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Use Aqueous Extract of *Tarragon* in Combination with Asacol on Cytomegalovirus Colitis Model: Synergistic Effect in Inflammatory Disease Therapy

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Abstract

In the current study, the effects of aqueous extract of aerial parts of tarragon in ulcerative colitis (UC) induced by acetic acid in Wistar rats were investigated. The participants were 70 male Wistar rats that were grouped into seven equal individuals. In this experimental study, luminal instillation of acetic acid was applied to induce ulcerative colitis in the male Wistar rats. Animals in the treatment groups received Mesalazine, Asacol or Tarragon and combination of Asacol and aqueous extract (orally or enema–daily) for 10 consecutive days. At the end, the rats were sacrificed, and the levels of myeloperoxidase, nitric oxide, the concentration of TNF-α and IL-6 and histopathological damage were assessed. Findings indicated a significant increase in inflammatory mediators' colon tissue levels and pathological damage of positive control group compared with the negative control group. Aqueous extract of *Tarragon* in combination with Asacol (intra-colonic) indicated a higher capability in remarkably reducing inflammatory mediators levels and pathological damage in comparison with the other treatment groups. The results showed that *Tarragon* extract with anti-colitis property can be a suitable candidate and a natural source of recent medications.

Keywords: *Tarragon*, Ulcerative Colitis, Rat, Inflammation.

Introduction

Cytomegalovirus (CMV) colitis is the most common infection of the CMV gastrointestinal disease. CMV infection of the gastrointestinal tract is widespread and it happens in 10% of all transplants including any part of the gastrointestinal tract (Le, Lin and Kuo, 2017; Nakase and Herfarth, 2016). Fever, abdominal pain, watery diarrhea, bloody stool, massive bleeding and sometimes mega colon and perforation are the symptoms of CMV colitis (Ko, Peck and Lee, 2015). Colonic ulcer bleeding can be self-limited, but can happen irregularly. The huge amount of colonic bleeding and perforation can be potentially fatal. Colonoscopy with biopsies is used to diagnose CMV colitis (Weng et al., 2017). There are variable endoscopic characteristics including diffuse erythema, hemorrhagic spots, ischemia, erosions, ulcers, strictures, polypoids, pseudo membranes, and pseudo tumors (Khan and Toms et al., 2016).

Recently, for examining the mechanisms and treatments of diseases, animal models have been used (Snider et al., 2016). Insights learned from such models have allowed designing novel therapeutic strategies and defining, in a preclinical setting, the safety and efficacy of such novel treatments before human clinical trials. Animal models have been used extensively to study the experimental ulcerative colitis syndromes (Goyal et al., 2014). Some compounds and chemical agents like acetic acid (AA), trinitrobenzene sulfonic acid (TNBS), iodoacetamide, indomethacin, oxazolone, dexran sodium sulphate (DSS) and peptidoglycan polysaccharide have been used for the induction of colitis (Pastrelo et al., 2017). Acetic acid induced colitis is a model which is normally used and easily inducible. The induction of colitis by chemical/compounds is an easily inducible model of the inflammatory phase bearing some similarities to acute human intestinal inflammation and damage caused by the CMV (Liu et al., 2016).

Plants have been the sources of isolates and extracts for huge numbers of medications. Therapeutically important metabolites and essential oils have been made from medicinal plants (Eidi et al., 2016). The safety beside economical, effective and easy availability of medicinal plants are their important therapeutically advantages in various diseases. *Artemisia dracunculus L.* (*Tarragon*) is a widespread traditional plant, and it has a varied genus with different species of the family *Asteraceae* as well as great therapeutic and economic importance (Kheterpal et al., 2014). A botanical extract obtained from *tarragon* has had antimalarial and anticancer activities. Furthermore, the experiments indicated that tarragon induced the generation of regulatory T cells with extraordinarily inhibitory effect on IL-17 production, diminishing the level of IL-6 in mouse model (Abtahi Froushani et al., 2016; Alasvand Zarasvand and Madani M, Modaresi, 2016).

Based on above investigations, the current study aimed at assessing the potent anti-inflammatory activity of *tarragon* in comparison with Mesalazine, and Asacol as a standard medication, on CMV colitis model induced by acetic acid in male Wistar rats.

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Experimental

Animals

Male Wistar rats (Urmia university, Urmia, Iran) weighting 200-250 g were used in this study. The animals were separately placed in wire-bottomed cages under a constant condition of light/dark cycle (12h/12 h), temperature (20 ± 4°C) and humidity (50-70%) with normal rat chow and tap water *adlibitum*. Animal care and the general protocols for animal management observed in compliance with the regulations of the Ministry of Health and Medical Education of the I.R. of Iran, were approved by the Medical Ethics Committee of the Baqiyatallah University of Medical Science, Tehran, Iran (IR.BMSU.REC.1397.177).

Grouping

In a total of 60 male Wistar rats after being fast for 24 h, 4% acetic acid (1 mL) was instilled rectally to induce CMV model UC (Varshosa et al., 2012). The animals were randomly divided to seven equal isolated groups. Excluding Group I as the negative control that not induced colitis, and in the other group, acetic acid was used to induce UC in the rats. Different treatments were applied after 24 h. Group II received 1 mL of normal saline as positive control, group III received 30 mg/kg of Mesalazine orally, Group IV received 10 mg/kg Asacol intra-colonic, group V received 100 mg/kg of Extract orally, group VI received 100 mg/kg of Extract intra-colonic, group VII received 100 mg/kg of Extract and 10 mg/kg Asacol as a combination treatment. All rats were subjected to euthanasia by cervical dislocation, and sampling on the 10^{th} day.

Plant material and preparation of extract

The fresh aerial parts of *tarragon* were collected from Urmia, Iran by an herbalist of the faculty of science, Urmia University (Herbarium code: 512). The plant was washed, cut into small pieces, and shade-dried. The percolation method in three steps was used to prepare aqueous extract of the dried and milled plant. At the end, the extract was dried by evaporation at 40 °C. Then, the extract was stored in a condition of without light exposure and −20°C (Abtahi Froushani et al., 2016).

Disease Activity Index (DAI)

Body weight, stool consistency and gross bleeding were monitored daily. As can be seen in Table 1, disease activity index (DAI) was assessed as the sum of the scores of weights loss, stool consistency and blood feces. The survival rate of rats was recorded daily during the study. Also, from 10 cm distal colon segments, the colon samples were dissected, and macroscopic examinations (hemorrhage and ulcer formation) were done on a white screen (Heidari barchi nezhad et al., 2018).

Evaluation of myeloperoxidase (MPO) levels

MPO activity was assessed according to a previous procedure and the manufacturer's instructions (Abcam, ab119605) (Obolskiy et al., 2011). The proteins obtained from the colonic tissues were employed to measure the MPO levels in the excised colon which was weighed, homogenized in 0.1 M phosphate buffer (pH 7.4), and centrifuged. The supernatant was used to determine the MPO concentration. The absorbance was measured at 460 nm. MPO activity was represented as U/g protein, and defined as the quantity of enzyme degrading 1 µmol peroxide per minute at 37 ◦C (Marteau, 2005).

Antioxidant enzyme activities

Determination of NO level activities in colon: The excised colons stored at -80°C were homogenized in 0.1 M phosphate buffer (pH 7.4), and then centrifuged at 15,000 g for 10 minutes. The supernatant fraction was utilized for the measurements of the nitrogen monoxide (NO) content using the corresponding kits (Abcam) (Gheibi, 2018).

Cytokine assay

The contents of IL-6 and TNF-α in the colon tissue were measured by a commercial enzyme-linked immunosorbent assay (ELISA) kit (Abcam, Germany) as instructed by the manufacturer. In Brief, Cytokine ELISA Kit was based on the standard principle of a sandwich enzyme-linked immunosorbent assay. A mouse monoclonal antibody specific to each cytokine was coated on a 96-well plate. Standards and test samples were added to the wells, and the immobilized antibody was used to bind cytokines existing in the samples. A cytokine-specific biotinylated polyclonal antibody from the goat was added subsequently. After the unbound biotinylated antibody was washed with PBS or TBS buffer, the avidin-biotin-peroxidase complex was added to the wells. To eliminate the unbound conjugates, the wells were washed again with PBS or TBS buffer. In order to visualize the HRP enzymatic reaction, HRP substrate TMB was used. TMB was catalyzed by HRP to generate a blue product that changes to yellow when an acidic stop solution was added. The density of yellow color was proportional to the cytokine captured onto the plate. The OD (optical density) values were measured by an ELISA reader at 450 nm wavelength. The cytokine amount of each sample was calculated using standard curves derived from standard samples (Esmaili Gourvarchin Galeh et al., 2018).

Histological investigation

The samples were prepared with H & E staining for the examination of the histopathologic pattern under a light microscope. The results of staining were scored from 0 to 3 (Fig.1). The scores were: 0 = normal; 1 = mucosal erythema only; 2 = mild mucosal edema, slight bleeding or slight erosion; 3 = sever ulceration, erosions, edema and tissue necrosis. Finally, the numbers obtained from each of the parameters were collected, and showed the severity of the lesion (Esmaili Gourvarchin Galeh et al., 2018).

Statistical analysis

The results were expressed as the Mean ± SD. The differences among groups were examined using one-way ANOVA with Tukey HSD as post-hoc test. Non-parametric data were analyzed by Mann-Whitney U test. All statistical analysis was performed by SPSS 21 software. The significance was assumed to occur at $p<0.05$.

Results and Discussion

Immunomodulation was required when the host defense mechanism had to be activated in immunodeficiency conditions or when a selective immunosuppression was needed in autoimmune disturbances (Abbas, Lichtman and Pillai, 2012). The aqueous extract of tarragon which was free from potentially harmful estragole or methyl-eugenol, possessed immunomodulatory effects, *in vivo*. The immunomodulatory benefits of the aqueous extract of *tarragon* were partly due to the inhibition of proinflammatory cytokines (IL-17 and IFN-γ), and the induction of anti-inflammatory macrophages. However, other mechanisms might also be involved (Obolskiy et al., 2011; Ghanadian et al., 2012).

Ulcerative colitis has been the main type of inflammatory bowel disease that has affected millions of people worldwide. It has been characterized by chronic uncontrolled inflammation of intestinal mucosa (Kim et al., 2012). However, the pathogenesis of IBD has not still completely understood. Researchers have suggested that the imbalance between proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-17, INF-γ and anti-inflammatory cytokines, such as IL-10, played a pivotal role in colitis inflammation (Nakase et al., 2010). CMV are normally observed in the colon, and they induce an inflammatory response. Cytomegalovirus latency, though common in the human being, has been known to cause colitis in both immunocompromised and immunocompetent hosts (Park et al., 2013). The aim of the present study was to assess the potent anti-inflammatory activity of *tarragon* in comparison with Mesalazine, and Asacol as a standard medication, on CMV colitis model induced by acetic acid in male Wistar rats.

A combination of DAI (body weight loss, stool consistency and stool blood) was considered to assess the therapeutic benefit of Tarragon extract. In mice with acid ascetic induced acute colitis, the body weight loss and marked remarkably diarrhea with bloody stools were observed, which resulted in an increase of the disease activity index (DAI), compared with negative control mice. However, it was observed that the DAI score was significantly decreased in all treated groups as compared to the positive control group (Fig. 1). As seen in the Fig. 1, the highest decrease group was group VII that received 100 mg/kg of Extract and 10 mg/kg Asacol (combination treatment) as compared to the other groups.

After scored damage of tissues (Fig.2), the negative control group receiving score 0, the lowest score possible. Groups receiving *Tarragon* extract (oral, enema), Mesalazine (orally) and Asacol (enema) represented that epithelium was not destroyed completely; hence, receiving 2 for the level of epithelium damage. Given the observed tissue changes, the score was given to the group receiving extract (enema) along with Asacol was 1 (Fig. 2). The results of statistical analysis represented that comparing with other groups, in the group receiving synergistic treatment of Asacol and extract intracolonically (enema), a higher decrease of acetic acid-induced ulcers ($p < 0.05$) was observed. Other treatment groups also represented significantly lower colon damage, compared with the positive control group ($p < 0.05$) (Table 2).

According to the obtained data, MPO concentrations of the colon tissue were significantly higher and lower in positive control and negative control groups, respectively, than all the other treatments ($p < 0.05$). The positive control group contained significantly lower tissue MPO concentration than those in Tarragon Orally, Tarragon Enema, Mesalazine and Asacol groups ($p < 0.05$). The group receiving synergistic treatment of Asacol and extract intracolonically (enema) represented a higher decrease of MPO concentrations (Fig. 3).

The NO level was also determined as antioxidant enzyme in colon tissue. As MPO, colonic levels of NO in mice were increased by acetic acid induction (Fig. 4). And the treatment of *Tarragon* extract (oral, enema), Mesalazine (orally) and Asacol (enema) significantly reduced the levels of NO as compared to acetic acid treated group (Fig. 4). The group receiving synergistic treatment of Asacol and extract intracolonically (enema) represented a higher decrease of NO concentrations.

Compared to the negative control group, positive control animals showed significantly elevated levels of TNF-α (Table 3) and IL-6 (Table 3) in the colon. Contrarily, the rats treated with *Tarragon* extract (oral, enema), Mesalazine (orally) and Asacol (enema) exhibited significantly lower values of TNF-α and IL-6. Fig. 4 displays more significant differences between synergistic treatment of Asacol and extract intracolonically (enema) treated animals and positive control group regarding the concentrations of TNF-α and IL-6.

According to the results, the extract of *Tarragon* could obviously reverse the inflammatory mediators of the trial colitis. A significant reversal in the severity of colitis was observed with oral and enema administration of *Tarragon* extract (oral, enema), Mesalazine (orally) and Asacol (enema) together with intracolonic instilment of 4% acetic-acid. Apparently, the extract was capable of resolving inflammatory mediators as demonstrated by the decreased biochemical markers MDA, NO and contents of TNF-α and IL-6 in the colon.

Dried aerial parts of *Tarragon* have been orally prescribed in Iranian folk medicine to control epilepsy, coagulopathy and hyperlipidemia. This herb also possesses antifungal and antioxidant activity as well as anti-bacterial, hepatoprotective properties and insecticide and radical scavenging activities

(Weinoehrl et al., 2012). Today, there are a lot of anti-inflammatory and immunosuppressive drugs which are normally utilized for curing inflammation-related diseases. However, long-term administration of these drugs can be associated with a high incidence of adverse side effects (Sharafati Chaleshtori et al., 2013). So, medicinal plants containing anti-inflammatory immunomodulatory characteristics and less side effects can be considered as a new vision in the traditional medicine.

Abtahi et al., 2015 indicated that the aqueous extract of tarragon can be utilized as a natural source to improve the immune system, since it can prevent pro-inflammatory cytokines and induce anti-inflammatory macrophages. Tarragon plant contains no disadvantages because it has

been categorized as nontoxic, and it does not provoke sensitization or irritation (Abtahi Froushani et al., 2016).

The inflammatory reaction and injurious nature are promoted and proliferated through the production of inflammatory cytokines (TNF-α and IL-6), which are known as the targets of curative interventions (Abdulkhaleq et al., 2018). The data obtained in this study suggested significantly decreased TNF-α and IL-6 levels and pathological damage in the treated animals and positive control group as a result of *Tarragon* extract (oral, enema), Mesalazine (orally) and Asacol (enema) administration.

Oxidative stress contributes essentially to the pathophysiology of UC. In UC, the migration of neutrophils to the colon tissue was induced by an initial elevation of free radicals, secondary hypoxic conditions, and inflammatory chemokines resulting in the spread of inflammation and oxidative stress in the colon by means of arachidonic acid metabolites, cytokines and another chemokine (Balmus et al., 2016). The reversal of antioxidant capacity of IBD patients is obvious, even in the asymptomatic phase of the disease. Intestinal cells have several enzymatic and non-enzymatic antioxidants, including superoxide dismutase (SOD), reduced glutathione (GSH) and catalase (CAT), for eliminating reactive oxygen and nitrogen substances. However, a surplus of free radical formation improves lipid peroxidation and may diminish antioxidant barriers (Zhang and Li, 2014).

Reactive NO radicals play important roles in the pathogenesis of human IBD. Many studies have indicated that excessive NO may exacerbate the pathological features of UC through mechanisms such as direct injury of gut epithelial cells, activation of neutrophils, and vasodilation (Pedersen et al., 2014). In addition, NO can interact with superoxide and form the highly toxic peroxynitrite radical, which reversibly increases the expression of iNOS by activating NF-κB, and leads to a cycle of deleterious events (Rana et al., 2014).

The aquase extract of *Tarragon* contains, presented substantial antioxidant properties through their ability to hinder reactive oxygen or nitrogen compounds. The anti-inflammatory and antioxidative activities of the tarragon compounds have also been advantageous by preventing the arachidonic acid cascade and hindering phospholipase-1, lipooxygenase and cyclooxygenase (Zhao et al., 2012). During the neutrophil respiratory burst and formation of reactive oxygen, Myeloperoxidase often emerges in neutrophils and generates hypohalous acids. The activity of Myeloperoxidase, therefore, can be applied as a neutrophil infiltration biomarker (Hansberry et al., 2017).

The present data further showed that the administration of *Tarragon* extract in two trans-rectal and oral forms can reverse MPO and NO activity in the colon.

Conclusion

The aqueous extract of *tarragon* can be recommended as an encouraging approach for UC treatment. This research, however, has been a preliminary animal study that calls for further investigations in the future.

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Conflict of Interest

The authors declared that they had no conflict of interest.

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Table 1. Criteria for Scoring of Colitis

Score	Weight Loss, %	Stool Consistency	Blood Feces
0	Negative	Normal	Negative
1	1-9	Soft	Red
2	10-19	Very Soft	Dark Red
3	< 20%	Diarrhea	Black

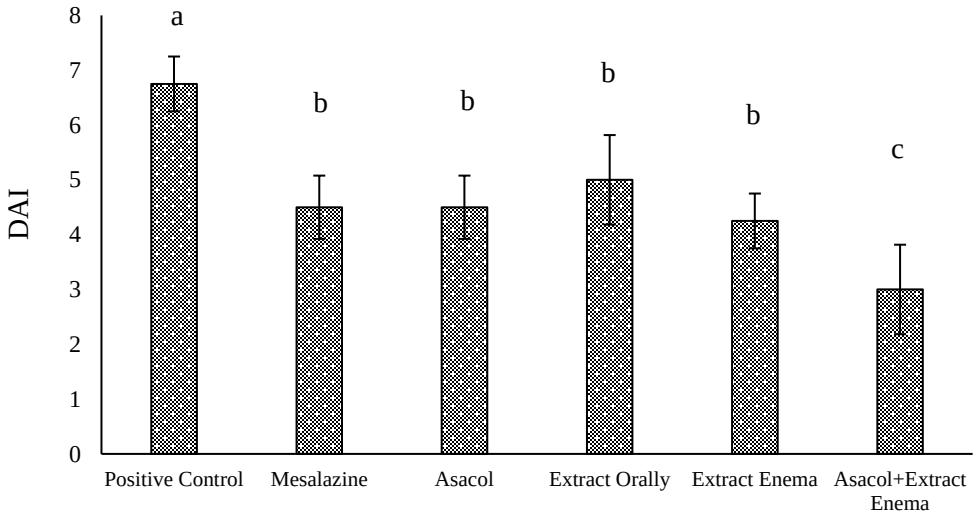

Fig. 1. Comparison of Disease Activity Index (DAI). Different superscript letters show statistically significant differences between the groups ($p < 0.05$).

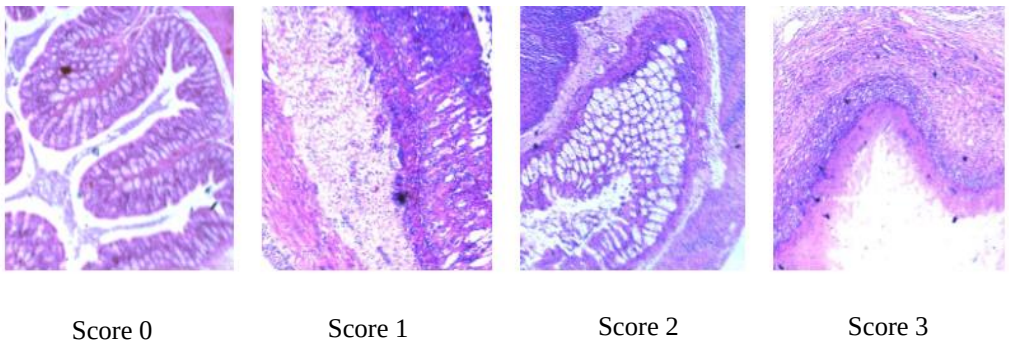

Fig. 2. Representative sections depict scoring system used for histopathological examinations (400×).

Table 2. Results of blind analysis of histopathological sections.

Groups	Score (0-3)
Negative	0^{a}
Positive Control	2.75 ± 0.50^{b}
Mesalazine	1.5 ± 0.57^{c}
Asacol	1.25 ± 0.50^{c}
Tarragon Extract Orally	1.75 ± 0.50^{c}
Tarragon Extract Enema	1.5 ± 0.50^{c}
Asacol+ Tarragon Extract Enema	0.5 ± 0.57^{c}

Different superscript letters show statistically significant differences between the groups ($p< 0.05$).

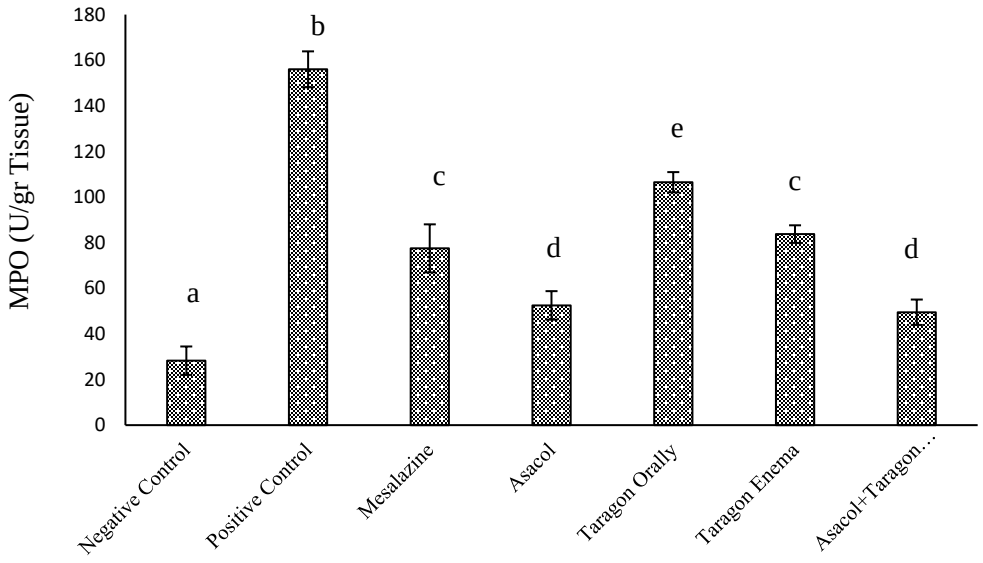

Fig. 3. Comparison of mean and SD MPO level in colon tissues of different experimental groups. Different superscript letters show statistically significant differences between the groups ($p<0.05$).

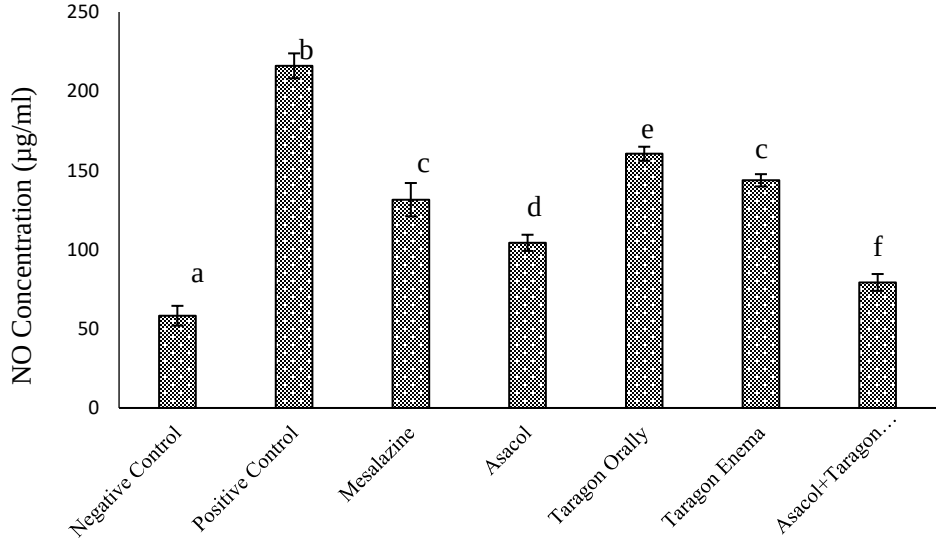

Fig. 4. Comparison of mean and SD NO level in colon tissues of different experimental groups. Different superscript letters show statistically significant differences between the groups ($p< 0.05$).

Table 3. Changes of inflammatory cytokine in colon tissues of rats in different groups.

Groups	IL-6	TNF-α
Negative	24.75 ± 16.83^{a}	10.25 ± 4.03^{a}
Positive Control	195.25 ± 7.63^{b}	169 ± 6^{b}
Mesalazine	118 ± 7.30^{c}	88.5 ± 7.54^{c}
Asacol	102.75 ± 6.94^{c}	77.75 ± 7.18^{c}
Tarragon Extract Orally	143 ± 6.83^{d}	93.5 ± 5^{c}
Tarragon Extract Enema	134.5 ± 9^{d}	82 ± 7.03^{c}
Asacol+ Tarragon Extract Enema	75.5 ± 5^{e}	57.75 ± 6.94^{d}

Different superscript letters show statistically significant differences between the groups ($p< 0.05$).