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Evaluation of *Salvia officinalis* in the Treatment of Acetic Acid-induced Ulcerative Colitis in a Rat Model

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Abstract

Introduction Ulcerative colitis (UC) is an inflammatory bowel disease that causes long-lasting inflammation and ulcers within the digestive tract. This study aims to determine the histochemical alteration of *Salvia officinalis* (sage), an anti-inflammatory and antioxidant herbal agent on UC.

Materials and Methods The disease was induced in 37 Sprague-Dawley rats with 2 mL of 3% acetic-acid (AA) enema. The rats were divided into five groups: a control group (AA), two 5-aminosalicylic (5-ASA) groups treated either orally (AO) or rectally (AR) with a dose of 100 mg/kg, and two salvia groups treated with 300mg/kg salvia orally (SO) or rectally (SR). Histopathological analyses of the colon were done on day 7, and markers such as C-reactive protein (CRP), superoxide dismutase (SOD), and complete blood count were measured.

Result In macroscopic evaluation, the AO group demonstrated the lowest involvement, followed by the SO, SR, AR, and AA groups, respectively ($p = 0.01$). There was no significant difference between the SO and AO groups ($p = 0.10$), and the SR and AR groups ($p = 0.58$). Regarding microscopic histopathological findings, the AO and SO group demonstrated the most satisfactory results, with no significant difference between the AO versus SO, and AR versus SR groups. Inflammation was resolved in all of the AO and SO subjects.

Conclusion Salvia can be beneficial in the treatment course of UC by inhibiting inflammatory responses, increasing the growth and viability of intestinal mucosa, and its antioxidant effects. Therefore, we propose the prescription of salvia as an adds-on or alternative therapy in the management of UC.

Keywords
- treatment protocol
- salvia officinalis
- ulcerative colitis

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that causes ulcers and mucosal barrier dysfunction. Although the exact causes for the illness is unclear, it's assumed that the effects may result from environmental and genetic factors. However, recent studies have shown that the cause of the disease is mainly because of the inflammatory defense and the antioxidative responses by the immune system.[1]

While current medical treatment protocols for UC may be helpful in reducing inflammation and damage, they are accompanied with various shortcomings and the patient may eventually end up undergoing emergency colectomy.[2] Medical treatments include the use of corticosteroids (such as prednisolone), aminosalicylates (such as 5-amino salicylic acid [5-ASA] and Sulfasalazine) immunomodulatory agents, antibiotics such as metronidazole, ciprofloxacin, and ampicillin, and biological therapies like anti-tumor necrosis factor (anti-TNF) drugs.[3–5] In spite of their beneficial antioxidative and anti-inflammatory properties, problematic side effects have been observed, including headaches, lung infections, mild diarrhea, nausea, abdominal pain, inflammation of the pancreas, and kidney problems, calling for the need of alternative treatment with fewer adverse effects.[3]

Salvia officinalis (salvia or sage) is an herb that contains tannins, a bitter substance with a digestion-facilitator effect increasing its function and antiseptic effect. The external use of the essence is commonly used for healing and disinfecting wounds.[6,7] Furthermore, the extract of this herb contains ursolic acid with anti-inflammatory properties, rosmarinic acid, 9-ethylrosmanol ether, and oleic acid with antioxidant effects.[8–10] On the other hand, IBD has been reported to be accompanied with the reduction of antioxidant factors and increased activated oxygen. Therefore, antioxidants can be useful in UC treatment.[11] Therefore, we designed this study to evaluate the therapeutic properties of salvia on UC in rat models as compared with the standard of treatment, 5-ASA.

Materials and Methods

Study Design

This study made use of 37 adult female Wister rats weighing 130 to 250 g provided from Animal House of the Shiraz University of Medical Science, Shiraz, Iran. The sample size was assigned based on previous studies, with assessing the risk of drop-out risk and along with the minimum requirement to attain reliable results.[12] The animals were housed in standard cages under stable conditions (40–50% humidity, 25 ± 3 temperature, 12:12 h dark-light cycle). They had free access to water ad libitum and a standard diet. All efforts to keep animal distress to a minimum were considered, and the animals were acclimatized to laboratory conditions for a week prior to the experiment. To avoid potential circadian effects, assessments and interventions were conducted between 9 and 12 a.m. during the light period. The health status and body weight of the animals were monitored daily and subjects failing to meet the threshold for a humane endpoint, which was a loss of more than 20% of body weight, were excluded.

The experimental protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran, under the ethical code IR.SUMS.REC.1394.S1075. All the criteria for taking care of laboratory animals outlined in the Guide for the Care and Use of Laboratory Animals were applied. All reagents not specifically described were purchased from Sigma-Aldrich (St. Louis, MO, United States).

Plant Extraction and Drug Preparation

Salvia extract was prepared by the method previously described by Kaith et al.[13] To facilitate extraction, a machine gel was prepared by the presented method.[14] The vehicle was prepared by using carboxy-methylcellulose (CMC) 0.3% (v/w) solution. The concentrated extract of the plant was introduced into the 10 and 20% v/v gel.

Before performing the main experiment, in a pilot study, oral and rectal administrations of the vehicle were evaluated and compared with an untreated group of rats with AA-induced colitis which showed no beneficial effect of the vehicle in contrast with the rats which received no treatment.

Induction of UC

Colitis was induced after 5 days of monitoring the rats and following previous reports regarding the standardized experimental model of UC. The rats were fasted for 24 hours with only access to water. Subsequently, under light ether anesthesia, acetic acid (AA) solution (2 ml, 3% v/v) in 0.9% normal saline was injected into the colon through a polypropylene tube (2 mm in diameter) which was inserted into the colon at a distance of 6 to 8 cm, depending on the size of the animal. The animal was kept in a supine Trendelenburg position for approximately 30 seconds to avoid solution leakage.[15]

Grouping of the Animals

At 24 hours after induction of UC, rats were weighed and divided into 5 groups, resulting in the same approximate 160 g average weight. Rats in the first group, assigned as the controls, received no treatment during the study (AA group) and consisted of 5 rats. The treatment groups each included 8 rats. The reference drug used was 5-ASA, administered by gavage to the rats in the second group with a dose of 100 mg/kg (AO). With the same dose as the second group, 5-ASA was given to the third group of rats rectally (AR). The fourth group received 300 mg/kg extract of salvia orally (SO). The fifth group was treated with 300 mg/kg extract of *S. officinalis* rectally (SR). For the rectal administration, a 2 mm diameter polypropylene tube was inserted into the colon to a distance of 5 to 8 cm, until the limit in which resistance was detected. The oral treatments were administered using oral gavage.

Assessment of the Colonic Damage

After 7 days of treatment, under light anesthesia, blood samples were taken via cardiac puncture to check complete

blood count (CBC), superoxide dismutase (SOD), hemoglobin levels (HGB), and C-reactive protein (CRP) levels. The enzymatic activities of SOD were based on the method developed by Misra and Fridovich.[16]

The rats were then sacrificed via decapitation. The abdomen was opened, and the colon exposed. The distal approximate 8 cm of the colon was excised and opened by a longitudinal incision. After washing the mucosa with saline solution, the samples were photographed and documented, and mucosal injury was macroscopically assessed using the Millar et al.[17] grading scale. Macroscopic inflammation scores were assigned based on clinical features of the colon using an arbitrary scale ranging from 0 to 4 as follows: 0 (no macroscopic changes), 1 (mucosal erythema only), 2 (mild mucosal edema, slight bleeding or small erosions), 3 (moderate edema, slight bleeding ulcers or erosions), 4 (severe ulceration, edema, and tissue necrosis). Additional samples were preserved in 10% formalin for histological examination.

Histological Assessment

Colonic samples were taken 2 to 4 cm proximal to the anus. After that, the tissue was fixed in phosphate-buffered formaldehyde, embedded in paraffin, and 5 mm sections were prepared.

The tissue was stained with hematoxylin and eosin and evaluated by light microscopy, being scored in a blinded manner by an expert pathologist. A histological grading scale was used to determine the extent of inflammatory reaction in the tissue. Each of the individual parameters estimated was graded 0 to 3 depending upon the severity of changes (0, none; 1, mild; 2, moderate; 3, severe). The evaluated parameters were: ulceration, inflammatory cell infiltration, destruction of the mucosa, disorganization, and crypt abscess. The severity of changes was subjectively graded and compared with controls.

Statistical Analysis

The laboratory data are expressed as mean ± standard deviation (SD) or median and quartiles (Q1–Q3). All the statistical analyses were performed via the Statistical Package Social Sciences (SPSS, IBM Corp., Armonk, NY, United States) software, version 26.0. The Fisher's exact test was used for categorical variables, while the independent sample *t*-test, Mann-Whitney U-test was used for two-parameter evaluation, or One-way analysis of variance (ANOVA) and Kruskal–Wallis test for multiple parameter evaluations. A *p*-value of less than 0.05 was considered statistically significant.

Results

Out of a total of 37 rats, 7died after the induction of AA, including 1 in the SO group, 1 in the SR, 2 in the AR, and 3 in the AO group. There was no significant difference among all groups regarding their initial weight ($p = 0.56$). Based on a repeated measures ANOVA, all groups had a significant decrease in their weight after the administration of AA until the end of their treatment ($p = 0.01$); however, this change had no statistically significant difference among the groups ($p = 0.23$).

In macroscopic evaluation, there was a significant difference among the study group scores. Severe macroscopic damage was observed after intra-rectal induction of AA. The AO group demonstrated the lowest scores, followed by the SO, SR, and AR groups, respectively ($p = 0.01$) (►**Table 1**). Based on pair-wise comparison, there was no significant difference between the SO and AO groups ($p = 0.10$), and the SR and AR groups ($p = 0.58$).

The next evaluations were performed based on microscopic findings. In relevance to ulceration, inflammation, destruction, disorganization, and crypt abscess, the AO and SO groups demonstrated the most satisfactory results, with no significant difference between them ($p = 0.47$) for all factors except inflammation, which was resolved in all of the AO and SO subjects. The other factors were either absent or mild in the SO group (►**Table 1**).

There was also no significant difference regarding the microscopic factors between the AR and SR group (ulcer: $p = 0.66$; inflammation: $p = 0.34$; destruction: $p = 0.59$; disorganization: $p = 0.48$; and crypt abscess: $p = 0.59$).

There was no significant difference between the groups regarding biochemical and laboratory evaluations (►**Table 1**). In pairwise comparisons, only the SO group demonstrated significantly higher SOD and HGB values than the AA group ($p = 0.047$ and 0.01 respectively).

Discussion

In our current report, salvia demonstrated satisfactory therapeutic properties in reversing colonic damaged subsequent to an experimental model of UC. The results were also similar to the current reference treatment, 5-ASA, with no noticeable difference between salvia and 5-ASA with respect to their route of administration. After histological grade evaluation, administration of salvia showed major improvement, with oral treatment (SO group) showing the more satisfactory results, causing a decrease in ulceration, inflammation, destruction, disorganization, and crypt abscess. The SOD levels were also significantly elevated following treatment with salvia. We believe that these findings are aligned with our main hypothesis, supporting the utilization of the anti-inflammatory and antioxidative properties of salvia in the treatment of UC.

A study by Jedidi et al.,[18] similar to our method, looked at salvia in a population of AA-induced UC demonstrated that *S. officinalis* leaf decoction extract (SOLDE) reversed all macroscopic and microscopic changes brought on by AA intoxication according to their doses. This colonic protection is partly attributed to SOLDE's abundance in phenolic compounds like flavonoids, anthocyanins, and tannins, which are among the cytoprotective substances with well-established antiulcerogenic efficacy.[19,20] They also reported a decrease in histopathological scores, indicating tissue healing and a significant reduction in inflammatory biomarkers were indicators of SOLDE's beneficial therapeutic effect.[18] Due to this, two main categories of phytochemicals' therapeutic effects

Table 1 Evaluation of microscopic, macroscopic, and laboratory features of acetic-acid induced ulcerative colitis in rats treated with *Salvia officinalis* and 5-ASA (mesalamine), compared with untreated rats

Factor		Group*					*p*-value**
		SO; $n=8$	SR; $n=8$	AO; $n=5$	AR; $n=6$	AA; $n=4$	
Gross examination							
Macroscopic grade***	Total	1 (0–2)	1 (1–2)	0 (0–0)	1.5 (1–3)	2.5 (1.3–3.8)	**0.01**
	0	2 (28.6)	1 (14.3)	5 (100)	0 (0)	0 (0)	0.07
	1	3 (42.9)	3 (42.9)	0 (0)	3 (50.0)	1 (25.0)	
	2	1 (14.3)	2 (28.6)	0 (0)	1 (16.7)	1 (25.0)	
	3	1 (14.3)	0 (0)	0 (0)	2 (33.3)	1 (25.0)	
	4	0 (0)	1 (14.3)	0 (0)	0 (0)	1 (25.0)	
Histological grade							
Ulcer	Total	0 (0–1)	1 (0–2)	0 (0–0)	0 (1–1.3)	0.5 (0–1.8)	0.14
	No Change	5 (71.4)	2 (28.6)	5 (100)	4 (66.7)	2 (50.0)	0.49
	Mild	2 (28.6)	3 (42.9)	0 (0)	1 (16.7)	1 (25.0)	
	Moderate	0 (0)	1 (14.3)	0 (0)	1 (16.7)	1 (25.0)	
	Severe	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	
Inflammation	Total	1 (1–1)	2 (1–3)	1 [1–1]	1 [1–2]	1 [1–2.5]	0.08
	Mild	7 (100)	3 (42.9)	5 (100)	4 (66.7)	3 (75.0)	0.06
	Moderate	0 (0)	1 (14.3)	0 (0)	2 (33.3)	0 (0)	
	Severe	0 (0)	3 (42.9)	0 (0)	0 (0)	1 (25.0)	
Destruction	Total	0 (0–1)	1 (0–2)	0 (0–0)	0.5 (0–1)	0.5 (0–1)	0.11
	No Change	5 (71.4)	2 (28.6)	5 (100)	3 (50.0)	2 (50.0)	0.23
	Mild	2 (28.6)	3 (42.9)	0 (0)	3 (50.0)	2 (50.0)	
	Moderate	0 (0)	2 (28.6)	0 (0)	0 (0)	0 (0)	
Disorganization	Total	0 (0–1)	1 (0–2)	0 (0–0)	0 (0–1)	0.5 (0–1)	0.10
	No Change	5 (71.4)	2 (28.6)	5 (100)	4 (66.7)	2 (50.0)	0.25
	Mild	2 (28.6)	3 (42.9)	0 (0)	2 (33.3)	2 (50.0)	
	Moderate	0 (0)	2 (28.6)	0 (0)	0 (0)	0 (0)	
Crypt abscess	Total	0 [0–1]	1 [0–2]	0 [0–0]	0.5 [0–1]	0.5 (0–1)	0.11
	No Change	5 (71.4)	2 (28.6)	5 (100)	3 (50.0)	2 (50.0)	0.23
	Mild	2 (28.6)	3 (42.9)	0 (0)	3 (50.0)	2 (50.0)	
	Moderate	0 (0)	2 (28.6)	0 (0)	0 (0)	0 (0)	
Biochemical Results							
CRP (mg/dL)		1.84 ± 0.25	1.83 ± 0.35	1.87 ± 0.20	1.98 ± 0.20	2.32 ± 0.63	0.17
SOD (units/mL)		6.44 ± 3.01	6.90 ± 4.58	3.84 ± 2.15	3.45 ± 1.66	2.70 ± 1.41	0.9
WBC ($x10^9$/L)		7.76 ± 2.83	10.97 ± 4.17	8.22 ± 3.15	11.50 ± 5.39	10.18 ± 5.60	0.45
HGB (g/dL)		13.77 ± 1.14	13.10 ± 1.07	12.16 ± 2.28	13.17 ± 1.80	11.50 ± 1.28	0.17

Abbreviations: 5-ASA, 5-amino salicylic acid; AA, control group; AO, oral 5-aminosalicylic group; AR, rectal 5-aminosalicylic group; CRP, C-reactive protein; HGB, hemoglobin; SO, oral salvia group; SOD, superoxide dismutase; SR, rectal salvia group; WBC, white blood cell.
Notes: Data are presented either as frequency (percentage), median [interquartile range], or mean ± standard deviation. * The groups are described as: SO – received 300 mg/kg oral treatment with *S. officinalis*; SR – received 300 mg/kg rectal treatment with *S. officinalis*; AO – received 100 mg/kg oral treatment with mesalamine; AR – received 100 mg/kg rectal treatment with mesalamine; and AA – the untreated animals with induced colitis. ** Fisher exact or one-way analysis of variance/Kruskal–Wallis test. *** Scores are defined as: 0–No macroscopic alterations; 1–just mucosal erythema, 2–mild mucosal edema, slight bleeding, or minor erosions; 3–moderate edema, slight bleeding ulcers, or erosions); and 4–severe ulceration, edema, and tissue necrosis.

in IBD models have been proposed: their antioxidant functions and their capacity to inhibit cytokines and proinflammatory enzymes like TNF-α, interleukin- 1 (IL-1), IL-6, interferon (IFN), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and myeloperoxidase (MPO).[18] Although our study differed in evaluated factors, mediators, and scoring method, it yielded the same final outcome and results demonstrating the therapeutic features of salvia through its anti-inflammatory and antioxidant activity, which enforces the effectiveness of this remedy in the treatment of UC.

In a molecular study by Jalalipour et al.,[21] macroscopic, microscopic, and biochemical analyses showed that salvia ethanolic extract and methanolic partition had therapeutic and/or preventive activity on rats with AA-induced colitis. The results[21] also showed that the acute induced colitis increased the weight of the rats' colon, as evidenced by edema, thickness, inflammation of tissue, necrosis of the colon, and infiltration of leukocytes in the control group.[22] Additionally, their findings showed that the myeloperoxidase and malondialdehyde levels in the control group's target tissue were elevated, suggesting that neutrophil and macrophage activation or migration were occurring. This, in turn, increased oxidative stress and lipid peroxidation, which led to the release of inflammatory mediators in the tissue.[23,24] The results of another study, by Jedidi et al.,[25] demonstrated that rats exposed to CO- and EtOH-induced diarrhea experienced a potential protective effect from the *S. officinalis* flowers' aqueous extract. These effects might be connected to its anti-inflammatory and antioxidant properties.

Additionally, patients with UC will have a higher risk of developing colon cancer.[26] Numerous studies have shown that salvia has cytotoxic and antitumor effects on cancer cells both in vitro and in vivo.[27–29] According to Pedro et al., drinking sage tea can reduce DNA damage and tumor cell proliferation, thereby preventing colon cancer.[30]

Our study has shown that AA-induced UC was associated with macroscopic, microscopic, and biochemical changes. Salvia administration, especially orally, reduced macroscopic damage due to its anti-inflammatory and antioxidative activities. The external use of the essence is commonly used for healing and disinfecting wounds, through re-epithelialization and the production of hydroxyproline, along with increased distribution of fibroblasts and new vessel formation.[6,7] Furthermore, this herb extract contains ursolic acid with anti-inflammatory properties, rosmarinic acid, and oleic acid with antioxidant effects.[8,9] Salvia oils inhibit lipopolysaccharide-induced nitric oxide, a proinflammatory mediator, production in macrophages to a very high extent, resulting in strong anti-inflammatory effects.[10,31] Due to compounds such as carnosol, rosmadial, rosmanol, and 9-ethylrosmanol ether, it has been proven that salvia has potent antioxidant effects.

Inflammation is affected by several acute-phase reactive proteins, such as CRP, which may worsen tissue damage in some settings.[32] In this study, after AA induction, we noted an increased level of CRP, most likely caused by the activation of the complementary system from the damage from AA. However, the administration of salvia decreased the CRP levels, therefore reducing the amount of inflammation, which is also supported by other studies.[18,31]

Crypt absence observed in UC is caused by lymphoplasmacytic infiltration into the lamina propria, which causes space between the crypts and muscularis mucosa and reduces the crypts' height.[33] It seems that salvia can reduce crypt absence by decreasing infiltration.

High levels of SOD may be caused by increased formation and accumulation of H2O2 in the tissues, inducing oxidative stress and causing inflammation.[34] The SOD levels significantly increased in all groups after treatment with salvia causing a decrease in inflammation. Similar results were observed in the Kontogianni research, in which salvia proved to have strong antioxidant properties against cancer cells. In our study, we believe that the increase in SOD levels alleviated inflammation.[35] Based on a study by Seguí et al.,[36] this increase improves colonic inflammation in UC. All things considered, it was determined that salvia not only has the potential to reduce colitis in experimental settings but also to heal ulcers and possibly prevent colon cancer.

No notable side effects have been reported in our study. Reported literature also support the finding of the herbal formulations are accompanied with less toxic substances and less side effects when compared with synthetic drugs. These side-effects have been evaluated both in biochemical and laboratory context, and also systematic involvement.[37,38] There are no previous studies for salvia toxicity and its limited household usage is considered very safe. Lima et al.[39] reported that sage tea has no toxic properties and is beneficial in improving glutathione levels in the liver. Nevertheless, Sharma et al.[40] stated that following excessive usage of salvia, some side effects might appear, which is associated to its content of thujone. However, since most of the available literature in this regard are based on in-vitro and animal studies, further human clinical trials are warranted to obtain more precise evidence regarding potential side effects of salvia in therapeutic settings.

Among the limitations of our study is that additional sensitive inflammatory mediators for bowel inflammation were not evaluated, including limited which were used, including colonic MPO, lipid peroxidation, glutathione (GSH), and serum lactate dehydrogenase (LDH). Additionally, the colonic specimen's net weight, which is thought to be a sensitive and accurate indicator of the intensity and scope of the inflammatory reaction, was not taken into consideration.

Conclusion

The result of this study demonstrates that *S. officinalis* can prove to be beneficial in the treatment of UC based on its anti-inflammatory and antioxidative effects, even achieving similar results with the reference drug, 5-ASA. The oral administration route established better results compared with the topical route. Based on our finding's, we propose salvia as a complementary or even alternative therapeutic measure in management of UC. However, further studies should be conducted to establish any potential side-effects or limitations.

Ethics Approval and Consent to Participate

The present study was approved by the Medical Ethics Committee of the Shiraz University of Medical Science. The experimental protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran, and all the criteria for taking care of laboratory animals outlined in the "Guide for the Care and Use of Laboratory Animals" were applied. Ethical code: IR.SUMS.REC.1394.S1075.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data regarding this study has been reported in the manuscript. Please contact the corresponding author if you are interested in any further information.

Authors' Contributions

In this study, the author contributions were as follows: Reza Shahriarirad was in charge of formal analysis, carried out investigative research, and wrote the initial manuscript draft. Sarvin Seifbehzad, Amirhossein Erfani, Fatemeh Nekouei, and Masood Hosseinzadeh contributed to the investigative research as well. Soheil Ashkani-Esfahani played a role in the study's conceptualization and oversaw project administration. Nader Tanideh was instrumental in the research concept and provided overall supervision. Omid Koohi-Hosseinabadi was responsible for developing the methodology and also engaged in investigative research. Lastly, Bahador Sarkari acted as a supervisor and was in charge of project administration.

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Conflict of Interests

The authors have no conflict of interests to declare.

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