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Original article

Evaluation of beneficial aspects of *Prunus avium L. (cherry)* extract in experimental model of acetic acid-induced colitis in rats

Khatereh Kharazmi[1, †], Seyedeh Najibeh Nasiri[2, †], Mohammad Saroughi[1, †], Akram Aminian[3], Mohammad Abavisani[4], Mahla Asadi[1], Seyedeh Elnaz Nazari[1], Majid Khazaei[5,*]

[1]*Department of Medical Physiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[2]*Tissue Engineering Research Group, Department of Anatomy and cell Biology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[3]*Department of Physiology and Pharmacology, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran*
[4]*Department of Microbiology & Virology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[5]*Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*

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† Equal first authors
**** Corresponding Author:***
Tel: +9851138002298
Fax: +985118002287
Khazaeim@mums.ac.ir

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Abstract

Objective: Cherry stems have strong anti-inflammatory properties. This study investigated the therapeutic potential of cherry stem extract in alleviating clinical symptom, colon histology, and inflammation and oxidative stress balance in this disease.

Materials and methods: Rats were divided into Control, Colitis, MSZ, and cherry stem groups. They received 2 ml of 4% acetic acid for colitis induction via intrarectal injection. They also received saline, MSZ 100 mg/kg/day, and cherry stem hydroalcoholic extract 300 mg/kg/day via oral gavage. Disease activity index (DAI) including diarrhea, rectal bleeding, and weight loss, was controlled daily after colitis induction. Colon macroscopic and microscopic damage, oxidative indicators including malondialdehyde (MDA), and antioxidant markers (superoxide dismutase (SOD), Catalase (CAT), and total thiol) were measured. Expression of pro-inflammatory genes including Interleukin-1β (*IL-1β*), Interferon gamma *(IFN-γ)*, and Tumor necrosis factor alpha *(TNF-α)*, and expression of *TGF-β*, pro-fibrotic gene, were evaluated.

Results: DAI, macroscopic ulcer, inflammation score, MDA and expression of pro-inflammatory and pro-fibrotic genes were significantly increased in the colitis group compared to control, and significantly decreased in the treatment groups compared to the colitis group.

Conclusion: Cherry stem extract has beneficial effects on clinical symptoms, and reduced inflammation and fibrosis in colon tissue through modulation of oxidant-antioxidant, pro-inflammatory, and pro-fibrotic factors. More studies are needed to clarify the combination of cherry stem and MSZ in treatment of UC.

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Introduction

Ulcerative colitis (UC) is a long-lasting inflammatory condition that impacts the lining of the colon, and it is classified under inflammatory bowel diseases (IBD) (Silaghi et al. 2022). The exact cause remains unclear, but most important key factors that are thought to contribute are gut microbiome, immune system, environmental influences, and genetics (Yuan et al. 2023). The disease presents with both intestinal and extraintestinal symptoms, affecting the colon and other organs like joints, skin, and eyes. Common intestinal symptoms include diarrhea, weight loss, hematochezia, and abdominal pain (Martins et al. 2021).

The exact mechanism of UC is unclear. However, it is suggested that increased mitochondrial activity in immune cells causes the release of reactive oxygen species (ROS), leading to oxidative stress in the colonic mucosa. This damages the colonic lining and weakens the tight junctions of mucosal cells, resulting in greater intestinal permeability and inflammation which are symptoms experienced by individuals with UC (Kurumi et al. 2024a). On the other hand, studies on colitis have shown elevated levels of leukotrienes, chemotactic substances, and inflammatory and fibrotic cytokines like *interleukin-1β (IL-1β), Tumor necrosis factor alpha (TNF-α), interferon-gamma (IFN-γ), and Transforming growth factor beta (TGF- β)* in the inflamed walls of the colon (Kurumi et al. 2024b; Langer et al. 2019). Thus, it seems that inhibiting these mediators may ease symptoms associated with IBD (Saez et al. 2023) and reduce the chance of tissue scarring and organ failure (Sinopoulou et al. 2021; Xin et al. 2024).

Despite extensive research on IBD, a definitive cure remains elusive. Current medications like salicylates, corticosteroids, immunomodulators, and TNF-α monoclonal antibodies primarily aim to control inflammation but are not always successful (Segal et al. 2021). Furthermore, the side effects of routinely prescribed drugs such as Mesalazine (MSZ) can be troublesome for patients, compounding their difficulties (Halawani et al. 2024) and a notable number of patients discontinue use due to adverse side effects.

Cherry fruits and their stems are high in flavonoids, making them a nutritious option. Sweet cherries, scientifically known as *Prunus avium* L., belong to the Rosaceae family and the *Prunus* genus, which includes both sweet and sour varieties (Merecz-Sadowska et al. 2021; Panche et al. 2016). Both the fruit and stems are rich in flavonoids which have potent antioxidant effects, highlighting the fruit's importance in studying treatments for inflammatory diseases due to the common imbalance of oxidants and antioxidants in tissue inflammation (Chagas et al. 2022).

Thus, in this study, we evaluated the therapeutic properties of cherry stem extract on improving colitis in acetic acid-induced colitis model in rats.

Materials and Methods

Animals

The research work involved 24 male Wistar rats, weighing 210 ± 20 g, sourced from the laboratory animal unit at Mashhad University of Medical Sciences, Iran. They were placed in equal groups in four cages under suitable conditions of 22±3°C, 40% humidity, and a 12-hr light/dark cycle. The rats had free access to food and water, except during fasting periods, and fed with standard pellets. The intervention was carried out in compliance with ethical standards, approved by the Animal Care Committee at the university (IR.MUMS.AEC.1403.087).

Chemicals

Glacial acetic acid (AA) was purchased from Merck (Darmstadt, Germany). Mesalazine (MSZ) was purchased from Iran Hormone Co., Tehran, Iran. Other reagents for oxidative stress tests were purchased from Sigma-Aldrich Chemical

Co. (St Louis, MO, USA). Total RNA extraction kit and cDNA synthesis kit were purchased from Pars Toos Company (Pars Toos, Tehran, Iran) and Yekta Tajhiz Azma Company (Yekta Tajhiz Azma, Tehran, Iran), respectively.

Cherry stem extraction

Cherry stem extract was prepared by the maceration method. In brief, fresh cherry stems were removed, freeze-dried, and then ground to a fine powder. The extract was created by combining a portion of the dry weight (DW) of powdered stems within ethanol 70% ethanol, in a ratio of 1 to 4, using a vortex for thorough mixing. The mixture was kept in a dark, room-temperature location for three days, during which it was occasionally shaken. Once the soaking period was completed, the mixture was filtered, and the solvent was carefully removed with a rotary device. The resulting dry powder was stored in a dark, cool environment, ready to be used for feeding animals (Nurcahyo et al. 2020).

Induction of colitis

Figure 1 provides an overview of the experimental design. After a fasting duration of 12 hr, the animals were anesthetized using ketamine and xylazine (50 mg/kg and 10 mg/kg respectively). Then, each rat was placed on its back, and 2 ml of 4% acetic acid was administered rectally over 30 sec using an 8 cm insertion of a soft tube. The rats were then placed in the Trendelenburg position to prevent acid leakage, followed by a flat position after two minutes to clear any remaining acid. The control group was given a 0.9% normal saline enema (Nazari-Khanamiri et al. 2023).

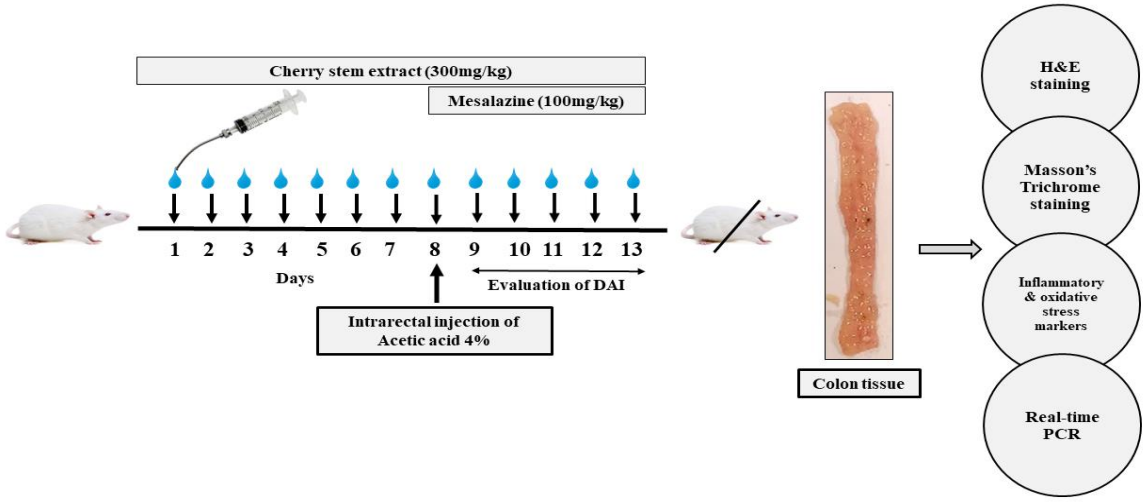

Figure 1. A schematic diagram of the study design

Experimental groups

Twenty-four rats were randomly assigned to following groups (n=6 each): Control group (without induction of colitis), which received 2 ml of 0.9% saline via oral gavage; Colitis group, which received 2 ml of 0.9% saline via oral gavage; MSZ group: colitis was induced and rats were treated by MSZ at 100 mg/kg/day via oral gavage (Kheradmand et al. 2025); and cherry stem group: colitis was induced and rats received cherry stem extract at 300 mg/kg/day via oral gavage (Akbari et al. 2020; Azaryan et al. 2017). All groups received the relevant drugs daily for seven days before the induction day, except for MSZ. After induction of colitis, treatment was given after two hours and continued for five days.

Evaluating of disease activity index (DAI)

After induction of colitis, the disease activity index (DAI) was evaluated, daily, including weight loss, stool consistency, and presence of blood in the stool. Score was allocated based on the cooper scoring system (Binabaj et al. 2019).

Evaluation of macroscopically colon changes

On the last day of the study, the animals were euthanized with ketamine 300 mg/kg and xylazine 30 mg/kg. The last 8 cm of the colon was removed, opened, cleaned, and examined through laparotomy. Tissue damage was assessed using the Miller method, focusing on erythema, edema, and ulcer appearance (Millar et al. 1996). The ulcer area was measured using Image J software, and the wet weight (mg) of the colon section was recorded. Following these assessments, the colon was divided into three parts: the distal section was fixed in formalin for histology, the middle section was frozen for biochemical studies, and the proximal section was stored at -80°C for molecular investigations.

Histological examination using H&E staining

Tissue samples were put in formalin 10%, rinsed with tap water, dehydrated through various ethanol concentrations, and then processed with xylene before being embedded in paraffin molds. They were sliced into 5 µm sections using a microtome and placed on glass slides. The sections underwent deparaffinization and stained with hematoxylin and eosin (H&E). A pathologist evaluated inflammatory changes, edema, crypt damage, and ulceration under a light microscope at 40x magnification without prior knowledge of the samples. Evaluation scores varied from 0 to 13, as shown in Table 1 (Eskandari et al. 2022).

Histological examination using Masson's trichrome staining

The Masson's trichrome staining technique was applied to the tissue sections, which were subsequently analyzed under a 10x light microscope. The blue regions and overall area of the tissue sections were assessed using Image J software, allowing for the calculation of collagen content and the percentage of tissue fibrosis.

Evaluation of oxidant/antioxidant markers

The levels of oxidative stress markers including Glutathione (GSH), Malondialdehyde (MDA), Superoxide dismutase (SOD), and Catalase (CAT) were assessed in colon tissue samples as previously described (Marjaneh et al. 2018; Mighani et al. 2024).

Evaluation of *IL-1β, IFN-γ, TNF-α, and TGF-β* mRNA expression

Total RNA was extracted using the kit according to the instructions provided with the kit. Then, complementary DNA (cDNA) was synthesized using a cDNA synthesis kit. Primer pairs for target genes (IL-1β, IFN-γ, TNF-α, and TGF-β) and reference housekeeping gene (GAPDH) are displayed in Table 2. Real-time PCR was performed using the ABI PRISM StepOne™ Instrument (Applied Biosystems, Foster City, CA, USA) with SYBR Green chemistry. Relative gene expression was calculated using the 2^(-ΔΔCt) method, normalized to housekeeping genes, and expressed as fold change compared to control group (Livak and Schmittgen 2001).

Statistical analysis

Data analysis was performed using SPSS version 22, employing One-way ANOVA with LSD for parametric data and Kruskal-Wallis and Mann-Whitney U tests for non-parametric data. Results are presented as mean ± standard error of mean (S.E.M), with significance set at $p<0.05$. Graphs were created using GraphPad Prism version 8.0.2.

Table 1. Histopathological scoring system (Alsharif et al. 2022)

Inflammatory Cell Infiltration	
0. None	
1. Intermittent, restricted to the submucosa	
2. Notable localized regions within the submucosa	
3. Prominent localized regions in both the submucosa and lamina propria	
4. Transmural infiltration extending from the mucosa to the muscularis	
5. Transmural infiltration extending from the mucosa to the muscularis	
Crypt Damage	
0. No change	
1. Damage to crypts observed, with noticeable gaps between them	
2. Loss of goblet cells and a reduction in crypt length, resulting in increased spacing	
3. Significant regions devoid of crypts	
4. Absence of crypts entirely	
Ulceration	
0. Absence of ulcers	
1. Small localized ulcers	
2. Numerous small ulcers	
3. Extensive regions lacking surface epithelium	
Edema	
0. Not present	
1. positive	
Total lesion score	0-13

Table 2. qPCR primers sequence

Gene	Source	Primer	Sequence
GAPDH	Rat	Forward	CTTCTCTTGTGACAAAGTGGACA
		Reverse	TTGACTGTGCCGTTGAACTTG
IL-1β	Rat	Forward	GACTTCACCATGGAATCCGT
		Reverse	TGCTCATTCACGAAAAGGGA
TNF-α	Rat	Forward	AGGCTGTCGCTACATCACTG
		Reverse	CTCTCAATGACCCGTAGGGC
IFN-γ	Rat	Forward	TGAGCATCGCCAAGTTCGAG
		Reverse	TCTGGTGACAGCTGGTGAATC
TGF-β	Rat	Forward	CACCCAGGTCCTTCCTAAA
		Reverse	GGAGAGCCCTGGATACCAAC

Results

DAI score

The DAI score, a collection of three scores including weight loss, rectal bleeding, and stool consistency, was reported in Figure 2. Our results indicated that rectal bleeding (Figure 2A), stool consistency (Figure 2B) and DAI score (Figure 2C) were significantly higher in colitis group compared to control group ($p<0.001$) and decreased in the MSZ and cherry stem groups compared to colitis group ($p<0.001$). There was no significant difference in these scores between MSA and cherry stem groups.

On the first day after induction of colitis, all the animals achieved the highest index scores. The colitis group's score was significantly higher than that of the control group, whereas the score of the treatment groups was lower compared to the colitis group. This decrease was particularly significant in the cherry stem group compared to control group ($p<0.05$) (Figure 2D).

Colon weight, ulcer area, and macroscopic changes

Figure 3A illustrates the macroscopic images of the rats' colon tissue. Our results showed that colon weight increased in the colitis group compared to the control group ($p<0.01$) which significantly decreased in treated groups with MSZ and cherry stem ($p<0.01$) (Figure 3B). Analysis of ulcer area (Figure 3C) and macroscopic score (Figure 3D) indicated that colitis group had higher ulcer area and macroscopic score compared to the control group ($p<0.001$) which notably decreased in treated groups especially in cherry stem group ($p<0.001$).

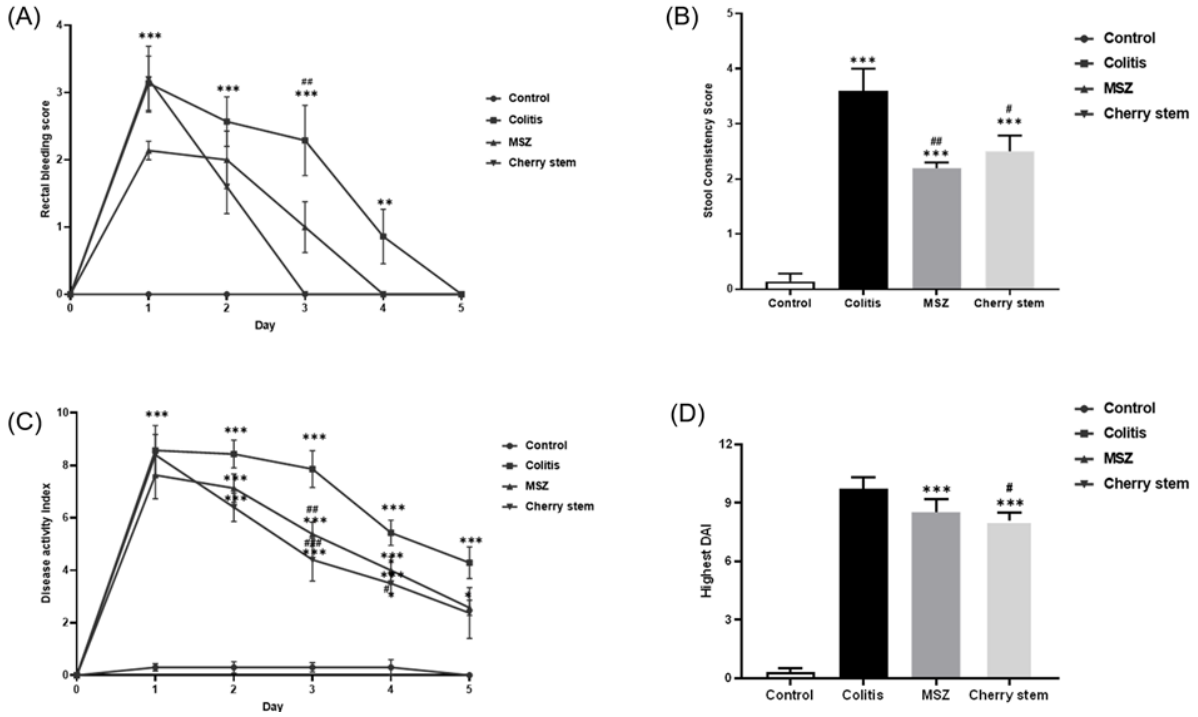

Figure 2. Effects of administering cherry stem extract on rectal bleeding (A), stool consistency (B), highest DAI score (C), and DAI changes (D). Data are presented as Mean ± SEM (n=6 per group). *p<0.005, **p<0.01, and ***p<0.001 vs. control group; $^{\#}$p<0.005, $^{\#\#}$p<0.01, and $^{\#\#\#}$p<0.001 vs. colitis group.

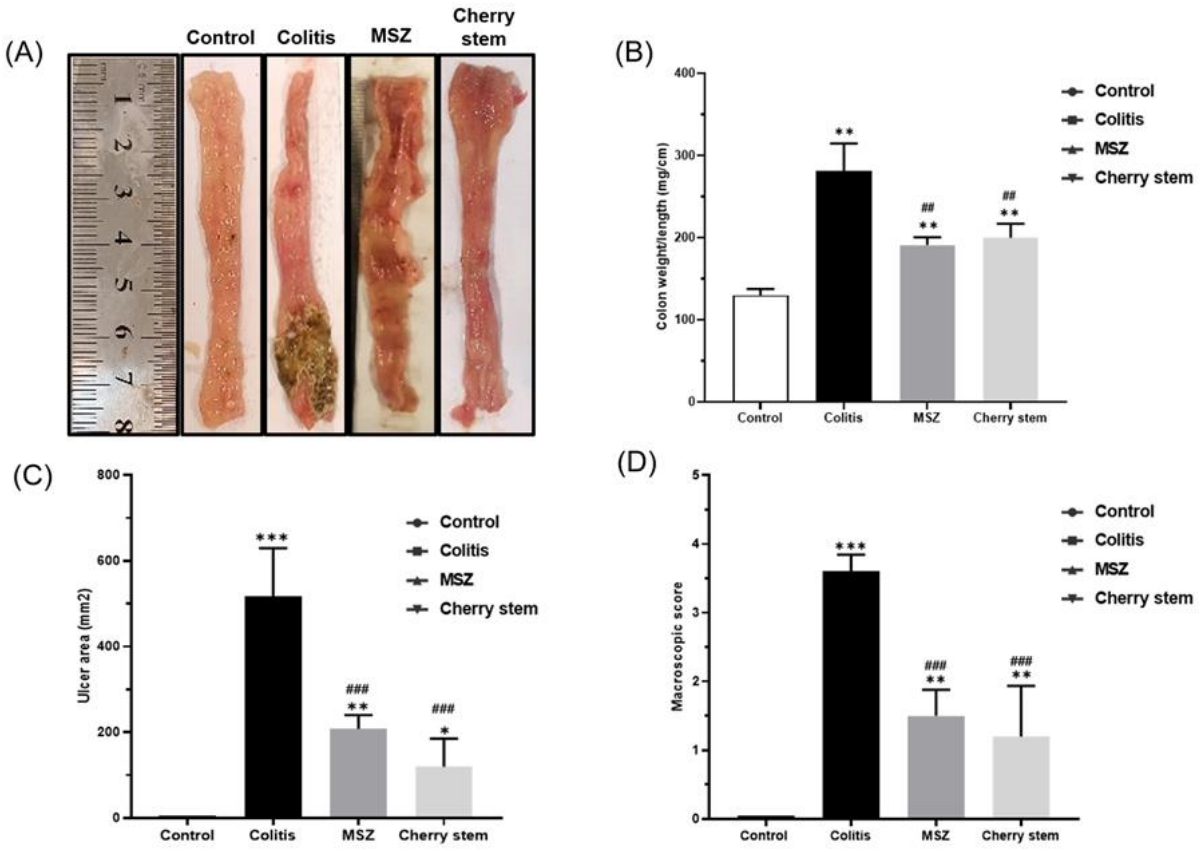

Figure 3. Macroscopic images of colon (A), colon weight (B), ulcer area (C), and macroscopic score (D). Data are presented as Mean ± SEM (n=6 per group). *p<0.005, **p<0.01, and ***p<0.001 vs. control group; $^{\#\#}$p<0.01, and $^{\#\#\#}$p<0.001 vs. colitis group.

Oxidative and antioxidative stress factors

Our finding showed that colitis induction decreased colon tissue level of antioxidative factors including total thiol level, and CAT, and SOD activity ($p<0.05$), and elevated tissue concentration of MDA, as oxidant marker, compared to control group. Administration of cherry stem extract, resulted in higher tissue levels of SOD, total thiol, and CAT, more effectively than MSZ, in comparison to the colitis group (Figure 4A-D).

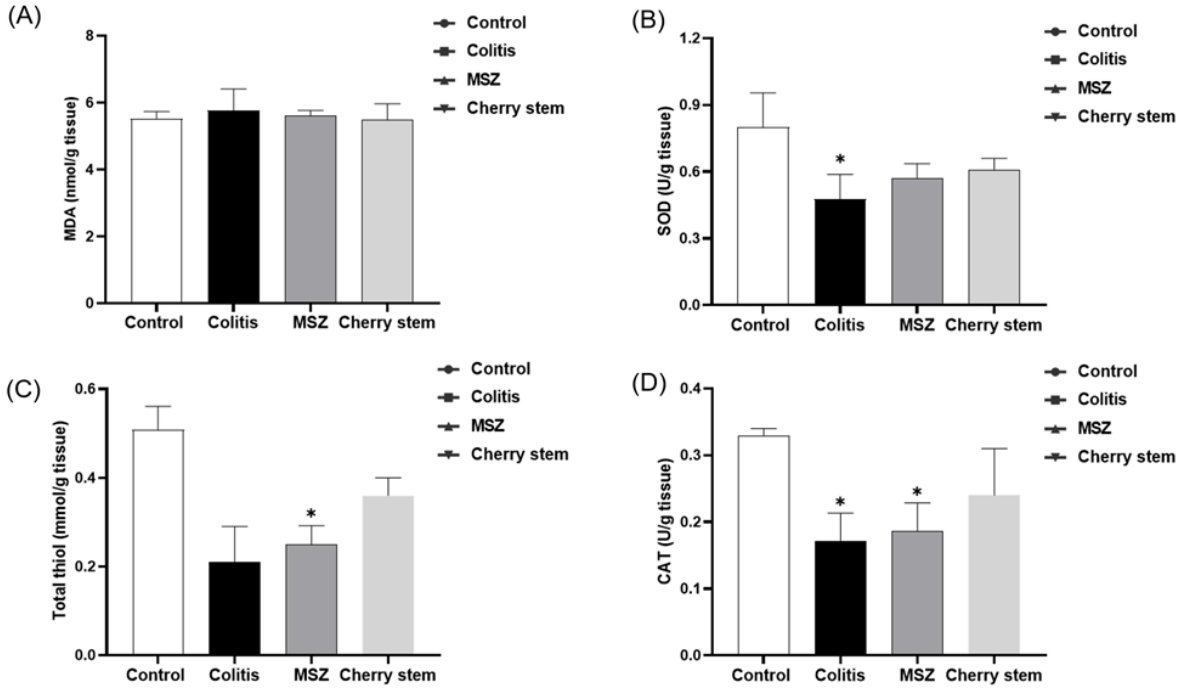

Figure 4. Colon tissue levels of MDA (A), SOD (B), total thiol (C), and CAT (D). Data are presented as Mean ± SEM (n = 6 per group). *$p<0.005$ vs. control group.

Histopathological changes

The histological score was calculated based on the combined scores of four factors: inflammation, crypt damage, ulceration, and edema in H&E-stained colon tissue. Our results showed a significant higher score in colitis group compared to control group ($p<0.001$), and a substantial reduction in the MSZ and cherry stem groups than colitis group ($p<0.01$) (Figure 5A-E).

Figure 6A illustrates the histological images of colon tissue stained by Masson trichrome. Our results revealed that collagen content in colon tissue of colitis group was higher than control group, which significantly decreased in the MSZ and cherry stem groups (Figure 6B).

IL-1β, IFN-γ, TNF-α, and TGF-β mRNA expression by real-time PCR

Real-time PCR analysis revealed significant upregulation in expression of inflammatory *(IL-1β, IFN-γ, and TNF-α)* and fibrotic *(TGF-β)* factors in colitis compared to control group ($p<0.05$) which markedly decreased in the treatment groups compared to the colitis group ($p<0.05$) (Figure 7A-D).

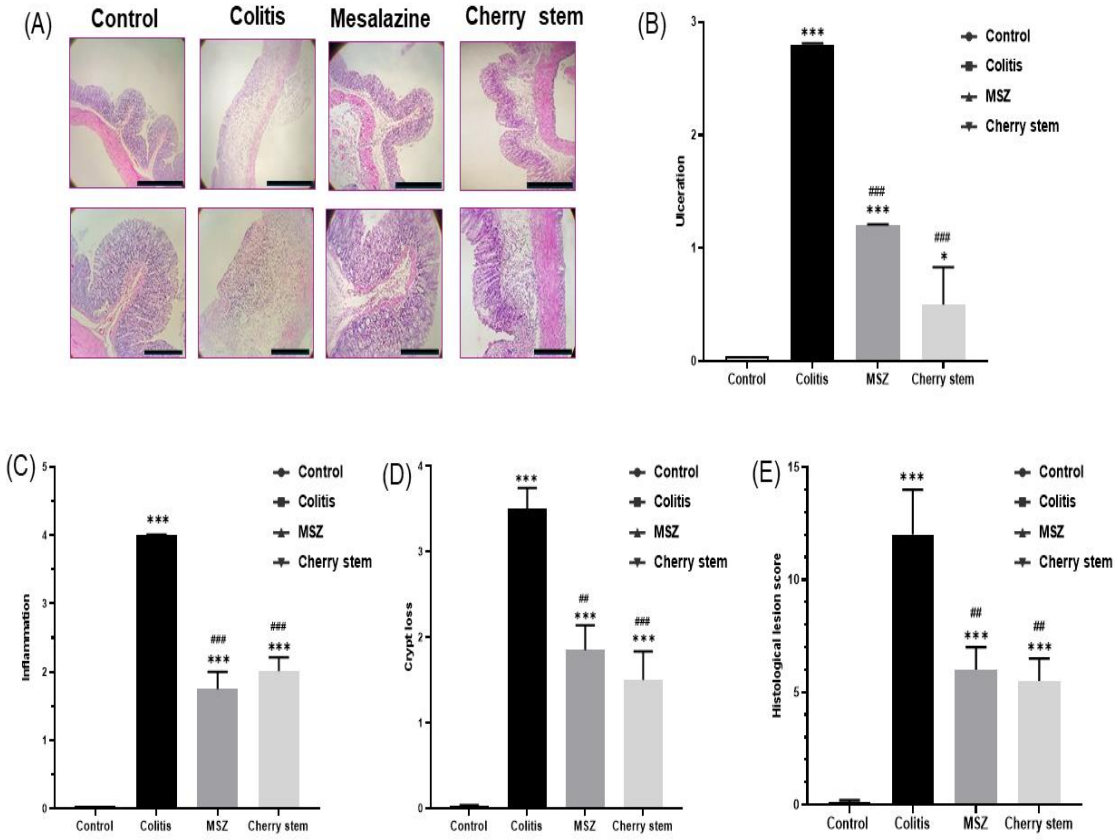

Figure 5. Microscopic images of rat colon tissue sections stained by H&E method, scale bar:200µm (A:above), scale bar:100µm (A:below), (A), ulceration (B), inflammation (C), crypt loss (D), and histological score (E). Data are presented as Mean ± SEM (n=6 per group). ***p<0.001 vs. control group; ##p<0.01, and ###p<0.001 vs. colitis group.

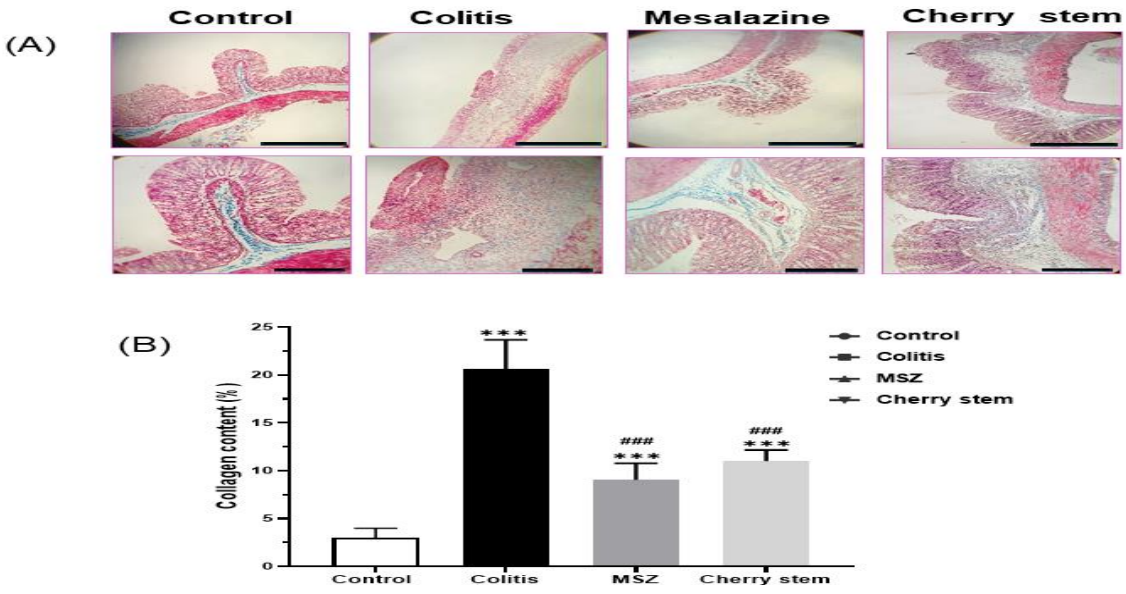

Figure 6. Microscopic images of rat colon tissue sections stained using the Masson's trichrome, scale bar:200µm (A:above), scale bar:100µm (A:below) (A) and collagen content (B). Black arrows indicate fibrotic areas. Data are presented as Mean ± SEM (n = 6 per group). ***p<0.001 vs. control group; ###p<0.001 vs. colitis group.

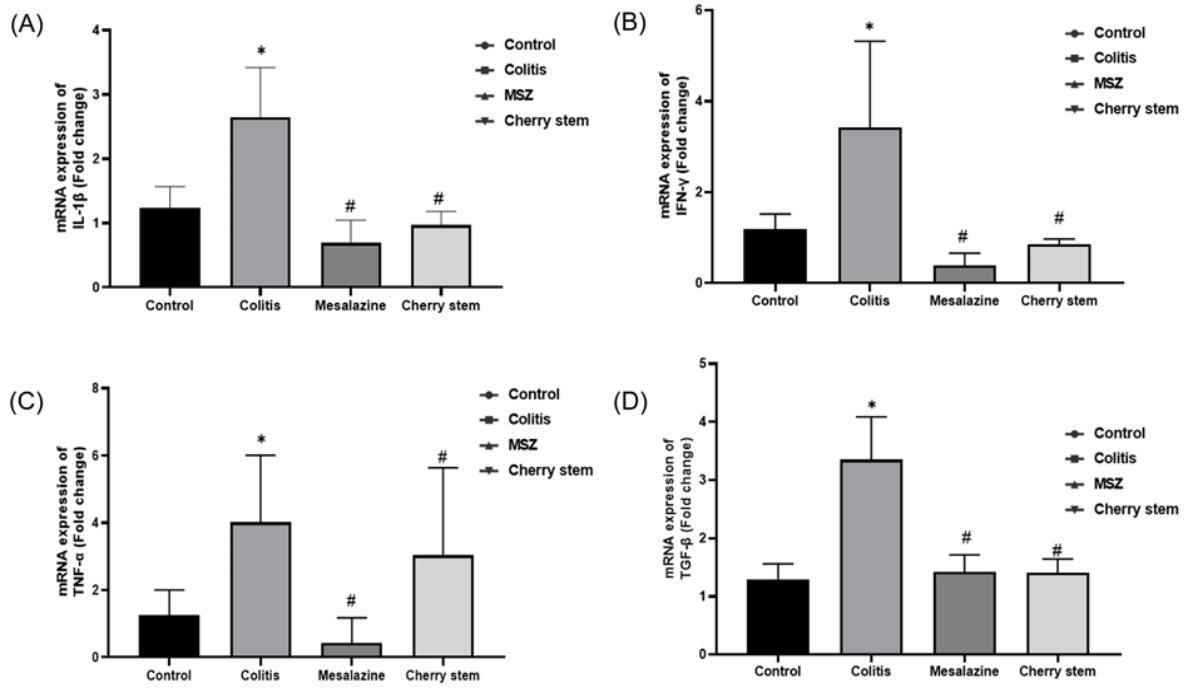

Figure 7. Colon tissue levels of mRNA expression of pro-inflammatory factors: IL-1β (A), IFN-γ (B), TNF-α (C), TGF-β (D). Data are presented as Mean ± SEM (n = 6 per group). *p<0.005 vs control group; #p<0.005 vs. colitis group.

Discussion

Our results showed that administration of cherry stem extract significantly reduced DAI including stool consistency and rectal bleeding and ulcer area in the colon were also improved, showing the beneficial effects comparable to mesalazine (MSZ). We also indicated that cherry stem could improve histological changes in colon such as crypt loss, reduced leukocyte infiltration and inflammation, and markedly decreased fibrotic tissue and collagen content in the colon.

Previous studies indicated the anti-inflammatory and antioxidative effects of cherry stem. It is indicated that Phenolic and flavonoid compounds extracted from cherry stems exhibit high antioxidant capacity and showed antimicrobial activities against *Escherichia coli*. Also, the extract inhibited some enzymes such as α-amylase and had antidiabetic and anti-inflammatory effects (Demir et al. 2020). A recent study on humans also indicates that cherry extract significantly reduces colon inflammation in UC patients (Sinclair et al. 2025) .

In this study, we also found that the animals treated with cherry stem extract exhibited more balanced levels of oxidant and antioxidant markers in colon tissue, along with a diminished expression of pro-inflammatory genes compared to the colitis group. A large body of research indicated an elevated expression of oxidative stress factors and the inflammatory genes *IL-1β, IFN-Y, and TNF-α* in animal models of acetic acid-induced colitis (Alfwuaires et al. 2021; Kurumi et al. 2024b; Langer et al. 2019). The anti-inflammatory properties of cherry have been already reported in human colon cell culture (Barreto-Peixoto et al. 2024). In addition, it is demonstrated that animals consuming a diet enriched with cherry extract exhibit significantly decreased inflammatory genes levels of TNFα and IL-1β in adipose tissue (Jayarathne et al. 2018).

Improvement in oxidative/antioxidative balance and reduced inflammatory genes levels in colon tissue of cherry stem-treated group may be attributed to their substantial

concentration of flavonoids such as catechin, genistein, and pronin, and anthocyanins, which are renowned for their potent antioxidant properties (Aires et al. 2017; Berni et al. 2018; Willig et al. 2022). These compounds probably have absorbed and neutralized free radicals with their phenolic rings and have played a role in reducing oxidative stress in this way. Additionally, they decreased inflammation by blocking NF-κB nuclear translocation and MAPK signaling pathways (Li et al. 2022). A recent study has indicated that cherry stem extract might impede the movement of NF-κB into the nucleus in macrophages, which could influence the expression of associated genes (Frusciante et al. 2025). Thereby, daily consuming of cherry extract was able to significantly decrease inflammatory flare-ups in the animal's colon tissue.

Another finding of this study indicated a notable reduction in collagen content and fibrotic gene expression, specifically TGF-beta, in the colon tissue of animals treated with cherry extract, as compared to the colitis group. Various experimental models of colitis have demonstrated elevated expression of fibrotic genes including TGF-beta, along with increased collagen content in colon tissue (Binabaj et al. 2019; Marjaneh et al. 2018; Rezaei et al. 2025). Elevated levels of TGF-beta lead to enhanced fibroblast activity and an increase in collagen production within the intercellular matrix of the colon mucosa (Moretti et al. 2022). Antifibrotic effects of cherry extract have been documented in other tissues such as liver tissue. It is indicated that there is a significant association between elevated inflammatory markers and enhanced cytokine production, particularly TNF- α, and upregulation of the TGF-beta gene (Van der Werf et al. 2018). In our study, reduced fibrotic tissue in colon may have been achieved by decreasing oxidative stress and limiting inflammation in cherry stem group. The plentiful phenols found in cherry stem extract have countered the inflammatory cytokines, thereby have reversed the collagen growth process and triggered fibrosis in the rat colon (Salaritabar et al. 2017). Furthermore, the abundant phenols in cherry stem extract have promoted granulation tissue formation, reduced collagenase activity and accelerated the tissue healing process which can be important in improving ulcer area and macroscopic improvement in colon in this group (García-Villegas et al. 2024; Merecz-Sadowska et al. 2021).

In conclusion, cherry stem extract has beneficial effects in improving clinical symptoms of colitis including rectal bleeding and stool consistency and reduced colon histological changes, inflammation and fibrosis by reducing inflammatory markers and improving oxidative stress balance which is comparable with standard drug MSZ. Further studies are needed to support the beneficial effects of cherry stem in combination with standard drugs in patients suffering UC.

Acknowledgment

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Conflicts of interest

The authors declare no conflicts of interest.

Funding

This study was supported by a grant from Mashhad University of Medical Sciences (Grant number: 4030978).

Ethical Considerations

Ethical approval for this study was obtained from the Ethics Committee of Mashhad University of Medical Sciences.

Code of Ethics

IR.MUMS.AEC.1403.087

Authors' Contributions

Conceptualization, All authors; Methodology, K.K., SN.N, M.S, A.A, and SE.N.; formal analysis, M.K.;investigation,

K.K, SN.N, M.S, A.A, M.AS, M.A, and SE.N.; writing—original draft preparation, K.K, SN.N, M.S and M.AS; writing—review and editing, K.K, SN.N, M.S ; supervision, M.K. All authors have read and agreed to the published version of the manuscript.

Data availability

Data will be made available on request.

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