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Original Research

Biochemical, histopathological, and histochemical effects of *Vitis vinifera* L. extract on acetic acid-induced colitis

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ABSTRACT

Background/Aim: Ulcerative colitis (UC) is a type of chronic inflammatory bowel disease with unknown etiology. Several therapeutic strategies such as consumption of medicinal plants have been used for its treatment. The aim of this study was to evaluate the possible ameliorative effects of the aqueous extract of *Vitis vinifera* L. seed in experimentally induced UC in mice. **Materials and Methods:** Twenty-four male mice, weighing 25-30 g each, were randomly divided into four equal groups. UC induced by 3% acetic acid and oral doses of *V. vinifera* L seed extract, 150 and 250 mg/kg, and negative control groups were given normal saline. On the day 5, intestinal histopathology and body weight (BW) changes, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and electrolyte profile plus oxidative stress markers were assayed. **Results:** Intrarectal administration of 3% acetic acid caused elevation of serum levels of ALT, AST, ALP, and a decrease in the other parameters such as colonic glutathione (GSH) level and catalase (CAT) enzyme activity. Treatment with *V. vinifera* L. seed extract for 5 days showed a significant increase in the BW of mice was seen in the group given treated with *V. vinifera* L seed extract 250 mg/kg orally compared with colitis control group during the experimental period. An increase in GSH and CAT activity in response to oral treatment with *V. vinifera* L seed extract was observed 5 days after treatment. Histological alterations and loss of polysaccharides content observed due to induced colitis and were compensated for after treatment with the *V. vinifera* L seed extract. **Conclusion:** Our results indicate that oral treatment from the *V. vinifera* L seed extract can be offered as potential therapeutic agents for UC in mice.

KEY WORDS: Catalase, electrolytes, glutathione, ulcerative colitis, *Vitis vinifera* L.

INTRODUCTION

Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD). IBD is a chronic disease that can involve gastrointestinal system. IBD remains a major gastrointestinal health-care issue [1]. The prevalence of IBD has been increasing, and higher incidence rates of IBD are seen in the developed countries [2].

Diarrhea, blood in the stool, abdominal pain, weight loss, loss of appetite, nutrient deficiencies, fever, and anemia are the main clinical symptoms of the UC [3], and inflammation and oxidative stress play an important role in the pathogenesis of UC [4].

Oxidative stress plays an important role in gastrointestinal diseases, and hence, chronic intestinal inflammation is concomitant with overproduction of both reactive oxygen and reactive nitrogen species leading to oxidative and nitrosative stress, correspondingly, which has been implicated in several human diseases, including UC [5]. Significant evidence proposed that UC is associated with an imbalance between reactive oxygen species and antioxidant activity which generates oxidative stress [5].

The conventional remedy for UC comprises aminosalicylates, corticosteroids, antibiotics, and immunomodulators [6]. Regardless of their effectiveness, these drugs on long-term use show side effects and compromise the quality of life of patients. Hence, there is a clinical need to recognize new and safe components for preventing (and treating) UC. Consequently, many patients turn to alternative strategies including traditional plant-based therapies. In particular, phytochemicals are an imperative naturally derived alternative therapy for UC [3].

Grapes (*Vitis vinifera* L., family: *Vitaceae*) are the most widespread and consumed berries, in the recent times. They received much attention from experts for its health benefits, due to remarkable pharmaceutically active ingredients, such as phenolic acids, anthocyanins, stilbenes (resveratrol), and proanthocyanidins [7,8].

Pharmaceutically active ingredients present in grape seed can clean off the free radicals and reduce the membrane lipid peroxidation, so they can reduce the occurrence of free radical-related diseases [9]. In traditional medicine, it is used for preventing diseases, such as myocardial infarction,

atherosclerosis, drug-induced liver, and kidney injury; moreover, used for diabetes complications such as nerve and eye problems, improving wound healing, and preventing cancer. It is hypothesized to be effective due to its antioxidant ingredients [10]. Therefore, this study has been carried out to evaluate the beneficial and therapeutic effects of grape seed extract (GSE) on the improvement of acetic acid-induced UC in mice through evaluation of biochemical and histopathological examinations.

MATERIALS AND METHODS

The study was carried out using 24 male albino mice weighing 23-30 g. The animals were obtained from the animal house of the College of Pharmacy, King Saud University, Riyadh, KSA. They were kept under observation for about 7 days before the onset of the experiment to exclude any intercurrent infection. The animals were kept in the animal house under standard conditions of light and temperature. They were housed in metal cages with free access to food and water. This study was carried out in accordance with the Institutional Scientific and Research Ethics Committees college of Medicine, Hail University, KSA.

Chemicals

All chemicals used in our study were of analytical or reagent grade. The seeds of the grapes were removed from the fresh fruits purchased from local market Hail city, KSA, and thoroughly washed and dried. The dried seeds were identified by an expert in phytochemistry, and then, it was powdered using a grinder.

Induction of Colitis

After an overnight fasting, colitis was induced under light ether anesthesia by intrarectal administration of 1 ml of 3% (v/v) acetic acid using 8 cm soft pediatric catheter [11]. To know that acetic acid was successful in induce colitis, we examined the rats for feces consistency which included loose feces, diarrhea, gross bleeding, and body weight (BW) loss.

Experimental Design

The animals were randomly divided into four groups (6 per group):

Group I (normal control group): Received 1 ml saline intrarectal.

Group II (colitis control): Colitis was induced in these animals by acetic acid, with a dose of 1 ml of 3% acetic acid intrarectally.

Group III (colitis treated with 150 mg/kg BW): Oral administration of GSE began after induction of colitis by 1 ml of 3% acetic acid intrarectally and was continued for 5 days.

Group IV (colitis treated with 250 mg/kg BW): Oral administration of GSE began after induction of colitis by 1 ml of 3% acetic acid intrarectally and was continued for 5 days.

Mice in Groups III and IV were fed orally with two different doses of GSE as 150 mg/kg and 250 mg/kg of BW, respectively. In our study, GSE doses were comparable to the daily consumption amounts recommended by practitioners of nutritional medicine to support optimal health [12].

At the end of the treatment period, the mice were sacrificed under diethyl ether anesthesia, and blood samples were collected from the jugular vein. After coagulation, blood samples were centrifuged. The supernatant sera were fractioned and kept at −30°C until used.

Biochemical Analysis

Serum AST and ALT activities were determined according to the method of Reitman and Frankel [13] using reagent kits purchased from Kashef diagnostic company (KSA). ALP activity in serum was determined using reagent kits purchased from United Diagnostics Industry (KSA). Electrolyte profile (Na^+, K^+, and Cl^-) levels were determined using reagent kits purchased from United Diagnostics Industry (KSA).

Colon tissues were quickly excised, weighed, and homogenized in a saline solution (0.9%), centrifuged at 3000 rpm for 15 min, and the supernatants were kept at −20°C for the assay of reduced glutathione (GSH) and catalase (CAT) activity according to the method of Moron *et al.* [14] and Hadwam [15], respectively.

Histopathological and Histochemical Studies

After scarification, decapitation, and dissection, colon from mice was rapidly excised and perfused in saline solution. Small pieces from the colon were taken and fixed in 10% neutral buffered formalin for histopathological examinations. Fixed organs were sent to histopathology laboratory for further processing, blocking in wax, sectioning, and staining with hematoxylin and eosin. For a demonstration of polysaccharides, sections were stained with periodic acid-Schiff (PAS) reaction [16].

Statistical Analysis

The SPSS program version 23 was used to analyze data. Data were expressed as a mean ± standard deviation. One-way ANOVA was used to study the difference between the studied groups. When ANOVA was significant, it was followed by Duncan test to study the details of differences between the animal groups. The fold change from control was calculated according to the equation (fold change = [treated−control]/control). All tests were considered statistically significant at a $P < 0.05$.

RESULTS

Table 1 shows the effect of intrarectal injection with 3% acetic acid on the BW of mice (initial and final). One-way ANOVA test showed a highly significant effect of treatment on the final BW in the different animal groups ($F = 73$, $P < 0.001$).

The control group showed a mean weight of 31.33 ± 2.42 g. Treatment with 3% acetic acid decreased this value significantly to 17.00 ± 1.26 g with a 0.46-fold decrease than the control. Treatment with 150 mg/kg BW GSE increased significantly the weight to 24.50 ± 1.05 g with a 0.22-fold decrease than the control. Treatment with 250 mg/kg BW GSE increased the animal weight to 27.33 ± 1.86 g with a 0.13-fold decrease than the control. The initial weight of animals in the four groups was non-significantly different.

Table 2 shows the effect of treatment with 3% acetic acid on the liver function tests. For ALT, one-way ANOVA test showed a highly significant effect of treatment in the different animal groups ($F = 77.3$, $P < 0.001$). The control group showed a mean ALT enzyme activity of 20.50 ± 2.74 U/L. Treatment with 3% acetic acid tripled this value significantly to 62.00 ± 6.72 U/L with a 2.02-fold increase than the control. Treatment with 150 mg/kg BW GSE decreased significantly the enzyme activity to 47.67 ± 4.59 U/L with a 1.33-fold increase than the control, whereas with 250 mg/kg BW GSE, ALT activity reduced to 38.33 ± 4.50 U/L with a 0.87-fold increase than the control. For AST, a very similar effect was shown ($F = 221.5$, $P < 0.001$).

Table 1: Effect of intrarectal injection with 3% acetic acid on initial and final body weight and the compensating role of GSE (150 and 250 mg/kg BW)

Groups	Initial body weight	Fold change	Final body weight	Fold change	*P*
Negative control	26.83±2.23	0.00	31.33±2.42[a]	0.00	0.007
3% acetic acid	27.33±2.16	0.02	17.00±1.26[d]	−0.46	0.000
150 mg (GSE)	26.50±2.43	−0.01	24.50±1.05[c]	−0.22	0.094
250 mg (GSE)	26.00±2.61	−0.03	27.33±1.86[b]	−0.13	0.332
F-ratio	0.338		73		
P	0.798		<0.001		

The different letters indicate statistically different means according to Duncan multiple range test. GSE: Grape seed extract, BW: Body weight

The fold increase than the control was 1.45, 0.89, and 0.62 for acetic acid, 150 mg, and 250 mg GSE, respectively. ALP had the same picture as shown in Table 2.

Table 3 shows the effect of treatment with 3% acetic acid on the electrolyte profile. For Na^+, one-way ANOVA test showed a highly significant effect of treatment in the different animal groups ($F = 57.1$, $P < 0.001$). The control group showed a mean Na^+ level of 140.33 ± 2.88 mmol/L. Treatment with 3% acetic acid decreased this value significantly to 123.50 ± 2.26 mmol/L with a 0.12-fold decrease than the control. Treatment with 150 mg/kg BW GSE increased significantly the ion level to 128.83 ± 2.04 mmol/L with a 0.08-fold decrease than the control. Treatment with 250 mg/kg BW GSE increased the ion level to 133.17 ± 1.94 mmol/L with only 0.05-fold decrease than the control. For Cl^- ions, a nearly similar effect was shown ($F = 38.5$, $P < 0.001$). The control Cl^- level was 122.17 ± 3.71 mmol/L. After injection with 3% acetic acid, the level was reduced significantly to 96.50 ± 6.28 mmol/L (0.21-fold decrease). When the animals were treated with 150 mg/kg GSE, the level of Cl^- was increased but insignificantly to 102.00 ± 5.10 mmol/L (0.17 fold decrease). On treatment with 250 mg/kg GSE, the level of Cl^- was significantly increased to 114.00 ± 2.37 mmol/L. The latter value is close to that of the control but still varies significantly from it (0.07 fold decrease). For K^+, the control level was 3.85 ± 0.34 mmol/L, and a value decreased significantly to 2.85 ± 0.24 mmol/L after acetic acid injection. When the animals were treated with 150 mg/kg GSE, the K^+ level was increased to 3.22 ± 0.26 mmol/L and restored a nearly normal level (3.58 ± 0.19 mmol/L) on treatment with 250 mg/kg GSE.

In regards to the oxidative stress markers, the CAT enzyme and GSH were studied. For CAT enzyme activity, one-way ANOVA test showed a highly significant difference between the different animal groups ($F = 87.4$, $P < 0.001$). The control group showed enzyme activity of 0.96 ± 0.11 UI/mg protein, a

Table 2: Effect of intrarectal injection with 3% acetic acid on liver function tests and the compensating role of GSE (150 and 250 mg/kg BW)

Groups	ALT (U/L)	Fold change	AST (U/L)	Fold change	ALP (U/L)	Fold change
Negative control	20.50±2.74[a]	0.00	71.83±6.37[a]	0.00	63.50±3.02[a]	0.00
3% acetic acid	62.00±6.72[d]	2.02	176.17±8.61[d]	1.45	268.83±9.50[d]	3.23
150 mg (GSE)	47.67±4.59[c]	1.33	135.83±7.36[c]	0.89	176.83±10.78[c]	1.78
250 mg (GSE)	38.33±4.50[b]	0.87	116.33±5.89[b]	0.62	137.67±5.16[b]	1.17
F-ratio	77.3		221.5		724.6	
P	<0.001		<0.001		<0.001	

The different letters indicate statistically different means according to Duncan multiple range test. GSE: Grape seed extract, ALT: Alanine transaminase, AST: Aspartate transaminase, ALP: Alkaline phosphatase, BW: Body weight

Table 3: Effect of intrarectal injection with 3% acetic acid on electrolytes (Na^+, Cl^-, and K^+) and the compensating role of GSE (150 and 250 mg/kg BW)

Groups	Na^+ (mmol/L)	Fold change	Cl^- (mmol/L)	Fold change	K^+ (mmol/L)	Fold change
Negative control	140.33±2.88[a]	0.00	122.17±3.71[a]	0.00	3.85±0.34[a]	0.00
3% acetic acid	123.50±2.26[d]	−0.12	96.50±6.28[c]	−0.21	2.85±0.24[c]	−0.26
150 mg (GSE)	128.83±2.04[c]	−0.08	102.00±5.10[c]	−0.17	3.22±0.26[b]	−0.16
250 mg (GSE)	133.17±1.94[b]	−0.05	114.00±2.37[b]	−0.07	3.58±0.19[a]	−0.07
F-ratio	57.1		38.0		16.2	
P	<0.001		<0.001		<0.001	

The different letters indicate statistically different means according to Duncan multiple range test. GSE: Grape seed extract, BW: Body weight

value that reduced to 0.23 ± 0.10 UI/mg protein after injection with 3% acetic acid (0.76-fold decrease from control). Treating the animals with 150 mg/kg GSE increased the CAT enzyme activity to 0.68 ± 0.06 UI/mg protein (0.29-fold decrease from control), whereas treatment with 250 mg/kg GSE increased the enzyme activity to 0.83 ± 0.05 UI/mg protein with an only 0.14-fold decrease from control. GSH showed the same trend as CAT enzyme activity [Table 4].

Histopathological Studies

Figure 1 shows the normal structure of colonic mucosa and submucosa including intact columnar epithelium and crypts. On intrarectal injection of 3% acetic acid, severe histological abnormalities appeared including congested blood vessels, leukocytic infiltration, and severe degradation of surface and crypt epithelium. Treatment with 150 mg/kg GSE reduced some of the degenerative effects on epithelium but with the presence of lymphocytic infiltration, whereas with 250 mg/kg GSE, nearly normal colonic mucosa tissue was restored.

Effect of Acetic Acid Injection on Polysaccharides

Figure 2 shows the effect of 3% acetic acid injection on polysaccharides content of colonic mucosa. PAS-positive material appeared well in the goblet cells, basement membrane, and brush border of surface epithelium. On intrarectal injection of 3% acetic acid, severe loss of PAS-positive material appeared in the crypt epithelium. Treatment with 150 mg/kg GSE restored the normal content of the PAS-positive material in some crypts. Treatment with 250 mg/kg GSE nearly restored the normal content of polysaccharides in the colonic mucosa.

DISCUSSION

The current study reveals the protection conferred by GSE against experimental UC in mice. In several studies, acetic acid was used as a model for induction of UC [17,18] where acetic acid causes colonic epithelial lesions, necrosis, and leukocyte infiltration to the damaged colon [19]. Moreover, the advantages of acetic acid-induced colitis are its low cost and the ease of administration.

In the current study, intrarectal administration of 3% acetic acid caused induction of UC, and there was marked decrease in BW of animals in colitis group in agreement with the results of the previous studies [1,17]. The BW reduction of animals is indicative of their weakened state due to colitis. Kumar *et al.* [20] stated that colonic inflammation causes bloody stool and diarrhea which contributing the BW loss of the animals. However, the treatment with GSE showed an improvement of the reduction of BW of animals. The BW improvement might have occurred due to the restoration of metabolism and cellular biosynthesis.

Oxidative stress plays an important role in the pathophysiology of UC [5]; it has been well-documented that levels of reactive oxygen species such as hydrogen peroxide, hydroxyl radicals, and

Table 4: Effect of intrarectal injection with 3% acetic acid on oxidative stress markers and the compensating role of GSE (150 and 250 mg/kg BW)

Groups	Catalase (UI/mg protein)	Fold change	GSH (μg/mg protein)	Fold change
Negative control	0.96±0.11[a]	0.00	1.02±0.08[a]	0.00
3% acetic acid	0.23±0.10[d]	−0.76	0.43±0.02[d]	−0.57
150 mg (GSE)	0.68±0.06[c]	−0.29	0.70±0.03[c]	−0.32
250 mg (GSE)	0.83±0.05[b]	−0.14	0.81±0.07[b]	−0.20
F-ratio	87.4		107.0	
P	<0.001		<0.001	

The different letters indicate statistically different means according to Duncan multiple range test. GSE: Grape seed extract, GSH: Glutathione, BW: Body weight

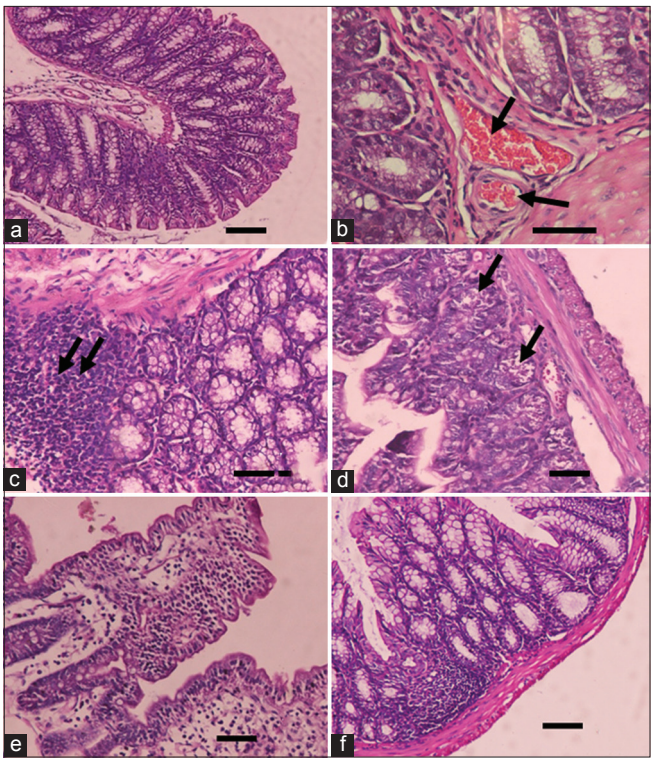

Figure 1: Effect of intrarectal injection of 3% acetic acid and the compensating role of grape seed extract (GSE) on the colonic mucosa of mice. (a) Normal mucosa with columnar epithelium and intact crypts. (b-d) Different pathological effects of acetic acid injection including congested blood vessels (arrows) (a), lymphocytic infiltration (arrows) (b), and severe degradation of crypt epithelium (arrows) (c). Treatment with 150 mg/kg GSE reduced some of the degenerative effects on epithelium but with the presence of leukocytic infiltration (predominantly polymorphs), (e) whereas with 250 mg/kg GSE, nearly normal colonic mucosa tissue was restored (f). H and E stain, magnification bar = 100 μm

nitrogen species are elevated in UC [21]. Protonation of acetic acid in the epithelial cells of the colon causes conversion of O_2 to H_2O_2 through superoxide dismutase enzyme; thereafter, it is converted to H_2O through CAT enzyme [22].

GSH is an important non-enzymatic antioxidant and has regulatory and protective roles in the body. Our findings indicate a lower CAT activity and GSH content in the colon

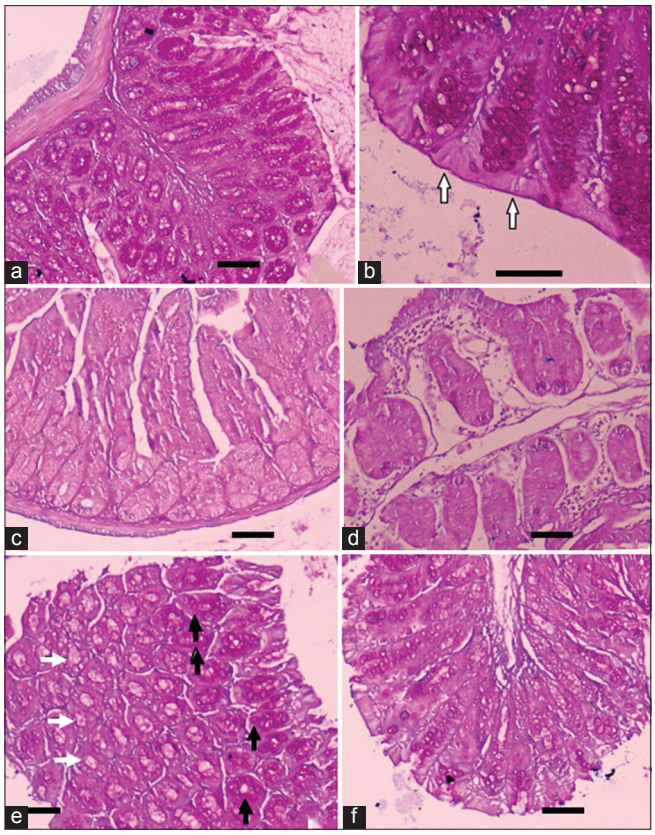

Figure 2: Effect of intrarectal injection of 3% acetic acid and the compensating role of grape seed extract (GSE) on polysaccharides of the colonic mucosa of mice. Normal mucosa with good content of polysaccharides in the goblet cells (a) and in the brush border (b). (c and d) Depletion of polysaccharides due to 3% acetic acid injection. Treatment with 150 mg/kg GSE restores normal polysaccharides in some crypts (black arrows), whereas, in other crypts, the polysaccharide content was less (white arrows) (e). Treatment with 250 mg/kg GSE restores polysaccharide content to nearly normal conditions (f). Periodic acid-Schiff stain, magnification bar = 100 μm

homogenate of the colitis group than normal group. Moreover, CAT activity and GSH content in GSE-treated groups were significantly elevated than colitis control group. These results are in agreement with the other studies [23,24] that reported diminished colonic CAT activity and GSH levels in acetic acid-induced colitis in mice. Furthermore, Somani *et al.* [24] found a significant elevation in CAT activity and GSH level in mice pretreated with *Dillenia indica* L. On acetic acid-induced colitis, gastrointestinal tract and hepatobiliary system are firmly connected anatomically. This makes the liver and the biliary system the immediate targets for injury during an exaggerated colonic inflammatory response [25].

Determination of AST and ALT in serum is a useful quantitative marker to indicate hepatocellular damage [26]. The increased activities of these serum markers observed in our study correspond to considerable liver damage induced in acetic acid-induced colitis in mice. Our results are in agreement with Trivedi and Gena [25] who reported that dextran sulfate sodium-induced colitis with a significant elevation in the plasma ALT and AST in mice. Administration of GSE significantly decreased the activities of AST and ALT, proposing that it offers protection by conserving the structural integrity of the hepatocellular membranes. On the other hand, there was a significant elevation in ALP activity in serum of colitis group. Elevated activity of ALP suggests inflammation during UC. GSE administration significantly attenuated the elevation of ALP in colitis-treated groups, which might be due to anti-inflammatory potential effects of GSE. Our results are in agreement with other authors [21,27] who reported a significant elevation of ALP activity in the serum of acetic acid-induced colitis in rats.

The most important function of the epithelial layer covering the inner surface of the colon is the transportation of electrolytes, moving of electrolytes from the mucosal site toward the blood stream, and *vice versa* [28]. Consequently, the major function of the colon is secretion of electrolytes, which is balanced by absorption. In UC, damage to epithelial layer of colon occurs due to peroxidation, which leads to an imbalance in secretion and absorption of electrolytes intern leads to electrolyte imbalance. Our results depict that serum electrolyte profile (Na^+, Cl^-, and K^+) significantly decreased after intrarectal administration of 3% acetic acid-induced UC in mice. Our findings are in consistent with other authors [29,30]. GSE administration significantly attenuated the electrolyte imbalance in colitis-treated groups, which might be due to its antioxidant action and improvement of the epithelial layer.

In our results, the biochemical alterations were confirmed by pathological examination. The observed histopathological alterations including congested blood vessels, leukocytic infiltration, and different degrees of cell degradation came in agreement with other authors who studied UC [3,31,32]. The protective effect of many plant extracts on colonic tissues against UC was studied in some plant species including *Helichrysum oligocephalum* [19], *Moringa oleifera* [33], *Coriandrum sativum* [34], and *Agave Americana* [35], but in fact, articles studying the effect of *V. vinifera* are few.

The main role of GSE in restoring normal colonic tissues after UC may be due to the antioxidant effects of the extract chemical components [36]. Antioxidant actions regarding the prevention of formation of reactive oxygen species usually occur through inhibition of enzymes or chelating trace elements involved in the production of free radicals or activating antioxidant enzymes [37,38]. The histochemical alterations observed due to acetic acid injection was compensated for after GSE treatment due to scavenging free radicals and restoration of normal tissue structure which reflected on the different biochemical activities regarding the synthesis of macromolecules such as proteins and polysaccharides. Similar observations were recorded in rats according to a very recent article [17,39].

CONCLUSION

In the present study, GSE had a significant ameliorative effect against acetic acid-induced colitis. This investigation has opened avenues for the use of GSE in the treatment of UC.

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