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Curcumin in inflammatory bowel diseases: Cellular targets and molecular mechanisms

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Abstract: Curcumin, a natural product, has exhibited promising effects in both animal models and clinical trials, interacting with a multitude of factors linked to Inflammatory Bowel Disease (IBD). These factors encompass cytokines, oxidative stress-associated enzymes, and modulation of the intestinal microbiota. Notably, curcumin has demonstrated therapeutic potential in animal models of colitis, wherein it exerts a negative regulatory influence on pivotal signaling pathways such as PI3/Akt, JAK/STAT, and β-catenin. Moreover, it inhibits the expression of pro-inflammatory enzymes and co-stimulatory molecules (including RANKL, ICAM-1, CD205, CD256, TLR4, among others), while curbing immune cell chemotaxis, thereby attenuating the characteristic neutrophil infiltration observed in IBD. Another facet of curcumin's action involves its modulation of the intestinal microbiota. Notably, the microbiota itself contributes to beneficial biotrans formations of curcumin, thereby enhancing its effectiveness in IBD treatment. On a clinical front, curcumin has demonstrated the ability to induce clinical and/or endoscopic remission without any reported toxic effects. Hence, curcumin warrants consideration as an adjunctive therapy in IBD management. Subsequent clinical investigations should concentrate on meticulously evaluating curcumin's impact on these precise therapeutic targets.

Abbreviation List

AP-1	Activator Protein 1
ARE	Antioxidant Response Element
ATG5	Autophagy-Related 5
BCL-2	B Cell Lymphoma 2
CAT	Catalase
CRP	C-Reactive Protein
CD	Crohn's Disease
C. Longa	Curcuma Longa
CUR	Curcumin
COX	Cyclooxygenases
DAMP	Damage-Associated Molecular Patterns
DNA	Deoxyribonucleic Acid
Nrf2	Erythroid Nuclear Factor 2
γGCL	Gamma-Glutamylcysteine Ligase
Gpx	Glutathione Peroxidase
GSH	Glutathione Reduced
GR	Glutathione Reductase
GST	Glutathione S-Transferase
HO-1	Heme-Oxygenase 1
IBD	Inflammatory Bowel Disease
IFNγ	Interferon-Gamma
IL	Interleukin
JAK	Janus Kinases

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JNK	Jun N-Terminal Kinase
Keap1	Kelch-Like ECH-Associated Protein
LPS	Lipopolysaccharide
LOX	Lipoxygenase
MDA	Malondialdehyde
MGO	Methylglyoxal
MAPK	Mitogen-Activated Protein Kinases
MCP-1	Monocyte Chemotactic Protein 1
MDR1	Multidrug Resistance Protein 1
MPO	Myeloperoxidase
NOS	Nitric Oxide Synthase
Nox	Nitrogen Oxid
NLRP3	NOD-Like Receptor Pyrin Domain-Containing 3
NF-κB	Nuclear Factor Kappa-B
PAMP	Pathogen-Associated Molecular Patterns
Prx	Peroxidase
PI3K	Phosphatidylinositol-3-Kinase
PXR	Pregnane X Receptor
PPAR	Proliferator-Activated Receptor-Gamma
NQQ1	Quinone Oxidoreductase 1
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
RONS	Reactive Species of Oxygen and Nitrogen
RIP	Receptor-Interacting Serine/Threonine Kinase
NADPH	Reduced Nicotinamide Adenine Dinucleotide Phosphate
SCFAS	Short-Chain Fatty Acids
STAT	Signal Transducer and Activator of Transcription Proteins
Srxn1	Sulfiredoxin
SOD	Superoxide Dismutase
Th	T-Helper Cells
TLRs	Toll-Like Receptors
TGF-β1	Transforming Growth Factor β–1
TNF-α	Tumor Necrosis Factor—α
UC	Ulcerative Colitis
XO	Xanthine Oxidase

Introduction

Complementary alternative medicine employs non-traditional therapies provided by professionals extending beyond Western allopathic medicine (Duff *et al.*, 2018). In managing inflammatory bowel disease (IBD), a chronic gastrointestinal inflammatory disorder, alternative or complementary approaches encompass bioactive components from food, psychotherapeutic practices, and hypnosis (Mijan and Lim, 2018; Torres *et al.*, 2019).

These approaches are adopted by 30%–56% of IBD patients, given potential adverse effects of conventional drug treatments (aminosalicylates, corticosteroids, antibiotics, immunomodulators, and biological therapy targeting tumor necrosis factor α—TNF-α) (Schmidt *et al.*, 2010, Torres *et al.*, 2019). Prolonged use of these drugs, associated with the chronicity of the disease, can cause adverse effects, many of them directly affect Gut Intestinal Transit (GIT), leading to dependence and therapeutic failure (Hvas *et al.*, 2018).

Curcuminoids, which include curcumin, demethoxycurcumin, and bisdemethoxycurcumin (Fig. 1), are polyphenols found in the plant species *Curcuma longa* (*C. longa*) which is being used for at least 2500 years in traditional Asia and Indian medicine as a food additive, and/or a dye, and/or a condiment (Kocaadam and Sanlier, 2017; Akaberi *et al.*, 2021).

Studies in animal models have shown that curcuminoids, particularly curcumin, have efficacy in reducing IBD activity (Altinel *et al.*, 2020; Wei *et al.*, 2021) through their antioxidant and anti-inflammatory modulation effects (Cooney *et al.*, 2016; Kocaadam and Sanlier, 2017). In addition, *C. longa* polyphenols are part of the group of selected phytochemicals studied as a complementary therapy for IBD in randomized clinical trials (Sugimoto *et al.*, 2020; Banerjee *et al.*, 2021). However, unlike studies in animal models, clinical trials have focused more heavily on the anti-colitis action of curcumin and have not given as much attention to its effects on redox and/or anti-inflammatory biochemical markers.

A recent review on curcumin delves into its potential adverse effects, including gallstone formation, moderate anemia, and elevated lipid peroxidation. This underscores the fact that not all mechanisms and cellular targets of this polyphenol are fully understood (Karthikeyan *et al.*, 2021). Another crucial point highlighted in the review conducted by Mazieiro *et al.* (2018) is the imperative for further clinical trials focusing on curcumin's impact on IBD. This is primarily due to the lack of knowledge regarding safe and efficacious dosage levels, a challenge compounded by its low bioavailability (Mazieiro *et al.*, 2018).

On this context, this review aims to discuss the effects and mechanisms of action of curcuminoids as an alternative therapy for IBD.

Inflammatory Bowel Disease

Immunological pathophysiology of IBD

IBD is a chronic disorder marked by periods of remission and symptom exacerbation. IBD comprises Crohn's disease (CD), which can affect any part of the gastrointestinal tract, and ulcerative colitis (UC), primarily occurring in the rectum, ascending colon, or both (Mahdipour *et al.*, 2019). Globally, IBD exhibits a widespread presence, with a consistent occurrence in developed regions such as Western Europe, the United States, and Canada, and a significant rise in incidence and prevalence in newly industrialized regions (Kaplan *et al.*, 2019). While seldom fatal, severe cases can result in infections, surgeries, and colorectal cancer (Brunet *et al.*, 2018). This disease substantially impacts patients' quality of life due to its recurrent, chronic symptoms, often emerging during periods of high productivity (Sairenji *et al.*, 2017).

The pathophysiology of IBD requires further investigation, though recent evidence highlights its multifactorial nature, involving external environmental factors, intestinal microbiota, individual genetic predisposition, and immune responses. Inflammation and redox imbalance play crucial

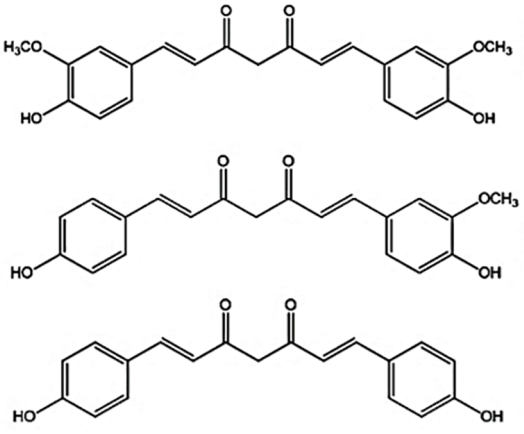

FIGURE 1. Chemical structures of Curcumidoids present in *Curcuma longa*.

roles at the molecular level in the initiation and progression of this disease (Moura *et al.*, 2015).

External contributors to IBD encompass factors like smoking, stress, medication use, and dietary composition. Genetic susceptibility evidence underscores around 240 *loci* heightening IBD risk, with approximately 30 being common between CD and UC. Gene alterations linked to maintaining intestinal homeostasis, such as epithelial barrier function, immunity, and cellular autophagy, are observed. Intestinal microbiota's influence on immunological factors is significant, and dysbiosis—favoring pathogenic over commensal bacteria—can lead to metabolic changes impacting gastrointestinal development. Immunological dysregulation, marked by exaggerated immune responses and uncontrolled inflammation, contributes to IBD (Guan, 2019).

A key IBD pathophysiological mechanism involves immune response dysregulation against antigens from luminal content, which normally triggers controlled inflammation. In genetically susceptible hosts, such as in IBD, this homeostatic balance breaks, resulting in persistent inflammation (Lim and Hanauer, 2004). Inflammatory cascade activation involves cell types like macrophages and dendritic cells, stimulating CD4+ T lymphocyte activation and differentiation. These differentiate into T-helper cells (Th) 1, 2, and 17, secreting various cytokines. Th-1 cells release interferon-gamma (IFNγ) and interleukin (IL)-2, IL-12, and IL-18, while Th-2 cells release IL-4, IL-5, IL-6, IL-10, and IL-13 (Piechota-Polanczyk and Fichna, 2014). Thus, the IBD pro-inflammatory signaling relies on the cytokine network and interactions (Ansari *et al.*, 2021).

IL-6 and Tumor Necrosis Factor-alpha (TNF-α) are critical mediators of chronic intestinal inflammation. TNF-α, produced by phagocytes, drives intestinal inflammation, influencing various intestinal cells. TNF-α effects include macrophage activation, enhanced T cell response, adhesion molecule expression, granuloma formation, and neutrophil recruitment. TNF-α can also regulate other inflammatory mediators like IL-6 and IL-1β, amplifying the initial inflammatory cascade (Cukovic-Cavka *et al.*, 2013).

Oxidative stress in IBD

In IBD, oxidative stress, an imbalance favoring oxidants over antioxidants, leads to redox signaling disruption, molecular damage, and apoptosis, along with promoting carcinogenesis. Reactive species interactions with cellular components cause injury and functional impairment, increasing permeability and chronic inflammation in the intestinal mucosa (Balmus *et al.*, 2016). Endogenously generated reactive oxygen species (ROS) and reactive nitrogen species (RNS) involve enzymes like peroxidase (POD), xanthine oxidase (XO), lipoxygenase (LOX), glucose oxidase, myeloperoxidase (MPO), nitric oxide synthase (NOS), cyclooxygenases (COX), and the NOX complex (Martins *et al.*, 2021). XO, particularly active in the intestinal mucosa, contributes to ROS generation and tissue damage. These enzymes play roles in pathological intestinal processes (Beaugerie and Itzkowitz, 2015).

Numerous cell mediators change during IBD. Erythroid nuclear factor 2 (Nrf2), involved in antioxidant and anti-inflammatory responses, has its activity inhibited in IBD. Protein 53 gene (p53) mutations in IBD may indicate early cancerous cell changes in UC patients. Nuclear factor kappa B (NFκB), a transcription factor regulating many pro-inflammatory cytokines and chemokines, has increased expression in IBD (Moura *et al.*, 2020).

Microbiota in IBD

The clinical course of IBD is profoundly influenced by shifts in the intestinal microbiota composition. Numerous studies have documented substantial differences between the gut microbiota of IBD patients and healthy individuals, particularly in terms of microbial diversity and the relative abundance of specific bacteria (Ni *et al.*, 2017). Characterization studies of IBD patient microbiota reveal a widespread reduction in biodiversity, coupled with diminished levels of specific taxa like Firmicutes, Bacteroidetes, Lactobacillus, and Eubacterium (Mentella *et al.*, 2020).

The various ways in which the host is impacted by microbial metabolite production are pivotal to IBD pathogenesis. A microbial metabolic pathway with relevance to IBD is the production of short-chain fatty acids (SCFAs) through the fermentation of non-digestible carbohydrates. SCFAs play a crucial role in immune regulation and metabolic homeostasis. Their loss or reduction could potentially disrupt host-microbe interactions, which are essential for intestinal mucosa and immune homeostasis (Ni *et al.*, 2017; Lee and Chang, 2021).

Although intestinal dysbiosis is undeniably associated with IBD, discerning whether these alterations are a cause or consequence of the disease remains challenging. While these changes might not be the primary drivers of IBD development, they do contribute to disease progression by exacerbating and perpetuating the immune-inflammatory process (Wu *et al.*, 2023). This, in turn, leads to tissue damage, impaired wound healing, complications like fibrosis and strictures, and the formation of fistulas and abscesses. Moreover, the decline or even eradication of key commensal microbiota necessary for immune system restoration and intestinal homeostasis further compounds the issue (Quaglio *et al.*, 2022; Yang and Li, 2022).

Integral to the dynamics of IBD is the engagement of innate immunity—the body's initial defense line—which recognizes invasive pathogens through Toll-like receptors (TLRs). These receptors respond to damage-associated and pathogen-associated molecular patterns (DAMPs and PAMPs), instigating immune responses (Li and Chang, 2021).

Curcumin

Curcumin chemical features and bioavailability

The effects of *C. longa* may be attributed to curcuminoids, including curcumin, demethoxycurcumin, bisdemethoxycurcumin, and cyclocurcumin, present in approximate proportions of 70%, 17%, 3%, and 10%, respectively (Trujillo *et al.*, 2013; Stanic, 2017; Li and Chang, 2021).

Curcumin has a structure consisting of two methoxy-and two hydroxyl-substituted benzene rings linked to an α,β-unsaturated β-diketone. The other curcuminoids, demethoxycurcumin (4-hydroxycinnamoyl-(4-hydroxy-3-methoxycinnamoyl) methane) and bis-demethoxycurcumin (bis-(4-hydroxy cinnamoyl) methane) (Fig. 1), have curcumin-like structures and differ by the presence or absence of the methoxy groups. Most studies suggest that curcumin is the most active component of *C. longa*, demonstrating significant anti-inflammatory, antioxidant, anti-tumor, anti-coagulant, antimicrobial, hypoglycemic, neuroprotective, cardioprotective, and other activities in experimental models and clinical trials (Peng *et al.*, 2021).

The β-diketone moiety exhibits keto-enolic tautomerism and cis-trans isomerism (Fig. 2), which can exist in different proportions depending on the medium (Slika and Patra, 2020). In media with acidic and neutral pH values (ranging between 3 and 7), the keto-enolic balance tends to shift towards the enol form. This is because, in addition to the molecule presenting greater planarity, there is an intramolecular hydrogen bond that contributes to the stability of the carbon chain. In the keto form, the substance becomes able to donate hydrogen with ease, since it presents an electron-deficient methylene due to the electrophilic vicinal carbonyl groups. This ability to donate hydrogen atoms is likely the mechanism behind the antioxidant properties of curcumin (Sueth-Santiago *et al.*, 2015). The presence of two phenolic groups can enhance the biological activities of this substance (Slika and Patra, 2020).

Curcumin has reduced bioavailability, as the compound is absorbed in a precarious manner, rapidly metabolized, and eliminated from the body (Liu *et al.*, 2016) (Fig. 2). The reduced solubility in an aqueous environment contributes to this process (Prasad *et al.*, 2014). Some studies have evaluated serum curcumin levels after administration by different routes (Yang *et al.*, 2007; Sun *et al.*, 2013; Cheng *et al.*, 2019). While oral administration resulted in reduced serum concentrations in animal models (Yang *et al.*, 2007) and humans (Cheng *et al.*, 2019), intravenous administration in rats resulted in higher serum concentrations (Sun *et al.*, 2013). These studies point to the influence of the route of

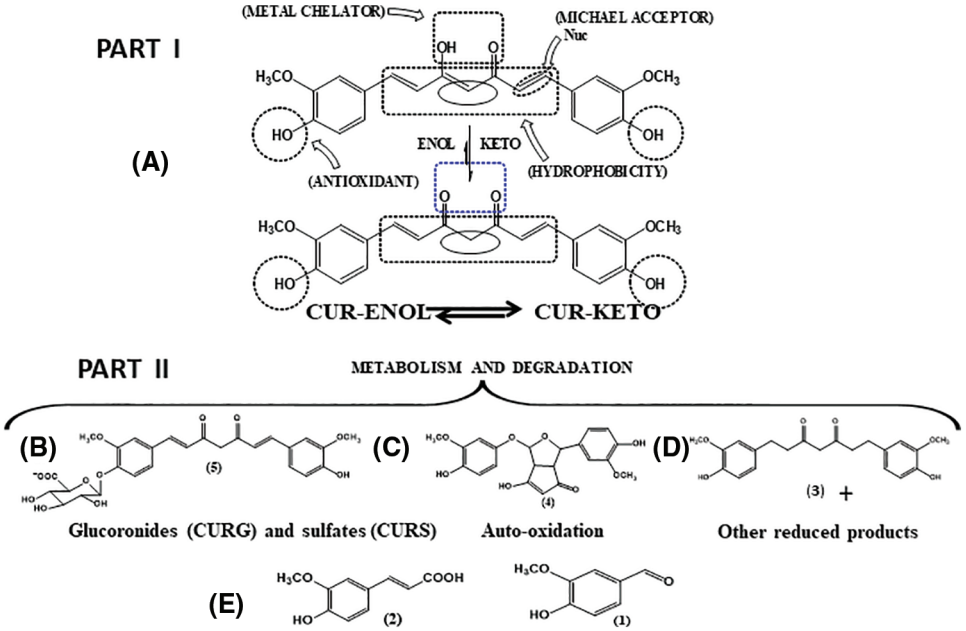

FIGURE 2. (I-A): Enol (CUR-ENOL)-keto (CUR-KETO) tautomerism of curcumin (CUR), along with the organic functions related to some of the biological activities and chemical properties of CUR. (II) Some pathways related to metabolism of CUR. (B) Conjugation, generating CURG and CURS; (C) Representative compound from the auto-oxidation of CUR; (D) Reduction; (E) Some products resulting from degradation (cleavage) of CUR. Adapted from Schneider *et al.* (2015).

administration on the bioavailability of this polyphenol (Prasad *et al.*, 2014). Curcumin is metabolized in two phases—reduction and conjugation—resulting in different metabolites (Kunnumakkara *et al.*, 2017; Kotha and Luthria, 2019) (Fig. 2).

Curcumin: metabolism

Curcumin metabolism unfolds in the liver, intestine, and gut microbiota. Its limited stability under physiological conditions leads to reactions like solvolysis (resulting in 90% degradation), photodegradation, and self-oxidation, producing ferulic acid, ferulic aldehyde, vanillin, vanillic acid, and others (Dei Cas and Ghidoni, 2019) (Fig. 2).

Upon absorption, curcumin undergoes first and second-pass metabolisms in the liver and intestine, mainly through reduction (phase I) and conjugation (phase II). Phase I involves di-, tetra-, hexa-, and octahydrocurcumin formation. In phase II, curcumin and phase I metabolites conjugate with monoglucuronide/sulfate, forming sulfate or glucuronide of curcumin/di-, tetra-, hexa-, and octahydrocurcumin (Anand *et al.*, 2007). Curcumin and metabolites from the first pathway can undergo further conjugation, forming di-glucuronides, tetra-, hexa-, and octahydrocurcumin, and di-, tetra-, hexa-, and octahydrocurcumin sulfates (Nelson *et al.*, 2017).

Curcumin's pharmacological effects stem from its modulation of various targets and molecular pathways. It curtails inflammation by inhibiting the nuclear factor kappa-B (NF-κB) pathway via binding to peroxisome proliferator-activated receptor-gamma (PPAR) and TLRs. Additionally, it negatively regulates activator protein 1 (AP-1), mitogen-activated protein kinases (MAPK), and p53 pathways (Zhang *et al.*, 2019). NOD-like receptor pyrin domain-containing 3 (NLRP3), involved in cytokine maturation via caspase-1, is directly compromised by curcumin through assembly prevention and indirectly via NFκB blockade (Hasanzadeh *et al.*, 2020).

Curcumin also exhibits effects on cell death that do not rely on caspases (necroptosis), which is inherently linked to increased inflammatory activity. In an *in vitro* model involving intestinal epithelial cells (human colon cancer HT-29 cells), curcumin inhibited the activity of receptor-interacting serine/threonine kinase (RIP) 1. As a result, the activation of NFκB and MAPKs was suppressed, leading to cellular survival (Zhong *et al.*, 2023).

Curcumin's effects encompass inhibition of signaling pathways, proteins, and enzymes like Janus kinases/signal transducer and activator of transcription proteins (JAK/STAT), phosphatidylinositol-3-kinase/protein kinase B

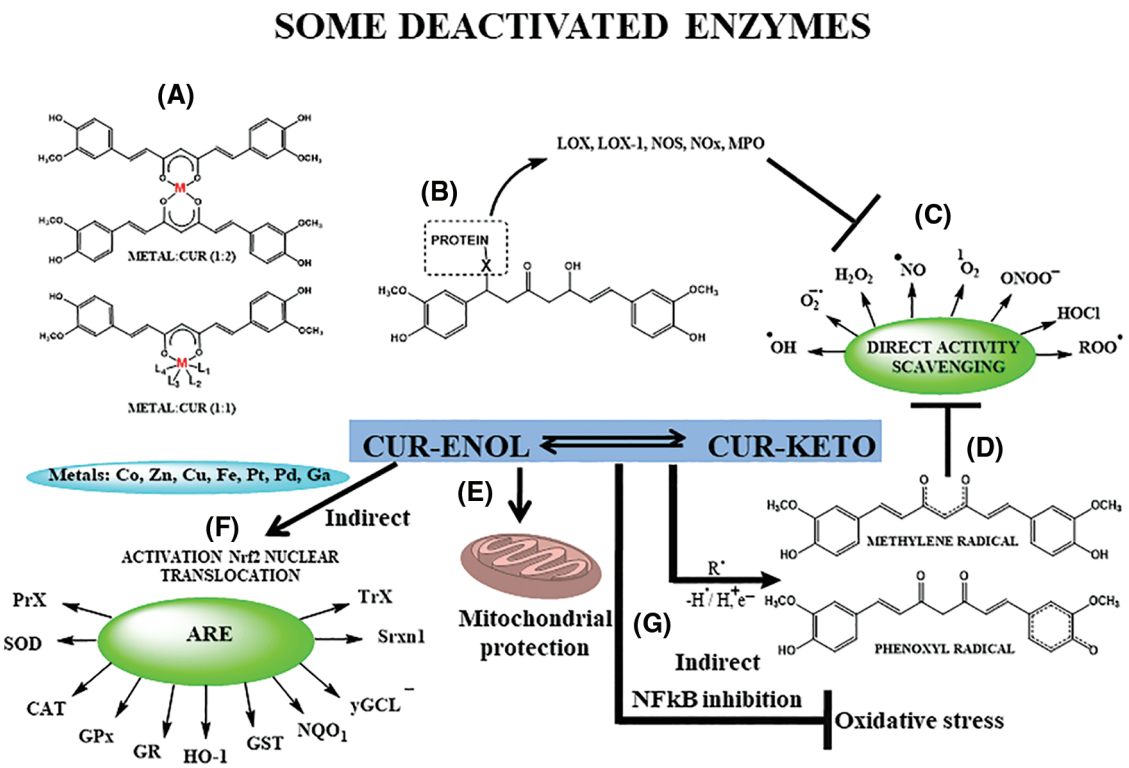

FIGURE 3. Direct and indirect antioxidant effects of Curcumin (CUR). (A) Metal chelation, especially Zn, Cu, Fe; (B) protein-binding, through Michael addition, mainly of oxidant enzymes (lipoxygenase—LOX—and LOX-1, nitric oxide synthase—NOS, myeloperoxidase—MPO, nitrogen oxid—NOx, and others), responsible for generating of reactive species of oxygen and nitrogen (RONS), thus regulating indirectly oxidative stress; (C) direct scavenging of RONS and some carbonyl derivatives (MGO—methylglyoxal); (D) organic moieties responsible for radical, ionic and molecular species capture; (E) mitochondrial protection; (F) generation of antioxidant enzymes (peroxidases—PrX, superoxide dismutase—SOD, catalase—CAT, glutathione peroxidase—GPx, glutathione reductase—GR, heme-oxygenase 1—HO-1, glutathione S-transferase—GST, quinone oxidoreductase 1—NQQ1, gamma-glutamylcysteine ligase—γGCL, sulfiredoxin—Srxn1, and thioredoxin—TrX) through nuclear translocation of erythroid nuclear factor 2/antioxidant response element (Nrf2/ARE); (G) inhibition of nuclear factor kappa-B (NF-κB), decreasing oxidative stress. Adapted from Trujillo *et al.* (2014), Schneider *et al.* (2015), Sueth-Santiago *et al.* (2015), Sun *et al.* (2016), Costantino *et al.* (2022).

(PI3K/Akt), jun n-terminal kinase (JNK), COX, and transforming growth factor β–1 (TGF-β1). This leads to diminished cytokines and chemokines with inflammatory properties, including TNF-α, IL-1β, IL-6, IL-8, and monocyte chemotactic protein 1 (MCP-1) (Ashrafizadeh *et al.*, 2020). C-reactive protein (CRP) and TNF-α, inflammatory mediators, are also reduced by curcumin (Alizadeh *et al.*, 2018). Moreover, curcumin curbs inflammation by acting on immune cells, inhibiting the IL-23/Th17 pathway, maintaining Treg/Th17 balance (Peng *et al.*, 2021).

Beyond its anti-inflammatory effects, curcumin lessens oxidative stress by inducing the Nrf2-Kelch-like ECH-associated protein (Keap1) signaling pathway (Fig. 3F), triggering antioxidant defense mechanisms that shield cells from ROS-induced oxidative damage. It also directly reacts with reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and others (Fig. 3B), elevating antioxidant enzyme levels like catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) (Lin *et al.*, 2019) (Fig. 3). Both mechanisms (antioxidant and anti-inflammatory) are interconnected.

Curcumin's distinctive chemical structure (Figs. 1 and 2)—the phenolic hydroxyl groups acting as a hydrogen donor, the α,β-unsaturated carbonyl group as a Michael acceptor, and the adjacent methoxy groups conferring metal-chelating ability (Fig. 3)—underlies its biological properties. These reactive sites enable curcumin's interaction with biomolecules, modulating proteins, enzymes, and transcription factors, leading to anti-inflammatory, antioxidant, and anti-cancer effects. The methoxy group is proposed as the preferred site for hydrogen donation due to weakened carbon-hydrogen bonds. The behavior as a Michael reaction acceptor (Fig. 3B) reactions occur between the β-unsaturated β-diketone and nucleophiles (-OH, -SH, -SeH, aminoacids residues), contributing to its antioxidant action (Fig. 3A), through deactivation of some oxidant enzymes. Curcumin's metal-chelating ability (Fig. 3A) is harnessed for various therapeutic purposes (Garcia-Nino and Pedraza-Chaverri, 2014; Wanninger *et al.*, 2015) including Alzheimer's disease, arthritis, cancer, neurological, metabolic, cardiovascular diseases, psoriasis, COVID-19, and inflammatory disorders (Patel *et al.*, 2020; Peng *et al.*, 2021).

Curcumin toxicity

The therapeutic use of turmeric/curcuminoid in humans is considered safe, as evidenced by studies involving high doses (Ryan *et al.*, 2013). Adverse events are rare and include dermatitis and platelet activation suppression, although the latter is not fully understood. Given its intrinsic relation to the dose, as demonstrated by Rukoyatkina *et al.* (2021) in their *in vitro* study, high concentrations of this polyphenol (50 μM) reduced platelet viability but in low doses (5 μM), it potentiates platelet autophagy (Rukoyatkina *et al.*, 2021).

In a recent review, the role of curcumin as an anti-thrombotic agent was discussed in the context of conditions involving thromboembolism, atherothrombosis, leukemia, and cardiovascular diseases. This review suggests the need for conducting clinical trials to evaluate the therapeutic potential of this bioactive compound (Hussain *et al.*, 2022). Furthermore, important questions such as the combination of this therapy with natural products and conventional drugs, whether pro-thrombotic or anti-thrombotic, need to be further explored to better understand the safety of curcumin in these situations.

A population-level study in India found curcumin intake up to 100 mg/day safe and associated with reduced cancer prevalence (Jutooru *et al.*, 2010) FAO/WHO Joint Expert Committee on Food Additives (JECFA) considers 4 to 10 g of turmeric daily safe for healthy adults (Kocaadam and Sanlier, 2017).

Apart from curcumin extract, turmeric oil has also been subject to testing in human trials (Table 1). Doses of 0.6 mL/d, administered three times a day for one month, and 1 mL/d, divided into three doses over two months, were assessed for their impact on haemoglobin, blood counts, liver and kidney functions, bleeding and clotting time and serum electrolytes. Over a 12-week observation period, no discernible alterations were noted in heart rate, blood pressure, tolerability, body weight, or signs and symptoms, reaffirming its safety in humans (Joshi *et al.*, 2003).

The assessment of curcumin toxicity finds more comprehensive exploration through animal models. In a study, a dosage equivalent to 20 times the therapeutic recommendation for humans was administered to treat arthritis in female rats, both orally and intraperitoneally. Intriguingly, oral administration exhibited no discernible toxicity, albeit with modest protective effects. In contrast, intraperitoneal administration significantly escalated morbidity and mortality among the animals (Funk *et al.*, 2010). Conversely, a dose of curcuminoids powder extract 25 times higher than the safe dosage (250 mg/kg body weight/day for 6 months) administered orally induced elevated serum levels of alkaline phosphatase and liver weight, but had no effect on hematological parameters or other liver enzymes (Chavalittumrong *et al.*, 2002).

However, in recent years, concerns regarding curcumin's hepatotoxicity have come to light (Lukefahr *et al.*, 2018; Sohal *et al.*, 2021). These case reports have triggered discussions regarding the quality of this polyphenol available in commercial outlets, as well as the formulations aimed at enhancing its bioavailability (Bucchini, 2019; Girme *et al.*, 2020). In light of these emerging hepatotoxicity questions, Pancholi *et al.* (2021) evaluated a new curcumin formulation, the curcumin-galactomannoside complex (CGM), in healthy volunteers at a dosage of 1000 mg per day (~380 mg curcuminoids). Following a 90-day intervention, the authors concluded that CGM was safe, as no discernible alterations in hepatic markers were identified (Pancholi *et al.*, 2021).

According to Qiu *et al.* (2016), the potential mechanism underlying the hepatotoxic action of curcumin in mega-doses could involve the pronounced overexpression of ROS and IL-6, alongside a reduction in SOD and glutathione-S-transferase levels. This proposed mechanism suggests that the excessive intake of curcumin might disrupt the delicate balance between oxidative stress and antioxidant defenses within the liver. The overproduction of reactive oxygen species and the

TABLE 1

Examples of human studies that evaluated the dose and safety of oral curcumin consumption

Author (year)	Type of study/n	Dose/time	Effects
Cheng *et al.* (2001)	Phase I clinical study (premalignant cells of cervix, bladder, skin, stomach, and oral mucosa)/n = 25	500 mg to 8 g/day 3 months	Well tolerated, without any toxic effect
Dhillon *et al.* (2008)	Phase II clinical study (patients with advanced pancreatic cancer)/n = 25	8 g/day 2 months	No toxic effect
Sharma *et al.* (2004)	Phase I clinical study (patients with advanced colorectal cancer refractory to chemotherapy)/n = 15	0.45 to 3.6 g/day 1–4 months	Minimal elevation of Alkaline phosphatase and lactate dehydrogenase, nausea and diarrhea
Epelbaum *et al.* (2010)	Patients with advanced pancreatic cancer/n = 17	8 g/day curcumin + topic gemcitabine (1000 mg/m²) Up to 2 weeks	Intractable abdominal pain
Lukefahr *et al.* (2018)	Case report	'low cost' turmeric, consumed 8 months prior to transaminitis testing	Autoimmune hepatitis (increased of transaminases, lactate dehydrogenase, perinuclear anti-neutrophil cytoplasmic antibody, actin smooth-muscle antibody, IgG and IgE. Acute (neutrophils) and chronic (lymphocytes and plasma cells) moderate to marked portal inflammation with sparse inflammatory cells in the liver lobules and mild portal fibrosis with sparse focal bridging. Focal piecemeal portal necrosis, focal ballooning hepatocellular degeneration adjacent to the portal inflammation)
Dei Cas and Ghidoni (2019)	Literature review (patients with ulcerative colitis, diabetes mellitus, Alzheimer's disease, osteoarthritis, nonalcoholic fatty liver disease, anxiety and breast cancer undergoing radiotherapy)	70 mg to 6 g/day 1–6 months	Nausea and constipation
Sohal *et al.* (2021)	Two case report	Case 1: Curcumin + piperine: 2000 mg/d/3 months Case 2: Turmeric tablets two times a day	Case 1—Highly probable hepatic dysfunction due to a specific drug (increased of transaminases; hepatocyte ballooning and necrosis—suggestive of acute hepatitis); Case 2—Abdominal pain and nausea; probable hepatic dysfunction due to a specific drug (increased of transaminases, total bilirubin and direct bilirubin; cavernous hemangioma and hepatic steatosis)

subsequent elevation of pro-inflammatory IL-6 could contribute to cellular damage and inflammation. At the same time, the diminished activity of SOD and Glutathione S-transferase (GST) enzymes, might compromise the liver's ability to counteract the damaging effects of oxidative stress (Qiu *et al.*, 2016).

Special physiological situations, such as pregnancy and lactation, lack studies on safe dosages of curcumin. Recent reviews have explored the potential applications of this polyphenol in pregnancy-related conditions, such as preeclampsia, gestational diabetes, intrauterine growth, and more. However, all these scenarios have been tested only *in vitro* or in animal models, yielding favorable results. Nonetheless, no human studies have assessed the safety and effectiveness, making impractical to recommend this compound during high-risk pregnancies or otherwise (Filardi *et al.*, 2020; Ghaneifar *et al.*, 2020; Tossetta *et al.*, 2021).

Regarding the impact of curcumin on breastfeeding, studies are even scarcer. Kobayashi *et al.* (2021) evaluated the influence of curcumin on milk production in lactating mammary epithelial cells (MECs) and observed a downregulation in milk production without triggering increased inflammatory activity. This phenomenon could be beneficial in certain situations where reducing breast milk production is desired, such as in cases of galactorrhea and hyperprolactinemia (Kobayashi *et al.*, 2021).

Topical use of curcumin was tested by Afshariani *et al.* (2014) for the treatment of mastitis in breastfeeding women.

In this randomized clinical trial, curcumin was found to successfully decrease markers of lactational mastitis, including pain, breast tension, and erythema within 72 h of administration, without any side effects. Similarly, oral use of turmeric in combination with fenugreek and ginger (3 capsules, 3 times/day for 4 weeks—100 mg turmeric per capsule) was investigated by Bumrungpert *et al.* (2018) in a randomized clinical trial. This combination exhibited promising effects within 2 weeks (49% increase in breast milk volume), and by 4 weeks, an increase of 103% was observed, all without any adverse effects. While curcumin shows potential in breastfeeding support, the available literature lacks sufficient information to confirm a safe dosage (Bumrungpert *et al.*, 2018).

Therefore, in both pregnancy and breastfeeding contexts, the use of curcumin remains a subject that requires further rigorous investigation to ascertain its safety and efficacy, especially in human populations.

Curcumin: new formulations

Due to its hydrophobicity, curcumin is insoluble in physiological media, where it rapidly degrades or self-oxidizes, impairing its absorption (Fig. 2). Furthermore, in the bloodstream, it is immediately metabolized in part by the action of glycoprotein-P, a transmembrane protein that depends on adenosine triphosphate (ATP) and leads to the efflux of curcumin, as well as by enzymes of first-pass metabolism in the liver and small intestine, which reduce it to its metabolites di-, tetra-, hexa-, and octa-hydrocurcumin (Fig. 2). When passing through second-pass metabolism, curcumin and its products are conjugated to glucuronide and sulfate, forming inactive products (Dei Cas and Ghidoni, 2019; Ipar *et al.*, 2019), However, some studies show that curcumin metabolites exhibit biological activity (Heger *et al.*, 2014; Edwards *et al.*, 2017). The low bioavailability, rapid degradation, and physical-chemical instability of curcumin have been attributed to the β-diketone portion of the molecule (Peng *et al.*, 2021).

Numerous studies have evaluated and demonstrated a wide variability in the systemic distribution of curcumin. In healthy individuals who received doses of curcumin ranging from 0.5 to 12 g/d, serum levels of this curcuminoid were only noticeable in volunteers who received doses higher than 4 g/d (Lao *et al.*, 2006). In patients with pancreatic cancer who supplemented with 8 g/d of curcumin, only their conjugated metabolic forms were detected in plasma (Chen *et al.*, 2020). Conversely, the concentration of curcumin in colonic tissue was found to be higher than the plasma levels of this polyphenol after supplementation with doses ranging from 3 to 66 g of curcumin per day (Garcea *et al.*, 2005) and with a dose of 3.25 g (Irving *et al.*, 2013), suggesting the potential pharmacological significance of the large intestine for curcumin's effects.

Efforts to augment curcumin's bioavailability have led to diverse formulations modifying its solubility, circulation time, permeability, and metabolic stability. These encompass associations with adjuvants, polymers, nanoparticles, liposomes, micelles, phospholipids, metal complexation, and derivatives/analogues (Prasad *et al.*, 2014; Kotha and Luthria, 2019). Recently, nanotechnology has been explored as a drug delivery system for therapeutic agents with bioavailability issues, such as curcumin. Examples of nanoparticles used include poly (butyl-cyanoacrylate) (PBCA), poly (lactide-co-glycolide) (PLGA), chitosan, albumin, and solid lipids (Slika and Patra, 2020).

Among the compounds investigated for adjuvant therapy, piperine, a component of black pepper (*Piper nigrum*), stands out. Piperine has been shown to prevent the degradation of curcumin and increase its concentration in aqueous solution by interacting with and inhibiting P-glycoprotein and glucuronidation in the liver and intestine, improving its bioavailability by up to 2000% (Singh *et al.*, 2013; Hewlings and Kalman, 2017; Ipar *et al.*, 2019). When 2 g of curcumin was administered to healthy adults, low plasma levels (0.006 ± 0.005 μg/mL, within 1 h) were observed. However, when this dosage was combined with 20 mg of piperine, the concentrations increased significantly (0.18 ± 0.16 μg/mL, up to 0.75 h) (Shoba *et al.*, 1998). Some studies have demonstrated the positive effects of this formulation in certain pathophysiological conditions, including metabolic syndrome, chronic pulmonary complications, and type II diabetes mellitus (Panahi *et al.*, 2015, 2016, 2018).

Curcumin in IBD

Anti-inflammatories targets

As mentioned, curcumin is a promising candidate for the treatment of IBD and has been shown to exert anti-inflammatory and antioxidant actions (Figs. 2 and 3) through the modulation of multiple targets and pathways involved in the pathophysiology of these diseases. The interruption of intestinal homeostasis and dysregulation of cytokine pathways, as discussed earlier, contribute to the inflammatory responses observed in IBD (Friedrich *et al.*, 2019). Additionally, the oxidative stress-induced damage to cellular components further exacerbates tissue injury (Moura *et al.*, 2020). On this context, curcumin's ability to target and modulate these cellular mechanisms and cytokine networks provides a rationale for its therapeutic potential in IBD. By exerting its anti-inflammatory and antioxidant effects, curcumin may help restore intestinal homeostasis and mitigate the pathophysiological processes underlying IBD.

Evidence in the literature suggests that the TLR4/NF-κB/AP-1 signaling pathways are overactivated IBD. Both *in vitro* and *in vivo* studies have consistently reported that curcumin reduces the levels of pro-inflammatory cytokines, such as TNF-α, IL-6, IL-1β, and IL-8, by inhibiting these pathways, thereby improving intestinal inflammation in patients with IBD (Zhao *et al.*, 2016; Wang *et al.*, 2018; Burge *et al.*, 2019). Curcumin exerts its effects by suppressing NFκB translocation, inhibiting MAPK phosphorylation, and reducing the expression of inflammatory mediators and reactive oxygen and nitrogen species (RONS). This modulation also impairs the activity of dendritic cells and macrophages that induce Th1 and Th17 responses. Animal models of induced colitis have further demonstrated the efficacy of curcumin in attenuating colonic injury, inflammation markers, lipid peroxidation, and cell death

through modulation of the p38 MAPK and TLR4-MyD88/NFκB pathways (Lubbad *et al.*, 2009; Topcu-Tarladacalisir *et al.*, 2013; Li *et al.*, 2015). Additionally, curcumin promotes the expansion of regulatory T cells (Treg) and increases the levels of anti-inflammatory products, such as IL-10 and TGF-β (Zeng *et al.*, 2013; Wang *et al.*, 2018).

The action of curcumin on NF-κB, coupled with its inhibition of the Notch-1 gene, confers to this compound an action that goes beyond anti-inflammatory effects, encompassing inhibition of angiogenesis and tumorigenesis. This multifaceted action is supported by numerous *in vitro* studies (Wang *et al.*, 2006; Li *et al.*, 2012; Zhdanovskaya *et al.*, 2022).

An important consequence of curcumin's action on NF-κB and TNF-α is the improvement in insulin resistance, leading to a subsequent reduction in glycemic levels. Several *in vivo* studies conducted both in animal models (Zou *et al.*, 2021; Lee *et al.*, 2022; Zhong *et al.*, 2022) and in humans (Thota *et al.*, 2018; Marton *et al.*, 2021) have consistently confirmed the hypoglycemic potential of this bioactive compound. In addition to the previously mentioned NF-κB and TNF-α inhibition, it is suggested that curcumin's action includes the suppression of Notch-1 signaling and the modulation of intestinal microbiota (Zhao *et al.*, 2018; Zhong *et al.*, 2022).

TNF-α, produced by phagocytes, monocytes, and T cells, has multiple effects on various intestinal cells, including cell proliferation and differentiation. This cytokine can stimulate the production of IL-1, IL-6, and fibroblasts, as well as the expression of other molecules (Guan, 2019). Excessive cytokine production may disrupt the functionality and integrity of the intestinal barrier by inducing apoptosis in epithelial cells (Friedrich *et al.*, 2019). IL-6 is produced by macrophages, T cells in the lamina propria (Mudter and Neurath, 2007), as well as epithelial and mesenchymal cells (Ansari *et al.*, 2021). These latter two cell types play a crucial role in the healing process by recruiting polymorphonuclear leukocytes and macrophages. IL-6 also prevents apoptosis of T cells (Zmora *et al.*, 2017) and its elevated levels have been associated with increased inflammatory activity, as indicated by elevated levels of fecal calprotectin (Bourgonje *et al.*, 2018) or disease activity (Slowinska-Solnica *et al.*, 2021).

IL-10, a critical anti-inflammatory cytokine, is produced by activated innate or adaptive immune system cells, primarily macrophages (Ip *et al.*, 2017). This cytokine regulates the production of pro-inflammatory cytokines and modulates the genetic expression of co-stimulatory molecules and chemokines. Mice genetically modified to lack IL-10 or the IL-10 receptor beta (IL-10Rβ) spontaneously develop enterocolitis (Wei *et al.*, 2020). Therefore, the stimulatory effect of curcumin on IL-10 may provide a protective effect against inflammation. Other cytokines, such as IL-4, IL-10, and IL-13, also appear to be molecular targets of curcumin, with their expression or levels being reduced by this curcuminoid (Ukil *et al.*, 2003; Jian *et al.*, 2005; Gopu *et al.*, 2015; Zhang *et al.*, 2016; Zhao *et al.*, 2017; Kesharwani *et al.*, 2018; Wei *et al.*, 2021).

Additionally, the administration of curcumin has demonstrated therapeutic potential by negatively regulating various signaling pathways (PI3/Akt, JAK/STAT, and β-catenin), inhibiting the expression of COX-2, iNOS, and co-stimulatory molecules (RANKL, ICAM-1, CD205, CD256, TLR4, among others), and suppressing immune cell chemotaxis, including the infiltration of neutrophils into inflamed regions (Zhao *et al.*, 2016; Wang *et al.*, 2018; Karthikeyan *et al.*, 2021). These effects contribute to the reduction of tissue damage. Several studies have supported these findings, including a model of 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis, where curcumin decreased the expression of pro-inflammatory cytokines (TNF-α and IFN-γ) by inhibiting COX-2 expression (Jiang *et al.*, 2006). The therapeutic effects of curcuminoids were also observed in other experimental models, attributed to the blockade of the STAT3 pathway (Liu *et al.*, 2013).

COX is an enzyme involved in the endogenous generation of ROS, while COX-2 is specifically associated with the formation of ulcers (Balmus *et al.*, 2016). Ulcer formation is closely linked to the development of precancerous features in the colon (Tian *et al.*, 2017). On the other hand, inducible nitric oxide synthetase (iNOS) is an enzyme highly expressed in inflammatory cells in response to immune system stimuli and cytokines. The iNOS catalyzes the production of nitric oxide (•NO) from L-arginine, which is normally produced under physiological conditions. However, in cases of IBD, where there is an excessive production of •NO, various cell types, including epithelial ones, can be affected, leading to vasodilation, formation of edema, and alteration of mucosal permeability (Kamalian *et al.*, 2020). Studies using cell and animal models of colitis have indicated that curcumin treatment significantly reduces iNOS activity and tissue levels of •NO (Camacho-Barquero *et al.*, 2007; Venkataranganna *et al.*, 2007; Mouzaoui *et al.*, 2020).

In addition, curcumin's protective effect is also attributed to its ability to inhibit NLRP-3 inflammasome activation and reduce IL-1β production, thereby resulting in improvements in weight loss, disease activity index, and colon length (Gong *et al.*, 2018; Yue *et al.*, 2019). Although the precise role of IL-1β in intestinal inflammation remains uncertain, it should be noted that patients treated with IL-1β receptor inhibitors did not show a favorable response (Mao *et al.*, 2018). Nonetheless, experimental studies have demonstrated elevated levels of this cytokine in colitis models (Liu *et al.*, 2013; Gopu *et al.*, 2015).

In IBD, histologically characteristic features include the infiltration and accumulation of immune cells, such as neutrophils and monocytes, which release MPO (Altinel *et al.*, 2020). This enzyme is associated with both the inflammatory process and oxidative mechanisms in the inflamed colon, including the generation of ROS such as hypochlorous acid (HOCl) through halogenation cycles or peroxidase (Chami *et al.*, 2018). Curcumin has been shown to inhibit MPO activity (Salh *et al.*, 2003; Ukil *et al.*, 2003; Deguchi *et al.*, 2007; Venkataranganna *et al.*, 2007; Lubbad *et al.*, 2009; Liu *et al.*, 2013; Zeng *et al.*, 2013; Gopu *et al.*, 2015; Bastaki *et al.*, 2016; Yildirim *et al.*, 2016; Zhang *et al.*, 2016; Altinel *et al.*, 2020), suggesting its potential antioxidant and anti-inflammatory effects, which may

potentially reduce immune cell infiltration and mucosal changes caused by intestinal inflammation.

In a murine model of colitis, curcumin was able to normalize the expression of autophagy-associated genes (Beclin-1, LC-3II, autophagy-related 5—ATG5, B cell lymphoma 2—BCL-2), leading to disease improvement. Additionally, it reduced the formation of autophagosomes in colonocytes and the levels of IL-17, IL-6, and TNF-α, promoting anti-inflammatory effects, as well as restoring IL-10 expression (Yue *et al.*, 2019).

Oxidative targets

Due to its antioxidant action, curcumin has been found to be effective in combating oxidative stress present in IBD. Several experimental studies have demonstrated that this polyphenol significantly reduces levels of malondialdehyde (MDA), HOCl, hydrogen peroxide (H_2O_2), and $^{\bullet}NO$, while increasing the activity of SOD and other phase II enzymes involved in xenobiotic detoxification processes mediated by the Nrf2 pathway, which is known to regulate antioxidant responses (Mouzaoui *et al.*, 2012, 2020; Goulart *et al.*, 2021; Lucas *et al.*, 2021) (Fig. 3).

Another therapeutic target of curcumin is the pregnane X receptor (PXR), a nuclear receptor that regulates inflammatory responses, glucose metabolism, and protects normal cells against carcinogenesis. Curcumin appears to activate the human PXR and significantly reduce the histological signs of colonic inflammation through the induction of multidrug resistance protein 1 (MDR1) expression. MDR1 is involved in the transport of various xenobiotics, toxins, as well as physiological substrates (Niu *et al.*, 2022).

As previously noted, oxidative stress plays a decisive role in the pathophysiology of IBD, leading to cellular and molecular damage in various components such as membrane lipids, proteins, and deoxyribonucleic acid (DNA) in mitochondria and nuclei, ultimately resulting in tissue injury (Tian *et al.*, 2017; Dudzinska *et al.*, 2018). The inhibition of lipid peroxidation by curcumin is crucial as it prevents the accumulation of MDA, a metabolite generated during lipid peroxidation. This process is significant because lipid peroxidation not only disrupts the cellular environment's metabolism and balance but also results in the production of harmful end products that can damage protein complexes (Alemany-Cosme *et al.*, 2021). The distinct antioxidant mechanisms of curcumin can be visualized in Fig. 3.

In animal models of colitis, supplementation with curcumin has been shown to increase or normalize the activity of SOD, CAT, and/or GPx enzymes in colonic tissue and/or serum, compared to groups without supplementation (Topcu-Tarladacalisir *et al.*, 2013; Gopu *et al.*, 2015). Furthermore, curcumin has been observed to elevate serum or tissue glutathione reduced (GSH) levels (Gopu *et al.*, 2015; Bastaki *et al.*, 2016). These findings indicate that apart from its direct effects on pro-oxidant enzymes and reactive species, curcumin can alleviate oxidative stress by stimulating the production of both enzymatic and non-enzymatic antioxidant complexes.

The effects and molecular targets of curcumin in IBD are listed in Table 2.

Effect on gut microbiota

As discussed previously, oxidative stress and inflammation play crucial roles in initiating, progressing, and sustaining tissue damage that leads to intestinal barrier dysfunction and increased permeability. This dysfunction results in the loss of immune tolerance to microbiota, making

TABLE 2

Effects and molecular targets of curcumin in inflammatory bowel disease

Authors	Compound	Type of study	Dose/route of administration	Biological effects
Zhao *et al.* (2017)	Curcumin (purity ≥ 95%)	TNBS-induced colitis model	200 mg/kg/day, oral	• ↑ Treg cells • ↑ IL-2, IL-6, IL-12, IL-21 and TNF-α • ↑ Expression of co-stimulatory molecules (ICAM-1, TLR4, OX40 L, RANK and RANK L) of dendritic cells
Lubbad *et al.* (2009)	Curcumin (aqueous suspension)	TNBS-induced colitis model	100 mg/kg/day, oral	• ↑ MPO, MDA, TLR-4, MyD88 and NFκB
Topcu-Tarladacalisir *et al.* (2013)	Curcumin (suspension in 1 mL of dimethylsulfoxide—DMSO)	Model of acetic acid-induced colitis	100 mg/kg/day, oral	• ↑ MPO, MDA, apoptosis, p38 and MAPK
Li *et al.* (2015)	Curcumin	DSS-induced colitis model	15, 30, and 60 mg/kg, intraperitoneal injection	• ↑ MPO, TNF-α, p-p38 MAPK • ↑ p38 and MAPK expression

(Continued)

Table 2 (continued)

Authors	Compound	Type of study	Dose/route of administration	Biological effects
Zeng *et al.* (2013)	Curcumin (purity ≥ 90%)	TNBS-induced colitis model	100 mg/kg/day, oral	• ↑ disease activity index, colonic mucosa damage index and histological score • ↑ MPO and expression of mRNA and NF-κB, TLR4 and IL-27 proteins
Cong *et al.* (2009)	Curcumin	Culture of bone marrow-derived dentritic cells from C57BL/6 and Rag2$^{-/-}$OT-II mice	1, 3, 10, 20, 50 and 100 mM/	• ↑ Treg cells • ↑ IL-10 and TGF-β • ↑ NF-κB, TNF-α and IL-6
Yang *et al.* (2018)	Curcumin and tetrahydrocurcumin (0,05% emulsion of carboxymethylcellulose)	DSS-induced colitis model	0.1 or 0.25 mmol/kg/day, oral	• (−) NF-κB and STAT3 pathway • ↑ COX-2 and iNOS expression
Liu *et al.* (2013)	Curcumin	DSS-induced colitis model	50 mg/kg/day, oral	• (−) STAT3 pathway • ↑ MPO, TNF-α and IL-1β
Jiang *et al.* (2006)	Curcumin (purity ≥ 95%)	TNBS-induced colitis model	30 and 60 mg/kg/day, Intraperitoneal	• ↑ MPO and COX-2 expression • ↑ PGE2
Gong *et al.* (2018)	Curcumin	Peritoneal and bone marrow macrophages/ DSS-induced colitis model	10, 25 and 50 μM 100 mg/kg/day, intraperitoneal	• (−) NLRP3 activation, K+ efflux, ROS and cathepsin B • ↑ MPO, caspase-1 • ↑ IL-1β, IL-6 and MCP-1 expression
Yue *et al.* (2019)	Curcumin	DSS-induced colitis model	15, 30 and 60 mg/kg, intraperitoneal injection	• ↑ ATG5, LC-3II, beclin-1 and bcl-2 (genes that regulate autophagy) • ↑ IL-17, IL-6 and TNF-α • ↑ IL-10
Mouzaoui *et al.* (2012)	Curcumin	TNF-α induced colitis model	25 mg/kg, intraperitoneal	• ↑ MPO, MDA and nitrite
Camacho-Barquero *et al.* (2007)	Curcumin	TNBS-induced colitis model	50–100 mg/kg/day, oral	• ↑ COX-2 and iNOS expression • ↑ p38 MAPK, nitrite, MPO, TNF-α • ↑ IL-10
Venkataranganna *et al.* (2007)	Standardized Curcumin Preparation (NCB-02)	Model of dinitrochlorobenzene-induced colitis	25, 50 and 100 mg/kg, intraperitoneal	• ↑ NF-κB and iNOS expression • ↑ MPO
Ukil *et al.* (2003)	Curcumin (2,5% emulsion of CMC)	TNBS-induced colitis model	25–300 mg/kg/day, oral	• ↑ MPO, MDA, $^{\bullet}$NO, $O_2^{\bullet-}$, NFκB • ↑ iNOS expression

Note: Legend: ↓ = decreased; ↑ = increased; (−) = inhibition; ATG5 = autophagy Related 5; CMC = carboxymethylcellulose; COX = cyclooxygenase; DSS = dextran sodium sulphate; IL = interleukin; ICAM1 = intercellular adhesion molecule 1; iNOS = inducible nitric oxide synthetase; LC3 = Microtubule-associated protein 1A/1B-light chain 3; MCP-1 = monocyte chemotactic protein 1; MAPK = mitogen-activated protein kinases; MDA = malondialdehyde; MPO = myeloperoxidase; MyD88 = myeloid differentiation primary response 88; $^{\bullet}$NO = oxide nitric; NFκB = nuclear factor kappa B; NLRP3 = NOD-, LRR- and pyrin domain-containing protein 3; $O_2^{\bullet-}$ = superoxide radical anion; Ox40 L = ligand of Tumor necrosis factor receptor superfamily, member 4; p38 = protein 38; RANK = receptor activator of nuclear factor kappa-B; RANK-L = receptor activator of nuclear factor kappa-B ligand STAT = signal transducer and activator of transcription proteins; TGF-β = transformative growth factor β–1; TNBS = trinitrobenzenesulfonic acid; TNF-α = tumor necrosis factor α; Treg = regulatory T cells; TLR4 = toll like receptor 4; PGE2 = prostaglandin E2.

the organism susceptible to attacks by various antigens from the lumen, primarily bacteria and their products such as lipopolysaccharide (LPS) (Pasternak *et al.*, 2011). In this regard, curcumin and its metabolites generated in the gut exhibit biological activity and promote beneficial effects on the intestinal microbiota.

Several animal models have demonstrated positive effects on the microbiota in induced colitis, such as increased abundance of butyrate-producing bacteria and fecal butyrate levels (Ohno *et al.*, 2017), as well as increased relative abundance of Lactobacillus and decreased Coriobacteriaceae order (McFadden *et al.*, 2015). These effects suggest two distinct influences of curcumin on the microbiota: firstly, curcumin modulates microbiota composition, and secondly, microbiota causes biotransformation of curcumin (Scazzocchio *et al.*, 2020).

However, human studies in this area are still limited and have presented conflicting results. In a double-blind, randomized, placebo-controlled pilot study, Peterson *et al.* (2018) compared the administration of 1000 mg of C, longa

+ 1.25 mg black pepper or 1000 mg of curcumin + 1.25 mg black pepper *vs.* placebo. According to the authors, both turmeric and curcumin altered the gut microbiota in a highly similar manner in healthy subjects. Nevertheless, there were some concerns regarding the study, including the small number of subjects evaluated (3 placebo, 6 turmeric, and 5 curcumin), the absence of a controlled diet group, and the potential for piperine to promote the growth of certain gut microbiota (Peterson *et al.*, 2018).

More recently, Lopresti *et al.* (2021) conducted a double-blind, randomized, placebo-controlled study to test the efficacy of a curcumin extract in adults with self-reported digestive complaints. After 8 weeks of treatment (500 mg curcumin extract *vs.* placebo), post-stool samples were available for 50 participants (25 per group). The study did not observe a significant effect on small intestinal bacterial overgrowth (SIBO) and intestinal microbial profile. However, the authors suggest conducting more detailed microbial analyses to examine the effects of curcumin on intestinal barrier function, inflammation, neurotransmitter activity, and visceral sensitivity (Lopresti *et al.*, 2021).

In a review by Jabczyk *et al.* (2021), discussing the impact of curcumin on the microbiota, the authors state that the benefits of curcumin on the microbiota depend on its dietary and supplementary intake, an individual's capacity for metabolism, and the biodiversity of their microbiota. Consequently, the influence of curcumin on the intestinal microbiota remains unclear. On this context, curcumin metabolites may exhibit higher bioactivity than the parent compound (Jabczyk *et al.*, 2021).

The anti-colitis efficacy of curcumin can be attributed to its multitarget action, which includes the modulation of inflammation and oxidative stress markers, regulation of microbiota and intestinal immune function, and improvement of mucosal barrier dysfunction, among other mechanisms. Experimental studies have demonstrated improvements in disease activity, macroscopic and histological evaluations of the colon, and a reduction in animal mortality (Ohno *et al.*, 2017; Yang *et al.*, 2018).

Another significant aspect of curcumin's action revolves around its interaction with *Escherichia coli*, a bacterium abundantly found within the human microbiota. Notably, a substantial proportion of ingested curcumin reaches the cecum and colon regions. Here, it undergoes a conversion process facilitated by the enzyme NADPH reductase, which is present in human fecal *E. coli*. This enzyme orchestrates the stepwise reduction of the four double bonds within curcumin's heptadiene-3,5-dione structure, resulting in the formation of dihydrocurcumin and subsequently tetrahydrocurcumin (Hassaninasab *et al.*, 2011).

Evidence from clinical trials

Numerous studies have demonstrated that the use of curcumin as an adjuvant agent is safe and effective in the treatment of IBD. These studies have reported beneficial effects on clinical symptoms, endoscopic remission, and reduction of certain inflammation markers (Burge *et al.*, 2019; Cunha Neto *et al.*, 2019; Fallahi *et al.*, 2021).

Sugimoto *et al.* (2020) conducted pioneering research on the therapeutic use of curcumin for the treatment of mild to moderate CD. A total of 30 patients from five independent medical centers were enrolled in the study and received Theracurmin®, an orally administered formulation containing 360 mg/day of curcumin, or a placebo for a duration of 12 weeks. It is important to note that Theracurmin® has a significantly higher absorption rate compared to curcumin powder, being 27 times more bioavailable. The effects of the treatment were assessed based on clinical, endoscopic, healing, and laboratory parameters. The study's findings revealed significant clinical and endoscopic improvements, reduced disease activity, and anal healing in the treatment group. The endoscopic remission rate was 15% in the curcumin group, while no remission was observed in the placebo group. Importantly, no serious adverse effects were reported, indicating the safety of Theracurmin® as a treatment option for CD (Sugimoto *et al.*, 2020).

The number of clinical trials investigating curcumin has been increasing, leading to the conduction of several meta-analyses, including a recent one conducted by our research group (Alves *et al.*, 2022). However, despite the reported positive effects, several critical factors and the absence of evaluation of more robust markers may limit our conclusions, as can be seen below.

Similarly, a randomized, double-blind, placebo-controlled study demonstrated that the administration of 1500 mg of curcumin for 8 weeks, in conjunction with pharmacological therapy, resulted in improved clinical parameters and reduced levels of CRP and erythrocyte sedimentation rate in patients with mild to moderate ulcerative colitis (UC), without any changes in TNF-α levels (Sadeghi *et al.*, 2020).

Masoodi *et al.* (2018) investigated the use of curcuminoid nanomicelles (80 mg, orally three times a day) for 4 weeks in patients with mild to moderate ulcerative colitis. Due to its better bioavailability, curcuminoid nanomicelles were used. Although improvements in clinical variables were observed, the study did not include endoscopic investigation or evaluation of other important laboratory and inflammatory markers (Masoodi *et al.*, 2018). Sadeghi *et al.* (2020) conducted a study with 70 patients using 1500 mg/day of curcumin as adjunctive therapy. The intervention group showed clinical remission, improved disease activity, and reduced inflammatory markers compared to the control group, indicating a positive response. However, the specific drug and dosage used in each group were not described (Sadeghi *et al.*, 2020).

Banerjee *et al.* (2021) evaluated a novel bioenhanced hydrophilic curcumin compound (BEC) as adjuvant therapy in ulcerative colitis patients. Treatment with BEC induced clinical and endoscopic remission and showed long-term efficacy without adverse effects. However, the study could have included additional inflammatory markers for a more robust analysis (Banerjee *et al.*, 2021). Similarly, the study conducted by Lang *et al.* (2015) in patients with mild to moderately active ulcerative colitis, using 5-aminosalicylic acid (5-ASA) at an optimized dose, demonstrated that curcumin supplementation (3 g/day) for 4 weeks improved clinical response and induced remission in patients with ulcerative colitis, but did not affect CRP and hemoglobin

levels. The study lacked evaluation of other inflammatory markers and had a short intervention time (Lang *et al*., 2015).

Interesting results were also reported by Hanai *et al.* (2006), in their multicenter study that demonstrated that oral administration of curcumin (2 g/day) as an adjuvant to sulfasalazine/mesalamine (1–3 g/day) for 6 months promoted clinical and endoscopic improvement in ulcerative colitis patients in remission. However, the study did not include patients with mild to moderate disease activity (Hanai *et al*., 2006). Also used as adjuvant therapy for 8 weeks, Kedia *et al.* (2017), reported that oral use of curcumin (450 mg/day) as was not effective in inducing clinical and endoscopic remission in patients with mild to moderate ulcerative colitis, possibly due to the low dosage used and limitations in sample size (Kedia *et al*., 2017).

Lastly, Singla *et al.* (2014) evaluated for 8 weeks the effects of the standardized preparation of *C. longa* extract (NCB-02), by enema, associated with 5-ASA, in patients with mild to moderate ulcerative colitis. Treatment with NCB-02 was effective in inducing clinical remission and endoscopic improvement, but the study had significant losses during the research period (Singla *et al*., 2014).

In general, most randomized clinical trials have reported satisfactory and promising outcomes with the use of curcumin as an adjunctive therapy for IBD (Grammatikopoulou *et al*., 2018; Alves *et al*., 2022). However, the significant variability among studies, including variations in dosage, formulation type, route of administration, intervention duration, and limited sample sizes, restricts its applicability in clinical practice. Therefore, there is a need for standardization in clinical studies with respect to these variables to establish more effective therapeutic approaches.

Conclusions

It is evident, considering the information presented, that the biological characteristics of curcumin, particularly its effects on various therapeutic targets, underscore its potential as an adjunct therapy for IBD. This warrants discussion by medical societies in their guidelines to provide scientific guidance for healthcare professionals involved in the care of these patients. Notably, curcumin has demonstrated effects on multiple targets related to inflammation, oxidative stress, and the gut microbiota. For instance, it has been shown to modulate key pro-inflammatory cytokines such as TNF-α, IL-6, IL-10, and IL-1β, reducing the inflammatory burden in IBD patients. Additionally, curcumin exerts its antioxidant effects by modulating the activity of enzymes involved in oxidative stress, such as superoxide dismutase SOD and CAT. Moreover, curcumin has shown potential in modulating the gut microbiota composition, promoting a balanced microbial environment and influencing the gut-brain axis, as it can be visualized in the graphical abstract.

To comprehensively explore curcumin's potential, future clinical trials should incorporate these mechanisms. Robust biomarkers can illuminate its intricate cellular pathways. By evaluating cytokine profiles, oxidative stress markers, and gut microbiota dynamics, researchers can elucidate curcumin's therapeutic potential in IBD. This holistic approach enriches the foundation for evidence-based medical decisions.

However, prescribing curcumin demands caution. Factors like origin, dosage, and ongoing monitoring to detect early alterations, especially in hepatic markers should be considered. Such vigilance ensures patient safety and outcomes. Furthermore, as curcumin's therapeutic potential evolves with new formulations, robust studies are imperative. Evaluating efficacy and safety of these novel formulations will expand our understanding and guide curcumin's integration into medical practice.

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