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Nano-curcumin for Clinical Symptoms and Gastrointestinal Inflammation in Children with Celiac Disease: A Pilot Randomized Controlled Trial Protocol

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Abstract

Background: Celiac disease (CD) is a chronic, systemic immune-mediated condition triggered by gluten exposure in genetically predisposed individuals and characterized by intestinal inflammation, mucosal injury, and impaired nutrient absorption. Lifelong adherence to a strict gluten-free diet remains the cornerstone of treatment, yet inflammatory and gastrointestinal manifestations may persist despite dietary adherence. Curcumin has anti-inflammatory and antioxidant properties and may modulate T-cell activation, antigen-presenting cell function, inflammatory signaling, oxidative stress, intestinal barrier integrity, and gut microbial balance. This pilot randomized controlled trial was designed to investigate whether adjunctive nano-curcumin can improve disease-related clinical manifestations and inflammatory biomarkers in children with CD.

Methods: This prospective, single-center, double-blind, placebo-controlled, parallel-group pilot trial will be conducted at Akbar Children's Hospital, Mashhad, Iran. Thirty eligible children aged 5–18 years with celiac disease of less than six months' duration will be randomly allocated in a 1:1 ratio to nano-curcumin (80 mg/day) or matched placebo for 12 weeks while receiving a gluten-free diet. The two primary outcomes are changes from baseline to week 12 in fecal calprotectin and serum tissue transglutaminase IgA (tTG-IgA). Secondary outcomes are gastrointestinal symptoms measured by the Gastrointestinal Symptom Rating Scale (GSRS) and standardized anthropometric measures. The primary analysis will use baseline-adjusted analysis of covariance (ANCOVA); logarithmic transformation will be considered for markedly right-skewed positive biomarker values. Because this is an exploratory pilot trial, the study is not powered to provide definitive evidence of efficacy.

Conclusion: This pilot trial will evaluate the feasibility and preliminary effects of adjunctive nano-curcumin on gastrointestinal symptoms and inflammatory and serological outcomes in children with newly diagnosed CD receiving a gluten-free diet. The study is intended to generate preliminary estimates of treatment effects and outcome variability rather than establish definitive clinical efficacy. Its findings may provide an empirical basis for the design of a subsequent adequately powered randomized controlled trial.

Trial registration: Iranian Registry of Clinical Trials IRCT20240721062501N1. Registered on October 19, 2024.

Key Words: Celiac disease; Curcumin; Inflammation; Immunomodulation; Pediatrics.

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1- INTRODUCTION

1-1. Background and Rationale

Celiac disease (CD) is a chronic systemic condition of immune origin that develops following gluten exposure among genetically predisposed individuals. It is marked by damage to the intestinal mucosal lining, leading to impaired nutrient absorption (1). The global prevalence of CD is estimated to be approximately 1%, although it varies across geographic regions and ethnic groups (2). Notably, the incidence of CD has been increasing over time, with an average annual percentage increase of 7.5% observed in recent decades (3). The clinical spectrum of CD ranges from typical features, including diarrhea and malabsorption, to less characteristic symptoms. Among pediatric patients, the disease is increasingly recognized with milder and atypical clinical patterns, particularly in older children (2, 4). Untreated CD in children may lead to long-term complications, including malnutrition, impaired growth, and an increased risk of autoimmune disorders and gastrointestinal neoplasia (5).

The management of CD primarily relies on lifelong adherence to a gluten-free diet, although this approach is accompanied by nutritional, financial, and psychosocial challenges (6). Moreover, recent research underscores the enduring nature of inflammation in CD, even in patients who have achieved remission. Studies have demonstrated that enterocytes in patients with CD exhibit constitutive inflammation and increased sensitivity to pro-inflammatory stimuli, including gliadin and viruses (7). This chronic inflammation has the potential to irreversibly alter the composition of tissue-resident immunity, resulting in a reduction in certain intraepithelial lymphocytes and an increase in gluten-sensitive T cells (8). The detection of low-grade inflammation before exposure to dietary gluten and the development of clinical disease suggests that inflammation is a key contributor to the pathogenesis of CD (9).

The persistence of inflammation in CD is a complex phenomenon that involves multiple factors, including oxidative stress, imbalances in cytokines, disturbances in the gut microbial community, and gut barrier dysfunction (10, 11).

In CD, an inappropriate immune response to gluten results in the production of reactive oxygen species (ROS). These ROS contribute to oxidative stress, resulting in structural damage at the cellular level that affects membrane lipids, proteins, and nucleic acids. The resulting oxidative injury can further aggravate inflammation within the intestinal mucosa, thereby promoting immune activation and tissue injury (12). Furthermore, the disruption of the intestinal barrier, often referred to as "leaky gut," is exacerbated by oxidative stress. Increased permeability allows antigens and pathogens to enter the bloodstream, intensifying the inflammatory response and worsening clinical symptoms. Oxidative stress is also accompanied by enhanced production of inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), thereby perpetuating the inflammatory cascade and promoting persistent intestinal inflammation (12, 13).

CD is accompanied by a decline in health-promoting bacterial populations, particularly Bifidobacterium species, together with an expansion of potentially pathogenic microorganisms, collectively contributing to increased intestinal permeability (14, 15). Several hypotheses have been put forth regarding the contribution of the gut microbiota to CD pathogenesis. Proposed mechanisms include the production of gliadin-mimicking epitopes by specific bacterial species and the involvement of lipopolysaccharides in initiating immune responses. Furthermore, the gut microbiota

may influence CD by modifying gluten metabolism, stimulating zonulin release, and regulating immune responses through cytokine production. Gut bacteria generate short-chain fatty acids (SCFAs), which are essential for preserving intestinal barrier integrity and regulating immune responses (10).

One condition associated with CD that can complicate management and affect patient outcomes is microscopic colitis (MC). CD and MC frequently co-occur, with a particularly strong relation between CD and the lymphocytic colitis (LC) subtype of MC. The coexistence of CD and collagenous colitis (CC), the other principal MC subtype, is less robust but noteworthy (16, 17). A study examining a cohort of CD patients from 1981 to 2006 revealed a 70-fold increased risk of developing MC in comparison to the general population (18). A systematic review has identified a strong epidemiological link between celiac disease and microscopic colitis, further supporting the close relationship between these inflammatory conditions (19). A systematic review and meta-analysis demonstrated elevated fecal calprotectin levels in patients with microscopic colitis, supporting its use as a non-invasive biomarker of gastrointestinal inflammation (20). Recent studies have demonstrated that elevated fecal calprotectin levels are associated with disease activity and diarrhea in patients with microscopic colitis (21). A retrospective analysis demonstrated the utility of fecal calprotectin as a non-invasive marker for assessing intestinal inflammation in both collagenous and lymphocytic colitis (22).

These findings suggest that effective management of CD requires a multifaceted approach, including strict adherence to a gluten-free diet, the use of biomarkers such as fecal calprotectin, and novel therapies to address persistent inflammation and oxidative stress.

Among the potential therapeutic candidates, curcumin, the principal active compound of turmeric (Curcuma longa), has attracted considerable attention because of its anti-inflammatory and antioxidant properties (23, 24). Curcumin has demonstrated therapeutic potential in several inflammatory disorders, particularly gastrointestinal inflammatory diseases (25, 26).

Nevertheless, no study has specifically focused on the impact of curcumin on the inflammatory progression of CD in children. Accordingly, the current study aims to investigate the effect of curcumin as an adjuvant treatment on gastrointestinal inflammatory markers and clinical symptoms in children with CD. Given the limited bioavailability of curcumin, primarily due to its low solubility in water and poor intestinal permeability, this study will utilize a nano-curcumin formulation that exhibits enhanced absorption.

1-2. Study Objectives

The primary objective is to estimate the preliminary effects and variability of adjunctive nano-curcumin, compared with placebo, on the two prespecified primary serological and inflammatory outcomes in children with CD. Secondary objectives are to obtain preliminary estimates for gastrointestinal symptom burden and anthropometric outcomes and to assess the feasibility and acceptability of the trial procedures.

1-3. Trial Methodology

A prospective pilot clinical trial will be undertaken using a single-center, double-blind, placebo-controlled, parallel-group design. Participants will be individually allocated to the intervention or placebo group in a 1:1 ratio. The study protocol was developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guideline (Table 1). Because the

study is exploratory, its primary statistical purpose is estimation of preliminary between-group treatment effects and variability for planning a subsequent confirmatory trial; it is not intended to provide definitive efficacy evidence.

2- MATERIALS AND METHODS

2-1. Study Site

The eligible participants comprise patients with a confirmed diagnosis of CD who have been referred to the Gastroenterology Clinic of Akbar Children's Hospital in Mashhad, Iran. A screening process will be conducted to identify eligible participants, who will then be recruited for the study.

2-2. Participant Eligibility

2-2-1. Inclusion Requirements

Participants will be eligible if they meet the following criteria: 1) a definitive diagnosis of CD based on the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) criteria (27); 2) newly diagnosed CD within the past six months, with initiation of a strict gluten-free diet (GFD) no more than 4 weeks before trial enrollment; 3) children aged 5–18 years; and 4) informed consent for participation.

2-2-2. Exclusion Requirements

Participants meeting any of the following conditions will be excluded: 1) cardiovascular, liver, or kidney failure; 2) presence of other autoimmune disorders; 3) a history of hospitalization in the preceding four weeks due to celiac crisis; and 4) acute gastroenteritis.

2-2-3. Obtaining Informed Consent

At the start of the trial, the principal investigator will explain the study objectives to the children's parents or legal guardians. Their written informed consent will be obtained before study enrollment.

2-2-4. Consent for the Collection and Use of Participant Data and Biological Specimens

The consent process will ask whether participants agree to the continued use of data collected before withdrawal, as permitted by the approved consent form and applicable regulations. The research team will obtain the necessary permissions to disclose relevant study information to designated academic specialists and regulatory authorities. Clinical specimens collected for the prespecified outcome assessments will be used only for the analyses described in this protocol and will not be retained for genetic or other future molecular analyses.

2-3. Study Interventions

2-3-1. Rationale for Comparator Selection

Participants assigned to the placebo group will continue the standard first-line management of CD, namely a strict gluten-free diet, while nano-curcumin is evaluated as an adjunctive intervention. A matched placebo is therefore used to isolate the incremental effect of nano-curcumin while keeping the background dietary treatment comparable between groups.

2-3-2. Intervention description

The study will utilize nano-curcumin, available in the form of 40 mg soft gelatin capsules under the trade name SinaCurcumin® in the Iranian pharmaceutical market. The placebo will be prepared with the same shape, color, and taste, containing polysorbate 80, vitamin C, vitamin E, soybean oil, and water. In accordance with the double-blind design, curcumin and placebo packs coded as A and B by Exir Nano Sina Company will be assigned to enrolled children. The children will receive either placebo or nano-curcumin at a total dose of 80 mg/day, administered as two 40-mg doses,

for 12 weeks while continuing the prescribed gluten-free diet.

2-3-3. Criteria for Intervention Discontinuation or Modification

If a clinically important intervention-related effect occurs, the study intervention will be withheld or discontinued, the participant will receive appropriate clinical assessment and care, and the principal investigator will document the event and notify the Ethics Committee of Mashhad University of Medical Sciences (MUMS) in accordance with institutional requirements. Intervention discontinuation will also occur at the participant's or parent/legal guardian's request or when the investigator judges continued participation to be unsafe because of clinical deterioration. Discontinuation of the investigational product will not by itself prevent continued outcome assessment or follow-up, unless the participant withdraws consent.

2-3-4. Measures to Promote Intervention Adherence

At enrollment, participants and their parents or legal guardians will receive standardized instructions on taking the study product and on the importance of maintaining the gluten-free diet. Research staff will contact families periodically by telephone to identify problems affecting adherence and to reinforce study instructions. Medication adherence will be assessed by pill count at each four-week follow-up. Non-adherence to the study product will be defined a priori as intake of less than 70% of the prescribed doses. Any interruptions, missed doses, or reasons for non-adherence will be documented.

2-3-5. Permitted and Prohibited Concomitant Care During the Study

The background treatment will be the same in both groups: a gluten-free diet excluding wheat, barley, and rye. Use of additional curcumin-containing products, other investigational anti-inflammatory supplements, or medications that could materially affect the inflammatory outcomes will be prohibited when clinically feasible and otherwise recorded as protocol-concomitant care. Adherence to the gluten-free diet will be assessed at each follow-up by clinical interview and dietary review, and suspected dietary lapses will be documented.

Table-1. Schedule of enrolment, intervention, and assessment based on the SPIRIT guidelines.

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT	**$-t_1$**	**0**	**t_1**	**t_2**	**t_3**	**t_x**
ENROLMENT:						
Eligibility screen	×					
Informed consent	×					
Allocation		×				
INTERVENTION:						
[Gluten-free diet + Nano-curcumin]			◆—	—	—◆	
[Gluten-free diet + Placebo]			◆—	—	—◆	
ASSESSMENT:						
[Demographics Information]	×					
[Serum tTG-IgA]	×	×				×
[Fecal Calprotectin]		×				×
[BMI z-score]		×				×
[GSRS]		×				×
[Adverse Event]			×	×	×	

2-3-6. Post-Trial Care Arrangements

Post-trial care will follow the routine clinical care pathway available at Akbar Children's Hospital. The protocol does not anticipate a high risk of adverse events, but any adverse event occurring during follow-up will be documented and managed according to clinical need and institutional requirements. The absence of anticipated severe adverse events should not be interpreted as an absence of monitoring or as a waiver of appropriate safety assessment. No compensation will be provided.

2-3-7. Outcomes

The two prespecified primary outcomes are the between-group differences in change from baseline to week 12 in fecal calprotectin and serum tTG-IgA. Each primary outcome will be analyzed separately because the outcomes are measured on different scales and represent different biological domains. Secondary outcomes are changes from baseline to week 12 in the GSRS total score and prespecified domain scores, together with changes in weight, height, and BMI-for-age z-score. Fecal calprotectin and serum tTG-IgA will be measured at both baseline and week 12. Fecal calprotectin will be interpreted as a non-specific marker of intestinal inflammation rather than as a disease-specific measure of celiac mucosal activity (28).

2-3-8. Participant Timeline

At baseline, serum tTG-IgA will be measured, and a stool specimen will be collected for fecal calprotectin assessment. Each participant will undergo GSRS assessment and standardized anthropometric measurement. Parents or legal guardians will receive nutritional counseling and an individualized gluten-free diet plan, and adherence to the diet will be assessed at subsequent contacts. Participants will then be randomized to placebo or nano-curcumin and followed every four weeks for 12 weeks. At each visit, adherence will be assessed by pill count, and the next four-week supply will be dispensed. At week 12, blood and stool assessments, GSRS evaluation, and anthropometric measurements will be repeated using the same procedures as at baseline.

2-3-9. Sample size

Because no prior randomized trial has evaluated nano-curcumin for inflammatory outcomes in children with CD, the present study is explicitly designed as an exploratory pilot trial. The sample size was informed by the fecal calprotectin change observed in a randomized trial of nano-curcumin in children with cystic fibrosis Talebi et al., 2023 in which mean ± standard deviation changes were −25 ± 70 in the curcumin group and −4 ± 15 in the placebo group (29). The resulting standardized effect estimate was 0.42. Based on the pilot-trial framework described by Whitehead et al. (2016), 15 participants per group is a feasible external-pilot sample for an anticipated effect size in the range of 0.3–0.7 at a nominal two-sided α of 0.05 (30). Accordingly, 30 participants will be recruited. This sample size is intended to assess feasibility and obtain preliminary estimates of treatment effects and variability; it is not powered for a definitive efficacy test. The effect estimate was borrowed from a different pediatric inflammatory condition and is therefore treated as exploratory rather than as a disease-specific efficacy assumption.

The participants will be recruited from patients referred to a pediatric gastroenterology clinic. Data in the CD registry will be used to facilitate identification and follow-up of potentially eligible participants.

2-4. Randomization and Intervention Allocation

2-4-1. Generation of the Randomization Sequence

The randomization sequence will be generated using permuted blocks of four with the Allocation Random Software random-number table. The sequence will be prepared by an individual who is independent of participant recruitment, clinical assessment, and outcome analysis. The allocation list will use study codes A and B and will not disclose the treatment identity to the recruiting team.

2-4-2. Concealment mechanism

The allocation sequence will be printed and placed in sequentially numbered, identical, opaque, sealed envelopes. Each envelope will be prepared so that the allocation cannot be read through the material, and the seal will show visible evidence of opening or tampering. Envelopes will be stored securely and opened only after a participant has met all eligibility criteria, provided informed consent, and been entered into the trial. The envelope will then be opened in numerical order by the designated allocator, with the allocation assignment documented in the trial record. No member of the recruitment or outcome-assessment team will have access to the sequence before assignment.

2-4-3. Implementation

The primary researcher will identify and enroll eligible participants. An individual external to the clinical trial team will generate the randomization sequence, prepare the concealed envelopes, and control allocation at the time of enrollment. The personnel responsible for baseline and follow-up outcome assessment will not have access to the allocation sequence.

2-5. Randomization Process and Blinding Procedures

2-5-1. Blinding of Study Participants and Personnel

Curcumin and placebo packs will be labeled A and B by Exir Nano Sina and administered according to the double-blind design. Participants, treating investigators, and outcome assessors will remain blinded to treatment allocation. The statistical analyst will work with masked group labels (for example, Group A and Group B) during the prespecified analyses. The allocation code will be held by the designated trial manager and will remain inaccessible to the analyst until database lock and completion of the prespecified primary analysis dataset, except when emergency unblinding is required for participant safety. Routine data review and analysis will be conducted without access to the treatment identities.

2-5-2. Procedures for Emergency Unblinding

Routine unblinding is not permitted before database lock. Emergency unblinding may occur only when knowledge of the treatment assignment is considered essential for the immediate clinical management of a participant. Such an event will be authorized by the principal investigator or designated trial manager, documented with the reason, date, and personnel involved, and reported promptly to the MUMS Ethics Committee. After any emergency unblinding, the participant will continue to be followed whenever consent is maintained, and the incident will be included in the final trial report. The complete treatment code will otherwise be released only after database lock and completion of the prespecified primary analysis.

2.6. Data Recording and Management Procedures

2-6-1. Outcome Evaluation and Collection Methods

Peripheral blood specimens will be collected at baseline and week 12. Approximately 5 mL of blood will be obtained and promptly centrifuged, after

which serum will be separated from cellular components and stored at −80 °C until batch analysis. Serum tTG-IgA will be measured using ELISA in the laboratory of Akbar Children's Hospital. The laboratory will use the same assay platform and lot for baseline and post-intervention samples, and samples from both time points will be analyzed in the same analytical batch whenever feasible. For each analytical run, the laboratory will perform the manufacturer's recommended calibration and internal quality-control procedures and will document acceptance criteria, control results, and any repeat testing. The assay manufacturer's name, kit designation, catalog/lot information, analytical range, and relevant cutoffs used by the laboratory will be recorded in the study laboratory log and reported in the final trial report. Fecal calprotectin will be measured from stool collected at baseline and week 12 using ELISA. Stool samples will be processed promptly according to the laboratory's validated procedure and stored at −80 °C until batch analysis when immediate testing is not possible. Samples will be labeled with the study code, and any deviations in collection, transport, processing, or storage will be documented. Stool examination for overgrowth of bacteria and parasites, particularly Giardia, will be performed using the routine laboratory procedure already specified in the protocol, including assessment of stool pH and the presence of trophozoites or Giardia cysts. All laboratory tests will be carried out in the laboratory of Akbar Children's Hospital by experienced personnel. Histology and endoscopy are not study outcomes, and no research endoscopy is planned as part of the intervention trial; participants will undergo endoscopy only when clinically indicated as part of routine care.

Clinical outcomes will be assessed using the GSRS questionnaire and standardized anthropometric measurements at baseline and week 12. The GSRS is a 15-item instrument comprising five symptom clusters: reflux, abdominal pain, indigestion, diarrhea, and constipation. Each item uses a seven-point Likert scale, with higher scores indicating more troublesome symptoms. Anthropometric measurements will be obtained without shoes using the digital SECA scale and a standardized standing-height technique with the heels positioned against the wall and the head facing forward. Weight will be recorded to the nearest 0.1 kg and height to the nearest 0.5 cm. Measurements will be obtained twice at each assessment; if the two readings differ materially, a third measurement will be taken, and the closest two values will be averaged. The same equipment and standardized positioning will be used at each assessment whenever possible, with equipment checked according to the manufacturer's routine calibration and maintenance procedures. BMI (Body mass index) will be calculated as weight in kilograms divided by height in meters squared, and BMI-for-age z-scores will be derived using WHO growth reference charts. The GSRS refers to gastrointestinal symptoms experienced during the preceding week. It will be administered using standardized instructions; the mode of administration (self-completion or interviewer-assisted completion with parent/guardian support when needed for younger children) will be recorded and kept consistent across assessments for each participant.

2-6-2. Strategies for Enhancing Participant Retention and Follow-up Completion

As our study cohort consists exclusively of pediatric patients, we request that parents or legal guardians submit written reports regarding the outcomes observed in their children. Furthermore, routine follow-up will be

maintained through telephone contacts or complimentary clinic visits.

2-6-3. Data management

The trial database will be generated from clinical questionnaire data and laboratory results. Data will be entered by trained research staff into a password-protected Excel database and analyzed using SPSS version 25. The database will contain predefined variable fields and range checks where applicable. A random selection of 10% of electronic records will be cross-checked against the paper-based questionnaires twice monthly. In the event of discrepancies, source documents will be reviewed, and the affected records will undergo a 50% second review to minimize transcription errors.

2-6-4. Confidentiality

The data obtained from the participants will be securely stored at the designated storage location. The site coordinator will collect personal information for the purpose of facilitating follow-up visits. This information will not be entered into the trial database and will not be accessible to the central trial management team. Additional data were gathered from laboratory samples, questionnaires, and reports, which were then assigned a unique coded identification number. Only clinical staff responsible for recruitment and follow-up can link trial data with participant personal identity. Furthermore, anonymized data will be shared with other investigators to support future international prospective meta-analyses.

2-6-5. Plans for the Collection, Laboratory Assessment, and Storage of Biological Samples for Genetic or Molecular Analyses during the Trial and Future Research

No specimens will be collected or stored for genetic or other future molecular analyses. Blood and stool specimens are collected only for the prespecified clinical and inflammatory outcome assessments described in Section 2.6.1 and are handled and stored temporarily according to the laboratory procedures required to complete those analyses.

2-6-6. Statistical Analysis of Primary and Secondary Outcomes

Statistical analyses will be conducted using IBM SPSS Statistics (version 25 or later). Baseline characteristics will be summarized as frequencies (percentages) for categorical variables, and mean ± standard deviation (SD) or median (interquartile range [IQR]) for continuous variables, as appropriate. The primary analysis will compare the two randomized groups using analysis of covariance (ANCOVA), with the week-12 outcome as the dependent variable, treatment group as the fixed factor, and the corresponding baseline outcome as a covariate. Adjusted between-group mean differences, 95% confidence intervals (CIs), and two-sided P values will be reported separately for fecal calprotectin and serum tTG-IgA. Distributional assumptions will be assessed using histograms and Q-Q plots of the outcome and model residuals. Because fecal calprotectin and tTG-IgA may be right-skewed, a natural logarithmic transformation will be considered when the biomarker values are positive and show marked skewness. When a log transformation is used, results will be interpreted on the transformed scale and, where appropriate, back-transformed estimates will be reported. Model assumptions, including linearity, homogeneity of regression slopes, and homoscedasticity, will be assessed from model diagnostics. No repeated-measures or pairwise pre/post testing will be used for the primary analysis because only baseline and week-12 assessments are planned. The same baseline-adjusted ANCOVA approach will be used for

secondary continuous outcomes. Secondary-outcome P values will be adjusted using the Benjamini–Hochberg false-discovery-rate procedure. No multiplicity adjustment will be applied to the two prespecified primary outcomes because this is an exploratory pilot study focused on estimation rather than confirmatory efficacy testing; interpretation will emphasize effect estimates and 95% CIs. Paired t-tests, independent-samples t-tests, Wilcoxon signed-rank tests, or Mann–Whitney U tests will be used only for clearly labeled exploratory or descriptive comparisons when appropriate and will not replace the prespecified ANCOVA.

2-6-7. Interim Data Analyses

No interim efficacy analysis is planned. Safety information will be reviewed continuously. The occurrence of a serious adverse event, an unexpected clinically important adverse event, repeated treatment-related adverse events, or a pattern suggesting unacceptable risk will prompt immediate review by the principal investigator and notification of the MUMS Ethics Committee. The intervention may be suspended or discontinued when continuation is judged unsafe. No formal statistical stopping boundary will be used because this is an exploratory pilot trial.

2-6-8. Approaches to Additional Analyses (e.g., Subgroup Analyses)

Any exploratory subgroup analysis by disease severity, classified as mild or moderate-to-severe according to serum tTG-IgA using the prespecified cutoff of 148 IU/mL (31), will be considered hypothesis-generating. Because the pilot sample is small, subgroup estimates will be presented with 95% confidence intervals and interpreted cautiously; no formal claim of treatment-effect modification will be made.

2-6-9. Statistical Approaches to Address Protocol Non-adherence and Missing Data

All randomized participants will remain in their assigned treatment groups for analysis. The primary ANCOVA will use participants with both baseline and week-12 measurements available for the relevant outcome. Last observation carried forward will not be used. If more than 5% of randomized participants have missing week-12 data for a primary outcome, a sensitivity analysis using multiple imputation under a missing-at-random assumption will be conducted using 20 imputed datasets and including treatment group, baseline outcome value, age, sex, and other available prognostic variables relevant to the outcome. Complete-case and imputed results will be compared to assess robustness. If missingness is 5% or less, the amount and reasons for missingness will be reported, and no imputation will be performed unless clinically justified. A prespecified per-protocol sensitivity analysis will include participants who complete the 12-week assessment, have at least 70% adherence to the study product, and have no major protocol deviations. Reasons for missing assessments, intervention discontinuation, and withdrawal will be reported by treatment group.

2-6-10. Data Sharing Plan for the Full Protocol, Participant-Level Data, and Statistical Code

Following the publication of the main results, the corresponding author could, upon reasonable request, make available the anonymized trial data and statistical codes.

2-7. Oversight and Monitoring

2-7-1. Composition of the Coordinating Center and Trial Steering Committee

The Ethics Committee and Vice Chancellery for Research of MUMS

oversee all aspects of the study, ensuring that the highest standards of academic integrity and impartiality are maintained.

2-7-2. Organization and Responsibilities of the Trial Monitoring Team

A formal Data Monitoring Committee was not established because this is a small, single-center pilot study with a short intervention period and no anticipated high-risk procedure. Safety oversight will instead be provided continuously by the principal investigator and the MUMS Ethics Committee, with expedited review of any serious or unexpected safety signal.

2-7-3. Safety Monitoring and Reporting of Adverse Events

Adverse events will be actively assessed at each follow-up contact and visit, with additional reporting encouraged between visits. Each event will be recorded with its onset and resolution dates, clinical description, severity, action taken, outcome, and relationship to the study intervention. Severity will be graded as mild, moderate, or severe according to the clinical impact on daily activities and need for medical intervention. Causality will be assessed by the investigator as unrelated, unlikely, possible, probable, or definite, based on temporal relationship, alternative explanations, dechallenge, and rechallenge when applicable. A serious adverse event will be defined according to standard clinical-trial criteria, including death, a life-threatening event, hospitalization or prolongation of hospitalization, persistent or substantial disability, or another medically important event requiring urgent intervention. Serious adverse events will be reported promptly to the MUMS Ethics Committee according to institutional requirements. The intervention will be interrupted or discontinued for clinically significant toxicity, a serious or unexpected suspected intervention-related event, repeated treatment-related events indicating an emerging safety signal, or any event for which continued exposure is judged unsafe. An independent Data Monitoring Committee is not planned; the Ethics Committee provides independent oversight of participant safety within the institutional framework.

2-7-4. Trial Monitoring and Auditing Procedures

The Ethics Committee of MUMS will be kept informed throughout the study, from the initial development of the protocol until study completion, and will review trial conduct at least twice.

2-7-5. Communication of Protocol Revisions to Key Stakeholders

Any modifications to the study protocol arising during the course of the study shall be submitted to the institutional ethics board for approval before implementation and subsequently updated in the trial registry.

2-7-6. Dissemination plans

The results, regardless of the magnitude or direction of the findings, will be disseminated through peer-reviewed publication. All planned dissemination will follow the approved protocol and applicable reporting standards. The corresponding author will coordinate submission and communication, and the sponsor has not placed restrictions on publication.

3- DISCUSSION

Curcumin, a natural polyphenolic compound derived from turmeric, has demonstrated anti-inflammatory, antioxidant, antimicrobial, and other pharmacological activities, with relatively low intrinsic toxicity (24). Systematic reviews and meta-analyses further suggest that curcumin can modulate immune responses across several inflammatory and immune-mediated conditions (25, 26).

These properties provide a biological rationale for investigating curcumin as an adjunctive intervention in CD, particularly during the early period after diagnosis when intestinal inflammation and gastrointestinal symptoms may persist despite initiation of a GFD.

Curcumin may exert immunomodulatory effects through several complementary pathways. It has been shown to suppress T-cell activation through downregulation of CD69 expression and interference with calcium mobilization and nuclear factor of activated T cells (NFAT) signaling, with consequent reductions in pro-inflammatory cytokines such as interleukin-2 (IL-2) and interferon-γ (IFN-γ) (32). It may also modulate antigen-presenting cell (APC) activity and suppress the expression of co-stimulatory molecules (33). In addition, curcumin may attenuate nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling while enhancing nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated antioxidant defenses. Modulation of cyclooxygenase (COX), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS) pathways may further reduce inflammatory mediator production (34-36). Collectively, these mechanisms provide a plausible basis for an effect on the inflammatory and oxidative processes involved in CD.

Experimental evidence provides more direct support for this rationale. Gupta et al. demonstrated that gliadin exposure increased oxidative stress, inflammatory mediators, and cellular injury, including increases in advanced oxidation protein products (AOPPs), myeloperoxidase (MPO), NADPH oxidase (NOX), pro-inflammatory cytokines, and matrix metalloproteinases (MMP-2/MMP-9), together with reductions in IL-10 and integrin expression. Curcumin pretreatment attenuated these changes and contributed to preservation of cellular morphology and function (37). Curcumin may also influence intestinal homeostasis through modulation of the gut microbiota and epithelial barrier. Evidence suggests potential effects on bacterial populations, including increases in Lactobacillus and Bifidobacterium and inhibition of potentially pathogenic microorganisms (38, 39), as well as improvement of tight-junction-associated proteins such as zonula occludens-1 (ZO-1), occludin, and claudin (39-42). These mechanisms are relevant to CD, in which intestinal inflammation, oxidative stress, microbial alterations, and impaired epithelial barrier function are implicated in disease pathogenesis (Figure 1).

Clinical evidence, although indirect, provides additional support for evaluating curcumin in gastrointestinal inflammatory conditions. Sadeghi et al. reported that curcumin supplementation at 1,500 mg/day for eight weeks improved clinical outcomes and reduced serum erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hs-CRP) in patients with ulcerative colitis (43). Similarly, Ben-Horin et al. reported that eight weeks of treatment with a curcumin-containing herbal formulation resulted in a reduction of at least 50% in fecal calprotectin in 46% of treated patients compared with 15% of placebo-treated patients (44). However, differences in disease characteristics, formulations, doses, and treatment settings limit direct extrapolation of these findings to CD. Pediatric tolerability data are also limited but encouraging. Suskind et al. reported no significant adverse events in children with controlled inflammatory bowel disease receiving curcumin, although bloating occurred in 2 of 11 participants (45). Differences in disease type, formulation, dose, and clinical context nevertheless limit the applicability of these findings to children with CD.

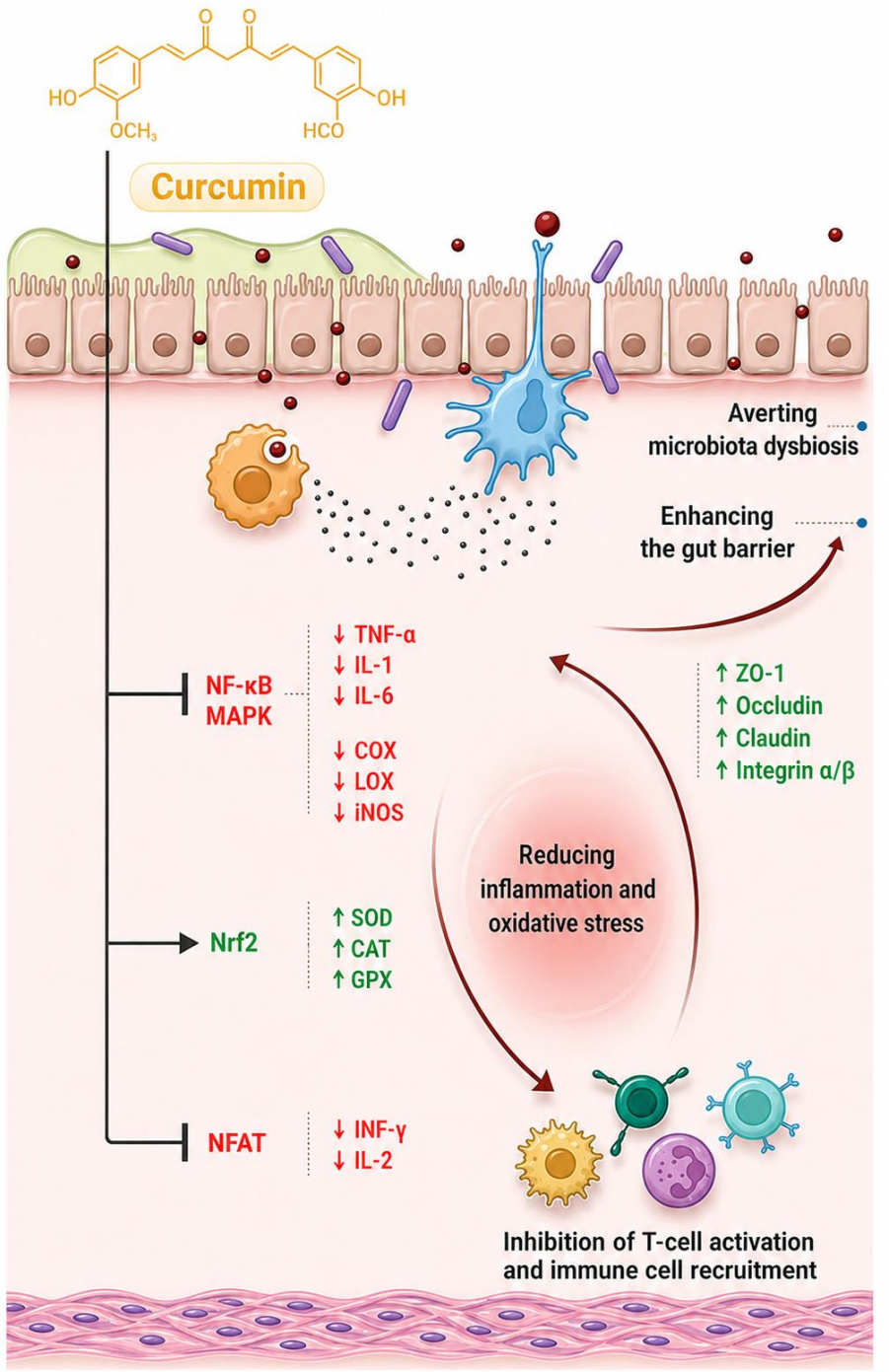

Figure-1: Schematic representation of the protective effects of curcumin against celiac disease.

Despite this biological rationale and indirect clinical evidence, no trial among the cited literature has specifically evaluated curcumin for gastrointestinal inflammation and clinical symptoms in children with CD. The present study therefore addresses an important evidence gap through an exploratory pilot randomized controlled trial. Its primary purpose is not to establish definitive efficacy, but to assess the feasibility of the trial procedures, evaluate the practicality of the planned clinical, anthropometric, serological, and inflammatory assessments, and generate preliminary estimates of treatment effects and outcome variability to inform a subsequent adequately powered trial.

The study has several methodological strengths, including its randomized, double-blind, placebo-controlled design and standardized evaluation of nano-curcumin as an adjunct to a GFD. The assessment of both gastrointestinal symptoms and objective inflammatory and serological outcomes may provide complementary information regarding potential treatment effects. Nevertheless, the small sample size, single-center setting, and relatively short follow-up will limit statistical precision, generalizability, and assessment of longer-term outcomes. In addition, fecal calprotectin is not specific to CD, and changes in tTG-IgA may partly reflect the expected response to a GFD. Accordingly, these biomarkers will be interpreted as exploratory between-group signals rather than definitive measures of mucosal healing or disease remission.

Overall, the existing evidence provides a plausible biological and preliminary clinical basis for evaluating nano-curcumin as an adjunctive intervention in children with newly diagnosed CD, while direct evidence in this population remains lacking. The present pilot trial is therefore intended to determine the feasibility of the proposed approach and provide preliminary estimates that can guide the design and sample-size planning of a future adequately powered multicenter randomized controlled trial.

4- CONCLUSION

This pilot randomized controlled trial is designed to evaluate the potential effects of adjunctive nano-curcumin on gastrointestinal symptoms and inflammatory and serological outcomes in children with newly diagnosed CD receiving a GFD. Given the absence of direct clinical evidence in this population, the study is primarily intended to assess feasibility and generate preliminary estimates of treatment effects and outcome variability rather than establish definitive efficacy. The findings may inform the design and justification of future adequately powered trials evaluating nano-curcumin as a potential adjunct to standard dietary management in pediatric CD.

5- ABBREVIATIONS

AOPP: Advanced oxidation protein product; **APC:** Antigen-presenting cell; **BMI:** Body mass index; **CAT:** Catalase; **CC:** Collagenous colitis; **CD:** Celiac disease; **COX:** Cyclooxygenase; **ESPGHAN:** European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; **ESR:** Erythrocyte sedimentation rate; **GPX:** Glutathione peroxidase; **GSRS:** Gastrointestinal Symptom Rating Scale; **hs-CRP:** High sensitive C-reactive protein; **IBD:** Inflammatory bowel disease; **IFN-γ:** Interferon-gamma; **IL:** Interleukin; **iNOS:** Inducible nitric oxide synthase; **LC:** Lymphocytic colitis; **LOX:** Lipoxygenase; **MAPK:** Mitogen-activated protein kinase; **MC:** Microscopic colitis; **MMP:** Matrix metalloproteinases; **MPO:** Myeloperoxidase; **NFAT:** Nuclear factor of activated T cells; **NF-κB:** Nuclear factor kappa B; **NOX:** NADPH oxidase; **Nrf2:** Nuclear factor E2-related factor 2; **RA:** Rheumatoid arthritis; **ROS:** Reactive oxygen species; **SCFA:** Short-chain fatty acid; **SOD:** Superoxide dismutase; **TNF-α:** Tumor necrosis factor-alpha; **tTG-IgA:** tissue Transglutaminase IgA

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7- FUNDING

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will supervise all aspects of the research, including the design of the study, data collection, analysis, and interpretation, as well as the preparation of the manuscript.

8- RESEARCH ETHICS AND INFORMED CONSENT

The research project was approved by the Ethics Committee of Mashhad University of Medical Sciences. Approval was granted under reference number IR.MUMS.REC.1403.263. Written informed consent will be obtained from all study participants or their legal guardians.

9- CONSENT FOR PUBLICATION

The report does not contain any personally identifiable information about individual participants. The participant information and informed consent materials are available from the corresponding author upon request.

10- AVAILABILITY OF DATA AND MATERIALS

Access to the final datasets will be granted exclusively to researchers who have obtained ethical approval. The datasets analyzed will be available from the corresponding author upon reasonable request.

11- COMPETING INTERESTS

The authors declare that they have no competing interests.

12- REFERENCES

1. Caio G, Volta U, Sapone A, Leffler DA, De Giorgio R, Catassi C, et al. Celiac disease: a comprehensive current review. BMC medicine. 2019 Jul 23;17(1):142.

2. Sahin Y. Celiac disease in children: A review of the literature. World journal of clinical pediatrics. 2021 Jul 9;10(4):53.

3. King JA, Jeong J, Underwood FE, Quan J, Panaccione N, Windsor JW, et al. Incidence of celiac disease is increasing over time: a systematic review and meta-analysis. American Journal of Gastroenterology. 2020 Apr;115(4):507-25.

4. Sansotta N, Amirikian K, Guandalini S, Jericho H. Celiac disease symptom resolution: effectiveness of the gluten-free diet. Journal of pediatric gastroenterology and nutrition. 2018 Jan;66(1):48-52.

5. Kårhus LL, Skaaby T, Petersen J, Madsen AL, Thuesen BH, Schwarz P, et al. Long-term consequences of undiagnosed celiac seropositivity. American Journal of Gastroenterology. 2020 Oct;115(10):1681-8.

6. Aljada B, Zohni A, El-Matary W. The gluten-free diet for celiac disease and beyond. Nutrients 2021; 13: 3993. Recent Advances and Remaining Challenges. 2021:265.

7. Porpora M, Conte M, Lania G, Bellomo C, Rapacciuolo L, Chirdo FG, et al. Inflammation is present, persistent and more sensitive to proinflammatory triggers in celiac disease enterocytes. International Journal of Molecular Sciences. 2022 Feb 10;23(4):1973.

8. Mayassi T, Ladell K, Gudjonson H, McLaren JE, Shaw DG, Tran MT, et al. Chronic inflammation permanently reshapes tissue-resident immunity in celiac disease. Cell. 2019 Feb 21;176(5):967-81.

9. Barone MV, Auricchio R, Nanayakkara M, Greco L, Troncone R, Auricchio S. Pivotal role of inflammation in celiac disease. International journal of molecular sciences. 2022 Jun 28;23(13):7177.

10. Rossi RE, Dispinzieri G, Elvevi A, Massironi S. Interaction between gut microbiota and celiac disease: from pathogenesis to treatment. Cells. 2023 Mar 7;12(6):823.

11. Ferretti G, Bacchetti T, Masciangelo S, Saturni L. Celiac disease, inflammation and oxidative damage: a nutrigenetic approach. Nutrients. 2012 Mar 27;4(4):243-57.

12. Maluf SW, Wilhelm Filho D, Parisotto EB, Medeiros GD, Pereira CH, Maraslis FT, et al. DNA damage, oxidative stress, and inflammation in children with celiac disease. Genetics and Molecular Biology. 2020 Jun 10;43(2):e20180390.

13. Moretti S, Mrakic-Sposta S, Roncoroni L, Vezzoli A, Dellanoce C, Monguzzi E, et al. Oxidative stress as a biomarker for monitoring treated celiac disease. Clinical and translational gastroenterology. 2018 Jun 8;9(6):157.

14. Sanz Y, Sánchez E, Marzotto M, Calabuig M, Torriani S, Dellaglio F. Differences in faecal bacterial communities in coeliac and healthy children as detected by PCR and denaturing gradient gel electrophoresis. FEMS Immunology & Medical Microbiology. 2007 Dec 1;51(3):562-8.

15. Collado MC, Donat E, Ribes-Koninckx C, Calabuig M, Sanz Y. Specific duodenal and faecal bacterial groups associated with paediatric coeliac disease. Journal of clinical pathology. 2009 Mar;62(3):264-9.

16. Villanueva MS, Alimi Y. Microscopic colitis (lymphocytic and collagenous), eosinophilic colitis, and celiac disease. Clinics in colon and rectal surgery. 2015 Jun;28(02):118-26.

17. Koskela R. Microscopic colitis: clinical features and gastroduodenal and immunogenetic findings. University of Oulu; 2011 May 10.

18. Green PH, Yang J, Cheng J, Lee AR, Harper JW, Bhagat G. An association between microscopic colitis and celiac disease. Clinical Gastroenterology and Hepatology. 2009 Nov 1;7(11):1210-6.

19. Nimri FM, Muhanna A, Almomani Z, Khazaaleh S, Alomari M, Almomani L, et al. The association between microscopic colitis and celiac disease: a systematic review and meta-analysis. Annals of Gastroenterology. 2022 Apr 8;35(3):281.

20. Songtanin B, Kahathuduwa C, Nugent K. Fecal calprotectin level in microscopic colitis: a systematic review and meta-analysis. InBaylor University Medical Center Proceedings 2023 Sep 3 (Vol. 36, No. 5, pp. 641-646). Taylor & Francis.

21. Ardelean MV, Kundnani NR, Sharma A, Dumitru M, Buzas R, Rosca CI, et al. Fecal calprotectin–a valuable predictor of microscopic colitis. European Review for Medical & Pharmacological Sciences. 2022 Dec 15;26(24):9382.

22. Songtanin B, Evans A, Nugent K, Costilla V. The utility of fecal calprotectin in the diagnosis and management of microscopic colitis. Journal of Community Hospital Internal Medicine Perspectives. 2023 Jun 29;13(4):71.

23. Witkin JM, Li X. Curcumin, an active constiuent of the ancient medicinal herb Curcuma longa L.: some uses and the establishment and biological basis of medical efficacy. CNS & Neurological Disorders-Drug Targets-CNS & Neurological Disorders). 2013 Jun 1;12(4):487-97.

24. Maheshwari RK, Singh AK, Gaddipati J, Srimal RC. Multiple biological activities of curcumin: a short review. Life sciences. 2006 Mar 27;78(18):2081-7.

25. Zeng L, Yang T, Yang K, Yu G, Li J, Xiang W, Chen H. Curcumin and curcuma longa extract in the treatment of 10 types of autoimmune diseases: A systematic review and meta-analysis of 31 randomized controlled trials. Frontiers in immunology. 2022 Aug 1;13:896476.

26. Haftcheshmeh SM, Mirhafez SR, Abedi M, Heydarlou H, Shakeri A, Mohammadi A, et al. Therapeutic potency of curcumin for allergic diseases: A focus on immunomodulatory actions. Biomedicine & Pharmacotherapy. 2022 Oct 1;154:113646.

27. Husby S, Koletzko S, Korponay-Szabó I, Kurppa K, Mearin ML, Ribes-Koninckx

C, et al. European society paediatric gastroenterology, hepatology and nutrition guidelines for diagnosing coeliac disease 2020. Journal of pediatric gastroenterology and nutrition. 2020 Jan;70(1):141-56.

28. Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. Quality of life research. 1997 Jan;7(1):75-83.

29. Talebi S, Day AS, Safarian M, Sayedi SJ, Jaafari MR, Abbasi Z, et al. Adjunctive nano-curcumin therapy improves inflammatory and clinical indices in children with cystic fibrosis: A randomized clinical trial. Food science & nutrition. 2023 Jun;11(6):3348-57.

30. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Statistical methods in medical research. 2016 Jun;25(3):1057-73.

31. Jafari SA, Khalesi M, Kianifar H, Shojaie H, Kiani MA. Serum Anti TTG Level as a Predictor for Severity of Iintestinal Damage in Children with Celiac Disease. Journal of Pediatric Perspectives. 2021;9(12):15076-82.

32. Kliem C, Merling A, Giaisi M, Köhler R, Krammer PH, Li-Weber M. Curcumin suppresses T cell activation by blocking Ca2+ mobilization and nuclear factor of activated T cells (NFAT) activation. Journal of biological chemistry. 2012 Mar 23;287(13):10200-9.

33. Lin Y, Liu H, Bu L, Chen C, Ye X. Review of the Effects and Mechanism of Curcumin in the Treatment of Inflammatory Bowel Disease. Front Pharmacol. 2022;13:908077.

34. Ali T, Shakir F, Morton J. Curcumin and inflammatory bowel disease: biological mechanisms and clinical implication. Digestion. 2012 Jun;85(4):249-55.

35. Molaei E, Molaei A, Abedi F, Hayes AW, Karimi G. Nephroprotective activity of natural products against chemical toxicants: The role of Nrf2/ARE signaling pathway. Food Science & Nutrition. 2021 Jun;9(6):3362-84.

36. Xu G, Gu Y, Yan N, Li Y, Sun L, Li B. Curcumin functions as an anti-inflammatory and antioxidant agent on arsenic-induced hepatic and kidney injury by inhibiting MAPKs/NF-κB and activating Nrf2 pathways. Environmental toxicology. 2021 Nov;36(11):2161-73.

37. Gupta KB, Mantha AK, Dhiman M. Mitigation of gliadin-induced inflammation and cellular damage by curcumin in human intestinal cell lines. Inflammation. 2021 Jun;44(3):873-89.

38. Di Meo F, Margarucci S, Galderisi U, Crispi S, Peluso G. Curcumin, gut microbiota, and neuroprotection. Nutrients. 2019 Oct 11;11(10):2426.

39. Jabczyk M, Nowak J, Hudzik B, Zubelewicz-Szkodzińska B. Curcumin and its potential impact on microbiota. Nutrients. 2021 Jun 10;13(6):2004.

40. Liu X, Zhu H. [Retracted] Curcumin Improved Intestinal Epithelial Barrier Integrity by Up-Regulating ZO-1/Occludin/Claudin-1 in Septic Rats. Evidence-Based Complementary and Alternative Medicine. 2022;2022(1):2884522.

41. Huang J, Guan B, Lin L, Wang Y. Improvement of intestinal barrier function, gut microbiota, and metabolic endotoxemia in type 2 diabetes rats by curcumin. Bioengineered. 2021 Dec 20;12(2):11947-58.

42. Zam W. Gut microbiota as a prospective therapeutic target for curcumin: A review of mutual influence.

Journal of nutrition and metabolism. 2018;2018(1):1367984.

43. Sadeghi N, Mansoori A, Shayesteh A, Hashemi SJ. The effect of curcumin supplementation on clinical outcomes and inflammatory markers in patients with ulcerative colitis. Phytotherapy Research. 2020 May;34(5):1123-33.

44. Ben-Horin S, Salomon N, Karampekos G, Viazis N, Lahat A, Ungar B, et al. Curcumin-QingDai combination for patients with active ulcerative colitis: a randomized, double-blinded, placebo-controlled trial. Clinical Gastroenterology and Hepatology. 2024 Feb 1;22(2):347-56.

45. Suskind DL, Wahbeh G, Burpee T, Cohen M, Christie D, Weber W. Tolerability of curcumin in pediatric inflammatory bowel disease: a forced-dose titration study. Journal of pediatric gastroenterology and nutrition. 2013 Mar;56(3):277-9.