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Experimental Research Article

Comparing the efficacy of sulfasalazine and an aqueous extract of tarragon in an experimental model of ulcerative colitis

Milad Qaderi, Ahmad Enferadi Qazanabad, Peyman Khademi, Parvin Mahdavi, Seyyed Meysam Abtahi Froushani*

Department of Microbiology, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran

ABSTRACT

Introduction: The anti-inflammatory and immunomodulatory properties of tarragon have been noted. Here, we examined the effects of an aqueous extract of the tarragon plant in a rat model of ulcerative colitis.

Methods: Ulcerative colitis was induced in Wistar rats using a 2 ml acetic acid (4%) intrarectal enema. Experimental groups received sulfasalazine (2 mg/kg) or tarragon aqueous extract (100 mg/kg) orally for ten consecutive days. After ten days, the animals were euthanized and evaluated for disease activity index (DAI), production of inflammatory and pro-inflammatory mediators in the intestinal tissue.

Results: Both the tarragon aqueous extract and sulfasalazine treatments were effective in reducing the disease severity index in experimental ulcerative colitis. Malondialdehyde intensity, nitric oxide level, and myeloperoxidase activity regressed in the colon of animals treated with the tarragon aqueous extract more than in the group treated with sulfasalazine. However, sulfasalazine significantly reduced TNF-α and IL-1 levels compared to the tarragon aqueous extract. There was no statistical difference in IL-6 and PGE2 reduction between the two groups.

Conclusion: These findings suggested that the aqueous extract of tarragon may be applied as a natural resource to control ulcerative colitis.

Keywords:
Ulcerative colitis
Sulfasalazine
Tarragon aqueous extract
Wistar rat

Introduction

Ulcerative colitis (UC) is a chronic inflammatory condition affecting the colon and rectum, typically characterized by symptoms such as rectal bleeding, diarrhea, tenesmus, and occasionally mild abdominal pain. The incidence of this disease peaks between the ages of 15 and 45 years. While the exact cause of UC remains elusive, research over the past decade has revealed that it stems from a dysregulated immune response in the intestinal region, triggered by interactions between the host genotype and the luminal microflora, or other potentially pathogenic factors (Hindryckx et al., 2016).

* Corresponding author: Seyyed Meysam Abtahi Froushani, sm.abtahi@urmia.ac.ir
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The most severe and potentially fatal complications of inflammatory bowel disease (IBD) encompass anemia resulting from significant blood loss due to multiple ulcers in the digestive system, obstruction of the gastrointestinal tract, and nutritional deficiencies stemming from malabsorption of nutrients in the intestines. Additionally, studies have highlighted a heightened risk of cancer development and progression, including colorectal carcinoma and lymphoma, among individuals with this condition, contributing to increased mortality rates among IBD patients (de Ridder et al., 2014; Landgren et al., 2011).

Currently, the first line of treatment for UC commonly involves anti-inflammatory medications, including aminosalicylates such as sulfasalazine, mesalazine, balsalazide, and olsalazine, as well as corticosteroids. However, these drugs are associated with significant side effects, including thinning of the skin, eye disorders, susceptibility to infections, indigestion, nausea, vomiting, headaches, diarrhea, bloating, and abdominal pain (D'haens 2016; Hauso et al., 2015; Hindryckx et al., 2016; Wang et al., 2016). Therefore, there is a pressing need for a safer and less hazardous approach for UC patients.

Tarragon (*Artemisia dracunculus*) is a perennial aromatic plant of the Asteraceae family (Sayyah et al., 2004; Weinoehrl et al., 2012) that has been applied in traditional medicine to treat fever, cold, cough, pain, dysmenorrhea, and amenorrhea (Aglarova et al., 2008; Obolskiy et al., 2011). In Iranian traditional medicine, dried parts of tarragon are also prescribed orally to control epilepsy, blood coagulation, and blood lipids (Sayyah et al., 2004; Shahriyary and Yazdanparast 2007). Additionally, this plant has antifungal and antioxidant activity (Kordali et al., 2005), as well as antibacterial properties, hepatoprotection (Nageeb et al., 2013), and significant insecticidal and antioxidant activities (Sayyah et al., 2004). Tarragon essential oil contains sabinene (approximately 35 percent), methyl eugenol (approximately 25 percent), and elmicine (up to 57 percent), constituting 40 to 85 percent of the oil composition. Other active compounds found in tarragon essential oil include beta-vocimene, terpinen-4-ol, α-trans-ocimenis, β-ocimene, trans-anethole, α-phellandrene, β-phellandrene (Z)-artemidin, capillene, and limonene (Ekiert et al., 2021). Recently, tarragon aqueous extract (TAE) has been shown to act as a natural source of immune modulation by inhibiting pro-inflammatory cytokines during T-lymphocyte responses and inducing anti-inflammatory macrophage responses (Abtahi Froushani et al., 2016). However, there is limited information about the potential benefits of TAE in auto-inflammatory diseases such as UC. Therefore, the current investigation aimed to investigate the potential role of TAE versus acetic acid-induced UC in Wistar rats.

Material and methods

Animals

Male Wistar rats weighing between 280-300 g were obtained from the animal center of Urmia University, Faculty of Veterinary Medicine, Urmia, Iran. The rats were housed under standard conditions, including humidity (55-60%), temperature (22-23 °C), and a 12-hour light:12-hour dark cycle. They had ad libitum access to water and food throughout the study. All experimental procedures were approved by the ethics committee at the Faculty of Veterinary Medicine, Urmia University.

Preparation of extract

Fresh aerial parts of the tarragon plant were collected and verified by a herbarium specialist. The plant parts were then washed, chopped into small pieces, and dried in the shade. An aqueous extract of the dried ground plant was prepared using a three-step percolation process. Subsequently, the extract was dried by evaporation at 40 °C and stored in a light-free environment at -20 °C (Abtahi Froushani et al., 2016).

Induction and evaluation of UC

Wistar rats were anesthetized with ether after fasting for 48 hours. Subsequently, 4% acetic acid (2 ml per animal) was injected into the rectum of the rats using a plastic cannula (8 cm in length). To ensure complete dispersion of the acetic acid in the colon, the rats were held in that position for 20 seconds and then flushed with 5.0 ml of saline before removal of the cannula (Low et al., 2013).

In this study, animals were randomly allocated into four groups of ten rats: UC rats receiving a placebo, UC rats administrated daily with oral sulfasalazine (sulfasalazine, 100 mg/kg), UC rats under daily oral treatment with TAE (100 mg/kg), and healthy rats. The healthy group also endured starvation for 48 h. Instead of acetic acid inoculation, this group of rats underwent intra-rec-

TABLE 1: Disease severity scoring system

Score	Rectal bleeding	Stool consistency	Blood
0	None	Normal	Normal
1	Red	Soft	Red
2	Dark red	Very soft	Dark red
3	Gross bleeding	Diarrhea	Black

tal inoculation of distilled water. Physiological serum was used as a placebo in this group of rats and in untreated UC animals.

Animals were examined daily for body weight, bleeding, and stool consistency. The disease activity index (DAI) was determined as the sum of stool consistency, bloody stool, and weight loss scores based on the characteristics outlined in Table 1. To evaluate the macroscopic schema (ulcer formation and bleeding), colon samples were collected from the distal 10 cm of colon sections.

Histopathological examination

After fixing the samples of the distal colons in 10% formaldehyde, they were embedded in liquid paraffin. Using a microtome, transverse sections were cut to a thickness of 5 µm. The samples were stained with hematoxylin and eosin (H&E). Histological changes, such as hyperemia, epithelial damage, wound, and leukocyte infiltration, were scored on a scale of 0-4, where 0 indicated no detectable damage and 4 indicated the most severe damage (Low et al., 2013).

Homogenization of colon samples

After weighing colon samples isolated from each group, an equal amount of the samples was separated and homogenized in a 10 w/v ratio in potassium chloride (11.5 g/L) by a glass homogenizer. Homogenized colon samples were centrifuged at 10,000 g for 10 min at 4 °C (Al-Rejaie et al., 2013a).

Myeloperoxidase activity in colon tissue homogenate

In brief, 10 µl of homogenized colon tissues were mixed with 110 µl of tetramethylbenzidine solution (2.9 mM of tetramethylbenzidine in 14.5% DMSO plus 150 mM of sodium phosphate buffer) and 80 µl of 0.75 mM hydrogen peroxide. The sample was kept at 37 °C for 5 min. Then, it was mixed with sulfuric acid (50 µl, 2 M) to terminate the reaction. The optical density (OD) was read at 450 nm by an ELISA reader. 10 µl of horseradish peroxidase (HRP) was used as a standard (2.5 and 25 mU/ml). MPO activity was calculated as the discrepancy in the OD of the HRP standard curve. The findings were reported as mU/mg of tissue protein.

Nitric oxide (NO) production intensity in homogenized colon samples

NO production intensity in the colon sample was examined using the Griess assay. 50 µl of Griess' reagent (3% phosphoric acid, 0.1% naphthylethylenediamine, and 0.1% sulfanilamide) was mixed with 50 µl of tissue sample homogenate and kept at room temperature for 10 min in the dark. Afterward, OD was recorded at 540 nm using a microplate reader. To estimate the nitrite level, a standard curve was drawn(Salamatian et al., 2019).

Estimation of malondialdehyde in colon samples

In short, 2.5 mL of the reaction solution (0.37% thiobarbituric acid, 0.25 M HCl, and15% trichloroacetic acid, 1:1:1 ratio) was mixed with 100 µL of colon homogenate and kept at 95 °C for 60 min. After cooling, the mixture was centrifuged at 3500 rpm for 15 min. Finally, the OD of the separated supernatant was read at 540 nm. Data were recorded as MDA/mg protein (Esmaeilnejad et al., 2018).

Determination of pro-inflammatory mediators in colon samples

The levels of IL-6, IL-1β, TNF-α, and PGE2 in colon sample homogenates were evaluated using commercial ELISA kits pursuant to the manufacturers' instructions.

Estimation of total protein level in colon homogenate

The protein content of the homogenized tissues was

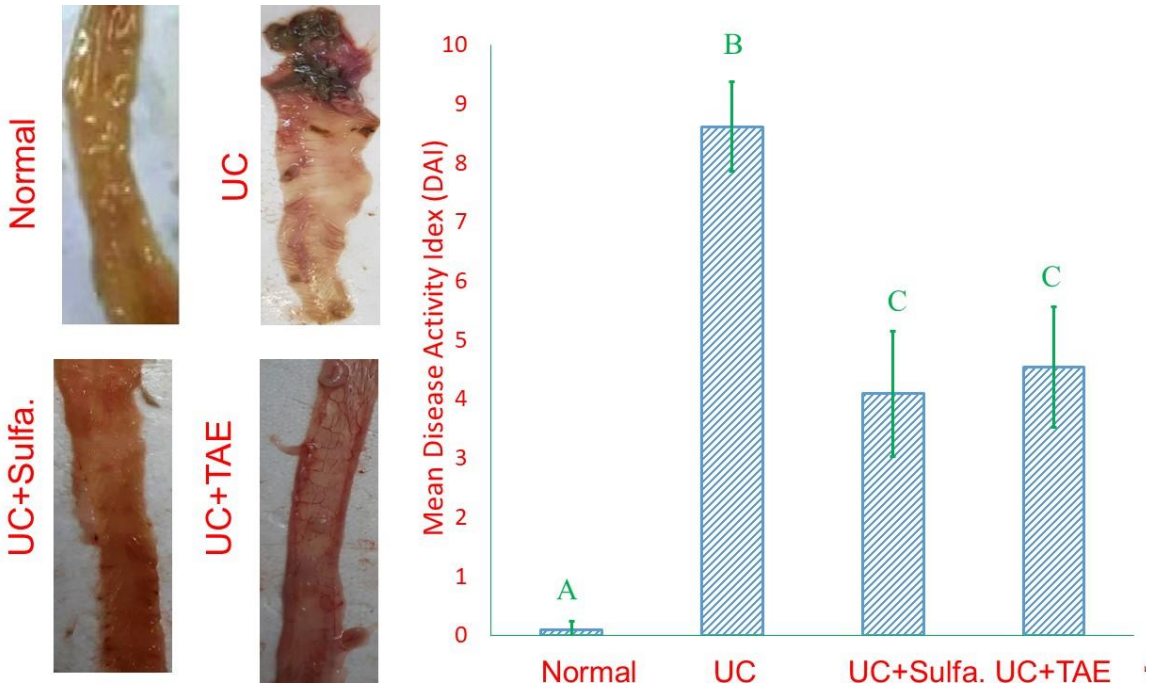

FIGURE 1. Assessment of Macroscopic (Right) And average changes in disease severity index during the study period (Left). Results were presented as mean ±S. D. Different letters indicate significant differences at the P<0.05 level. (UC., Rats with ulcerative Colitis; UC+Sulf., Rats with UC received sulfasalazine; UC+TAE, Rats with UC received aqueous extract of Tarragon).

analyzed using the pyrogallol red molybdate method according to the instructor's instructions (Orsonneau et al., 1989).

Statistical analyses

Non-parametric data (DAI) were analyzed using the Kruskal-Wallis test. Multiple and pair-wise comparisons of data were performed by the Mann-Whitney U test with Bonferroni adjustment. The remaining parametric findings were analyzed using one-way analysis of variance (Dubska et al., 2009) and Duncan's post hoc test. The findings were reported as mean ± standard deviation. P-values < 0.05 were considered statistically significant.

Results

The changes in the rats' weight and health were examined daily after the injection of acetic acid into the lumen of the animals' colons. According to Figure 1, no weight loss or bleeding was found in the control group. Stool consistency was normal, and no lesions were observed in colonic tissues. UC induction resulted in high DAI records in live mice. The data revealed that TAE and sulfasalazine could reduce the clinical index of UC in a similar manner (Figure 1).

Colon specimens of healthy rats exhibited no observable histopathological changes (Figure 2a). As expected, colons of UC rats showed ulcers and infiltration of inflammatory cells into the submucosa (Figure 2b). Treatment of rats with sulfasalazine or TAE significantly reduced the pathological changes in the micrographs (Figure 4c and d). Upon quantification, the mean histopathological score of UC rats exhibited severe inflammation, with a significant increase compared to healthy rats (Figure 2e). The analysis of quantified data showed that TAE and sulfasalazine could reduce the mean histopathological score of UC in a similar manner (Figure 2e).

As shown in Figure 3, the levels of TNF-α, IL-1β, and IL-6 in colon tissues increased significantly in UC rats compared to healthy animals. Both TAE and sulfasalazine treatments significantly reduced the levels of these cytokines in the colon samples of UC rats compared to placebo-treated UC rats (Figure 3). Sulfasalazine was more effective in reducing IL-1 and TNF-α levels than TAE (Figure 3). However, no statistical discrepancy was found in the ability to reduce IL-6 levels between UC rats treated with TAE and sulfasalazine (Figure 3). The

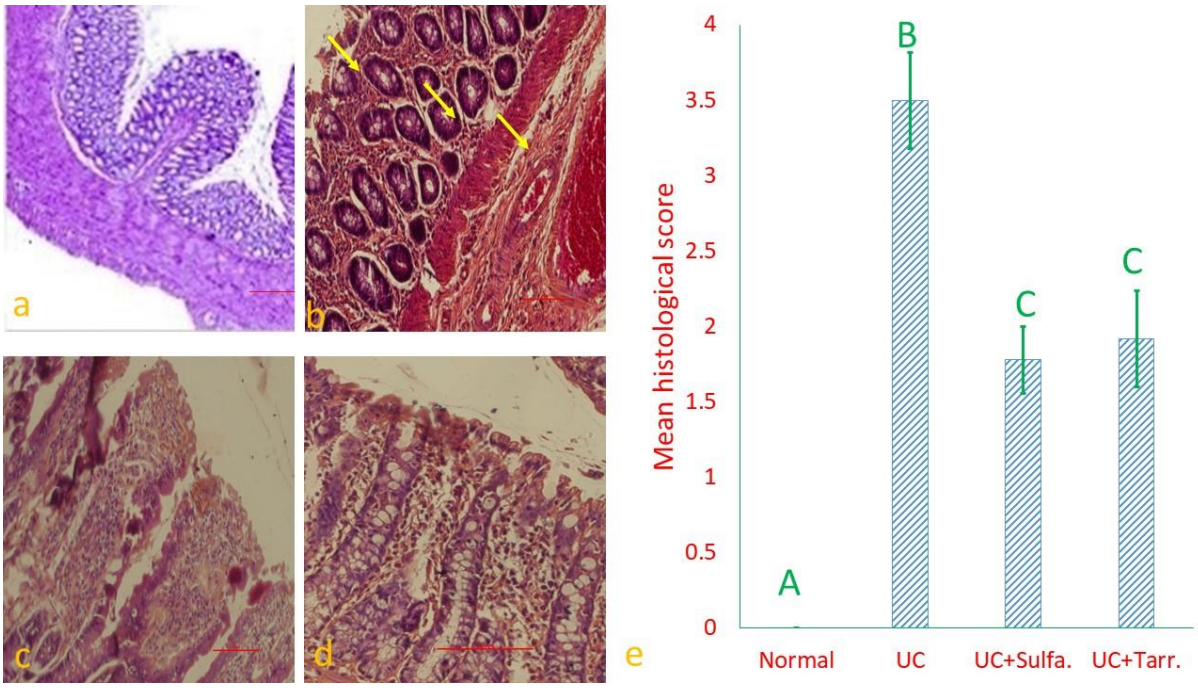

FIGURE 2. Histopathological analysis of colonic specimens. The samples were stained with H&E. Representative micrographs shown are colons of healthy control rats (a), UC rats (b), sulfasalazine-treated rats(c), and Rats with UC received aqueous extract of Tarragon (d). The red line drawn across each section represents 20 µm Histologic changes were quantified based on severity of damage (e). Results were reported as mean ± SD. Different letters indicate significant differences at the P<0.05 level. (UC., Rats with ulcerative Colitis; UC+Sulf., Rats with UC received sulfasalazine; UC+TAE, Rats with UC received aqueous extract of Tarragon).

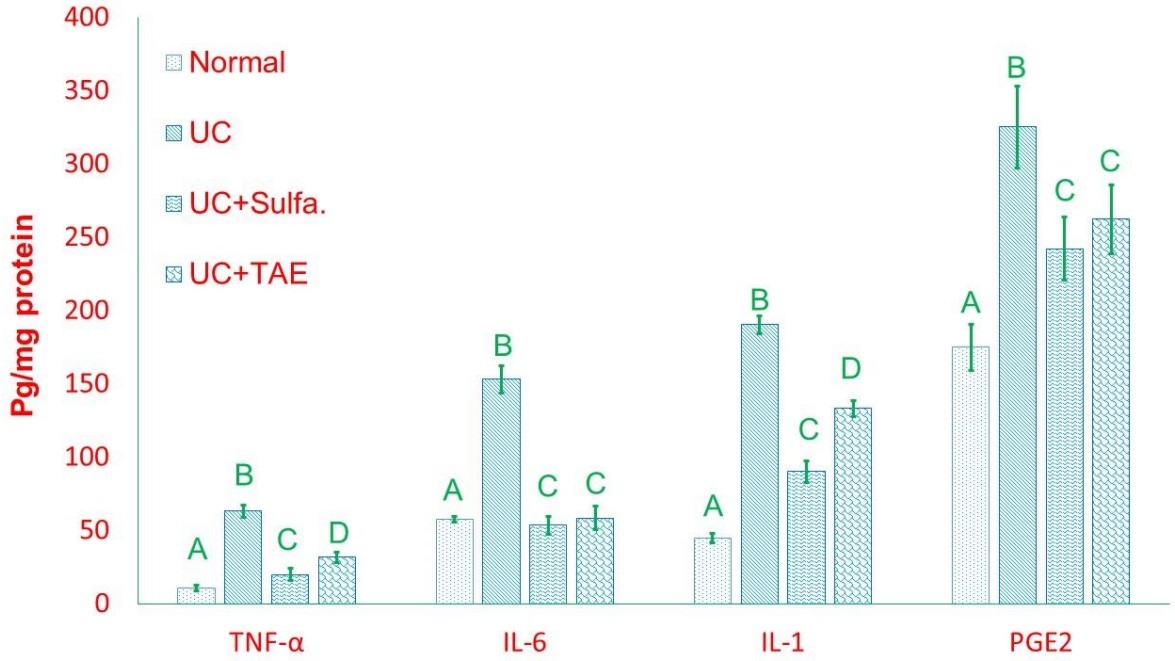

FIGURE 3. Evaluation of pro-inflammatory mediator in intestinal tissue homogenate. Findings were expressed as mean ±S. D. Different letters indicate significant differences at the P<0.05 level. (UC., Rats with ulcerative Colitis; UC+Sulf., Rats with UC received sulfasalazine; UC+TAE, Rats with UC received aqueous extract of Tarragon).

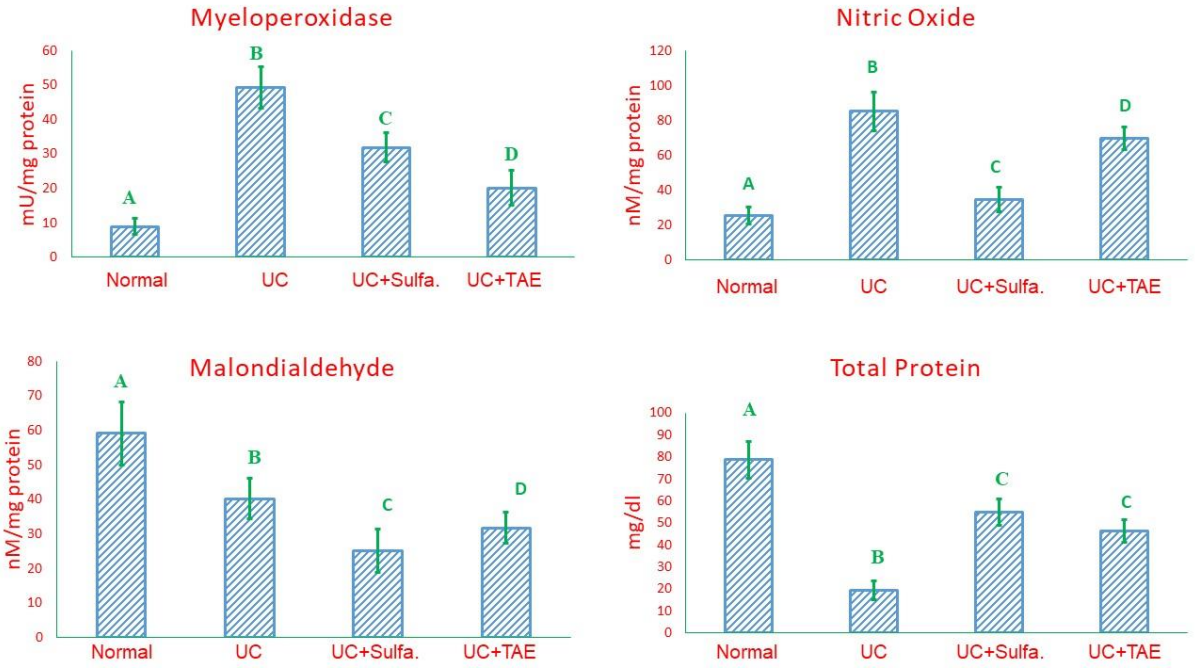

FIGURE 4. Biochemical changes in rats suffering from ulcerative colitis. Results were reported as mean ±SD. Different letters indicate significant differences at the P<0.05 level. (UC., Rats with ulcerative Colitis; UC+Sulf., Rats with UC received sulfasalazine; UC+TAE, Rats with UC received aqueous extract of Tarragon).

observed findings exhibited a remarkable progress in the level of PGE2 in UC rats compared to healthy rats. Treatment with sulfasalazine and TAE significantly decreased the upregulated level of PGE2 compared to UC rats, as shown in Figure 3.

The data obtained from biochemical changes in the colon tissue of the rat population indicated that MPO activity and MDA/NO intensities increased significantly in the colon homogenates of UC rats compared to healthy animals (Figure 4). The total protein content significantly decreased in the colon samples of UC rats compared with healthy ones (Figure 4). Both TAE and sulfasalazine significantly reduced MPO activity and MDA/NO production intensities in the colon homogenate of UC rats compared with untreated UC animals (Figure 4). The reductions in MPO activity, NO level, and MDA production intensity were significantly higher in TAE-treated colon homogenate than the same levels in sulfasalazine-treated groups (Figure 4). Finally, the total protein content of colon samples increased statistically in both therapeutic groups compared with untreated UC mice (Figure 4).

Discussion

Various anti-inflammatory and immunosuppressive medications are currently prescribed to manage inflammation-related disorders, including UC. Nonetheless, long-term use of these medications can lead to numerous side effects (Menichini et al., 2009; Saraiva et al., 2011). Therefore, medicinal herbs with immunomodulatory and anti-inflammatory potentials and lower side effects can provide new insights into alternative medicine (Visavadiya et al., 2009). However, contrary to popular belief, medicinal herbs are not always safer. For instance, chronic exposure to two toxic components of tarragon, estragole, and methyl eugenol, has been associated with an increased risk of hepatocarcinogenesis in rodents (De Vincenzi et al., 2000). Therefore, it was recommended to minimize the consumption of estragole and methyl eugenol (De Vincenzi et al., 2000; Weinoehrl et al., 2012). Interestingly, aqueous extract of tarragon does not possess this harmful compound according to recently published studies (Abtahi Froushani et al., 2016). Accordingly, this extract was chosen for use in the current study.

The present data indicated that both sulfasalazine and TAE similarly reduced the DAI in the animal model of UC. Intra-rectal administration of acetic acid is a

well-established method used to assess the efficacy of new drugs in controlling UC (Gupta et al., 2022; Shibrya et al., 2023). Intra-rectal injection of acetic acid can induce severe diffuse inflammatory responses, leading to the formation of colonic ulcers and erosion, accompanied by the deep migration of leukocytes, particularly neutrophils, into the colon (Mashhouri et al., 2020). MPO is a well-known peroxidase that originally forms the azurophilic granules of polymorphonuclear cells. The measuring of this enzyme can be indirectly used to monitor neutrophil infiltration intensity into a tissue sample, such as the colon, under UC conditions (Abtahi Froushani and Mashouri 2018; Mashhouri et al., 2020). The inhibitory effects of tarragon on the function of neutrophils have been evidenced recently. For example, the main phenolic compounds of tarragon aerial extract (flavonoids and caffeoylquinic acids) have been shown to inhibit the production of ROS, TNF-α, and IL-8 by neutrophils (Ekiert et al., 2021; Majdan et al., 2020). Pretreatment with tarragon essential oil has also been reported to inhibit human neutrophil chemotaxis following stimulation with f-MLF, indicating the potential anti-inflammatory benefits of tarragon on the function of human neutrophils (Schepetkin et al., 2022). Our results also showed lower MPO activity in UC rats receiving TAE (as an indicator of neutrophil infiltrations in homogenate samples) than in untreated UC animals or even in sulfasalazine -treated ones. MPO activity is characterized by ROS production by neutrophils (Abtahi Froushani and Mashouri 2018). NO is another potentially detrimental agent involved in UC pathogenesis (Mashhouri et al., 2020). Inappropriate or uncontrolled propagation of reactive substances, like NO and ROS, contributes to the prolongation and exacerbation of inflammation (Abtahi Froushani and Mashouri 2018). Interestingly, the NO level and MDA intensity further lessened in the colons of TAE-treated rats than in those of the sulfasalazine -treated groups, clearly showing the strong antioxidant activity of tarragon (Shahrivari et al., 2022). The antioxidant activity of tarragon extract has been confirmed using DPPH and ABTS tests (Ekiert et al., 2021). This partially confirms the proper results of TAE in the reduction of MPO and NO than sulfasalazine. Consistently, TAE reduced the production of NO and oxygen free radicals in the peritoneal macrophages of rats receiving TAE (100 mg/kg) for one month (Abtahi Froushani et al., 2016).

Obviously, free radicals produced in inflammatory conditions, such as UC, cause lipid peroxidation in colon tissues (de Carvalho et al., 2018; Liu et al., 2018). The lipid peroxidation intensity can be estimated by evaluating the level of MDA (Al-Rejaie et al., 2013b). According to our data, MDA production intensity was suppressed more deeply in the UC rats receiving TAE than in the UC animals receiving sulfasalazine, suggesting the direct antioxidant benefits of tarragon contrary to sulfasalazine.

Pro-inflammatory cytokines (e.g., TNF-α, IL-1, and IL-6) play an fundamental role in UC pathogenesis (Liu et al., 2018). This study demonstrated that TAE significantly reduced IL-1 and TNF-α levels in UC rats. However, the two groups were not significantly different in IL-6 reduction. The immunomodulatory effect and changes in cytokine production by TAE (100 mg/kg for 21 consecutive days) were previously investigated in mice immunized with sheep erythrocytes. TAE significantly reduced the production of IFN-γ and IL-17 in spleen cells of immunized mice (Abtahi Froushani et al., 2016).

PGE2 is one of the well-known mediators that can induce inflammatory edema and intestinal hyperemia, which exacerbates ROS/NO production and depletes the antioxidant system in colonic inflammation (Shahid et al., 2022). The current survey suggested that treatment with sulfasalazine and TAE statistically reduced the overexpression of PGE2 in animals with ulcerative colitis while suppressing oxidative-nitrative damage and pro-inflammatory cytokines and restoring the antioxidant system.

Extensive neutrophil infiltration and diffuse inflammation cause cell integrity interruption and mucosal healing in colonic tissues after induction of UC (Al-Rejaie et al., 2013a). The present study indicated that both treatments could inhibit the severity of the decreased total protein level.

The lesions caused by the instillation of acetic acid result in the invasion of the lamina propria by microflora and intensify the inflammatory process (Gupta et al., 2022). Considerable scientific evidence shows the direct antibacterial and antifungal properties of tarragon (Osanloo et al., 2022). Therefore, some of the beneficial effects of TAE related to its antimicrobial effect should be considered logically, along with its direct anti-inflammatory potentials.

Conclusion

Current findings demonstrate that treatment with TAE as a natural pharmacologic source is a promising approach to improve inflammation symptoms in the UC animal model. Along with its direct anti-inflammatory potentials, TAE also possesses antimicrobial and antioxidant properties. However, other mechanisms may be involved in the therapeutic benefits observed in the present study, which require further investigation.

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Conflict of interest

The authors have no conflicts of interest to declare.

Ethics approval

All protocols related to animal experiments were approved by our University Ethics Committee.

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