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Original Article

# Ameliorative effects of aqueous cinnamon extract on ulcerative colitis in rats

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## Abstract

**Introduction:** This study was designed to evaluate the effects of cinnamon extract on ulcerative colitis in rats.

**Methods:** Thirty-two male Wistar rats were divided into four groups: untreated control, positive control group (acetic acid-induced ulcerative colitis), cinnamon extract treated group (150mg/kg/day) and treated group with prednisolone (4mg/kg/day). After 10 consecutive days, the rats were euthanized and examined for the production of inflammatory mediators and oxidative stress indices in the intestinal tissue.

**Results:** Data showed that both therapies could reduce the cumulative disease score. The results also indicated that treatment with cinnamon caused a more benefit in restoring the total antioxidant capacity of the colonic specimens of the colitis-induced rats compared to treatment with prednisolone. The levels of myeloperoxidase and nitric oxide were down-regulated in the colons of cinnamon treated rats more than prednisolone groups. Prednisolone significantly decreased the levels of TNF-α and IL-6 cytokines more than colitis rats treated with cinnamon extract. The levels of COX-2 were decreased and conversely, the total protein content of colonic homogenates was increased in the colons of both treatment groups in a non-significant manner, compared to untreated colitis rats.

**Conclusion:** These results demonstrated cinnamon as herbal medicine is a promising strategy to improve the inflammation in a rat model of ulcerative colitis. It is logical to consider some of the beneficial effects of cinnamon extract associated with its direct antioxidant benefits, along with its direct anti-inflammatory benefits.

**Keywords:**
Ulcerative colitis;
Cinnamon extract;
Inflammation

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## Introduction

Ulcerative colitis (UC) is relapsed and idiopathic syndrome that classified under inflammatory bowel disorders (IBD). The exact etiology of ulcerative colitis is not clear until now. accelerated free radical production and decreased antioxidant capacity as well as pro-inflammatory cytokines are distinguished features of IBD. Reactive oxygen species and following lipid peroxidation decline cellular antioxidant capacity, causing noted inflammation in the colon. Extreme inflammation and oxidative stress have crucial roles in ulcerative colitis disease pathogenesis. Frequent symptoms of UC include diarrhea, bloody stools, the pain of the abdomen and

ulceration in the mucus of the large intestine (Bernstein et al., 2010). Currently, it is believed that the occurrence of UC may be related with different factors, such as genetics, microbes, food allergens and immune system dysfunction; however the exact etiology of this factors remain uncertain (Vasovic et al., 2016). Because of the increase in the incidence and prevalence of UC around the world, current is considered to be a worldwide disease (Ng et al., 2018). Often primary treatment for UC includes NSAIDs, corticosteroids and immunosuppressants (Triantafillidis et al., 2011). However, these drugs have adverse effects including allergies, nausea and lymphoma. Given according to these, many scientists have studied herbal medicine for the treatment of UC. Traditionally, cinnamon extract from the cinnamon bark of *Cinnamomum ceylanicum* gathered in Asian countries used as an old herbal medicine. Main components of cinnamon extract are cinnamic aldehyde, cinnamic acid, tannin and methylhydroxychalcone polymer (Kim et al., 2006). Antioxidant, anti-inflammatory and anti-diabetic effects of cinnamon related to these combinations (Kwon et al., 2011; Lopes et al., 2015). Previously, the effects of cinnamon extract on UC had not been studied. Therefore, the aim of this work was to determine the beneficial effects of cinnamon extract on ulcerative colitis in rats.

# Materials and methods

### Reagents

Fetal calf serum and Dulbecco's modified Eagle's medium (DMEM) were obtained from GIBCO/Life Technologies Inc. (Gaithersburg, MD). Total protein assay kit was provided from Zist chemi Co. (Tehran, Iran). The enzyme-linked immunosorbent assay (ELISA) kits were purchased from Peprotech (UK). Other reagents were purchased from Sigma-Aldrich (St. Louis, MO).

### Preparation of cinnamon extract

*Cinnamomum ceylanicum* bark was obtained from an herbal drug market in Urmia, Iran, defined by the Department of Botanical Sciences, Urmia University, Iran. *Cinnamomum ceylanicum* bark (500g) in tap water (5l) was extracted at 100°C for 3.5h, filtered by a filter (150µm) and dried using the freeze dryer. The prepared cinnamon extract was stored at -20°C (Moselhy and Ali, 2009).

### Gas chromatography–mass spectrometry (GC-MS) analysis

GC-MS was performed with an Agilent 7890A GC (USA) instrument coupled to an Agilent 5973 mass spectrometer and an Agilent ChemStation software (Agilent Technologies).

### Animals

Male Wistar albino rats (150–200g) were obtained from animal house care center of Urmia University and were housed there. The animals were kept with a 12-hour light/dark cycle and had standard diet pellets and water *ad libitum*. Before the start of the trial, adaptation period of animals took (room temperature 25±5°C) for ten days. All the procedures were performed according to the standard animal experimentation protocol of the ethics committee of the Urmia University for Animal Studies (AECVU-182-2018).

### Experimental protocols

Induction of colitis was conducted as designated previously (Low et al., 2013). Briefly, after fasting of rats for 24 hours, the animals were anesthetized using ether and catheter was then placed in the colon and through the rectum instillation of 2ml solution of 4% acetic acid was conducted. Rats were assigned to follows groups (n=8): group 1 was intact group and received only isotonic saline; group 2; UC control, received only oral phosphate buffer solution (0.5ml/day). In cinnamon treated animals and positive control, colitis treated rats with oral cinnamon (150mg/kg/day) or prednisolone (4mg/kg/day), respectively (Kumar and Mukkadan, 2013). Treatments were started on induction day and continued until 10 days, then rats were sacrificed (Froushani and Mashouri S, 2018). In all days of the experiment, weight of the body, consistency of stool and gross bleeding were examined. Disease activity index (DAI) was calculated as factors defined in Table 2.

### Sample collection and immunohistochemical (IHC) evaluation

After scarification of rats, colonic segments were excised, rinsed with saline, then colon samples were fixed in formalin solution (10%). Hematoxylin and

eosin (H&E) staining and IHC assay of samples were done.

**Myeloperoxidase (MPO) activity assay**

The level of malondialdehyde (MDA) in the colonic homogenates was monitored like to a protocol defined former (Pulli et al., 2013). Briefly, 10µl of the homogenized colon was mixed with 110µl tetramethylbenzidine solution (2.9mM tetramethylbenzidine in 14.5% dimethyl sulfoxide along with 150mM PBS at pH 5.4) and 80µl of 0.75mM hydrogen peroxide. Immediately, the optical density was recorded at 450nm. After incubation of the sample for 15 minutes at 37°C, we added 50µl of 2M sulfuric acid to terminate the reaction. The absorbance was read spectrophotometrically at 450nm. The 10µl of horseradish peroxidase (2.5 and 25 milliunits/ml) were used as internal standards. The activity of MPO was estimated as the difference of the absorbance relating to the horseradish peroxidase standard curve. Results were reported as milliunits per milliliter (mU/ml).

**MDA determination**

The level of MDA in the colonic homogenates was evaluated similarly to a protocol defined former (Al-Rejaie et al., 2013). Briefly, 2.5ml reaction buffer (0.37% thiobarbituric acid, 0.25M HCl and 15% trichloroacetic acid, 1:1:1 ratio) were mixed to 100µl of colon homogenate and heated at 96°C for 60min. After cooling, it was centrifuged at 3500g for 10min. We monitored absorbance of the supernatant at 540nm. Results were reported as nM of MDA/mg protein.

**Nitric oxide (NO) determination**

The level of NO in the colonic homogenates was measured with the colorimetric method using the commercial kit (Cib biotech Co, Tehran, Iran) in accordance with manufacturer instruction (Bryan and Grisham, 2007).

**Total antioxidants capacity**

Total antioxidants capacity levels were measured using a commercial kit according to the manufacturer's guidelines (Navand Lab kit, Tehran, Iran).

**Total protein levels assessment in colonic tissues**

Total protein levels in colonic the homogenates using pyrogallol red-molybdate method was determined according to the manufacturer's guidelines (Orsonneau et al., 1989).

**Determination of pro-inflammatory cytokine levels in colon samples**

Interleukin (IL)-1β, tumor necrosis factor (TNF)-α and IL-6 levels were measured in colonic homogenate by the commercial ELISA kits (Peprotech, London,UK) according to the manufacturer's instructions (Gao et al., 2016).

**Cyclooxygenase (COX)-2 immunohistochemical staining**

Immunohistochemical staining was conducted by the method described former (Xu et al., 2005). After 25min, colonic sections were heated at 60°C in a hot oven (Binder, Germany). After de-paraffinization, the process of retrieval of antigen was done in 10mM sodium citrate buffer. Based on the manual (Biocare, Pacheco, USA), we stained the sample immunohistochemically. To eliminate the endogenous peroxidase, a solution of peroxidase blocking (0.03% hydrogen peroxide containing sodium azide) was used for 5min. Tissue sections were rinsed gently with PBS and then incubated with COX-2 primary antibody at a dilution of (1:500) (Elabsciences, Houston, USA) at 4°C, overnight. The sections were washed gently with PBS and allocated in a buffer bath. Afterward, we put the slides in a humidified chamber with an adequate streptavidin conjugated to horseradish peroxidase for 15min. Afterward, sections were washed and incubated with a DAB chromogen for 5min. Then, hematoxylin was used to stain the specimen. The sections were rinsed in weak ammonia (0.037ml) 10 times. After that, the slides were washed with deionized water and cover slipped. The COX-2 cells were counted in one $mm^2$ of the tissue and compared among groups quantitatively.

**Statistical analysis**

Results were reported as mean±SD. The Kruskal Wallis test was used to analysis the disease activity index. The rest of the findings were evaluated by the one-way ANOVA and Dunnett's post hoc test. Monitoring of survival function of lifetime data was measured by the Kaplan–Meier estimator. *P* values <0.05 were considered significance.

# Results

The contents of investigated components in sample of *Cinnamomum ceylanicum* extract are summarized in Table 1. The DAI of each rat were monitored every day after the instillation of acetic acid into the colon of rats. As expected, colonic instillation of acetic acid led to a high DAI score and high mortality rate in the positive control group (Fig. 1). Obtained data showed that both therapies could reduce the DAI index (Fig. 1). The survival rate over 10 days of the survey in cinnamon extract and prednisolone treated groups were 80% and 90% respectively (Fig. 1).

Induction of colitis resulted in noteworthy reduction in the antioxidant properties of the colonic homogenate specimens of the colitis rats in comparison with normal animals (Table 3). The obtained data indicated that treatment with cinnamon caused a more prominent benefit in restoring the total antioxidant capacity of the colonic homogenate specimens of the colitis rats compared to treatment with prednisolone. So that, cinnamon could return the antioxidant capacity to the level of normal rats in colonic specimens (Table 3). As exhibited in Table 3, instillation of acetic acid into the colon of animals also led to a prominent increase in the levels of NO and MPO activity in the colonic homogenate specimens. (Table 3). Both medications induced a significant decrease in the activity of MPO and the levels of NO in the colonic homogenate of colitis animals in comparison with positive control animals (Table 3). Of note, the values of MPO and NO were down-regulated in the guts of cinnamon treated rats more than prednisolone groups (Table 3). Moreover, the total protein content of the colonic homogenate of colitis rats was significantly disappeared in comparison with a normal animal (Table 3). The level of total protein of colonic specimens was increased in both treatment groups, without any significant difference, compared to control positive rats in a significant manner (Table 3).

As shown in Figure 2 the content of the TNF-α, IL-6 and IL-1β in the colonic tissues were significantly increased in the colonic specimens compared to specimens of normal rats. Based on the results, both medications caused a significant regression in the content of these cytokines in the colonic specimens of rats instilled with acetic acid (Fig. 2). Nevertheless,

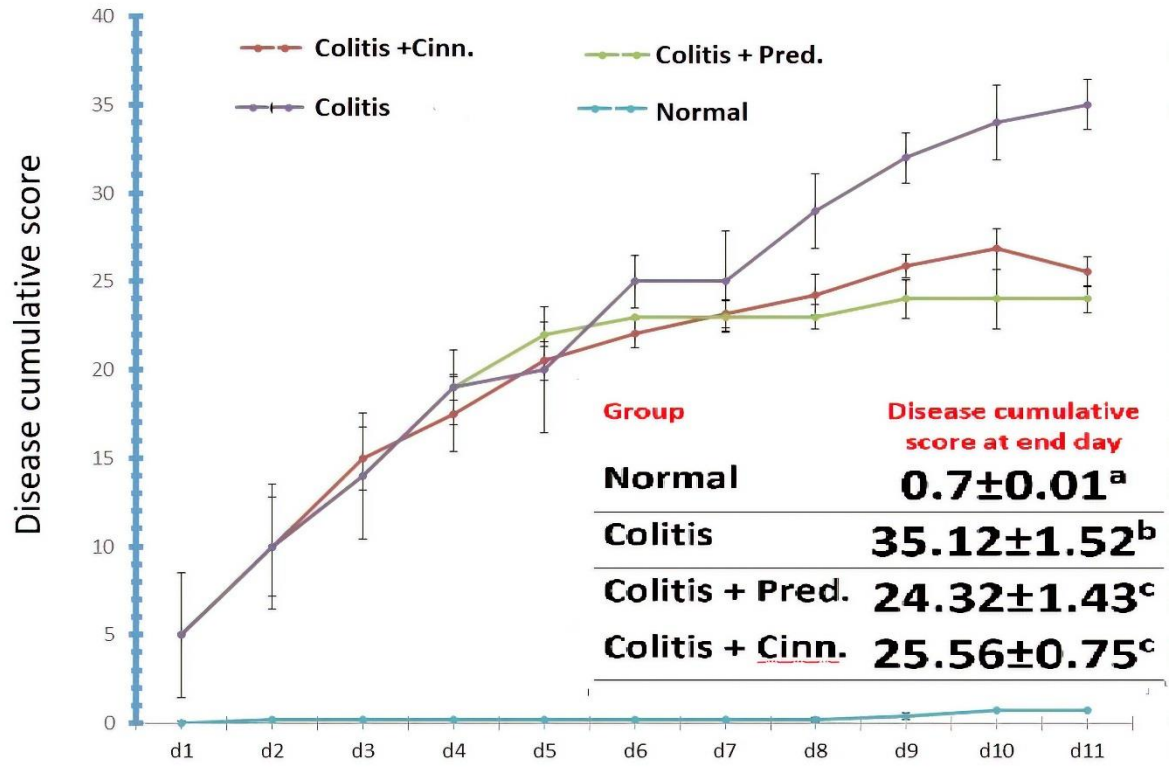


**Fig.1.** Assessment of cumulative disease score**.** The obtained data demonstrated that both cinnamon and prednisolone could ameliorate disease score of rats with ulcerative colitis in a comparable manner (different letters indicate a significant difference at the level of $P<0.001$). Col: Colitis; Pred: Prednisolone; Cinn: Cinnamon.

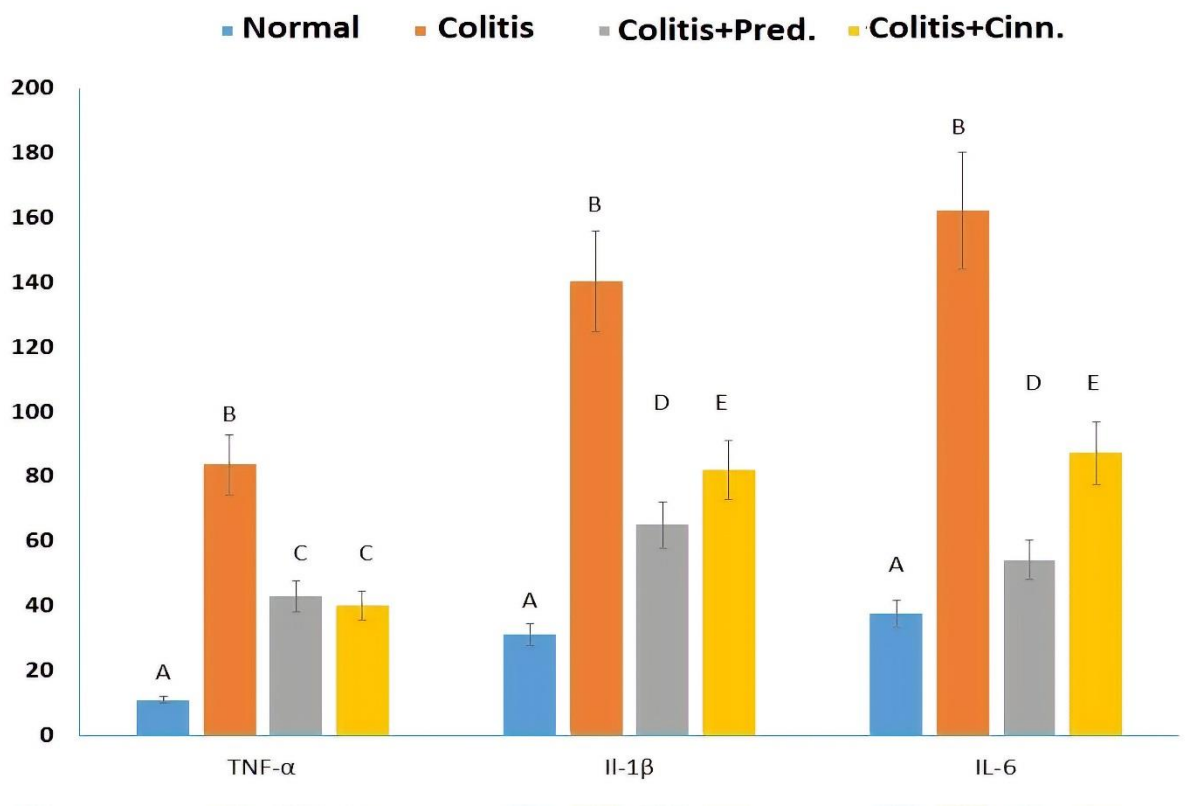


**Fig.2.** Evaluation of cytokine profile in the colonic specimens (pg/mg pr tissue). The content of TNF-α, IL-1β and IL-6 in colonic homogenates was markedly regressed in both treatment groups compared to colitis rats (different letters [A-E] indicate a significant difference at the level of $P<0.001$). Col: Colitis; Pred: Prednisolone; Cinn: Cinnamon.

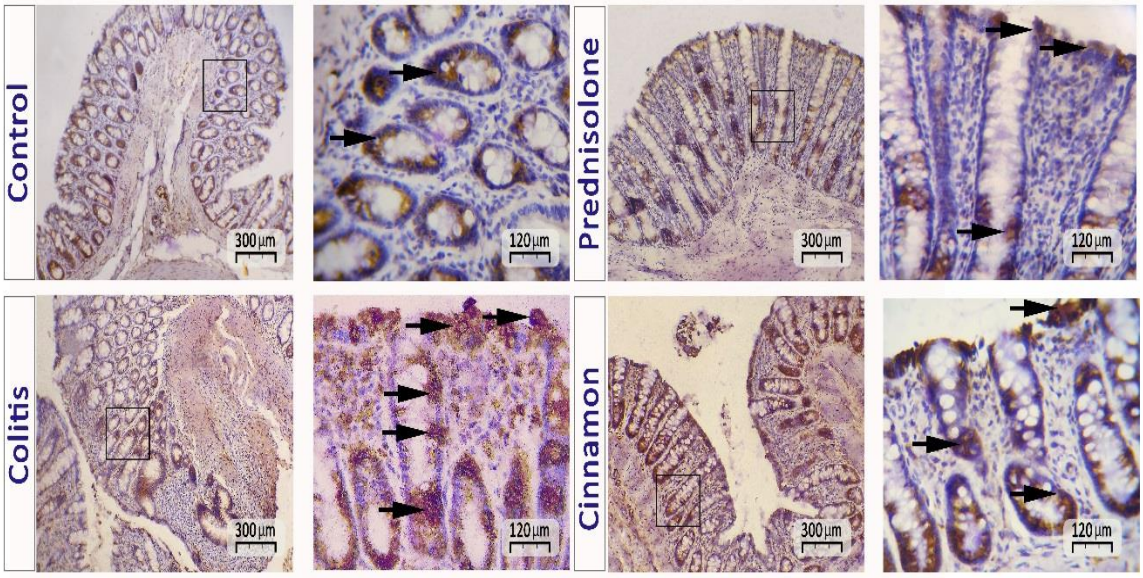


**Fig.2.** Immunohistochemical evaluation of the colonic tissues. The expression of COX-2 was significantly decreased in the colons of cinnamon treated rats more than prednisolone groups. Note arrows representing positive reaction for COX-2. Note diminished COX-2 expression (arrows) in cross section from prednisolone and cinnamon extract received groups. Con: Control; Col: Colitis; Pred: Prednisolone; Cinn: Cinnamon.

prednisolone significantly decreased the levels of TNF-α and IL-6 cytokines more than colitis rats treated with cinnamon extract (Fig. 2).

As exhibited in Figure 3, IHC examination indicated that the expression of COX-2 was markedly increased in the colonic homogenates of colitis rats

**Table 1:** Contents of the investigated compounds in *Cinnamomum ceylanicum* extract by GC-MS.

| Results of GC-MS Analysis of extract of cinnamon | | | |
|---|---|---|---|
| Components | Retention index | Retention time | (%) |
| Alpha.-thujene | 926 | 5.12 | 0.59 |
| Alpha.-pinene | 934 | 5.28 | 0.40 |
| 1 octen 3 ol | 975 | 6.09 | 0.34 |
| 3-octanone | 984 | 6.26 | 1.06 |
| Beta.-myrcene | 990 | 6.38 | 0.85 |
| 3-octanol | 993 | 6.44 | 0.18 |
| 1-phellandrene | 1005 | 6.69 | 0.14 |
| Alpha.-terpinene | 1017 | 6.96 | 1.48 |
| P-Cymene | 1026 | 7.15 | 9.69 |
| L-Limonene | 1029 | 7.23 | 0.31 |
| 1,8-cineole | 1033 | 7.31 | 0.06 |
| Cis-Ocimene | 1036 | 7.38 | 0.31 |
| Trans-Ocimene | 1047 | 7.62 | 0.07 |
| Gamma.-terpinene | 1060 | 7.91 | 8.03 |
| Cis-Sabinenehydrate | 1068 | 8.10 | 0.26 |
| .Alpha.-terpinolene | 1090 | 8.58 | 0.10 |
| Linalool | 1100 | 8.81 | 0.13 |
| Borneol | 1169 | 10.42 | 0.10 |
| 4-terpineol | 1180 | 10.68 | 0.67 |
| Alpha. Terpineol | 1193 | 11.00 | 0.69 |
| Cumarin | 1200 | 11.11 | 0.07 |
| Beta-(E)-Cinnamyl | 1246 | 12.18 | 8.17 |
| Cinnamal | 1275 | 12.85 | 0.54 |
| Thymol | 1293 | 13.26 | 11.20 |
| Alpha- (E)Cinnamaldehyed | 1307 | 13.57 | 52.21 |
| Trans-caryophyllene | 1425 | 16.15 | 0.29 |
| Beta.-bisabolene | 1510 | 17.91 | 0.11 |
| Cis-.alpha.-bisabolene | 1544 | 18.58 | 1.17 |
| Caryophyllene oxide | 1590 | 19.50 | 0.08 |
| SUM | | | 99.36 |

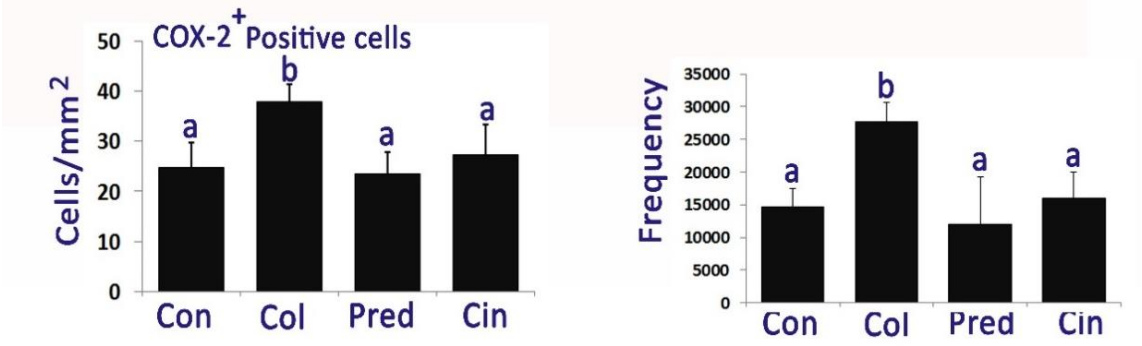


**Fig.4.** Quantitative COX-2 positive cells count per one $mm^2$ of the colonic tissue of rats following experimental colitis and treated with cinnamon extract (different letters [a,b] indicate a significant difference at the level of $P<0.001$). All data are represented as mean±SD.

**Table 2:** Scoring system for assessment the severity of ulcerative 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 |

The disease activity index (DAI) was calculated as the sum of scores.

**Table 3:** Results of biochemical changes in the colonic tissues.

| Group | Total antioxidant capacity (mmol/mg pr) | Nitric oxide (µM/mg pr) | Myeloperoxidase (U/mg pr) | Malondialdehyde (µM/mg pr) | Total protein (mg/g tissue) |
|---|---|---|---|---|---|
| **Intact** | 52.63±9.40$^{a}$ | 0.88±0.09$^{a}$ | 0.79±0.09$^{a}$ | 1.53±0.17$^{a}$ | 247.3±20.1$^{a}$ |
| **Colitis** | 27.64±2.74$^{b}$ | 22.58±4.51$^{b}$ | 18.88±3.90$^{b}$ | 41.20±6.00$^{b}$ | 65.3±10.6$^{b}$ |
| **Colitis + Prednisolone (4mg/kg)** | 31.35±4.09$^{c}$ | 8.13±1.56$^{c}$ | 6.44±1.10$^{c}$ | 15.22±1.88$^{c}$ | 122.6±12.04$^{b}$ |
| **Colitis + Cinnamon.** | 49.82±5.39$^{d}$ | 4.04±0.52$^{d}$ | 2.70±0.52$^{d}$ | 8.64±1.30$^{c}$ | 119.19±11.9$^{a}$ |

The levels of nitric oxide activity, myeloperoxidase and malondialdehyde were down-regulated in the guts of cinnamon treated rats more than prednisolone groups. Furthermore, both medication could equally increase the level of total protein in the colonic specimens compared to control positive rats (different letters indicate a significant difference at the level of $P<0.01$). Col: Colitis; Pred: Prednisolone; Cinn: Cinnamon. Different letters (a-d) in each column indicate significant differences at $P<0.01$.

compared to normal rats (Fig. 3). In this regard, the levels of COX-2 were decreased in the guts of prednisolone group rats more than cinnamon treated in a non-significant manner (Fig. 3).

# Discussion

Destruction of the intestinal mucosa by acetic acid leads to acute local inflammation in the rectum and the colon and induces a pathologic pattern similar to the UC (Rezaie et al., 2007). Severe infiltration of neutrophils and oxidative and nitrative damages are thought to be the principal actors of the pathology (Wallace et al., 1998). Although inflammation could be controlled relatively by corticosteroids like prednisolone, tissue oxidative or nitrative damages are not influenced by corticosteroids. Also, the immunosuppressive properties of corticosteroids and many other side effects have made investigators to find a substitute therapy. The findings of this study suggested that both cinnamon and prednisolone could reduce the DAI of UC in a comparable manner.

As mentioned above, the inflammatory condition like UC caused the peroxidation of lipids in the colonic tissues (Rodrigues et al., 2018; Gupta et al., 2018). Therefore, the application of antioxidants in the food and pharmaceutical industries is a logical decision to control inflammation like UC (Lee et al., 2018; Sabzevary-Ghahfarokhi et al., 2018). It is clear that cinnamon spice, especially its flavonoid compounds, is one of the sources of natural antioxidants. Previous results showed that the essential oils of cinnamon, like cinnamaldehyde, eugenol and linalool can regress the peroxynitrite-induced nitration and lipid peroxidation (Shahid et al., 2018). The obtained data showed that treatment with cinnamon caused a more prominent benefit in restoring the total antioxidant capacity of the colonic homogenate specimens of the colitis rats, so that, cinnamon could return the antioxidant capacity to the level of normal rats in colonic specimens. Unlike cinnamon extract,

prednisolone hasn't direct antioxidant benefits. Therefore, the partial restoration of total antioxidants capacity in prednisone treated UC rats was indirectly occurred by inflammatory mediators.

MPO is an enzyme found in the azurophilic granules of neutrophils which can be used in an indirect way to evaluate the rate of neutrophil infiltration into a tissue in the inflammatory conditions (Kondamudi et al., 2015). The inhibitory effect of cinnamon on the leukocyte attachment and migration by interacting with sialosides of selectins has been reported (Lin et al., 2015). Also MPO is a key enzyme for the propagation of reactive oxygen species by infiltrating neutrophils. NO is another potent player that participate in the pathogenesis of UC. Attained data in this study showed that, the levels of MPO and NO were reduced in the guts of cinnamon treated rats more than prednisolone group. In this regard, some previous *in vitro* surveys showed that cinnamon derivatives could inhibit the expression of inducible nitric oxide synthase (iNOS) via up-regulation of suppressor of cytokine signaling 3 or MAPKs pathway regulation (Chakrabarti et al., 2018; Kim et al., 2018). In addition to direct damage induced by acetic acid, the normal microflora also attacks the lamina propria and intensify the inflammation (Fabia et al., 1993). Despite prednisolone, it is obviously documented that cinnamon extract possesses direct antifungal and antibacterial benefits (Hajimonfarednejad et al., 2019).

Nowadays, the direct anti-inflammatory agents like 5-aminosalicylate and glucocorticoids and prescribed to control UC (Auphan et al., 1995; Joshi et al., 2005). This medication can inhibit COX enzymes and inflammatory cytokines like TNF-α, IL-1 and IL-6 that participate in the propagation of inflammation (Consalvi et al., 2015). Targeting selectivity for COX-2 isoenzyme can reduce some of the adverse effects of this medication such as the risk of peptic ulceration (Clemett and Goa, 2000). Obtained data in this study showed that, the levels of COX-2 were decreased in both treatment groups in a non-significant manner. In this regard, a former study suggested that cinnamaldehyde, an essential oil in cinnamon, can reduce cerebral ischemia-induced brain injury by a significant decrease in expressions of iNOS, COX-2 and NFκ-B signaling pathway (Chen et al., 2016). Based on results, both medications made a significant reduction in the content of TNF-α, IL-1 and IL-6 cytokines in the colonic specimens of rats instilled with acetic acid. An interesting former survey showed that cinnamon polyphenol extract markedly decreased infarct and edema formation in traumatic brain injury via a significant decrease in oxidative and inflammatory parameters, including NF-κB, IL-1, IL-6, GFAP, NCAM and Nfr2 expressions (Yulug et al., 2018). It has been reported that cinnamic acid can up-regulate the level of SOCS3 and decrees the expression of IL-6, IL-1β and TNF-α in LPS-stimulated BV-2 microglial cells (Chakrabarti et al., 2018).

After UC induction, propagation of inflammation due to extensive infiltration of neutrophils disrupt the integrity of cell and mucosal improvement in the colonic tissues (Al-Rejaie et al., 2013). The current study showed that both medications could encourage the tissue healing because both could reverse the amount of decrease in total protein levels in a similar manner.

# Conclusion

In summary, these results suggest that treatment with natural antioxidants is a promising strategy to alleviate the inflammation in a rat model of UC. It is logical to consider some of the beneficial effects of cinnamon extract associated with its direct antioxidant benefits, along with its direct anti-inflammatory benefits. However, other mechanisms may also be involved and these remain to be illuminated.

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## Conflict of interest

The authors declare that they have no conflict of interest.

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