



The Effect of Vitamin D in Reducing C-reactive Protein Levels in Ulcerative Colitis: Evidence-based Case Report

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ABSTRACT

Introduction: Ulcerative colitis (UC) is a chronic gastrointestinal inflammatory disease characterized by immune dysregulation. C-reactive protein (CRP) is used as a marker of inflammation and disease severity. Vitamin D has an immunomodulatory role, and low serum levels are associated with increased disease activity in UC. However, the effect of vitamin D supplementation on inflammatory markers in UC remains unclear. This study aims to evaluate the effect of vitamin D supplementation on CRP levels in patients with UC. **Methods:** A systematic literature search was conducted across three databases: PubMed, Scopus, and the Cochrane Library. The search strategy was developed based on the PICO approach, with filters for randomized controlled trials and meta-analyses. Duplicates were removed, and selection was carried out based on titles, abstracts, and full texts. The selected studies were critically appraised using the validity, significance, and applicability approach from the Centre for Evidence-Based Medicine. **Results:** Two studies met the criteria, one systematic review and meta-analysis, and one meta-analysis. Although both studies showed a significant reduction in CRP levels after vitamin D administration, the validity of these studies remains doubtful. **Conclusion:** Current evidence is insufficient to support a definitive recommendation for the use of vitamin D supplementation in patients with ulcerative colitis. High-quality randomized controlled trials are needed.

Keywords: C-reactive protein, inflammation, ulcerative colitis, vitamin D.

ABSTRAK

Pendahuluan: *Ulcerative colitis* (UC) merupakan penyakit inflamasi kronik saluran cerna yang ditandai dengan disregulasi imun. *C-reactive protein* (CRP) digunakan sebagai penanda inflamasi dan keparahan penyakit. Vitamin D memiliki peran imunomodulator, dan kadar serum yang rendah dikaitkan dengan peningkatan aktivitas penyakit pada UC. Namun, efek suplementasi vitamin D terhadap penanda inflamasi pada UC masih belum jelas. Studi ini bertujuan untuk mengevaluasi efek suplementasi vitamin D terhadap kadar CRP pada pasien UC. **Metode:** Penelusuran literatur secara sistematis pada tiga basis data: PubMed, Scopus, dan Cochrane Library. Strategi pencarian berdasarkan pendekatan PICO, dengan filter studi *randomized controlled trials* dan meta-analisis. Duplikasi dihapus dan seleksi berdasarkan judul, abstrak, dan teks lengkap. Studi yang terpilih ditelaah kritis menggunakan pendekatan validitas, signifikansi, dan aplikabilitas dari Centre for Evidence-Based Medicine. **Hasil:** Sebanyak dua studi terdiri dari satu *systematic review and meta-analysis* dan satu meta-analisis memenuhi kriteria. Meskipun kedua studi ini menunjukkan penurunan kadar CRP yang signifikan setelah pemberian vitamin D, validitasnya masih diragukan. **Simpulan:** Bukti saat ini belum cukup untuk menghasilkan rekomendasi pemberian vitamin D pada kolitis ulseratif. Uji klinis acak terkontrol dengan kualitas tinggi diperlukan untuk memastikan efektivitasnya dalam menurunkan kadar CRP. **Irawati Friana Batubara, Steffi Sonia. Efek Vitamin D dalam Menurunkan Kadar C-reactive protein pada Kolitis Ulserativa: Laporan Kasus Berbasis Bukti.**

Kata Kunci: *C-reactive protein*, inflamasi, kolitis ulseratif, vitamin D.

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INTRODUCTION

Ulcerative colitis (UC) is a subtype of chronic inflammatory bowel disease characterized by symmetric, diffuse mucosal inflammation of the rectum and proximal colon, with alternating periods of relapse and remission.¹ The prevalence in Europe and North America

is reported as 505 and 249 per 100,000 population, respectively. Data from developing countries are limited, but recent studies suggest rising incidence rates in Africa, South America, and Asia.² UC typically presents in two age peaks: 20–30 and 50–80 years, with a male-to-female ratio of approximately

1 : 1.³ Its etiology is multifactorial, involving genetic, immunologic, and environmental factors.^{4,5}

Clinical symptoms of UC vary depending on the location and severity of inflammation. Rectal bleeding is a hallmark feature, reported

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in over 90% of cases. Diarrhea may include mucus, blood, or both, occurring more than three times daily. Urgency is common in 75%–90% of patients and significantly impacts quality of life.⁶ Other symptoms include abdominal pain, tenesmus, urinary incontinence, fever, dehydration, and malnutrition. Extraintestinal manifestations such as arthritis, erythema nodosum, and ocular inflammation can also occur.⁷

UC is anatomically classified into proctitis, left-sided colitis, and pancolitis, depending on the extent of colon involvement.⁸ Diagnosis is based on clinical presentation, endoscopy, and histopathology. Colonoscopy often shows mucosal erythema and ulceration, while biopsies reveal chronic inflammation, crypt distortion, and basal plasmacytosis.^{4,5} Disease severity guides treatment decisions and includes clinical, biochemical, and endoscopic evaluations.¹ In hospitalized patients with severe UC, CRP is recommended to be monitored every 1–2 days as a surrogate of treatment response.⁹

CRP is a key acute-phase protein and inflammatory biomarker. Levels typically range from 5 to 200 mg/L during inflammation. Hepatocytes are rapidly stimulated by pro-inflammatory cytokines to produce CRP during systemic inflammatory responses. CRP levels decline rapidly, with a half-life of 48 hours after inflammation resolves.¹⁰ CRP contributes to complement activation, cytokine release, and microbial elimination, but elevated levels can promote further pathological processes, including atherosclerosis, hypercoagulability, gut dysbiosis, and increased mucosal permeability due to lipopolysaccharide exposure.⁹

The primary goals of UC treatment are remission induction and maintenance, prevention of complications, and improvement in quality of life.¹¹ With growing understanding of UC pathogenesis, recent studies have shown that vitamin D plays roles beyond calcium regulation, including mucosal healing and anti-inflammatory effects. Experimental animal models demonstrated that vitamin D supplementation significantly improved outcomes in UC.⁴

Mathur, *et al.*, found that vitamin D

supplementation improved quality of life and reduced disease activity in vitamin D-deficient UC patients.¹² Gubatan, *et al.*, reported that serum vitamin D levels < 35 ng/mL during remission were associated with increased relapse risk, greater disease severity, and higher mucosal inflammation.¹³

CASE ILLUSTRATION

A 43-year-old female presented to the Emergency Department with complaints of worsening watery diarrhea over the past 24 hours, approximately 15 episodes, accompanied by mucus and minimal solid content, without visible blood. She also reported lower left abdominal pain, epigastric discomfort, and nausea. The patient had a history of recurrent episodes of bloody and mucous stools. She was only able to tolerate liquid food due to postprandial pain, resulting in progressive weight loss. Imaging and histopathologic findings confirmed active ulcerative colitis, characterized by severe chronic colitis, mucosal ulceration, epithelial regeneration, and moderate dysplasia. Laboratory tests revealed elevated C-reactive protein (CRP) levels at 68 mg/L, indicative of systemic inflammation. Her serum 25-hydroxyvitamin D [25(OH)D] concentration was 41.4 ng/mL. Pharmacological therapy included systemic corticosteroids, immunosuppressive agents, and anticoagulants. Nutritional support comprised an oligomeric liquid diet along with oral cholecalciferol (vitamin D3) at a dose of 5,000 IU/day. By day 3 of treatment, CRP levels had declined to 39 mg/L, suggesting a favorable response to therapy. This case raises a clinical question regarding the potential immunomodulatory role of vitamin D supplementation in reducing systemic inflammation, particularly as measured by CRP in patients with active ulcerative colitis.

CLINICAL QUESTION

- P** : Patients with ulcerative colitis
- I** : Vitamin D supplementation
- C** : No supplementation/placebo
- O** : Reduction in C-reactive protein (CRP) levels

Clinical Question: Does vitamin D supplementation reduce C-reactive protein (CRP) levels in patients with ulcerative colitis?

METHODS

A systematic literature search was conducted

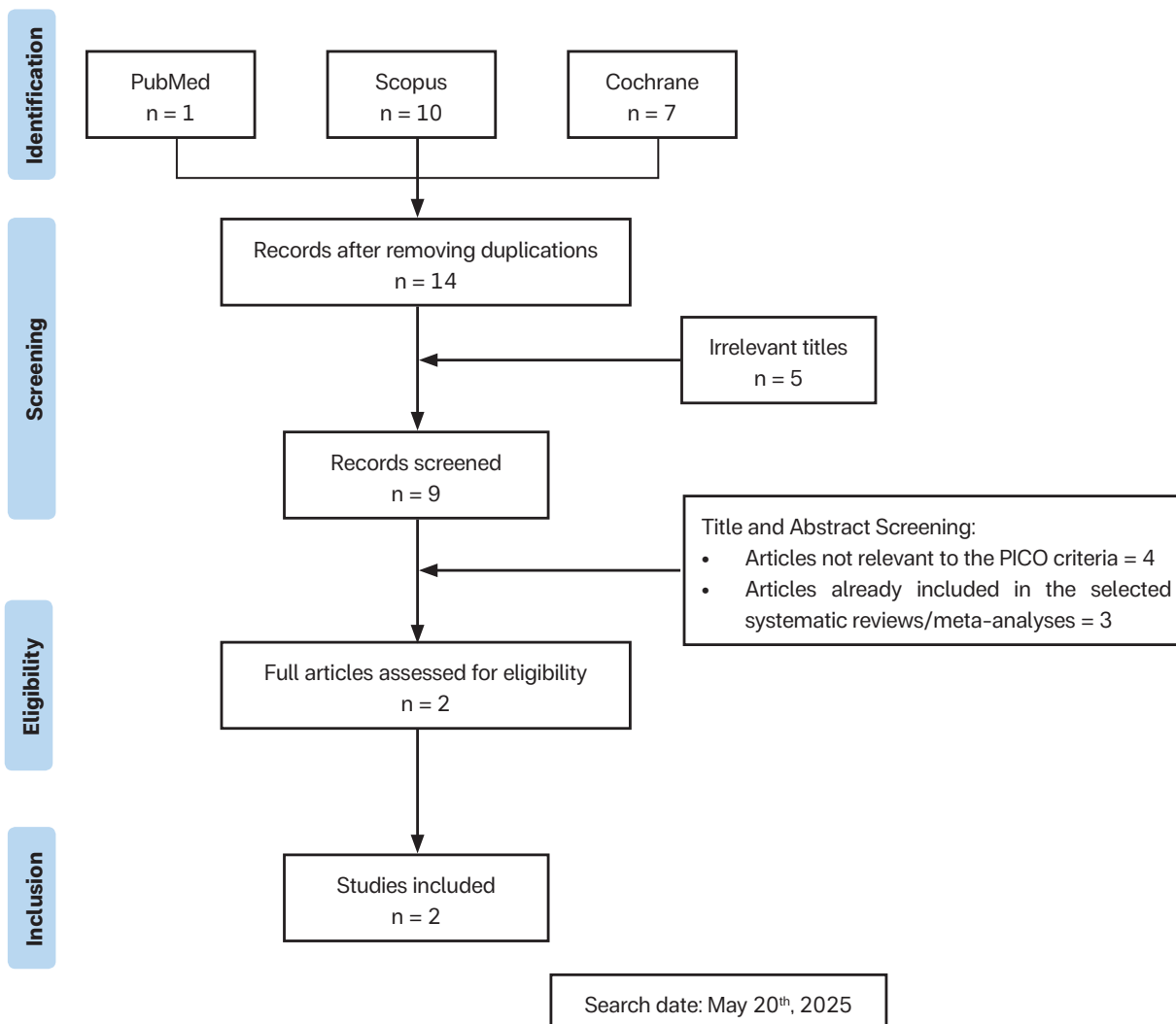
on May 20th, 2025, using three major electronic databases: PubMed, Scopus, and the Cochrane Library. Keywords included: "vitamin D supplementation," "cholecalciferol," "ulcerative colitis," "C-reactive protein," "CRP," and "inflammatory biomarkers." The search strategy was developed based on the PICO framework. Filters were applied to identify relevant randomized controlled trials (RCTs), systematic reviews, and meta-analyses. Articles were screened in two stages: initial screening based on title and abstract, followed by full-text review to determine final eligibility.

ELIGIBILITY CRITERIA

Inclusion criteria included publications in English, available in full-text format, and involving adult human subjects (≥ 18 years) diagnosed with ulcerative colitis. Eligible studies evaluated vitamin D supplementation, either as a primary or adjunctive therapy, with outcomes including inflammatory biomarkers such as C-reactive protein (CRP). The included study designs were randomized controlled trials (RCTs), systematic reviews, and meta-analyses. Exclusion criteria included studies involving patients with Crohn's disease, pregnant or breastfeeding women, individuals with active malignancy or severe infections, animal studies, or articles without full-text availability. The methodological quality and level of evidence were assessed using the Oxford Centre for Evidence-Based Medicine (CEBM) guidelines.¹⁴

RESULTS

A total of 1 article was identified from PubMed, 10 from Scopus, and 7 from the Cochrane Library, as summarized in **Table 1**. The selection process is illustrated in **Scheme**. After duplicate removal and screening based on the PICO framework and predefined eligibility criteria, two studies were included in the final review. Study characteristics, including design, population, interventions, and outcomes, are presented in **Table 2**. Relevance to the clinical question was evaluated based on the similarity of populations, determining factors, and outcome measures (**Table 3**). Critical appraisal of the included studies was conducted using the Centre for Evidence-Based Medicine approach, focusing on validity, importance, applicability, and level of evidence (**Table 4**).



Scheme. Prisma's flow chart.

Table 1. Resources and search strategy.

Database	Terminology	Hits
PubMed	("ulcerative colitis"[tiab] OR "colitis ulcerosa"[tiab]) AND ("vitamin D"[tiab] OR "cholecalciferol"[tiab] OR "calcitriol"[tiab] OR "ergocalciferol"[tiab]) AND ("placebo"[tiab] OR "no intervention"[tiab] OR "control group"[tiab]) AND ("C-reactive protein"[tiab] OR "CRP"[tiab]) AND ("randomized controlled trial"[Publication Type] OR "meta analysis"[Publication Type])	1
Scopus	(TITLE-ABS-KEY ("ulcerative colitis") AND TITLE-ABS-KEY ("vitamin D" OR "cholecalciferol") AND TITLE-ABS-KEY ("inflammatory biomarkers" OR "CRP") AND (TITLE-ABS-KEY ("randomized controlled trial") OR TITLE-ABS-KEY ("meta-analysis")))	10
Cochrane	"ulcerative colitis" AND "vitamin D" AND (placebo OR control) AND ("C-reactive protein" OR CRP)	7



Table 2. Study characteristics.

Author	Study Design	Population Characteristics	Number of Subjects	Outcomes	Results
Guo, et al. ¹⁵ 2022	Meta-analysis of randomized controlled trials (RCTs)	Adult patients diagnosed with ulcerative colitis (some with vitamin D deficiency; with/without co-interventions such as mesalazine or Chinese medicine)	1,077 (10 RCTs)	<ul style="list-style-type: none"> Serum vitamin D C-reactive protein (CRP) Erythrocyte sedimentation rate (ESR) TNF-α IL-6 Ulcerative Colitis Disease Activity Index (UCDAI) 	Vitamin D supplementation significantly reduced CRP ($p < 0.001$) and increased serum 25(OH)D ($p < 0.001$). Improvements were also seen in TNF- α , IL-6, and UCDAI, though some studies used combination therapies.
Guan, et al. ¹⁶ 2022	Systematic review and meta-analysis of 7 RCTs	Adult patients with ulcerative colitis	539 (7 RCTs)	<ul style="list-style-type: none"> Serum vitamin D ESR CRP Parathyroid hormone (PTH) Serum calcium UCDAI 	Vitamin D supplementation significantly increased serum 25(OH)D (SMD = 0.69; 95% CI: 0.36 to 1.03; $p < 0.001$), reduced CRP (SMD = -0.43; 95% CI: -0.67 to -0.20; $p = 0.0003$), and decreased ESR (WMD = -1.10; 95% CI: -1.97 to -0.24; $p = 0.01$). Serum calcium also increased (SMD = 0.92; 95% CI: 0.09 to 1.74; $p = 0.03$). However, no significant effect was found on PTH ($p = 0.42$) or UCDAI ($p = 0.38$). Subgroup analysis showed better efficacy with doses $\geq 300,000$ IU.

Abbreviations: TNF- α : Tumor necrosis factor-alpha; IL-6: Interleukin-6; SMD: Standardized mean difference; WMD: Weighted mean difference.

Table 3. Relevance criteria.

Article	Year	Similarity Population	Similarity	
			Determinant/Intervention/Indicators	Similarity Outcome
Guo, et al. ¹⁵	2022	+	+	+
Guan, et al. ¹⁶	2022	+	+	+

Table 4. Summary of the critical review process: validity, importance, applicability, and level of evidence.

Questions	Guo, et al. ¹⁵ (2022)
Validity	
Does the systematic review address a focused question (PICO)? and use it to direct the search and select articles for inclusion?	Yes
Did the search find all the relevant evidence?	Yes
Have the studies been critically appraised?	Yes
Did they only include high-quality studies?	No, the studies included varied in quality, and not all were high-quality. The overall evidence was considered low due to methodological limitations and potential publication bias.
Have the results been summarized with appropriate tables and plots?	Yes
And heterogeneity between studies was assessed and explained?	Yes

EVIDENCE-BASED CASE REPORT



Importance	What measure was used, and how large was the effect (could it have been due to chance)? How are the results presented?	Mean difference shown in a forest plot with 95% CI and p -value (MD = -1.49 ; 95% CI: -1.76 to -1.23 ; $p < 0.00001$), $I^2 = 3\%$ The results are presented in tabular form and combined in a forest plot.
Applicability	Are the characteristics of the patients we will encounter similar to those of the study patients? Are the exposures in the study similar to those in our patients?	Yes Unclear: due to the lack of transparency and specificity in the reporting of the intervention, the similarity of exposures to local patients cannot be confirmed, and thus, the applicability is unclear.
Level of evidence		2

Questions	Guo, et al. ¹⁵ (2022)	
Validity	Does the systematic review address a focused question (PICO)? And use it to direct the search and select articles for inclusion? Did the search find all the relevant evidence? Have the studies been critically appraised? Did they only include high-quality studies? Have the results been summarized with appropriate tables and plots? And heterogeneity between studies was assessed and explained?	Yes Yes Unclear, no CRP data in one of the sub-studies. Unclear. Although the included studies were reportedly appraised, the presence of two studies sharing the same registered trial number raises concerns regarding possible duplication or misclassification. This limits the ability to independently assess the methodological quality of the evidence. No, only some included studies were clearly of high quality. While they used double-blind methods and reported dropouts, most did not describe the details of randomization or allocation concealment. Yes Yes
Importance	What measure was used, and how large was the effect (could it have been due to chance)? How are the results presented?	SMD shown in a forest plot with 95% CI and p -value, SMD = -0.43 (95% CI -0.67 to -0.20 ; $p = 0.0003$). The $I^2 = 0\%$ ($p = 0.71$) The results are presented in tabular form and combined in a forest plot.
Applicability	Are the characteristics of the patients we will encounter similar to those of the study patients? Are the exposures in the study similar to those in our patients?	Yes No. Although the intervention involved vitamin D supplementation, some included studies used intramuscular injections or oral formulations that are not currently available in Indonesia.
Level of evidence		2

DISCUSSION

This evidence-based case report synthesized findings from two key sources: a systematic review with meta-analysis by Guan, et al., (2025)¹⁶ which evaluated vitamin D supplementation as a stand-alone intervention, and a meta-analysis conducted by Guo, et al., (2024),¹⁴ which assessed vitamin D supplementation in combination

with mesalazine. Both studies included randomized controlled trials investigating the effect of vitamin D supplementation on CRP levels in patients with UC. While they shared similar study designs and broadly comparable inclusion criteria (adult patients diagnosed with UC), their methodological rigor and intervention strategies differed significantly. These differences were critically

appraised using the Validity, Importance, and Applicability (VIA) framework.

One key distinction lies in the intervention approach: Guan, et al., (2025) evaluated vitamin D as a stand-alone treatment, whereas Guo, et al., (2024) assessed vitamin D combined with mesalazine. Notably, the meta-analysis by Guo, et al., (2024) did not



specify the exact dosage, type of vitamin D, or route of administration in the included trials, limiting the assessment of clinical reproducibility.^{15,16}

Furthermore, the lack of methodological clarity in Guo, *et al.*, (2024) was compounded by limited access to several primary studies, likely due to language barriers, as many were published in Chinese-language databases. This limitation hindered independent critical appraisal and raised concerns about the validity and reproducibility of the findings. Additionally, the small number of included studies and the asymmetry of the funnel plot, particularly for the CRP outcome, suggest potential publication bias, thereby reducing confidence in the overall results.¹⁵

Similarly, methodological concerns were also identified in the Guan, *et al.*, (2025). The quality of evidence for CRP was rated as very low due to high risk of bias, indirect outcome measures, imprecise effect estimates, and limited RCT data. Additionally, two sub-studies in Guan's meta-analysis shared the same trial registration number and lacked clear CRP reporting, introducing uncertainty into the pooled estimate and further contributing to the GRADE downgrading.¹⁶

This duplication may "interfere with" or affect the analysis because:

1. **Risk of effect size bias** – Double-counting the same study can give disproportionate weight to its results, potentially inflating or underestimating the true intervention effect.
2. **Reduced internal validity** – Duplication without correction compromises the accuracy of a meta-analysis by violating the assumption of data independence.
3. **Lower confidence in the results** – As noted in the critical appraisal, the quality of evidence for the CRP outcome was

rated as "very low" due to high risk of bias, unclear outcome reporting, and a limited number of RCTs.

Nevertheless, despite the identified methodological shortcomings in both reviews, the findings consistently indicated a beneficial effect of vitamin D supplementation on CRP levels. Several biological mechanisms may support this effect. Vitamin D receptors (VDRs) inhibit NF- κ B activation, suggesting an intrinsic anti-inflammatory role. NF- κ B, a key molecular target of vitamin D, promotes the release of pro-inflammatory cytokines and the endogenous production of CRP. Moreover, NF- κ B activation can enhance STAT3 signaling, further amplifying inflammation. Its inhibition by vitamin D may therefore attenuate CRP synthesis. Studies have shown that the active form of vitamin D (1,25-dihydroxyvitamin D₃) suppresses NF- κ B activity. It is thus hypothesized that vitamin D supplementation may reduce CRP levels through modulation of NF- κ B and STAT3 pathways.¹⁷

To evaluate the clinical relevance of these mechanistic pathways, both studies included CRP as an inflammatory outcome. As an acute-phase protein produced in response to interleukin-6, CRP reflects systemic inflammation but may not always align with mucosal disease activity in ulcerative colitis. Nevertheless, its clinical value remains significant.¹⁸ A study by Croft, *et al.*, (2022) demonstrated that a CRP threshold of ≥ 12 mg/L had high diagnostic accuracy for acute severe ulcerative colitis, with 95% sensitivity, 85% positive predictive value, and 82% overall accuracy.¹⁹ Furthermore, several sub-studies included in Guan's analysis used high-sensitivity CRP as an inflammatory marker. High-sensitivity CRP can reliably detect concentrations below 0.3 mg/L, and its levels correlate closely with both clinical

and endoscopic activity in ulcerative colitis.²⁰ While CRP, particularly high-sensitivity CRP (hs-CRP), demonstrates significant diagnostic value in ulcerative colitis, current findings don't yet offer definitive evidence regarding the therapeutic efficacy of vitamin D supplementation. Consequently, the existing research is insufficient to recommend its use as an anti-inflammatory agent in the management of UC. Variations in dosage, duration, and co-interventions across studies, coupled with their low methodological quality, result in an overall low to very low certainty of evidence (as reflected in GRADE assessments). These limitations underscore the urgent need for robust, well-designed, double-blind randomized controlled trials with adequate sample sizes, standardized vitamin D regimens, and CRP as a core inflammatory outcome.

CONCLUSION

Current findings do not provide convincing evidence for vitamin D supplementation as a therapeutic approach in ulcerative colitis, particularly for reducing CRP levels. This limitation is due to variations in intervention methods across studies, insufficient reporting of vitamin D dosage, type, and route of administration, and the overall low methodological quality of the available studies, characterized by a high risk of bias, unclear outcomes, and a limited number of randomized controlled trials. Therefore, high-quality randomized controlled trials with robust study designs, standardized interventions, and CRP as a primary inflammatory marker are needed to establish the clinical efficacy of vitamin D in managing inflammation in ulcerative colitis.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this article.

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