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Research Article

Azilsartan Mitigates Dextran Sodium Sulfate-induced Colitis in Rats via Modulating Inflammation and Oxidative Stress

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Abstract

Background: Ulcerative colitis is a persistent mucosal inflammation of the bowel that impacts a high portion of the population worldwide. Preclinical data highlighted the role of the renin-angiotensin system in mucosal inflammation, and its inhibition improves colitis inflammation in animal models. Azilsartan is a new angiotensin II receptor blocker that was reported to be associated with the inhibition of intracellular inflammation and oxidative stress. ***Objective***: To investigate the potential anti-inflammatory effects of azilsartan on dextran sodium sulfate-induced ulcerative colitis in rats. ***Methods***: Thirty-two healthy adult albino rats were divided into 4 groups, as follows: group I is the normal control group, group II is the dextran sodium sulfate group, group III was administered dextran sodium sulfate+prednisolone (10 mg/kg/day) orally, and group IV was administered dextran sodium sulfate+azilsartan (10 mg/kg/day) orally. The colitis induction was prompted in rats by administering 3% dextran sodium sulfate in drinking water for 7 days. ***Results***: The administration of azilsartan decreased edema index, spleen index, macroscopic changes scores, and microscopic changes scores that were produced by dextran sodium sulfate. Additionally, azilsartan markedly reduced the pro-inflammatory cytokine expression, including tumor necrosis factor-α and interleukin-6 in colon tissue. Furthermore, azilsartan significantly attenuated oxidative stress in colonic tissue by decreasing upregulated myeloperoxidase enzyme activity and increasing downregulated catalase antioxidant activity. ***Conclusions***: Azilsartan has anti-inflammatory and antioxidant effects on experimentally induced colitis. It may have a beneficial therapeutic role in the treatment of ulcerative colitis.

Keywords: Anti-inflammatory activity; Azilsartan; Dextran sulfate; Ulcerative colitis.

أزيلسارتان يخفف التهاب القولون المُستحث بكبريتات ديكستران الصوديوم لدى الجرذان عن طريق تعديل الالتهاب والإجهاد التأكسدي

الخلاصة

الخلفية: التهاب القولون التقرحي هو مرض مزمن في الغشاء المخاطي للأمعاء، يصيب نسبة كبيرة من سكان العالم. وقد أبرزت البيانات ما قبل السريرية دور نظام الرينين-أنجيوتنسين في التهاب الغشاء المخاطي، كما أن تثبيطه يُحسّن من التهاب القولون في النماذج الحيوانية. يُعد أزيلسارتان مُثبّطًا جديدًا لمستقبلات الأنجيوتنسين ويقترن بتثبيط الالتهاب داخل الخلايا والإجهاد التأكسدي. **الهدف:** دراسة التأثيرات المضادة للالتهاب المحتملة لأزيلسارتان على التهاب القولون التقرحي المُستحث بكبريتات دكستران الصوديوم في الجرذان. **الطرائق:** قُسّم اثنان وثلاثون جرذا أبيض بالغاً سليماً إلى أربع مجموعات: المجموعة الأولى هي مجموعة التحكم الطبيعية، و الثانية هي مجموعة كبريتات دكستران الصوديوم، و الثالثة أُعطيت كبريتات دكستران الصوديوم مع بريدنيزولون (10 ملغم/كغم/يوم) عن طريق الفم، و الرابعة أُعطيت كبريتات دكستران الصوديوم مع أزيلسارتان (10 ملغم/كغم/يوم) عن طريق الفم. حُفّز التهاب القولون في الفئران بإعطائها 3% من كبريتات دكستران الصوديوم في ماء الشرب لمدة سبعة أيام. **النتائج:** أدى إعطاء أزيلسارتان إلى انخفاض مؤشر الوذمة، ومؤشر الطحال، ودرجات التغيرات العيانية، ودرجات التغيرات المجهرية التي نتجت عن كبريتات دكستران الصوديوم. بالإضافة إلى ذلك، قلل أزيلسارتان بشكل ملحوظ من التعبير عن السيتوكينات المحفزة للالتهاب، بما في ذلك عامل نخر الورم ألفا والإنترلوكين-6 في نسيج القولون. علاوة على ذلك، خفّف أزيلسارتان بشكل ملحوظ من الإجهاد التأكسدي في أنسجة القولون عن طريق خفض نشاط إنزيم المايلوبيروكسديز المُرتفع وزيادة نشاط إنزيم الكاتالاز المضاد للأكسدة. **الاستنتاجات:** يتمتع أزيلسارتان بتأثيرات مضادة للالتهاب ومضادة للأكسدة على التهاب القولون المُستحث تجريبياً. وقد يكون له دور علاجي مفيد في علاج التهاب القولون التقرحي.

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INTRODUCTION

Ulcerative colitis (UC) is a complex, persistent, and idiopathic disorder of the gastrointestinal tract (GIT) characterized by relapsing and remitting inflammation of the colonic mucosa that usually begins in the rectum and extends proximally in a contiguous pattern [1]. Clinically, it presents with symptoms of diarrhea, weight reduction, abdominal pain, and perianal bleeding, significantly impacting patients' quality of life [2], but it is believed to result from a complex interaction between genetic predisposition, alterations in the gut microbiota, and immune system dysregulation in response to unidentified environmental influences [3]. The pathological features include loss of mucosal barrier integrity and upregulation of nuclear factor (NF-κB)-dependent inflammatory mediators like TNF-α and IL-6, IL-1β, and IL-17. These mediators have an important role in recruiting and activating immune cells, perpetuating the inflammatory cycle [4]. Also, it is related with excessive production of oxidative byproducts, along with depleted antioxidant defense capacity of the colon [5]. There is growing dissatisfaction with

existing ulcerative colitis treatments—such as steroids, aminosalicylates, and immunomodulators—because many cause intolerable side effects and lose effectiveness with long-term use. [6]. In addition, the increasing prevalence of ulcerative colitis indicates the urgent need to discover new treatments that can effectively control or potentially cure the disease, which significantly impairs patients' quality of life [7]. Azilsartan is a new angiotensin II receptor blocker (ARB) [8]. Its antihypertensive mechanism is like other ARBs, which relax blood vessels and reduce the workload on the heart by blocking the angiotensin II receptor [9]. In addition, azilsartan has higher efficacy and a longer duration of action and showed better antihypertensive effects when compared to other ARBs [10]. Recent studies have indicated that azilsartan has notable anti-inflammatory properties. In the diabetic cardiomyopathy mouse model and the doxorubicin-induced cardiotoxicity rat model**,** azilsartan treatment significantly lowered the expressions of pro-inflammatory mediators, including IL-6, IL-1β, and TNF-α [11,12]. Azilsartan also lowered the higher levels of IL-6, IL-1β, and monocyte chemoattractant protein-1 (MCP-1) in cells that were stimulated by lipopolysaccharides (LPS) in a dose-dependent way. This shows that it could be a very strong anti-inflammatory drug [13]. Moreover, several studies have highlighted the role of the local renin-angiotensin system in the GIT, not only in regulating blood glucose and electrolyte balance but also in contributing to carcinogenesis and inflammation [14]. In addition, evidence from various studies showed the protective effect of ARBs against gastric ulcers [15] since angiotensin II can promote the generation of reactive oxygen species (ROS) and activate the nuclear factor (NF-κB), leading to inflammatory processes and cellular injury. These effects are primarily mediated through its ability to induce mucosal vasoconstriction [16]. Circumstantial evidence suggests that angiotensin II has pro-inflammatory properties that may participate in the pathogenesis of colitis [17]. One study reported increased concentrations of angiotensin I and II in the colonic tissue of patients with Crohn's disease experiencing active inflammation [18]. Also, mice lacking angiotensin receptors exhibited significantly milder colitis than wild-type mice [17]. Moreover, several studies have demonstrated that certain ARBs, such as telmisartan and olmesartan, exert beneficial effects in experimentally induced colitis models, potentially due to their anti-inflammatory and antioxidant properties [19,20]. Some preclinical studies have shown that azilsartan is superior to other ARBs due to its high affinity to the angiotensin receptor and its slow dissociation from it. Additionally, azilsartan exhibits strong inverse agonist activity at the angiotensin receptor. These characteristics give it a more persistent ability to ameliorate angiotensin II-derived effects than other ARBs, resulting in a stronger anti-inflammatory effect [21,22]. Therefore, the present study was conducted to explore the potential anti-inflammatory effect of azilsartan against colitis model induced by DSS in rats.

METHODS

Animals

Thirty-two male albino rats (180 ± 20 grams) were provided from the College of Veterinary Medicine, University of Baghdad. All animals were housed in the animal house at standard condition (25 ± 2°C) with a 12 hr light/dark cycle and 50% humidity and had free access to tap water and commercial pellets. After acclimation for 7 days, the rats were separated randomly in four groups (8 rats in each).

Drugs and chemicals

DSS (mol. wt. 40,000) (Sigma Aldrich), prednisolone and azilsartan (Hangzhou Jinlan Pharm-Drugs Technology, China), TNF-α immunohistochemistry kit (Abcam, UK), and IL-6 ELIZA kit (BD Bioscience, San Diego, USA) were purchased. Diethyl ether and ethanol (BDH Chemical Ltd., England).

Colitis induction and study design

The induction of colitis was prompted by administering 3% DSS (mol. wt. 40,000) via drinking water for 7 days according to the procedure described by Jeon *et al*. [23]. After acclimation for 7 days, the rats were separated into 4 groups in a random manner (each group have 8 rats). Group I (normal control group): The rats in this group were allowed normal water every day. Group II (DSS group): The rats in this group received tap water with 3% DSS only. Group III (prednisolone group): The rats in this group received tap water with 3% DSS and prednisolone (10 mg/kg/day) orally [6], and in group IV (azilsartan group) the rats in this group received tap water with 3% DSS and azilsartan (10 mg/kg/day) orally [24]. The oral administration of these drugs was initiated simultaneously with water containing DSS. After 24 h from the last oral dose of all agents, every rat was anesthetized with diethyl ether and then sacrificed. The spleen and colon tissues were excised from all rats and cleaned with cold normal saline for macroscopical assessment. Then, the colon tissues were cut into 2 parts: one fixed in 10% neutral formalin for histopathological assessment. The 2nd one was preserved at −80°C for tissue homogenization to measure oxidative stress and pro-inflammatory parameters.

Assessments of colitis severity

Colon weight /length ratio was utilized as a marker of colon edema and colitis severity. The colon weight and length between cecum to rectum were measured after longitudinally opening and cleaning the colon gently under water, and then this ratio was calculated for each animal, as well as the spleen weight/body weight index [25]. The scoring pattern mentioned by Appleyard and Wallace (1995) [26] served as a visual indicator of the macroscopic colonic score. Briefly, the grading system is as follows: (grade 1): Mucosal

erythema alone; (grade 2): slight mucosal edema, mild erosion; (grade 3): moderate edema, small erosion or ulcer; and (grade 4): severe edema, extensive ulceration, and tissue necrosis.

Evaluation of oxidative stress parameters

The myeloperoxidase (MPO) activity in tissue homogenate was assessed chemically using spectrophotometry using a modified dianisidine-H_2O_2 method as previously described [27], and─MPO activity was calculated as U/g (units/gram). Catalase (CAT) enzyme activity was measured in tissue homogenates using a chemical method as described by Góth (1995) [28]. The assay was based on the reaction of 0.2 ml of tissue homogenate with 1 ml of substrate solution (65 µmol/ml H_2O_2 in 60 mmol/L sodium-potassium phosphate buffer pH 7.4), incubated for 1 minute. Following incubation, 1 ml of 32.4 mM ammonium molybdate was added to terminate the reaction. The resulting yellow complex formed between ammonium molybdate, and residual hydrogen peroxide was quantified by measuring absorbance at 405 nm using a spectrophotometer.

Measurement of IL-6 tissue levels

Tissue level of the IL-6 mediator was measured using an enzyme-linked immunosorbent assay (ELISA) kit following the protocol of the manufacturer.

Histopathological study and assessment of TNF-α

For histopathological study, one piece of colonic tissue was kept in 10% phosphate-buffered formalin, processed, and then embedded in paraffin blocks. Then, 5 µm thick sections were prepared, mounted on slides, and stained with hematoxylin and eosin (H&E) [29]. All slides were examined in a blind fashion. Assessment of histopathological changes of colonic tissue according to previously reported scoring criteria [30]. The scoring pattern is as follows (normal= 0; focal= 1; zonal= 2; sever= 3) and was used to evaluate the extent of epithelial and glandular damage, crypt dilation, formation of crypt abscess, goblet cells destruction, leukocyte infiltration, edema, dysplasia and mucosal hemorrhage. A TNF-α polyclonal antibody (Abcam, ab220210) was used to do an immunohistochemical (IHC) study on paraffin-embedded tissue. This technique depends on the specific binding of antibodies to their corresponding antigens within biological tissues. The resulting antigen–antibody complex can be visualized by conjugating the antibody to an enzyme or fluorescent dye, which produces a detectable color reaction. This histochemical signal is then observed using a light microscope. The TNF-α expression was evaluated semi-quantitatively depending on the proportion of positively stained cells, using the previously reported scoring system [31] as follows: (no staining = 0), (≤ 25% = score 1), (26–50% = score 2), (51–75% = 3), and (76–100% = score 4).

Ethical considerations

All procedures for this experiment followed the standard principle of laboratory animal care and were reviewed and approved by a local ethics committee, the Animal Experiment Committee, under the approved document number 20200865 on 8/12/2022.

Statistical analysis

The results were expressed as mean ±SD (standard deviation) and were analyzed using a one-way ANOVA test followed by Tukey's *post hoc* test to evaluate the significant difference among the variables at p-value < 0.05 [32]. SPSS program version 23 was used for statistical analysis.

RESULTS

Colon weight-to-length ratio acts as an indicator of colon edema and colitis severity. This ratio was significantly elevated after administering DSS (p< 0.001). This increment in colon weight/length ratio was reduced by treatment with azilsartan and prednisolone (p< 0.001), as shown in Figure 1A.

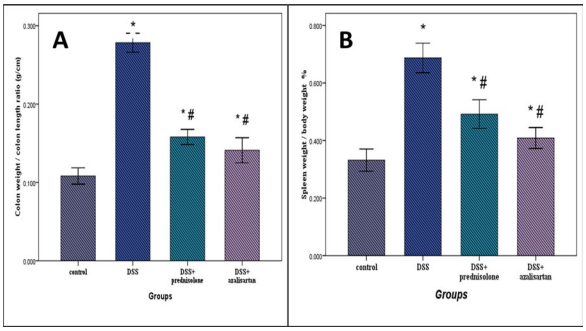

Figure 1: The impact of azilsartan and prednisolone on (**A**) colon weight-to-length ratio and **(B)** spleen weight/body weight index. (* p< 0.001 vs. normal control group; and # p< 0.001 vs. DSS group. DSS=dextran sulfate sodium.

The spleen, as a very important lymphoid organ, often enlarges in response to infection or inflammation. To assess the effect of azilsartan, we measured the spleen weight/body weight index. Our findings showed that azilsartan restored the DSS-induced increase in spleen index (p< 0.001) as shown in Figure 1B. Administration of DSS induced a high elevation in MPO activity (p< 0.001) in the colitis group. Azilsartan markedly decreased the elevated MPO activity that was mediated by DSS administration (p< 0.001) as shown in Figure 2C.

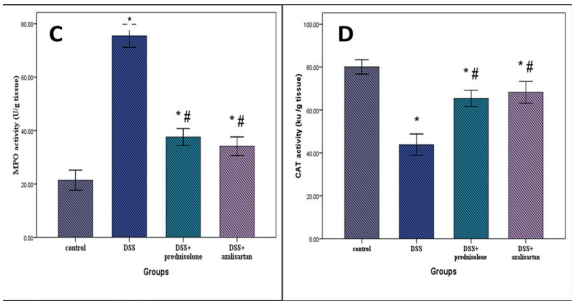

Figure 2: Impact of azilsartan and prednisolone on **(C)** Myeloperoxidase (MPO) activity and **(D)** Catalase (CAT) activity. (* p< 0.001 against normal control group; and # p< 0.001 against dextran sulfate group. DSS: dextran sulfate sodium.

CAT antioxidant activity was significantly depleted in the colitis group by administration of DSS ($p< 0.001$) revealing depletion in free radical scavenging activity. The treatment with azilsartan causes significant replenishment in CAT antioxidant activity compared to the DSS group, indicating restoration of free radical scavenging activity (Figure 2D). DSS administration causes a highly significant elevation in the pro-inflammatory mediator IL-6 level. However, treatment with azilsartan decreased this elevated level of IIL-6 ($p< 0.001$), as shown in Figure 3E.

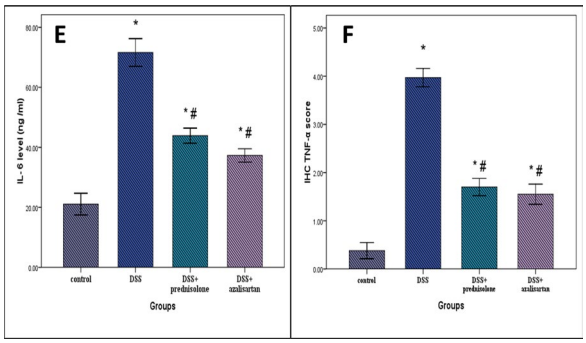

Figure 3: The impact of azilsartan and prednisolone on **(E)** IL-6 level in colon tissue and **(F)** Immunohistochemical TNF-α expression. (* $p< 0.001$ against normal control group; and # $p< 0.001$ against DSS group. DSS=dextran sulfate sodium.

Additionally, DSS administration markedly increased the IHC expression of TNF-α cytokine in colonic tissue. Oral administration of azilsartan and prednisolone highly reduced the increment in TNF-α expression upon comparison with the DSS group ($p< 0.001$) (Figures 3F and 4).

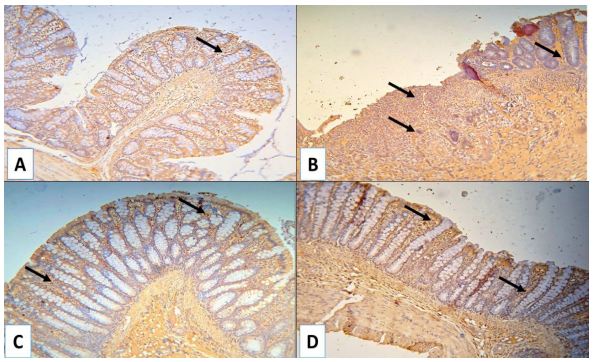

Figure 4: Images represent IHC expression of TNF-α in colonic tissue for study groups presenting: **A**) normal control group shows a very little appearance of TNF-α including mild chronic non-specific mucosal inflammation (black arrow); **B**) DSS group displays strong expression of TNF-α in inflammatory cells that infiltrated in mucosal and submucosal layers (black arrow); **C**) prednisolone treated group; and **D**) azilsartan treated group both display weak appearance of TNF-α in few inflammatory cells that infiltrated mucosal layer (black arrow). IHC, 10X.

Macroscopic features were evaluated according to a grading scale (0-4). No visible changes were observed in the normal control group. In contrast, the DSS-treated group showed significant damage, including colonic edema and severe tissue erosion and ulceration. Administration of azilsartan significantly reduced the intensity of all observed microscopic injuries ($p< 0.001$) as shown in Figure 6G. As illustrated in Figure 5, the colon tissues from the control group appeared normal, showing well-preserved colonic tissue layers, including intact colonic mucosa and submucosa with preservation of goblet cells. In contrast, the oral administration of DSS caused widespread tissue damage and necrosis, along with extensive ulceration of the mucosal lining and intense leukocyte infiltration. As a result, the histopathological changes score showed a more pronounced increase in the DSS group than that in the normal control group ($p< 0.001$).

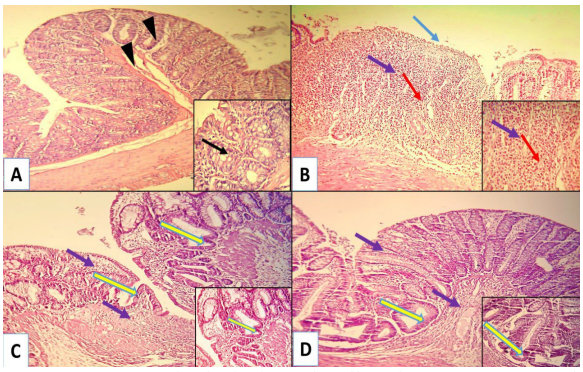

Figure 5: Images of colonic tissue for all study groups. **A)** normal control group stays whole colon layers (arrow heads) and preserved goblet cells (black arrow). **B)** DSS group shows extensive ulceration (blue arrow) with massive inflammatory cells infiltration(purple arrow) and vascular congestion and edema (red arrows). These are features of ulcerative colitis. **C)** prednisolone treated group and **D)** azilsartan treated group both showing improved histological picture with mild inflammatory cells infiltration (purple arrows) with mucosal glands and goblet cells regeneration (yellow arrows). H&E stain, 10X; inset 40X.

However, the administration of azilsartan and prednisolone noticeably improved the histopathological pattern, including preservation of the crypt architecture, fewer small ulcers, and a marked reduction in leukocyte infiltration with mucosal gland and goblet cell regeneration. Therefore, the azilsartan-treated group and prednisolone-treated group have a lower histopathological score than that in the untreated DSS group ($p< 0.001$) (Figure 6H).

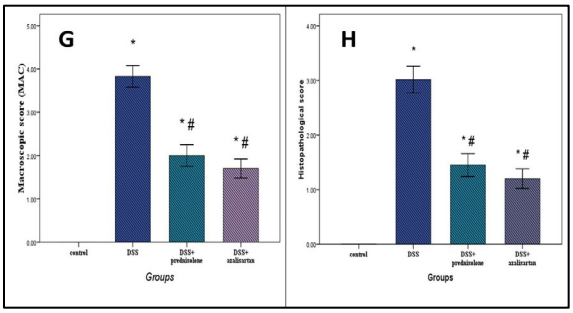

Figure 6: Impact of azilsartan and prednisolone on **(G)** Macroscopic changes scores and **(H)** histopathological score (* $p< 0.001$ against normal control group; and # $p < 0.001$ against dextran sulfate group. DSS=dextran sulfate sodium.

DISCUSSION

Inflammatory bowel diseases are chronic relapsing diseases that negatively impact patient quality of life by impacting them mentally and physically, and they are closely related to increased risk of colorectal cancer [33]. The available treatments that are used to treat IBD symptoms and inflammation have many

serious side effects, and they lose their efficacy with chronic use. Therefore, these limitations highlight the urgent need for the development of safer and more efficacious therapeutic alternatives [34]. In this study, a rat model of DSS-induced colitis was utilized. This model is mostly recognized as one of the established experimental models for studying ulcerative colitis. This is due to its ability to closely mimic the disease's clinical symptoms, such as diarrhea, weight reduction, and perianal bleeding. Moreover, it reflects several histopathological features characteristic of human UC, including ulceration, crypt damage, edema, and inflammatory cell infiltration. Also, by adjusting the concentration and duration of DSS exposure, it can induce acute or chronic colitis models [35,36]. There are many studies that have demonstrated that the administration of 3% DSS in drinking water to rats for 5-10 days induced severe colitis characterized by elevated edema index, spleen index, and symptoms of bloody diarrhea and sustained weight loss. Furthermore, colonic tissue sections from rats that have DSS-induced colitis exhibited revealing ulcerated regions, disrupted crypt architecture, infiltration of inflammatory cells, and significant microscopic tissue damage [37-39]. These findings are in line with results of the present study. In the present study, we evaluated the impact of administering azilsartan orally on colitis induced by DSS in rats. Our findings elucidated that the azilsartan administration significantly mitigated the edema index and spleen index more than prednisolone in DSS-induced colitis in rats and improved microscopic and macroscopic changes in colitis rats. The edema index (colon weight to length ratio) is an indicator of colitis severity. This ratio is elevated due to inflammatory cell infiltration, edema, mucosal hyperplasia, and overgrowth of muscularis mucosa. All these are signs of inflammation [40]. The spleen is a key lymphoid organ that often undergoes enlargement as a primary response to infection or inflammation in the body [23]. There are many previous studies that have indicated splenomegaly in patients with IBD [41,42]. Additionally, another previous retrospective study showed that the spleen volume reduced in IBD patients who had a good response to drug treatment [43]. In this study, azilsartan administration effectively inhibited MPO activity that was mediated by DSS administration and restored free radical scavenging activity, which was manifested by replenishment in CAT antioxidant activity compared to the DSS group. Oxidative stress is a critical factor contributing to tissue damage in UC. Excessive production of free radicals by activated macrophages and neutrophils in inflamed mucosa leads to the pathophysiology of UC and damages the intestinal mucous membranes [44]. In addition, azilsartan reduced inflammatory markers such as IL-6 and TNF-α, which aligns with the findings of previous studies [13.24.45]. These effects can be attributed to the blockage of angiotensin II, which is directly associated with reduced oxidative stress and suppression of inflammatory pathways [12,14,46]. The histopathological findings of this study were compatible with the biochemical and immunohistochemical results, where azilsartan provided marked amelioration of the DSS-induced colitis, demonstrated by reduced inflammatory cell infiltration with preservation of the crypt architecture, fewer small ulcers, and mucosal gland regeneration. In addition, our findings are further supported by results of some previous studies that documented that the other angiotensin antagonists, such as telmisartan and olmesartan, have a potential therapeutic effect on experimentally induced colitis [19,20]. Moreover, another study found that azilsartan had a gastroprotective effect against gastric ulcers induced by ethanol in rats through improving blood flow to the stomach, anti-inflammatory activity, and free radical scavenging capacity [24].

Study limitations

It is worth noting that the present study used a single dose of azilsartan based on previous reports, without performing a detailed dose-response analysis. Additionally, although the study includes macroscopic and microscopic assessments, as well as measurement of key inflammatory and oxidative stress markers, additional biomarkers such as IL-17, nuclear factor erythroid 2-related factor 2 (Nrf2), cyclooxygenase-2 (COX-2), and caspase-3 could provide deeper insights into the underlying mechanistic pathways. Nevertheless, this study has several notable strengths that enhance the clinical significance of its results. To our knowledge, this is the first study to explore the effect of azilsartan on colitis. It lays the basis for further research and highlights the potential anti-inflammatory effects of azilsartan that extend beyond its established role in managing hypertension.

Conclusion

Based on present data, we conclude that azilsartan has a therapeutic role in the treatment of ulcerative colitis. It attenuates inflammation and oxidative stress by reducing pro-inflammatory cytokines (IL-6 and TNF-α), inhibiting MPO activity, and enhancing the antioxidant enzyme CAT activity in colonic tissues upon comparison with prednisolone in dextran sodium sulfate-induced colitis.

Conflict of interests

The authors declared no conflict of interest.

Funding source

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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