Efficacy of Curcumin as Adjuvant Therapy to Induce or Maintain Remission in Ulcerative Colitis Patients: an Evidence-based Clinical Review

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ABSTRAK

Latar belakang: *panduan tatalaksana untuk kolitis ulseratif (KU) belum tersedia. Saat ini, mesalazine, kortikosteroid, dan imunomodulator merupakan pilihan terapi untuk KU. Namun, obat-obatan tersebut memiliki efek samping yang tidak menyenangkan, misalnya mual, muntah, sakit kepala, hepatitis, dan infertilitas pria. Curcumin terdapat dalam tanaman Kunyit (Curcuma longa L.) yang memiliki aktivitas anti-inflamasi dan anti-oksidan. Artikel ini bertujuan menentukan apakah curcumin sebagai terapi adjuvan dapat menginduksi atau memelihara status remisi pada KU.* ***Metode:*** *pencarian terstruktur pada tiga database (Cochrane, PubMed, Proquest) menggunakan "Curcumin", "remisi" dan "kolitis ulseratif" sebagai kata kunci. Kriteria inklusi adalah uji klinis acak terkontrol, meta-analisis, atau review sistematis yang meneliti curcumin sebagai terapi adjuvan pada pasien KU dewasa.* ***Hasil:*** *dari 49 artikel yang ditemukan, didapatkan 3 uji klinis acak terkontrol setelah eksklusi artikel – 2 meneliti efektivitas curcumin dalam menginduksi remisi, dan 1 untuk memelihara remisi pada kolitis ulseratif. Curcumin lebih efektif secara signifikan dibandingkan plasebo pada semua uji klinis. Efektivitas curcumin dapat dijelaskan oleh aktivitas anti-inflamasi yang dimilikinya, yaitu dengan inhibisi jalur NF-kB. Regulasi keseimbangan oksidan/anti-oksidan dapat memodifikasi pelepasan sitokin. Meski demikian, metode yang digunakan bervariasi antara uji klinis satu dengan yang lain. Oleh karena itu, sulit untuk membandingkannya secara objektif. Selain itu, jumlah sampel yang digunakan juga kecil (n= 50, 45, 89), sehingga tidak terdapat kekuatan statistik yang cukup untuk mewakili seluruh populasi pasien kolitis ulseratif dewasa.* ***Kesimpulan:*** *studi yang ada menunjukkan bahwa curcumin memiliki potensi untuk menginduksi dan memelihara status remisi pada pasien KU tanpa menimbulkan efek samping yang serius. Meski demikian, diperlukan studi lebih lanjut dengan jumlah sampel yang lebih besar sebelum curcumin dapat direkomendasikan sebagai terapi adjuvan untuk KU.*

Kata kunci: *curcumin, kolitis ulseratif, pemeliharaan, remisi.*

ABSTRACT

Background: *treatment guidelines for ulcerative colitis (UC) not yet established. Currently, mesalazine, corticosteroids, and immunomodulators are treatment options for UC. However, they are known to have unpleaseant side effects such as nausea, vomiting, headaches, hepatitis, and male infertility. Curcumin is found in Turmeric plants (*Curcuma longa L.*), which possesses both anti-inflammatory and antioxidant properties. This study aimed to determine whether curcumin as adjuvant therapy can induce or maintain remission in UC*

patients. ***Methods:*** *structured search in three database (Cochrane, PubMed, Proquest) using "Curcumin", "remission" and "Ulcerative Colitis" as keywords. Inclusion criteria is randomized controlled trials (RCTs), meta-analysis, or systematic review using curcumin as adjuvant therapy in adult UC patients.* ***Results:*** *we found 49 articles. After exclusion, three RCTs were reviewed; two examined curcumin efficacy to induce remission and one for remision maintenance in UC. Curcumin was significantly more effective than placebo in all RCTs. The efficacy of curcumin could be explained by its anti-inflammatory properties, which inhibit NF-kB pathway. Regulation of oxidant/anti-oxidant balance can modify the release of cytokines. However, methods varied between RCTs. Therefore, they cannot be compared objectively. Futhermore, the sample size were small (n= 50, 45, 89) therefore the statistical power was not enough to generate representative results in all UC patients.* ***Conclusion:*** *Available evidence showed that curcumin has the potential to induce and maintain remission in UC patients with no serious side effects. However, further studies with larger sample size are needed to recommend it as adjuvant therapy of ulcerative colitis.*

Key words: *curcumin, remission, maintenance, ulcerative colitis (UC).*

INTRODUCTION

Ulcerative colitis (UC) is an immune-mediated chronic intestinal condition that causes inflammation and ulcers on the large intestine's inner lining. It is one of the two major types of inflammatory bowel disease (IBD). The incidence of UC varies between geographic areas, the highest incidence occurs in Europe, United Kingdom, and North America; its prevalence ranges from 21.4 – 246 cases per 100,000 person per year. However, the incidence of UC is rising in regions previously thought to have low incidence, for example in Hong Kong the incidence of UC has increased six-fold in the past two decades. UC's peak age of onset is between 15 – 30 years old, and second peak occurs between 60 – 80 years old. Mortality is the highest during the first years of disease, and in long-duration disease due to the risk of colon cancer. In a large population study, the standardized mortality ratios for UC was 1.1.[1] In addition, UC also produces symptoms that impair quality of life and ability in carrying work or daily activities.[2] Therefore, an effective treatment regimen for UC is needed to relieve its symptoms and maintain disease remission.

However, treatment guidelines for UC has not been established yet. Currently, 5-aminosalicylates (5-ASA), corticosteroids, sulfasalazine (SZ), mesalazine, and immunomodulators are treatment options for patients with active UC. Nonetheless, they are known to have unpleaseant side effects such as nausea, vomiting, headaches, hepatitis, and male infertility.[3-6] Moreover, 20 – 30% patients failed to respond to the drugs given for induction of remission.[7] Hence, new alternatives for UC treatment are being sought.

Inappropriate and persistent immune response against commensal intestinal bacterial flora plays a central role in the pathogenesis of UC. There is an enhanced T-cell response to the bowel luminal contents accompanied by excessive neutrophil influx in colonic tissue, leading to uncontrolled inflammation. The role of proinflammatory cytokines interleukin (IL)-1β, IL-6, tumour necrosis factor (TNF)-α, IL-12, and interferon (IFN)-γ in initiating and sustaining the mucosal inflammation has been established in animal models as well as in human studies. Nuclear Factor kappa B (NF-κB) is the main up-regulator of expression of these cytokines, and is strongly activated in UC, suggesting important role in its pathogenesis.[1,8] Curcumin is found in Turmeric plants (*Curcuma longa L.*), which possesses both anti-inflammatory and antioxidant properties. Recently, its use for treatment of inflammatory diseases, including UC, has gained increasing interest for research. Therefore, this review is focused on curcumin's efficacy as adjuvant therapy to induce or maintain remission in adult UC patients.

METHODS

The search strategy and study selection criteria were based on problem-intervention-

comparison-outcome (PICO) model to answer the clinical question, as described in **Table 1.** Since the clinical question type is intervention, searching would be focused to find meta-analysis, systematic review, or clinical trial to answer the clinical question.

Data Sources and Search Strategy

We screened Pubmed, Proquest, and Cochrane database on June 10th – 17th, 2016 for data comparing UC standard therapy with curcumin and UC standard therapy alone. We used "curcumin", "remission", and "ulcerative colitis" as keywords. Filters were used to limit article types, which is "meta-analysis", "systematic review", "randomized clinical trial", or "clinical trial". No filter for date of publication was used, and the articles found were published between 2005 and 2015. The keywords and articles found in each search were listed in **Table 2**.

Selection Criteria

Articles included in this review were systematic review, meta-analysis, randomized clinical trial, or clinical trial comparing UC standard therapy with curcumin and UC standard therapy alone. Exclusion criteria for this review were: articles with observational design, studies using patients <18 years old, studies using pregnant patients, animal studies, studies assessing endpoint other than maintenance or induction of disease remission, and studies assessing the effects of drug other than the combination of curcumin and standard UC therapy. Articles written in languages other than English or Indonesian were also excluded. The literature screening, study selection, and reasons for exclusion were described in the flowchart (**Figure 1**). Eligible studies, which conformed to the inclusion and exclusion criteria, were assessed for their risk of bias. Publication bias was graded using the components of evidence-based medicine (EBM) toolkit recommended by the British Medical Journal (BMJ), which consist of randomization, allocation concealment, blinding of participants, and other sources of bias. The characteristics of included studies, along with potential sources of bias were summarised in **Table 3**.

RESULTS

From the 49 studies, 46 did not meet the inclusion criteria. Three RCTs were finally included in the review (**Figure 1**); two examined curcumin efficacy to induce remission and one for maintenance in UC. Curcumin as adjuvant therapy was signifiantly more effective than placebo in all RCTs (**Table 3**).

Curcumin as Adjuvant to Induce Remission in Ulcerative Colitis

Lang et al used patients with active mild to moderate UC who did not respond to maximum dose of 5-ASA oral and topical therapy; they were randomly assigned to groups given curcumin capsules (3 g/day) or placebo for

Table 1. PICO components

Problem	Intervention	Comparison	Outcome
Adult patients (>18 years old) with ulcerative colitis, both in active and remission phase.	Standard UC therapy (e.g corticosteroids, mesalazine) plus curcumin, administrated via rectal or oral route	Standard UC therapy (e.g corticosteroids, mesalazine) plus placebo	Remission, as measured by Ulcerative Colitis Disease Activity Index (UCDAI) < 3 or Colitis Activity Index (CAI) <4

Table 2. Searching strategy in several database

Engines	Search Terms	Hits
Pubmed	(curcumin [MeSH Terms] AND ulcerative colitis [MeSH Terms]) AND remission	21
Cochrane	"curcumin" AND "ulcerative colitis" AND "remission"	15
Proquest	"curcumin" AND "ulcerative colitis" AND "remission"	13

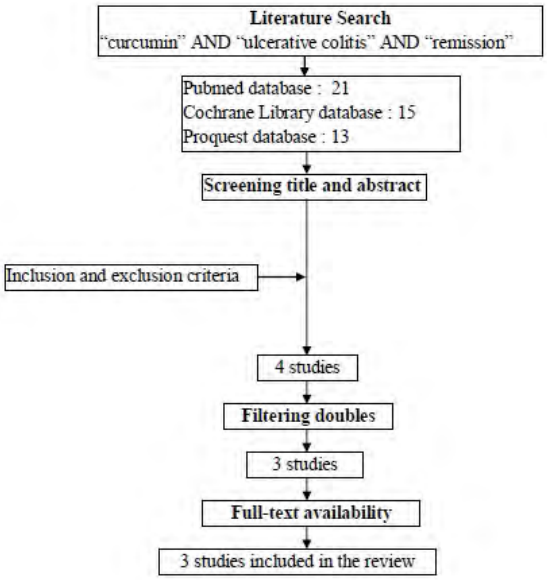

Figure 1. Flow chart of search strategy

1 month with continued 5-ASA. This study reported 53.8% patients in curcumin group experienced remission compared to none in the placebo group (odds ratio (OR) 42, 95% CI 2.3 – 760). Clinical response (i.e. decrease in clinical score, but did not fulfill remission criteria) was also higher in the curcumin group (65.3% vs 12.6%, OR 13.2, 95% CI 3.1 – 56.6).[9]

Singla et al[8] used patients with active mild to moderate UC in distal colon (<25 cm disease involvement from anal verge) who were already on oral mesalamine for at least 8 weeks. They were randomly assigned to groups given curcumin enema (NCB-02) plus oral 5-ASA or placebo enema plus oral 5-ASA once daily. This study reported 43.4% remission in curcumin group compared to 22.7% in placebo group. Clinical response was also higher in the curcumin group (56.5% vs. 36.4%). Number needed to treat in both studies were small, less than 50 patients.

Curcumin as Adjuvant to Maintain Remission in Ulcerative Colitis

Hanai et al[10] used patients with quiescent UC and randomly assigned to oral curcumin (2 g/day) plus sulfasalzine or mesalamine (depending on which drug the patients already used before trial), or placebo capsules plus sulfasalazine or mesalamine (depending on which drug the patients already used before trial). Patients experienced recurrence were fewer in curcumin group both at 6-month follow-up (10% vs. 14%) and 12-month follow-up (22.2% vs 31.8%).[10] Number needed to treat was small, less than 50 patients.

DISCUSSION

In all studies that we found, curcumin was significantly more effective as adjuvant therapy to induce or maintain UC remission, compared to placebo.[8-10] A small number needed to treat showed that curcumin had significant benefit for patients and could potentially be used in

Table 3. Critical appraisal of the randomized clinical trial

Articles (years)	Numbers of sample	Relevance				Validity						Importance				
		P	I	C	O	Random	Long follow up	All patients analyzed	Blind	Treated equally	Similiar at start	CER (%)	EER (%)	RRR (%)	ARR (%)	NNT (CI 95%)
Lang (2015)[9]	50	+	Oral, 3g/day	+	+	+	-	+	+	+	+	0	53.8	-	53.8	2 (1–3)
Singla (2014)[8]	45	+	Enema, 1x/day	+	+	+	-	+	+	+	+	22.7	43.5	91.6	20.8	5 (3–17)
Hanai (2006)[10]	89	+	Oral, 2g/day	+	+	+	+	+	+	+	+	68.2	77.8	14.1	9.6	11 (4–12)

P:patient, I: intervention, C: comparison, +: placebo. O: outcome, +: remission. In validity, +: yes, -: no. CER: control event rate, event=outcome. EER: experimental event rate, event=outcome. RRR: relative risk reduction, minus (-):RRR cannot be counted because the CER is 0 (zero) percent. ARR: absolute risk reduction. NNT: number needed to treat.
CI : confidence interval

clinical settings. This effect might be explained by curcumin's anti-inflammatory properties. Inhibition of NF-κB was postulated as its main anti-inflammatory properties. The mechanism of action involves inhibition of IKK (IκB kinase) which leads to inhibition of both cytokine mediated phosphorylation and degradation of IκB, which is an inhibitor of NF-κB. As a result of NF-κB inhibition, IL-2 synthesis, as well as IL-2 and mitogen activation of human leukocytes are also inhibitied. Curcumin is also indicated to have inhibiting effect on tumor necrosis factor α (TNF-α) and phorbol ester-induced binding of NF-κB transcription factors to sites located on the GSTP-1 (glutathione S-transferase P1-1) gene promoter – therefore, it could induce apoptosis by inhibiting GSTP-1 expression at the transcription level. In animal studies, curcumin also showed ability to suppresss CD4+ T-cell infiltration, thereby reducing the inflammatory response.[8-11]

Adverse events were not significantly different in the placebo and curcumin groups in all trials.[8-10] The most common side effects of curcumin was gastrointestinal complaint, such as nausea and sensation of abdominal distension; it was usually mild, transient and no subjects in the studies dropped out because of curcumin's side effects.[10] This side effects could be reduced by administering curcumin via rectal route (enema), especially for patients with distal UC. Futhermore, topical preparation can bypass first pass metabolism in the liver, which is high for oral preparation of curcumin.[8] The good safety profile of curcumin places it as a promising agent in UC treatment. Moreover, not only curcumin could improve clinical symptoms, it could also improve endoscopic findings of the colon, as described by Lang, et al.[9] In animal models of colon cancer, curcumin was reported to inhibit dysplasia and neoplasia. This chemopreventive activities might be mediated by inhibition of cyclo-oxygenase-2 expression.[8] Curcumin also strongly inhibited proliferation of HT-29 and HCT-15 human colon cancer cell lines. Therefore long treatment with curcumin might also inhibit colorectal cancer development in UC patients, which needed to be studied further.[11] However, all studies we found used a relatively small sample size (50,45, and 89), and one trial only conducted one month follow-up – the statistical power is not enough to generate representative results in all UC patients. Moreover, the studies each used different curcumin dosage and routes of administration, and different follow-up period; it could not be objectively compared. Futhermore, clinical scoring system used in each trial was slightly different from each other. As a result, the quantitative data from those trials could not be integrated to form a pooled analysis. We concluded that further studies with larger sample size are needed to recommend it as adjuvant therapy of ulcerative colitis.

Additionally, studies comparing the effectivity of various combination of curcumin and standard UC therapy were also needed, e.g curcumin-mesalamine, curcumin-steroids, etc. Similar to curcumin, mesalamine also acts by inhibiting NF-κB pathway. The combination of curcumin and mesalamine had shown increased efficacy compared to mesalamine therapy alone. This might be due to synergistic action of curcumin with mesalamine, or inhibition of other inflammatory pathways by curcumin.[8] Comparison of synergistic effect between curcumin and various drugs used in UC therapy has not been established. Furthermore, studies comparing various curcumin dosage (e.g 2 g/day, 3 g/day, etc). were needed to obtain curcumin dosage and avoid gastrointestinal side effects caused by unneccessarily high curcumin dosage. Recently, various formulation of oral curcumin is also developed to increase its absorption rate, because curcumin is a poorly water-soluble drug. Li et al[12] used curcumin and piperine (PIP) co-encapsulated into the nanoformulation called self-microemulsifying drug delivery system (SMEDDS) to improve the stability and water-solubility of curcumin and enhance its anticolitis activity. Lately, oral colon-specific drug delivery has been developed, using microparticles as drug carrier to achieve controlled drug-release in the colon. Curcumin-loaded microparticles has been used in animal and in-vivo studies, and showed promising results.[13] These methods might hold promis for more efficient clinical treatment of UC. Therefore, studies comparing curcumin efficacy between different routes and formulation were also needed.

CONCLUSION

Available evidence showed that adjuvant therapy using curcumin has potential to induce and maintain remission in UC patients with no serious side effects. However, further studies with larger sample size are needed to recommend it as adjuvant therapy of ulcerative colitis.

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