



Zingiber officinale and oxidative stress in patients with ulcerative colitis: A randomized, placebo-controlled, clinical trial



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ABSTRACT

Objectives: Oxidative stress plays an essential role in ulcerative colitis (UC) initiation and severity. We aimed to investigate the effect of ginger as a well-known antioxidant agent on the quality of life, disease activity index and oxidative stress in patients with UC.

Methods: Forty six patients with active mild to moderate UC randomly assigned to consume 2000 mg/day dried ginger powder in 4 capsules or similar placebo capsules for 12 weeks. Disease activity index, quality of life and some oxidative stress factors were measured before, at the middle and at the end of the intervention through valid and reliable questionnaires and blood sampling.

Results: Ginger reduced Malondialdehyde (MDA) significantly after 6 weeks ($p = 0.003$) and 12 weeks ($p < 0.001$) of intervention, whereas it did not affect serum total anti-oxidant capacity (TAC). The scores of severity of disease activity at 12th week was significantly improved in ginger group in comparison to placebo ($p = 0.017$). Moreover, ginger increased patients quality of life significantly at 12th week ($p = 0.039$).

Conclusion: Our data indicate that ginger supplementation can improve treatment of patients with UC. Further clinical trials with different dosages and duration of ginger or its standard extract supplementation are needed to obtain firm conclusion.

1. Introduction

Ulcerative colitis(UC), as one of the two major forms of inflammatory bowel disease (IBD), is a chronic inflammatory disorder with frequent relapses and remissions.¹ It is often associated with incessant lesions of the colon, bloody diarrhea, bloating, abdominal cramp, weight loss, and generally has a notable impact on patient's quality of life due to its usual occurrence at early adulthood and continuing for lifelong. UC pathogenesis includes interaction among genetic susceptibilities, immune response, intestinal flora, and environmental factors.¹

It seems that oxidative stress plays a pivotal role in UC initiation and occurrence of relapses.² In the condition of impaired immune system, excessively produced Reactive Oxygen Species (ROS) metabolites injures the integrity of intestinal mucosa, and delay recovery of them.³

Recently, UC prevalence is increasing especially among western diet consumers all over the world, even areas where the disease had previously been reported to be rare such as African and Asian countries.^{4–6}

Medical therapy of UC including anti-inflammatory and immune suppressants are often reported to induce some side effects on eyes, bones, GI tract, liver, pancreas and immune system.¹ Thus, exploration of therapies with less adverse effects, high efficacies, low toxicities, and low prices seems to be necessary. Diet and dietary supplements are the most modifiable environmental factor involved in pathogenesis of UC.^{6–9} The beneficial effects of anti-oxidative agents on UC have been shown previously.^{10–13} Ginger (*Zingiberofficinale* root) is known as an anti-oxidative agent with known beneficial effects on some gastrointestinal diseases such as nausea and vomiting.^{14–16}

Although the effects of ginger and its phenolic components on UC were examined in experimental models and resulted in improvement of oxidative stress and microscopic and macroscopic scores of colonic tissue,^{5,17–23} there is no evidence of ginger application in human trials. So, we conducted a clinical trial to investigate whether supplementation with dried ginger powder can improve UC patients response to routine treatments, quality of life, disease activity index, and serum oxidative status or not

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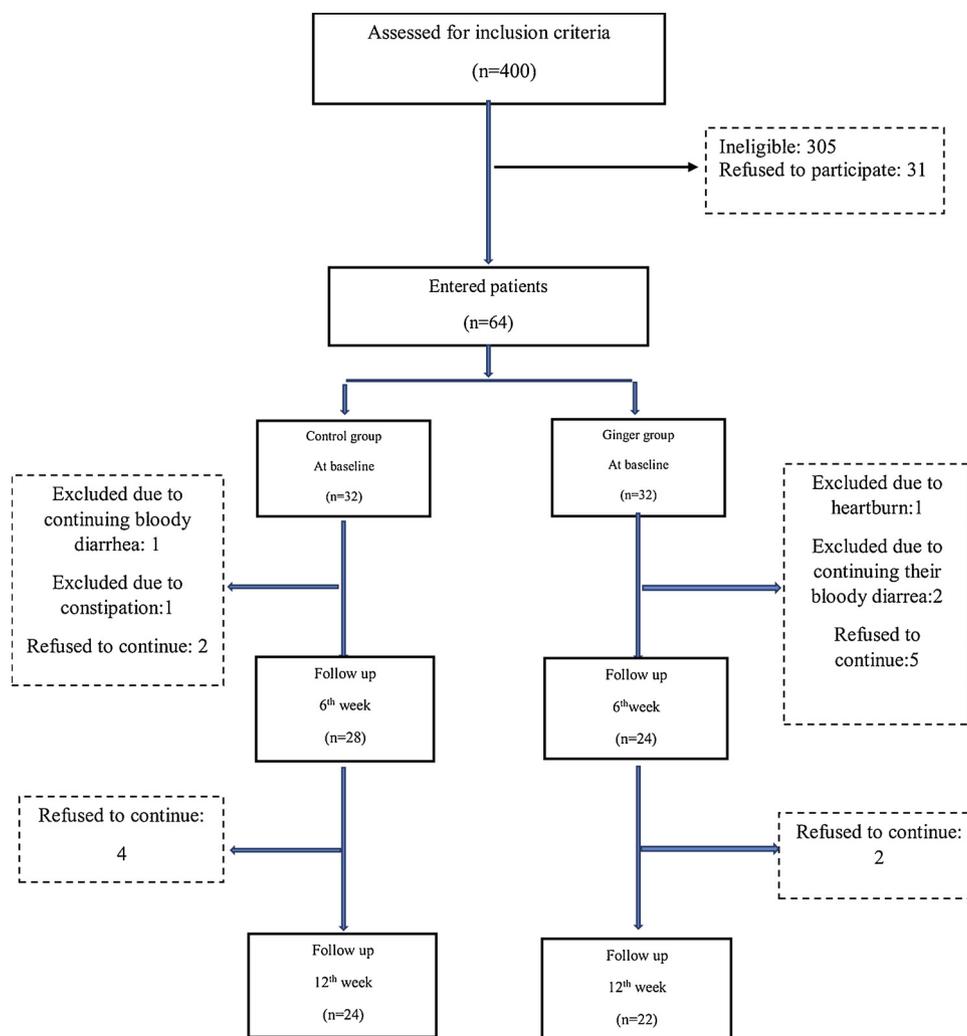


Fig. 1. The study consort flowchart.

Table 1

Individual characteristics of patients with ulcerative colitis participated in the two groups of ginger and placebo supplement before intervention.

p	Ginger group(n = 22)	Control group(n = 24)	
0.351	15 (68.2%) 7 (31.8%)	14 (58.3%) 10 (41.7%)	Sex number(percent) Male female
0.524	41.41 ± 11.4	39.21 ± 11.81	Age (year)
0.638	5.23 ± 5	6 ± 5.89	Duration of disease (year)

2. Material and methods

2.1. Trial design and participants

This study was a prospective, randomized, double-blind, placebo-controlled trial (NO. IRCT201703164010N17). Through convenience sampling method, patients with active mild to moderate UC were recruited from three gastroenterology clinics in Tehran and Sari, Iran. All patients' diagnosis of UC was previously confirmed by gastroenterologist using histopathology exams. Patients more than 18 years old, free of cancer or other inflammatory, autoimmune, infectious and intestinal diseases were included. Pregnant/lactating women, as well as those consuming some medications such as antihistamines, anti-coagulants, calcium channel antagonists, NSAIDs (non-steroidal anti-

inflammatory drugs) or oral contraceptive drugs during the past month before starting intervention were not enrolled in this trial. Participants visited three times during the study period (at the first (T1), middle (T2) and end (T3) of study). At first visit, participants consciously signed a written consent form approved by the ethics committee of the National Nutrition and Food Technology Research Institute (Ethics committee reference number IR.SBMU.NNFTRI.1395.109).

2.2. Intervention

Patients who agreed to participate were randomly assigned to receive either ginger (containing 500 mg dried ginger powder) or placebo capsules (maltodextrin powder). Ginger powder was made by drying and milling the fresh edible ginger from the same farm. Randomization was conducted using the random number table. Patients were recommended to have 4 capsules (2000 mg) during a day along with their meals (two capsules with breakfast, and two capsules with dinner) for 12 weeks. We asked participants not to change their usual dietary habits and physical activity during intervention. Capsules needed for the first and second 6 weeks of intervention were delivered to participants at the first and second visits respectively. Before beginning of the study, the medicine cans were coded as A or B by someone other than the researchers so that the researchers did not know which kind of capsules received by each group. At each visit, anthropometric data including weight (with light clothes to the nearest 0.1 kg), height (without shoes to the nearest 0.5 cm), and BMI (weight (kg)/height (m²)) were

Table 2

Mean and standard deviation of anthropometric indices and dietary intake in patients with ulcerative colitis participated in the two groups of ginger and placebo supplement at the beginning, middle and end of the study.

		Before (T1)	Mid (T2)	After (T3)	P2 (trend)
Weight (kg)	ginger	78.56 ± 12.04	79.09 ± 12.50	78.88 ± 12.11	0.419
	control	68.43 ± 14.39	68.82 ± 14.32	68.7 ± 14.22	0.380
	P1 (between group)	0.007	0.015	0.014	
BMI (kg/m ²)	ginger	26.35 ± 3.93	26.53 ± 4.1	26.48 ± 4.08	0.368
	control	24.73 ± 3.67	24.86 ± 3.6	24.83 ± 3.6	0.259
	P1 (between group)	0.151	0.159	0.052	
Energy (Kcal)	ginger	1467.7 ± 488.58	1547.69 ± 550.26	1658.2 ± 441.63	0.314
	control	1410.71 ± 349.31	1530 ± 306.73	1596.71 ± 356.65	0.197
	P (between group)	0.664	0.709	0.622	
protein	ginger	55.81 ± 20.14	51.7 ± 19.33	51.86 ± 9.78	0.395
	control	53.82 ± 8.71	55.41 ± 6.97	54.22 ± 7.33	0.627
	P (between group)	0.680	0.489	0.321	
carbohydrate	ginger	184.27 ± 74.86	191.71 ± 80.28	184.55 ± 65.58	0.784
	control	202 ± 51.15	183.77 ± 38.66	174.25 ± 35.5	0.120
	P (between group)	0.372	0.804	0.702	
fiber	ginger	15.46 ± 5.17	15.2 ± 9.24	12.69 ± 3.08	0.164
	control	16.58 ± 3.35	13.89 ± 2.95	12.04 ± 2.56	< 0.001
	P (between group)	0.408	0.695	0.355	
Total fat	ginger	58.24 ± 19.7	49.54 ± 18.96	54.82 ± 10.69	0.118
	control	53.02 ± 12.04	50.22 ± 13.52	51.43 ± 11.72	0.890
	P (between group)	0.292	0.890	0.410	
Saturated fat	ginger	16.39 ± 7.24	14.83 ± 7.39	17.06 ± 5.6	0.239
	control	16.17 ± 4.23	15.7 ± 3.71	15.16 ± 5.18	0.766
	P (between group)	0.902	0.760	0.611	
Mono-un saturated fat	ginger	20.31 ± 7.32	18.1 ± 6.92	17.69 ± 5.87	0.099
	control	18.59 ± 8.3	16.99 ± 8.2	18.53 ± 6.41	0.614
	P (between group)	0.475	0.700	0.623	
Poly-unsaturated fat	ginger	13.44 ± 5.47	12.07 ± 5.18	13.69 ± 4.36	0.341
	control	15.73 ± 6.41	13.73 ± 5.66	15.89 ± 7.21	0.504
	P (between group)	0.231	0.312	0.225	
Omega-3	ginger	0.59 ± 0.46	0.49 ± 0.45	0.62 ± 0.47	0.490
	control	0.72 ± 0.29	0.59 ± 0.21	0.74 ± 0.37	0.340
	P (between group)	0.297	0.308	0.456	
Omega-6	ginger	7.22 ± 3.56	6.72 ± 3.76	6.54 ± 3.56	0.291
	control	8.96 ± 6.33	6.84 ± 5.43	5.98 ± 5.02	0.146
	P (between group)	0.271	0.821	0.481	
Cholesterol	ginger	161.82 ± 113.91	155.07 ± 114.84	177.06 ± 43.44	0.715
	control	147.79 ± 53.14	150.96 ± 48.71	158.06 ± 33.22	0.503
	P (between group)	0.610	0.763	0.210	
Selenium	ginger	53.41 ± 21.36	74.45 ± 48.48	68.96 ± 32.61	0.115
	control	52.81 ± 27.2	73 ± 41.17	66.33 ± 36.66	0.155
	P (between group)	0.935	0.968	0.683	
Zinc	ginger	8.34 ± 3.48	7.68 ± 3.99	9.59 ± 4.08	0.069
	control	7.76 ± 1.51	7.47 ± 1.34	8.9 ± 3.54	0.136
	P (between group)	0.488	0.956	0.850	
Vitamin C	ginger	47.82 ± 26.98	42.64 ± 26.16	57.74 ± 32.03	0.128
	control	45.84 ± 20.64	44.75 ± 18.17	57.13 ± 26.98	0.135
	P (between group)	0.788	0.689	0.896	
Vitamin E	ginger	14.93 ± 5.94	13.7 ± 6.39	14.7 ± 6.65	0.079
	control	13.92 ± 3.36	12.5 ± 5.38	12.5 ± 5.38	0.249
	P (between group)	0.494	0.330	0.136	

measured. Furthermore, four questionnaires were filled out by an expert interviewer including "general questionnaire" requesting general information about age, sex, duration of the disease, smoking history, current medications, etc; "Inflammatory Bowel Disease Questionnaire-9 (IBDQ-9)"^{24,25} assessing UC patient's quality of life, "Simple Clinical Colitis Activity Index Questionnaire (SCCAIQ)"²⁶ determining disease activity index of UC patients and finally, 3-day dietary recalls of 2 weekdays and 1 weekend day assessing patients dietary intake of energy, macro/ micronutrients. For assessing the differences between serum oxidative stress factors, before, at the middle and after intervention, we collected 10cc of 12–14 h fasted blood samples, poured into heparinized laboratory tubes and immediately centrifuged. Separated plasma was kept in –80 °C freezer for further examinations. Adverse events of treatment were monitored during visits as well as follow up phone calls at third and ninth weeks. During intervention, participants with disease relapse leading to hospitalization or patients who did not want to continue the study protocol were excluded. Adherence to

treatment was evaluated by counting the number of pills remaining in medicine can at the second and third visits. If > 10% of capsules were remained, the patient was excluded from the study.

2.3. Measurements

Serum total antioxidant capacity (TAC) and malondialdehyde (MDA) levels, as indicators of oxidative stress status, were determined using ELISA. We analyzed dietary intake values of energy and nutrients through modified Nutritionist 4 using national food composition tables. We rated IBDQ-9 to evaluate each participant's quality of life. IBDQ questionnaire is the most utilized questionnaire for evaluating the quality of life in patients with IBD in clinical and epidemiological studies, regarding due to its high validity, reliability, sensitivity and intercultural adaptation.^{24,25} Our questionnaire had 9 questions about patient's emotional and social challenges such as the levels of satisfaction or happiness in personal life, patient's energy, feeling of

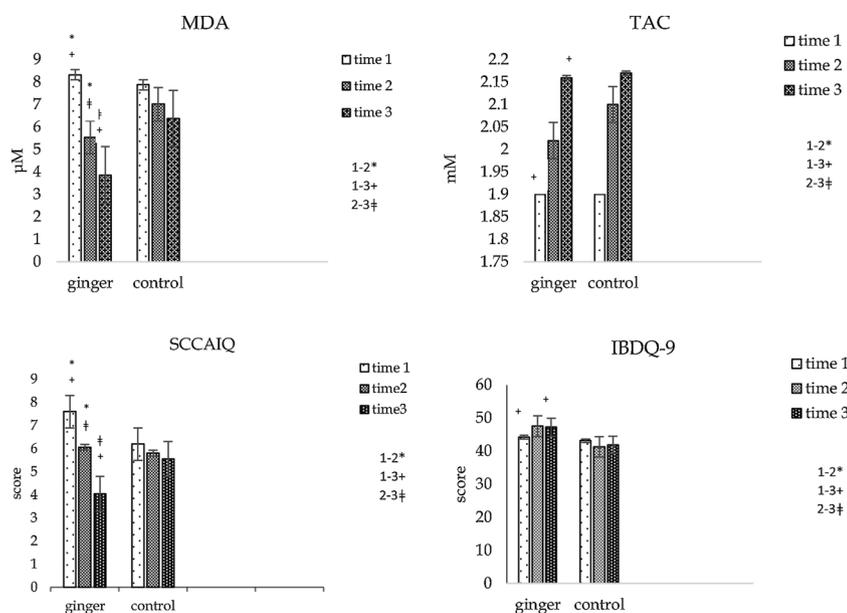


Fig. 2. Schematic pattern of changes in serum oxidative stress factors concentration, IBDQ-9 score and SCCAIQ score in patients with Ulcerative Colitis participated in two groups of ginger and placebo before, at the middle and at the end of the study.

Table 3

-Mean and standard deviation of the serum oxidative stress factors concentration in patients with ulcerative colitis participated into groups of ginger and placebo before, at the middle and the end of the study.

		Before (T1)	Mid (T2)	After (T3)	P2 (trend)
MDA	ginger	8.33 ± 1.82	5.54 ± 2.03	3.87 ± 1.95	< 0.001
	control	7.88 ± 2.24	7.02 ± 0.87	6.38 ± 2.42	0.119
	P1 (between group)	0.348	0.003	< 0.001	
TAC	ginger	1.9 ± 1.2	2.02 ± 1.27	2.16 ± 1.16	0.110
	control	1.99 ± 1.33	2.1 ± 1.23	2.17 ± 1.17	0.548
	P1 (between group)	0.723	0.705	0.640	

*Adjusted for baseline values and weight.

sickness, feeling tired, cancel or delay a scheduled task as well as bowel habits such as gas excretion, flatulence, stool frequency and cramps during past two weeks. Each question has 7 items and each item has its own corresponding score; so each question covers points 1 to 7. The total score of questionnaire can be from 9 to 63. The higher score reflects the better quality of life of patient.²⁷ Evidence have shown that

Table 4

The mean and standard deviation of the quality of life questionnaire score and the index of disease activity in patients with ulcerative colitis participated in the two groups of ginger and placebo before, at the middle and at the end of the study.

		Before (T1)	Mid (T2)	After (T3)	P2 (trend)
IBDQ score	ginger	44.22 ± 9.79	47.54 ± 10.07	47.23 ± 9.24	0.134
	control	43.12 ± 6	41.29 ± 13.86	41.87 ± 14.18	0.636
	P1 (between group)	0.644	0.089	0.140	
stool frequency score	ginger	6.2 ± 1.84	6.09 ± 1.6	6.54 ± 1.1	0.502
	control	5.78 ± 0.97	5.59 ± 0.59	5.82 ± 1.2	0.705
	P (between group)	0.215	0.183	0.041	
Bowel distress and cramp score	ginger	5.04 ± 1.98	5.91 ± 1.85	5.64 ± 1.78	0.073
	control	4.64 ± 1.49	5 ± 1.19	4.59 ± 1.22	0.264
	P (between group)	0.331	0.060	0.029	
gas excretion of bowel score	ginger	4.86 ± 2	5.14 ± 1.42	5.27 ± 1.42	0.467
	control	4.55 ± 1.44	4.9 ± 1.27	4.54 ± 1.74	0.217
	P (between group)	0.830	0.579	0.136	
Flatulence score	ginger	4.73 ± 2.09	4.64 ± 1.81	4.77 ± 1.82	0.945
	control	4.59 ± 0.9	4.14 ± 1.28	4.54 ± 1.14	0.146
	P (between group)	0.963	0.297	0.623	
SCCAIQ score	ginger	7.6 ± 4.03	6.05 ± 3.02	4.05 ± 1.23	0.438
	control	6.2 ± 3.22	5.8 ± 2.66	5.55 ± 2.39	0.194
	P (between group)	0.233	0.825	0.017	

IBDQ score is significantly correlated with clinical and colonoscopy results.²⁵ We also rated SCCAIQ to evaluate each participant’s disease activity. This questionnaire score correlates closely to laboratory data and is reported to be a reliable tool for initial assessment of UC outpatients.²⁶ This questionnaire has multiple items with total score between 0–19; which higher scores reflect more severity of UC symptoms during past week.

2.4. Primary and secondary outcomes

The primary outcome measure was a significant reduction in SCCAIQ score. Secondary outcome measures were IBDQ-9 score, serum concentration of MDA, and TAC.

2.5. Statistical analysis

Estimation of sample size for this study was based on detection of 4 score difference in mean SCCAIQ score with power of 80% (β = 20%).¹² In this study, the calculated sample size for each group was 21 patients. Due to the potential loss of samples, 25 patients in each group were considered.

We applied SPSS 19 for the statistical analysis. The collected data normality distribution was assessed by Shapiro-Wilks test. We used chi-square test in order to compare the qualitative confounding variables and independent *t*-test in order to compare the variable means between ginger and control groups. We also compared three times averages of quantitative variables within each group by repeated measures test. In order to eliminate the impact of quantitative confounding factors, that had been found statistically different between groups at baseline, analysis of covariance was conducted. We assumed *p* value < 0.05 as statistically significant.

3. Results

From sixty four patients who were enrolled in the study at baseline, 46 patients completed intervention period (12 weeks). Number of cases and controls were 22 and 24 respectively (Fig. 1). There was no smoker in study participants, and medications were similar in both groups. None of the study participants had any extra-intestinal symptoms. As it is shown in Table 1, there was no significant difference in baseline characteristics of participants at the beginning of the study.

The mean and standard deviation of anthropometric data and dietary intakes are shown in Table 2. There was no significant difference between the amounts of energy, macronutrients and micronutrients intake between two groups at each time of intervention except for fiber intake, which was significantly reduced during the study in control group.

Serum level of oxidative stress related factors are shown in Fig. 2. Although two groups were statistically similar in oxidative stress factors, quality of life, and disease activity scores at the base line, independent *t*-test showed that MDA in the ginger group was significantly lower than the control group after 6 weeks (*p* = 0.003) and 12 weeks (*p* < 0.001) of intervention (Table 3). The mean difference between groups at the end of the study was significantly higher than at 6 weeks (2.52 vs. 1.47). Serum level of MDA decreased significantly in ginger group (*p* < 0.001). As it is shown in Table 3, the difference in mean of MDA relative to the previous time was significant (*p* < 0.001 for T2-T1, T3-T1, T3-T2) in ginger group. During the study time MDA concentration was significantly lower in ginger group in comparison to placebo group (*p* < 0.001) and this change remained significant after adjustment for weight and baseline values.

No significant difference was observed in TAC level between two groups; only in ginger group TAC was significantly more at the end of study compared to the beginning of the intervention (*p* = 0.01).

The scores of severity of disease activity at 12th week was significantly improved in ginger group in comparison to placebo (*p* = 0.017) (Table 4).

IBDQ score increased significantly at T3 in ginger group (*p* = 0.039). The difference in mean of patient's disease activity relative to the previous time was significant in ginger group (*p* T2-T1 = 0.04, *p* T3-T1 = 0.004, *p* T3-T2 = 0.04) (Fig. 2).

4. Discussion

To our knowledge, this is the first clinical trial that has investigated the effects of ginger on oxidative stress in patients with UC. Our results have shown that consumption of 2 g/day dried ginger powder for 90 days can improve some aspects of oxidative stress and disease activity. It seems that this dosage and duration of supplementation was too low to induce significant improvement in patients with UC. Ginger supplementation reduced MDA significantly; however, it could not affect TAC. Thus, it could significantly decrease the total score of SCCAIQ, and IBDQ; however, the difference with placebo did not reach to a significant point for IBDQ.

In inflammatory conditions, the migration of inflammatory cells such as neutrophils into the colon causes the production of ROS, oxidative stress and lipid peroxidation, which affects cell macromolecules

and imbalances in membrane integrity leading to mucosal disorders, chronic inflammation and ulcers.^{18,19} Studies have indicated gingerols and shogaols, the active compounds of ginger, protect colonic mucosa from ulceration through their antioxidant aspects and restoring the redox state of colonic tissue. They also have protecting roles against UC by their spasmolytic activity, mediated by blockage of calcium channels.^{28–30}

Recently, the beneficial effects of various ginger extracts and its bioactive constituents have been reported in experimental models of UC.^{17,20–23,31}

Ginger restored parameters of the redox state of the colonic mucosa through improving colonic enzymatic and non-enzymatic defense systems to the extent that approaches the normal values. It is shown in experimental studies that ginger active derivatives prohibit peroxidation of lipids, expression of p38 protein and activity of myeloperoxidase, as well as decrease mucosal MDA, hydrogen peroxide (H₂O₂), and protein carbonyl (PCO) levels in a dose-dependent manner.^{17,19–21} In addition, antioxidant properties of ginger have been reported in clinical trials of other diseases with oxidative stress condition such as type 2 diabetes and Tuberculosis.^{32,33} Our study confirmed the results of these studies in patients with UC. However, serum MDA improved more than TAC in our study, which might be due to relatively short duration and low dosage of supplementation.

This study had some advantages; it was the first randomized, double blind, placebo controlled, clinical trial evaluated the effects of ginger on oxidative stress in UC patients, all known covariates were controlled during study, and study outcomes were measured every 6 weeks that have shown the trend of study outcome measurements.

This study had some limitations; we could not use invasive methods such as colonoscopy and tissue biopsy to measure the severity of the disease and the tissue oxidative stress indices because patients did not accept to undertake colonoscopy at the end of the study. However, we used SCCAIQ, which has been shown as an effective indicator of the severity of UC.²⁶

In our study, most patients claimed that intestinal gas excretion, bloating and abdominal pain decreased after taking ginger; although we received slight complaints of ginger supplement during study. Some patients, who used ginger capsules with an empty stomach, not during a meal or snack, claimed that the capsules caused heartburn. Some participants were unhappy with the severe smell of ginger in their digestive system.

In conclusion, this randomized, placebo controlled trial found that 2000 mg/day ginger supplementation can improve disease severity index and oxidative stress in patients with active mild to moderate UC. Further clinical trials with different dosages and duration of ginger or its standard extract supplementation are needed to obtain firm conclusion.

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References

- Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut*. 2011;60(5):571–607.
- La Kruidenier, Verspaget H. oxidative stress as a pathogenic factor in inflammatory bowel disease—radicals or ridiculous? *Aliment Pharmacol Ther*. 2002;16(12):1997–2015.
- Buffinton GD, Doe WF. Depleted mucosal antioxidant defences in inflammatory bowel disease. *Free Radic Biol Med*. 1995;19(6):911–918.
- Amre DK, D'souza S, Morgan K, et al. Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children. *Am J Gastroenterol*. 2007;102(9):2016.
- Hsiang C-Y, Lo H-Y, Huang H-C, et al. Ginger extract and zingerone ameliorated

- trinitrobenzene sulphonic acid-induced colitis in mice via modulation of nuclear factor- κ B activity and interleukin-1 β signalling pathway. *Food Chem.* 2013;136(1):170–177.
6. Rashvand S, Somi MH, Rashidkhani B, et al. Dietary protein intakes and risk of ulcerative colitis. *Med J Islam Repub Iran.* 2015;29:253.
 7. Hekmatdoost A, Feizabadi MM, Djazayeri A, et al. The effect of dietary oils on cecal microflora in experimental colitis in mice. *Indian J Gastroenterol.* 2008;27(5):186–189.
 8. Shivappa N, Hébert JR, Rashvand S, et al. Inflammatory potential of diet and risk of ulcerative colitis in a case–control study from Iran. *Nutr Cancer.* 2016;68(3):404–409.
 9. Rashvand S, Somi MH, Rashidkhani B, et al. Dietary fatty acid intakes are related to the risk of ulcerative colitis: A case–control study. *Int J Colorectal Dis.* 2015;30(9):1255–1260.
 10. Hekmatdoost A, Mirshafiey A, Feizabadi MM, et al. Polyunsaturated fatty acids, microflora and colitis. *Ann Nutr Metab.* 2009;55(4):325.
 11. Hekmatdoost A, Wu X, Morampudi V, et al. Dietary oils modify the host immune response and colonic tissue damage following *Citrobacter rodentium* infection in mice. *Am J Physiol Gastrointest Liver Physiol.* 2013;304(10):G917–28.
 12. Samsamikor M, Daryani NE, Asl PR, et al. Resveratrol supplementation and Oxidative/Anti-Oxidative status in patients with ulcerative colitis: A randomized, double-blind, placebo-controlled pilot study. *Arch Med Res.* 2016;47(4):304–309.
 13. Samsami-kor M, Daryani NE, Asl PR, et al. Anti-inflammatory effects of resveratrol in patients with ulcerative colitis: A randomized, double-blind, placebo-controlled pilot study. *Arch Med Res.* 2015;46(4):280–285.
 14. Giacosa A, Morazzoni P, Bombardelli E, et al. Can nausea and vomiting be treated with ginger extract. *Eur Rev Med Pharmacol Sci.* 2015;19(7):1291–1296.
 15. Haniadka R, Saldanha E, Sunita V, et al. A review of the gastroprotective effects of ginger (*Zingiber officinale* Roscoe). *Food Funct.* 2013;4(6):845–855.
 16. Lete I, Allué J. The effectiveness of ginger in the prevention of nausea and vomiting during pregnancy and chemotherapy. *Integr Med Insights.* 2016;11 IMI. S36273.
 17. Ajayi B, Adedara I, Farombi E. Protective mechanisms of 6-gingerol in dextran sulfate sodium-induced chronic ulcerative colitis in mice. *Hum Exp Toxicol.* 2018 0960327117751235.
 18. Ajayi BO, Adedara IA, Farombi EO. Pharmacological Activity of 6-Gingerol in Dextran Sulphate Sodium-induced Ulcerative Colitis in BALB/c Mice. *Phytother Res.* 2015;29(4):566–572.
 19. El-Abhar HS, Hammad LN, Gawad HSA. Modulating effect of ginger extract on rats with ulcerative colitis. *J Ethnopharmacol.* 2008;118(3):367–372.
 20. Zhang F, Ma N, Gao YF, et al. Therapeutic Effects of 6-Gingerol, 8-Gingerol, and 10-Gingerol on Dextran Sulfate Sodium-Induced Acute Ulcerative Colitis in Rats. *Phytother Res.* 2017;31(9):1427–1432.
 21. Zhang M, Viennois E, Prasad M, et al. Edible ginger-derived nanoparticles: A novel therapeutic approach for the prevention and treatment of inflammatory bowel disease and colitis-associated cancer. *Biomaterials.* 2016;101:321–340.
 22. Zhang M, Wang X, Han MK, et al. Oral administration of ginger-derived nanolipids loaded with siRNA as a novel approach for efficient siRNA drug delivery to treat ulcerative colitis. *Nanomedicine.* 2017;12(16):1927–1943.
 23. Zhang M, Xu C, Liu D, et al. Oral delivery of nanoparticles loaded with ginger active compound, 6-shogaol, attenuates ulcerative colitis and promotes wound healing in a murine model of ulcerative colitis. *J Crohns Colitis.* 2017.
 24. Casellas F, Alcalá M-J, Prieto L, et al. Assessment of the influence of disease activity on the quality of life of patients with inflammatory bowel disease using a short questionnaire. *Am J Gastroenterol.* 2004;99(3):457.
 25. Verissimo R. *Quality of Life in Inflammatory Bowel Disease: Psychometric Evaluation of an IBDQ Cross-Culturally Adapted Version.* 2008; 2008.
 26. Walmsley R, Ayres R, Pounder R, et al. A simple clinical colitis activity index. *Gut.* 1998;43(1):29–32.
 27. Gholamrezaei A, Haghani S, Shemshaki H, et al. Linguistic validation of the inflammatory bowel disease questionnaire-short form (IBDQ-9) in Iranian population. *J Isfahan Med Sch.* 2011;28(123).
 28. Blomhoff R. Antioxidants and oxidative stress. *Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin, ny raekke.* 2004;124(12):1643–1645.
 29. Ghayur MN, Gilani AH. Pharmacological basis for the medicinal use of ginger in gastrointestinal disorders. *Dig Dis Sci.* 2005;50(10):1889–1897.
 30. Masuda Y, Kikuzaki H, Hisamoto M, et al. Antioxidant properties of gingerol related compounds from ginger. *Biofactors.* 2004;21(1-4):293–296.
 31. Vavricka SR, Gubler M, Gantenbein C, et al. Anti-TNF treatment for extraintestinal manifestations of inflammatory bowel disease in the Swiss IBD cohort study. *Inflamm Bowel Dis.* 2017;23(7):1174–1181.
 32. Shidfar F, Rajab A, Rahideh T, et al. The effect of ginger (*Zingiber officinale*) on glycemic markers in patients with type 2 diabetes. *J Complement Integr Med.* 2015;12(2):165–170.
 33. Kulkarni RA, Deshpande AR. Anti-inflammatory and antioxidant effect of ginger in tuberculosis. *J Complement Integr Med.* 2016;13(2):201–206.