Clinical and Endoscopic Improvement of Inflammatory Bowel Disease with Curcumin Therapy: Experiences from Clinical Studies

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ABSTRACT

Inflammatory bowel disease, including Crohn's disease and ulcerative colitis, is a chronic inflammatory condition of the intestine and one of etiological factor for colon cancer development. Incidences of inflammatory bowel disease is still high around the world, even with current therapy, emerging the need for innovational approach to increase the achievement of disease improvement and remission. Curcumin is a natural compound derived from Curcuma longa and has been well known with its anti-inflammatory properties which is possible to be beneficial for inflammatory bowel disease. This review aims to provide clinical evidences of effectively and safety profile of curcumin in treating inflammatory bowel disease, both Crohn's disease and ulcerative colitis, and viewing the future prospect of curcumin to be an effective adjuvant therapy to prevent the relapse of inflammatory bowel disease.

Keywords: *curcumin, inflammatory bowel disease, Crohn's disease, ulcerative colitis*

ABSTRAK

Penyakit radang usus, termasuk penyakit Crohn dan kolitis ulserativa, adalah kondisi peradangan kronis pada usus dan salah satu faktor etiologi perkembangan kanker usus besar. Insiden penyakit radang usus masih tinggi di seluruh dunia, bahkan dengan pengobatan yang ada saat ini, sehingga muncul kebutuhan akan pendekatan inovatif untuk meningkatkan pencapaian dalam perbaikan dan remisi penyakit. Kurkumin adalah senyawa alami yang berasal dari Curcuma longa dan telah dikenal dengan sifat anti-inflamasinya yang mungkin bermanfaat untuk penyakit radang usus. Ulasan ini bertujuan untuk memberikan bukti klinis profil efektif dan keamanan kurkumin dalam mengobati penyakit radang usus, baik penyakit Crohn dan kolitis ulserativa, serta melihat prospek masa depan kurkumin menjadi terapi adjuvant yang efektif untuk mencegah kekambuhan penyakit radang usus.

Keywords: *kurkumin, penyakit radang usus, penyakit Crohn, kolitis ulserativa*

INTRODUCTION

Inflammatory bowel disease (IBD) is chronic idiopathic relapsing inflammatory condition which affecting the intestinal tract.[1–3] Pathologically, this disease is marked by inflammation of the intestinal and epithelial injury.[3] IBD has been a world-wide health challenge and has emerged with its continuous increasing incidences.[1,4] Prevalence of IBD is variable between countries around the world.[4–7] In 2015, there were 3 million people that were estimated suffered from IBD in United States, while North America and Europe reported 1.5 and 2 million people suffered from this disease in 2013.[4,5] Meanwhile, IBD prevalence in Asia is varies beyond the countries.[6] Totally, there are more than 6.8 people living with this disease worldwide.[7]

IBD has unknown exact cause with multiple predisposing factors, but genetics and environment are the two most attributable factors of IBD.[8,9] Several predisposing factors which involving in IBD including genetic, gut dysbiosis, smoking, nutrition and diet, environmental pollution, and psychological stress.[8–20] Several genes have been discovered to be associated with IBD, such as NOD2, CARD9, CARD15, ATG16L1, IRGM, IL-23R, IL-12B, STAT3, MUC2, IL-10R, IL-10, XIAP, etc. Genes polymorphism which contributes to IBD are very significant of each other, but they are commonly related to inflammatory pathways of the disease.[9,13,14] Besides genes, IBD was also found to be correlated with ethnical factors, where certain ethnicities shows higher incidences of IBD while other ethnics shows the opposite.[15] Gut microbiota composition and its relation with IBD has been proven in many studies where dysbiosis is seem to be associated with intestinal inflammatory conditions.[16–19] Dysbiosis is linked with IBD by some mechanism such as immune alteration, T-helper cells imbalance, fermentation products alteration, and biochemical processes disruption.[10,20] Antibiotics use is also related to IBD and its subtypes, especially systemic antibiotics, probably due to its effect to gut microbiota.[11] In addition, psychological stress also contributes symptoms exacerbations of IBD because of its role in lowering intestinal pain thresholds, thus enhancing pain sensation and disrupting mucosal barrier function.[12]

IBD comes with varies clinical manifestations, depends on its subtypes.[21–25] Ulcerative colitis usually manifests with tenesmus especially in left lower quadrant though along of entire colon area can be found in patients with pancolitis, accompanied by defecation urgency, and commonly bloody diarrhea. Fever and peritoneal signs can be present as alarm sign in poor prognosis cases.[21–23] Different with ulcerative colitis, Crohn's disease often comes with watery diarrhea, colicky abdominal pain, and perirectal ulcers. Bleeding was less frequent in Crohn's disease.[21,22,24] Common abdominal complaints is also the same with pediatric IBD, but growth failure can happened.[25] Besides clinical examination, endoscopy is very important as diagnostic approach for IBD. Endoscopic findings that are typical for IBD are mucosal inflammation, vascular abnormality, erythema, ulcerations, edema, and pseudo-polyp formation. Endoscopic findings then will be scored to determine the severity of the disease.[26,27] As continuation to endoscopic approach, a histopathological study is usually performed to confirm the diagnosis of IBD, with typical findings of crypt abnormality, inflammatory cells infiltration, paneth cells metaplasia, and gland metaplasia.[28] In addition, laboratories examination including C-reactive protein (CRP) and fecal calprotectin also radiology modalities such as magnetic resonance (MR) can also be utilized as helpful diagnostic and controlling tools for IBD.[29–33] The nature of IBD that often recurs with increasing incidence have emerged the need of a safe and effective adjuvant therapy that can increase achievement of the disease improvement and remission for the patients, as an addition to the main therapy.[1–7] Recently, curcumin, a compound derived from *Curcuma longa*, has been well known for decades of having many benefits for several disease, including anti-inflammatory properties.[34,35] This study is aimed to provide clinical evidences of curcumin effectivity in improving IBD outcome, both clinically and endoscopically.

CURCUMIN AND ITS EFFECTS TO PATHOGENESIS OF INFLAMMATORY BOWEL DISEASE

In IBD, macrophages are upregulated due to dysregulated some signaling pathways, leading to increased pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6; leucocytes attracting chemokines such as IL-8; monocyte chemoattractant proteins (MCPs); and macrophage inflammatory proteins (MIPs). Various kinds of leucocytes such as monocytes, neutrophils, and T-cells then recruited due to leucocytes attracting molecules such as MCPs, IL-8 and macrophage-related-cytokines. Macrophages-derived-TNF-α can also induce expression of adhesion molecules that are responsible for recruitment and activation of lymphocytes to the inflammation areas. Antigen presenting cells (APC) which is dominated

by dendritic cells also penetrates the mesenteric lymph nodes, driving macrophages proliferation and T-lymphocytes differentiation into several subsets such as Th1, Th17 in Crohn's disease and Th2, Th9, Th17 in ulcerative colitis. Increased levels of IFN-γ, TNF-α, and IL-2 then be found in Crohn's disease lesion due to Th1 activity. On the other hand, tissue destruction is detected in ulcerative colitis as an impact of released IL-13 from Th2 which increase intestinal cells apoptosis, as well as IL-9 that produced by Th9 which responsible for barrier dysfunction. In both Crohn's disease and ulcerative colitis, there is also Th17 that secretes IL-17 which also contributes to intestinal inflammation.[36] Interestingly, some studies have demonstrated curcumin ability in decreasing some of these cytokines, including IL-1β, IL-6, TNF-α, IFN-γ, IL-13, and IL-17, reflecting the anti-inflammatory properties of curcumin.[37–46] These findings are possibly related to curcumin effect in regulating levels of leucocytes which produce the pro-inflammatory cytokines, such as macrophage, neutrophil, Th1, Th2, and Th17, that are also observed in several experiments.[39,40,42,44,47–51]

Anti-inflammatory effects of curcumin may be possible explained with its ability in regulating several signaling pathways. TLR-4, NF-κB, and AP-1 are signaling pathways which are dysregulated in IBD. TLR-4 plays an important role for immune cells in marking the self and non-self-molecules, while upregulating NF-κB and AP-1, which occurred in both intestinal and immune cells. TLR-4 pathway is also responsible for maturation of dendritic cells and differentiation of Th1 and Th2. TLR-4 signaling pathway also modulate macrophage differentiation to M1 phenotype which are typical with pro-inflammatory cytokines production. Together with TLR-4, NF-κB is also an important and dominant transcription factor that involved in inflammatory bowel disease. Binding of NF-κB to DNA promoter will initiate inflammatory genes transcriptions, leading to releasing of several cytokines from leucocytes such as IL-1β, TNF-α, IL-12, inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), IL-6, and IL-23. NF-κB is found in both intestinal epithelial and immune cells. In addition, AP-1 is also one of important signaling pathway in pathogenesis of IBD. Resemblant with NF-κB, binding of several families of AP-1 can regulates expression of several genes related to pro-inflammatory cytokines and even matrix metalloproteinases (MMPs). This pathway is active in both intestinal epidermal cells and immune cells, influencing intestinal healthy and gut microbiota balance. Under certain circumstances including inflammatory bowel disease, these signaling pathways can be dysregulated, resulting in imbalance of pro-inflammatory cells and their-related-cytokines.[36] Surprisingly, some experiments have revealed curcumin capability in regulating TLR-4, NF-κB, and AP-1 signaling pathways in inflammatory conditions, providing explanation anti-inflammatory properties of curcumin.[52–58]

ANTIOXIDANT AND INTESTINAL PROTECTIVE EFFECT OF CURCUMIN

Tissue injury of intestinal mucosa is closely related to the role of oxidative stress. Normally, nitric oxide act as a protective substance for intestinal mucosa, as long as its level is within physiological limit, but in case of IBD, nitric oxide is produced in a large amount, due to upregulation of iNOS and potentially endothelial nitric oxide synthase (eNOS). Together with reactive nitrogen species (RNS), reactive oxygen species (ROS) is also generated continuously in IBD, leading to membrane peroxidation, DNA injury, and cellular proteins denaturation, resulting in tissue damage.[36] In several studies, curcumin was found to controlling oxidative stress in some inflammatory conditions, including colitis, by various mechanism, either by inhibiting iNOS and neutrophils, and by upregulating antioxidant enzymes production.[59–61] These findings have become indication of intestinal protection properties of curcumin against oxidative stress which is beneficial for endoscopic improvement and remission.

CLINICAL IMPROVEMENT OF INFLAMMATORY BOWEL DISEASE WITH CURCUMIN THERAPY

Several studies, including randomized control trials, have provides proofs of clinical improvement with curcumin therapy, both as single therapy or as adjunctive to standard therapy regiment, for both ulcerative colitis and Crohn's disease. Clinical parameters that used was variable beyond the studies, varies from SCCAI, CDAI, UCDAI, and IBDQ-9, PUCAI, PCDAI.[62–67]

The effect of curcumin therapy in inducing clinical remission for patients with ulcerative colitis was studied by Lang et al. In their randomized control study, 18-70 years old patients with ulcerative colitis diagnosis were included. The patients then randomly divided into two groups. One group achieved combination

therapy of curcumin and mesalamine, while another group was given combination of mesalamine and placebo. In the end of the fourth week, the study was ended and the simple clinical colitis activity index (SCCAI) score was counted between the two groups to compare the difference between two groups from the beginning of the study until the end of the study. The intention to treat (ITT) analysis results showed that 14/26 (53.8%) of the patients from the curcumin groups achieved clinical remission (SCCAI score value ≤ 2), while none of the patients from placebo group achieved the same result with the curcumin group ($p = 0.01$). Clinical improvement (defined as a reduce of ≥ 3 points of SCCAI score) was shown in 65.3% (17/26) patients from curcumin groups compared to placebo groups where clinical improvement only achieved by 12.5% (3/24) patients (p value < 0.001). Per protocol analysis (PP) results exhibited more significant differences between these two groups. A total of 14/25 (56%) patients from curcumin group attained clinical remission, while none of the patients from placebo group achieving it ($p < 0.01$). Clinical improvement was also reached by more patients from curcumin group (17/25 or 68%) compared to placebo group (3/22 or 13.6%) ($p < 0.01$).[62]

Similar with Lang et al, clinical improvement effect of curcumin was also found by Masoodi et al in their randomized control study. The study was conducted for 4 weeks. The 56 patients with mild to moderate ulcerative colitis was involved in their study and was randomly grouped into case group which was given combination therapy of curcuminoid nanomicelles 80 mg three times daily and mesalamine 3 grams per day; and placebo group that received placebo together with mesalamine 3 grams daily. The SCCAI score was assessed in the baseline and in the end of the study to determine clinical improvement of the patients. In the end of the study at the fourth week, the defecation urgency was found to be reduced significantly in case group compared to placebo group, though there was no significantly reduction in bowel habit, stool blood, frequency, and other clinical symptoms. The general condition and main SCCAI was found to significantly better in curcumin group than the placebo group at the fourth week. Generally, the patients that given curcumin experienced better clinical outcome which was measured with SCCAI after four weeks therapy with curcumin compared to patients receiving placebo.[63]

Table 1. Clinical, endoscopic, and laboratory improvement of inflammatory bowel disease after curcumin therapy

No	Study	Population	Intervention	Comparison	Outcome
1	Lang et al, 2015	Fifty patients with active mild-moderate ulcerative colitis who didn't respond to 2 weeks therapy of maximal dose 5-ASA and topical therapy	Combination of oral curcumin capsules and 5-ASA	Combination of identical oral placebo and 5-ASA	Higher proportion of participants from curcumin group achieved both clinical and endoscopic remission and improvement compared to placebo group ($p < 0.01$)[62]
2	Masoodi et al, 2018	Fifty-six patients with mild to moderate ulcerative colitis	Combination of curcumin and mesalamine	Combination of placebo and mesalamine	Better general condition and significantly improvement of SCCAI score in curcumin group compared to placebo group ($p = 0.05$)[63]
3	Sadeghi et al, 2020	Seventy patients with mild to moderate	Curcumin supplementation	Placebo	Significant improvement in SCCAI score ($p = 0.001$), IBDQ-9 score ($p = 0.006$), hs-CRP concentration ($p = 0.01$), and ESR level ($p = 0.02$)[64]
4	Singla et al, 2014	Ulcerative colitis patients with mild to moderate disease activity	Curcumin enema and oral 5-ASA	Placebo enema and oral 5-ASA	Significantly better outcomes in clinical response ($p = 0.01$), clinical remission ($p = 0.03$), and mucosal healing in endoscopic examination ($p = 0.04$)[65]
5	Sugimoto et al, 2020	Patients with active mild to moderate Crohn's disease from 5 independent medical centers	Addition of curcumin to the established standard therapy	Administration of placebo to the established standard therapy	Significantly lower CDAI score in curcumin group ($p = 0.035$), reduction of stool frequency and abdominal pain in curcumin group, and significantly decreased SESCD score in curcumin group ($p = 0.032$) vs in placebo group ($p = 0.220$)[66]
6	Suskind et al, 2013	Children with Crohn's disease or ulcerative colitis	All patients received addition of oral curcumin to the standard therapy	None	Better improvement in PUCAI and PCDAI score. Some of patients achieved clinical remission

5-ASA: 5-aminosalycilate, SCCAI: simple clinical colitis activity index, IBDQ-9: the 9-item inflammatory bowel disease questionnaire, hs-CRP: high-sensitivity C-reactive protein, ESR: erythrocyte sedimentation rate, CDAI: Crohn's disease activity index, SESCD: simple endoscopic score for Crohn's disease, PUCAI: pediatric ulcerative colitis activity index, PCDAI: pediatric Crohn's disease activity index

Curcumin supplementation alone has also exhibited clinical restoration capability for patients with ulcerative colitis. A randomized control trial conducted by Sadeghi et al was able to proof that curcumin supplementation alone can resulting in larger number of participants achieving clinical remission (83.9% patients) compared to placebo (43.8% patients), measured using SCCAI. Clinical improvement which was determined by drop of SCCAI score for 3 or more points was also found in 93.5% patients treated with curcumin, while only 59.4% of placebo-treated patients get this clinical achievement. The 9-item inflammatory bowel disease questionnaire (IBDQ-9) parameter was also higher in curcumin group than the placebo group in their study.[64]

Clinical enhancement was not only found by administration of oral preparation of curcumin, but also in the enema administration of curcumin. As many as 45 patients with mild to moderate distal ulcerative colitis were included in a study by Singla et al and randomized into two different groups that received different kinds of enema; curcumin enema for one group and placebo enema for another group. Both groups were also treated orally with mesalamine 800 mg twice daily during the 8 weeks study. The ulcerative colitis disease activity index (UCDAI) score was used as measurement tool in assessing clinical progression between the two groups. At the end of the study, intention to treat analysis presented 56.5% (13/23) patients from enema curcumin group achieved clinical respond to treatment, while only 36.4% (10/23) patients in placebo group achieved it. Clinical remission was also reached by more patients from curcumin group (43.5%) than patients from placebo group (22.7%). Meanwhile, per protocol analysis showed more significant differences between clinical improvement of these two groups. Proportion of patients who achieved clinical improvement was significantly higher (92.9% or 13/14) for curcumin group, while only 50% (8/16) patients from placebo group achieved the same outcome ($p = 0.01$). The same significant difference was also observed in 71.4% (10/14) patients from curcumin group who achieved clinical remission compared to 31.3% (5/16) patients from placebo group ($p = 0.03$).[65]

Besides enhancing clinical outcome for ulcerative colitis, curcumin is also proven to inducing clinical improvement in Crohn's disease patients. Sugimoto et al proofed that adding curcumin to standard therapy for Crohn's disease patients was able to lowering the Crohn's disease activity index (CDAI) score compared to standard therapy only. Their randomized control study reported significantly higher proportion of patients reaching disease remission (CDAI < 150) in curcumin group compared to standard therapy group. Besides CDAI, reduction of stool frequency and abdominal pain parameters after adding curcumin to the therapy was also observed in the study, indicating the effectivity of curcumin in improving clinical outcome of Crohn's disease.[66]

Not only for adults, curcumin effectivity in inducing clinical improvement was also observed in pediatric population. An experimental study by Suskind et al provided the evidence of better clinical outcome by adding curcumin to the standard treatment of children with both ulcerative colitis or Crohn's disease, marked by lower pediatric ulcerative colitis activity index (PUCAI) and pediatric Crohn's disease activity index (PCDAI) score. Beyond the children with ulcerative colitis, two of them reached even clinical remission after receiving curcumin, providing the clinical evidence of curcumin effectivity as adjunctive inflammatory bowel disease therapy in pediatric population.[67]

CURCUMIN INDUCING INTESTINAL MUCOSA IMPROVEMENT ON INFLAMMATORY BOWEL DISEASE, AN ENDOSCOPIC APPROACH

Curcumin has been proven not only affects IBD improvement clinically, but also endoscopically. Several clinical trials have been conducted to study the effect of curcumin for endoscopic improvement on patients with inflammatory bowel disease, using some parameters, including disease activity index/ Mayo score and simple endoscopic score for Crohn's disease (SESCD).[62,65,66]

In a randomized placebo-controlled trial in 2015, Lang et al demonstrated endoscopic improvement on ulcerative colitis after oral curcumin therapy, where patients with mild to moderate ulcerative colitis from different medical centers from three different countries were included into the study and were divided into two group with different therapy: curcumin plus 5-aminosalycilate (5-ASA) combination for curcumin group; and placebo plus 5-ASA for control group. Sigmoidoscopy was performed to consenting patients and Mayo score was measured in the baseline and in the end of the study. The study results revealed that 8/22 (36.3%) of patients in curcumin group achieved endoscopic remission (defined as drop of Mayo score to 0 or 1), meanwhile there were no patients who received placebo reached endoscopic remission in the

end of the study. Endoscopic improvement (drop of ≥ 1 points of Mayo score) was reported in 10/22 (45.4%) in participants receiving curcumin, where 0/16 (0%) of patients in placebo group achieved ≥ 1 points drop in Mayo score.[62]

Singla et al also stated that curcumin enema was also able to heal the mucosa lesion of patients with distal ulcerative colitis. ITT analysis of the randomized placebo-controlled trial showed 52.2% (12/23) of respondents that given curcumin enema as addition to their mesalamine oral reached mucosal healing endoscopically, where only 36.4% (8/22) patients from placebo group experienced mucosal healing in endoscopy examination. More significant difference was presented by the PP analysis, where mucosal improvement was observed in 85.7% (12/23) patients from curcumin group and 50% (8/22) participants from placebo group ($p = 0.04$).[65]

Furthermore, curcumin also exhibited therapeutical effect endoscopically for Crohn's disease cases that has been proven in a randomized control study by Sugimoto et al in 2020. The SESCD score was significantly decreased at the end of the 12th week of the study in group receiving curcumin therapy ($p = 0.032$) but not in participants receiving placebo ($p = 0.220$). Higher amount of participant achieving endoscopic remission (defined as SESCD value ≤ 4) was also reported from curcumin group (15%) than in placebo group (0%).[66]

REDUCED CLINICAL INFLAMMATORY MARKERS DUE TO CURCUMIN EFFECT

Besides giving better outcome both clinically and endoscopically, curcumin administration was also leading to improvement of laboratory aspect for patients with IBD. This finding was obtained in a trial where 70 participants with mild to moderate ulcerative colitis was randomly given 1500 mg curcumin once daily or placebo orally. The venous blood then was collected from the participants before and after the treatment in order to assess the levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and TNF-α while evaluating the complete blood counts. In the end of the trial at the 8th week, levels of ESR were found reduced significantly compared to in the beginning of the study in both curcumin group ($p = 0.02$) and placebo group ($p = 0.01$). Unsimilar to ESR, significant decreased of CRP was observed only in curcumin group (p value = 0.02 in PP analysis and p value = 0.01 in ITT analysis), where there is no significant decreased of CRP in placebo group. Decreased TNF-α was also found in curcumin group in both PP and ITT analysis while increased of TNF-α was found in placebo group in both PP and ITT analysis, although the difference is not significant.[64]

Table 2. Curcumin effects on inflammatory bowel disease pathophysiology pathway

No	Studies	Results
1	Zhang et al, 2016	Curcumin pretreatment inhibit levels of TNF-α and IFN-γ while increasing levels of IL-10[37]
2	Ali et al, 2018	Curcumin was able to reduce to level of inflammatory cytokines IL-1β, IL-6 and TNF-α[38]
3	Bakir et al, 2016	Curcumin can control the levels of IL-17 and IL-23[39]
4	Chen et al, 2018	Curcumin can ameliorate IL-13 production and controlling the activity of Th2 signaling pathway[40]
5	Saadati et al, 2019	Curcumin supplementation was associated with significant decrease in tumor necrosis-α (TNF-α)[41]
6	Sharma et al, 2020	Curcumin treatment was able to depress the expression of Th2 cytokine IL-13[42]
7	Silva et al, 2017	Curcumin suppresses IL-1b and IL-6 in plasma[43]
8	Skyvalidas et al, 2020	Curcumin attenuates pro-inflammatory interferon-γ and interleukin 17[44]
9	Wang et al, 2021	Curcumin has protective effect to intestinal epithelial cells by inhibiting IL-6/STAT3 signaling pathway[45]
10	Yin et al, 2018	Curcumin suppresses IL-1β secretion[46]
11	Yeh et al, 2020	Curcumin have attenuating effect to neutrophil infiltration in dependent dose manner[47]
12	Antoine et al, 2013	Curcumin has ability in inhibiting lipopolysaccharide-induced neutrophilic infiltration in vivo[48]
13	Gong et al, 2018	Curcumin alleviates IL-1β production in DSS-induced colitis experiment[49]
14	Nonose et al, 2014	Oral administration of *Curcuma longa* inhibits the inflammatory response of the neutrophil[50]
15	Wang et al, 2019	Curcumin attenuates macrophage inflammatory response by inducing macrophage apoptosis[51]
16	Kumari et al, 2019	Regulatory effect of curcumin to TLR-4 and MMP-9[52]
17	Tu et al, 2020	Curcumin can regulate Toll-like receptor 4 and 2 expression[53]
18	Wang et al, 2020	Curcumin ability in inhibiting the TLR4/NF-κB signaling pathway[54]
19	Buhrmann et al, 2021	Anti-inflammatory property of curcumin by attenuating Sox9/NF-kB signaling axis[55]
20	Ghasemi et al, 2019	Curcumin was able to inhibits the NF-kB signaling pathway[56]
21	Chu et al, 2015	AP-1-regulatory effect of curcumin[57]
22	Woo et al, 2020	Ability of curcumin in regulating AP-1[58]
23	Mouzaoui et al, 2011	Curcumin attenuated (TNF)-α-induced oxidative stress in colitis[59]
24	Lin et al, 2019	Curcumin reduce the oxidative stress by increasing the activity of antioxidant enzymes[60]

SAFETY OF CURCUMIN THERAPY FOR INFLAMMATORY BOWEL DISEASE

In this review, curcumin side effects were also reported besides its benefits. Data about the side effects of curcumin were collected from the clinical studies of curcumin therapy for both ulcerative colitis cases and Crohn's disease that have been explained in the previous parts.[62–67]

In study of Lang et al only one complaint of hospitalization due to peptic ulcer was reported from curcumin group, but the hospitalization due to peptic ulcer happened before initiation of the study medication, indicating that the peptic ulcer wasn't caused by the curcumin.[62] Side effects were also found by Masoodi et al in their randomized control study, where some of the participants complained about flatulence, increased appetite, headache, dyspepsia, nausea, and yellow stool. But the complaints were also obtained in control group which given placebo plus 5-ASA therapy with unsignificant differences between the curcumin and control groups ($p = 0.530$). No serious side effect was reported from the study.[63] Side effects of allergic skin symptoms, dyspepsia, and heartburn were also from curcumin group by Sadeghi et al but it was happened in only one participant.[64] In another randomized control trial, Singla et al also reported no serious side effects. Aggravation symptoms happened in 5 participants from curcumin group and 4 participants from placebo group but the difference was not significant between these two arms.[65] No serious adverse effect was also observed in curcumin group in Sugimoto et al study. Only one patient in that study reported symptoms of appetite loss in a very minor event that didn't interfere with the therapy.[66] In pediatric population, curcumin was also well tolerated. Only two participants complained about increase gassiness, but it felt only once and resolved by their own occurrence. The complaints were really mild, unclearly related to curcumin, and didn't need any degression of the curcumin dosage.[67]

From the clinical studies, the curcumin was well tolerable by the patients with only a few mild and unserious side effects. Overall, it can be concluded that curcumin therapy utilization as therapy for the patients with IBD is safe and well-tolerable.[62–67]

CONCLUSION

Based on data from clinical trials, curcumin therapy can be considered as an effective therapy for achieving clinical and endoscopic improvement and remission of inflammatory bowel disease, due to its anti-inflammatory and anti-oxidant mechanisms. Some side effects are reported but it remains within minimal limit.[62–67] Overall, curcumin is an effective and safe adjunctive therapy for inflammatory bowel disease.

RECOMMENDATION

Further studies are still needed to determine the ideal dosage, duration, safety, and effectivity of routine curcumin administration in preventing relapse of inflammatory bowel disease.

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