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Effect of colchicine on experimental acetic acid induced colitis

[Asetik asitle oluşturulan deneysel kolit modeline kolşisinin etkisi]

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ABSTRACT

Objectives: Ulcerative colitis (UC) is an inflammatory disease of the colonic mucosa with involvement from distal to proximal and characterized by neutrophil infiltration. There is no golden standart for the current state of therapy of the patients with UC. The aim of this study is to evaluate the possible effects of colchicine against acetic acid (AA)-induced colitis in rats.

Methods: Fifty three rats were divided into six groups. Rats with AA-induced colitis were treated by intraperitoneal or oral administration of colchicine (80 mcg/kg/day) on treated group. Other four groups formed as colitis control groups and sham groups. Superoxide dismutase (SOD), myeloperoxidase (MPO), lipid peroxidation end products (MDA, FOX) were evaluated from the tissue extracts of colon.

Results: The macroscopic and microscopic colitis scores were found to be significantly increased on AA-induced colitis compared to the sham groups (p<0.0001). However, there were no significant differences between oral or intraperitoneal treated groups and their control groups for those scores. Oral colchicine therapy was associated with decreased SOD (p<0.0001) and MPO (p=0.001), but increased FOX (p=0.013) levels.

Conclusions: Colchicine could be beneficial to control the inflammation in treatment of UC. However, in our study, there was not any protective effect to antioxidant activity neither inhibition on lipid peroxidation end products were observed.

Key Words: Colchicine, ulcerative colitis, experimental model

Conflict of Interest: The authors declare that there was no conflict of interest in this work.

ÖZET

Amaç: Ülseratif kolit (ÜK) tüm kolon mukozasını tutabilen, nötrofil infiltrasyonuyla karakterize inflamatuvar bir hastalıktır. Bu hastalarda altın standart denilebilecek güncel tedavi yaklaşımı bulunmamaktadır. Çalışmamızda asetik asitle (AA) oluşturulmuş deneysel kolit modeline kolşisinin olası etkisinin değerlendirilmesi amaçlanmıştır.

Yöntem: 53 sıçandan 6 grup oluşturuldu. Tedavi gruplarında AA'le kolit oluşturulmuş sıçanlara oral veya intraperitoneal kolşisin (80 mcg/kg/gün) verildi. Diğer 4 grup, kontrol grupları ve sham grupları olarak oluşturuldu. Kolon mukozasında superoksit dismutaz (SOD), miyeloperoksidaz (MPO) ve lipid peroksidasyon ürünlerinin (MDA ve FOX) ölçümleri yapıldı.

Bulgular: Makroskopik ve mikroskopik kolit skorları AA'le kolit oluşturulmuş gruplarda sham gruplarından anlamlı derecede yüksek bulundu (p<0.0001). Ancak oral ve intraperitoneal tedavi grupları ve onların kontrol gruplarının skorları arasında fark saptanmadı. Oral kolşisin tedavisiyle SOD (p<0.0001) ve MPO (p=0.001) düzeylerinde azalma, FOX (p=0.013) seviyelerinde artış saptandı.

Sonuç: Kolşisin ÜK'te inflamasyonun tedavisi için faydalı olabilir. Ancak çalışmamızda kolşisinin antioksidan sisteme koruyucu ve lipid peroksidasyonu önleyici etkisi bulunmamıştır.

Anahtar kelimeler: Kolşisin, ülseratif kolit, deneysel model

Çıkar Çatışması: Yazarlar çıkar çatışması bulunmadığını beyan eder.

Introduction

Chronic and recurrent ulcerative colitis (UC) and Crohn disease are studied under the common inflammatory bowel diseases (IBD) heading. Their etiologies have not been completely understood but environmental factors and genetic predisposition are thought to have important contributions. UC is a chronic mucosal inflammatory disease with neutrophil infiltration affecting the colon and progress from distal to proximal. Medical approach in IBD is towards controlling symptoms and decreasing the underlying inflammation however about half of patients with fulminant ulcerative colitis who are admitted to the hospital have the history of failure of conventional medical therapy [1]. Disease's treatment mainly remains unspecific and primarily directed towards to the relief of symptoms. Depending on all these reasons new therapeutic approaches are needed. Recently researchs have concentrated on drugs targeted at understanding pathophysiology of inflammatory diseases since despite developments in medical treatment, limited progress have been achieved in the treatment of medium to severe ulcerative colitis patients.

Colchicine is an alkaloid, which has been known as the most used drug in the prophylaxis of familial Mediterranean fever (FMF) [2]. It can reduce inflammation and relieve attacks. It was suggested that colchicines inhibited proliferation of fibroblast [3] and some leukocyte functions such as adhesiveness, motility and chemotaxis [4-7]. In addition to those, it is believed that colchicine's effects are attributed to interaction with microtubules [8]. All of these effects may led to new research areas about its indications.

Some recent studies have shown the increased frequency of mutations of MEFV in patients with UC [9] and this gene encodes for pyrin, which has been implicated in the regulation of neutrophil activity [10]. This togetherness may be a predisposition to aggressive inflammatory response. Recently, it was claimed that colchicine may help to control the inflammatory activity in some patients with both UC and FMF [11]. However, it is not known that colchicine which is used as an anti-inflammatory and antioxidant agent, may also be effective in UC. The aim of the present study was to determine the possible effects of colchicine on experimental acetic acid (AA)-induced colitis in rats.

Materials and Methods

Rats

Fifty three male Wistar-albino rats each weighting 225 ± 25 grams were obtained from Gazi University Faculty of Medicine Laboratory Animal Breeding and Experimental Research Laboratory (Ankara, Turkey). The animals were housed in special cages in a room with 12-hour light/ 12 hour dark cycle with air-conditioning at a controlled temperature between 20- 22°C. They were allowed free access to tap water and standard rat pellet diet. The study protocol was approved by the animal research ethics committee of Gazi University Faculty of Medicine. All experiment was performed according to the rules of the Guide for the Care and Use of Laboratory Animals.

Study design

Oral treatment groups formed as follows: A1 group (n=10) had AA-induced colitis and oral colchicine therapy, 80mcg/kg/day by intragastric gavage, for three days before and two days after colitis model. A2 group (n=8) had AA-induced colitis and oral isotonic saline solution by intragastric gavage for three days before and two days after colitis model. A3 group (n=9) received oral isotonic saline solution by intragastric gavage for five days and rectal isotonic saline solution on third day.

Intraperitoneal treatment groups formed as follows: B1 group (n=10) had AA-induced colitis and intraperitoneal colchicine therapy, 80mcg/kg/day, for three days before and two days after colitis model. B2 group (n=8) had AA-induced colitis and intraperitoneal isotonic saline solution for three days before and two days after colitis model. B3 group (n=8) received intraperitoneal isotonic saline solution for five days and rectal isotonic saline solution on third day. Rats were sacrificed on fifth day.

Experimental colitis model

After slight intraperitoneal anesthesia, a 5-F soft polyurethane cannule was placed through the lumen of colon into the anus and 1ml of 4% acetic acid was carefully instilled. After this procedure, rats were maintained in a head-down position for a minute to prevent leakage of the colonic installation. Blood samples were obtained just prior to sacrification of the rats. The distal 8 cm of the colon was excised, opened longitudinally and quickly observed for the macroscopically evident damage. The most distal segment was fixed in 10 % formalin solution, embedded in paraffin and 4-µm sections were prepared. The remaining materials were placed into liquid nitrogen and kept in - 80°C until future analysis.

Assessment of gross macroscopic and microscopic damages

Macroscopic examination was assessed by using the grading scale of Morris et al. as follows: (score 0) no damage; (score 1) localized hyperemia with no ulcers; (score 2) linear ulcers with no significant inflammation; (score 3) linear ulcer with inflammation at one site; (score 4) more sites of ulceration and inflammation, the size of ulcers < 1cm; (score 5) multiple inflammations and ulcers, the size of ulcers 1cm [12]. Colonic tissue sections were fixed in formaldehyde and embedded in paraffin. Hematoxylin-eosin staining was performed according to the standard procedure. Histological examination was evaluated by a pathologist according to the described criteria [13].

Biochemical analysis

Superoxide Dismutase (SOD) Enzyme Assay

SOD activity was determined by spectrophotometric assay to measure the antioxidant activity by using a very simple, convenient and sensitive SOD assay based on the method by Yi Sun et al [14]. According to the assay, superoxide dismutase activity was inhibited by nitroblue tetrazolium reduction, with xanthine-xanthine oxidase used as a superoxide generator and one IU was defined as the quantity of SOD required to produce 50 % inhibition. Protein concentrations were determined by the method of Lowry et al [15].

Myeloperoxidase (MPO) Activity

The MPO activity assay was used to quantitate polymorphonuclear neutrophils accumulation in the colon tissue. The first step, tissue preparation was determined by the method of Grishan et al. with minor modifications and the supernatants were used for MPO assay [16]. MPO activity was assessed by measuring the H_2O_2-dependent oxidation of homogenate with the reduction of o-dianisidin and the absorption of reduced o-dianisidin was determined. One unit of enzyme activity was defined as the amount of MPO present that caused a change in absorbance of 1.0/min at 410 nm and 37ºC. Results expressed as U/g tissue [17].

Malondialdehyde (MDA) assay

Tissue MDA levels were determined by using TBARS assay which is a major aldehyde species for lipid peroxidation. Difference in absorbance of the two measurements from the butanol phase was used as the MDA value (nmol/g tissue) [18].

Lipid Peroxidation (FOX) Assay

Assay is intended for the quantitative determination of the low levels of lipid hydroperoxide in the samples. It is based on the oxidation of ferrous ions (Fe^{2+}) to ferric ions (Fe^{3+}) by hydrogen peroxide under acidic conditions. The ferric ion binds with the indicator dye xylenol orange to form a stable colored complex which can be measured at 560 nm as an indirect measure of hydroperoxide concentration. HP Equivalents (HPE/g wet weight) were calculated according to Hermes-Lima et al [19].

Statistical Analysis

Variables were expressed as median and IQR. Differences in non parametric values were tested with Mann Whitney-U tests. The differences were considered to be statistically significant according to the Bonferroni correction when p value < 0.017. Spearman's correlation coefficient was analyzed to the correlation of the markers of oxidative and anti-oxidative stress in groups. Correlation coefficients were considered significant at a level of $p < 0.05$.

Results

In our two AA-induced colitis control groups, intrarectal administration of 4% AA-induced extensive macroscopic damage to the colon and developed acute colitis. The macroscopic and microscopic colitis scores were found to be significantly increased in AA colitis control groups compared to the sham groups ($p < 0.0001$). However, there were no statistically significant differences between oral or intraperitoneal treated groups and between oral or intraperitoneal treated groups and their AA colitis control groups for those scores.

In oral treatment groups, the colonic SOD activity was decreased; MPO, MDA and FOX levels were increased by administration of AA compared to sham group. In intraperitoneal treatment groups, the colonic SOD activities were decreased; MPO and MDA levels were increased by administration of AA compared to sham group. Only the differences of SOD values in oral and intraperitoneal groups were significant (p=0.001). The median values of SOD for AA colitis control group and sham group in oral treatment groups were found 12.94 U/mg protein (IQR 12.01 to 15.75) and 22.31 U/mg protein (IQR 18.92 to 24.65), respectively. These values in intraperitoneal treatment groups were found 15.44 U/mg protein (IQR 12.31 to 20.97), and 30.75 U/mg protein (IQR 24.94 to 35.53), respectively. The results were presented in Figures 1-4.

The colonic SOD and MPO levels were decreased; MDA and FOX levels were increased in oral treatment group compared to its AA colitis control group. The median values of SOD for colchicine group and AA colitis control group in oral treatment groups were found 7.82 U/mg protein (IQR 6.64 to 8.14) and 12.94 U/mg protein (IQR 12.01 to 15.75); the values of MPO were found 0.21 U/g tissue (IQR 0.12 to 0.29) and 0.57 U/g tissue (IQR 0.37 to 0.71); the levels of FOX were found 2084.3 HPE/g wet tissue (IQR 1888.5 to 3107.5) and 1432.6 HPE/g wet tissue (IQR 1203.9 to 1714.6), respectively. Oral colchicine therapy was associated with decreased SOD ($p < 0.0001$) and MPO (p=0.001), but significantly increased FOX (p=0.013) levels. The colonic SOD, MPO, MDA, and FOX levels increased in intraperitoneal treatment group compared to its AA colitis control group. However, statistically significant results were not found.

Discussion:

In this study, we aimed to evaluate the possible effects of colchicine against AA-induced colitis in rats. Colchicine is an anti-inflammatory and antioxidant agent, known to be beneficial to control the inflammation in the treatment of UC [10-11]. However, in our study, there was not any protective effect on antioxidant activity neither inhibition on lipid peroxidation end products were observed.

In our study colchicine therapy was begun before 72 hours and continued for 48 hours of AA administration.

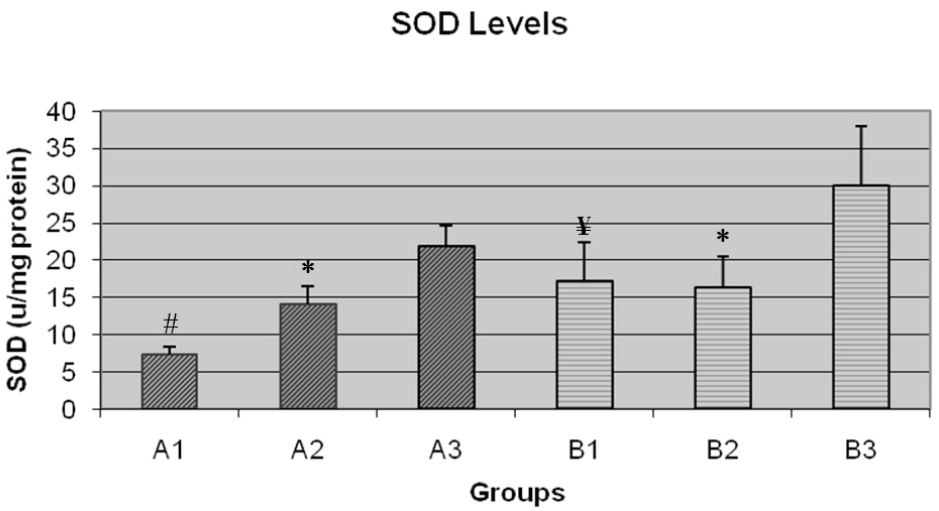

Figure 1. Effects of colchicine on colonic superoxide dismutase (SOD) activity in oral and intraperitoneal therapy groups. #, oral colchicine treated group significantly different from control and sham groups ($p<0.0001$); ∗, both of acetic acid (AA)-induced colitis control groups significantly different from sham groups ($p=0.001$); ¥, intraperitoneal colchicine treated group significantly different from sham group ($p=0.001$); A1=AA-induced colitis+oral colchicine; B1=AA-induced colitis+intraperitoneal colchicine; A2, B2=AA-induced colitis; A3,B3=Sham groups

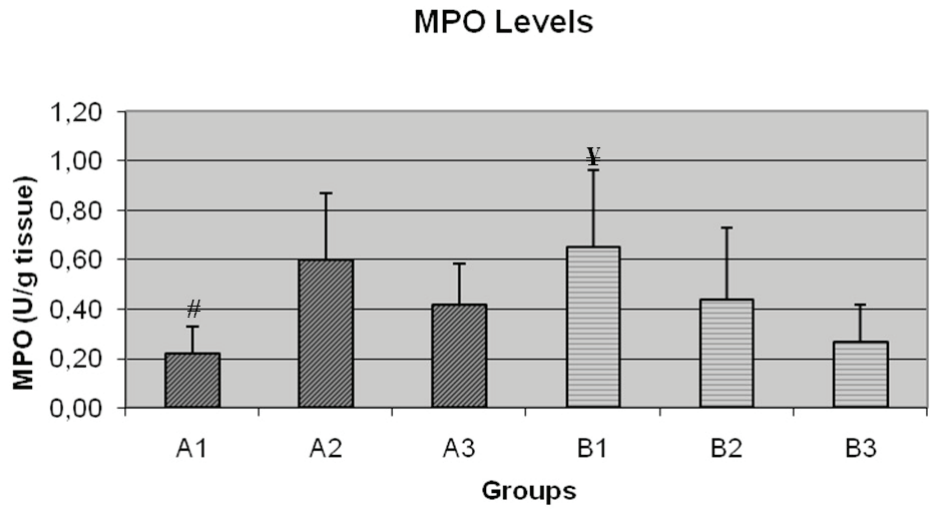

Figure 2. Effects of colchicine on colonic myeloperoxidase (MPO) activity in oral and intraperitoneal therapy groups. #, oral colchicine treated group significantly different from control ($p=0.001$) and sham ($p=0.010$) groups; ¥, intraperitoneal colchicine treated group significantly different from sham group ($p=0.009$); A1=Acetic acid(AA)-induced colitis+oral colchicine; B1=AA-induced colitis+intraperitoneal colchicine; A2, B2=AA-induced colitis; A3,B3=Sham groups

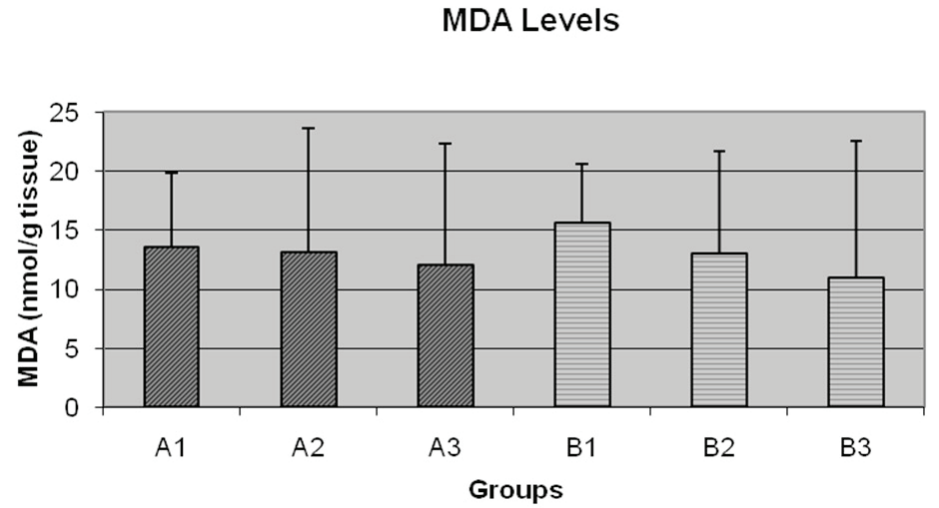

Figure 3. Effects of colchicine on colonic malondialdehyde (MDA) levels in oral and intraperitoneal therapy groups; A1=Acetic acid(AA)-induced colitis+oral colchicine; B1=AA-induced colitis+intraperitoneal colchicine; A2, B2=AA-induced colitis; A3,B3=Sham groups

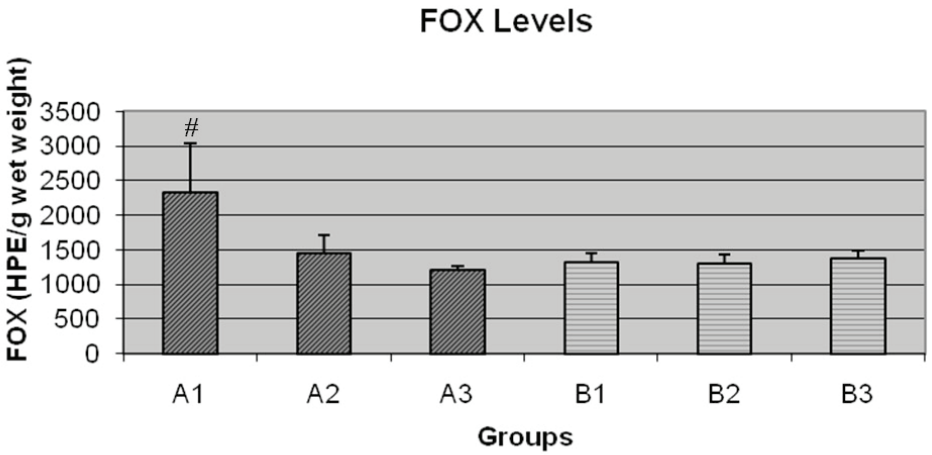

Figure 4. Effects of colchicine on colonic lipid peroxidation assay (FOX) levels in oral and intraperitoneal therapy groups. #, oral colchicine treated group significantly different from control ($p=0.013$) and sham ($p<0.0001$) groups; A1=Acetic acid(AA)-induced colitis+oral colchicine; B1=AA-induced colitis+intraperitoneal colchicine; A2, B2=AA-induced colitis; A3,B3=Sham groups.

It was known that twenty four to forty eight hours were required to develop the inhibition of chemotaxis [20] or adhesion [21] on leukocyte for colchicine effects. We also performed intraperitoneal colchicine therapy group in order to eliminate and observed the various absorption differ from 24-88% after oral ingestion [22] and gastrointestinal side effects [23] and toxicity. However colchicine can enter all tissues, it is lipophilic and quickly absorbed in the jejenum and ileum. Peak in plasma levels is obtained about two hours after oral administration [24, 25]. In our study oral or intraperitoneal colchicine therapy did not provide any marked improvement on macroscopic and microscopic scores.

Similar to other studies, induction of colitis by AA is frequently used as an experimental model of UC [26, 27]. The observed significant macroscopic and microscopic colonic damage in AA colitis groups implied that the experimental model was done effectively. The colonic MPO activity was decreased and FOX levels significantly increased with oral colchicine therapy compared to both AA-induced colitis and sham groups. There were no statistical significant differences observed between the intraperitoneal colchicine therapy group and its controls. However, decreased MPO activity in oral treatment group may be an important finding as the marker of neutrophilic infiltration that colchicine therapy may effect as a systemic anti-inflammatory agent. The anti-inflammatory effects are the decreased IL-1 activation, TNF-alfa and leukotriene levels and decreased inflammasome activation which is known as an inhibition of key inflammatory signaling networks [28]. Sari et al. reported that familial Mediterranean fever mutations were detected highly in resistant pediatric UC cases and colchicine therapy may be beneficial in these patients [11]. Our finding can also support that colchicine may help to control the inflammatory activity in UC patients characterized by neutrophils infiltration. Hovewer, colchicine's antioxidant effect was not found in our study.

Excessive production of oxidants has been well described in the plasma, colonic mucosa and peripheral blood leukocytes of IBD patients [29, 30]. In addition, the oxidant activity was found to be correlated with IBD activity [29] and Ozyilmaz et al. suggested that the oxidants produced in the bowel in IBD could migrate to other sites of the body [31]. In our study, SOD activities were decreased in oral colchicines treatment and its colitis group compared to sham group. Besides, SOD activities decreased; MPO activity and MDA levels increased in AA-induced colitis and intraperitoneal therapy groups compared to sham group. However, only the change of SOD activity was significant in two groups. In different studies, AA-induced colitis was increased the MPO activity [26, 27, 32-34] and MDA levels [26, 27, 32-34] and could decrease SOD activity [26, 27, 32, 34]. The levels of colonic MPO and MDA, indicating infiltration of neutrophils, are decreased by lithium, ginger extract, and sulfasalazine in AA-induced colitis in rats [32]. Ran et al. described an induction of colonic SOD activity and a reduction of MDA in AA-induced colitis by Epigallocatechin-3-gallate [35].

Supporting to our results Menekşe et al [36] observed increase lipid peroxidation products as MDA levels in colitis and 3-aminobenzamide (poly [ADP-ribose] polymerase, PARP inhibitor) treated groups. We used 80mcg/kg/day colchicine, near minimal toxic dose, on experimental colitis model. Depending on our findings, it was claimed that prolonged therapy times and reduced doses of colchicine may decrease MDA levels on experimental colitis model. The poor changes of SOD activity and FOX levels may also related to colchicines

dose. However statistically significant changes were not found with intraperitoneal therapy. The reason why we did not observed that effect could also be related with the dose and the duration of the treatment of colchine without absorption variety in this group. Disel et al. declareted that 30mcg/kg/day of colchicine (four week) on the cyclosporine nephrotoxicity decreases MDA levels [37]. Mourelle et al. found that colchicine 10 micrograms/rat/day for 7 days prevents partially and 50 micrograms/rat/day for 7 days prevents almost completely the liver damage induced by galactosamine and claimed that colchicine inhibits lipoperoxidation [38]. Colchicine (10 micrograms/day/rat, for 7 days) also completely prevents the lipid peroxidation induced by CCl4 [39]. In 2009, the FDA approved colchicine for the treatment of gout and FMF. It is a powerful spindle poison and could exert anti-inflammatory effects. Whenever has been used at low doses, it can be found in white blood cells interfering with many functions as migration and degranulation, blocking tubulin polymerization, microtubule generation and stability [28].

In conclusion, this study appears to be the first in the literature showing the effect of colchicine on experimental colitis. Our results show that colchicine administration may only exert beneficial effects on experimental colitis model by decreasing MPO activity.

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Conflict of Interest: The authors declare that there was no conflict of interest in this work.

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