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Experimental Research Article

Protective effects of *Pistacia Atlantica* leaves hydroalcoholic extract against acetic acid-induced colitis damage in rats

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ABSTRACT

Introduction: Ulcerative colitis (UC) is an inflammatory bowel disease (IBD), in which the role of pro-inflammatory cytokines and oxidative stress in its underlying pathogenesis has come into focus. *Pistacia Atlantica (P. atlantica)* is used in traditional Persian medicine for the management of gastrointestinal disorders. Hence, the present study aimed to investigate the protective effects of hydroalcoholic extract of *P. atlantica* leaves on acetic acid-induced UC in a rat model.

Methods: Male Sprague-Dawley rats were assigned to six groups: normal, colitis by transrectal administration of 4% acetic acid, colitis + sulfasalazine (sulfa, 500 mg/kg/day, intraperitoneally (i.p.)), and colitis + *P. atlantica* leaves hydroalcoholic extract (at 50, 100, 200 mg/kg/day doses). *P. atlantica* was administered via oral gavage for 3 consecutive days. After 7 days, colons were resected for macroscopic damage score and histopathological assessment. Furthermore, antioxidant status and inflammatory markers were measured in the serum.

Results: Macroscopic and histopathological analysis of the mucosa showed that *P. atlantica* significantly alleviated colonic damage in a concentration-dependent manner ($P<0.001$ to $P< 0.01$). Importantly, in the group treated with *P. atlantica*, there was a significant reduction in serum nitric oxide (NO) levels ($P<0.001$), along with restoration of antioxidant systems, as indicated by increased superoxide dismutase (SOD) activity and glutathione (GSH) levels, compared to the colitis rats ($P<0.001$).

Conclusion: These findings indicate the therapeutic potential of *P. atlantica* leaves in alleviating the severity of colitis in rats by suppressing inflammation and oxidative states in the serum, which could be used as an appropriate drug for the management of UC.

Keywords:
Inflammation
Oxidative stress
Pistacia atlantica
Ulcerative colitis
Rat

Introduction

Ulcerative colitis (UC) is a type of immune-mediated chronic intestinal disease that poses a significant burden on the healthcare system. It is a disabling and idiopathic

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condition characterized by chronic diarrhea, unintentional weight loss, rectal bleeding, abdominal pain, and ulceration in the rectal and colonic mucosa (Marinelli et al., 2019; Ostovan et al., 2020; Shih and Targan 2008). Although UC was once regarded as a Western disease, it is now increasing in developed countries due to modern lifestyle (Kaplan and Windsor 2021; Ng et al., 2013). For now, its etiology remains elusive; however, it is most likely associated with the complex interplay among genetic, environmental factors, and immune disturbances, which results in overproduction of reactive oxygen and nitrogen species (ROS/RNS) (Bourgonje et al., 2020), modulation of signaling pathways such as nuclear factor-kappa B (NF-kB) (Raish et al., 2021), nuclear factor erythroid 2–related factor 2 (Nrf2) (Alsharif et al., 2022), and apoptosis (Raish et al., 2021). These factors contribute to lipid peroxidation, reduction of antioxidant capacity (Wang et al., 2016), and impaired mucosal barrier function (Xie et al., 2022).

Oxidative stress is one of the most significant phenotypes in the initiation and progression of colitis (Balmus et al., 2016). Corresponding studies have found a correlation between oxidative stress and the upregulation of inflammatory response-related genes in inflamed mucosa (Tian et al., 2017). Moreover, it is a major cause of colorectal cancer in colitis patients (Tian et al., 2017; Wang et al., 2016). Accordingly, glucocorticoids, immunosuppressive antibiotics, probiotics, anti-TNF-α antibodies, etc., which interfere with inflammatory processes and oxidative stress, have been used as routine drugs for UC treatment (Bressler and Sands 2006). However, these therapeutic options have undesirable side effects (Danese 2012). Therefore, there is a rising trend in the world to use natural antioxidants and anti-inflammatory against the development of UC.

Pistacia Atlantica (Atlas pistachio) is a polyphenol belonging to the Anacardiaceae family, that comprises 15 different species and is native to parts of North Africa, Middle East, and Asia (Ahmed et al., 2021). Several studies showed that *P. atlantica* contains bioactive components including carotenes, tocopherols, alcohols, and phenols (Benhammou et al., 2008). *P. atlantica*, also known as "Baneh" in Iran, is widely consumed in a variety of industries, traditional Persian medicine, and as food by the local populations. Pharmacological investigation on different parts of *P. atlantica* claims anti-oxidant, gastro-protective, anti-inflammatory, neuroprotective, and antinociceptive activities (Amri et al., 2018; Heidarian et al., 2017). Treatment of cardiovascular diseases (anti-atherosclerosis), dermatitis, diabetes, and hyperlipidemia are other well-known properties of *P. atlantica* (Bagheri et al., 2019; Tolooei and Mirzaei 2015). Interestingly, it has been reported to have anti-cancer and anti-apoptotic effects (Dousti et al., 2022). Given the lack of data regarding the protective role of leaves of *P. atlantica* on UC damage, the present experiment evaluated the both anti-oxidant and anti-inflammatory effects of hydroalcoholic extract of *P. atlantica* leaves against an acetic acid-induced rat colitis model.

Materials and methods

Preparation of hydroalcoholic extract of P. atlantica leaves

Leaves of *P. atlantica*, which were the focus of this study, were collected in July 2022 from the mountain Kermanshah province, in Iran's west, and verified by the Herbarium Committee of Kermanshah University of Medical Sciences, with voucher specimen (No. PMP-818). To prepare hydroalcoholic extract, plant leaf parts were shade-dried and powdered by electric mills. About 100 g of powder was immersed in a solution of ethanol-water (80: 20 (v/v), filtered, and condensed under vacuum and maintained at 4°C.

Animals

In total, 30 male Sprague-Dawley rats (180-220 g), aged 8-10 weeks were selected in the present experiments. The animals were obtained from the animal house of Faculty of Pharmacy, Lorestan University of Medical Sciences, Iran. Rats were group-housed (2 rats per cage) under controlled conditions with a 12-hour light/dark schedule (lights on at 7:00 a.m.), temperature (22 ± 3 °C), and ad libitum access to standard diet and tap water. Animals were adapted to the test environment for one week (Ahmed et al., 2022) All experiments were done according to previously delivered guidelines (National Institutes of Health Publication, NO. 82–23, revised 1996) and approved by the Ardabil University of Medical Sciences Ethics Committee (Code: IR.ARUMS.AEC.1400.024).

Colitis model

Colitis was induced according to the method of Fakhraei et al. (2014) (Fakhraei et al., 2014). Briefly, the

TABLE 1: Criteria for scoring microscopic colonic damage.

Inflammation				Depth of lesion					Fibrosis		
Non	Mild	Medium	Severe	Non	Laminapropria	Submucose	Muscular	Serosa	Non	Mild	Severe
–	+	++	+++	–	+	++	+++	++++	–	+	++

overnight fasted rats were lightly anesthetized by an intraperitoneal (i.p.) injection of mixed ketamine/xylazine (70/6 mg/kg) (Struck et al., 2011) Afterward, 1 mL of 4% acetic acid (Sigma-Alrich) dissolved in 0.9% NaCl was administered intra-rectum with a rubber catheter (8-cm length), while the rats were maintained in a head-down position to prevent acetic acid leakage. To monitor the effects of the procedure, the animals were checked daily for body weight, diarrhea, anorectal bleeding, and mortality.

Experimental procedure

Animals were randomly allocated into six groups (5 rats/group) including: Normal group: healthy rats received 1 mL of distilled water (DW) through gavage for three consecutive days; colitis group: colitis rats received 1 mL of distilled water through gavage for three consecutive days; Sulfasalazine (sulfa) group: colitis rats received sulfasalazine (Sigma-Alrich) as a reference drug (500 mg/kg, i.p; intraperitoneally) (Naseri et al., 2022). The remaining three groups were *P. atlantica*-treated groups, which received oral gavage injections of *P. atlantica* leaves hydroalcoholic extract at doses of 50, 100, and 200 mg/kg for three consecutive days after induction of colitis.

The doses of *P. atlantica* leaf extract and intervention duration were chosen based on previous research (Naseri et al., 2022). After the treatment period, fasted rats were anesthetized with ketamine/xylazine (Sigma, 100/10 mg/kg, i.p. respectively), blood samples were taken from the tail vein, collected in Eppendorf tubes, and centrifuged at 664 ×g for 10 min at 4°C. Serums were preserved at -70°C to measure glutathione (GSH), nitrite oxide (NO) levels, and superoxide dismutase (SOD) activity. Finally, rats were sacrificed, and colon tissue was excised and post-fixed in buffered formalin (10%) for histopathological analysis.

Measurement of body weight change

The rats' body weight was recorded at baseline on day 1 and at the end of the study on day 7, using a weighing scale.

Biochemical assays

To monitor the effect of *P. atlantica* leaves extract on serum NO, GSH levels, and SOD activity in a UC rat model, ELISA kits for NO (Kiazist, Iran) and commercial colorimetric kits for GSH and SOD (Kiazist, Iran) were used according to the manufacturer's recommendations.

Evaluation of colon macroscopic damage

At the end of the experiments, animals were euthanized under ketamine and xylazine anesthesia (Sigma, 100/10 mg/kg, i.p. respectively) then 7 cm of the distal colon was dissected and based on the extent of the ulcer, inflammation, and hyperemia were scored by Morris's scoring system (Morris et al., 1989). No damage: (score = 0), Localized hyperemia, no ulcers: (score = 1), Ulceration with absence of inflammation: (score = 2), Ulceration with inflammation at 1 site: (score = 3), Two or more sites of ulceration and/or inflammation: (score = 4), Two or more sites of ulcer and inflammation extending over 1 cm along the length of the colon: (score = 5).

Histopathological evaluations

For histopathological evaluation, appropriate tissue samples were removed from the colon and immediately fixed with formalin-10%, embedded in paraffin wax, cut into 5-µm sections, and stained with hematoxylin-eosin (Merck, Germany) for light microscopic examination. Scoring of lesions was performed using a modified Wallace method, as described in Table 1 (Wallace et al., 1992).

Data analysis

Data were analyzed by Graph Pad Prism software (version 8). Two-way repeated measures ANOVA detected differences in body weight between groups. For other parameters, one-way ANOVA was used to evalu-

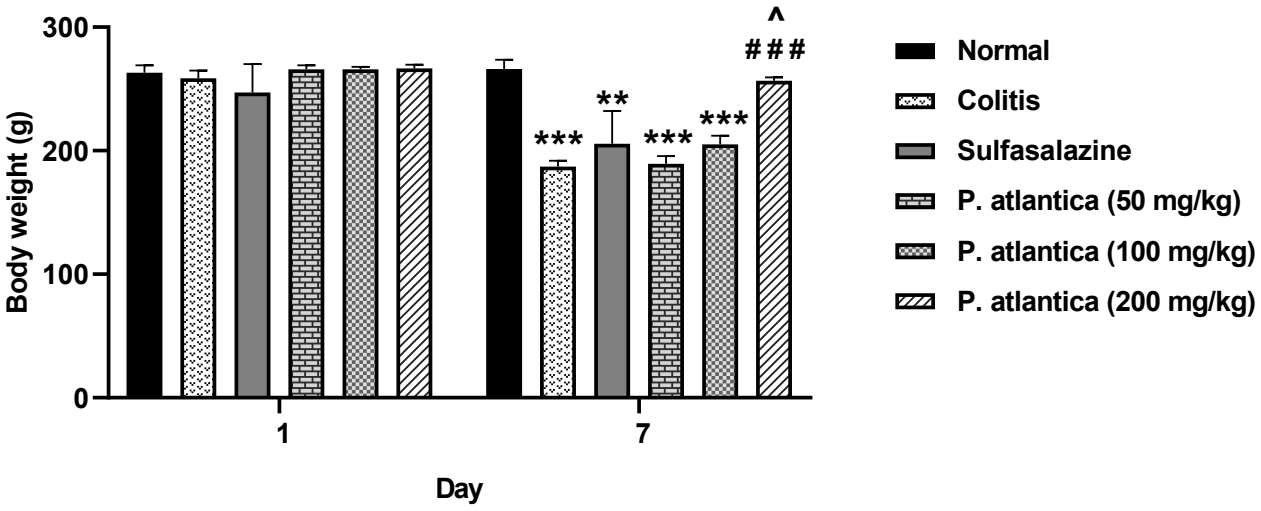

FIGURE 1. Effects of *P. atlantica* leaves hydroalcoholic extract on body weight changes of acetic acid-induced colitis rats. Results are expressed as mean ± S.E.M and were analyzed by two-way repeated measures ANOVA followed by Tukey's post hoc test (n = 5). **p<0.01, ***p<0.001 versus Normal group, ###p<0.001 versus Colitis group, and ^p< 0.05 versus Sulfa group.
P. atlantica: Pistacia Atlantica.

ate differences between groups with Tukey's post-hoc analysis. Results are expressed as mean+ standard error of the mean (SEM), and P values less than 0.05 were considered significant.

Results

Effect of hydroalcoholic extract of P. atlantica leaves on body weight changes in the UC rats

As shown in Figure 1, the body weight of animals did not differ significantly among the groups at the start of the study (day 1). Whereas the colitis group had significantly lower body weight compared to the normal group at the end of the study (day 7) (p<0.001 to p<0.01, Figure 1). In general, three days of *P. atlantica* treatment led to a significant increase in animal body weight compared with the colitis group, and these increases were significant at the dose of 200 mg/kg (p<0.001). Moreover, there were significant differences in this parameter between the *P. atlantica* (200 mg/kg) and sulfa groups (p<0.05, Figure 1).

Effect of hydroalcoholic extract of P. atlantica leaves on serum GSH levels and SOD activity in the UC rats

As expected, in the colitis rats, serum GSH levels were significantly lower as compared to the normal group (p<0.001, Figure 2A). Whereas, the sulfa group and *P. atlantica*-treated groups displayed a significant increase in serum level of GSH in colitis rats (p<0.001). There was a significant increase in serum GSH levels in the *P. atlantica* at 100 and 200 mg/kg compared with the sulfa group (p<0.001, Figure 2A).

Serum SOD activity in colitis rats was significantly declined as compared to the normal group (p<0.001 to p<0.05). While treatment with *P. atlantica* in 50, 100, and 200 mg/kg doses and also sulfa caused a significant increment in serum activity of SOD in colitis rats (p< 0.001). Besides, a significant increase was observed by comparing the *P. atlantica* (50, 100, and 200 mg/kg) groups and the sulfa group (p<0.001, Figure 2B).

Effect of hydroalcoholic extract of P. atlantica leaves on serum NO levels in the UC rats

The inflammatory status of rats with ulcerative colitis led to an increase in serum NO level compared with the normal group (p<0.001). When all of the treated groups, including *P. atlantica* (50, 100, and 200 mg/kg) and sulfa, were compared with the colitis group, a noticeable decrease was realized in the results (p<0.001). Furthermore, the serum levels of NO in the *P. atlantica* 50 mg/kg (p<0.001) and 100 mg/kg (p<0.05) groups were significantly different from the sulfa group (Figure 3).

Effect of hydroalcoholic extract of P. atlantica leaves on colonic macroscopic scores in the UC rats

According to Fig.4, administration of acetic acid to the rat exhibited considerable tissue damage with signs of ulcers and colon inflammation (p<0.001)(Figure 4). The lowest score among the therapeutic group belonged

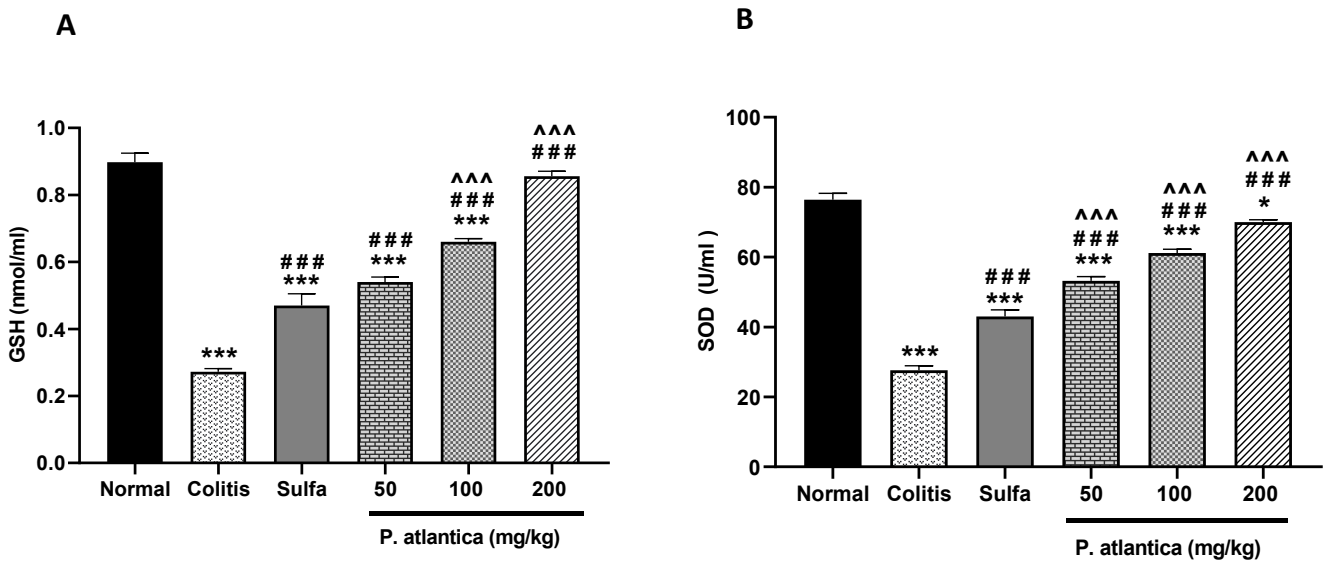

FIGURE 2. Effects of *P. atlantica* leaves hydroalcoholic extract on GSH (A) levels, and SOD (B) activity in the serum of acetic acid-induced colitis rats. Results are expressed as mean ± S.E.M and were analyzed by one-way ANOVA followed by Tukey's post hoc test (n = 5). *p<0.05, ***p<0.001 versus Normal group, ###p<0.001 versus Colitis group, and ^^^p< 0.001 versus Sulfa group. *P. atlantica: Pistacia Atlantica*; Sulfa: sulfasalazine.

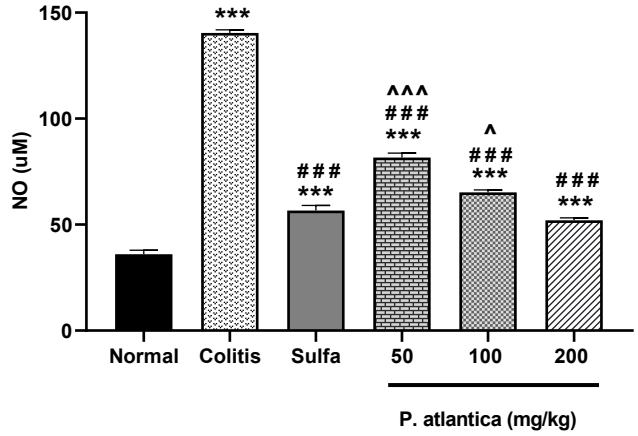

FIGURE 3. Effects of *P. atlantica* leaves hydroalcoholic extract on NO levels in the serum of acetic acid-induced colitis rats. Results are expressed as mean ± S.E.M and were analyzed by one-way ANOVA followed by Tukey's post hoc test (n = 5). ***p<0.001 versus Normal group, ###p<0.001 versus Colitis group, ^p< 0.05, ^^^p< 0.001 versus Sulfa group.
P. atlantica: Pistacia Atlantica; Sulfa: Sulfasalazine.

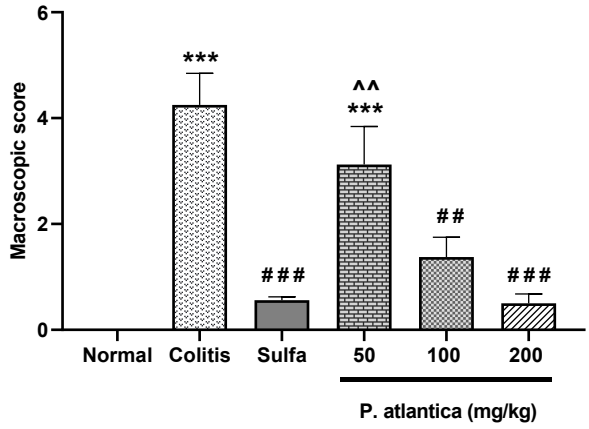

FIGURE 4. Effects of *P. atlantica* leaves hydroalcoholic extract on macroscopic damage of the colon tissue in acetic acid-induced colitis rats. Results are mean ± S.E.M (n=4). Data were analyzed using one-way ANOVA followed by Tukey's post hoc test. ***p<0.001 versus Normal group, ##p<0.01, ###p<0.001 versus Colitis group, and ^^p< 0.01 versus Sulfa group.
P. atlantica: Pistacia Atlantica; Sulfa: sulfasalazine.

to *P. atlantica* 200 mg/kg (p<0.001), followed by *P. atlantica* 100 mg/kg (p<0.01), compared to the colitis group (Figure 4). As well as this score was markedly attenuated in sulfa-treated rats compared to the colitis group (p<0.001).

Effect of hydroalcoholic extract of P. atlantica leaves on the histopathological changes in the UC rats

Microscopic examination of the colon sections in the control group displayed normal architecture (Figure 5A), however, this organ in the colitis groups showed mild, moderate, and severe tissue changes. The group treated only with acetic acid exhibited extensive ulcerative areas in the mucosa extending through the muscularis mucosa, severe mucosal necrosis, and crypt disarray with goblet cell depletion, marked interstitial edema, severe hemorrhages and inflammatory cells infiltration in the serosa, muscularis, submucosa, and mucosa lay-

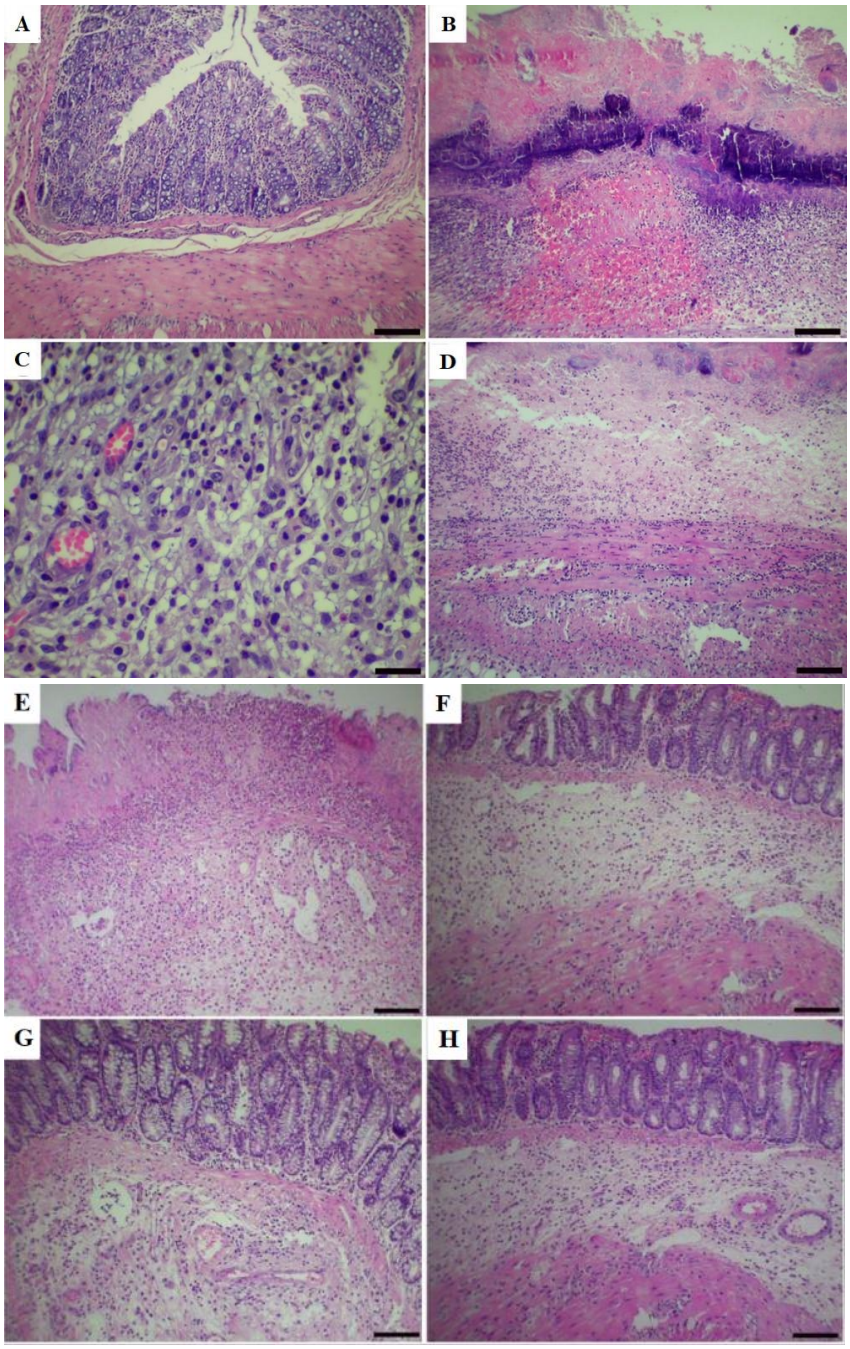

FIGURE 5. Histopathological lesion in the colon tissue of normal and acetic acid groups (H&E staining). A) Normal group, normal architecture of colon tissue (Scale bar=150 µm); B) Colitis group, focal ulceration, severe necrosis, and crypt destruction in the mucosal layer (Scale bar=150 µm); C) Colitis group, severe infiltration of mono- and polymorphonuclear cells in the submucosal layer (Scale bar=70 µm); D) Necrosis of muscle tissue and infiltration of inflammatory cells in the muscularis layer with severe edema in the submucosal and muscularis layers (Scale bar=150 µm). E) *P. atlantica* (50 mg/kg) group, focal ulceration and severe necrosis in the mucosal layer, moderate inflammatory cells infiltration, and moderate edema and hemorrhages in the mucosa, submucosa, and muscularis layers; F) *P. atlantica* (100 mg/kg) group, moderate necrosis in the mucosal layer, mild to moderate inflammatory cells infiltration, edema and hemorrhages in the mucosa, submucosa and muscularis layers; G) *P. atlantica* (200 mg/kg) group, mild crypt destruction and necrosis with mild inflammation in the mucosal layer; H) Sulfasalazine group, mild crypt destruction with minimal mucosal inflammation.

ers. In this group, the depth of lesions was observed to serous layer, but there was no evidence of fibrosis (Figure 5B-D).

Treatment with sulfa and *P. atlantica* significantly reduced the histopathological scores of colonic lesions compared with the colitis group, particularly the depth of lesions and inflammation (Table 2). The colon of rats treated with *P. atlantica* at concentrations of 50 and 100

TABLE 2: Results of pathological evaluation using the modified Wallace method in different groups

	Inflammation				Depth of lesion					Fibrosis		
	Non	Mild	Medium	Severe	Non	Laminapropria	Submucose	Muscular	Serosa	Non	Mild	Severe
Normal group	-				-					-		
Colitis group				+++					++++	-		
sulfasalazine		+					++			-		
P. atlantica (50 mg/kg)			++					+++		-		
P. atlantica (100 mg/kg)			++					+++		-		
P. atlantica (200 mg/kg)		+					++					

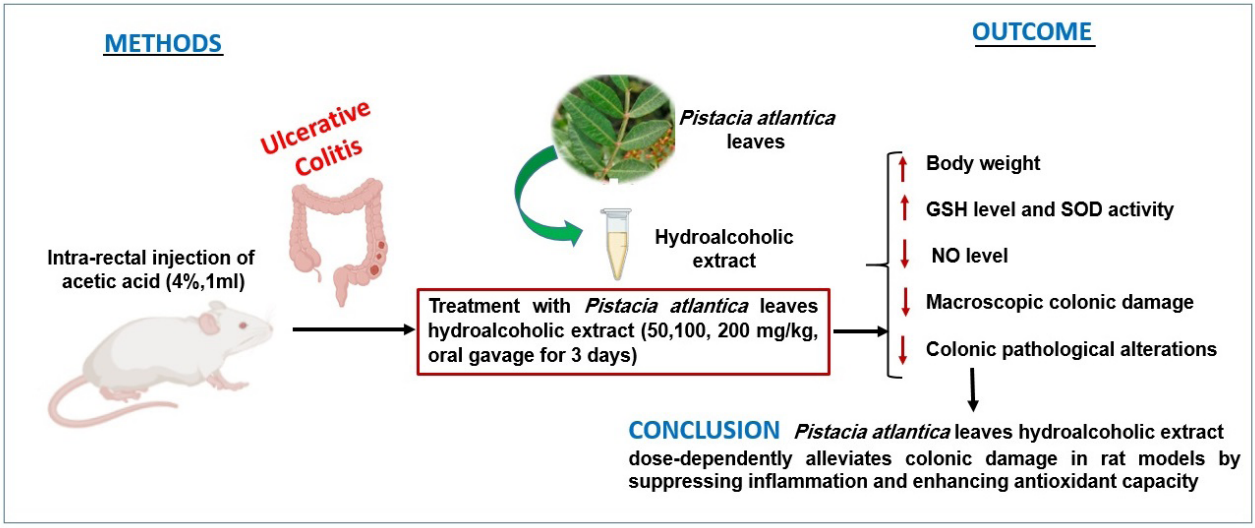

FIGURE 6. Summary of conclusion

mg/kg showed moderate to severe focal ulceration and necrosis accompanied by moderate inflammatory cells infiltration and mild to moderate edema and hemorrhages in the mucosa, submucosa, and muscularis layer. Histological features observed in sulfasalazine and *P. atlantica* at doses of 200 mg/kg groups were similar to those observed in the group treated with *P. atlantica* at doses of 50 and 100 mg/kg but with minimal lesions. In detail, the extent of lesions was limited to the mucosa and submucosa layers including mild necrosis with minimal epithelial loss and mild inflammatory infiltration of the submucosa with mild interstitial edema and congestion. Moreover, fibrosis was not detected in the treated animals (Figure 5E-H).

Discussion

In the current study, the body weight of rats was significantly increased following treatment with *P. atlantica* leaves hydroalcoholic extract, which was accompanied by a significant reduction in macroscopic scores and histopathological damage of colon tissue. Moreover, the *P. atlantica* leaves hydroalcoholic extract treatment reduced serum NO levels, and remarkably enhanced SOD activity and GSH levels as compared with the colitis group (Figure 6).

It is well documented that an imbalance of oxidant/antioxidant systems and an enhanced release of ROS as well as pro-inflammatory cytokines are key processes that lead to chronic inflammation in UC (Guerra et al., 2015; Wang et al., 2020). These risk factors induce DNA damage, cellular dysfunction, apoptosis, and cell death in colitis tissue (Pereira et al., 2015). It has been shown that in UC, chronic inflammation results from the disruption of acute inflammatory mechanisms to eliminate mucosal damage (Soufli et al., 2016). Therefore, regulation of immune response and antioxidant defense

systems could be a promising approach for colitis therapy. On the other hand, natural products/plant-based drugs contain a variety of bioactive components and are used to treat various inflammatory diseases (Calixto et al., 2003). Natural products are characterized by anti-oxidant and anti-inflammatory activities along with minimal side effects (Zahouani et al., 2021). Consistent with our findings, Gholami et al. have shown that *P. atlantica* extracts administration for 10 days decreased colon oxidative stress markers and improved macroscopic and histology scores in the trinitrobenzene sulfonic acid (TNBS)-induced rat colitis model (Gholami et al., 2016). Treatment with *P. atlantica* fruit oil extract at a dose of 600 mg/kg/day was shown to significantly decrease malondialdehyde (MDA) levels and restore the intensity of histopathological deterioration of colon in rats with acetic acid (AA)-induced colitis (Tanideh et al., 2014). Boutemine et al. also found that oral administration of *pistacia lentiscus* aqueous extract significantly reduced the inflammatory status (NO, IL-6, and TNF-α levels) and mucosal damage in dextran sulfate sodium (DSS)-induced acute colitis (Boutemine et al., 2021). Recently, Ostovan et al. showed that *Pistacia lentiscus* Oil administration to colitis rats significantly reduced the total colitis index, inflammation cytokines, and oxidative stress (Ostovan et al., 2020). Other authors showed that oral administration of *Pistacia* suppressed the expression of cyclooxygenase type-2 (COX-2) and inducible nitric oxide synthase (iNOS), and the levels of NO *in vitro* and *in vivo* models (Bahrami et al., 2019; Paterniti et al., 2017). Moreover, these antioxidant and anti-inflammatory activities have been demonstrated in different experimental models such as asthma (Shakarami et al., 2019), Ethanol-induced gastric ulcers (Karampour et al., 2019), and busulfan-induced infertile (Norasteh et al., 2019). It seems that improved damage to the colon in UC animals by *P. atlantica* treatment might be related to the existence of bioactive compounds. In this regard, several reports have shown that *P. atlantica* extract are rich in flavonoids (such as quercetin) and polyphenolic compounds (such as caffeic acid and sinapic acid) that exhibit anti-inflammatory and oxidative stress effects (Hatamnia et al., 2016; Kohnepoushi et al., 2020; Shapiro et al., 2007). Therefore, *P. atlantica* leaves extract, especially in the high dose, may provide a more effective treatment compared with sulfa for UC patients.

Conclusions

To conclude, *P. atlantica leaves* hydroalcoholic extract treatment dose-dependently, mitigates ulcerative colitis induced by acetic acid in rats, probably by suppressing NO production and promoting SOD activity and GSH levels, as well as reducing body weight loss. However, the therapeutic significance of this plant in clinical settings should be clarified in future studies.

Acknowledgements

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Conflict of interest

The authors declare that there is no conflict of interest.

Ethics approval

All experiments were done according to previously delivered guidelines (National Institutes of Health Publication, NO. 82–23, revised 1996) and approved by the Ardabil University of Medical Sciences Ethics Committee (Code: IR.ARUMS.AEC.1400.024).

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