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Administration of dietary antioxidants for patients with inflammatory bowel disease: A systematic review and meta-analysis of randomized controlled clinical trials

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ABSTRACT

Objective: Accumulating evidence has been reported regarding the effect of dietary antioxidants on clinical variables in IBD patients, however, findings are controversial. This systematic review and meta-analysis aimed to investigate effect of dietary antioxidants on clinical variables in patients with IBD or its subtypes.

Methods: We searched PubMed, Scopus, and ISI Web of Science from inception to January 2021 using relevant keywords. Data were pooled by using the random-effect model. All statistical analyses were done using STATA version 14.

Results: Our meta-analysis was exclusively done on studies about the effect of curcumin on IBD patients, because limited studies were done on other antioxidants. Curcumin administration resulted in significant increment of clinical remission in patients with IBD (SMD: 0.86%, 95% CI: 0.16, 1.56, $p = 0.016$), significant remission in clinical symptoms (SMD: −0.96 score, 95% CI: −1.34, −0.57, $p < 0.001$), and significant increment in endoscopic remission in IBD patients (SMD: 0.51%, 95% CI: 0.16, 0.85, $p = 0.004$), comparing to control group. Curcumin supplementation also made better clinical response than control group (SMD: 0.74%, 95% CI: 0.22, 1.26, $p = 0.005$) and also resulted in significant improvement in quality of life of patients with IBD, as compared to control group (SMD: 1.23 score, 95% CI: 0.72, 1.74, $p < 0.001$).

Conclusions: Our meta-analysis showed that curcumin significantly improved clinical and endoscopic remissions in IBD patients. This supplementation also caused significant reduction in clinical symptoms of IBD patients along with better clinical response and the increased quality of life. Further researches with larger sample size and longer period of intervention are required to evaluate efficacy of dietary antioxidants on clinical variables in patients with IBD.

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1. Introduction

Inflammatory bowel disease (IBD) is an idiopathic intestinal inflammatory disease which includes two main subtypes including ulcerative colitis (UC) and crohn's disease (CD)[1]. The global prevalence of IBD is increasing rapidly [2]. IBD has several complications, which interfere with a normal life of the suffering patients [3]. In addition, it is a known risk factor for many other chronic diseases [4,5].

Exact etiology of IBD is unknown. However, it seems that inflammation has a crucial role in the pathogenesis of this disease [6,7]. Administration of dietary antioxidants in patients with IBD resulted controversial findings in previous studies[8]. Various treatments have been used by individuals to improve the condition of inflammatory bowel disease[9]. For example, In Western countries, the use of complementary and alternative drugs to improve chronic diseases increased significantly in the 1990s and then reached a relatively constant level[10]. Some studies have also shown that supplementation with curcumin has been associated with the improvement in clinical outcomes, quality of life, and inflammatory factors in UC patients in one study[11] By down-regulating inflammatory transcription factors such as NFkB, important enzymes such as cyclooxygenase 2 and 5 lipoxygenase and a variety of cytokines such as tumor necrosis factor, interleukin 1 and interleukin 6 can have anti-inflammatory effects [12]. Another study showed that resveratrol supplementation improved quality of life and simple clinical colitis activity index (SCCAI) in patients with UC[13]. However, the administration of oral curcumin at a dose of 450 mg/d in another study had no significant influence on clinical remission of such patients[14]. These discrepancies might be due to the different dosages of supplementation, and also differences in antioxidant type and administration routes. Although lower doses of curcumin (140 mg/day) were used in Singla et al[15]. as compared to the Kedia et al. study [14] (450 mg/day), clinical findings were obviously better in patients with IBD. The authors said that this finding might be partially explained by the different curcumin administration rout (enema vs. oral administration), such that those received lower dose of curcumin via their enema had a better prognosis. In Singla et al. study despite lower dose of curcumin comparing to other RCTs, they found a significant improvement in clinical remission and clinical responses of patients with IBD[15]. A recent meta-analysis of the effects of polyphenols on IBD showed that there is a significant association between curcumin supplementation and better clinical response and endoscopic remission in patients with IBD [16]. The meta-analysis only included studies on supplementing curcumin. Moreover, no subgroup analysis was done in that study. In addition, they used odds ratios to calculate final effect sizes, which might result in misleading conclusions for clinical trials in which two groups of intervention and control are comparing.

Although the results of early studies on the effects of dietary antioxidants on the clinical symptoms of patients with IBD are controversial, a comprehensive and conclusive study on this topic has not yet been conducted. The early meta-analysis only focused on a single dietary antioxidant, and it also needs to be updated. Therefore, the current study aims to systematically review existing randomized controlled trials on the effects of dietary antioxidant supplementation on clinical variables in patients with IBD or its subtypes.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were followed in conducting this systematic review and meta-analysis [17]. The PRISMA checklist has been fulfilled for the current study (Appendix A).

2.1. Search strategy

Online medical databases, including PubMed, Scopus, and Web of Science were searched up to January 2021. Detailed search algorithm using MESH and non-MESH terms including ("RCT"[tiab] OR "randomized clinical trial"[tiab] OR "clinical trials as topic"[MeSH] OR "trial*"[tiab] AND "curcumin"[MeSH] OR "curcumin"[tiab] OR "curcuma"[tiab] OR OR "Resveratrol"[tiab] OR "Resveratrol"[MESH] OR "antioxidants"[MeSH] OR "Antioxidant"[tiab] OR "Anti-Oxidant"[tiab] OR "vitamin C"[tiab] OR "vitamin E"[MESH] OR "vitamin E"[Title/Abstract] OR "N acetylcysteine"[Title/Abstract] OR "Acetylcysteine"[MeSH] OR "Acetylcysteine"[Title/Abstract] OR "ascorbic acid"[MeSH] OR "ascorbic acid"[Title/Abstract] AND "Inflammatory bowel disease"[Title/Abstract] OR "Inflammatory bowel diseases"[MeSH] OR "Crohn disease"[Title/Abstract] OR "Crohn disease"[MeSH] OR "colitis, ulcerative"[MeSH] OR "ulcerative colitis"[Title/Abstract] OR "IBD"[Title/Abstract] OR "Crohn's disease"[Title/Abstract]) No time and language restrictions were made. In addition, the reference lists of all included studies were manually searched to avoid missing any relevant study. Grey literatures, including dissertations, letters, congress abstract, and etc. were removed.

2.2. Eligibility criteria

Potentially relevant studies that met the following criteria were included: (a) original papers with either parallel or cross-over randomized clinical trials (RCT) design; (b) studies conducted on individuals aged 18 years old or more; (c) investigated the impact of oral supplementation with any dietary antioxidant on patients with IBD or its subtypes, and (d) reported mean (SD) or percent changes or baseline and final clinical remission rates, clinical response rates, endoscopic remission simple clinical colitis activity index questionnaire (SCCAIQ) score, inflammatory bowel disease questionnaire-9 (IBDQ-9) score, SCCAI score or other outcomes related to clinical symptoms of IBD patients in intervention and control group. If different articles were published on data from the same population, we included only the most complete one.

Studies were excluded if they were reviews, meta-analyses, and ecologic studies, or if they were conducted on animals, pregnant or lactating women or children, or had no control group or studies assessed influence of antioxidant supplementation along with other interventions. We also excluded studies in which food items or herbs containing antioxidants were used as the intervention.

2.3. Data extraction

Study selection and data extraction were performed at least twice by two independent researchers (HSH and NP). Any disagreement was discussed and resolved by a third reviewer (AM). Following data were collected from each study: study characteristics (first author's name, year of publication, study location, publishing year, and study design), participant characteristics (mean age and gender of participants separately by intervention and control group, health condition of participants, and number of participants in each group), intervention (type, dose, and duration of supplementation), mean and SD or percentage of clinical variables at baseline, and end of study or changes between baseline and post-intervention in both groups, and any adjustment for confounding factors.

2.4. Quality assessment of included studies

The methodological quality of studies was assessed by using the Cochrane Collaboration risk of bias tool[18]. The following methodological domains were considered: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential threats to validity. According to Cochrane Handbook recommendation, studies were stratified as low risk of bias, high risk of bias, or unclear regarding each domain.

2.5. Statistical analysis

Pooled effect sizes and corresponding 95% confidence interval (CI) were calculated using the mean changes and SDs of outcomes of interest in intervention comparing to control group. All analyses were done by the random-effect model. When means (±SD) of outcomes was not directly available and a standard error of the mean (SEM) was presented, we converted it to SD using this formula: $SD = SEM \times \sqrt{n}$, being "n" the number of subjects in each group. If medians and inter-quartile range were reported, mean and SD values were estimated using the method described by Hozo et al[19]. Ultimately, we used the GetData Graph Digitizer version 2.24 to extract data from studies that reported outcomes in the graphical form. We also converted all percentages to mean and SDs for the current meta-analysis to made final results easy to read. We assessed the magnitude of inter-study heterogeneity by the I^2 statistics, where values greater than 50% were considered as evidence of moderate to high between-study heterogeneity. A priori subgroup analysis by the predefined variables was performed to detect potential sources of heterogeneity. Any publication bias was investigated by visually inspecting at funnel plots and quantitatively evaluated using the Egger's regression test. In case of detecting potential publication bias, Duval & Tweedie "trim and fill" approach was applied to adjust final results [20]. Sensitivity analysis was done by excluding a single study in each stage to find influence of each included study on overall results. All analyses were undertaken using Stata software version 14 (Stata Corp. College Station, Texas, USA). P-values less than 0.05 were considered to be statistically significant.

3. Results

3.1. Selected studies

After searching databases, 316 relevant articles were included at the initial stage. After removing duplicates, 211 relevant articles were screened by title and abstract. After this stage, 31 articles remained for the final evaluation. The full texts of the potentially eligible articles were retrieved for independent further screening. Finally, 12 articles were included in the present systematic review. Of these articles, 7 studies had information for meta-analysis. Fig. 1 demonstrates the process by which articles were selected.

3.2. Studies characteristics

General characteristics of included studies have been summarized in

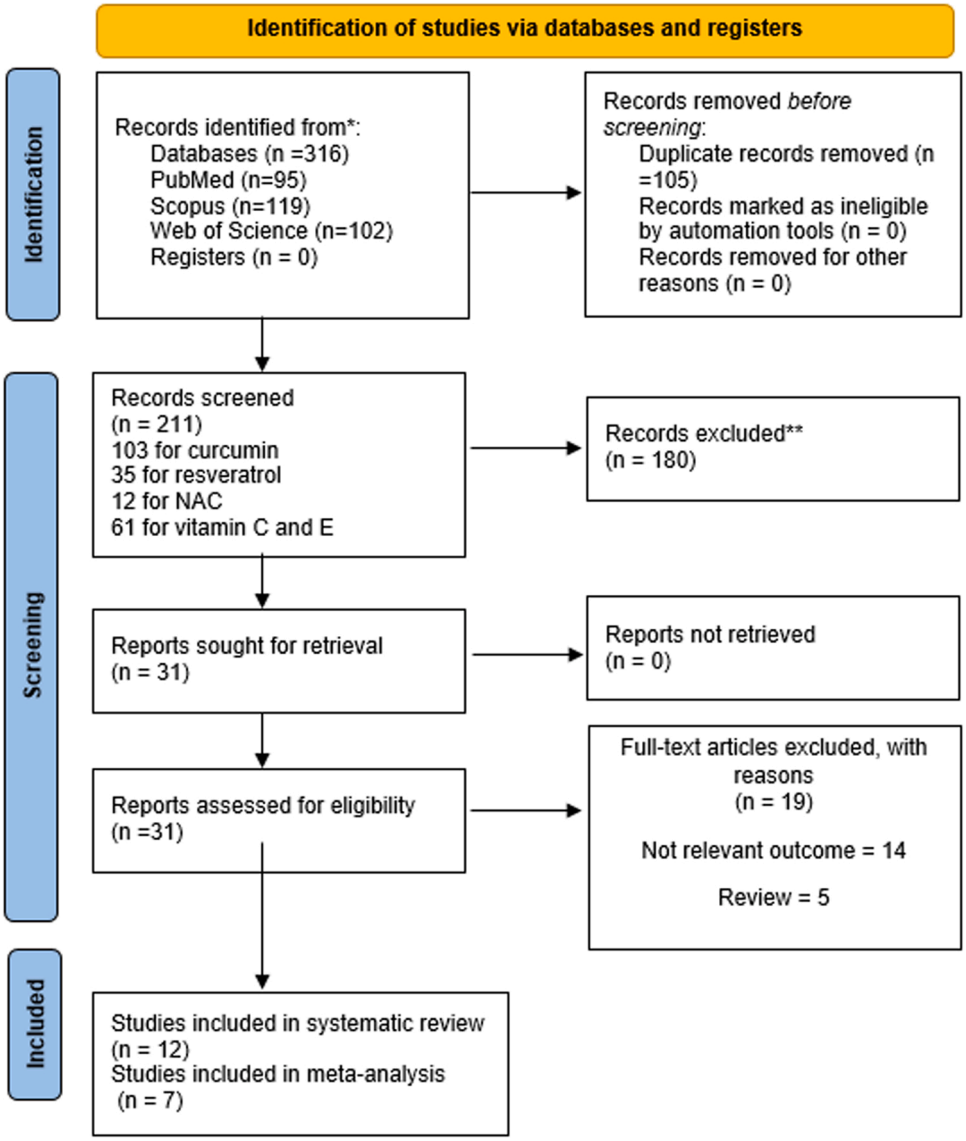

Fig. 1. Flow chart of the number of studies identified and selected into the meta-analysis.

Table 1
Demographic characteristics of the included studies.

Author (year)	Country	Disease	Subjects and gender	Age range (y) And mean	Design	Antioxidant	Route of administration	Dose	Intervention type		Duration (week)	Outcomes	Outcome assessment method	outcome	
									Intervention (name and composition)	**Control (Name and composition)**				**Intervention** mean±SD and number	**Control** mean±SD and number
Banerjee et al.[22]	India	UC	Both: 47 Int:22 Con:25	18-70 (44)	RCT, Parallel	Curcumin	Capsule (Oral)	100 mg/d	Curcumin capsules + mesalamine	Placebo + mesalamine	12	endoscopic remission	partial mayo score (%)	44% (16/34)	5.7% (2/35)
												Clinical response	partial mayo score (%)	58.8% (20/34)	28.6% (10/35)
												Clinical Remission	partial mayo score (%)	55.9% (19/34)	5.7% (2/35)
Hanai et al.[24]	Japan	UC	F: 40 M: 49 Both: 89 Int:45 (23/22) Con: 44 (26/18)	13–65 (39)	RCT, Parallel	Curcumin	Capsule (Oral)	2000 mg/d	Curcumin + sulfasalazine or mesalamine	Placebo + sulfasalazine or mesalamine	24	Clinical remission	clinical activity index (%)	ITT:4.44 PP:4.65	ITT:15.15 PP:20.51
Kedia et al.[14]	India	UC	F: 21 M: 41 Both: 62 Int:29 (13/16) Con: 33 (8/25)	≥18	RCT, Parallel	Curcumin	Capsule (Oral)	450 mg/d	Curcumin capsules + mesalamine	Placebo + mesalamine	8	Clinical remission,	Ulcerative Colitis Disease Activity Index. (mean ± SD)	Before: 5.2 ± 2.0 After: 3.4 ± 3.1	Before: 5.5 ± 1.9 After: 3.8 ± 2.8
												clinical remission,	Ulcerative Colitis Disease Activity Index. (%)	ITT:31.03 PP:56.25	ITT:27.27 PP:36
												endoscopic remission	Ulcerative Colitis Disease Activity Index.(%)	ITT: 34.5 PP:62.5	ITT:30.3 PP:40
Lang et al.[26]	Hong Kong	UC	F: 17 M: 33 Both: 50 Int:26 (9/17) Con: 24 (8/16)	18–70 (44)	RCT, Parallel	Curcumin	Capsule (Oral)	3000 mg/d	Curcumin capsules + 5-aminosalycilate	Placebo + 5-aminosalycilate	4	Clinical remission	Simple Clinical Colitis Activity Index (%)	53.8	0
												clinical response	Simple Clinical Colitis Activity Index (%)	65.3	12.5
												endoscopic remission	Simple Clinical Colitis Activity Index(SCCAI) (%)	36.3	0
Bommelaer et al.[23]	France	CD	In: ITT31/PP26 Con: ITT31/PP27	36.3 y	RCT, Parallel	curcumin	Capsule (Oral)	3000 mg/d	Placebo+ azathioprine	oral curcumin+azathioprine	24	endoscopic remission	Endoscopic POR (Rutgeerts index i2a) N (%)	ITT: 21 (67.7) PP:16 (61.5)	ITT: 18 (58.1) PP: 14 (51.8)

(*continued on next page*)

Table 1 (*continued*)

Masnadi Shirazi et al.[27]	Iran	UC	F=89/m=79 Both=168 in = 82 p=86	38.8	RCT, Parallel	Nacetylcysteine (NAC)	Capsule (Oral)	800 mg/d	Nacetylcysteine	Placebo	16	Clinical remission	Partial mayo score (mean ± SD)	Baseline 3.57±1.17 After 2.8±0.25	Baseline 3.43±1.13 After 4.09±0.31
Sugimoto et al.[31]	Japan	CD	F: 9 M: 21 Both: 30 Int:20 (7/13) Con: 10 (2/8)	20-60 (40)	RCT, Parallel	Curcumin		360 mg/d	Theracurmin	Placebo	12	Clinical remission	Crohn's disease activity index (CDAI) (%)	40	0
												endoscopic remission	Simple Endoscopic Score for Crohn's Disease (SESCD) (%)	15	0
Sadeghi et al.[29]	Iran	UC	Curcumin: 8M/27F Placebo : 13M/22F	Curcumin: 40.1 ± 13.2 Placebo: 40.6 ± 12.4	RCT, Parallel	Curcumin	Capsule (Oral)	1500 mg/d	curcumin	Placebo (maltodextrin.)	8	Quality of life	Questionnaire (mean ± SD)	ITT:39.3±9.6 b ITT:48.9±7.5 a PP:38.4 ± 9.7 b PP:48.9 ± 8.0 a	ITT:44.6±9.5 b ITT:48.9±7.5 a PP:45.2 ± 9.2 b PP:49.6 ± 7.3 a
												Clinical remission	SCCAI (mean ± SD)	ITT:6.7±2.1 b ITT:1.6±1.4 a PP:6.3 ± 1.6 b PP:1.1 ± 1.4 a	ITT:5.5±1.1 b ITT:3.3±2.4 a PP:5.5 ± 1.2 b PP:2.8 ± 1.7 a
												Clinical remission	SCCAI (%)	83.9	43.8
												Clinical improvement	SCCAI (%)	93.5	59.4
Samsami-Kor et al.[13]	Iran	UC	Both: 49 Int:25 Con: 24	≥18	RCT, Parallel	Resveratrol	Capsule (Oral)	500 mg/d	Resveratrol capsule	Placebo	6	Clinical remission	Simple Clinical Colitis Activity Index Questionnaire (mean ± SD)	ITT: Before: 12.34 ±2.51 After: 8.14 ±2.1	ITT: Before: 10.76 ±2.55 After: 9.34 ±2.65
												Quality of life	Inflammatory Bowel Disease Questionnaire -9 (mean ± SD)	ITT: Before: 32.72 ±7.52 After: 47.64 ±8.59	ITT: Before: 35.54 ±9.50 After: 41.08 ±8.59
Samsamikor et al.[30]	Iran	UC	Both: 56 Int:28 Con: 28	≥18	RCT, Parallel	Resveratrol	Capsule (Oral)	500 mg/d	Resveratrol capsule	Placebo	6	Clinical remission	Simple Clinical Colitis Activity Index Questionnaire (mean ± SD)	ITT: Before: 11.67 ± 2.72 After: 8.14 ± 2.1	ITT: Before: 10.88 ± 2.69 After: 9.34 ± 2.65
												Quality of life	Inflammatory Bowel Disease Questionnaire -9 (mean ± SD)	ITT: Before: 34.85 ±7.67 After: 47.64 ±8.59	ITT: Before: 35.67 ±9.89 After: 41.08 ±8.59

(*continued on next page*)

Table 1 (*continued*)

Singla et al.[15]	India	UC	F: 22 M: 23 Both: 45 Int:26 (11/12) Con: 24 (11/11)	≥18	RCT, Parallel	NCB-02 (curcumin)	Enema (Rectal)	140 mg/d	NCB-02 (curcumin) enema + 5-aminosalycilate oral	Placebo + 5-aminosalycilate oral	8	Clinical remission	Ulcerative Colitis Disease Activity Index (%)	ITT: Inter:10(43.5 %) PP: 10(71.4%)	ITT: con: 5(22.7%) PP: 5(31.3%)
												clinical response	Ulcerative Colitis Disease Activity Index (%)	ITT: Inter:13(56.5 %) PP: Inter:13(92.9 %)	ITT: con: 8(36.4%) PP:8(50%)
												improvement on endoscopy	Ulcerative Colitis Disease Activity Index (%)	ITT: Inter:12(52.2 %) PP:12(85.7%)	ITT: con: 8(36.4%) PP:8(50%)
Aghdassi et al.[21]	Canada	UC	Both:57 Int:28 Cont:29	37.5	RCT, Parallel	Vitamin C and E	Capsule (Oral)	Vit E: 800 IU Vit C:1000 mg	Vit E, Vit C oral capsule	Placebo	4	Clinical remission	Crohn's disease activity index (CDAI) (mean ±SD)	121±18 b 137±24 a	138±18 b 136±20 a

ITT: intention to treat; PP: per protocol; Int: intervention; Con: control; IU: international unit; UC: Ulcerative Colitis; CD: Crohn's disease; vit: vitamin; mg: milligram; d: day; a: after; b: before

Table 1. We identified 12 randomized controlled clinical trials (RCTs) that assessed effects of various antioxidant supplementation on ameliorating symptoms of inflammatory bowel disease [13–15,21–31]. These studies were carried out in various countries including Iran [13,27–30], India [14,15,22], Japan [24,25,31], Hong Kong [26] Canada [21], and France [23]. Publication dates ranged from 2006 to 2020. Overall, 1060 participants were enrolled in these studies. All RCTs were done on both genders and had parallel design. Different antioxidants including Curcumin, N-acetylcysteine, resveratrol, combination of vitamin C and E were used in our included RCTs. Antioxidants were administrated through different routes, including oral [13,14,21–31] and enema [15]. Supplements were administrated in doses ranging from 100 and 3000 mg/day. The intervention duration varied between 4 and 24 weeks. Most studies were conducted on patients with ulcerative colitis [13–15,21–24,26,27,29,30]. However, a few papers enrolled patients with crohn's disease [31]. The severity of disease in the patients was as follows: severe disease [27], mild-to-moderate [13–15,21–23,26,29–31], and Quiescent [24]. RCTs had analyzed effectiveness of antioxidants on these outcomes: clinical remission [13–15,21,22,24,26,27,29–31], clinical response [15,22,26], endoscopic remission [14,15,22,23,26,31] and quality of life [13,23,29,30]. Some studies had adjusted for confounding factors [13,24,27,30], however, most of them did not control for covariates [14,15,21–23,26,29,31].

4. Quality assessment

All studies reported random allocation of participants [13–15,21–24,26,27,29–31]. Allocation concealment was reported in all papers [13–15,21–24,26,27,29–31]. Low risk of bias in eight trials in terms of blinding of participants, personnel, and outcome assessment was demonstrated [13,23,24,26,27,29–31] and other 4 studies revealed high risk of bias [14,15,21,22]. Ten studies indicated low risk of bias in domain of "incomplete outcome data" [13–15,21,22,24,27,29–31], while two other papers had high risk of bias [23,26]. Eleven trials showed low risk of bias on selective outcome reporting [13–15,22–24,26,27,29–31] and only one research had unclear risk of bias [21]. Details about risk of bias assessment are described in Table 2.

5. Systematic review

The only RCT in this review evaluated the effect of antioxidant vitamin supplementation in patients with inactive or mildly active crohn's disease. A total of 57 subjects were supplemented with vitamin E (800 IU) and vitamin C (1000 mg) or their placebo for 4 weeks. A blood test measuring breath pentane and ethane output, plasma lipid peroxides and F2-isoprostane was analyzed at baseline and after four weeks. A plasma orosomucoid measurement was also taken to measure disease activity. The plasma levels of vitamin C and alpha-tocopherol increased, and virtually all indices of oxidative stress decreased during supplementation. Disease activity remained unchanged during supplementation. [21]

Two studies reported the effect of resveratrol supplementation on inflammation and oxidative stress status in patients with ulcerative colitis (UC). In study of Samsamikor et al. for 6 weeks, 56 patients with mild to moderate disease were randomly assigned to receive 500 mg/day of resveratrol or an equivalent amount of placebo. Before and after the intervention, disease activity, quality of life, and oxidative stress were assessed using the Simple Clinical Colitis Activity Index Questionnaire (SCCAIQ), Inflammatory Bowel Disease Questionnaire-9 (IBDQ-9), and serum level of malondialdehyde (MDA), superoxide dismutase (SOD), and total antioxidant capacity (TAC), respectively. The results indicated that resveratrol supplementation significantly increased serum SOD, TAC, and quality of life and decreased serum MDA and disease activity [30]. In another study investigated the effect of resveratrol supplementation on inflammatory biomarkers in patient with ulcerative colitis. Six weeks of resveratrol or placebo supplementation was given to 50 mild to moderately active UC patients. At baseline and the end of the study, serum inflammatory markers, NF-kB activity in peripheral blood mononuclear cells (PBMC), and quality of life were assessed. The results of resveratrol supplementation led to significant reduction in plasma levels of TNF-α, hs-CRP, and NF-kB activity. The score of inflammatory bowel disease questionnaire -9 (IBDQ-9) increased, whereas the clinical colitis activity index score decreased significantly in the resveratrol group.

There was also one study that assessed the effect of N-acetylcysteine (NAC) on remission maintenance in patients with ulcerative colitis by Masnadi Shirazi et al. They recruited 168 volunteers who were already taking high-dose corticosteroids and Mesalamine for flare-up management. These patients received either 800 mg of NAC or a placebo for 16 weeks concurrently with tapering their prednisolone dose. The primary efficacy of the treatment was remaining in remission. The secondary outcomes were the endoscopic relapse, serum level of hs-CRP, hemoglobin, and fecal calprotectin level. In terms of the relapse-free period, they showed NAC differed significantly from placebo. The mean fecal calprotectin, serum erythrocyte sedimentation rate, and hs-CRP levels were significantly lower in the NAC group compared with the placebo group. Also, they found NAC supplementation led to significant positive effect on the maintenance of remission in UC patients that were in steroid therapy [32].

Table 2
Cochrane risk of bias assessment.

Study	Random Sequence Generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other bias
Banerjee et al. [22]	L	L	H	L	L	U
Hanai et al. [24]	L	L	L	L	L	U
Kedia et al. [14]	L	L	H	L	L	L
Lang et al. [26]	L	L	L	H	L	U
Bommelaer et al. [23]	L	L	L	H	L	U
Masnadi Shirazi et al. [27]	L	L	L	L	L	U
Sugimoto et al. [31]	L	L	L	L	L	U
Sadeghi et al. [29]	L	L	L	L	L	H
Samsami-Kor et al. [13]	L	L	L	L	L	U
Samsamikor et al. [30]	L	L	L	L	L	U
Singla et al. [15]	L	L	H	L	L	L
Aghdassi et al. [21]	L	L	H	L	U	U

L, low risk of bias; H, high risk of bias; U, unclear risk of bias

6. Meta-analysis

6.1. Effect of curcumin supplementation on clinical remission

A pooled analysis of seven papers that reported clinical remission in percent, showed significant increment of clinical remission in patients with IBD (SMD: 0.86%, 95% CI: 0.16, 1.56, p = 0.016), with considerable heterogeneity (I^2 = 90.4%; p < 0.001) (Fig. 2). This finding remained unchanged in all subgroups, except for studies done on patients with < 40 years old, in which no significant change was seen (SMD: −0.05%, 95% CI: −0.33, 0.23, p = 0.741) (Table 3). Furthermore, two studies reported mean (SD) changes in clinical symptoms score following antioxidant supplementation in patients with IBD. Pooling these studies, we found significant remission in clinical symptoms of IBD patients following antioxidants supplementation (SMD: −0.96 score, 95% CI: −1.34, −0.57, p < 0.001), with significant heterogeneity between included studies (I^2 = 96.7%; p < 0.001). Subgroup analyses were conducted based on supplementation dosage and duration. Findings remained unchanged among all subgroups (Table 3).

6.2. Effect of curcumin supplementation on endoscopic remission

Combining six studies that evaluated endoscopic remission in patients with IBD, we revealed that antioxidants supplementation significantly caused in the increased endoscopic remission in comparison to control group (SMD: 0.51%, 95% CI: 0.16, 0.85, p = 0.004) with moderate heterogeneity (I^2 = 52.0%; p = 0.064) (Fig. 3). Similar to clinical remission, subgroup analysis showed no significant effect of antioxidant only on those aged < 40 years (SMD: 0.19%, 95% CI: −0.11, 0.49, p = 0.224) (Table 3).

6.3. Effect of curcumin supplementation on clinical response

Meta-analysis of three studies showed that antioxidants

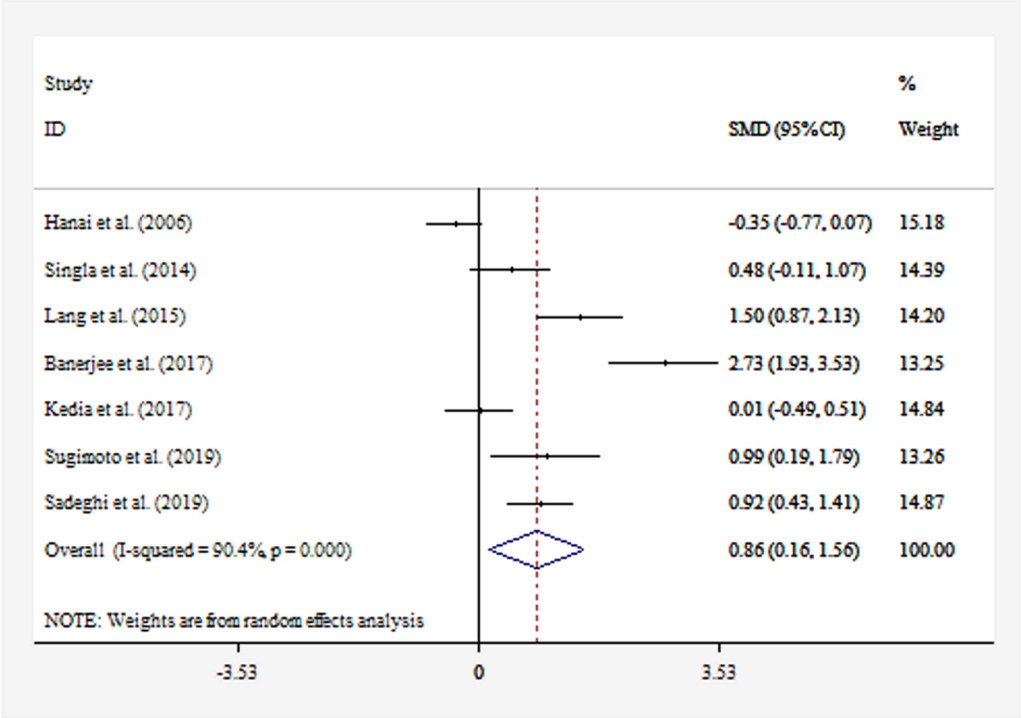

Fig. 2. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of curcumin supplementation on clinical remission.

Table 3
Subgroup analysis of included randomized controlled trials in meta-analysis of the effect of antioxidants on clinical and endoscopic remission.

Group	No. of trials	SMD (95% CI)	P value	I^2 (%)	P-heterogeneity	P for between subgroup heterogeneity
Clinical Remission						
Population						< 0.001
< 50	3	1.20 (0.79, 161)	< 0.001	89.9	< 0.001	
≥ 50	4	0.34 (0.09, 0.59)	0.007	90.1	< 0.001	
Age						< 0.001
< 40	3	-0.05 (−0.33, 0.23)	0.741	61.0	0.077	
≥ 40	4	1.37 (1.05, 1.69)	< 0.001	80.3	0.002	
Dose						0.211
< 1000	4	0.72 (0.40, 1.04)	< 0.001	90.9	< 0.001	
≥ 1000	3	0.45 (0.16, 0.73)	0.002	92.9	< 0.001	
Duration						0.282
< 12	4	0.66 (0.39, 0.94)	< 0.001	79.5	0.002	
≥ 12	3	0.43 (0.09, 0.76)	0.013	95.7	< 0.001	
Endoscopic Remission						
Population						0.313
< 50	3	0.62 (0.25, 0.92)	0.001	25.6	0.261	
≥ 50	3	0.38 (0.07, 0.68)	0.015	70.2	0.035	
Age						0.003
< 40	3	0.19 (−0.11, 0.49)	0.224	0.0	0.840	
≥ 40	3	0.91 (0.54, 1.28)	< 0.001	0.0	0.503	
Dose						0.654
< 1000	4	0.43 (0.14, 0.73)	0.004	45.5	0.138	
≥ 1000	2	0.54 (0.16, 0.93)	0.005	78.8	0.030	
Duration						0.738
< 12	3	0.44 (0.12, 0.76)	0.007	67.0	0.048	
≥ 12	3	0.52 (0.17, 0.86)	0.003	52.9	0.120	

Abbreviations: N: number; CI, confidence interval; SMD: Standardize mean differences.

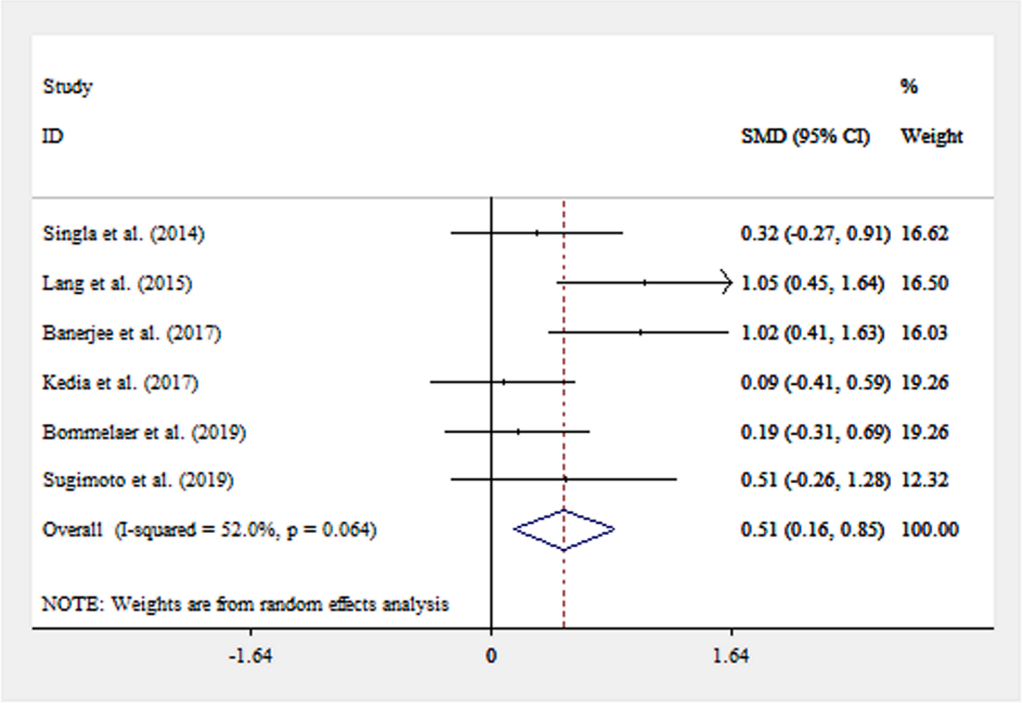

Fig. 3. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of curcumin supplementation on endoscopic remission.

supplementation made better clinical response than control group (SMD: 0.74%, 95% CI: 0.22, 1.26, p = 0.005), with moderate heterogeneity (I^2 = 56.2%; p = 0.102) (Fig. 4). Due to the limited number of included studies, it was impossible to do any subgroup analysis.

6.4. *Effect of curcumin supplementation on quality of life*

Pooling one study showed antioxidant supplementation resulted in significant improvement in quality of life of patients with IBD, as compared to control group (SMD: 1.23 score, 95% CI: 0.72, 1.74, p < 0.001).

7. Discussion

Current systematic reviews and meta-analysis showed that supplementing with dietary antioxidants significantly reduced the clinical and endoscopic symptoms of IBD patients. Antioxidants also lead to better clinical responses in patients with IBD. Moreover, we found that

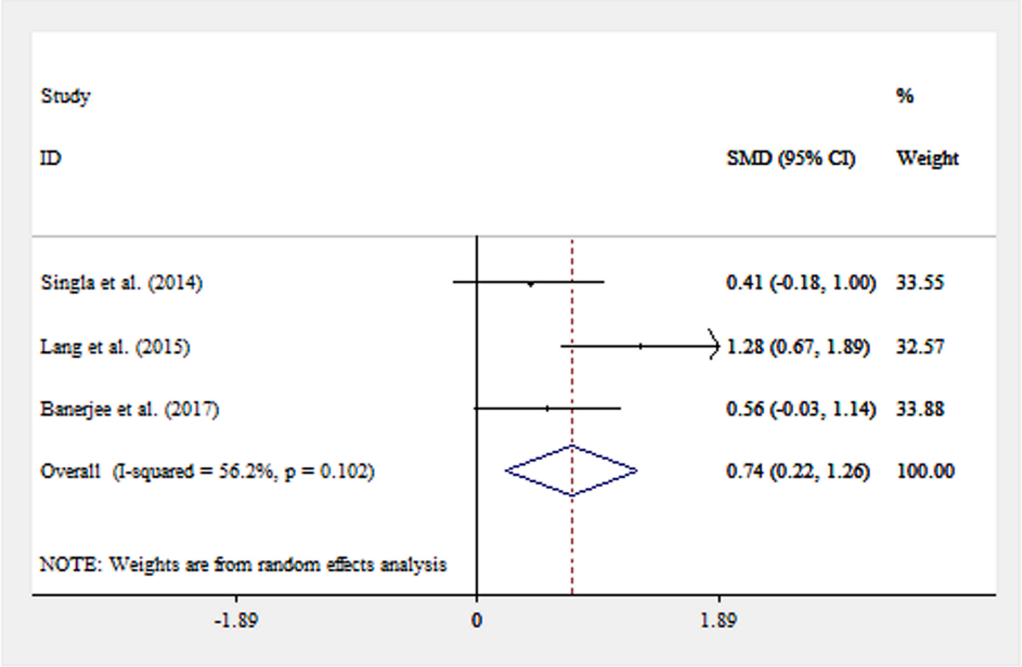

Fig. 4. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of curcumin supplementation on clinical response.

antioxidants supplementation can improve the quality of life of patient with IBD.

Consistent with our results, supplementation with 500 mg of resveratrol per day in a randomized double-blind placebo-controlled trial significantly improved the quality of life of patients with active mild to moderate UC [13]. Some other studies reported that the use of polyphenols can improve IBD-related complications [16,33–35]. Another study by Samsami et al. showed that supplementation with resveratrol for 6 weeks at a dose of 500 mg/day can significantly affect the disease progression of UC patients and improve their quality of life [30]. A meta-analysis by Liu et al. in 2020 regarding the effect of polyphenols on IBD patients showed that polyphenols may be an effective supplementary treatment to improve clinical remission rate, endoscopic remission rate and clinical response rate, especially in UC patients [16]. However, other studies failed to find significant effect of antioxidants on clinical and subclinical variables in patients with IBD. Although Sugimoto, et al. study showed significant effects of a new and rapid derivative of curcumin on clinical and endoscopic markers in patients with active mild-to-moderate CD, no significant improvements were seen in systemic biomarkers or quality of life of those patients [31]. Studies have shown that curcumin can regulate different cell signaling pathways, which are important in prognosis of most chronic diseases[12]. However, some studies in which low-dose (150 mg/day) oral curcumin was used for 8 weeks showed no significant effect on the clinical remission or response of patients with mild to moderate UC[14]. Differences in stages of disease, disease types, and different dosages of various types of antioxidants may be the reasons for these discrepancies. Moreover, as we showed in our subgroup analyses, participants' age might be a detrimental factor for the effects of antioxidants on clinical and subclinical variables in patients with IBD. Therefore, further researches are needed to expand existing knowledge in this field.

Inflammatory bowel disease (IBD) is an idiopathic inflammatory bowel disease with multiple complications, and its global prevalence is rapidly increasing [36,37]. In addition, IBD itself is also a known risk factor for many other chronic diseases [38]. It is well known that the cause of IBD is unknown, but it seems that inflammation plays a crucial role in the pathogenesis of this disease [36]. High intake of dietary fats, obesity, and low intake of fruits and vegetables may be associated with elevated inflammation [39–41]. Adherence to a diet high in total fat, oleic acid, SAFA, total PUFA, trans fat, MUFA, and linoleic acid is associated with an increased risk of ulcerative colitis[39]. Some of the other most common risk factors for IBD are genetic factors, immune response disorders, mucosal barrier dysfunctions, and loss of immune tolerance to intestinal flora [35,36,42,43]. Increased production of inflammatory mediators (including oxygen and nitrogen active substances, prostaglandins and cytokines) can lead to uncontrolled inflammation in these patients [35]. Dietary antioxidants such as resveratrol reduce oxidative stress and through which might influence clinical responses in IBD patients. Dietary antioxidants reduce neutrophil infiltration of intestinal mucosa, inhibit TNF-α production and NF-κB activation [30,35]. Inhibition of NF-κB, cyclooxygenase-2 [44,45], TNF-α activities, and blockage of the JAK/STAT pathway [46], along with up-regulation of IL-22 [47,48] restrains inflammatory cascades in these patients. Reduction in inflammatory reactions will reduce frequency of attacks against gut mucosa. By this mechanism, we will be able to explain why antioxidants might cause clinical and endoscopic remission and finally increase the quality of life in patients with IBD. Significant reductions in endogenous production of lipid peroxides and reactive species of oxygen are other mechanisms through which antioxidants might reduce clinical problems in patients with IBD [21].

Our meta-analysis has some advantages. To the best of our knowledge, current study is the first comprehensive meta-analysis on the effect of dietary antioxidants on clinical variables in patients with inflammatory bowel disease and its subtypes. Moreover, the literature search is so precise. However, we had sufficient data only for some specific types of antioxidants to do meta-analysis. Moreover, we were not able to do our analyses separately for each type of antioxidants. We tried to solve this problem by subgroup analysis. In addition, different types of IBD, different dosages of the supplements, various study sample size and duration were other concerns that needs to be investigated in further trials. Lack of adjustment for important confounders was seen in most included studies. Furthermore, most included studies were done among Eastern populations and more studies are required from other nations. Finally, current systematic review and meta-analysis was not registered in a relevant database, because of time restrictions.

8. Conclusion

In summary, supplementation with antioxidants significantly increased the clinical and endoscopic remissions in patients with IBD. Antioxidants also improved the clinical responses in these patients and improved their quality of life. More randomized clinical trials using different types of antioxidants are required to shed light on this issue.

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CRediT authorship contribution statement

HSH and ARM designed the study. HSH, NP and ME did the literature search and screening data. HSH, ME, and NP performed data extraction and quality assessment, independently. AM, ME, NP and HSH analyzed and interpreted data and wrote the manuscript. AM edited and finalized the manuscript. AM supervised the study. All authors read and approved the final manuscript.

Conflicts of interest statement

The authors declared no conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ctim.2021.102787.

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