

## Original Article



# Effects of Soybean Consumption on Disease Severity, Quality of Life, IBD-Related Disabilities, and Mental Health in Patients with Ulcerative Colitis: A Clinical Trial

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## Abstract

**Background:** Several dietary and non-dietary approaches have been recommended to help managing the clinical symptoms of ulcerative colitis (UC). One potential approach is the consumption of soybean due to its anti-inflammatory properties, which may aid in controlling disease severity. However, no research has been conducted on the effects of soybean consumption on disease activity in individuals with UC. To address this gap, a randomized controlled clinical trial was conducted to investigate the effect of soybean consumption on disease severity, quality of life, disability caused by the disease, and mental health in patients with mild to moderate UC. **Methods:** Thirty participants were assigned to either receive 30 g/d of soybean plus routine UC treatments (n=15) in the intervention group or only routine UC treatments (n=15) in the non-intervention group for 8 weeks.

**Results:** At the end of the trial, anxiety score of the patients in the soybean group was significantly reduced compared to the control group ( $P=0.02$ ). However, no significant differences were observed in depression and psychological distress scores between groups. Moreover, there were no significant differences between groups in terms of quality of life, disease severity, and inflammatory bowel disease (IBD)-related disabilities.

**Conclusion:** Findings from this study provide evidence that soybean consumption significantly improves anxiety of patients with UC, while no significant changes were found in terms of quality of life, disease severity, IBD-related disabilities, depression, and psychological distress. Further studies are required to confirm these findings.

**Keywords:** Soybean, Quality of life, Mental health, Ulcerative colitis, Inflammation

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## Introduction

Inflammatory bowel disease (IBD) is an autoimmune condition characterized by chronic inflammation of the digestive tract.<sup>1</sup> It encompasses two main diseases: Crohn's disease (CD) and ulcerative colitis (UC).<sup>2</sup> Similar to other gastrointestinal diseases, IBD places a significant burden on the healthcare system worldwide. Estimates indicate

that 10 576 000 individuals are affected by IBD worldwide. In Iran, a review study reported a prevalence of 40.67 per 100 000 people.<sup>3</sup>

Various environmental factors, including dietary intakes, can influence the symptoms and frequency of IBD flare-ups.<sup>4,5</sup> Epidemiological studies and clinical trials have demonstrated that a high intake of fermented



dairy products, probiotics, and omega-3 fatty acids can improve UC symptoms and reduce disease severity.<sup>6</sup> Conversely, consumption of fermentable carbohydrates, spicy foods, red meat, fried foods, alcohol, and coffee has been shown to aggravate the symptoms.<sup>7-11</sup> Additionally, some studies suggest that vitamin D deficiency and high iron intake can exacerbate UC by increasing inflammatory processes.<sup>12,13</sup> Therefore, dietary intakes seem to play a crucial role in both preventing UC flares and managing its symptoms.

Soybean is rich in fiber, phytoestrogens, phytosterols, phospholipids, and biologically active peptides, all of which possess antioxidant, anti-inflammatory, and immune-regulating properties.<sup>14</sup> As such, soybean could serve as a complementary treatment for UC, given that oxidant/antioxidant imbalance and inflammatory conditions significantly contribute to disease recurrence and progression. However, most studies in this area have focused on the effects of soy-derived compounds, and no research has examined the effects of whole soybean, which contains all these beneficial compounds. In an experimental study, soy protein intake in mice with UC reduced weight loss, colon shortening, splenomegaly, and colonic inflammation, leading to decreased disease activity and increased remission periods.<sup>15</sup> Similarly, in a randomized clinical trial, the administration of Bowman-Birk inhibitor (BBI) to patients with UC reduced disease activity and increased remission periods.<sup>16</sup> These findings underscore the need for further research to explore the effects of whole soy intake in individuals with UC.

Given the aforementioned points, we hypothesized that soybean consumption might positively impact several clinical outcomes in individuals with UC. This parallel clinical trial was designed to investigate the effect of soybean consumption on disease severity, quality of life, IBD-related disabilities, and mental health in patients with UC.

## Methods

The present investigation is a randomized controlled clinical trial. Participants were recruited from Shariati and Imam Khomeini Hospitals, affiliated with Tehran University of Medical Sciences, Tehran, Iran. The study was registered on the Iranian Registry of Clinical Trials website (<http://www.irct.ir>) on January 24, 2020, with the code number IRCT20191113045432N1.

Participants of the current study were patients with UC, who met the following inclusion criteria: aged between 20–60 years, diagnosed with UC by a gastroenterologist using Porto diagnostic criteria based on clinical, endoscopic, radiological, histopathologic, and surgical findings, and presenting with mild to moderate disease severity. Exclusion criteria included pregnancy, lactation, smoking, alcohol consumption, intake of multivitamins, changes in the type or dosage of medications over the last three months, hospitalization in the last three months, and other pathological conditions affecting the gut such as

cancer and infectious diseases. Additionally, individuals who had an infection over the past three months were not included.

## Sample Size

The sample size was calculated based on disease severity.<sup>17</sup> The minimal sample size was determined to be 13 patients per group, considering a 95% confidence interval (CI) and 80% power. The sample size was expanded to 15 patients per group to account for a possible 10% dropout rate.

## Randomization

The patients were randomly allocated into either a “soybean” or “control” group in a 1:1 ratio using Random Allocation Software (RAS). Allocation was performed by a third person not involved in the study, and sequentially numbered concealed envelopes were used for allocation concealment.

## Study Design and Intervention

All participants provided written informed consent and completed a comprehensive questionnaire via face-to-face interviews, which included demographic characteristics, past medical and medication history, and socioeconomic status (SES). The intervention group was instructed to consume 30 g of soybean daily in addition to their routine treatment regimens, while the non-intervention group only received routine treatment regimens. Patients in both groups also received usual nutritional recommendations for patients with IBD based on the European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines.<sup>18</sup>

## Outcomes

The outcomes of the present clinical trial were disease activity, quality of life, disability caused by the disease, and mental health.

## Assessment of Disease Severity

Disease activity was measured at the beginning and end of the trial using the 9-point partial Mayo Clinic score developed by Sutherland et al.<sup>19,20</sup> This score considers stool frequency, rectal bleeding, and the physician's assessment of disease activity, with higher scores indicating greater severity.

## Assessment of Disability Caused by the Disease

Disability caused by the disease was assessed using the inflammatory bowel disease disability index (IBD-DI).<sup>21,22</sup> This questionnaire consists of 28 questions related to health, body functions, activities, and environmental factors. The answers to these questions are “yes” and “no” or based on a 5-point Likert scale (1 indicating no difficulty and 5 indicating extreme difficulty). Scores from each question were combined to obtain a total score for each domain. The final score of the questionnaire ranges from -80 (maximum disability) to 22 (no disability), with zero as the anticipated point of neutrality.

### Assessment of Quality of Life

Quality of life was evaluated using the inflammatory bowel disease questionnaire-9 (IBDQ-9),<sup>23</sup> containing nine questions about gastrointestinal disorders, and systemic, emotional, and social symptoms, with higher scores indicating a better quality of life.

### Assessment of Mental Health

Given the high prevalence of psychological disorders such as depression, anxiety, and psychological distress among patients with IBD,<sup>24,25</sup> mental health was also evaluated. The Iranian-validated version of the Hospital Anxiety and Depression Scale (HADS) was used to screen for depression and anxiety, as it is a brief and effective questionnaire for measuring the severity of anxiety and depression symptoms.<sup>26</sup> The General Health Questionnaire (GHQ) was also employed to assess psychological distress, consisting of 28 items scored on a 4-option Likert scale.<sup>27-29</sup>

### Dietary Intake and Physical Activity Assessment

Dietary intake was assessed using a three-day food recall (two non-consecutive weekdays and one day on the weekend) at baseline, middle, and end of the study. The nutrient intakes of study participants were computed using Nutritionist IV software, modified for Iranian foods. To evaluate physical activity levels, participants were asked to record their physical activity at the beginning, middle, and end of the intervention, and responses were converted to metabolic equivalent task hours per day (MET-hour/day).

### Adherence

Adherence to the study intervention was evaluated using three-day dietary records. Moreover, patients were asked to return the rest of the soy packets, and weekly phone calls were made to all subjects to ensure their regular consumption.

### Statistical Analysis

All analyses were conducted using an intention-to-treat (ITT) approach. The normality of variable distribution was assessed using the Shapiro-Wilk test, skewness, Q-Q diagram, and Kolmogorov-Smirnov test. Results were presented as mean (standard deviation) or frequency (percentage). Differences in categorical variables between the soybean and control groups were examined using the Chi-square test. The independent samples t-test was also used to compare the means (standard deviation) of normally distributed variables between the two groups. Within-group variations were assessed using the paired samples t-test for data with normal distribution. Additionally, the analysis of covariance (ANCOVA) was conducted to examine the effects of soybean consumption on outcome variables after controlling for potential confounding factors. Baseline values of outcome variables and age were adjusted to detect independent results. Analyses were performed using SPSS software version 18.0, and  $P < 0.05$  was considered statistically significant.

### Results

Figure 1 displays the CONSORT flowchart of the trial. A total of 26 participants completed the trial, with 2 patients in each arm lost to follow-up due to non-adherence to dietary recommendations. No side effects were reported by those who completed the trial, except for diarrhea, which was reported by some participants. Table 1 provides the baseline characteristics of the patients, which were well balanced between two groups. Table 2 illustrates the dietary intakes of participants, with a significant difference in fiber intake between the study groups ( $P = 0.04$ ), indicating a higher fiber intake in the soybean group than in the control group. Other dietary intakes did not show statistically significant differences between the study groups.

Table 3 illustrates no significant differences in study outcomes between the study groups at baseline. Disease severity and quality of life did not differ significantly between the groups at the end of the study, and there were no statistically significant changes in IBD-related disabilities within or between the groups. Additionally, there was no significant effect of soybean consumption on psychological distress and depression. However, soybean consumption did significantly improve anxiety in patients with UC compared to the control group ( $P = 0.02$ ).

### Discussion

In the current study, soybean consumption was found to significantly improve anxiety in patients with UC, while no significant changes were observed in terms of quality of life, disease severity, IBD-related disabilities, depression, and psychological distress.

UC is a prevalent chronic gastrointestinal disease. The clinical symptoms of IBD, including diarrhea, abdominal pain, fatigue, and bleeding, are characterized by periods of relapse and remission. Long-standing inflammation in IBD can lead to the development of colorectal cancer.<sup>30</sup> First-line therapies for IBD typically involve medications such as 5-aminosalicylates, corticosteroids, and immunosuppressive drugs. While these medications are often effective, long-term usage can result in adverse

**Table 1.** Baseline Characteristics of the Study Patients

	Soybean (n = 15)	Control (n = 15)
Age (y)	34.6 (10.38)	38.2 (11.04)
BMI (kg/m <sup>2</sup> )	24.8 (3.89)	26.7 (6.02)
Gender (male), n (%)	9 (60.0)	11 (73.3)
Education (educated), n (%)	6 (40)	9 (60)
Marital status (married), n (%)	10 (66.7)	12 (80)
Physical activity (MET-h/day)	20.0 (6.22)	19.6 (9.25)
Abdominal pain, n (%)	5 (33.3)	2 (13.3)
Diarrhea, n (%)	4 (26.7)	3 (20)
Constipation, n (%)	0 (0.0)	1 (6.7)

Note. BMI: Body mass index; MET: Metabolic equivalent task. Data are presented as mean (standard deviation) or n (percent). Obtained from independent samples t-test or chi-square test, where appropriate.

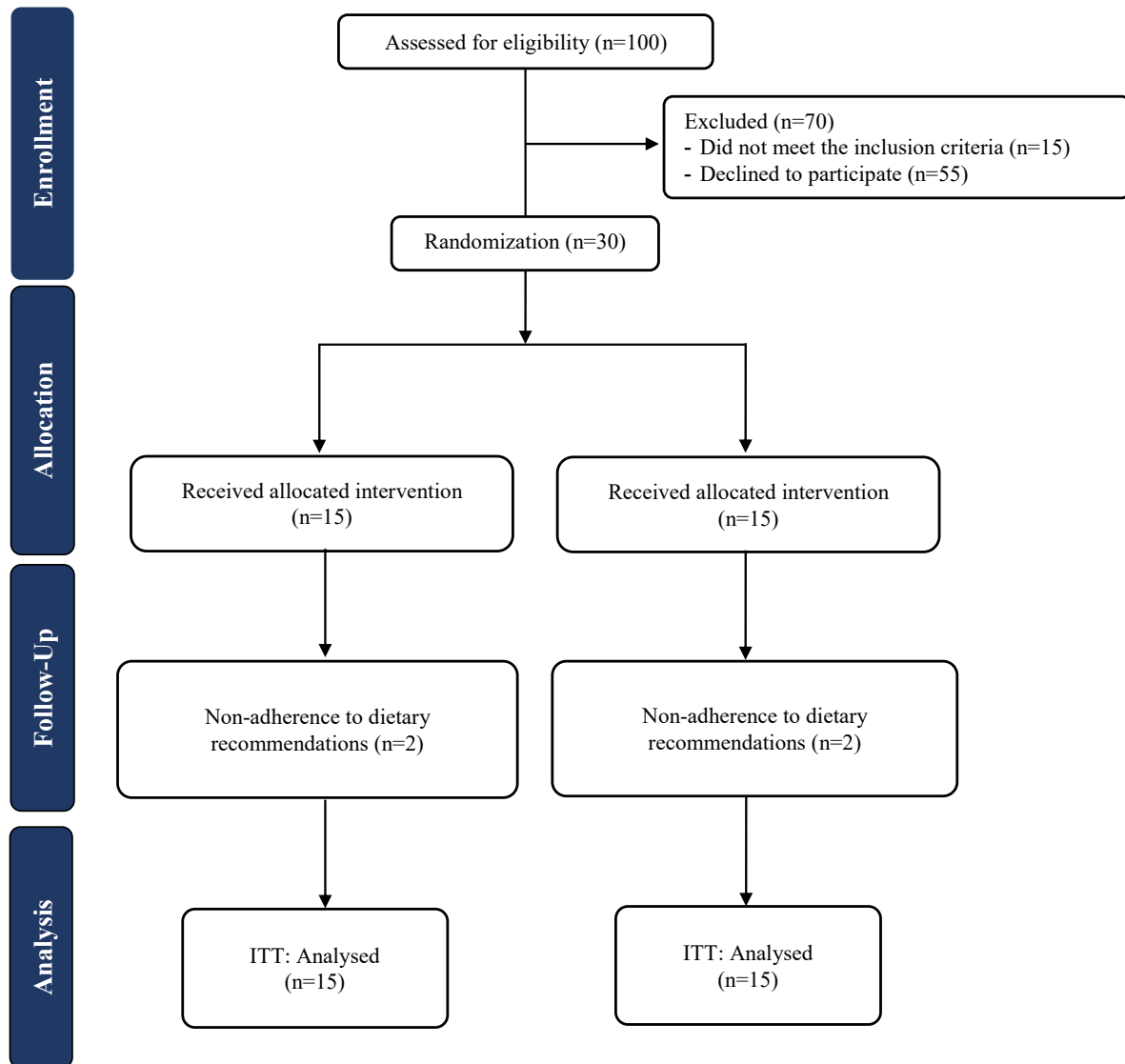


Figure 1. Study flow diagram. Note. ITT: Intention to treat

Table 2. Dietary Intake of the Patients Throughout the Study

	Soybean (n=15)	Control (n=15)	P value <sup>a</sup>
Energy (kcal/d)	1837 (534)	1730 (719)	0.64
Carbohydrate (g/d)	295 (96.5)	265 (98.9)	0.41
Total fat (g/d)	40.2 (16.3)	41.6 (30.7)	0.94
Protein (g/d)	70.9 (32.6)	76.4 (37.4)	0.67
SFA (g/d)	11.8 (5.3)	11.6 (7.31)	0.90
PUFA (g/d)	11.6 (8.66)	12.4 (16.5)	0.87
Dietary fiber (g/d)	15.9 (5.08)	12.41 (3.79)	0.04
Vitamin E (mg/d)	3.14 (3.30)	3.71 (2.01)	0.57
Vitamin C (mg/d)	66.9 (58.4)	126 (106)	0.07
Iron (mg/d)	15.5 (6.08)	12.7 (4.71)	0.18
Calcium (mg/d)	511 (218)	600 (374)	0.43
Magnesium (mg/d)	217 (46.6)	207 (91.8)	0.71
Potassium (mg/d)	2212 (553)	2235 (1233)	0.92

Note. PUFA: Polyunsaturated fatty acid; SFA: Saturated fatty acid. Data are presented as mean (standard deviation).  
<sup>a</sup> Obtained from independent samples t-test.

side effects.<sup>31-33</sup> Maintaining remission in IBD is a clinical challenge that is currently under-researched. Evidence suggests that diet plays a crucial role in managing the severity of IBD and improving quality of life. Soybean, known for its anti-inflammatory and immunomodulatory properties, is considered a good option for inflammatory diseases such as IBD. Previous studies have reported the beneficial effects of consuming soybean components on patients with IBD. However, these effects have not yet been assessed with soybean. This study is the first clinical trial to investigate the effects of soybean consumption on disease severity, IBD-related disabilities, quality of life, and mental health in patients with UC. In the current study, soybean consumption had no significant effect on the severity of UC. Consistent with our finding, results of a randomized clinical trial showed that supplementation with soy and whey protein for 16 weeks does not affect CD disease activity.<sup>34</sup> Jalili et al<sup>35</sup> also reported that simultaneous use of soy isoflavone and vitamin D supplement does not affect the severity of symptoms of irritable bowel disease.

**Table 3.** Effect of Soy Intake on Study Outcomes

	Soybean (n=15)	Control (n=15)	MD	95% CI	P-value
<b>Disease severity</b>					
Baseline	3.46 (1.06)	2.93 (1.03)	0.53	-0.24, 1.31	0.17 <sup>a</sup>
End	3.53 (0.91)	2.86 (1.30)	0.23	-0.46, 0.93	0.49 <sup>c</sup>
MD	0.06	-0.06			
95% CI	-0.46, 0.59	-0.55, 0.42			
$p^b$	0.79	0.77			
<b>IBD-DI</b>					
Baseline	-6.00 (15.51)	-3.53 (17.13)	-2.46	-14.69, 9.76	0.68 <sup>a</sup>
End	-4.13 (16.92)	-3.93 (13.36)	1.34	-5.55, 8.24	0.69 <sup>c</sup>
MD	1.86	-0.40			
95% CI	-1.95, 5.68	-6.87, 6.07			
$p^b$	0.31	0.89			
<b>Quality of life</b>					
Baseline	41.60 (7.70)	45.06 (8.14)	-3.46	-9.39, 2.46	0.24 <sup>a</sup>
End	42.20 (6.61)	44.26 (6.09)	-0.27	-3.79, 3.24	0.87 <sup>c</sup>
MD	0.60	-0.80			
95% CI	-2.37, 3.57	-4.00, 2.40			
$p^b$	0.67	0.60			
<b>Psychological distress</b>					
Baseline	48.46 (8.35)	50.20 (11.97)	-1.73	-9.45, 5.98	0.65 <sup>a</sup>
End	49.20 (8.23)	48.26 (9.70)	2.25	-2.79, 7.24	0.37 <sup>c</sup>
MD	0.73	-1.93			
95% CI	-2.74, 4.21	-6.66, 2.79			
$p^b$	0.65	0.39			
<b>Depression</b>					
Baseline	9.20 (3.60)	10.46 (2.58)	-1.26	-3.61, 1.08	0.28 <sup>a</sup>
End	8.93 (4.43)	9.86 (2.99)	0.23	-2.05, 2.52	0.83 <sup>c</sup>
MD	-0.26	-0.60			
95% CI	-1.86, 1.33	-2.39, 1.19			
$p^b$	0.72	0.48			
<b>Anxiety</b>					
Baseline	9.06 (3.71)	9.93 (2.37)	-0.86	-3.19, 1.46	0.45 <sup>a</sup>
End	8.00 (3.52)	10.86 (2.53)	-2.43	-4.45, -0.42	0.02 <sup>c</sup>
MD	-1.06	0.93			
95% CI	-2.89, 0.76	-0.41, 2.28			
$p^b$	0.23	0.16			

Note. MD: Mean of difference; CI: Confidence interval; IBD-DI: Inflammatory bowel disease disability index.

Data are presented as mean (standard deviation).

<sup>a</sup> Obtained from independent samples t-test.

<sup>b</sup> Obtained from paired sample t-test.

<sup>c</sup> Obtained from ANCOVA adjusted for age and baseline values.

In contrast, daily consumption of 30 grams of flaxseed or 20 grams of flaxseed oil for 12 weeks significantly reduced the severity of UC.<sup>36</sup> The conflicting results in these studies may be due to differences in the content of bioactive compounds in soybean and flaxseed products. For example, the predominant polyunsaturated fatty acid (PUFA) in flaxseed is alpha-linolenic acid, while the predominant PUFA in soybeans is linoleic acid. In addition, difference in the duration of intervention could

be another reason for the conflicting results of the studies.

In the present study, an increase in the incidence of diarrhea was observed in the soybean group compared to the control group. This finding is consistent with results of a study in which consumption of soy milk, compared to yogurt or hydrolyzed formula, in infants with chronic diarrhea non-significantly increased the severity of diarrhea.<sup>37</sup> In another study, consuming 200 mg of soy isoflavones for two years had no significant

effect on reducing constipation in postmenopausal women. Additionally, consumption of soy isoflavones did not reduce headaches, bloating, and dry mouth in postmenopausal women.<sup>38</sup> Unlike our finding, administration of soy-based formulas in healthy infants who were intolerant to milk-based formulas significantly reduced gastrointestinal symptoms.<sup>39</sup> The increased diarrhea associated with soy consumption is not well understood. One hypothesis is that the presence of short-chain carbohydrates in the carbohydrate composition of soybean can cause this effect. Furthermore, short-chain carbohydrates play an important role in creating osmotic pressure in the intestine, leading to diarrhea.

The finding of the present study showed that soybean consumption, compared to the control group, does not improve the quality of life in patients with UC. Consistent with our finding, Nourozi et al reported that daily consumption of 500 mL of soy milk for 8 weeks does not affect the quality of life of postmenopausal women.<sup>40</sup> Our finding was also consistent with another clinical trial, which indicated that supplementation with soy isoflavones and vitamin D for 6 weeks does not improve the quality of life in patients with irritable bowel syndrome.<sup>35</sup> In another study, supplementation with soy isoflavones had no significant effect on the quality of life of postmenopausal women.<sup>41</sup> Nevertheless, our finding contrast with a randomized clinical trial that reported supplementation with fermented soybeans for three weeks significantly improves the quality of life in adults experiencing heartburn.<sup>42</sup> These conflicting results might be explained by differences in the duration of studies and the evaluation of individuals with different clinical conditions across studies.

Our finding displayed that the consumption of soybean does not significantly affect the disability caused by UC. Results of a case-series study showed that adherence to an anti-inflammatory diet, which also contains soy products, can reduce fatigue, bloating, diarrhea, and pain in patients with IBD, all of which contribute to the disabilities caused by the disease.<sup>43</sup> An underlying cause for the difference in the findings of this study and our results could be related to the different designs of the interventions. For example, in the case-series study, soy products were given to participants as part of an anti-inflammatory diet, and the presence of other anti-inflammatory compounds could have also reduced the mentioned symptoms.

Our findings demonstrated that soybean consumption significantly impacts anxiety in patients with UC. However, it had no significant effect on the levels of depression and psychological distress of the patients. A cross-sectional study showed that legume consumption has an inverse and significant relationship with anxiety in adults, while legume consumption was not associated with psychological stress in this study.<sup>44</sup> Another study reported a non-significant association between adherence to a diet rich in soy or its products and psychological stress.<sup>45</sup> In the study by Balk et al, daily consumption of 100 mg of soy

isoflavone for 6 months did not have a significant effect on depressive symptoms in postmenopausal women.<sup>46</sup> In contrast, consumption of soybeans for 3 months in 40 depressed postmenopausal women improved depression and increased response to antidepressants.<sup>47</sup> These conflicting results of studies may be due to differences in mental health assessment tools, participants with different clinical conditions, and different durations of interventions across studies. In addition, the lack of effect of soybean on depression and psychological distress could be due to the short duration of the intervention, as available evidence suggests that depression is affected later than anxiety in interventions.<sup>48</sup> Overall, clinical trials with longer intervention durations are needed to draw definitive results.

In the literature, several mechanisms have been proposed for the anticolic effects of soy. Soy is rich in phytoestrogens, phospholipids, phytosterols, saponins, and bioactive peptides. Isoflavones, for instance, are believed to function as antioxidants in patients with colitis by directly scavenging free radicals and increasing antioxidant enzyme systems.<sup>49,50</sup> Phytosterols, despite being well-known for their cholesterol-lowering effects, also exhibit anti-inflammatory properties.<sup>51</sup>  $\beta$ -Sitosterol, the most abundant phytosterol in soybeans, has immunomodulatory properties,<sup>52</sup> and soyasaponins, though not highly bioavailable orally, were found to be beneficial to the colon.<sup>53,54</sup> In a mouse model of colon tumorigenesis, crude soyasaponin extracts exhibited anticancer potential and antioxidant properties. Soyasaponins also demonstrated anti-inflammatory effects in vitro and in mouse models of intestinal inflammation.<sup>55,56</sup> Additionally, an early study in rats revealed that rectal administration of glycerophospholipids improves histological signs of colitis and reduces the permeability of the colonic mucosa.<sup>57</sup> The therapeutic potential of phosphatidylcholine in IBD was supported by studies showing that patients with UC in remission had lower levels of phosphatidylcholine and lysophosphatidylcholine (an intermediate of phospholipase A2) in rectal mucus samples.<sup>58,59</sup>

### Strengths

To the best of our knowledge, it seems that the present study is the first to investigate the effect of soybean consumption on individuals with UC. Several outcomes were examined in patients at the study baseline and at the end of the trial. Using the ITT approach and including all randomized subjects allowed us to obtain an unbiased estimate of the intervention's effect. Moreover, adherence to the intervention and information about participants' food intake and physical activity were assessed throughout the study.

### Limitations

The duration of the study might not have been long enough to affect some of the study outcomes. Although the study groups were well-balanced for baseline characteristics,

potential differences in unknown confounders between the groups cannot be ruled out. In this study, a single dose of soy was investigated, preventing the establishment of a dose-response relationship. Funding restrictions prevented us from measuring urine levels of isoflavonoids to assess patient compliance. Due to the relatively small sample size, we were unable to examine the effect of soy consumption on study outcomes stratified by gender or other demographic variables. Furthermore, the results may not be generalizable to patients with CD. Financial constraints also prevented us from investigating the effects of soy intake on inflammatory biomarkers. Finally, due to the nature of the food intervention in the present study, it was not possible to blind study participants, which could affect the findings. Larger trials are needed to address these limitations and further explore the effects of soy intake on study outcomes, stratified by gender or other demographic variables.

### Conclusion

In summary, soybean consumption significantly improved anxiety of patients with UC, while no significant changes were observed in terms of quality of life, disease severity, IBD-related disabilities, depression, and psychological distress. To confirm our findings, further studies are required.

### Ethics statement

The study design was approved by the Bioethics Committee of Tehran University of Medical Sciences, Tehran, Iran (identifier: IR.TUMS.VCR.REC.1398.973).

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### Conflict of interests declaration

The authors declare no conflict of interests.

### Author contributions

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**Writing—review & editing:** Ahmad Esmailzadeh, Leila Azadbakht, Amir Ali Sohrabpour.

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