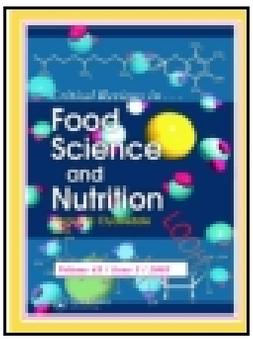

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CURCUMINOIDS FROM *CURCUMA LONGA:* NEW ADJUVANTS FOR THE TREATMENT OF CROHN'S DISEASE AND ULCERATIVE COLITIS?

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ABSTRACT

Crohn's Disease (CD) and Ulcerative Colitis (UC) result from an overreaction of the bowel to multifactorial stimuli leading to discomfort, pain, and it is associated with high morbidity and lethality. The medications commonly used are expensive and associated with multiple side effects. *Curcuma longa* exerts anti-inflammatory and antioxidant actions and has shown positive effects on CD and UC treatment, possibly due to the presence of curcuminoids. The objective of this review was to evaluate the role of curcuminoids in the treatment of IBD. A search for articles associating curcuminoids and CD and UC was performed using MEDLINE–PubMed. It has been found that curcumin can reduce oxidative stress and inhibit the migration of neutrophils and inducible nitric oxide synthase in the intestine. It may also improve micro and macroscopic lesions, prevent apoptosis of intestinal cells and also induce the restoration of the mitogen-activated protein kinase immune reaction. As the incidence of CD and UC is growing in many populations, there is an urgency to find an appropriate and accessible therapeutic approach to improve quality of life of patients. The use of curcumin is cheap, efficient and associated with no side effects, and may become an alternative to the IBD treatment.

Keywords: Curcuminoids, *Curcuma longa, Crohn's Disease, Ulcerative Colitis*

INTRODUCTION

Crohn's Disease (DC) and Ulcerative Colitis (UC) are Inflammatory Bowel Diseases (IBD) and are characterized by chronic and destructive inflammatory process of the gastrointestinal tract. This inflammation results from a reaction to multifactorial stimuli such as eating habits, hyperactivity of the immune response, and genetic factors (Hemperly, Vande-Casteele, 2018; Ilhara, Hirata, Koike, 2017). IBD causes extreme discomfort, as they affect intestinal mucosal homeostasis, as well as leading patients to morbidity and lethality if they are not treated correctly (Lanis, Arshd et al., 2017)

The treatment usually involves drug therapy (aminosalicylates and immunosuppressants) or surgical procedure. It is worth mentioning that the intervention currently used in addition to bringing a cost of US $ 8,265 to DC and US $ 5,066 to UC (annual *per capita* expenditure in the United States) also causes numerous side effects due to the marked suppression of the immune response. For these reasons the conventional therapy cannot be used for a long time as the therapy usually demands (Kappelman et al., 2008; Rajasekaram, 2011).

Since ancient times, many plants have been used by populations for medicinal purposes, either in the alleviation of pain or the treatment of different diseases. Previously, the use of medicinal plants was given empirically and was based on accidental discoveries, but in the last decades, plants have been used as primary therapy or as adjuvants in the treatment of various illness (Sueth-Santiago et al., 2015).

Curcuma longa besides exerting an expectorant, antibacterial, antidiabetic, cardioprotective, antimutagenic, radioprotective and hepatoprotective effects, also exerts anti-inflammatory, antioxidant, and anticancer actions and therefore may play beneficial effects in the treatment of IBD (Liu et al., 2018; Kondamundi, 2015). It is popularly known as saffron or turmeric and is originated in Indian. This spice is widely used in traditional Indian and Chinese medicine as well as having culinary uses (Hemachandra et al., 2018; Chin, 2016; Rajasekaram, 2011). Due to the anti-inflammatory and anticancer effects, *C. longa* may exert beneficial effects for the IBD patients (Algieri et al., 2015).

Due to the increase of the incidence of IBD especially in many developing countries and the significant burden for Health Systems, the objective of this study was to review the positive effects of curcuminoids on Crohn's Disease and Ulcerative Colitis.

METHODS

Focused question and combination of terms

The question raised to build this revision was "Is there any association between Ulcerative Colitis, Crohn's Disease, and curcuminoids?".

The databases consulted for this review was MEDLINE (US National Library of Medicine's – NLM, National Institutes of Health) – PubMed/PMC (from 2013 to November 2017).

The articles query was performed by combining the following terms: “Crohn’s Disease” and “curcumin” or “bisdemethoxycurcumin” or “demethoxycurcumin”. The combination was also performed with the use of the term “Ulcerative colitis” and curcumin, or “bisdemethoxycurcumin” or “demethoxycurcumin.”

Inclusion and exclusion criteria

The inclusion criteria for the search were full-texted articles, original studies with animals or human models and *in vitro* studies. The exclusion was based on articles not in English or that did not present full-text; reviews, poster presentations, editorials, letters, and articles not available for free in the databases accessed by the authors.

Each author independently searched articles with the above combination of terms, and all authors discussed the inclusion or exclusion according to the criteria previously discussed.

RESULTS

The selected articles obtained with the search and obeying the inclusion criteria are shown in the flow diagram in Figure 1.

The combination of the terms selected (Figure 1) resulted in 15 articles that fulfilled the inclusion criteria (Figure 1). The final selection of the articles is shown in Table 1. We did not find articles associating CD and UC with the curcuminoids Bisdemethoxycurcumin and Demethoxycurcumin.

Apart from these studies associating CD and UC and Curcumin, we performed another search to find relevant manuscripts that presented relevant information to help in the discussion section.

DISCUSSION

Inflammatory Bowel Diseases

Inflammatory bowel diseases are chronic, multifactorial, and inflammatory diseases characterized by periods of activation and remission of intestinal inflammation, with potential for severe complications, sometimes leading to mortality (Shalkami, Hassan, Bacr, 2017).

The intestinal mucosa acts as an intestinal epithelial physical barrier, with the function of preventing the entrance of antigens and external microorganisms. Such a barrier is formed by enterocytes, firmly connected through membrane specializations, as intercellular junctions. These cells secrete cytokines and chemokines, which are responsible for triggering the inflammatory response, as the second line of defense. Also, there are goblet cells responsible for the secretion of mucin, which forms a mucosal layer that protects the surface against antigens and helps maintain the function of the intestinal barrier (Gadaleta, Garcia-Irigoyen, Moschetta, 2017).

T lymphocytes perform the third line of defense; T-cell subsets are stimulated by antigen presenting cells (APCs) that have the unique ability to activate näive T cells. They are found inactive, but when they contact bacterial contents, they migrate to the mesentery or lymph nodes, where they stimulate T cells. The stimulus can be performed by binding to other signs, presenting an antigen on the MHC surface, which is recognized by the appropriate T cell receptor, or by the secretion of cytokines such as Interleukin-6 (IL-6), IL-12, IL-23, IL-10 or Transforming Growing Factor β (TGFβ). Each of these signals contributes to the activation state of T cells. In patients with IBD, dendritic cells are present in increased numbers in the intestinal mucosa, which leads to higher activation of T cells and consequently more severe inflammation (Shalmami, Hassan, Bacr. 2017; Barbalho, 2017; Hart et al., 2005).

Crohn´s Disease and Ulcerative Colitis

CD is a chronic inflammation of transmural characteristic (Azevedo et al., 2014) that affects the digestive tract, and can occur from the oral cavity to the anus (Yu et al., 2017), affecting mainly the small intestine and colon with intermittent regions between healthy and affected areas. This disease can affect any age of both sexes and is increasing worldwide (Sairenji, Collins, 2017).

CD patients have an atypical immune response mediated by TH1 and TH17 cells leading to the release of Interferon- γ (IFN-γ), Tumor Necrosis Factor (TNF-α), IL-1β, IL-6, and IL-17. The main symptoms of CD include abdominal pain, diarrhea and weight loss (Akobeng, Elawad, Gordon, 2016). During endoscopy, it is possible to observe inflammation with linear or aphthous ulcers, stenoses, fistulas, and fissures (Yu et al., 2017; Wang et al., 2017; Ganju-Arjenaki, Nasri, Rafieian-Kopaei, 2017; (Sairenji, Collins, 2017).

The inflammation observed in UC is usually limited to the colon or rectum (Henriksen et al., 2017) and has an atypical TH2 and TH9 response mediated by Natural Killers T cells (NKT) secreting IL-13. NKTs are activated by APCs that express compatibility to MHC CD1d, which presents T-cell lipid and non-protein antigens. The main symptoms also include abdominal pain, diarrhea and weight loss (Khan, Samson, Grover, 2017; Sartor, 2006).

According to the Clinical Protocol and Therapeutic Guidelines for IBD, the primary drugs used in Brazil are Sulfasalazine, Mesalazine, Corticosteroids, Ciprofloxacin, Azathioprine, Methotrexate, Ciclosporin, Infliximab, Adalimumab, and Allopurinol. The use of these medications brings varying costs, and the use of these medications does not eliminate the possible need for surgical intervention.

Infliximab and Adalimumab have a better long-term response, increasing disease remission time, but are costly and associated with some side effects (Kotze et al., 2009). The costs of the allopathic medications mean a significant problem for the patient. For example, in Brazil, the majority of the population receives a minimum wage of US$283.30. If we consider the prices of the medications, that range between US$ 9,00 to US$ 2,585,244 in this country, we may say that the costs are very high.

The data presented above shows that is evident the need of adjuvant treatments. Moreover, the augment in the risk of infections and malignancy by immune suppressive therapies has been disrupting the need for alternatives for IBD patients to focus on acceptable, non-toxic and cheap natural products. Curcumin may be a new expectancy of reaching a not expensive and effective compound to reduce inflammation, maintain remission and improve quality of life of the patient.

General Aspects of *Curcuma longa*

Beyond its primary use as a condiment, it has antioxidants, antimicrobials, and dyes that give it the possibility of employment in several areas (Seo, Fischer, Efferth, 2017; Ameruoso et al., 2017).

Curcuma longa L. belongs to the family Zingiberaceae that may grow naturally throughout the Indian subcontinent and also in tropical countries, especially in Southeast Asia. It has traditionally been used both as a spice, cosmetic or medication and there are records of its use in Indian Ayurvedic medicine for more than 6,000 years (Schaffer et al., 2011; Santel et al., 2008). The medicinal effects can be

attributed to the presence of curcuminoids designated curcumin (diferuloylmethane), bisdemethoxycurcumin, and demethoxycurcumin in the proportions of 77%, 17%, and 3% (Kuo et al., 2018; Chin, 2016; Rajasekaram, 2011).

Its main compound, curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene- 3,5-dione) is a flavonoid present in the rhizomes (Hu et al., 2015). The presence of this hydrophobic phenolic compound is related to its therapeutic potentials such as producing significant immunosuppressive actions due to the inhibition of the production of IL-2 and IL-12, and mitogen activation mediated by the inhibition of NF-κB, which exerts a significant effect on the regulation of pro-inflammatory gene expression transcription. This compound inhibits the expression of iNOS (inducible Oxide Nitric Synthase), COX-2 (Cyclooxygenase-2), Lipoxygenase-5, and many pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-8, IL-12, and TNF-α. It is also capable of regulating apoptosis and suppresses neurotoxic factors in lipopolysaccharide-stimulated alveolar macrophages and monocytes. Furthermore, inhibits the phosphorylation and degradation of IκBα and activate the peroxisome-proliferator-activated receptor γ mechanism, reducing inflammation by inducing the inhibition of the NF-κB pathway (Seo, Fischer, Efferth, 2017; Baliga et al., 2012; Hanai, Sugimoto, 2009; Hatcher et al., 2008).

Curcuma, Crohn's Disease and Ulcerative Colitis

Some studies have shown that the use of the curcuminoids extracted from *Curcuma longa* may bring unique benefits in the inflammatory processes and oxidative stress. Turmeric compounds may reduce oxidative stress, neutrophil influx, and ROS-related cellular damage, and inhibits migration of neutrophils and iNOS in the intestine and liver of animals with colitis reducing oxidative damage in the intestine in

IBD patients (Figure 2) (Mouzaoui, Rahim, Djerdiouri, 2011). It may also improve micro and macroscopically lesions, a decrease of myeloperoxidase and malonaldehyde, prevent the apoptosis of intestinal cells and also induce the restoration of the immune reaction of mitogen-activated protein kinase (MAPK). For these reasons curcumin decreases injury to the colon and is still associated with inflammatory reactions, lipid peroxidation, apoptosis, and further modulates p38 and JNK-MAPK (Topcu-Tarladacalisir et al., 2013).

Other study showed that the treatment with curcumin reduced lipid peroxidation and increased levels of superoxide dismutase, glutathione peroxidase, catalase, and protected the intestine from methotrexate-induced damage in an animal model due to the antioxidant properties of this compound (Moghadam et al., 2013).

Turmeric may reduce the abnormal transport function of the SLC22A4 503F variant (Authenticated cell lines Flp-In ™ 293 (Flp293) and 293 / TLR4-MD2-CD14) and may increase the activity of the IL-10 promoter variant having reduced activity in IBD (McCann et al., 2014).

Mayura, et al. (2014) studied culture of differentiated human colon cancer cells (Caco-2 cells), and treated with IL-1β, TNF-α, IFN-γ and LPS for 24, 48, 72 and 96 hours. Differentiated cells were treated with 65 μM of active curcumin for four hours and found that it can modulate intestinal inflammation by downregulation of iNOS induction both in transcription and translation factors, leading to a decrease in NO (nitric oxide) production.

Kim et al. (2016) studied the effects of Curcuma in lesions of gastric mucosa of Spray-Dawley rats with gastric ulcerations induced by naproxen and showed that curcumin blocks gastric ulceration formation and prevents lipid peroxidation and the activation of enzymes that damage the epithelium.

Bastaki et al. (2016) used curcumin powder (1, 10, and 100mg/kg/day) in an animal model of IBD before and after induction and observed a reduction of macro and microscopic ulcers; reduction of IL-23, myeloperoxidase, and GSH (reduced glutathione peroxidase). They also observed an increase in the body weight and reduction of oxidative stress related to colitis.

Intestinal epithelial cells (HT29 lineage) from humans submitted to IFNγ stimulation (to reproduce damage in the intestinal epithelium) were pre-treated with curcumin and resulted in a reduced rate of cellular apoptosis and IL-7 production, and negatively interfered on the phosphorylation of proteins in inflammatory signaling cascade (Longanes et al., 2017).

In table 1 we may find the results of the selection of articles described in the Methods section. We may observe with these studies that curcumin may produce several benefits in the outcomes presented by patients with IBD. The use of curcumin produces benefic effects by oral administration alone, in combination with other components, stabilized in nanoparticle technology or even in enemas. These studies indicate that are necessary new curcumin delivery technology in order to improve its bioavailability what would bring a new horizon in the treatment of patients with IBD. Furthermore, the studies found to perform this review reveal that only curcumin has been used to the therapeutic approach of IBD once we did not find studies with bisdemethoxycurcumin and demethoxycurcumin to treat or prevent UC or CD.

Conclusion

The incidence of IBD is growing sharply in many countries, and there is an urgency to find an appropriate therapeutic approach to improve quality of life of patients. The available medications commonly used are associated with high costs and several side effects. On the other hand, the use of curcumin is cheap, efficient and associated with no side effects. For these reasons, it may become an alternative or an adjuvant in the treatment of IBD once it may reduce the inflammatory process and oxidative stress that is associated with the primary symptoms related by the patients.

Conflict of Interests

Authors declare no conflict of interests.

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Figure legends

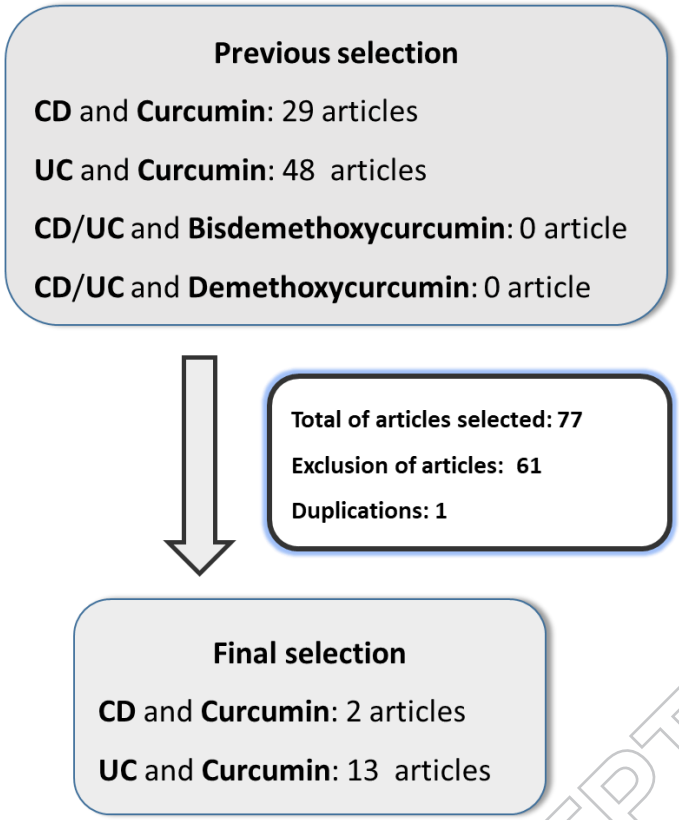

Figure 1. Flow diagram demonstrating the selection of the studies involving Crohn's Disease and Ulcerative Colitis and the curcuminoids (curcumin or diferuloylmethane, bisdemethoxycurcumin, and demethoxycurcumin).

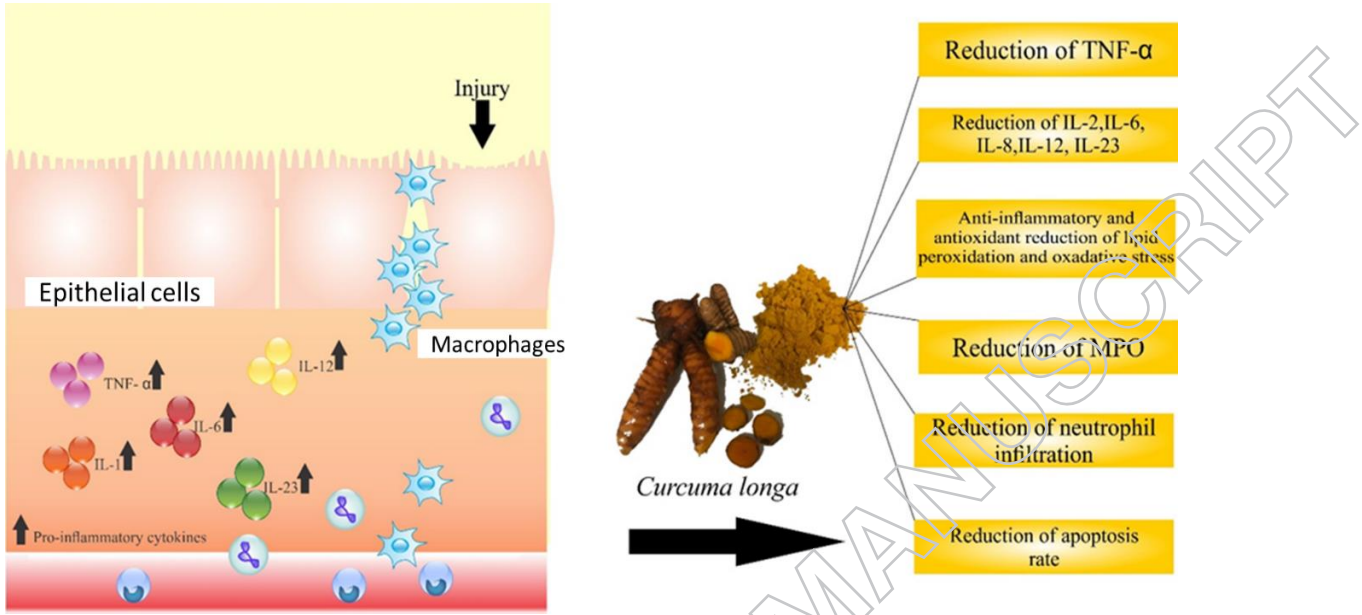

Figure 2. The injury of the epithelial cells and the inflammatory appearance of the intestine of individuals with Inflammatory Bowel Disease are characterized by the increase in the pro-inflammatory cytokines such as TNF-α (Tumor Necrosis Factor-α), IL-1 (Interleukin-1), IL-6, IL-12, and IL-23.

Table 2. Main aspects of the use of curcuminoids in animal models for UC and humans with Inflammatory Bowel Diseases.

Reference	Model	Methods	Main results	Other relevant comments
Gopi et al., 2017	Wistar rats (colitis induced by dextran sulfate sodium (DSS).	After induction of colitis, animals were treated with a product named GHP (that contains Asafoetida and turmeric). The index of disease activity was evaluated by stool formation weight loss and fecal occult blood.	Colitis score, myeloperoxidase (MPO) and histopathology GHP effectively improved the characteristic symptoms of UC and histological scores. Reduced inflammation and preserved intestinal integrity.	GHP may work as an effective therapeutic approach for UC.
Chen et al., 2017	Macrophages.	Use of non-porous curcumin (CUR)-loaded polymeric nanoparticles (NPs) and porous CUR-loaded polymeric NPs.	Cells showed time-dependent accumulation of NPs for the initial two h of incubation. The porous NPs inhibited the production of the TNF-α, IL-6 and IL-12, and reactive oxygen species with more	Oral administered porous NPs exhibited superior therapeutic efficiency in reducing UC suggesting that porous polymeric NPs may become an alternative and efficient drug

			efficiency when compared to non-porous NPs.	carrier for the treatment of UC.
Huang et al., 2017	Sprague–Dawley rats/model of UC.	Animals were divided into groups normal, sulfasalazine, model, and curcumin plus soy oligosaccharide for four weeks.	UC model showed the worst scores for histological injury and macroscopic damage of colonic mucosa. TNF-α and IL-8 reduced significantly in curcumin group compared with the UC model and similar to sulfasalazine.	The use of curcumin plus soy oligosaccharide reduced the expression of TNF-α and IL- 8 and decreased the inflammation in the colonic mucosa and tissue damage.
Yang et al., 2017	Sprague–Dawley rats/model of UC / induction with dextran sodium sulfate (DSS).	Curcumin (20, 60 mg/kg) was orally used once/d/10 days, starting from the 3rd day after induction of UC.	Curcumin inhibited the augment in abdominal withdrawal reflex score. A significant augment in colonic TRPV1, and pTRPV1 expression was observed in DDS rats but was reversed by oral administration of curcumin.	Oral use of curcumin reduces visceral hyperalgesia UC model rats in part. Through the downregulation of the colonic expression and TRPV1 phosphorylation.

Rachmawati et al., 2017	Wistar rats model for UC (induction withTNBS: 2,4,6-trinitrobenzene sulfonic acid).	Animals were separated into two groups, and treated with TPGS-stabilized curcumin nanosuspension or TPGS-curcumin suspension orally (10 mg/kg).	The use of stabilized curcumin nanoparticles showed higher local anti-inflammatory actions in UC due to the shift of parameters to a similar pattern found in the health status.	The improvement of anti-inflammatory actions of the stabilized curcumin nanoparticle was obtained with a very low dose that would be a promise alternative approach to improve the actions of curcumin.
Kadri et al., 2017	Rats submitted to a proximal colostomy and distal colonic fistulation.	Animals were subjected to application of enemas with saline or an oily curcumin extract (50mg/kg/d or 200 mg/kg/d. UC was seen with histological analysis.	Enemas with curcumin improved inflammatory process of the mucosa, decrease the tissue contents of myeloperoxidase (same results for the two concentrations).	Enemas containing curcumin improved the inflammatory process of the colonic mucosa, decreased the inflammatory grade, and myeloperoxidase in colon segments without a faecal stream.
Xiao et al.,	*In vitro:* Colon-26	Deliver of CD98 siRNA	Use of CD98 siRNA (siCD98) plus	Co-delivered siCD98 plus CUR

2016	cells and Raw 264.7 macrophages; *In vivo:* mice/induction of UC with Dextran sulphate sodium.	(siCD98) plus curcumin using hyaluronic acid - functionalized polymeric nanoparticles (NPs) that are capable of guiding the drugs to the targeted cells linked to UC therapy (macrophages and colonic epithelial cells).	curcumin using hyaluronic acid - functionalized polymeric NPs may bring combinational actions against UC due to the reduction of inflammation and protection of the mucosal layer *in vitro* and *in vivo.*	is a structurally simple way for drugs orally administered targeting cells in UC therapy.
Zhao et al., 2016	Male C57BL/6 mice/induction of colitis with 2, 4, 6-trinitrobenzene sulfonic acid (TNBS)/ethanol solution.	Mice were separate in the groups: normal, TNBS + Curcumin, TNBS + mesalazine and TNBS. Inflammation scores and cytokines, and costimulatory molecules (CD205, ICAM-1, TLR4, CD252, RANK and	Curcumin reduced: weight loss, inflammatory injury in the colonic mucosa, and histological scores. It also restored the colonic length, increased the number of Treg cells and strongly inhibited the release of TNF-α, IL-2, IL-6, IL-12 p40, IL-17 and IL-21 and the expression of	Curcumin highly modulates activation of DCs and increase the suppressive functions of Treg cells and lead to the recovery of damaged colonic mucosa in the animals.

		RANK L were evaluated.	costimulatory molecules.	
Yildrim et al., 2016	Balb/C mice/induction of colitis with DSS.	Curcumin and sulfasalazine were mixed in olive oil (100 mg/kg/mouse) resulting in the therapeutic group and the prophylactic group (evaluation of curcumin prophylactic effects on the occurrence of acute colitis).	Prophylactic use of curcumin led to effects on the activity of serum and liver paraoxonase, erythrocyte carbonic anhydrase activity, and b-glucosidase activity.	In the in the prophylactic group, the body weight loss and the shortening of the colon length was less than in the therapeutic group.
Li et al., 2015	BALB/c mice / Induction of colitis with DSS.	Groups were divided in control; model; dexamethasone, and groups that received curcumin 15, 30, and 60 mg/kg.	Levels of TNF-α, myeloperoxidase, and p38MAPK significantly reduced in the groups treated with dexamethasone and curcumin.	Curcumin produced a therapeutic effect on the UC mice models possibly due to the inhibition of p38MAPK signaling pathway, (reducing TNF-α).

Lang et al. 2015	Fifty patients with active mild to moderate UC treated with mesalazine and that was irresponsive to 2 additional weeks of the maximum dose of this drug orally used and topical therapy.	Irresponsive patients treated with 5-aminosalicylate (5ASA)and topical therapy were divided into groups that received curcumin (3g/day) or placebo/30 d, and continued 5ASA. Clinical remission and endoscopic responses were recorded.	From the patients that received curcumin, 53.8% achieved clinical remission at week 4; 65,3% achieved clinical remission and 38% endoscopic remission, compared to none of the placebo group. For these reasons, curcumin may be a safe and promising agent for treatment of UC.	Curcumin may be an important and safe therapy for UC.
Fontani et al., 2014	Intestinal subepithelial myofibroblasts (ISEMFs) from CD patient	Evaluation of the effects of N-acetylcysteine and curcumin.	ISEMFs are linked to the high oxidative pattern in the higher MMP-3 production in intestinal mucosa of CD patients. N-acetylcysteine and curcumin leads	Curcumin and N-acetylcysteine exhibits direct action on transcriptional factors and could be used in the prevention or in the treatment of fistulaes

	colon		the levels of MMP-3 to normal mainly in the cells stimulated by TNFα.	in CD.
Singla et al., 2014	Forty-five patients with mild-to-moderate UC.	Patients received oral 5-ASA plus standardized preparation of curcumin enema or oral 5-ASA, and placebo enema Disease scores were evaluated.	A positive response was seen in 56.5% in the curcumin group and 36.4% in the placebo group. At week 8: clinical remission was seen in 43.4% in Curcuma group (22.7% in placebo group); endoscopy improvement was seen in 52.2% in Curcuma group (36.4% in placebo). In clinical response: 92.9% in Curcuma group and 50% in placebo.	Results show that the use of Curcuma enema may improve overall UC scores when comparing to placebo.
Liu et al., 2013	BALB/c mice / Induction of colitis	Curcumin was used and evaluation of the disease	Curcumin promoted significant improvement in DAI and in the	The benefits produced by curcumin in a colitis model is

	with DSS.	activity index (DAI) and histological score, DNA-binding activity of STAT3 dimers, the activity of myeloperoxidase and expression of TNF-α and IL-1β was performed.	histological score and reduced the DNA-binding activity of STAT3 dimers, myeloperoxidase activity, and expression of TNF-α and IL-1β.	due to the downregulation of STAT3 pathway. Curcumin is a well-tolerated, cheap, and may become an effective therapeutic for UC.
Suskindet al., 2013	Pediatric patients with CD or UC (remission or with mild disease)	Children received curcumin and standard therapy (initially received 500mg 2x/day/3 weeks and then, 1g 2x/day/3 weeks. Then patients received 2g 2x/day/3 weeks.	Curcumin was well tolerated and lead to reduced PUCAI or PCDAI scores.	Turmeric may help individuals with IBD.

UC: Ulcerative Colitis; CD: Crohn's Disease; IFNγ: Interferon gamma; IBD: Inflammatory Bowel Disease; IL: Interleukin; TNF-α: Tumor Necrosis Factor-alfa; TRPV: transient receptor potential vanilloid; ICAM: Intercellular Adhesion Molecule; RANK: Receptor activator of

nuclear factor kappa-B; RANKL: Receptor activator of nuclear factor kappa-B ligand; TLR: Toll like Receptor; PUCAI: Pediatric ulcerative colitis activity index; PCDAI: Pediatric Crohn's Disease Activity Index; MAPK: mitogen-activated protein kinase.