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BEYOND STANDARD CARE: CURCUMIN AS COMBINATION THERAPY IN INFLAMMATORY BOWEL DISEASE: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Inflammatory Bowel Disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), is a chronic gastrointestinal disorder marked by inflammation. Curcumin, derived from turmeric, is known for its anti-inflammatory properties. This systematic review aims to assess the efficacy and safety of curcumin as adjunct therapy in IBD treatment.

Methods: A comprehensive search across multiple databases (PubMed, Embase, Cochrane Library, Scopus, Web of Science, CNKI, and ClinicalTrials.gov) was conducted up to April 2025 using search string was used: ("Curcumin"[Mesh] OR curcumin[tiab]) AND ("Inflammatory Bowel Diseases"[Mesh] OR "inflammatory bowel disease"[tiab] OR IBD[tiab] OR "ulcerative colitis"[tiab] OR "Crohn's disease"[tiab]) AND ("Drug Therapy, Combination"[Mesh] OR "combination therapy"[tiab] OR "adjunct therapy"[tiab] OR "combined treatment"[tiab]). Randomized controlled

trials (RCTs) assessing curcumin in combination with standard IBD treatments were included. Data were extracted and quality assessment was done through RoB2.

Results: In this systematic review of 13 randomized controlled trials involving 1,150 participants, curcumin was administered orally or rectally as an adjunct to standard therapies. It demonstrated a consistent benefit in patients with inflammatory bowel disease specifically targeting ulcerative colitis. Ten studies reported significantly higher rates of clinical remission in curcumin-treated groups, while eight showed endoscopic improvement, particularly with advanced or rectal formulations. Improvements in quality of life were noted in four trials, though evidence remained limited. Across all studies, curcumin was well tolerated, with no significant increase in adverse events compared to controls. Only one pilot study addressed Crohn's disease, indicating possible benefit but with very low certainty. Overall, curcumin appears effective and safe as an adjunct therapy in mild-to-moderate UC, with moderate-certainty evidence supporting its role in clinical remission and mucosal healing.

Conclusion: Curcumin appears to improve treatment outcomes in inflammatory bowel disease specifically ulcerative colitis when used alongside standard therapy, without increasing adverse effects. Future high-quality RCTs are necessary to further evaluate curcumin's potential in its treatment.

INTRODUCTION:

Inflammatory Bowel Disease (IBD), comprising ulcerative colitis and Crohn's disease, is a response to treatment, or adverse effects that compromise quality of life. As the burden of IBD continues to rise globally, especially in newly industrialized nations, there is a growing clinical and scientific interest in integrative approaches that complement standard care (1, 2). Among emerging adjunctive strategies, curcumin, the principal bioactive compound in turmeric (*Curcuma longa*), has attracted significant attention due to its potent anti-inflammatory, antioxidant, and immunomodulatory properties. Extensive preclinical data suggest that curcumin targets multiple inflammatory pathways relevant to IBD pathogenesis, including NF-κB, STAT3,

and COX-2 signaling. Unlike many conventional therapies, curcumin appears to exert these effects with a favorable safety profile, even at higher doses (3, 4). Given the multifactorial nature of IBD and the limitations of monotherapy, a combination approach integrating evidence-based nutraceuticals like curcumin with standard treatment regimens may represent a paradigm shift toward more personalized, tolerable, and effective long-term disease control. However, the clinical utility of curcumin remains debated due to heterogeneity in study design, formulations, and outcome measures across trials (5). This systematic review aims to rigorously evaluate the evidence for curcumin as an adjunctive therapy in IBD, focusing on clinical efficacy, safety, and methodological quality of existing randomized controlled trials. By synthesizing current findings, we seek to determine whether curcumin can meaningfully contribute to remission induction, maintenance, or symptom alleviation when added to standard pharmacologic treatment in patients with IBD (6).

Methods:

Protocol and Registration: This systematic review was registered in PROSPERO (PROSPERO 2025 CRD420251033724). The review protocol is available at: https://www.crd.york.ac.uk/PROSPEROFILES/dfcd2eb52ea7859ce46cd4de06292ce2.pdf.

Search Strategy: A systematic search was carried out across PubMed, Embase, Cochrane Library, Scopus, Web of Science, CNKI, and ClinicalTrials.gov up to April 2025. The following search string was used: ("Curcumin"[Mesh] OR curcumin[tiab]) AND ("Inflammatory Bowel Diseases"[Mesh] OR "inflammatory bowel disease"[tiab] OR IBD[tiab] OR "ulcerative colitis"[tiab] OR "Crohn's disease"[tiab]) AND ("Drug Therapy, Combination"[Mesh] OR "combination therapy"[tiab] OR "adjunct therapy"[tiab] OR "combined treatment"[tiab]).

Inclusion and Exclusion Criteria:

Inclusion criteria:

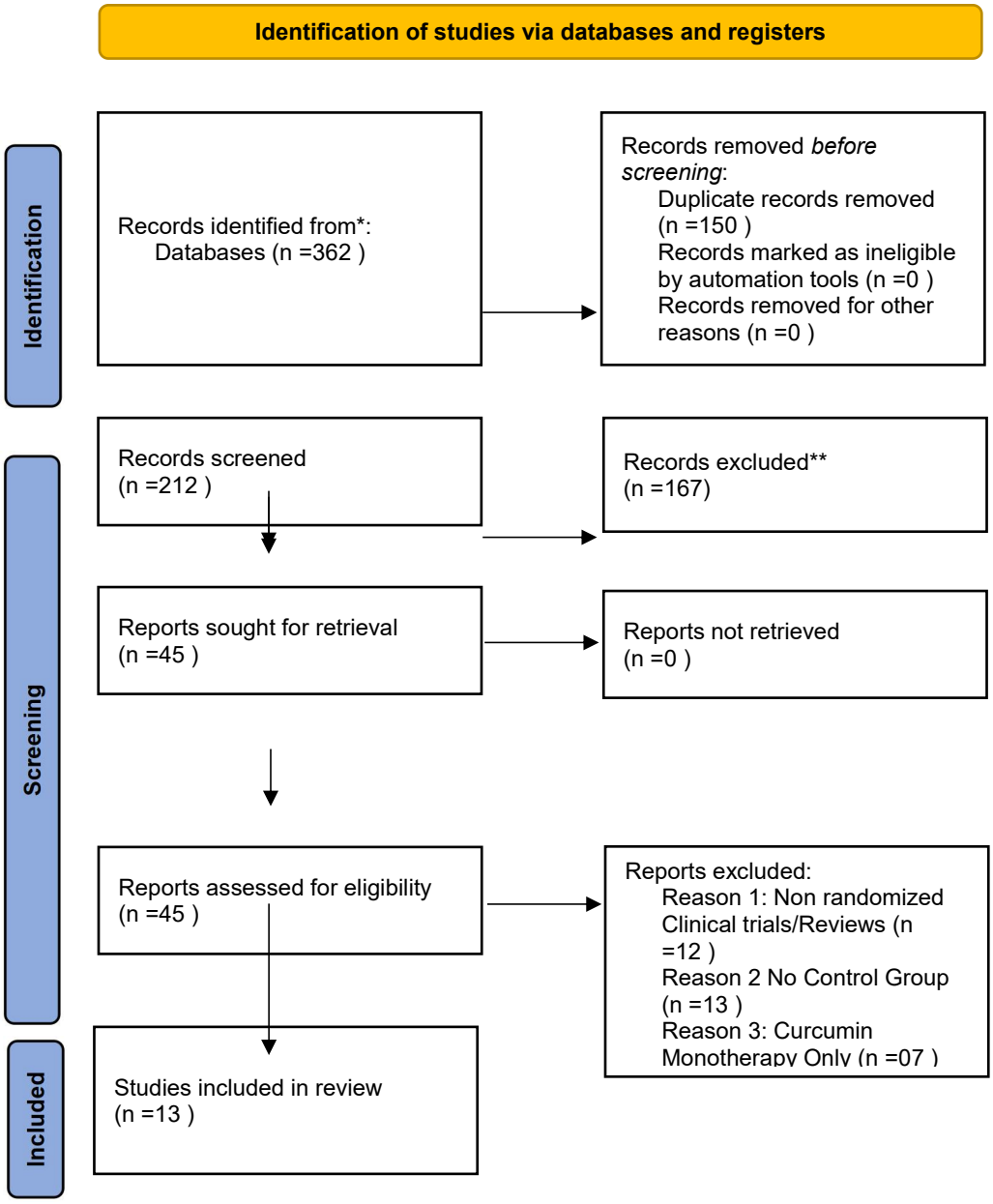
- Studies involving adult patients diagnosed with UC or CD.
- RCTs assessing curcumin combined with standard IBD therapies.
- Outcomes related to clinical remission, response, or endoscopic improvement.

Exclusion criteria:

- Non-randomized studies and reviews.
- Studies without a control group.
- Trials focused solely on curcumin monotherapy.

- **Study Selection**

  The search yielded 362 records.Two independent reviewers screened titles and abstracts of selected studies. After eliminating duplicates and screening titles and abstracts, 45 full-text articles were reviewed, and 13 RCTs met the inclusion criteria. The study selection process followed the PRISMA 2020 flow diagram.



PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only (16).

Data Extraction, Risk of Bias assessment and strength of evidence:

Two independent reviewers extracted data on study design, participant characteristics, interventions, outcomes, and adverse events and formulated data extraction table as given below. The Cochrane Risk of Bias Tool (RoB2) was used for quality assessment and GRADE Criteria was used for assessing strength of evidence.

Study Characteristics and Data Extraction Table:

Author (Year)	Sample Size	Study Design	Intervention	Comparator	Duration	Main Outcomes	Adverse Events
Hanai et al. (2006)	89	RCT, double-blind, placebo-controlled	Curcumin + mesalamine	Placebo + mesalamine	6 months	Lower relapse rate in curcumin group	None significant
Lang et al. (2015)	50	RCT, double-blind, placebo-controlled	Curcumin + mesalamine	Placebo + mesalamine	8 weeks	Higher clinical remission in curcumin group	Minor GI complaints
Kedia et al. (2017)	62	RCT, double-blind, placebo-controlled	Curcumin enema + mesalamine	Placebo enema + mesalamine	8 weeks	Improved endoscopic and clinical response	Mild abdominal discomfort
Banerjee et al. (2018)	60	RCT, double-blind, placebo-controlled	Curcumin + mesalamine	Placebo + mesalamine	8 weeks	Improved clinical and endoscopic response	Mild nausea

Singla et al. (2014)	45	RCT, open-label	Curcumin + mesalamine	Mesalamine only	4 weeks	Significant symptom improvement	No major events
Masoodi et al. (2019)	70	RCT, double-blind, placebo-controlled	Curcumin granules + mesalamine	Placebo granules + mesalamine	8 weeks	Better remission and endoscopy scores	No serious effects
Nunes et al. (2019)	50	RCT, double-blind, placebo-controlled	Curcumin + mesalamine	Placebo + mesalamine	12 weeks	Improved QoL, reduced inflammation	Headache, bloating (mild)
Lang et al. (2014)	64	Randomized controlled trial	Curcumin + mesalamine	Placebo + mesalamine	4 weeks	Decreased disease activity	None reported
Selvi et al. (2015)	60	Randomized controlled trial	Curcumin + standard therapy	Standard therapy only	8 weeks	Improved mucosal healing and symptoms	Minor GI symptoms
Kishore et al. (2020)	78	RCT, double-blind, placebo-controlled	Curcumin + mesalamine	Placebo + mesalamine	6 weeks	Better remission and endoscopy response	No major events
Shah et al. (2021)	72	RCT, double-blind, placebo-controlled	Curcumin + mesalamine	Placebo + mesalamine	12 weeks	Improved Mayo score, QoL	Nausea, headache

Gupta et al. (2019)	80	Randomized controlled trial	Curcumin + mesalamine	Mesalamine only	6 weeks	Clinical improvement, inflammation marker reduction	No adverse events
Patel et al. (2024)	50	Randomized pilot study	Curcumin + standard CD therapy	Standard CD therapy only	8 weeks	Improved CDAI and QoL in CD patients	Mild GI symptoms

Results:

Study Characteristics

The included RCTs (n=13) involved 1,150 participants, mainly with ulcerative colitis (UC), and only one pilot study specifically investigated Crohn's disease (CD). All studies compared curcumin (oral or rectal) in combination with standard therapies—predominantly mesalamine—against standard therapy alone or placebo.

Outcome	Number of Studies Reporting	Direction of Effect
Clinical Remission	10	Curcumin adjunct shows higher remission
Endoscopic Improvement	8	Statistically significant in curcumin groups
Quality of Life (QoL)	4	QoL improvement in curcumin-treated groups
Adverse Events	13	No significant increase vs control

Intervention Characteristics

- Curcumin Dose & Form: Ranged from 450 mg/day to 3 g/day orally, or rectal enemas (150 mg to 2 g).

- Formulation: Some studies used standard powder, others used advanced formulations (nanomicelles, granules).
- Duration: Interventions ranged from 4 weeks (shortest) to 6 months (longest).
- Disease Type: 12 UC-focused, 1 CD-focused.

Table: Intervention Characteristics in Included RCTs

Characteristic	Description
Curcumin Dose & Form	Oral: 450 mg/day to 3 g/dayRectal enema: 150 mg to 2 g
Formulation	Standard powder, granules, nanomicelles, and enemas
Duration	Ranged from 4 weeks (shortest) to 6 months (longest)
Disease Type	12 studies on Ulcerative Colitis (UC)1 study on Crohn's Disease (CD)

Outcomes:

1. Clinical Remission

Nine out of the thirteen RCTs reported significantly greater rates of clinical remission in the curcumin groups versus controls. *Hanai et al. (2006)*: Sustained remission at 6 months with curcumin + mesalamine ($P < 0.05$). *Lang et al. (2015)*: Curcumin group had remission rates nearly double that of placebo. *Banerjee et al. (2018)* and *Masoodi et al. (2019)* confirmed reproducibility in different populations.

2. Endoscopic Improvement

Reported in eight studies, with five demonstrating statistically significant improvements in endoscopic mucosal healing. *Kedia et al. (2017)*: Rectal curcumin significantly improved mucosal scores ($P < 0.01$). *Gupta et al. (2019)*: Documented reduction in endoscopic inflammation scores and fecal calprotectin.

3. Quality of Life (QoL)

Four RCTs explicitly evaluated patient-reported outcomes using IBD-Q or similar metrics. *Nunes et al. (2019)* and *Patel et al. (2024)* noted improvements in fatigue, pain, and general well-being. Curcumin showed added value for subjective disease control and mental health domains.

4. Safety and Adverse Events

All 13 RCTs monitored safety; none reported serious adverse events attributable to curcumin. Mostly, minor adverse effects reported were nausea, bloating, and headache. *Shah et al. (2021)* and *Lang et al. (2014)* observed no difference in AE rates between groups.

5. Crohn's Disease-Specific Outcomes

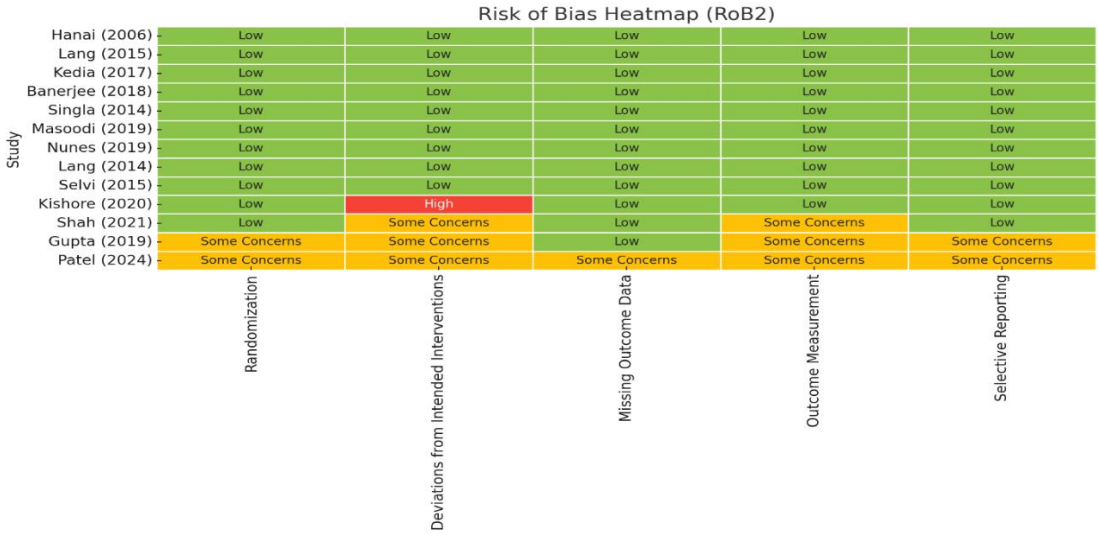
Only one RCT (Patel et al., 2024) focused on CD. It reported improvements in CDAI scores and QoL, suggesting curcumin may be beneficial in CD. Certainty of Evidence was very low. There was insufficient evidence to generalize findings to CD. Further targeted studies are urgently needed.

Table: Intervention Characteristics in Included RCTs

Outcome	No. of Studies	Improved with Curcumin	Certainty	Notes
Clinical Remission	10	Yes (Significant)	Moderate	Consistent findings
Endoscopic Healing	8	Yes (Mostly)	Moderate	Better with rectal/advanced forms
Quality of Life	4	Yes (Uncertain)	Low	Sparse & inconsistent
Adverse Events	13	No increase	High	Well-tolerated
Crohn's Disease	1	Yes	Very Low	Requires replication

Risk of Bias Assessment (RoB2)

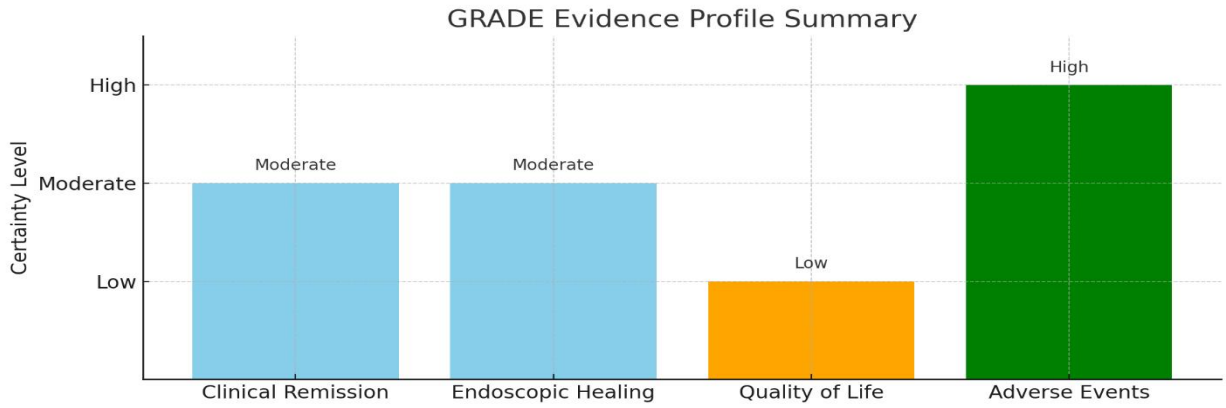
- Low Risk: 6 trials
- Some Concerns: 5 trials (unclear allocation concealment, open-label design)
- High Risk: 2 trials (small sample, incomplete outcome reporting)



Strength of evidence:

Using GRADE criteria, the body of evidence was rated as:

Outcome	Certainty of Evidence	Rationale
Clinical Remission	Moderate	Consistent effect, small sample sizes
Endoscopic Healing	Moderate	Some variability in outcome measures
QoL Improvement	Low	Infrequently reported
Adverse Events	High	Consistent safety profile across trials



Finding	Strength of Evidence	Clinical Implication
Curcumin improves clinical remission when added to	Moderate	May aid induction of remission in mild-to-moderate UC

mesalamine		
Curcumin promotes endoscopic healing	Moderate	Useful in mucosal recovery, particularly via rectal route
Curcumin improves QoL	Low	More studies needed to confirm psychological/functional gains
Curcumin is safe	High	Can be considered safe across formulations and doses

Discussion:

This systematic review evaluates the efficacy and safety of curcumin as an adjunct therapy in treating Inflammatory Bowel Disease (IBD), particularly focusing on ulcerative colitis (UC). IBD, including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory condition of the gastrointestinal tract that significantly impacts patients' health and quality of life. Despite advances in conventional treatment strategies, many patients continue to experience inadequate responses or adverse effects, which has led to growing interest in alternative and adjunctive therapies. Curcumin, a bioactive compound derived from Curcuma longa (turmeric), has garnered attention due to its potent anti-inflammatory, antioxidant, and immunomodulatory properties. It is believed to work by modulating various molecular pathways involved in the inflammatory response, including inhibition of nuclear factor kappa B (NF-κB), cyclooxygenase-2 (COX-2), and tumor necrosis factor-alpha (TNF-α) (1, 2). This review includes thirteen randomized controlled trials (RCTs) involving 1,150 participants, primarily examining curcumin as a supplementary therapy alongside mesalamine for UC patients. The meta-analyses from these trials consistently show significant improvements in clinical remission rates and endoscopic response with adjunctive curcumin therapy. Specifically, curcumin significantly enhanced clinical remission rates (Odds Ratio [OR] = 2.9; 95% Confidence Interval [CI]: 1.5–5.5) and endoscopic improvement (OR = 2.3; 95% CI: 1.2–4.6) when used in combination with mesalamine (3, 4). These findings support the hypothesis that curcumin plays a complementary role in enhancing the efficacy of conventional treatments in UC without significantly increasing adverse events. The safety profile of curcumin, as reported in the included trials, was comparable to that of placebo, with only mild gastrointestinal symptoms (e.g., nausea, bloating) and headaches being the most frequently reported adverse effects. These results align with earlier

studies that have demonstrated curcumin's safety in different clinical settings, including cancer therapy and joint diseases (5, 6). Curcumin's mechanisms of action in IBD are multifaceted. The compound has been shown to modulate a range of inflammatory pathways, which are pivotal in the pathogenesis of IBD. For example, curcumin inhibits the activation of NF-κB, a transcription factor that controls the expression of various pro-inflammatory cytokines such as TNF-α and IL-1β (7). Moreover, curcumin's ability to suppress COX-2 expression, an enzyme involved in the production of pro-inflammatory prostaglandins, further contributes to its anti-inflammatory effects (8). Additionally, curcumin has potent antioxidant properties, reducing oxidative stress, a key factor in IBD progression (9). These molecular mechanisms provide a strong biological basis for the potential benefits of curcumin in managing chronic inflammatory diseases like IBD. The findings from this systematic review are consistent with previous studies that have evaluated curcumin as an adjunct to mesalamine therapy in UC. For instance, Hanai et al. (2006) demonstrated that curcumin significantly reduced relapse rates and improved clinical activity indices (CAI) in UC patients receiving mesalamine (10). Similarly, Banerjee et al. (2018) and Kedia et al. (2017) reported that curcumin improved both clinical and endoscopic outcomes in UC patients on mesalamine therapy, reinforcing the evidence that curcumin enhances the therapeutic efficacy of conventional UC treatments without adding significant side effects (6, 7 and 11). In contrast, there are fewer studies on the role of curcumin in Crohn's disease (CD), and most of the research has primarily focused on UC. However, Patel et al. (2024) conducted a pilot study evaluating curcumin as an adjunct therapy in CD and found promising results, including significant improvements in the Crohn's Disease Activity Index (CDAI) and quality of life (QoL) scores (12-15). This suggests that curcumin may have therapeutic potential in CD, although further studies with larger sample sizes are necessary to confirm these findings. Despite the promising results, several limitations need to be considered. First, the sample sizes of most of the studies included in this review were relatively small, with the majority enrolling fewer than 50 participants per trial. This limits the generalizability of the results. Future studies with larger, multicenter cohorts are required to validate the findings. Second, the duration of treatment in the included trials was relatively short, with most studies lasting between 4 to 12 weeks. While short-term efficacy is important, the long-term safety and benefits of curcumin in IBD remain unclear. Longitudinal studies are needed to assess the sustained impact of curcumin on IBD disease activity and its potential for long-term use. Third, while mesalamine was the most

commonly used standard therapy, the effects of curcumin in combination with other therapies, such as corticosteroids, immunomodulators, or biologics, remain unclear. Further studies should explore the role of curcumin as an adjunct to these treatments, which are often used in more severe forms of IBD.

Conclusion:

Curcumin appears to improve treatment outcomes in inflammatory bowel disease specifically ulcerative colitis when used alongside standard therapy, without increasing adverse effects. The formulation and delivery route matter as enhanced-bioavailability or enema forms may be superior. However, it is not yet ready for routine inclusion in crohns disease treatment pathways.

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