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Effects of bromelain supplementation on disease activity and quality of life in patients with ulcerative colitis: a randomized, triple-blind, placebo-controlled study

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Bromelain is a proteolytic enzyme found in pineapple fruit. This study was conducted to evaluate the effects of bromelain supplementation on disease activity and quality of life (QoL) in patients with ulcerative colitis (UC). Seventy individuals with mild-to-moderate UC participated in a randomized, triple-blind clinical trial. Participants were randomly assigned to receive either maltodextrin as a placebo or 400 mg of bromelain daily for eight weeks. QoL and Simple Clinical Colitis Activity Index (SCCAI) scores were assessed. All results were analyzed using both intention-to-treat (ITT) and per-protocol (PP) approaches. The only demographic factor that differed between the two groups statistically significantly was gender ($p = 0.01$). Additionally, the mean difference in vitamin B6 consumption variations between the bromelain and placebo groups was significant (0.39 ± 0.86 vs. -0.44 ± 1.43; $p < 0.001$). There was no considerable difference detected for the other nutrients. The bromelain group had considerably higher changes in their SCCAI score in comparison with the placebo group (-3.29 ± 2.17 vs. -1.11 ± 1.71; $p < 0.001$). There was no considerable difference in changes in QoL questionnaire scores between the intervention and control groups (3.76 ± 6.18 vs. 3.91 ± 4.30; $p = 0.90$). After correcting for baseline, the findings remained significant for the SCCAI variable but not for the QoL variable ($p < 0.001$ and $p = 0.99$). In UC patients, the severity of the disease is reduced by bromelain supplementation, which is an alternative therapy.

Trial registration: The study protocol received approval from the Ethics Committee at Iran University of Medical Sciences "IR.IUMS.REC.1402.125" and was registered with the Iranian Clinical Trials Registry "IRCT20191105045340N2" on 09/07/2023.

Keywords Bromelain, Inflammatory bowel disease, Disease activity, Quality of life, Ulcerative colitis

Inflammatory bowel disease (IBD) is a chronic gastrointestinal disorder that includes both crohn's disease (CD) and ulcerative colitis (UC), with UC being more prevalent than CD[1,2]. In UC, continuous inflammation is limited to the intestinal mucosa, submucosa, and crypt cells, leading to the formation of ulcers in the colonic mucosal lining[3–5]. Generally, UC presents with symptoms such as fatigue, diarrhea, bloody stools, abdominal discomfort, weight fluctuations, mucin deficiency, and shortening or loss of intestinal crypt cells[1,6–9]. IBD has emerged as a global health concern. Its epidemiologic evolution can be categorized into four stages: (1) Emergence, (2)

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Acceleration of Incidence, (3) Compounding Prevalence, (4) Prevalence Equilibrium[10]. Western countries are currently in the third epidemiologic stage (compounding prevalence)[11]. In contrast, newly industrialized nations are in the second stage (acceleration of incidence) characterized by low prevalence but rapidly rising case numbers[12]. By 2035, incidence in Western countries is expected to remain stable at approximately 30 per 100,000 annually, with an average annual change of 0.36%[13]. Projections indicate a marked rise in ulcerative colitis cases in Asian nations and Iran by 2035[14,15]. Enhancing quality of life (QoL) is a primary goal in the treatment of IBD[4,16]. Currently, patients with IBD are treated with a variety of medications, including tumor necrosis factor-α (TNF-α) blockers, aminosalicylates, corticosteroids, antibiotics, and thiopurines. These drugs are associated with a range of potential adverse effects, from moderate to severe, such as infections, osteoporosis, depression, stress, anxiety, and mutagenesis. As a result, alternative therapeutic agents may be considered to help manage IBD, maintain remission, and support gastrointestinal health in affected individuals[17]. In pineapple fruit, bromelain is a predominant proteolytic enzyme that has anti-inflammatory, anticoagulant, fibrinolytic, and edema-inhibiting properties[18]. After oral ingestion, it has no adverse effects because of its high efficiency[18,19]. Bromelain reduces the production and activity of cyclooxygenase-2 (COX-2) and nuclear factor kappa light chain enhancer of activated B lymphocytes (NF-κB), which are involved in the manufacturing of pro-inflammatory factors like interferon, according to both in vitro and in vivo investigations. Interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (1 L-8), interferon gamma (IFN-γ), and TNF-α are all involved[17]. Research indicates that chronic illnesses such as IBD can negatively impact a person's quality of life and symptom severity, while also increasing susceptibility to mental health disorders, including depression[18,19]. While the anti-inflammatory properties of bromelain are well-documented in vitro and in animal models, our search indicates that no human studies have yet been conducted on its effects in patients with inflammatory bowel disease. Considering the adverse effects associated with long-term use of conventional UC medications, there is an urgent need to explore alternative, safe, and natural adjunct therapies that may improve disease outcomes and patients' quality of life. Our study aims to contribute to this emerging area by investigating the effects of bromelain supplementation as a complementary intervention alongside standard treatments. Given the increasing prevalence of IBD and the limited human research on bromelain, this study aimed to investigate the effects of bromelain supplementation on disease activity and quality of life in patients with UC.

Materials and methods

Participants

The effects of bromelain on quality of life and disease activity were evaluated in seventy patients with UC who were referred to the gastrointestinal clinic at Rasoul Akram Hospital between October 2023 to October 2024. This eight-week, triple-blind, parallel-group, randomized controlled trial included patients diagnosed with mild to moderate UC based on clinical symptoms and physician assessment. To be eligible, participants had to be between 18 and 70 years old, willing to participate, and have active mild-to-moderate UC symptoms, confirmed by a Simple Clinical Colitis Activity Index (SCCAI) score between 3 and 11. The exclusion criteria included smoking, alcohol consumption in the last one month, pregnancy and breastfeeding, use of antioxidant supplements, such as vitamin C, E, selenium, curcumin, pomegranate peel and any other antioxidant supplements in the last one month, use of anticoagulants, using drugs against TNF-α, use of anti-inflammatory drugs, steroidal and non-steroidal, antibiotics, fiber or probiotics or synbiotic supplements during two weeks before the start of the intervention, patients in the stage of vitamin D deficiency, immigration and unavailability of people, emergency withdrawal of people from the study based on the diagnosis of a specialist doctor, non-acceptance of supplement (acceptance less than 80%), abdominal surgery or radiotherapy, any abnormal reaction to the supplement, gastrointestinal bleeding, rapid weight loss, change in the type or dose of medicine, change in diet or daily physical activity, suffering from other chronic inflammatory diseases, mental illnesses or neurological conditions (such as Parkinson's disease, Alzheimer's disease, intracranial hemorrhage, or traumatic brain or head injury), Cushing's syndrome, polyovarian syndrome cystic, anemia, hemophilia, leukopenia, thrombocytopenia, asthma, cancer, anorexia and bulimia nervosa, other autoimmune diseases and extensive gastrointestinal surgeries that affect the condition of disease, altering the kind and dosage of UC medications. The required sample size was calculated based on a study by Tahvilian et al. (2020), which investigated the effects of saffron supplementation on oxidative/anti-oxidative status and disease severity in patients with UC[20]. Their findings demonstrated a statistically significant improvement ($p<0.05$) in both oxidative balance and disease severity among UC patients receiving saffron. Aligned with the objectives of the present study, sample size estimations were conducted for each outcome. The largest required sample size corresponded to the comparison of disease activity before and after the intervention between the two groups. To achieve a 95% confidence level and 80% statistical power, 35 participants were needed per group. Considering a projected dropout rate of 20%, the final sample size was adjusted to 42 participants per group. The following formula was used to calculate the sample size:

$$n = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 \sigma^2}{\left(\mu_1 - \mu_2\right)^2} \qquad n = \frac{(1.96 + .84)^2 (0.03 + 0.05)}{(-0.82 - (-0.02))^2} \sim 35 \quad 35 * 1.2 = 42$$

We confirm that this study adhered to the ethical principles outlined in the Helsinki Declaration[21], and all stages of the study were communicated to the participants in the form of informed consent. Additionally, we confirm that the study proposal, with tracking code "25425" and project code "25425-2-1-1402", was approved by the reviewers of the Medical Ethics Committee at Iran University of Medical Sciences. Sampling commenced on 09/07/2023, following the receipt of the ethical approval code "IR.IUMS.REC.1402.125" and the registration of

the study protocol with the Iranian Registry of Clinical Trials under the number "IRCT20191105045340N2". The link to the protocol for this study is as follows: https://irct.behdasht.gov.ir/trial/70387.

Study design

The intervention (n = 35) and control (n = 35) groups were divided among 70 UC patients in this randomized, triple-blind, placebo-controlled study. Participants in the study were randomly assigned to two groups using a computerized random sampling matrix. The intervention group received bromelain at a dose of 500 gelatin dissolving units (GDU), equivalent to 200 mg, administered twice daily in capsule form. Clinical evidence from previous human studies confirms the safety of a 1000 mg dose of bromelain and indicates that it has been reported without adverse effects[22]. In another study, the toxic dose of bromelain was reported to be approximately 5000 mg per day, which supports the safety of the dosage used in the present study[23]. Maltodextrin was present in placebo capsules in the same quantity. The pharmaceutical company Salamat Parmoon Amin, located in Tehran, Iran, manufactured the bromelain supplements and placebo. The bromelain capsules and the placebo supplement were identical in terms of appearance, color, smell, and packaging. The manufacturer coded the supplements as (AH-402007 or AH-402008) for one category and (AH-402999) for the other to preserve blinding for the researchers. Because of this, neither the participants nor the researchers knew what kind of supplements were given to each group. During the initial visit, participants were given all 120 capsules, and instructed to take one capsule an hour before or two hours after lunch and dinner, for a daily total of two capsules to maximize absorption and enhance bioavailability. Throughout the study period, participants were cautioned against changing their medication schedule, food preferences, or level of physical activity. Throughout the study, frequent phone calls were used to track compliance. During the study, the phone calls were made to gauge participant compliance. To ensure complete adherence, participants were asked to return the empty supplement boxes at the conclusion of the trial. The study excluded participants who took fewer than 80% of the capsules. The main results at week eight were improvements in disease activity as determined by SCCAI-questionnaire and in QoL as assessed by the IBD-QoL questionnaire. Above questionnaires were used in previous studies in Iran[24–26].

Data assessment

To collect general patient information—including age, gender, height, weight, body mass index (BMI), waist circumference (WC), physical activity level, educational background, marital status, economic status, water intake, family history of UC, and medication use a demographic survey was administered at the beginning of the study. Participants completed the SCCAI and the IBD-QoL questionnaire at both baseline and the end of the trial. The SCCAI was used to evaluate the severity of UC, given its strong correlation with colonoscopic findings in affected patients[27]. This questionnaire consists of 13 items that evaluate both gastrointestinal and extraintestinal symptoms experienced by the patient during the past week. The gastrointestinal items include: frequency of daytime and nighttime bowel movements, ability to retain stool during urgency, changes in daily activities due to the need for proximity to a toilet, presence of stool in clothing, visible blood in stool, and a self-rated general health score. The extraintestinal items assess joint pain at rest, joint swelling or redness, sleep disturbance due to joint pain, and physician-diagnosed dermatologic (erythema nodosum and pyoderma gangrenosum) and ophthalmologic (uveitis) conditions. Multiple-choice items such as bowel frequency, blood in stool, and general health are scored from 0 to 3 based on severity. The general health item is reverse-scored using the formula: (11 - selected score) ÷ 3. Yes/no questions are scored as follows: "yes" = 1 and "no" = 0. The total score reflects the overall disease activity and is categorized as follows: 0–2: Remission; 3–5: Mild activity; 6–11: Moderate activity; 11< : Severe activity. In this study, all 13 items were included in the total score to provide a comprehensive assessment of the patient's condition. The nine-item IBD-QoL questionnaire assesses patients' QoL in four domains: gastrointestinal disturbances, emotional state, systemic function, and social function. The instrument consists of nine items, each addressing a distinct aspect of the patient's experience. The first two items assess abdominal symptoms: (1) changes in bowel movement frequency compared to the stable phase of the disease, and (2) frequency of abdominal cramps or pain. Systemic symptoms are evaluated through two items: (3) feelings of helplessness, fatigue, or worry related to the disease, and (4) the level of energy available for daily activities. Emotional symptoms are covered by four items: (5) concern about the possibility of needing surgery, (6) fear of not finding a toilet in urgent situations, (7) sense of psychological relief or relaxation, and (8) episodes of irritability or moodiness. The final item (9) assesses social functioning, specifically the extent to which IBD has interfered with participation in sports and leisure activities. Each item offers seven response options that reflect the frequency or severity of the experience. Responses are scored on a 7-point scale, where 1 indicates the most unfavorable condition and 7 represents the most favorable. Higher scores reflect better quality of life, while lower scores indicate greater symptom burden or functional limitation. In this study, all nine items were included in the total score to provide a comprehensive assessment of the patient's overall quality of life. At the beginning of study and eight weeks following the intervention, anthropometric indices were measured. IBD-QoL score ranges from 1 to 63, with each item having a score between 1 (worst state) and 7 (best state). Less impairment in QoL is indicated by higher scores[28]. Anthropometric measurements involve the use of a stadiometer without shoes to measure height and a digital scale with an accuracy of 100 g to measure weight while wearing light garments. The body mass index (BMI) was determined by dividing the weight in kilograms by the height in meters squared. The WC was measured using a tape measure while the subject was standing with their hands at their sides, midway between the last rib and the iliac crest. Dietary intake was evaluated during the first three days of the intervention and again during the final three days of the 8-week intervention period. To assess patients' dietary intake and control for potential confounding factors, we used a 3-day food record method. Specifically, participants recorded their dietary intake for three consecutive days during the week prior to the start of the intervention and for three consecutive days during the final week of the intervention. Each

3-day period included two weekdays and one weekend day to better reflect typical dietary patterns. The average intake of each nutrient over the three days was calculated and considered as the pre- and post-intervention dietary values. Nutritionist IV software (First Databank, San Bruno, CA) was used to analyze dietary intake, which was adjusted for Iranian foods. Throughout the research, all participants were asked to stick to their regular food and exercise regimens. The classified physical activity questionnaire was applied to measure the level of physical activity based on metabolic equivalent tasks performed before and after the study[29].

Statistical analysis

Pair t-tests were applied to compare the participants' scores before and after the intervention. In addition, the two groups were compared applying independent t-tests. The chi-square test was utilized to compare the two groups across a variety of category variables. The scores of bromelain group were compared using analysis of covariance (ANCOVA) following the study. All primary and secondary results were subjected to the intention-to-treat (ITT) and per-protocol (PP) analytical techniques. SPSS version 27.0 (SPSS Inc. Chicago, IL) was employed to handle the data analysis. The significance level of each efficacy measure was established at 0.05.

Results

General information

Of the 130 patients screened for eligibility, 60 were excluded from the study. Fifty individuals were excluded due to the use of antibiotics, nonsteroidal anti-inflammatory drugs, anticoagulants, or a history of surgery or gallbladder cancer. An additional ten patients declined to sign the informed consent form. Among the remaining 70 participants, 35 were assigned to receive bromelain capsules (500 gelatin dissolving units (GDU), twice daily), while the other 35 received placebo capsules. During the study, five participants from the bromelain group and three from the placebo group withdrew. The flow chart for the study design is indicated in Fig. 1.

Demographic information

Table 1 displays the demographic information of the participants, which includes the mean age, sex, weight, height, BMI, WC, duration of the disease, degree of disease activity, QoL, physical activity, educational attainment, marital status, economic status, history of UC, water intake, and anti-inflammatory medication dosage. The two groups did not exhibit any significant differences in these general characteristics. Nevertheless, the two groups exhibited a significant difference in sex ($p = 0.01$).

Dietary intakes information

The paired sample t test results in both the PP and ITT analyses, as shown in Table 2, indicate that the bromelain group's intake of vitamin B6 increased at the conclusion of the trial ($p = 0.02$ in PP analyses and $p = 0.01$ in ITT analyses). The mean difference in vitamin B6 intake changes between the bromelain group and the placebo group was significant in both the PP and ITT analyses ($p < 0.001$). The other nutrients did not exhibit a significant difference.

Results of the main outcomes analysis

Table 3 indicates that the SCCAI mean scores in both groups decreased at the conclusion of the trial ($p < 0.001$), as indicated by the results of the paired sample t test in both PP and ITT analyses. The results were still significant ($p = 0.01$ in PP analyses and $p < 0.001$ in ITT analyses) even after controlling for the baseline value, as bromelain significantly reduced the mean difference in SCCAI changes between the two groups ($p < 0.001$ in both PP and ITT analyses). QoL mean scores rose in both groups at the end of trial, based on the paired sample t test in both the PP and ITT analyses ($p = 0.005$ and $p < 0.001$ in PP analyses for the bromelain and placebo group, respectively, and $p = 0.001$ and $p < 0.001$ in ITT analyses for bromelain and placebo group, respectively). Compared to the placebo group, the bromelain group's mean difference in QoL changes was not statistically varied ($p = 0.87$ in PP analyses and $p = 0.90$ in ITT analyses). After controlling for the baseline values, this difference was also not statistically varied ($p = 0.84$ in PP analyses and $p = 0.99$ in ITT analyses).

Discussion

The findings demonstrated that UC patients' SCCAI scores could be reduced by taking 400 mg of bromelain daily for eight weeks. The severity of disease has significantly decreased, according to the SCCAI questionnaire. Similarly, evidence of bromelain's efficacy in improving IBD has been reported in previous studies. A research on mice showed that daily oral treatment of bromelain at levels from 2 to 20 mg/kg substantially reduced the incidence and severity of colitis by decreasing inflammatory factors. A further animal research indicated that 200 mg/kg of bromelain suppressed the activation of Nf-κB, therefore reducing the inflammatory response[30]. Purified bromelain decreased inflammation by blocking TNF-α type 1 receptors (TNFR-1) and type 2 receptors (TNFR-2), in another animal study[23]. Cellular studies showed that bromelain treatment decreases the secretion of various proinflammatory cytokines and chemokines, which is in line with our findings[31–34]. Another animal study discovered that fresh pineapple juice, which contains active bromelain enzymes, decreased the severity of inflammation in IBD, and had no detrimental effects on the body weight or general health of mice with colitis when taken as a long-term supplement. On the other hand, purified bromelain treatment did not reduce inflammation over an extended period of time[35]. This is likely due to the fact that pineapple juice contains a greater quantity of antioxidants and anti-inflammatory substances than purified bromelain. According to other research, bromelain has not always been associated with improved intestinal barrier function and decreased expression of inflammatory cytokines. As per Chakraborty (2021), this discrepancy suggests that the outcomes are significantly influenced by the dose and specific circumstances of each study[36]. On the other hand, the

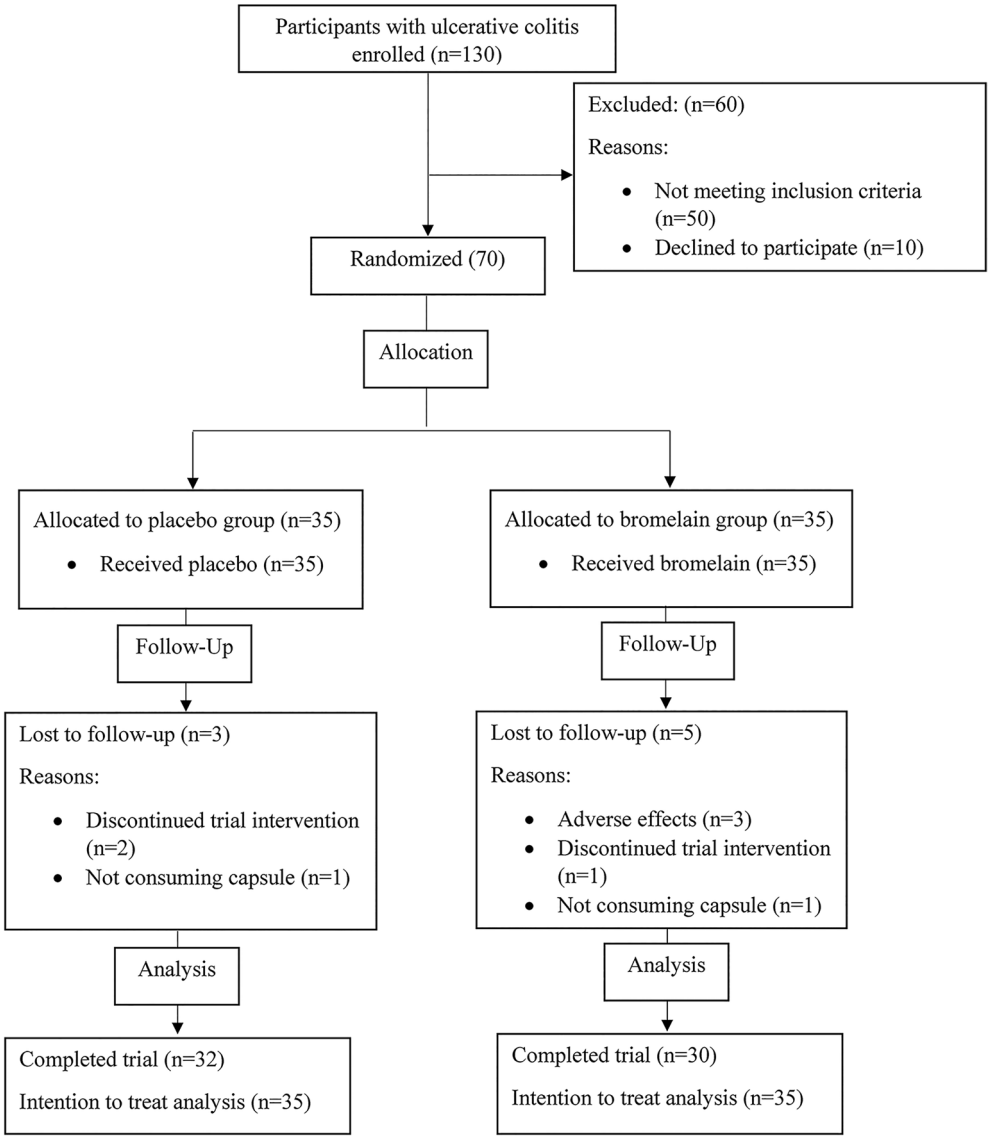

Fig. 1. Flow chart of the study.

supplement did not significantly improve QoL according to our results. Furthermore, in a study handled by Bjarnason et al., the patients with mild to moderate UC and CD received probiotic supplementation at a dose of 1 ml per kilogram of body weight for 4 weeks. The results indicated that the probiotic did not significantly affect the patients' quality of life[37]. In a controlled intervention study investigating the efficacy of curcumin supplementation (1600 mg) in conjunction with a Mediterranean dietary regimen, as well as resveratrol supplementation (500 mg) alongside a Mediterranean diet in subjects experiencing mild to moderate colitis, the findings demonstrated that these interventions, over an 8-week duration, substantially enhanced patients' quality of life[38]. Nevertheless, attaining more pronounced enhancements in quality of life may necessitate prolonged intervention durations or the incorporation of supplements in conjunction with a nutrient-dense dietary plan specifically designed to ameliorate the condition of individuals suffering from inflammatory bowel disease. Quality of life typically exhibits more significant alterations in severe cases, as individuals afflicted with mild to moderate disease generally encounter lesser degrees of impairment. Thus, in this investigation, the identified enhancements in quality of life were comparatively less pronounced, likely attributed to the mild to moderate classification of intestinal inflammation among the participants. A recent development in the management of inflammatory diseases is using complementary therapies with potent natural anti-inflammatory products[39]. Although molecular mechanisms were not directly assessed in this study, prior evidence provides a compelling context for interpreting our findings. Bromelain has been shown to exert anti-inflammatory effects through multiple pathways. It suppresses the expression of cyclooxygenase-2 (COX-2) and nuclear factor kappa B (NF-κB), both of which are central to the regulation of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6[40–43]. COX-2, in particular, is upregulated in response to inflammatory stimuli and contributes to the synthesis of prostaglandin E2, amplifying mucosal inflammation[40,41]. In addition, bromelain may modulate intestinal

Characteristic	Bromelain group $N=35$	Placebo group $N=35$	P-value
Age (years)	44.11 ± 13.34	41.97 ± 13.20	0.50[a]
Sex, n (%)			0.01[b]
Male	17 (70.8)	7 (29.2)	
Female	18 (39.1)	28 (60.9)	
Weight (kg)	72.82 ± 13.03	69.65 ± 16.68	0.37[a]
Height (cm)	169.71 ± 8.80	166.37 ± 6.67	0.07[a]
BMI (kg/m ^{2})	25.27 ± 3.96	25.02 ± 4.97	0.82 [a]
Waist circumference (cm)	82.97 ± 16.63	82.63 ± 17.75	0.93 [a]
Disease duration (mounth)	112.67 ± 121.86	89.70 ± 76.85	0.35 [a]
SCCAI score	4.94 ± 3.33	3.63 ± 2.68	0.07 [a]
Qol score	43.06 ± 9.07	45.74 ± 8.27	0.20 [a]
IPAQ (MET-minutes/week)	1309.67 ± 1077.40	1272 ± 867.80	0.87 [a]
Educational level, n (%)			0.86[b]
Elementary	5 (55.6)	4 (44.4)	
Diploma	12 (46.2)	14 (53.8)	
College	18 (51.4)	17 (48.6)	
Married status, n (%)			0.78[b]
Single	9 (47.4)	10 (52.6)	
Married	26 (51)	25 (49)	
Economic status, n (%)			0.28[b]
Lower-middle	4 (50)	4 (50)	
Middle	8 (36.4)	14 (63.6)	
Upper-middle	23 (57.5)	17 (42.5)	
History of UC, n (%)			0.59[b]
No	24 (48)	26 (52)	
Yes	11 (55)	9 (45)	
Water (glass/day)	6.51 ± 2.21	6.58 ± 1.78	0.88[a]
Dose of anti-inflammatory drugs (mg)			0.61[b]
500	10 (41.7)	14 (58.3)	
1000	9 (50)	9 (50)	
1200	14 (53.8)	12 (46.2)	
2400	1 (100)	0 (0)	

Table 1. Baseline traits of participants in the placebo and bromelain-treated groups. P-value <0.05 was considered significant. BMI; Body Mass Index, SCCAI; Simple Clinical Colitis Activity Index, QoL; Quality Of Life, IPAQ; International Physical Activity Quastionnaire, MET; Metabolic Equivalent Task, UC; Ulcerative Colitis. [a] Based on the independent sample t test (mean ± standard deviation). [b] Based on the chi-squared test (n (%)).

barrier function by downregulating myosin light chain kinase (MLCK) and tumor necrosis factor receptor 2 (TNFR-2), which are implicated in tight junction disruption and increased epithelial permeability[23,44,45]. Its proteolytic activity also enables the cleavage of cell surface molecules such as CD-44 and CD-128, which mediate leukocyte adhesion and migration[46–49]. By targeting these molecules, bromelain may reduce neutrophil infiltration and dampen local inflammatory responses[34]. Taken together, these mechanisms provide a plausible biological basis for the observed reduction in disease activity following bromelain supplementation. While speculative in the context of our study, they align with previous findings and support the potential of bromelain as a complementary therapeutic agent in ulcerative colitis. This study has several benefits, including the exclusion of patients with different medication types or dosage changes during the intervention due to the similar distribution of medication types between the two groups. Second, this is the first triple-blind, placebo-controlled clinical trial to look at how well bromelain supplements work for UC patients' QoL and disease activity. Third, the study's sample size was suitable, and patients were closely watched during the intervention. Fourth, another noteworthy benefit was high medication compliance rate among participants (> 80%). Nonetheless, it is necessary to acknowledge several significant limitations. First, because of financial limitations and patient resistance, endoscopic or colonoscopic examinations were not carried out. Second, it is recommended that extended intervention studies be conducted to confirm the long-term effects of supplementing with bromelain in UC patients. Third, it is recommended that additional research be conducted with extended intervention durations and higher dosages of bromelain, as the efficacy of bromelain on QoL was not demonstrated in this study. Despite the promising outcomes observed in this trial and prior experimental evidence, the clinical application of bromelain as a complementary treatment for ulcerative colitis remains underexplored. Most

Variable	Per-protocol analysis			Intention to treat analysis		
	Bromelain group ($n=30$)	Placebo group ($n=32$)	P-value[a]	Bromelain group ($n=35$)	Placebo group ($n=35$)	P-value[a]
Energy (kcal/day)						
Baseline End of trial Change P-value[b]	1869.60 ± 466.41 1889.73 ± 31.66 20.12 ± 461.51 0.81	1748.85 ± 413.19 1696.67 ± 323.55 -52.18 ± 485.60 0.54	0.55	1873.71 ± 446.97 1893.84 ± 363.38 20.12 ± 426.23 0.78	1780.75 ± 414.03 1728.56 ± 333.48 -52.18 ± 463.68 0.51	0.49
Protein (g/day)						
Baseline End of trial Change P-value[b]	77.88 ± 19.28 74.97 ± 17.13 -2.90 ± 22.02 0.47	75.06 ± 20.03 69.96 ± 20.50 -5.10 ± 19.34 0.14	0.67	78.52 ± 18.67 75.61 ± 16.79 -2.90 ± 20.34 0.40	75.78 ± 19.59 70.68 ± 20.02 -5.10 ± 18.47 0.11	0.63
Carbohydrate (g/day)						
Baseline End of trial Change P-value[b]	257.86 ± 74.64 242.36 ± 51.29 -15.49 ± 75.90 0.27	226.18 ± 68.16 217.75 ± 48.64 -8.42 ± 66.99 0.48	0.69	256.79 ± 72.57 241.04 ± 52.55 -15.75 ± 70.10 0.19	228.07 ± 66.51 219.04 ± 48.19 -9.03 ± 64 0.40	0.67
Fat (g/day)						
Baseline End of trial Change P-value[b]	61.16 ± 18.86 72.84 ± 23.23 11.68 ± 25.93 0.02	63.71 ± 19.98 67.39 ± 19.56 3.68 ± 23.61 0.38	0.20	62.05 ± 17.69 73.74 ± 21.67 11.68 ± 23.95 < 0.001	66.13 ± 21.57 69.81 ± 21.21 3.68 ± 22.54 0.34	0.15
Omega3 (g/day)						
Baseline End of trial Change P-value[b]	1.39 ± 2.17 1.52 ± 1.96 0.13 ± 1.28 0.57	1.66 ± 3.91 1.77 ± 3.03 0.11 ± 3.68 0.86	0.97	1.56 ± 2.30 1.69 ± 2.13 0.13 ± 1.18 0.51	1.58 ± 3.74 1.70 ± 2.91 0.11 ± 3.52 0.85	0.97
Omega6 (g/day)						
Baseline End of trial Change P-value[b]	11.93 ± 5.86 14.11 ± 9.18 2.17 ± 10.78 0.27	11.64 ± 4.75 11.77 ± 5.96 0.12 ± 6.90 0.91	0.38	11.50 ± 5.78 13.67 ± 8.71 2.17 ± 9.96 0.20	12.11 ± 5.53 12.24 ± 6.51 0.12 ± 6.59 0.90	0.31
PUFA (g/day)						
Baseline End of trial Change P-value[b]	15.69 ± 7.38 18.79 ± 10.16 3.10 ± 12.46 0.18	15.81 ± 6.63 16.51 ± 7.50 0.70 ± 9.22 0.67	0.38	15.25 ± 7.12 18.35 ± 9.60 3.10 ± 11.51 0.12	16.60 ± 7.27 17.25 ± 7.95 0.64 ± 8.80 0.66	0.31
MUFA (g/day)						
Baseline End of trial Change P-value[b]	19.24 ± 7.14 21.82 ± 6.99 2.58 ± 9.45 0.14	20.92 ± 8.86 21.92 ± 8.54 1 ± 8.35 0.50	0.48	19.91 ± 7.21 22.49 ± 7.09 2.58 ± 8.73 0.09	21.41 ± 8.72 22.42 ± 8.42 1 ± 7.97 0.46	0.43
Cholestrol (mg/day)						
Baseline End of trial Change P-value[b]	338.53 ± 219.29 306.25 ± 155.99 -32.27 ± 189.47 0.35	319.61 ± 207.84 288.60 ± 183.89 -31.01 ± 193.46 0.37	0.97	346.74 ± 229.39 314.47 ± 179.88 -32.27 ± 174.99 0.28	312.33 ± 200 281.32 ± 177.32 -31.01 ± 184.73 0.32	0.97
Satureted fat (g/day)						
Baseline End of trial Change P-value[b]	16.87 ± 5.72 18.77 ± 5.51 1.89 ± 6.92 0.14	15.44 ± 5.32 17.86 ± 6.39 2.41 ± 5.95 0.02	0.75	17.04 ± 5.39 18.94 ± 5.20 1.89 ± 6.39 0.08	16.08 ± 5.74 18.49 ± 6.66 2.41 ± 5.68 0.01	0.72
Total fiber (g/day)						
Baseline End of trial Change P-value[b]	4.57 ± 1.53 4.41 ± 1.56 -0.16 ± 1.94 0.63	4.92 ± 1.97 4.64 ± 2.02 -0.28 ± 2.29 0.49	0.83	4.69 ± 1.55 4.52 ± 1.58 -0.16 ± 1.79 0.58	4.94 ± 1.99 4.65 ± 2.04 -0.28 ± 2.19 0.45	0.80
Vitamin A (RE/day)						
Baseline End of trial Change P-value[b]	673.89 ± 456.11 720.33 ± 515.21 46.44 ± 392 0.52	634.92 ± 311.16 614.63 ± 195.24 -20.29 ± 314.76 0.71	0.46	724.95 ± 557.53 771.39 ± 599.83 46.44 ± 362.03 0.45	629.84 ± 303.38 609.55 ± 196.25 -20.29 ± 300.55 0.69	0.40
Vitamin E (mg/day)						
Baseline End of trial Change P-value[b]	5.45 ± 5.70 8.98 ± 9.09 3.52 ± 11.39 0.10	3.66 ± 3.88 5.11 ± 5.62 1.45 ± 6.59 0.22	0.38	5.26 ± 5.48 8.78 ± 8.35 3.52 ± 10.52 0.05	4.13 ± 4.49 5.58 ± 5.93 1.45 ± 6.29 0.18	0.32
Vitamin D (µg/day)						
Baseline End of trial Change P-value[b]	0.91 ± 1.19 0.87 ± 0.97 -0.03 ± 0.77 0.79	0.85 ± 1.65 1.02 ± 1.24 0.17 ± 1.37 0.48	0.46	0.92 ± 1.16 0.88 ± 0.98 -0.03 ± 0.71 0.76	0.83 ± 1.58 1 ± 1.20 0.17 ± 1.31 0.44	0.41
Continued						

Variable	Per-protocol analysis			Intention to treat analysis		
	Bromelain group ($n=30$)	Placebo group ($n=32$)	P-value[a]	Bromelain group ($n=35$)	Placebo group ($n=35$)	P-value[a]
Vitamin K (μg/day)						
Baseline End of trial Change P-value[b]	63.76 ± 33.03 58.92 ± 32.32 -4.84 ± 40.57 0.51	52.80 ± 30.03 48.37 ± 23.10 -4.42 ± 29.55 0.40	0.96	61.95 ± 31.08 57.10 ± 30.44 -4.84 ± 37.46 0.45	51.59 ± 30.70 47.16 ± 24.64 -4.42 ± 28.22 0.36	0.95
Vitamin C (mg/day)						
Baseline End of trial Change P-value[b]	63.85 ± 28.17 60.24 ± 32.27 -3.61 ± 39.08 0.61	59.85 ± 26.93 63.01 ± 30.96 3.16 ± 40.42 0.66	0.50	65.71 ± 29.36 62.09 ± 32.77 -3.61 ± 36.09 0.55	60.23 ± 27.35 63.39 ± 30.98 3.15 ± 38.59 0.63	0.45
Vitamin B1 (mg/day)						
Baseline End of trial Change P-value[b]	1.76 ± 0.79 1.63 ± 0.71 -0.13 ± 0.60 0.23	1.82 ± 1.30 1.69 ± 1.05 -0.13 ± 1.23 0.55	0.98	1.83 ± 0.86 1.67 ± 0.73 -0.15 ± 0.57 0.11	1.79 ± 1.25 1.66 ± 1.01 -0.13 ± 1.17 0.51	0.89
Vitamin B2 (mg/day)						
Baseline End of trial Change P-value[b]	1.39 ± 0.84 1.29 ± 0.72 -0.09 ± 0.64 0.42	1.52 ± 1.33 1.47 ± 1.05 -0.05 ± 1.20 0.81	0.85	1.51 ± 0.92 1.41 ± 0.83 -0.09 ± 0.59 0.35	1.50 ± 1.28 1.45 ± 1.01 -0.05 ± 1.15 0.79	0.84
Vitamin B3 (mg/day)						
Baseline End of trial Change P-value[b]	20.80 ± 5.84 19.93 ± 5.04 -0.86 ± 7.60 0.53	20.10 ± 6.68 18.05 ± 6.32 -2.04 ± 6.82 0.10	0.52	20.75 ± 5.65 19.89 ± 4.95 -0.86 ± 7.02 0.47	20.19 ± 6.45 18.15 ± 6.11 -2.04 ± 6.52 0.07	0.47
Vitamin B5 (mg/day)						
Baseline End of trial Change P-value[b]	4.52 ± 1.51 3.96 ± 1.04 -0.56 ± 1.53 0.05	4.34 ± 1.71 4.14 ± 1.59 -0.20 ± 1.64 0.49	0.37	4.54 ± 1.48 3.99 ± 1.09 -0.55 ± 1.41 0.02	4.29 ± 1.64 4.09 ± 1.53 -0.19 ± 1.57 0.45	0.33
Vitamin B6 (mg/day)						
Baseline End of trial Change P-value[b]	1.84 ± 0.73 2.23 ± 0.93 0.39 ± 0.93 0.02	2.44 ± 1.42 1.98 ± 1.01 -0.46 ± 1.49 0.08	< 0.001	1.99 ± 0.92 2.39 ± 1.06 0.39 ± 0.86 0.01	2.39 ± 1.37 1.95 ± 0.98 -0.44 ± 1.43 0.07	< 0.001
Vitamin B7 (μg/day)						
Baseline End of trial Change P-value[b]	7.30 ± 4.56 8.03 ± 5.98 0.72 ± 6.72 0.55	7.04 ± 5.60 7.47 ± 4.10 0.42 ± 5.53 0.66	0.84	7.03 ± 4.36 7.75 ± 4.64 0.72 ± 6.20 0.49	7.19 ± 5.66 7.62 ± 4.32 0.42 ± 5.28 0.63	0.82
Vitamin B9 (μg/day)						
Baseline End of trial Change P-value[b]	212.42 ± 74.78 203.86 ± 86.10 -8.56 ± 101.46 0.64	193.30 ± 61 197.03 ± 60.91 3.73 ± 78.89 0.79	0.59	218.05 ± 79.11 209.48 ± 88.38 -8.56 ± 93.70 0.59	198.39 ± 74.39 202.12 ± 74.32 3.73 ± 75.33 0.77	0.54
Vitamin B12 (μg/day)						
Baseline End of trial Change P-value[b]	3.86 ± 2.35 3.28 ± 1.16 -0.58 ± 2.35 0.18	3.60 ± 1.73 3.52 ± 1.87 -0.08 ± 1.91 0.80	0.36	3.90 ± 2.21 3.31 ± 1.15 -0.58 ± 2.17 0.12	3.58 ± 1.68 3.49 ± 1.80 -0.08 ± 1.83 0.78	0.30
Magnesium (mg/day)						
Baseline End of trial Change P-value[b]	190.68 ± 49.11 187.08 ± 42.22 -3.59 ± 57.83 0.73	197.72 ± 54.49 192.44 ± 43.64 -5.27 ± 62.85 0.63	0.91	193.10 ± 49.21 189.51 ± 43.42 -3.59 ± 53.41 0.69	200.33 ± 54.73 195.20 ± 45.09 -5.12 ± 60.02 0.61	0.91
Calcium (mg/day)						
Baseline End of trial Change P-value[b]	603.73 ± 203.33 556.84 ± 188 -46.88 ± 247.91 0.30	543.24 ± 180.51 580.61 ± 179.41 37.36 ± 210.40 0.32	0.15	624.83 ± 233.97 577.94 ± 212.25 -46.88 ± 228.95 0.23	563.49 ± 197.45 600.86 ± 196.53 37.36 ± 200.91 0.27	0.10
Selenium (mg/day)						
Baseline End of trial Change P-value[b]	0.25 ± 0.72 0.22 ± 0.68 -0.02 ± 0.43 0.71	0.43 ± 1.27 0.40 ± 0.97 -0.02 ± 1.19 0.89	0.99	0.31 ± 0.78 0.29 ± 0.74 -0.02 ± 0.40 0.69	0.40 ± 1.21 0.37 ± 0.94 -0.02 ± 1.13 0.88	0.99
Iron (mg/day)						
Baseline End of trial Change P-value[b]	10.99 ± 2.98 11.55 ± 3.44 0.55 ± 3.84 0.43	11.53 ± 3.14 11.02 ± 2.65 -0.50 ± 3.87 0.46	0.28	11.25 ± 2.97 11.81 ± 3.36 0.55 ± 3.55 0.35	11.60 ± 3.06 11.10 ± 2.61 -0.50 ± 3.69 0.42	0.22
Continued						

Variable	Per-protocol analysis			Intention to treat analysis		
	Bromelain group ($n=30$)	Placebo group ($n=32$)	*P*-value[a]	Bromelain group ($n=35$)	Placebo group ($n=35$)	*P*-value[a]
Zinc (mg/day)						
Baseline End of trial Change P-value[b]	9.18 ± 2.81 8.91 ± 2.70 -0.26 ± 2.80 0.60	9.32 ± 2.78 8.76 ± 2.29 -0.55 ± 3 0.30	0.70	9.33 ± 2.81 9.06 ± 2.72 -0.26 ± 2.58 0.54	9.42 ± 2.72 8.86 ± 2.27 -0.55 ± 2.87 0.26	0.66
Copper (mg/day)						
Baseline End of trial Change P-value[b]	1.26 ± 0.77 1.23 ± 0.64 -0.02 ± 0.54 0.80	1.45 ± 1.27 1.42 ± 1.02 -0.03 ± 1.24 0.87	0.96	1.34 ± 0.83 1.31 ± 0.74 -0.02 ± 0.50 0.77	1.43 ± 1.22 1.40 ± 0.98 -0.03 ± 1.18 0.86	0.96
Manganese (mg/day)						
Baseline End of trial Change P-value[b]	2.52 ± 1.01 2.27 ± 0.88 -0.24 ± 1.02 0.19	2.61 ± 1.46 2.46 ± 1.34 -0.15 ± 1.63 0.60	0.78	2.55 ± 1.08 2.31 ± 0.98 -0.24 ± 0.94 0.13	2.58 ± 1.42 2.43 ± 1.31 -0.15 ± 1.55 0.56	0.76
Sodium (mg/day)						
Baseline End of trial Change P-value[b]	5953.28 ± 3431.47 5494.91 ± 2519.79 -458.37 ± 3075.63 0.68	8223.50 ± 3526.34 8018 ± 1561.21 -205.50 ± 2542.25 0.94	0.93	5768.82 ± 4737.92 5310.45 ± 3898.87 -458.37 ± 4611.14 0.63	7844.32 ± 6646.32 7639.06 ± 4232.75 -205.26 ± 5819.57 0.93	0.92
Potassium (mg/day)						
Baseline End of trial Change P-value[b]	2080.16 ± 486.64 2110.83 ± 589.04 30.67 ± 648.17 0.79	2151.04 ± 658.92 2061.30 ± 508.40 -89.74 ± 794.09 0.52	0.51	2130.74 ± 511.39 2161.41 ± 596.21 30.67 ± 598.62 0.76	2161.72 ± 646.39 2071.97 ± 507.68 -89.74 ± 758.25 0.48	0.46
Phosphorus (mg/day)						
Baseline End of trial Change P-value[b]	894.38 ± 204.50 866.63 ± 166.45 -27.75 ± 210.69 0.47	888.97 ± 205.94 864.18 ± 188.53 -24.78 ± 233.69 0.55	0.95	908.94 ± 204.16 881.19 ± 172.18 -27.75 ± 194.58 0.40	899.69 ± 204.83 874.90 ± 188.93 -24.78 ± 223.14 0.51	0.95
Chromium (mg/day)						
Baseline End of trial Change P-value[b]	0.24 ± 0.73 0.20 ± 0.68 -0.03 ± 0.44 0.66	0.41 ± 1.27 0.39 ± 0.98 -0.01 ± 1.18 0.94	0.92	0.31 ± 0.78 0.27 ± 0.75 -0.03 ± 0.41 0.62	0.37 ± 1.22 0.36 ± 0.94 -0.01 ± 1.13 0.94	0.91

Table 2. Results of per-protocol and intention to treat analysis for dietary intake at baseline and after 8 weeks of intervention in the bromelain-treated and placebo groups. P-value < 0.05 was considered significant. All data are presented as mean ± standard deviation. MUFA; Mono Unsaturated Fatty Acid, PUFA; Poly Unsaturated Fatty Acid, RE; Retinol Equivalents. [a] Based on the independent sample t test. [b] Based on the paired t test.

Variable	Per-protocol analysis			Intention to treat analysis		
	Bromelain group ($n=30$)	Placebo group ($n=32$)	*P*-value	Bromelain group ($n=35$)	Placebo group ($n=35$)	*P*-value
SCCAI score						
Baseline End of trial Change P-value[d]	4.37 ± 3.21 1.07 ± 1.46 -3.30 ± 2.35 < 0.001	3.94 ± 2.59 2.75 ± 1.84 -1.18 ± 1.76 < 0.001	< 0.001[a], 0.01[b]	4.94 ± 3.33 1.65 ± 2.05 -3.29 ± 2.17 < 0.001	3.63 ± 2.68 2.51 ± 1.93 -1.11 ± 1.71 < 0.001	< 0.001[a], < 0.001[c]
QoL score						
Baseline End of trial Change P-value[d]	44.87 ± 8.52 48.60 ± 7.40 3.73 ± 6.70 0.005	44.66 ± 7.69 48.63 ± 6.32 3.96 ± 4.46 < 0.001	0.87[a], 0.84[b]	43.06 ± 9.07 46.82 ± 8.15 3.76 ± 6.18 0.001	45.74 ± 8.27 49.66 ± 7.01 3.91 ± 4.30 < 0.001	0.90[a], 0.99[c]

Table 3. Results of per-protocol and intention to treat analysis for outcomes at baseline and after 8 weeks of intervention in the bromelain-treated and placebo groups. P-value < 0.05 was considered significant. All data are presented as mean ± standard deviation. SCCAI; Simple Clinical Colitis Activity Index, QoL; Quality of Life. [a] Based on the independent sample t test. [b] Based on the parametric ANCOVA test adjusted for sex and vitamins B6. [c] Based on the parametric ANCOVA test adjusted for sex and vitamins B6. [d] Based on the paired t test.

previous investigations have focused on animal models or in vitro settings, leaving a notable gap in the clinical literature. The current study addresses this limitation by providing preliminary human evidence on the efficacy of bromelain supplementation in reducing disease activity among patients with mild to moderate UC. Given the increasing burden of IBD and the potential adverse effects associated with conventional pharmacological

treatments, there is a growing need for complementary therapies that are both safe and effective. Bromelain, as a natural compound with multifaceted anti-inflammatory mechanisms, offers a promising adjunct to existing treatment regimens. Future long-term and large-scale clinical trials are warranted to further elucidate its role in improving not only disease activity but also quality of life and intestinal barrier function in patients with UC.

Conclusion

The study showed a significant reduction in SCCAI scores in both groups by the end of the trial. This reduction remained statistically robust after adjusting for baseline values. Bromelain demonstrated a notable effect in reducing the between-group differences in SCCAI changes. Although quality of life scores improved in both groups, no statistically significant difference was found between bromelain and placebo groups, even after baseline adjustment. Given the existing limitations, these findings should be considered preliminary and may serve as a basis for future investigations. Further studies with more rigorous designs and the use of clinical and biochemical markers are necessary to accurately assess the true effects of bromelain on disease activity.

Data availability

All data will be made available upon request. In case the data of the present study is required, access can be obtained by contacting the corresponding author.

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Author contributions

S. T. R. and P. D. designed the research. P. D. conducted research (hands-on conduct of data collection). P. D. and J. A. analysed data. M. M. and N. E. D. conducted part of the research. P. D. wrote the paper, which is finally edited and approved by S. T. R. and J. A. supervised the study. All authors approved the final version of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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