic postoperative recurrence rate (Rutgeerts index ≥ i2a), clinical postoperative recurrence rate (CDAI > 150), and quality of life (IBD-Q)	**UNEVALUATED PARAMETERS**
(Sadeghi *et al.*, 2020) Iran	Mild to moderate ulcerative colitis in active form	• 70 patients; • 18–70 years; • 21 M/49 F	• Curcumin (turmeric extract)[3]; • 1.500 mg/day; • for 8 weeks	• Current drug treatment	• Placebo (maltodextrin) + medications	• ↑ Clinical remission rate (SCCAI ≤ 2) [83,9% *vs.* 43,8%; $p = 0,001$]; • ↑Clinical improvement rate (reduction ≥ 3 in SCCAI) [93,5% *vs.* 59,4%; $p < 0,001$]; • ↑ Quality of life (IBDQ-9) [9.6 ± 7.1 *vs.* 4.1 ± 7.8; $p = 0,006$][4]; • ↓ SCCAI score [−5.3 ± 1.4 *vs.* −2.7 ± 2.0; $p = 0,001$][4]	• ↓ High-sensitivity C-reactive protein levels (μg/ml) [−6.3 ± 13.6 *vs* 3.7 ± 11.6; $p = 0,01$][4]; • ↓ Erythrocyte sedimentation rate levels (mm/hr) [−1.6 ± 2.7 *vs.* −0.09 ± 2.4; $p = 0,02$][4]; • ↓ Monocytes (%) [−0.5 ± 2.2 *vs.* 0.82 ± 1.7; $p = 0,01$][4]

(Continued)

Table 2 (continued).

Author, year/country	Clinical situation	n/age/sex	Supplementation/ dose/duration	Treatment association	Control	Clinical, histological, and imaging parameters effects	Nitroxidative stress/inflammation biomarkers, serum, and fecal biomarkers effect
(Masoodi *et al.*, 2018) Iran	Mild to moderate ulcerative colitis in active form	• 56 patients; • ≥18 years; • 28 M/28F	• Curcuminoids nanomicelles; • 240 mg/day; • 4 weeks	• Mesalamine (3 g/day)	• Unspecified Placebo + mesalamine	• ↓ Score for urgency of defecation [p = 0,041]; • ↓ SCCAI score [1.71 ± 1.84 *vs.* 2.68 ± 2.09; p = 0.05]; • ↑ Self-reported well-being condition [p = 0,05]	**UNEVALUATED PARAMETERS**
(Kedia *et al.*, 2017) India	Mild to moderate ulcerative colitis in active form	• 62 patients; • ≥18 years; • 41 M/21F	• Curcumin (unspecified purity); • 450 mg/day; • 8 weeks	• Mesalamine (2,4 g/day)	• Placebo (starch with a • yellow edible dye-caramel yellow) + mesalamine	• **NO SIGNIFICANT DIFERENCE** for clinical remission (UCDAI ≤ 2) and clinical response rates (reduction in UCDAI), treatment failure (increase at UCDAI) and sigmoidoscopic remission rate (Baron endoscopic score of 0/1)	• **NO SIGNIFICANT DIFERENCE** for hemoglobin, erythrocyte sedimentation rate, total leukocyte count, urea, alanine aminotransferase, total protein, and albumin levels
(Lang *et al.*, 2015) Israel, China (Hong Kong), Cyprus	Mild to moderate ulcerative colitis in active form, in treatment with optimized dose[5] of mesalamine	• 50 patients; • 18–70 years; • 33 M/17 F	• Curcumin (95% purity); • 3 g/day; • 1 month	• Rectal (1 g/4 g via enema or 1 g via suppository) + oral (4,0 g) mesalamine	• Unspecified Placebo + mesalamine	• ↑ Clinical remission rate (SCCAI ≤ 2) [OR, 42.2; 95% CI: 2.3–760; p = 0,01]; • ↑ Clinical response rate (reduction ≥ 3 in SCCAI) [OR, 13.2; 95% CI: 3.1–56.6; p < 0,01]; • ↑ Endoscopic remission rate (reduction ≥ 1 and final of 0 or 1 in the Mayo endoscopic score) [OR, 20.7; 95% CI, 1.1–393; p = 0,043]; • ↑ Endoscopic improvement rates (reduction ≥ 1 in the Mayo endoscopic score) [OR, 30.1; 95% CI,1.6–567; p < 0.01]; • ↓ mean endoscopic rate [−0.55 ± 0.79 *vs.* +0.15 ± 0.49; p = 0,04]	**UNEVALUATED PARAMETERS**

Note: [1]Maximal dose of oral (4.8 g/d) and rectal mesalamine (1 g/d suppository/enema); [2]Composition: *Curcuma longa* variety containing 4% of curcumin with cocoa and dextrose powder; [3]Composition: turmeric extract, magnesium stearate, stearic acid, silicon dioxide, and gelatin capsule; [4]Average change values; [5]Oral (4.0 g/d) and rectal mesalamine (1 a 4 g/d via enema or 1 g via suppository); ALT, alanine aminotransferase; CDAI; Clinical Disease Activity Index; CD; Chron's disease; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; FC, fecal calprotectin; Hb, hemoglobin; IBDQ, Inflammatory Bowel Disease Questionnaire; IBDQ-9, Inflammatory Bowel Disease Questionnaire composed of only 9 items; M = male; OR, odds ratio; SCCAI = Simple Clinical Colitis Activity Index; SESCD = Simple Endoscopic Score for Crohn's Disease; TLC = total leukocyte count; UC = ulcerative colitis; UCDAI = Ulcerative Colitis Disease Activity Index; *vs.*, *versus*

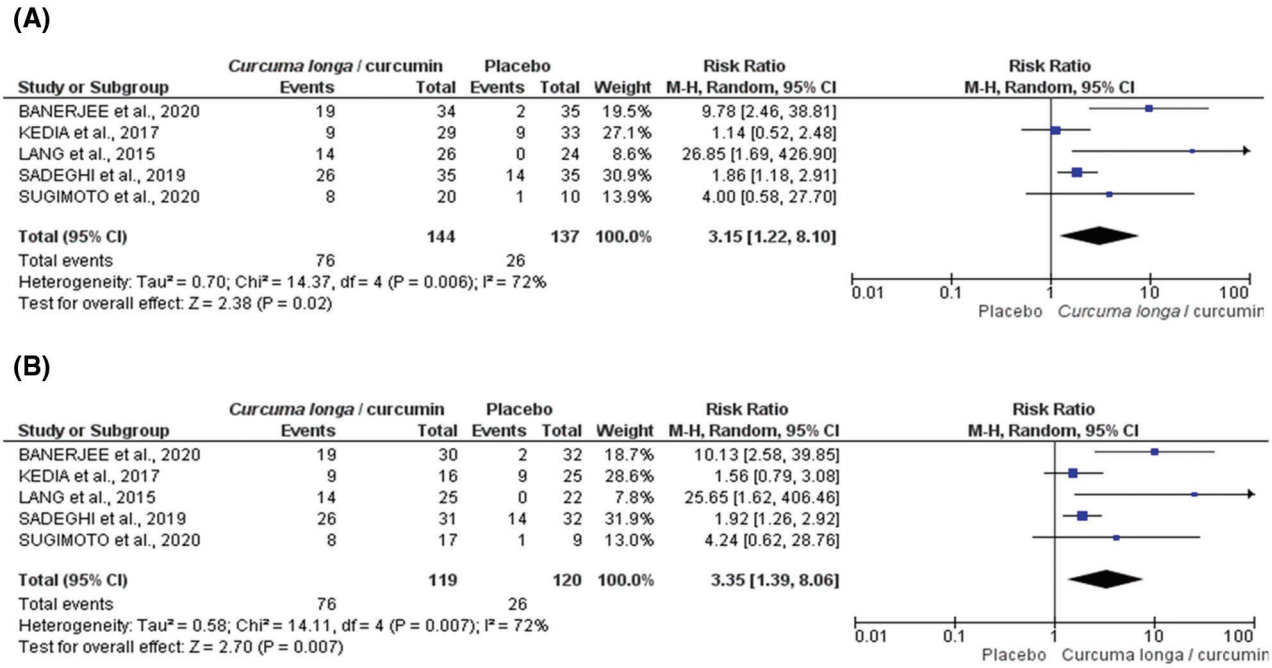

FIGURE 2. Forest plot for clinical remission induced by *Curcuma longa* extract or curcumin associated with drug therapy according to randomized clinical trial included in meta-analysis: ITT (intention-to-treat) (A) or PP (per protocol) (B).

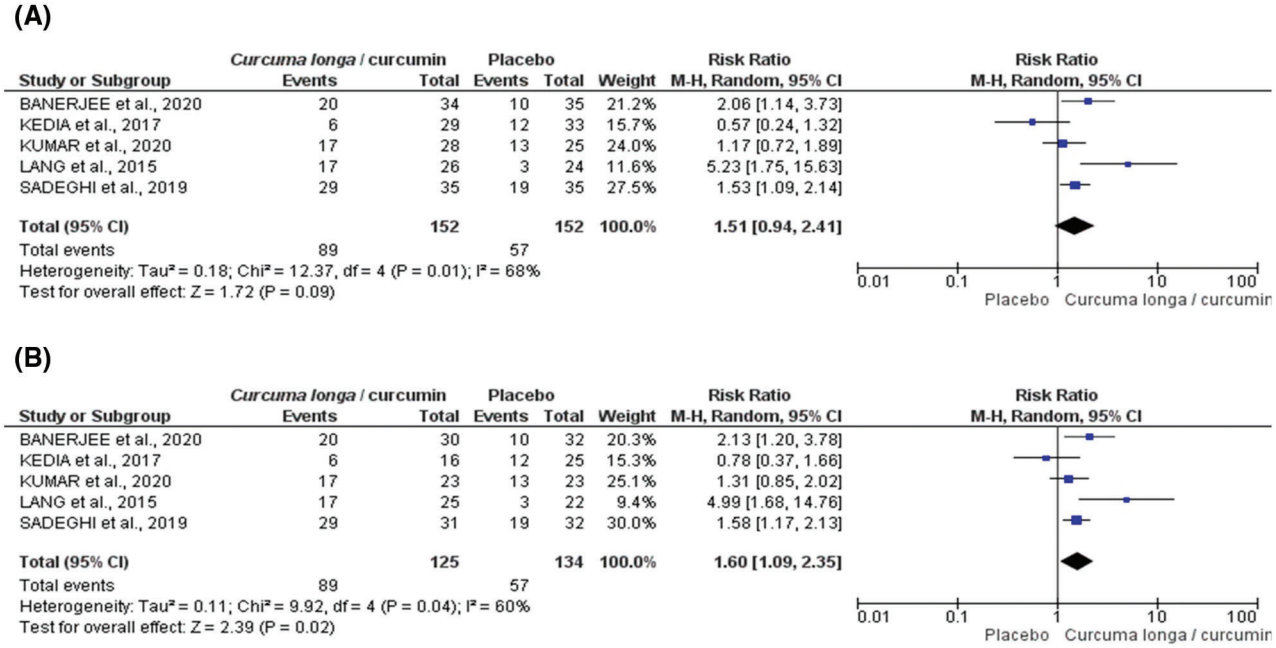

FIGURE 3. Forest plot for clinical response induced by *Curcuma longa* or curcumin associated with drug therapy according to randomized clinical trial included in meta-analysis: ITT (intention-to-treat) (A) or PP (per protocol) (B).

healing process, as it participates in the recruitment of polymorphonuclear leukocytes and macrophages (Mudter and Neurath, 2007). It also acts to prevent apoptosis of type T cells. On the other hand, IL-10, one of the main cytokines, is produced by innate and adaptive immune cells such as dendritic cells, macrophages, mast cells, natural killer cells, and Treg cells, among other cell types (Moore *et al.*, 2001).

In IBD, the reduction in IL-10 production has already been associated with more severe clinical cases (Engelhardt and Grimbacher, 2014). IL-10 may trigger different signaling pathways related to anti-inflammatory activity and has already been considered a potential therapeutic target in IBD (Katsanos and Papadakis, 2017). Thus, by associating with higher levels of anti-inflammatory cytokines and decreased pro-inflammatory mediators, curcumin seems to exert a protective effect against inflammation.

Another line of evidence identified in the results of this systematic review indicates that curcumin can inhibit or reduce NF-κB activation. NF-κB is a factor that plays a

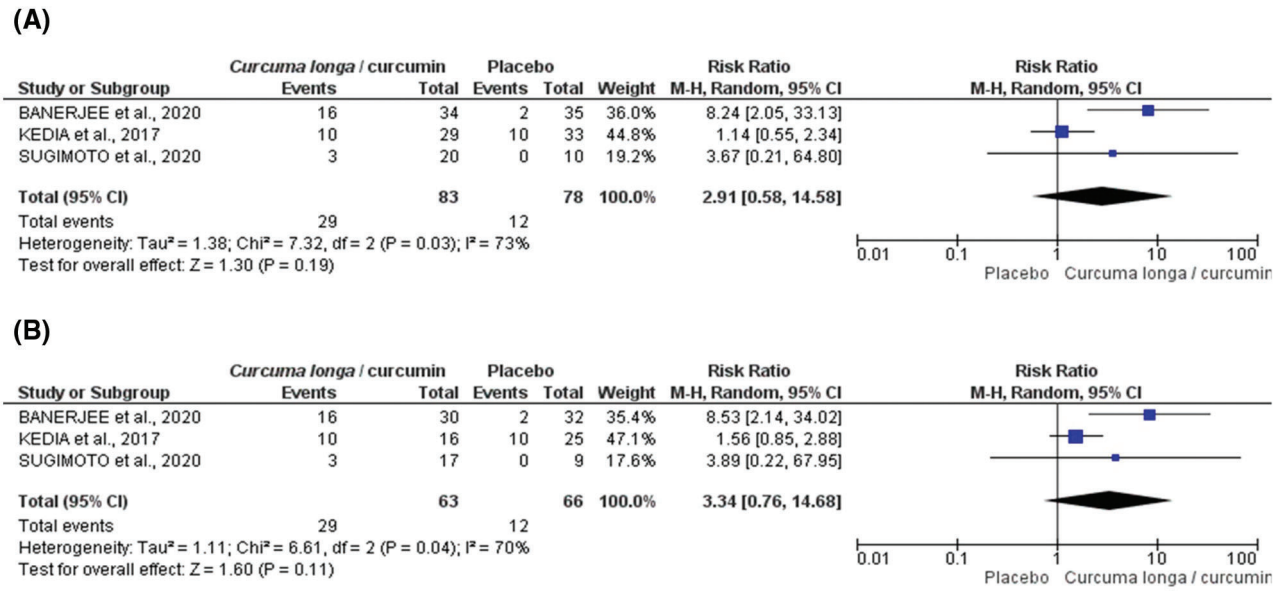

FIGURE 4. Forest plot for endoscopic remission induced by *Curcuma longa* or curcumin associated with drug therapy according to randomized clinical trial included in meta-analysis: ITT (intention-to-treat) (A) or PP (per protocol) (B).

TABLE 3

Summary of findings for assessment quality of evidence according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Quality assessment[a]							Number of patients		Effects		
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Curcuma longa*/ curcuminoids + conventional medicines	Placebo + conventional medicines	Relative (CI 95%)	Quality GRADE	Importance
Clinical remission (ITT)											
5	RCT	No serious limitations	Serious[b]	Not serious	Not serious	None	144	137	RR: 3,15 (1,22–8,10)	⨁⨁ Low	Important
Clinical response (ITT)											
5	RCT	No serious limitations	Serious[c]	Not serious	Not serious	None	152	152	RR: 1,51 (0,94–2,41)	⨁⨁ Low	Important
Endoscopic remission (ITT)											
3	RCT	No serious limitations	Serious[b]	Not serious	Serious[d]	None	83	78	RR: 2,91 (0,58–14,58)	⨁ Very low	Important

Note: RCT, randomized clinical trials; CI, confidence interval; ITT, intention to treat; RR: relative risk; a. due to the small number of studies included, it was not possible to evaluate publication bias; b. heterogeneity with I^2 value > 70%; c. heterogeneity with I^2 value > 60%; d. small number of studies and a wide confidence interval.

central role in regulating the transcription of proinflammatory cytokine genes. Physiologically, the NF-κB transcription factor family in mammals consists of five proteins, p65 (RelA), RelB, c-Rel, p105/p50 (NF-κB1), and p100/52 (NF-κB2) that associate with each other to form distinct transcriptionally active homo and heterodimeric complexes (Oeckinghaus and Ghosh, 2009). By inhibiting the activation of transcription factors, curcumin interferes with the start-up of the process and the subsequent cascade of characteristic reactions of the inflammatory process by negatively regulating the suppression of multiple proinflammatory genes (Katsanos and Papadakis, 2017).

Some stimuli that culminate in NF-κB activation pass through cellular receptors that recognize pathogen-associated molecular patterns (PAMPs), especially TLR-4 (Ni *et al.*, 2015). The stimulation of the TLR-4 isoform and the polymorphism of these receptors were identified as important mechanisms in the inflammatory stimulus in IBD (De Jager *et al.*, 2007; Fukata and Abreu, 2008). The TLR-4-MyD88-NF-κB signaling pathway is activated when TLR-4 activates myeloid differentiation factor 88 (MyD88), which stimulates other molecules that act together for NF-κB activation with consequent expression of proinflammatory genes (Lubbad *et al.*, 2009; Luo *et al.*, 2020). Through these results, it seems that curcumin presents a mechanism of action: inhibition of the TLR-4-MyD88-NF-κB signaling pathway.

Intestinal tissue in IBD is histologically characterized by infiltration and accumulation of immune system cells in the

TABLE 4

Tools used by randomized clinical trials included in the meta-analysis to assess signs and symptoms of ulcerative colitis and Crohn's disease: Simple Clinical Colitis Activity Index (SCCAI), Ulcerative Colitis Disease Activity Index (Mayo/UCDAI) and Crohn's Disease Activity Index (CDAI)

Simple clinical colitis activity index (SCCAI) (Walmsley, 2014)		Mayo score* (Schroeder *et al.*, 1987)		Ulcerative colitis disease activity index (UCDAI) (Sutherland *et al.*, 1987)		Crohn's disease activity index (CDAI) (Best *et al.*, 1976)	
Bowel frequency (day) - 1 per occurrence	**Score**	**Stool frequency**	**Score**	**Stool frequency**	**Score**	**For seven days**	**Score**
0–3	0	Normal n° of stools for this patient	0	Normal	0	Number of liquid or very soft stools per day	2 points per stool
4–6	1	1–2 stools more than normal	1	1–2 stools/day > normal	1	Adjustment if using diarrhea - control medications	30
7–9	2	3–4 stools more than normal	2	3–4 stools/day > normal	2		
> 9	3	5 or more stools than normal	3	> 4 stools/day > normal	3		
Bowel frequency (night)	**Score**	**Rectal bleeding**	**Score**	**Rectal bleeding**	**Score**	**Abdominal pain rating**	**Score (x5)**
0	0	No blood observed	0	No	0	None	0
1–3	1	Streaks of blood with stool less than half the time	1	Streaks of blood	1	Mild	1
4–6	2	Obvious blood with stool most of the time	2	Obvious blood	2	Moderate	2
		Blood alone passed	3	Mostly blood	3	Severe	3
Urgency of defecation	**Score**	**Findings of flexible sigmoidoscopy**	**Score**	**Mucosal appearance**	**Score**	**General well-being rating**	**Score (x7)**
None	0	Normal or inactive disease	0	Normal	0	Well	0
Hurry	1	Mild disease (erythema, decreased vascular pattern, mild friability)	1	Mild friability	1	Slightly under par	1
Immediately (toilet nearby)	2	Moderate friability	2	Moderate friability	2	Poor	2
Incontinence	3	Severe disease (spontaneous bleeding, ulceration)	3	Exudation, spontaneous bleeding	3	Very poor	3
						Terrible	4
Blood in stool	**Score**	**Physician's global assessment**	**Score**	**Physician's rating of disease activity**	**Score**	**Number of complications - 20 per manifestation**	**Score (x20)**
None	0	Normal	0	Normal	0	Arthralgias, erythema nodosum, iritis, uveitis, anal disease (fissure, fistula, etc.), external fistula (enterocutaneous/vesicle/vaginal, etc.), fever > 38.7°C	Yes = 1 No = 0
Trace	1	Mild disease	1	Mild	1		
Occasionally frank (<50% of defecation)	2	Moderate disease	2	Moderate	2		
Usually, frank (>50% of defecation)	3	Severe disease	3	Severe	3		
General well-being (0 - 10)	**Score**					**Abdominal mass**	**Score (X10)**
≥ Very well	0					None	0
6 = Slightly below par	1					Equivocal	2
5 = Poor	2					Present	10
4 = Very poor	3						
<4 Terrible	4						
Extracolonic features (1 per manifestation)	**Score**					**Haematocrit, % decrease from expected**	**Score**
Arthritis, uveitis, erythema nodosum, pyoderma gangrenosum	Yes = 1 No = 0					Absolute deviation of haematocrit from 47% in males or 42% in females	6 points per percent deviation
						Body weight, % decrease from expected	**Score**
						Percentage deviation from standard weight	1 point per percent deviation
MAXIMUM SCORE	**19**	**MAXIMUM SCORE**	**12**	**MAXIMUM SCORE**	**12**	**MAXIMUM SCORE**	**600**

mucous region, such as neutrophils and monocytes (Gui *et al.*, 2018). In a complex tissue environment and loaded with proinflammatory molecules, these immune cells are probably recruited by chemotaxis mechanisms (Harbord *et al.*, 2006). Neutrophils and monocytes release the MPO enzyme, whose activity may be able to indirectly reflect colonic inflammation (Chami *et al.*, 2018). MPO may also be associated with the oxidative mechanisms of the inflamed colon, since this enzyme generates reactive species of oxygen (ROS), including hypochlorous acid (HOCl), through halogenation or peroxidase cycles (Myzak and Carr, 2002). The great number of experimental studies that observed a decrease in MPO activity, independent of dose, supplementation time, or moment of colitis, seem to indicate that curcuminoids can attenuate the infiltration of immune cells and reduce changes in the mucous region generated by intestinal inflammation in animals (Zeng *et al.*, 2013).

Redox imbalance is related to inflammation and is characterized by an imbalance between oxidants and antioxidants, with a predominance of oxidation reactions (Vasconcelos *et al.*, 2007). The gastrointestinal tract, which commonly interacts with food metabolites, microorganisms, and its own immune system, is a region that favored pro-oxidant molecules (Moura *et al.*, 2015). Research conducted with animals and humans demonstrated the presence of redox imbalance in the disease by increasing the levels of markers of oxidative damage and reducing the level of antioxidant systems present in the blood, saliva, or colonic tissue. Lipid peroxidation, protein denaturation, and deoxyribonucleic acid (DNA) mutation are examples of damage caused by nitroxidative stress and interfere with the integrity of the intestinal mucosal barrier (Wang *et al.*, 2016). Additionally, the evolution of IBD symptoms such as ulcer, toxic megacolon, and colorectal cancer has been related to the action of RONs (Moura *et al.*, 2015; Moura *et al.*, 2020).

The process of inflammation characteristic of IBD may incur gene transcription of some enzymes implicated in the endogenous generation process of reactive species. Peroxidases such as xanthine oxidase (XO), lipoxygenases (LPO), MPO, iNOS, COX, and the NADPH oxidase complex (NOX) (Balmus *et al.*, 2016a; Balmus *et al.*, 2016b) COX-2 are directly involved in ulceration formation and may be associated with inflammatory processes in the colon region and precancerous changes in the gastrointestinal tract (Binion *et al.*, 2008; Camacho-Barquero *et al.*, 2007; Mccarty, 2012). The results of the experimental studies in this systematic review demonstrate that oral curcumin supplementation can inhibit these enzymes directly or by blocking NF-κB.

In this systematic review, damage to the lipid membrane was the most evaluated cell damage and showed the best results after curcumin supplementation. Lipid peroxidation results in the formation of products such as TBARS and MDA (Niki, 2013). In this context, it has been shown that MDA is increased in IBD in animals and humans in different biological environments, such as saliva (Jahanshahi *et al.*, 2004; Rezaie *et al.*, 2006; Szeląg *et al.*, 2012) and blood (Boehm *et al.*, 2012; Alzoghaibi *et al.*, 2007). Another finding of the study points to the existence of a positive correlation of MDA with Crohn's Disease Activity Index (CDAI) and C-reactive protein (CRP) and a negative correlation with antioxidant defense (Szczeklik *et al.*, 2018), composed of enzymatic and nonenzymatic biomarkers. The positive effects of curcumin/*Curcuma longa* on this cell damage marker suggest that this polyphenol/extract may act, protecting membrane integrity.

Although few studies, pointed out in this review, have evaluated the antioxidant defense system, represented by enzymes SOD, CAT, and GPx, and nonenzymatic system GSH, several studies on humans confirm that these biomarkers are altered in IBD (Guan and Lan, 2018; Szczeklik *et al.*, 2018). SOD–represented by its three main isoforms SOD1 (Cu/ZnSOD) present in the cytosol, SOD2 (MnSOD) located in mitochondria, and SOD3 (Cu/ZnSOD) present in extracellular medium–catalyzes the conversion from anion radical superoxide (O2•-) to oxygen (O2); in sequence CAT–present in peroxisomes–and GPx–found in cytosol–convert O_2 in hydrogen peroxide (H_2O_2). In turn, the GSH system (reduced glutathione–GSH–, oxidized (GSSG) and glutathione reductase–GR), a nonenzymatic system defense, also responds against oxidative damage, and their levels are altered in CD or UC (Pinto *et al.*, 2013; Sido *et al.*, 1998). The improvement or normalization of the levels of antioxidant defense in animals that received oral curcumin/*Curcuma longa* indicates that they may directly stimulate enzymatic end nonenzymatic synthesis/activity.

In the inflamed colon, the presence of macrophages and neutrophils that are stimulated by proinflammatory cytokines, as well as the recognition of bacterial lipopolysaccharides (LPS) by TRL-4, and the action of IFN-γ are associated with super expression of iNOS and consequent production of •NO (Camacho-Barquero *et al.*, 2007; Motawi *et al.*, 2012), which appears to be associated with a more severe inflammatory response and tissue injury, in experimental colitis (Motawi *et al.*, 2012). On the other hand, •NO may interact with O2•- and generate peroxynitrate (-OONO) that can react with DNA (Cooke *et al.*, 2003). In this context, the decrease in •NO levels observed in some animal studies (Altinel *et al.*, 2020; Camacho-Barquero *et al.*, 2007; Kao *et al.*, 2016; Motawi *et al.*, 2012; Venkataranganna *et al.*, 2007; Ukil *et al.*, 2003) may reflect the scavenging action of curcumin/*Curcuma longa* or their role in inhibiting iNOS activity. The alteration of the microbiome stands out as a factor involved in the pathogenesis of IBD (Guan, 2019). It is hypothesized that curcumin may interfere in the microbiome, either through the action of the compound and/or metabolites or the action of products resulting from the microbial metabolism of the substance itself. Regulatory effects can be attributed to modulation in the intestinal biome's amount, diversity, and composition (Scazzocchio *et al.*, 2020). This relationship between curcumin and microbiota can be confirmed in the study by Ohno *et al.* (2017), which when evaluating mice with DSS-induced colitis, observed that a diet consumption containing 2.0% (w/w) of curcumin for 18 days was able to stimulate the proliferation of bacteria Clostridium cluster IV and XIVa, which was accompanied by increased levels of fecal butyrate. Unfortunately, human studies have not yet tested this hypothesis, leaving this gap in the beneficial actions of curcumin in the health of patients with IBD.

Together, these beneficial actions reveal the protective role of curcuminoids/*Curcuma longa* against inflammation, redox imbalance, and dysbiosis and suggest the necessity of evaluating these biomarkers in human studies.

RCT: Systematic review and meta-analysis

The IBD is not a disease with an established cure; therefore, the treatment adopted in current protocols is nonspecific and aims to minimize symptoms, improve quality of life, achieve remission, and decrease complications of the disease (Abraham *et al.*, 2017). In addition, IBD pathogenic mechanisms remain unclear, and global epidemiologic data suggest an important crosslink with socioeconomic development (Molodecky *et al.*, 2012). Furthermore, IBD has a low mortality rate and is usually associated with complications such as colorectal cancer (CRC), infections and surgical complications. Its clinical manifestations, such as diarrhea, weight loss, and low digestive bleeding, have a great impact on the quality of life of its patients (Moura *et al.*, 2015). Together, these data confirm IBD as an important global public health problem.

Conventional IBD therapy involves, in general, the use of sulfasalazine, corticosteroids, immunosuppressive agents, such as azathioprine, mercaptopurine or methotrexate (Lamb *et al.*, 2019). In addition, is used the biological therapy, represented especially by the anti-TNF, anti-integrin, and anti-IL 12/23 drugs (Hindryckx *et al.*, 2018). On the other hand, the adverse effects associated with the prolonged use of these drugs and the high rate of relapses significantly limit their use (Xu *et al.*, 2004). In this context, the estimate indicates that 10%–30% of patients with UC and 38%–70% of patients with CD, with complications, will undergo some surgical intervention (Palacio *et al.*, 2021) and the long-term collateral effects of drug therapy, together with the high cost of surgical management, leads the scientific community to investigate alternative treatments for IBD.

In the present meta-analysis, even with the variation in the rates of assessment of disease severity among RCTs, curcumin/*Curcuma longa* oral supplementation combined with conventional drug therapy was able to induce clinical remission and response in adult IBD patients. These outcomes were assessed by the score of different tools, such as Crohn's Disease Activity Index (CDAI) (Sugimoto *et al.*, 2020), Simple Clinical Colitis Activity Index (SCCAI) (Lang *et al.*, 2015; Masoodi *et al.*, 2018; Sadeghi *et al.*, 2020) and Ulcerative Colitis Disease Activity Index (Mayo/UCDAI) (Banerjee *et al.*, 2020; Kedia *et al.*, 2017; Kumar *et al.*, 2020), which measure disease activity through the severity of the presented symptoms (Table 4).

The SCCAI includes assessing six questions, including the number of nighttime evacuations and fecal urgency. This index was proposed by Walmsley *et al.* (1998) and has been used by several authors (Lang *et al.*, 2015; Sadeghi *et al.*, 2020; Schroeder *et al.*, 1987; Walmsley, 2014). The Mayo Clinic Score and UCDAI are similar tools composed of four questions, and in addition to including clinical symptoms, they also evaluate endoscopic changes. Such tools are the most adopted in the methodology for assessing disease activity in RCTs (Bewtra *et al.*, 2014). Although the CDAI is one of the tools commonly used in CD and evaluates the severity of several signs and symptoms, such as weight loss and anemia, it is considered an insufficient form since the questions included in the tool can be influenced by subjectivity, in addition to presenting little agreement with histological altars identified by the Global Histologic Activity Score (GHAS) (Tajra *et al.*, 2019).

Despite the different methods used, clinical activity is an important parameter to assess IBD. The intensity with which symptoms manifest in the patient and endoscopic and histological changes can predict whether the disease is active. However, few tools have been validated to categorize the severity of the disease (Peyrin-Biroulet *et al.*, 2016). Patients with active disease have a worse quality of life, increasing between 70% and 80% chances of having a recurrent episode in one year (Sairenji *et al.*, 2017). In addition, IBD clinical activity can be an independent risk factor for extraintestinal manifestations, such as acute arterial disease, ischemic heart, and cerebrovascular arterial disease (Le Gall *et al.*, 2018) and anemia (Parra *et al.*, 2020).

Endoscopic evaluation is known to be recommended for diagnosis, monitoring and therapeutic evaluation of patients with IBD. Although endoscopic remission is not statistically evidenced in this meta-analysis, it is important to highlight those other methods are emerging as an alternative for the accompaniment of these patients, such as fecal markers (such as calprotectin), because they have lower cost and impact for these individuals, facilitating their performance, including in places of difficult access to imaging methods (common in poor or developing countries). In this context, we strongly suggest that the new human trials include these biomarkers aiming at an expanded view of the effects of curcumin (and other antioxidants) on the intestinal health of patients with IBD.

In this context, identifying therapies that reduce clinical activity, and consequently, lead and keep the patient in the remission phase is one of the main objectives of clinical research in IBD.

Strengths and Limitations

This study presents to the scientific community two-point of view about oral supplementation of curcumin/*Curcuma longa*: the impact of this polyphenol/extract on animal models of UC, and a systematic review and meta-analysis of RCTs. In both, beneficial effects were observed. However, RCTs still do not carry out analysis on the nitroxidative and anti-inflammatory impacts of curcumin, even with several confirmations observed both *in vitro* and in animal models. Additionally, the curcumin administration led to different effects in animal experiments and in clinical trials. Probably, these differences occurred because colitis in animal models is induced by external factor. Since IBD is a multifactorial disease, its induction cannot mimic the various risk factors involved, and for that, it is not possible to have the same results in animals and humans. However, the results in animals serve as a basis for conducting human trials.

Another unanswered question is whether curcumin changes its beneficial effects in symptomatic or asymptomatic colitis. Although animal studies show different models of colitis, in randomized studies, curcumin/curcuminoids were mostly tested in the acute phase of the disease. Likewise,

studies are still insufficient to determine whether curcuma/curcuminoids is more effective among patients with CD or UC.

Given this information, new clinical studies' objectives should confirm whether curcumin shows similar results in humans, which would justify its positive result on the clinical improvement found in this meta-analysis.

Future studies should evaluate the effect of *Curcuma longa*/curcuminoids on nitroxidative stress and its crosslink with inflammation and disease activity and remission.

Some questions, as listed below, should direct research efforts.

Which is the better moment to initiate supplementation: the symptomatic or the asymptomatic phase?

What are the better doses and period of treatment?

Does modified curcumin (nanoparticles, microparticles, combined, and other formulations) show beneficial effects *vs*. pure curcumin in humans?

In addition to these issues, it is necessary to be established reproducible models that ensure the evaluation of this bioavailability in different IBD scenarios.

However, despite these still unanswered questions, the analysis of the present data, allow to suggest that the oral prescription of *Curcuma longa* and/or curcumin, when associated with drug therapy, is safe and effective in the treatment of patients with IBD.

Author Contribution: Fabiana Andréa Moura designed the study; Nassib Bezerra Bueno analyzed data and performed statistical analysis; Marla de Cerqueira Alves, Monise Oliveira Santos and Orlando Roberto Pimentel de Araújo wrote the paper; Fabiana Andréa Moura and Nassib Bezerra Bueno had primary responsibility for the final content; Marília Oliveira Fonseca Goulart critically revised the paper for intellectual content and provided final approval of the manuscript; all authors reviewed the results and approved the final version of the manuscript.

Funding Statement: This work was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq–Brazil) [Grant No. 435704/2018-4]; and Fundação de Amparo à Pesquisa do Estado de Alagoas (FAPEAL)/PPSUS/Ministério da Saúde (MS) [Grant No. 60030-000876/2016].

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

References

Abraham BP, Ahmed T, Ali T (2017). Inflammatory bowel disease: Pathophysiology and current therapeutic approaches. *Handbook of Experimental Pharmacology* **239**: 115–146. DOI 10.1007/978-3-319-56360-2.

Actis GC, Pellicano R, Fagoonee S, Ribaldone DG (2019). History of inflammatory bowel diseases. *Journal of Clinical Medicine* **8**: 1970. DOI 10.3390/jcm8111970.

Aldini R, Budriesi R, Roda G, Micucci M, Ioan P et al. (2012). *Curcuma longa* extract exerts a myorelaxant effect on the ileum and colon in a mouse experimental colitis model, independent of the anti-inflammatory effect. *PLoS One* **7**: e44650. DOI 10.1371/journal.pone.0044650.

Altinel Y, Yalçın Ş, Ercan G, Yavuz E, Erçetin C et al. (2020). The efficacy of curcumin on PDGF expression and NF-Kappa B pathway: TNBS-Induced colitis. *Ulusal Travma ve Acil Cerrahi Dergisi = Turkish Journal of Trauma & Emergency Surgery: TJTES* **26**: 663–670. DOI 10.14744/tjtes.2019.45570.

Alzoghaibi MA, Al IA, Al-jebreen AM (2007). Lipid peroxides in patients with inflammatory bowel disease. *Saudi Journal of Gastroenterology: Official Journal of the Saudi Gastroenterology Association* **13**: 187–190. DOI 10.4103/1319-3767.36750.

Balmus IM, Ciobica A, Trifan A, Stanciu C (2016a). The implications of oxidative stress and antioxidant therapies in inflammatory bowel disease: Clinical aspects and animal models. *Saudi Journal of Gastroenterology* **22**: 3–17. DOI 10.4103/1319-3767.173753.

Balmus IM, Ciobica A, Antioch I, Dobrin R, Timofte D (2016b). Oxidative stress implications in the affective disorders: Main biomarkers, animal models relevance, genetic perspectives, and antioxidant approaches. *Oxidative Medicine and Cellular Longevity* **3975101**: 1–25. DOI 10.1155/2016/3975101.

Banerjee R, Pal P, Penmetsa A, Kathi P, Girish G et al. (2020). Novel bioenhanced curcumin with mesalamine for induction of clinical and endoscopic remission in mild-to-moderate ulcerative colitis: A randomized double-blind placebo-controlled pilot study. *Journal of Clinical Gastroenterology* **55**: 702–708. DOI 10.1097/MCG.0000000000001416.

Bastaki SMA, Al Ahmed MM, Al Zaabi A, Amir N, Adeghate E (2016). Effect of turmeric on colon histology, body weight, ulcer, IL-23, MPO and glutathione in acetic-acid-induced inflammatory bowel disease in rats. *BMC Complementary and Alternative Medicine* **16**: 72. DOI 10.1186/s12906-016-1057-5.

Beloqui A, Coco R, Memvanga PB, Ucakar B, Des Rieux A et al. (2014). PH-Sensitive nanoparticles for colonic delivery of curcumin in inflammatory bowel disease. *International Journal of Pharmaceutics* **473**: 203–212. DOI 10.1016/j.ijpharm.2014.07.009.

Beloqui A, Memvanga PB, Coco R, Reimondez-Troitiño S, Alhouayek M et al. (2016). A comparative study of curcumin-loaded lipid-based nanocarriers in the treatment of inflammatory bowel disease. *Colloids and Surfaces B: Biointerfaces* **143**: 327–335. DOI 10.1016/j.colsurfb.2016.03.038.

Best WR, Becktel JM, Singleton JW, Kern F Jr (1976). Development of a crohn's disease activity index. *Gastroenterology* **70**: 439–444. DOI 10.1016/S0016-5085(76)80163-1.

Bewtra M, Brensinger CM, Tomov VT, Hoang TB, Sokach CE et al. (2014). An optimized patient-reported ulcerative colitis disease activity measure derived from the mayo score and the simple clinical colitis activity index. *Inflammatory Bowel Diseases* **20**: 1. DOI 10.1097/MIB.0000000000000053.

Billerey-Larmonier C, Uno JK, Larmonier N, Midura AJ, Timmermann B et al. (2008). Protective effects of dietary curcumin in mouse model of chemically induced colitis are strain dependent. *Inflammatory Bowel Diseases* **14**: 780–793. DOI 10.1002/ibd.20348.

Binion DG, Otterson MF, Rafiee P (2008). Curcumin inhibits VEGF-Mediated angiogenesis in human intestinal microvascular endothelial cells through COX-2 and MAPK inhibition. *Gut* **57**: 1509–1517. DOI 10.1136/gut.2008.152496.

Boehm D, Krzystek-Korpacka M, Neubauer K, Matusiewicz M, Paradowski L et al. (2012). Lipid peroxidation markers in

crohn's disease: The associations and diagnostic value. *Clinical Chemistry and Laboratory Medicine* **50**: 1359–1366. DOI 10.1515/cclm-2011-0817.

Bommelaer G, Laharie D, Nancey S, Hebuterne X, Roblin X et al. (2020). Oral curcumin no more effective than placebo in preventing recurrence of crohn's disease after surgery in a randomized controlled trial. *Clinical Gastroenterology and Hepatology* **18**: 1553–1560.e1. DOI 10.1016/j.cgh.2019.08.041.

Camacho-Barquero L, Villegas I, Sánchez-Calvo JM, Talero E, Sánchez-Fidalgo S et al. (2007). Curcumin, a *Curcuma longa* constituent, acts on MAPK P38 pathway modulating COX-2 and INOS expression in chronic experimental colitis. *International Immunopharmacology* **7**: 333–342. DOI 10.1016/j.intimp.2006.11.006.

Chami B, Martin NJJ, Dennis JM, Witting PK (2018). Myeloperoxidase in the inflamed colon: A novel target for treating inflammatory bowel disease. *Archives of Biochemistry and Biophysics* **645**: 61–71. DOI 10.1016/j.abb.2018.03.012.

Chen Q, Gou S, Huang Y, Zhou X, Li Q et al. (2018). Facile fabrication of bowl-shaped microparticles for oral curcumin delivery to ulcerative colitis tissue. *Colloids and Surfaces B: Biointerfaces* **169**: 92–98. DOI 10.1016/j.colsurfb.2018.05.012.

Chen Q, Gou S, Ma P, Song H, Zhou X et al. (2019). Oral administration of colitis tissue-accumulating porous nanoparticles for ulcerative colitis therapy. *International Journal of Pharmaceutics* **557**: 135–144. DOI 10.1016/j.ijpharm.2018.12.046.

Chen Q, Si X, Ma L, Ma P, Hou M et al. (2017). Oral delivery of curcumin via porous polymeric nanoparticles for effective ulcerative colitis therapy. *Journal of Materials Chemistry* **5**: 5881–5891. DOI 10.1039/C7TB00328E.

Cooke MS, Evans MD, Dizdaroglu M, Lunec J (2003). Oxidative DNA damage: Mechanisms, mutation, and disease. *FASEB Journal* **17**: 1195–1214. DOI 10.1096/fj.02-0752rev.

Cooney JM, Barnett MP, Dommels YE, Brewster D, Butts CA et al. (2016). A combined omics approach to evaluate the effects of dietary curcumin on colon inflammation in the Mdr1a-/- Mouse model of inflammatory bowel disease. *Journal of Nutritional Biochemistry* **27**: 181–192. DOI 10.1016/j.jnutbio.2015.08.030.

Cunha Neto F, Marton LT, de Marqui SV, Lima TA, Barbalho SM (2019). Curcuminoids from curcuma longa: New adjuvants for the treatment of crohn's disease and ulcerative colitis? *Critical Reviews in Food Science and Nutrition* **59**: 2136–2143. DOI 10.1080/10408398.2018.1456403.

de Jager PL, Franchimont D, Waliszewska A, Bitton A, Cohen A et al. (2007). The role of the Toll receptor pathway in susceptibility to inflammatory bowel diseases. *Genes and Immunity* **8**: 387–397. DOI 10.1038/sj.gene.6364398.

Deguchi Y, Andoh A, Inatomi O, Yagi Y, Bamba S et al. (2007). Curcumin prevents the development of dextran sulfate sodium (DSS)-Induced experimental colitis. *Digestive Diseases and Sciences* **52**: 2993–2998. DOI 10.1007/s10620-006-9138-9.

Dinarello CA, Novick D, Kim S, Kaplanski G (2013). Interleukin-18 and IL-18 binding protein. *Frontiers in Immunology* **8**: 289. DOI 10.3389/fimmu.2013.00289.

Duque AG, Descoteaux A (2014). Macrophage cytokines: Involvement in immunity and infectious diseases. *Frontiers in Immunology* **5**: 491. DOI 10.3389/fimmu.2014.00491.

Engelhardt KR, Grimbacher B (2014). IL-10 in humans: Lessons from the gut, IL-10/IL-10 receptor deficiencies, and IL-10 polymorphisms. *Current Topics in Microbiology and Immunology* **380**: 1–18. DOI 10.1007/978-3-662-43492-5.

Esatbeyoglu T, Huebbe P, Ernst IM, Chin D, Wagner AE et al. (2012). Curcumin-from molecule to biological function. *Angewandte Chemie-International Edition* **51**: 5308–5332. DOI 10.1002/anie.201107724.

Friedrich M, Pohin M, Powrie F Cytokine (2019). Cytokine networks in the pathophysiology of inflammatory bowel disease. *Immunity* **50**: 992–1006. DOI 10.1016/j.immuni.2019.03.017.

Fukata M, Abreu MT (2008). Role of toll-like receptors in gastrointestinal malignancies. *Oncogene* **27**: 234–243. DOI 10.1038/sj.onc.1210908.

Gopu B, Dileep R, Rani MU, Kumar CS, Kumar MV, Reddy AG (2015). Protective role of curcumin and flunixin against acetic acid-induced inflammatory bowel disease via modulating inflammatory mediators and cytokine profile in rats. *Journal of Environmental Pathology, Toxicology and Oncology* **34**: 309–320. DOI 10.1615/JEnvironPatholToxicolOncol.2015013049.

Guan G, Lan S (2018). Implications of antioxidant systems in inflammatory bowel disease. Bowel Disease. *BioMed Research International* **1290179**: 1–7. DOI 10.1155/2018/1290179.

Guan Q (2019). A comprehensive review and update on the pathogenesis of inflammatory bowel disease. *Journal of Immunology Research* **7247238**: 1–16. DOI 10.1155/2019/7247238.

Gui X, Li J, Ueno A, Iacucci M, Qian J et al. (2018). Histopathological features of inflammatory bowel disease are associated with different CD4+T cell subsets in colonic mucosal lamina propria. *Journal of Crohn's and Colitis* **12**: 1448–1458. DOI 10.1093/ecco-jcc/jjy116.

Harbord MW, Marks DJ, Forbes A, Bloom SL, Day RM et al. (2006). Impaired neutrophil chemotaxis in Crohn's disease relates to reduced production of chemokines and can be augmented by granulocyte-colony stimulating factor. *Alimentary Pharmacology & Therapeutics* **24**: 651–660. DOI 10.1111/j.1365-2036.2006.03016.x.

Hindryckx P, Casteele NV, Novak G, Khanna R, D'Haens G et al. (2018). The expanding therapeutic armamentarium for inflammatory bowel disease: How to choose the right drug [s] for our patients? *Journal of Crohn's & Colitis* **12**: 105–119. DOI 10.1093/ecco-jcc/jjx117.

Jahanshahi G, Motavasel V, Rezaie A, Hashtroudi AA, Daryani NE et al. (2004). Alterations in antioxidant power and levels of epidermal growth factor and nitric oxide in saliva of patients with inflammatory bowel diseases. *Digestive Diseases and Sciences* **49**: 1752–1757. DOI 10.1007/s10620-004-9564-5.

Jantawong C, Priprem A, Intuyod K, Pairojkul C, Pinlaor P et al. (2021). Curcumin-loaded nanocomplexes: Acute and chronic toxicity studies in mice and hamsters. *Toxicology Reports* **8**: 1346–1357. DOI 10.1016/j.toxrep.2021.06.021.

Jian YT, Mai GF, Wang JD, Zhang YL, Luo RC et al. (2005). Preventive and therapeutic effects of NF-kappaB inhibitor curcumin in rats colitis induced by trinitrobenzene sulfonic acid. *World Journal of Gastroenterology* **11**: 1747–1752. DOI 10.3748/wjg.v11.i12.1747.

Jurenka JS (2009). Anti-Inflammatory properties of curcumin, a major constituent of *Curcuma longa*: A review of preclinical and clinical research. *Alternative Medicine Review* **14**: 141–153.

Kao NJ, Hu JY, Wu CS, Kong ZL (2016). Curcumin represses the activity of inhibitor-κb kinase in dextran sulfate

sodium-induced colitis by S-Nitrosylation. *International Immunopharmacology* **38**: 1–7. DOI 10.1016/j.intimp.2016.05.015.

Katsanos KH, Papadakis KA (2017). Inflammatory bowel disease: Updates on molecular targets for biologics, **11**: 455–463 DOI 10.5009/gnl16308.

Kedia S, Bhatia V, Thareja S, Garg S, Mouli VP et al. (2017). Low dose oral curcumin is not effective in induction of remission in mild to moderate ulcerative colitis: Results from a randomized double blind placebo controlled trial. *World Journal of Gastrointestinal Pharmacology and Therapeutics* **8**: 147–154. DOI 10.4292/wjgpt.v8.i2.147.

Kesharwani SS, Ahmad R, Bakkari MA, Rajput MKS, Dachineni R et al. (2018). Site-Directed non-covalent polymer-drug complexes for inflammatory bowel disease (IBD): Formulation development, characterization and pharmacological evaluation. *Journal of Controlled Release* **290**: 165–179. DOI 10.1016/j.jconrel.2018.08.004.

Kotha RR, Luthria DL (2019). Curcumin: Biological, pharmaceutical, nutraceutical, and analytical aspects. *Molecules* **24**: 2930. DOI 10.3390/molecules24162930.

Kumar A, Singh R, Yadav A, Giri DD, Singh PK et al. (2016). Isolation and characterization of bacterial endophytes of *Curcuma longa* L. *3 Biotech* **6**: 60. DOI 10.1007/s13205-016-0393-y.

Kumar S, Dutta U, Shah J, Singh P, Vaishnavi C et al. (2020). Impact of curcuma longa on disease activity in patients with ulcerative colitis: A double-blind randomized trial (Data no published).

Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ et al. (2019). IBD guidelines e delphi consensus group, British society of gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* **68**: s1–s106. DOI 10.1136/gutjnl-2019-318484.

Lang A, Salomon N, Wu JCY, Kopylov U, Lahat A et al. (2015). Curcumin in combination with mesalamine induces remission in patients with mild-to-moderate ulcerative colitis in a randomized controlled trial. *Clinical Gastroenterology and Hepatology* **13**: 1444-9.e1. DOI 10.1016/j.cgh.2015.02.019.

Larmonier CB, Uno JK, Lee KM, Karrasch T, Laubitz D et al. (2008). Limited effects of dietary curcumin on Th-1 driven colitis in IL-10 deficient mice suggest an IL-10-dependent mechanism of protection. *American Journal of Physiology. Gastrointestinal and Liver Physiology* **295**: G1079–G1091. DOI 10.1152/ajpgi.90365.2008.

Le Gall G, Kirchgesner J, Bejaoui M, Landman C, Nion-Larmurier I et al. (2018). Clinical activity is an independent risk factor of ischemic heart and cerebrovascular arterial disease in patients with inflammatory bowel disease. Edited by Emiko Mizoguchi. *PLoS One* **13**: e0201991. DOI 10.1371/journal.pone.0201991.

Liu L, Liu YL, Liu GX, Chen X, Yang K et al. (2013). Curcumin ameliorates dextran sulfate sodium-induced experimental colitis by blocking stat3 signaling pathway. *International Immunopharmacology* **17**: 314–320. DOI 10.1016/j.intimp.2013.06.020.

Lubbad A, Oriowo MA, Khan I (2009). Curcumin attenuates inflammation through inhibition of TLR-4 receptor in experimental colitis. *Molecular and Cellular Biochemistry* **322**: 127–135. DOI 10.1007/s11010-008-9949-4.

Lucas M, Freitas M, Xavier JA, Moura FA, Goulart MOF et al. (2021). The scavenging effect of curcumin, piperine and their combination against physiological relevant reactive pro-oxidant species using *in vitro* non-cellular and cellular models. *Chemical Papers* **75**: 5269–5277. DOI 10.1007/s11696-021-01710-y.

Luo R, Lin M, Zhang C, Shi J, Zhang S et al. (2020). Genipin-crosslinked human serum albumin coating using a tannic acid layer for enhanced oral administration of curcumin in the treatment of ulcerative colitis. *Food Chemistry* **330**: 127241. DOI 10.1016/j.foodchem.2020.127241.

Maiti P, Dunbar GL (2018). Use of curcumin, a natural polyphenol for targeting molecular pathways in treating age-related neurodegenerative diseases. *International Journal of Molecular Sciences* **19**: 1637. DOI 10.3390/ijms19061637.

Martelli L, Ragazzi E, di Mario F, Martelli M, Castagliuolo I et al. (2007). A potential role for the vanilloid receptor TRPV1 in the therapeutic effect of curcumin in dinitrobenzene sulphonic acid-induced colitis in mice. *Neurogastroenterology and Motility: The Official Journal of the European Gastrointestinal Motility Society* **19**: 668–674. DOI 10.1111/j.1365-2982.2007.00928.x.

Martínez N, Herrera M, Frías L, Provencio M, Pérez-Carrión R et al. (2019). A combination of hydroxytyrosol, omega-3 fatty acids and curcumin improves pain and inflammation among early stage breast cancer patients receiving adjuvant hormonal therapy: Results of a pilot study. *Clinical and Translational Oncology* **21**: 489–498. DOI 10.1007/s12094-018-1950-0.

Martins ASP, Campos SBG, Goulart MOF, Moura FA (2021). Extraintestinal manifestations of inflammatory bowel disease, nitroxidative stress and dysbiosis: What is the link between them? *BIOCELL* **45**: 461–481. DOI 10.32604/biocell.2021.014332.

Masoodi M, Mahdiabadi MA, Mokhtare M, Agah S, Kashani AHF et al. (2018). The efficacy of curcuminoids in improvement of ulcerative colitis symptoms and patients' self-reported well-being: A randomized double-blind controlled trial. *Journal of Cellular Biochemistry* **119**: 9552–9559. DOI 10.1002/jcb.27273.

Mccarty MF (2012). Minimizing the cancer-promotional activity of Cox-2 as a central strategy in cancer prevention. *Medical Hypotheses* **78**: 45–57. DOI 10.1016/j.mehy.2011.09.039.

Mohammadi E, Tamaddoni A, Qujeq D, Nasseri E, Zayeri F et al. (2018). An investigation of the effects of curcumin on iron overload, hepcidin level, and liver function in β-thalassemia major patients: A double-blind randomized controlled clinical trial. *Phytotherapy Research* **32**: 1828–1835. DOI 10.1002/ptr.6118.

Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M et al. (2012). Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* **142**: 46–54.e42. DOI 10.1053/j.gastro.2011.10.001.

Momtazi-Borojeni AA, Haftcheshmeh SM, Esmaeili SA, Johnston TP, Abdollahi E, Sahebkar A (2018). Curcumin: A natural modulator of immune cells in systemic lupus erythematosus. *Autoimmunity Reviews* **17**: 125–135. DOI 10.1016/j.autrev.2017.11.016.

Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A (2001). Interleukin-10 and the interleukin-10 receptor. *Annual Review of Immunology* **19**: 683–765. DOI 10.1146/annurev.immunol.19.1.683.

Motawi TK, Rizk SM, Shehata AH (2012). Effects of curcumin and ginkgo biloba on matrix metalloproteinases gene expression and other biomarkers of inflammatory bowel disease.

Journal of Physiology and Biochemistry **68**: 529–539. DOI 10.1007/s13105-012-0168-9.

Moura FA, de Andrade KQ, Dos Santos JCF, Araújo ORP, Goulart MOF (2015). Antioxidant therapy for treatment of inflammatory bowel disease: Does it work? *Redox Biology* **6**: 617–639. DOI 10.1016/j.redox.2015.10.006.

Moura FA, Goulart MOF, Campos SBG, Martins ASP (2020). The close interplay of nitro-oxidative stress, advanced glycation end products and inflammation in inflammatory bowel diseases. *Current Medicinal Chemistry* **27**: 2059–2076. DOI 10.2174/0929867325666180904115633.

Mudter J, Neurath MF (2007). IL-6 signaling in inflammatory bowel disease: Pathophysiological role and clinical relevance. *Inflammatory Bowel Diseases* **13**: 1016–1023. DOI 10.1002/ibd.20148.

Myzak MC, Carr AC (2002). Myeloperoxidase-Dependent caspase-3 activation and apoptosis in HL-60 cells: Protection by the antioxidants ascorbate and (Dihydro) lipoic acid. *Redox Report: Communications in Free Radical Research* **7**: 47–53. DOI 10.1179/135100002125000181.

Nones K, Dommels YE, Martell S, Butts C, McNabb WC et al. (2009). The effects of dietary curcumin and rutin on colonic inflammation and gene expression in multidrug resistance gene-deficient (Mdr1a-/-) mice, a model of inflammatory bowel diseases. *British Journal of Nutrition* **101**: 169–181. DOI 10.1017/S0007114508009847.

Ni H, Jin W, Zhu T, Wang J, Yuan B et al. (2015). Curcumin modulates TLR4/NF-κB inflammatory signaling pathway following traumatic spinal cord injury in rats. *Journal of Spinal Cord Medicine* **38**: 199–206. DOI 10.1179/2045772313Y.0000000179.

Niki E (2013). Biomarkers of lipid peroxidation in clinical material. *Biochimica et Biophysica Acta* **1840**: 809–817. DOI 10.1016/j.bbagen.2013.03.020.

Oeckinghaus A, Ghosh S (2009). The NF-kappaB family of transcription factors and its regulation. *Cold Spring Harbor perspectives in biology* **1**: a000034. DOI 10.1101/cshperspect.a000034.

Ohno M, Nishida A, Sugitani Y, Nishino K, Inatomi O et al. (2017). Nanoparticle curcumin ameliorates experimental colitis via modulation of gut microbiota and induction of regulatory T cells. *PLoS One* **12**: e0185999. DOI 10.1371/journal.pone.0185999.

Oliver JM, Stoner L, Rowlands DS, Caldwell AR, Sanders E et al. (2016). Novel form of curcumin improves endothelial function in young, healthy individuals: A double-blind placebo controlled study. *Journal of Nutrition and Metabolism* **1089653**: 1–6. DOI 10.1155/2016/1089653.

Oshi MA, Lee J, Naeem M, Hasan N, Kim J et al. (2020). Curcumin nanocrystal/PH-responsive polyelectrolyte multilayer core-shell nanoparticles for inflammation-targeted alleviation of ulcerative colitis. *Biomacromolecules* **21**: 3571–3581. DOI 10.1021/acs.biomac.0c00589.

Palacio F, de Souza L, Moreira J, Luiz RR, de Souza H, Zaltman C (2021). Hospitalization and surgery rates in patients with inflammatory bowel disease in Brazil: A time-trend analysis. *BMC Gastroenterology* **21**: 192. DOI 10.1186/s12876-021-01781-x.

Panahi Y, Khalili N, Sahebi E, Namazi S, Simental-Mendía LE et al. (2018). Effects of curcuminoids plus piperine on glycemic, hepatic and inflammatory biomarkers in patients with type 2 diabetes mellitus: A randomized double-blind placebo-controlled trial. *Drug Research* **68**: 403–409. DOI 10.1055/s-0044-101752.

Parra RS, Feitosa MR, Ferreira SDC, Rocha JJRD, Troncon LEA et al. (2020). Anemia and iron deficiency an inflammatory bowel disease patients an a referral center in Brazil: Prevalence and risk factors. *Arquivos de Gastroenterologia* **57**: 272–277. DOI 10.1590/s0004-2803.202000000-51.

Peyrin-Biroulet L, Panés J, Sandborn WJ, Vermeire S, Danese S et al. (2016). Defining disease severity in inflammatory bowel diseases: Current and future directions. *Clinical Gastroenterology and Hepatology* **14**: 348–354.e17. DOI 10.1016/j.cgh.2015.06.001.

Pinto MA, Lopes MS, Bastos ST, Reigada CL, Dantas RF et al. (2013). Does active crohn's disease have decreased intestinal antioxidant capacity? *Journal of Crohn's and Colitis* **7**: e358–e366. DOI 10.1016/j.crohns.2013.02.010.

Qiao H, Fang D, Chen J, Sun Y, Kang C et al. (2017). Orally delivered polycurcumin responsive to bacterial reduction for targeted therapy of inflammatory bowel disease. *Drug Delivery* **24**: 233–242. DOI 10.1080/10717544.2016.1245367.

Qiu P, Man S, Li J, Liu J, Zhang L et al. (2016). overdose intake of curcumin initiates the unbalanced state of bodies. *Journal of Agricultural and Food Chemistry* **64**: 2765–2771. DOI 10.1021/acs.jafc.6b00053.

Rezaie A, Ghorbani F, Eshghtork A, Zamani MJ, Dehghan G et al. (2006). Alterations in salivary antioxidants, nitric oxide, and transforming growth factor beta-1 in relation to disease activity in crohn's disease patients. *Annals of the New York Academy of Sciences* **1091**: 110–122. DOI 10.1196/annals.1378.060.

Rotrekl D, Šalamúnová P, Paráková L, Bađo O, Saloň I et al. (2021). Composites of yeast glucan particles and curcumin lead to improvement of dextran sulfate sodium-induced acute bowel inflammation in rats. *Carbohydrate Polymers* **252**: 117142. DOI 10.1016/j.carbpol.2020.117142.

Sadeghi N, Mansoori A, Shayesteh A, Hashemi SJ (2020). The effect of curcumin supplementation on clinical outcomes and inflammatory markers in patients with ulcerative colitis. *Phytotherapy Research* **34**: 1123–1133. DOI 10.1002/ptr.6581.

Sairenji T, Collins KL, Evans DV (2017). An update on inflammatory bowel disease. *Primary Care-Clinics in Office Practice* **44**: 673–692. DOI 10.1016/j.pop.2017.07.010.

Salh B, Assi K, Templeman V, Parhar K, Owen D et al. (2003). Curcumin attenuates DNB-induced murine colitis. american journal of physiology. *Gastrointestinal and Liver Physiology* **285**: G235–G243. DOI 10.1152/ajpgi.00449.2002.

Samba-Mondonga M, Constante M, Fragoso G, Calvé A, Santos MM (2019). Curcumin induces mild anemia in a DSS-induced colitis mouse model maintained on an iron-sufficient diet. *PLoS One* **14**: e0208677. DOI 10.1371/journal.pone.0208677.

Sands BE, Kaplan GG (2007). The role of TNFα in ulcerative colitis. *Journal of Clinical Pharmacology* **47**: 930–941. DOI 10.1177/0091270007301623.

Sareen R, Jain N, Rajkumari A, Dhar KL (2016). PH triggered delivery of curcumin from eudragit-coated chitosan microspheres for inflammatory bowel disease: Characterization and pharmacodynamic evaluation. *Drug Delivery* **23**: 55–62. DOI 10.3109/10717544.2014.903534.

Sareen R, Nath K, Jain N, Dhar KL (2014). Curcumin loaded microsponges for colon targeting in inflammatory bowel disease: Fabrication, optimization, and *in vitro* and pharmacodynamic evaluation. *BioMed Research International* **340701**: 1–7. DOI 10.1155/2014/340701.

Scazzocchio B, Minghetti L, D'Archivio M (2020). Interaction between gut microbiota and curcumin: A new key of understanding for the health effects of curcumin. *Nutrients* **12**: 2499. DOI 10.3390/nu12092499.

Schroeder KW, Tremaine WJ, Ilstrup DM (1987). Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. *New England Journal of Medicine* **317**: 1625–1629. DOI 10.1056/NEJM198712243172603.

Sheethal S, Ratheesh M, Jose SP, Asha S, Krishnakumar IM et al. (2020). Anti-ulcerative effect of curcumin-galactomannoside complex on acetic acid-induced experimental model by inhibiting inflammation and oxidative stress. *Inflammation* **43**: 1411–1422. DOI 10.1007/s10753-020-01218-9.

Shigeshiro M, Tanabe S, Suzuki T (2013). Dietary polyphenols modulate intestinal barrier defects and inflammation in a murine model of colitis. *Journal of Functional Foods* **5**: 949–955. DOI 10.1016/j.jff.2013.02.008.

Sido B, Hack V, Hochlehnert A, Lipps H, Herfarth C et al. (1998). Impairment of intestinal glutathione synthesis in patients with inflammatory bowel disease. *Gut* **42**: 485–492. DOI 10.1136/gut.42.4.485.

Soleimani V, Sahebkar A, Hosseinzadeh H (2018). Turmeric (*Curcuma Longa*) and its major constituent (Curcumin) as nontoxic and safe substances: Review. *Phytotherapy Research* **32**: 985–995. DOI 10.1002/ptr.6054.

Stanić Z (2017). Curcumin, a compound from natural sources, a true scientific challenge–A review. *Plant Foods for Human Nutrition* **72**: 1–12. DOI 10.1007/s11130-016-0590-1.

Sueth-Santiago V, Mendes-Silva GP, Decoté-Ricardo D, de Lima MEF (2015). Curcumina, o Pó Dourado Do Açafrão-Da-Terra: Introspecções sobre química e atividades biológicas. *Quimica Nova* **38**: 538–552. DOI 10.5935/0100-4042.20150035.

Sugimoto K, Hanai H, Tozawa K, Aoshi T, Uchijima M et al. (2002). Curcumin prevents and ameliorates trinitrobenzene sulfonic acid-induced colitis in mice. *Gastroenterology* **123**: 1912–1922. DOI 10.1053/gast.2002.37050.

Sugimoto K, Ikeya K, Bamba S, Andoh A, Yamasaki H et al. (2020). Highly bioavailable curcumin derivative ameliorates crohn's disease symptoms: A randomized, double-blind, multicenter study. *Journal of Crohn's and Colitis* **14**: 1693–1701. DOI 10.1093/ecco-jcc/jjaa097.

Sutherland LR, Martin F, Greer S, Robinson M, Greenberger N et al. (1987). 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology* **92**: 1894–1898. DOI 10.1016/0016-5085(87)90621-4.

Szczeklik K, Krzyściak W, Cibor D, Domagała-Rodacka R, Pytko-Polończyk J et al. (2018). Markers of lipid peroxidation and antioxidant status in the serum and saliva of patients with active crohn disease. *Polish Archives of Internal Medicine* **128**: 362–370. DOI 10.20452/pamw.4273.

Szeląg M, Mikulski D, Molski M (2012). Quantum-chemical investigation of the structure and the antioxidant properties of α-lipoic acid and its metabolites. *Journal of Molecular Modeling* **18**: 2907–2916. DOI 10.1007/s00894-011-1306-y.

Tajra JB, Calegaro JU, de Paula AP, Bachour D, Silveira D et al. (2019). Correlation and concordance measures between clinical, endoscopic and histological scores activity in Crohn's disease under treatment. *Scandinavian Journal of Gastroenterology* **54**: 441–445. DOI 10.1080/00365521.2019.1596305.

Toden S, Theiss AL, Wang X, Goel A (2017). Essential turmeric oils enhance anti-inflammatory efficacy of curcumin in dextran sulfate sodium-induced colitis. *Scientific Reports* **7**: 814. DOI 10.1038/s41598-017-00812-6.

Topcu-Tarladacalisir Y, Akpolat M, Uz YH, Kizilay G, Sapmaz-Metin M et al. (2013). Effects of curcumin on apoptosis and oxidoinflammatory regulation in a rat model of acetic acid-induced colitis: The roles of c-Jun N-Terminal kinase and P38 mitogen-activated protein kinase. *Journal of Medicinal Food* **16**: 296–305. DOI 10.1089/jmf.2012.2550.

Ukil A, Maity S, Karmakar S, Datta N, Vedasiromoni JR et al. (2003). Curcumin, the major component of food flavour turmeric, reduces mucosal injury in trinitrobenzene sulphonic acid-induced colitis. *British Journal of Pharmacology* **139**: 209–218. DOI 10.1038/sj.bjp.0705241.

Ung VY, Foshaug RR, MacFarlane SM, Churchill TA, Doyle JS et al. (2010). Oral administration of curcumin emulsified in carboxymethyl cellulose has a potent anti-inflammatory effect in the IL-10 gene-deficient mouse model of IBD. *Digestive Diseases and Sciences* **55**: 1272–1277. DOI 10.1007/s10620-009-0843-z.

Vasconcelos SML, Goulart MOF, de Moura JB, Manfredini V, Benfato MS et al. (2007). Espécies reativas de oxigênio e de nitrogênio, antioxidantes e marcadores de dano oxidativo em sangue humano: Principais métodos analíticos para sua determinação. *Química Nova* **30**: 1323–1338. DOI 10.1590/S0100-40422007000500046.

Venkataranganna MV, Rafiq M, Gopumadhavan S, Peer G, Babu UV et al. (2007). NCB-02 (standardized curcumin preparation) protects dinitrochlorobenzene-induced colitis through down-regulation of NFkappa-B and INOS. *World Journal of Gastroenterology* **13**: 1103–1107. DOI 10.3748/wjg.v13.i7.1103.

Walmsley RS (2014). Comment on an optimized patient-reported ulcerative colitis disease activity measure derived from the mayo score and the simple clinical colitis activity index. *Inflammatory Bowel Diseases* **20**: E25–E26. DOI 10.1097/MIB.0000000000000248.

Walmsley RS, Ayres RCS, Pounder RE, Allan RN (1998). A simple clinical colitis activity index. *Gut* **43**: 29–32. DOI 10.1136/gut.43.1.29.

Wang Z, Li S, Cao Y, Tian X, Zeng R et al. (2016). Oxidative stress and carbonyl lesions in ulcerative colitis and associated colorectal cancer. *Oxidative Medicine and Cellular Longevity* **9875298**: 1–15. DOI 10.1155/2016/9875298.

Wei C, Wang JY, Xiong F, Wu BH, Luo MH et al. (2021). Curcumin ameliorates DSS-induced colitis in mice by regulating the Treg/Th17 signaling pathway. *Molecular Medicine Reports* **23**: 34. DOI 10.3892/mmr.2020.11672.

Xiao B, Si X, Zhang M, Merlin D (2015). Oral administration of ph-sensitive curcumin-loaded microparticles for ulcerative colitis therapy. *Colloids and Surfaces B: Biointerfaces* **135**: 379–385. DOI 10.1016/j.colsurfb.2015.07.081.

Xu CT, Meng SY, Pan BR (2004). Drug therapy for ulcerative colitis. *World Journal of Gastroenterology* **10**: 2311. DOI 10.3748/wjg.v10.i16.2311.

Yadav VR, Suresh S, Devi K, Yadav S (2009a). Effect of cyclodextrin complexation of curcumin on its solubility and antiangiogenic and anti-inflammatory activity in rat colitis model. *AAPS PharmSciTech* **10**: 752–762. DOI 10.1208/s12249-009-9264-8.

Yadav VR, Suresh S, Devi K, Yadav S (2009b). Novel formulation of solid lipid microparticles of curcumin for anti-angiogenic and anti-inflammatory activity for optimization of therapy of inflammatory bowel disease. *Journal of Pharmacy and Pharmacology* **61**: 311–321. DOI 10.1211/jpp.61.03.0005.

Yang JY, Zhong X, Kim SJ, Kim DH, Kim HS et al. (2018). Comparative effects of curcumin and tetrahydrocurcumin on dextran sulfate sodium-induced colitis and inflammatory signaling in mice. *Journal of Cancer Prevention* **23**: 18–24. DOI 10.15430/JCP.2018.23.1.18.

Yang JY, Zhong X, Yum HW, Lee HJ, Kundu JK et al. (2013). Curcumin inhibits STAT3 signaling in the colon of dextran sulfate sodium-treated mice. *Journal of Cancer Prevention* **18**: 186–191. DOI 10.15430/JCP.2013.18.2.186.

Yang M, Wang J, Yang C, Han H, Rong W, Zhang G (2017). Oral administration of curcumin attenuates visceral hyperalgesia through inhibiting phosphorylation of TRPV1 in rat model of ulcerative colitis. *Molecular Pain* **13**: 1744806917726416. DOI 10.1177/1744806917726416.

Yavarpour-Bali H, Ghasemi-Kasman M, Pirzadeh M (2019). Curcumin-loaded nanoparticles: A novel therapeutic strategy in treatment of central nervous system disorders. *International Journal of Nanomedicine* **14**: 4449–4460. DOI 10.2147/IJN.

Yildirim H, Sunay FB, Sinan S, Köçkar F (2016). *In vivo* effects of curcumin on the paraoxonase, carbonic anhydrase, glucose-6-phosphate dehydrogenase and β-Glucosidase enzyme activities in dextran sulphate sodium-induced ulcerative colitis mice. *Journal of Enzyme Inhibition and Medicinal Chemistry* **31**: 1583–1590. DOI 10.3109/14756366.2016.1158173.

Zeng Z, Zhan L, Liao H, Chen L, Lv X (2013). Curcumin improves TNBS-induced colitis in rats by inhibiting IL-27 expression via the TLR4/NF-κB signaling pathway. *Planta Medica* **79**: 102–109. DOI 10.1055/s-00000058.

Zhang L, Xue H, Zhao G, Qiao C, Sun X et al. (2019). Curcumin and resveratrol suppress dextran sulfate sodium-induced colitis in mice. *Molecular Medicine Reports* **19**: 3053–3060. DOI 10.3892/mmr.2019.9974.

Zhang X, Wu J, Ye B, Wang Q, Xie X et al. (2016). Protective effect of curcumin on TNBS-induced intestinal inflammation is mediated through the JAK/STAT pathway. *BMC Complementary and Alternative Medicine* **16**: 299. DOI 10.1186/s12906-016-1273-z.

Zhao HM, Han F, Xu R, Huang XY, Cheng SM et al. (2017). Therapeutic effect of curcumin on experimental colitis mediated by inhibiting CD8(+)CD11c(+) cells. *World Journal of Gastroenterology* **23**: 1804–1815. DOI 10.3748/wjg.v23.i10.1804.

Zhao HM, Xu R, Huang XY, Cheng SM, Huang MF et al. (2016a). Curcumin suppressed activation of dendritic cells via JAK/STAT/SOCS signal in mice with experimental colitis. *Frontiers in Pharmacology* **7**: 455. DOI 10.3389/fphar.2016.00455.

Zhao HM, Xu R, Huang XY, Cheng SM, Huang MF et al. (2016b). Curcumin improves regulatory T cells in gut-associated lymphoid tissue of colitis mice. *World Journal of Gastroenterology* **22**: 5374–5383. DOI 10.3748/wjg.v22.i23.5374.

Zhou X, Chen Q, Ma Y, Huang Y, Gou S, Xiao B (2019). Porous polymeric microparticles as an oral drug platform for effective ulcerative colitis treatment. *Journal of Pharmaceutical Sciences* **108**: 2238–2242. DOI 10.1016/j.xphs.2019.02.001.

Supplementary Materials

SUPPLEMENTARY BOX 1

Search strategy used for different databases

MEDLINE (via PubMed)

((((((((((“inflammatory bowel disease”) OR “bowel diseases, inflammatory”) OR “idiopathic proctocolitis”) OR “ulcerative colitis”) OR “colitis”) OR “Crohn Disease”) OR “Crohn’s enteritis”) OR “Crohn’s disease”) OR “Crohn’s disease”)) AND ((((((“curcumin*”) OR “curcuma”) OR “tumeric”) OR “turmeric”) OR “curcuma longa”) OR “indian saffron”))

Search strategy used for Cochrane Controlled Register of Trials (CENTRAL)

(“inflammatory bowel disease” OR “idiopathic proctocolitis” OR “ulcerative colitis” OR “Crohn disease” OR “Crohn’s disease”) AND (“curcumin*” OR “curcuma” OR “turmeric”)

Search strategy used for LILACS

((((((((((((inflammatory bowel disease) OR (bowel diseases, inflammatory)) OR (idiopathic proctocolitis))) OR (ulcerative colitis)) OR (Crohn disease))))) AND (curcumin*)) OR (curcuma))) OR (turmeric)))

Search strategy used for Science Direct

(“inflammatory bowel disease” OR “bowel diseases inflammatory” OR “idiopathic proctocolitis” OR “ulcerative colitis” OR “Crohn Disease” OR “Crohn’s enteritis”) AND (“curcumin” OR “curcuma” OR “tumeric”)

Obs.: “Research articles” filter was active.

Search strategy used for Clinical Trials

Ulcerative colitis | Interventional Studies | Inflammatory Bowel Diseases | Curcumin | Adult, Older Adult

Obs.: “Advanced Search”; Condition or disease: Inflammatory Bowel Diseases + Other terms: ulcerative colitis + Study type: Interventional Studies (Clinical Trials); Age: Adult (18–64) + Older adult (65+); Intervention/treatment: curcumin

SUPPLEMENTARY TABLE 1

Bias risk assessment of animal studies according to Systematic Review Centre for Laboratory animal Experimentation (SYRCLE)

Study	Risk of bias									
	Sequence generation[1]	Baseline characteristics[1]	Allocation concealment[1]	Random housing[2]	Blinding[2]	Random outcome assessment[3]	Blinding[3]	Incomplete outcome data[4]	Selective outcome reporting[5]	Other sources of bias
≤5 mg.kg.d^{-1}/0.01 mmol.kg.d^{-1}										
(Chen *et al.*, 2019)	High	Low	High	High	High	High	High	High	Low	Low
(Zhou *et al.*, 2019)	High	Low	High	High	High	High	High	High	Low	Low
(Chen *et al.*, 2018)	High	Low	High	Low	High	High	High	High	Low	Low
(Sareen *et al.*, 2016)	Unclear	Low	High	Unclear	High	High	Low	High	Low	Low
>5–50 mg/kg day/0.01–0.15 mmol/kg day										
(Altinel *et al.*, 2020)	High	Low	High	Low	High	High	Low	High	Low	Low
(Oshi *et al.*, 2020)	High	Low	High	Low	High	High	Low	High	Low	Low
(Luo *et al.*, 2020)	Unclear	Low	High	Low	High	High	High	High	Low	Low
(Zhang *et al.*, 2019)	Unclear	Low	High	Low	High	Unclear	High	High	Low	Unclear
(Kesharwani *et al.*, 2018)	High	Low	High	High	High	High	Low	High	Low	Low
(Chen *et al.*, 2017)	High	Low	High	Low	High	High	High	High	Low	Unclear
(Qiao *et al.*, 2017)	High	Low	High	High	High	High	High	High	Low	Low
(Beloqui *et al.*, 2016)	High	Low	High	Unclear	High	High	High	High	Low	Unclear
(Gopu *et al.*, 2015)	Unclear	Low	High	Low	High	High	High	High	Low	Unclear
(Xiao *et al.*, 2015)	High	Low	High	Low	High	High	High	High	Low	Unclear
(Beloqui *et al.*, 2014)	High	Low	High	High	High	High	High	High	Low	Low
(Sareen *et al.*, 2014)	Unclear	Low	High	Unclear	High	High	High	High	Low	Low
(Liu *et al.*, 2013)	High	Low	High	Low	High	High	Low	High	Low	Unclear
(Martelli *et al.*, 2007)	Unclear	Low	High	Low	High	High	Low	High	Low	Unclear
60–200 mg/kg day/0.25–0.50 mmol/kg day										
(Wei *et al.*, 2021)	Unclear	Low	High	Low	High	High	High	Unclear	Low	Low
(Yang *et al.*, 2018)	High	Low	High	Low	High	High	High	High	Low	Low
(Zhao *et al.*, 2017)	Unclear	Low	High	Low	High	High	High	High	Low	Low
(Toden *et al.*, 2017)	High	Low	High	Low	High	Unclear	Low	High	Low	Low
(Yang *et al.*, 2017)	High	Low	High	Low	High	Unclear	Low	High	Low	Low
(Bastaki *et al.*, 2016)	High	Low	High	Low	High	Unclear	High	High	Low	Low
(Zhao *et al.*, 2016b)	Unclear	Low	High	Low	High	High	High	High	Low	Unclear

(Continued)

SUPPLEMENTARY Table 1 (continued).

Study	Risk of bias									
	Sequence generation[1]	Baseline characteristics[1]	Allocation concealment[1]	Random housing[2]	Blinding[2]	Random outcome assessment[3]	Blinding[3]	Incomplete outcome data[4]	Selective outcome reporting[5]	Other sources of bias
(Kao *et al.*, 2016)	High	Low	High	Low	High	High	High	High	Low	Low
(Yildirim *et al.*, 2016)	Unclear	Low	High	Low	High	High	High	High	Low	Low
(Zhao *et al.*, 2016a)	Unclear	Low	High	Low	High	High	High	High	Low	Low
(Topcu-Tarladacalisir *et al.*, 2013)	Unclear	Low	High	Low	High	Unclear	Low	High	Low	Unclear
(Yang *et al.*, 2013)	High	Low	High	Low	High	High	High	High	Low	Unclear
(Zeng *et al.*, 2013)	Unclear	Low	High	Unclear	High	High	Low	Unclear	Low	Low
(Aldini *et al.*, 2012)	Unclear	Low	High	Low	High	Unclear	Low	Unclear	Low	Unclear
(Lubbad *et al.*, 2009)	High	Low	High	Unclear	High	High	High	High	Low	Low
(Yadav *et al.*, 2009a)	Unclear	Low	High	Low	High	High	Low	High	Low	Unclear
(Yadav *et al.*, 2009b)	Unclear	Low	High	Low	High	High	Low	High	Low	Unclear
(Ung *et al.*, 2010)	High	Low	High	High	High	High	Low	High	Low	Unclear
(Venkataranganna *et al.*, 2007)	High	Low	High	Low	High	High	Unclear	High	Low	Unclear
(Camacho-Barquero *et al.*, 2007)	Unclear	Low	High	Low	High	High	Low	High	Low	Unclear
(Ukil *et al.*, 2003)	High	Low	High	Low	High	High	High	High	Low	Low
≥200 mg/kg day/0.54 mmol.kg.d^{-1}										
(Sheethal *et al.*, 2020)	High	Low	High	Low	High	High	Low	High	Low	Low
(Rotrekl *et al.*, 2021)	Unclear	Low	High	Low	High	High	High	High	Low	Low
<2.0% (w/w) of diet										
(Ohno *et al.*, 2017)	High	Low	High	Low	High	High	Low	High	Low	Low
(Cooney *et al.*, 2016)	Unclear	Low	High	Low	High	High	High	High	Low	Low
(Zhang *et al.*, 2016)	Unclear	Low	High	Alto	High	High	Low	High	Low	Low
(Shigeshiro *et al.*, 2013)	Low	Low	High	Low	High	High	Low	High	Low	Low
(Nones *et al.*, 2009)	Unclear	Low	High	Low	High	High	High	Low	Low	Low
(Larmonier *et al.*, 2008)	High	Low	High	Low	High	Unclear	Low	High	Low	Low
(Salh *et al.*, 2003)	High	High	High	High	High	High	Low	High	Low	Low
≥2.0% (w/w) of diet										

(Continued)

SUPPLEMENTARY Table 1 (continued).

Study	Risk of bias									
	Sequence generation[1]	Baseline characteristics[1]	Allocation concealment[1]	Random housing[2]	Blinding[2]	Random outcome assessment[3]	Blinding[3]	Incomplete outcome data[4]	Selective outcome reporting[5]	Other sources of bias
(Samba-Mondonga *et al.*, 2019)	High	Low	High	Low	High	High	Low	Unclear	Low	Unclear
(Motawi *et al.*, 2012)	High	Low	High	Low	High	High	Low	High	Low	Unclear
(Billerey-Larmonier *et al.*, 2008)	High	Low	High	Unclear	High	Low	Low	Unclear	Low	Unclear
(Deguchi *et al.*, 2007)	High	Low	High	Low	High	High	Low	High	Low	Unclear
(Jian *et al.*, 2005)	Unclear	Low	High	Unclear	High	High	High	Unclear	Low	Unclear
(Sugimoto *et al.*, 2002)	High	Low	High	Low	High	High	Alto	Unclear	Low	Unclear

Note: [1]Selection bias ; [2]Performance bias; [3]Detection bias; [4]Attrition bias; [5]Reporting bias; *Studies whose main objective was to manufacture and test formulations containing curcumin and, for that, the manuscript report tends to be less detailed, which may result in the risk assessment of high-level trends in various domains; SYRCLE, Systematic Review Centre for Laboratory animal Experimentation.

SUPPLEMENTARY TABLE 2

Risk of bias in human studies, according to cochrane collaboration tool

Study	Risk of bias					
	Sequence generation random[1]	Allocation concealment[1]	Blinding of participants and researchers[2]	Blinding outcome evaluators[3]	Outcome result incomplete[4]	Selective report of outcomes[5]
(Banerjee *et al*., 2020)	Low	Low	Low	Unclear	Low	Unclear
(Kumar *et al*., 2020)	Low	Low	Low	Low	Low	Unclear
(Sugimoto *et al*., 2020)	Low	Low	Low	Low	High	Unclear
(Bommelaer *et al*., 2020)	Low	Low	Low	Unclear	Low	Low
(Sadeghi *et al*., 2020)	Low	Low	Low	Unclear	Low	High
(Masoodi *et al*., 2018)	Low	Unclear	Low	Low	Low	Low
(Kedia *et al*., 2017)	Low	Low	Low	Unclear	Low	Unclear
(Lang *et al*., 2015)	Unclear	Low	Unclear	Unclear	Low	Unclear

Note: [1]Selection bias; [2]Performance bias; [3]Detection bias; [4]Friction bias; [5]Reporting bias; [6]Other sources of bias.