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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи.** Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и http://www.nlm.nih.gov/bsd/uniform_requirements.html. В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned
Requirements are not Assigned to be Reviewed.**

ავტორთა საყურადღებო!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე, დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემავსებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიის ფოტოსურათები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგების ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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ACEBROPHYLLINE REPROGRAMS INFLAMMATORY AND REDOX SIGNALLING IN EXPERIMENTAL ULCERATIVE COLITIS: A DOSE-DEPENDENT STUDY

Omar S. Salman^{1*}, Adeeb A. Al-Zubaidy².

¹Department of Pharmacology, College of Medicine, Al-Nahrain University, Baghdad, Iraq.

²Department of Pharmacology, College of Medicine, University of Warith Al-Anbiyaa, Karbala, Iraq.

Abstract.

Background: Ulcerative colitis (UC) is a chronic inflammatory disease mediated by dysregulated immune responses and oxidative stress, characterised by excessive production of pro-inflammatory cytokines and defective redox homeostasis that leads to mucosal damage. Few therapeutic strategies are therefore able to simultaneously modulate these unified pathways.

Objective: This study investigated the prophylactic dose-dependent immunomodulatory and antioxidant effects of acebrophylline in dextran sulfate sodium (DSS)-induced experimental colitis.

Methods: Male albino mice were treated with 3% DSS in drinking water for 10 days to induce experimental colitis. Animals were divided randomly into control, DSS, sulfasalazine reference, acebrophylline (5 mg/kg), and acebrophylline (10 mg/kg) groups. Sulfasalazine was included as a reference standard to provide pharmacological context for the effect of acebrophylline. Disease severity was assessed with the clinical disease activity index (DAI), macroscopic parameters, and histopathological analysis. Colonic inflammation levels (TNF- α , IL-1 β , IL-6, and IL-10) and oxidative stress markers (MDA, MPO, SOD, and GSH) were determined using ELISA-based assays.

Results: DSS exposure led to severe colitis features such as high DAI scores and increased levels of pro-inflammatory cytokines and oxidative stress parameters, as well as pronounced histopathological damage. In a dose-dependent manner, these changes were significantly reduced by acebrophylline treatment. A higher (10 mg/kg) dose showed more effective inhibition towards TNF- α , IL-1 β , and IL-6 and stronger restoration of IL-10. In addition, acebrophylline decreased MDA and MPO levels, indicating the inhibition of lipid peroxidation and neutrophil infiltration, respectively, as well as restored antioxidant defence via an increase in SOD activity and GSH levels. These findings were confirmed by histopathology, revealing enhanced mucosal architecture and less inflammatory infiltration, evident mainly at the high dose.

Conclusion: Acebrophylline has a strong protective effect on DSS-induced colitis with dose-dependent reprogramming of inflammatory and redox signalling. The latter findings indicate that it may fulfil the criteria of a standalone therapeutic candidate by targeting several important pathogenic mechanisms in ulcerative colitis.

Key words. Acebrophylline, ulcerative colitis, DSS, dose-dependent, inflammation, oxidative stress, redox signalling.

Introduction.

Ulcerative colitis (UC) is a chronic, relapsing type of

inflammatory disorder of the colon with both an increasing incidence and long-term complications that result in significant global healthcare burden. It is defined by a chronic process of inflammation, including mucosal inflammation, damage, and impairment of the epithelial barrier, associated with cumulative tissue injury due to inflammatory processes governed by inherited factors (genetic predisposition), environmental factors, and dysregulated immune responses [1-3]. The difficulties in achieving sustained remission despite significant improvements in therapeutic strategies indicate that improved, mechanism-based approaches are urgently needed.

Immune pathways are the main features of UC pathogenesis, particularly those related to pro-inflammatory cytokines such as tumour necrosis factor- α (TNF- α), interleukin 1 beta (IL-1 β), and interleukin 6 (IL-6). These cytokines orchestrate the inflammatory cascade, promote leukocyte recruitment, and are responsible for epithelial injury as well as mucosal ulceration [4-6]. In parallel, inflammatory regulation is disrupted, leaving the system with diminished anti-inflammatory defence, notably by way of decreased interleukin-10 (IL-10) signalling that further propagates inflammation and leads to a loss of homeostasis in immune function [7,8]. The imbalance between pro-inflammatory pathways and regulatory pathways is one of the major factors determining the severity and course of diseases.

Accompanying immune dysregulation, oxidative stress is another important factor contributing to mucosal injury in UC [9,10]. Overproduction of reactive oxygen species (ROS) results in lipid peroxidation, protein oxidation, and DNA damage that may amplify inflammatory responses and sustain tissue injury [10,11]. Elevated malondialdehyde (MDA) and myeloperoxidase (MPO), alongside depletion of the endogenous antioxidants superoxide dismutase (SOD) and glutathione (GSH), are reproducibly reported in experimental and clinical UC [11-13]. In particular, inflammatory and oxidative pathways are inextricably linked to each other and establish a positive self-reinforcing cycle that promotes disease progression [14-16].

Current therapeutic approaches for UC are largely directed at controlling inflammation; however, the multifactorial nature of the disease makes such actions incomplete. As current approaches are limited by incomplete response, adverse effects, and high relapse rates, there is a pressing need for novel treatments that can simultaneously modulate multiple interlinked pathogenic pathways [17-19]. Based on this, agents with dual actions of anti-inflammatory and antioxidant activity particularly merit attention in this context.

Acebrophylline is a xanthine derivative used to treat various respiratory disorders and has gained attention as one of the potential candidates because of its immunomodulatory properties

and antioxidant activity [20]. Its mechanisms of action include inhibition of phosphodiesterase activity and the subsequent rise in intracellular levels of cyclic adenosine monophosphate (cAMP), suppressing inflammatory cell activation (notably eosinophils) and cytokine secretion [21,22]. Furthermore, cAMP signalling modulates other important inflammatory processes, including inhibition of nuclear factor kappa B (NF- κ B), which is the archetypal cytokine-mediated inflammation regulator in UC [23-25]. In addition, acebrophylline could reduce the production of reactive oxygen species and help restore endogenous antioxidant levels, affecting oxidative stress parameters, which is consistent with an integrated effect on inflammatory and redox signalling pathways [26].

Despite these promising characteristics, its role as an independent medicinal compound in ulcerative colitis remains uncertain. For instance, limited direct evidence exists for its dose-dependent impact on balancing the integration of inflammatory & oxidative signalling pathways in experimental colitis [27,28]. Filling this gap is necessary to exploit its therapeutic potential and yield optimal use of this pharmacological agent.

Hence, the current study was designed to assess the dose-dependent effect of acebrophylline in dextran sulfate sodium (DSS)-induced ulcerative colitis. In particular, this study tests its effect on clinical severity, pattern of inflammatory cytokines, and markers of oxidative stress, as well as histopathological changes related to its ability to modulate central pathological pathways in disease progression. Sulfasalazine was included as a reference standard, while the main focus remained on evaluating the dose-dependent effects of acebrophylline.

Materials and Methods.

Study design and experimental animals: The present study was designed as a randomised controlled experimental study using a dextran sulfate sodium (DSS)-induced ulcerative colitis model in mice. This study included thirty 8–12-week-old adult male albino mice weighing 20–25 g each. The subjects were purchased from the Animal House of the Iraqi Centre for Cancer Research and Medical Genetics (Baghdad, Iraq) and acclimatised for a week before being used in the experiment. Mice were maintained in a controlled laboratory environment (12-hour light/dark cycle, controlled temperature, and free access to standard laboratory diet and tap water). Individual variations related to hormones were avoided by working with male mice. The procedures of the experiments were performed under relevant institutional oversight and approved by the Institutional Review Board, College of Medicine, Al-Nahrain University (Approval No. 20250926; 7 October 2025).

Drugs and chemicals: Induction of experimental colitis was accomplished by administration of dextran sulfate sodium (DSS; MW 40 kDa) [29,30]. Sulfasalazine was used as a reference standard and was administered orally at a dose of 100 mg/kg/day. Acebrophylline was used as the pharmacological agent for testing and was freshly prepared immediately before use. Acebrophylline was dissolved in distilled water and given orally by gastric gavage at the doses of 5 mg/kg/day and 10 mg/kg/day. The doses were chosen based on the results of preliminary dose selection and the finalised protocol.

Induction of experimental ulcerative colitis: Experimental colitis was induced by oral administration of 3% DSS in drinking water for 10 days. During the same period, control animals were provided with normal drinking water without DSS. DSS exposure was used to induce UC-like colonic inflammation characterised by mucosal injury, inflammatory infiltration, and biochemical alterations consistent with experimental ulcerative colitis [31,32].

Experimental groups and treatment protocol: Animals were randomly allocated into five experimental groups, with six mice in each group:

Group I (Control group): Mice received ordinary drinking water without DSS and did not receive acebrophylline treatment.

Group II (DSS-induced colitis group): Mice received 3% DSS in drinking water for 10 consecutive days without pharmacological treatment.

Group III (Sulfasalazine reference group): Mice received 3% DSS in drinking water and were treated with sulfasalazine at a dose of 100 mg/kg/day by oral gastric gavage.

Group IV (Acebrophylline 5 mg/kg group): Mice received 3% DSS in drinking water and were treated with acebrophylline at a dose of 5 mg/kg/day by oral gastric gavage.

Group V (Acebrophylline 10 mg/kg group): Mice received 3% DSS in drinking water and were treated with acebrophylline at a dose of 10 mg/kg/day by oral gastric gavage.

Acebrophylline and sulfasalazine treatment started 48 hours before DSS exposure and continued once daily throughout the 10-day DSS induction period. This design was employed to evaluate the dose-dependent protective effects of acebrophylline, with sulfasalazine included as a reference standard.

Sample collection: Twenty-four hours after the final oral dose, mice were anaesthetised using an intraperitoneal injection of ketamine and xylazine. After euthanasia, the abdomen was dissected, and the colon and spleen were carefully excised. The length of the colon and the weight of the colon and spleen were measured. The colon was opened longitudinally, washed with normal saline, and macroscopically inspected. Each column was split in half. One part was fixed in 10% neutral buffered formalin for histopathological evaluation, and the other part was processed for tissue homogenization to assess the cytokines of inflammation and levels of oxidative stress markers.

Disease activity index assessment: The Disease Activity Index (DAI) was used to assess the severity of clinical disease. The DAI score was calculated from body weight loss, stool consistency, and faecal blood. Each parameter was scored according to a specific range, and the overall DAI represented the total score of each animal. This score was applied to evaluate the clinical development of DSS-induced colitis as well as the therapeutic efficacy of acebrophylline treatment [33,34].

Macroscopic evaluation and general morphology score: Immediately after euthanasia, the colon was resected, washed, and examined for any gross morphologic alterations. Colonic inflammation and systemic immune activation were assessed using colon length, colon weight, and spleen weight. Mucosal congestion and ulceration determined the general morphology score. The scoring scale is between 0 and 4: a score of 0 (no mucosal damage), 1 (mucosal congestion), 2 (ulceration of

25–50% area damaged), and, finally, a score of 4 indicates ulcerations in >50% area damaged [35].

Biochemical assessment of inflammatory and oxidative stress markers: Colonic tissue homogenates were then prepared for biochemical analysis. Serum levels of inflammatory cytokines and oxidative stress markers in colonic tissue homogenates were measured by enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions [36]. The inflammatory cytokines assessed included tumour necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), and interleukin-10 (IL-10). Oxidative stress was evaluated by measuring malondialdehyde (MDA) and myeloperoxidase (MPO), while antioxidant status was assessed by measuring superoxide dismutase (SOD) and reduced glutathione (GSH).

Histopathological examination: Once obtained, colon samples were fixed in 10% neutral buffered formalin and paraffin-embedded using conventional histological methods. Tissues were dehydrated by gradients of ethanol, cleared with xylene, embedded in paraffin, sliced into approximately 4–5 μ m thick sections, and stained with hematoxylin and eosin (H&E) [37,38]. Histopathology was performed using light microscopy by a blinded pathologist. Parameters of tissue injury were assessed according to inflammation, extent of pathological change, mucosal damage and crypt loss. Each parameter was graded on a scale that reflects histopathological criteria for injury to colonic tissue.

Statistical analysis: Data were expressed as mean $\pm$ standard deviation (SD). Statistical analysis was conducted using SPSS (version 26.0 for Windows, IBM Corp., Armonk, NY, USA). Differences between groups were evaluated using one-way analysis of variance (ANOVA), followed by Duncan's post hoc test to perform multiple comparisons. Statistical significance was defined as a p -value < 0.05 .

Results.

Acebrophylline produces a graded reduction in clinical disease severity: DSS administration resulted in significantly higher DAI compared to the control group ($p < 0.05$), confirming successful induction of experimental colitis (Table 1). The DAI score in the control group was 0.00 ± 0.00 , and it increased to 3.83 ± 0.40 in the DSS group. Clinical disease severity was progressively attenuated by acebrophylline treatment ($p < 0.05$) in a dose-responsive manner. The DAI score of the group treated with 5 mg/kg was reduced to 2.33 ± 0.51 , while the DAI score of the group treated with 10 mg/kg was more strongly decreased (1.50 ± 0.54). The sulfasalazine reference group also showed a marked reduction in DAI score to 1.33 ± 0.51 compared with the DSS group, providing a reference response for interpreting the clinical effect of acebrophylline. These results suggest that acebrophylline mitigated DSS-induced clinical symptoms in a dose-dependent manner.

Acebrophylline improves colon and spleen parameters in a dose-responsive manner: Severe macroscopic damage followed DSS exposure, as evidenced by increased colon weight, reduced colon length, and enlarged spleen. Colon weight increased from 120.33 ± 1.86 mg in the control group to 206.00 ± 2.60 mg in the DSS group, and colon length decreased from 8.10 ± 0.18 cm to

4.83 ± 0.35 cm. Spleen weight also increased from 80.66 ± 1.75 mg to 150.00 ± 1.67 mg (Table 2).

Acebrophylline improved these DSS-induced alterations in a graded manner. At 5 mg/kg, colon weight decreased to 168.00 ± 2.00 mg, colon length improved to 7.18 ± 0.22 cm, and spleen weight decreased to 124.33 ± 1.75 mg. The 10 mg/kg dose produced greater improvement, with colon weight reduced to 150.30 ± 1.86 mg, colon length restored to 7.76 ± 0.22 cm, and spleen weight reduced to 106.50 ± 1.51 mg. In the sulfasalazine reference group, colon weight, colon length, and spleen weight were 140.00 ± 1.89 mg, 7.86 ± 0.15 cm, and 95.00 ± 1.41 mg, respectively, indicating effective macroscopic improvement compared with the DSS group.

Acebrophylline reduces morphological injury: DSS markedly increased the general morphology score, indicating severe mucosal congestion and ulcerative injury. The morphology score increased from 0.00 ± 0.00 in the control group to 3.83 ± 0.40 in the DSS group (Table 3, Figure 1A).

Acebrophylline reduced gross morphological damage in a dose-dependent manner, with corresponding macroscopic improvement observed in representative colonic images (Figure 1B). The 5 mg/kg dose reduced the score to 2.16 ± 0.40 , while the 10 mg/kg dose produced a greater reduction to 1.16 ± 0.40 . The sulfasalazine reference group showed a comparable reduction in the general morphology score to 1.16 ± 0.40 . This pattern suggests that acebrophylline preserved colonic mucosal integrity more effectively at the higher dose.

Acebrophylline shifts the cytokine profile toward an anti-inflammatory pattern: DSS-induced colitis was associated with a pronounced pro-inflammatory cytokine response. Compared with controls, DSS increased IL-6 from 67.21 ± 14.95 pg/mL to 182.57 ± 57.48 pg/mL, IL-1 β from 126.84 ± 42.00 pg/mL to 427.35 ± 35.09 pg/mL, and TNF- α from 138.87 ± 9.37 pg/mL to 274.12 ± 53.98 pg/mL. In contrast, IL-10 decreased markedly from 171.98 ± 10.05 pg/mL to 28.38 ± 2.04 pg/mL (Table 4).

Acebrophylline treatment moderated this inflammatory shift. At 5 mg/kg, IL-6, IL-1 β , and TNF- α were reduced to 118.60 ± 20.32 , 252.59 ± 66.14 , and 223.53 ± 39.92 pg/mL, respectively, while IL-10 increased to 62.04 ± 2.65 pg/mL. The 10 mg/kg dose showed stronger cytokine modulation, reducing IL-6, IL-1 β , and TNF- α to 109.04 ± 5.96 , 171.98 ± 20.94 , and 171.53 ± 37.12 pg/mL, respectively, while further increasing IL-10 to 81.17 ± 17.08 pg/mL (Table 4). The sulfasalazine reference group also shifted the cytokine profile toward an anti-inflammatory pattern, with IL-10 increased to 106.69 ± 26.49 pg/mL and IL-6, IL-1 β , and TNF- α reduced to 71.69 ± 3.71 , 163.86 ± 48.14 , and 208.89 ± 5.82 pg/mL, respectively.

Acebrophylline restores redox balance in DSS-induced colitis: DSS administration induced a clear oxidative stress response, demonstrated by increased MDA and MPO levels and depletion of antioxidant defences. MDA increased from 34.99 ± 11.88 ng/mL in controls to 220.77 ± 70.18 ng/mL in the DSS group, while MPO increased from 227.63 ± 52.89 ng/mL to 640.81 ± 87.70 ng/mL. Meanwhile, SOD decreased from 7.58 ± 0.50 ng/mL to 2.16 ± 1.00 ng/mL, and GSH decreased from 25.25 ± 2.32 ng/mL to 8.23 ± 2.20 ng/mL (Table 5).

Acebrophylline partially restored redox homeostasis. The 5 mg/kg dose reduced MDA and MPO to 150.75 ± 9.97 and 442.68 ± 57.76 ng/mL, respectively, while increasing SOD and GSH to 4.21 ± 0.68 and 13.24 ± 2.05 ng/mL. The 10 mg/kg dose produced a stronger antioxidant profile, reducing MDA and MPO to 125.64 ± 25.17 and 392.90 ± 66.73 ng/mL, while increasing SOD and GSH to 5.09 ± 0.23 and 15.45 ± 2.67 ng/mL, respectively. In the sulfasalazine reference group, MDA and MPO were reduced to 101.66 ± 17.15 and 417.33 ± 53.72 ng/mL, respectively, while SOD and GSH increased to 6.26 ± 0.39 and 24.98 ± 4.29 ng/mL (Table 5).

Histopathological Scoring Confirms Dose-Dependent Tissue Protection: Histopathological scoring showed severe colonic injury in the DSS group compared with controls. DSS increased the inflammation score from 0.00 ± 0.00 to 3.00 ± 0.00 , pathological change score from 0.00 ± 0.00 to 3.83 ± 0.40 , mucosal damage score from 0.00 ± 0.00 to 2.83 ± 0.40 , and crypt loss score from 0.00 ± 0.00 to 4.00 ± 0.00 (Table 6).

Acebrophylline reduced histological injury in a graded manner. At 5 mg/kg, inflammation, pathological change, mucosal damage, and crypt loss scores were 2.33 ± 0.51 , 2.33 ± 0.51 , 2.00 ± 0.00 , and 2.00 ± 0.00 , respectively. At 10 mg/kg, these scores improved further to 1.83 ± 0.40 , 1.50 ± 0.54 , 1.67 ± 0.51 , and 0.67 ± 0.51 , respectively. The sulfasalazine reference group

also showed marked histopathological improvement, with inflammation, pathological change, mucosal damage, and crypt loss scores of 1.50 ± 0.54 , 1.17 ± 0.40 , 1.33 ± 0.51 , and 0.67 ± 1.03 , respectively. These findings confirm that acebrophylline provides stronger mucosal and crypt protection at the higher dose (Table 6).

Histological examination supports quantitative scoring: Microscopic examination of control colonic tissues showed preserved mucosal crypts, intact epithelial lining, absence of goblet cell depletion, and no inflammatory cell infiltration. DSS-induced colitis produced severe tissue disruption, including mucosal erosions, ulceration, epithelial loss, crypt destruction, oedema, and marked inflammatory cell infiltration (Figure 2B). The sulfasalazine reference group showed clear histological improvement, with reduced mucosal injury, lower inflammatory infiltration, and better preservation of crypt architecture compared with the DSS group (Figure 2C).

Acebrophylline at 5 mg/kg produced partial histological improvement, but residual inflammatory infiltration, erosions, crypt shortening, and goblet cell depletion remained evident. In contrast, acebrophylline at 10 mg/kg showed better preservation of epithelial integrity, less inflammatory infiltration, milder crypt distortion, and reduced goblet cell depletion, supporting a dose-dependent tissue-protective effect (Figure 2D & E).

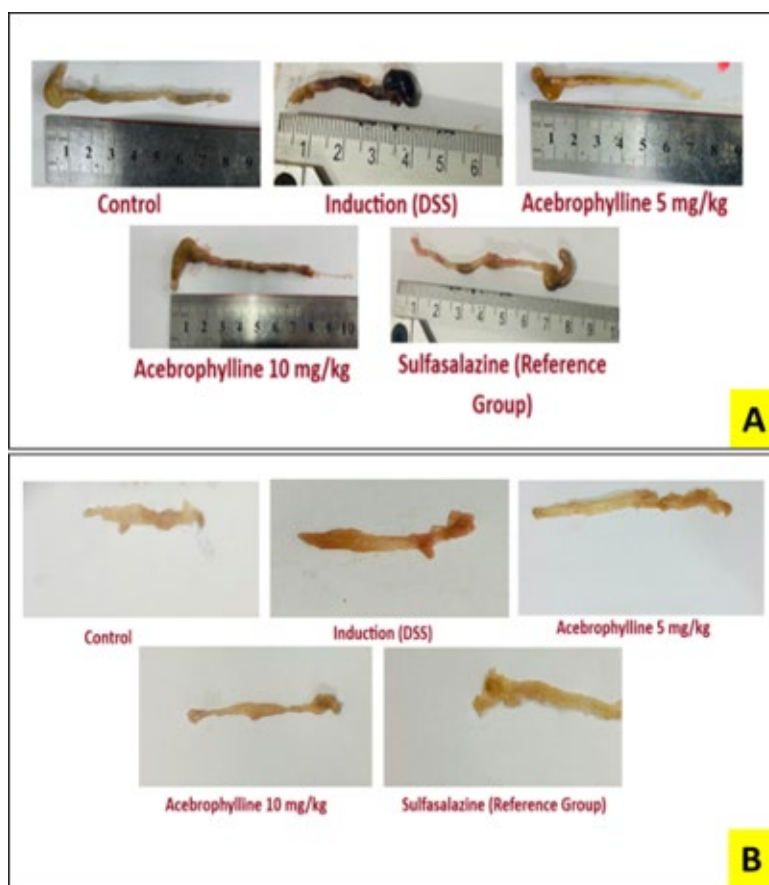


Figure 1. Gross morphological changes and morphology score among the experimental groups. (A) General morphology score demonstrating increased gross injury following DSS exposure and dose-dependent reduction after acebrophylline treatment. (B) Representative macroscopic appearance of colonic tissues showing DSS-induced mucosal damage and treatment-related improvement.

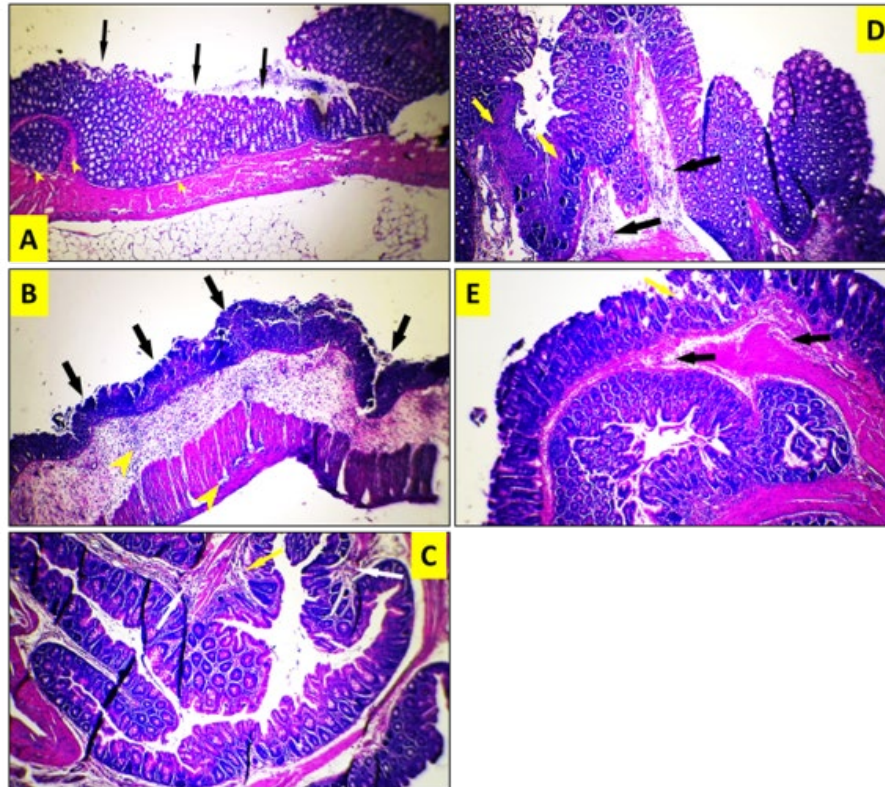


Figure 2. Representative histopathological changes of colonic tissues among the experimental groups. (A) Control group: The section shows well-preserved mucosal crypts with no atrophy or goblet cell depletion, a normal-appearing mucosal epithelial lining (black arrows), and a healthy thin submucosa without inflammatory cell infiltration (yellow arrows). (B) DSS-induced colitis group: The section demonstrates distorted colonic architecture with mucosal erosions, ulceration, epithelial destruction and loss (black arrows), crypt destruction and loss, together with marked mixed inflammatory cell infiltration in the mucosa and submucosa (yellow arrows). (C) Sulfasalazine reference group: The section shows mainly preserved colonic mucosa and epithelium, with few mixed chronic inflammatory cell infiltrates throughout the mucosa and submucosa and mild oedema (black arrow). The mucosa shows intact epithelium, mild structural variation, and few depleted goblet cells (yellow arrows), with no ulceration or haemorrhage. (D) Acebrophylline 5 mg/kg-treated group: The section shows marked chronic inflammatory cell infiltration in the mucosa and submucosa with oedema (black arrows), along with mucosal erosions, ulceration, cryptitis, crypt shortening, dilatation, structural obliteration, and goblet cell depletion (yellow arrows). (E) Acebrophylline 10 mg/kg-treated group: The section shows mixed chronic inflammatory cell infiltration in the mucosa and submucosa with oedema (black arrows). The mucosa demonstrates intact epithelium with focal erosions, mild crypt shortening, structural and size variation, and multifocal goblet cell depletion (yellow arrow).

Table 1. Effect of acebrophylline on disease activity index (DAI) in DSS-induced ulcerative colitis.

Parameters	Control (n=6)	Induction (DSS) (n=6)	Sulfasalazine (n=6)	Acebrophylline 5 mg/kg (n=6)	Acebrophylline 10 mg/kg (n=6)	P value
DAI Score (0-4)	0.0 ¹ ±0.0	3.83 ⁵ ±0.40	1.33 ^{2,3} ±0.51	2.33 ⁴ ±0.51	1.5 ³ ±0.54	<0.01 (HS)

Data are expressed as mean±SD. Different superscript numbers within the same row indicate statistically significant differences among groups according to Duncan's multiple range post hoc test. P<0.01 was considered highly significant at 95% confidence intervals.

Table 2. Effect of acebrophylline on colon weight, colon length, and spleen weight in DSS-induced colitis.

Parameters	Control (n=6)	Induction (DSS) (n=6)	Sulfasalazine (n=6)	Acebrophylline 5 mg/kg (n=6)	Acebrophylline 10 mg/kg (n=6)	P value
Colon Weight mg	120.33 ¹ ±1.86	206 ⁶ ±2.6	140 ³ ±1.89	168 ⁵ ±2	150.3 ⁴ ±1.86	<0.01 (HS)
Colon Length Cm	8.1 ⁴ ±0.18	4.83 ¹ ±0.355	7.86 ^{3,4} ±0.15	7.18 ² ±0.22	7.76 ³ ±0.22	<0.01 (HS)
Spleen Weight mg	80.66 ¹ ±1.75	150 ⁶ ±1.67	95 ³ ±1.41	124.33 ⁵ ±1.75	106.5 ⁴ ±1.51	<0.01 (HS)

Data are expressed as mean±SD. Different superscript numbers within the same row indicate statistically significant differences among groups according to Duncan's multiple range post hoc test. P<0.01 was considered highly significant at 95% confidence intervals.

Table 3. Effect of acebrophylline on general morphology score in DSS-induced colitis.

Parameters	Control (n=6)	Induction (DSS) (n=6)	Sulfasalazine (n=6)	Acebrophylline 5 mg/kg (n=6)	Acebrophylline 10 mg/kg (n=6)	P value
General morphology score (0-4)	0.0 ¹ ±0.0	3.83 ⁵ ±0.40	1.16 ³ ±0.40	2.16 ⁴ ±0.40	1.16 ³ ±0.40	<0.01 (HS)

Data are expressed as mean±SD. Different superscript numbers within the same row indicate statistically significant differences among groups according to Duncan's multiple range post hoc test. P<0.01 was considered highly significant at 95% confidence intervals.

Table 4. Effect of acebrophylline on colonic inflammatory cytokines in DSS-induced colitis.

Parameters	Control (n=6)	Induction (DSS) (n=6)	Sulfasalazine (n=6)	Acebrophylline 5 mg/kg (n=6)	Acebrophylline 10 mg/kg (n=6)	P value
IL-10, pg/ml	171.97 [±] 10.05	28.38 ¹ ±2.04	106.69 ⁴ ±26.49	62.04 ² ±2.65	81.17 ³ ±17.08	<0.01(HS)
IL-6, pg/ml	67.21 ¹ ±14.95	182.57 ³ ±57.48	71.69 ¹ ±3.71	118.60 ² ±20.32	109.04 ² ±5.96	<0.01(HS)
IL-1 β , pg/ml	126.84 ¹ ±42.004	427.35 ³ ±35.09	163.86 ¹ ±48.14	252.59 ² ±66.14	171.98 ¹ ±20.94	<0.01(HS)
TNF- α , pg/ml	138.87 ¹ ±9.37	274.12 ⁴ ±53.98	208.89 ^{2,3} ±5.82	223.53 ³ ±39.92	171.53 ^{1,2} ±37.12	<0.01(HS)

Data are expressed as mean $\pm$ SD. Different superscript numbers within the same row indicate statistically significant differences among groups according to Duncan's multiple range post hoc test. P<0.01 was considered highly significant at 95% confidence intervals.

Table 5. Effect of acebrophylline on oxidative stress and antioxidant markers in DSS-induced colitis.

Parameters	Control (n=6)	Induction (DSS) (n=6)	Sulfasalazine (n=6)	Acebrophylline 5 mg/kg (n=6)	Acebrophylline 10 mg/kg (n=6)	P value
MDA, ng/ml	34.99 ¹ ±11.88	220.77 ⁴ ±70.18	101.66 ^{2,3} ±17.15	150.75 ³ ±9.97	125.64 ^{2,3} ±25.17	<0.01(HS)
MPO, ng/ml	227.63 ¹ ±52.89	640.81 ³ ±87.70	417.33 ² ±53.72	442.68 ² ±57.76	392.90 ² ±66.73	<0.01(HS)
SOD, ng/ml	7.58 ⁵ ±0.50	2.16 ¹ ±1.003	6.26 ⁴ ±0.392	4.205 ² ±0.68	5.09 ³ ±0.228	<0.01(HS)
GSH, ng/ml	25.25 ³ ±2.32	8.23 ¹ ±2.20	24.98 ³ ±4.29	13.24 ² ±2.05	15.45 ² ±2.67	<0.01(HS)

Data are expressed as mean $\pm$ SD. Different superscript numbers within the same row indicate statistically significant differences among groups according to Duncan's multiple range post hoc test. P<0.01 was considered highly significant at 95% confidence intervals.

Table 6. Effect of acebrophylline on histopathological scoring parameters in DSS-induced colitis.

Parameters	Control (n=6)	Induction (DSS) (n=6)	Sulfasalazine (n=6)	Acebrophylline 5 mg/kg (n=6)	Acebrophylline 10 mg/kg (n=6)	P value
Inflammation Score (0-3)	0.0 ¹ ±0.0	3.0 ⁴ ±0.0	1.5 ² ±0.54	2.33 ³ ±0.51	1.83 ² ±0.40	<0.01 (HS)
Pathological change range Score (0-4)	0.0 ¹ ±0.0	3.83 ⁵ ±0.4	1.17 ^{2,3} ±0.40	2.33 ⁴ ±0.51	1.5 ³ ±0.54	<0.01 (HS)
Mucosal damage Score (0-3)	0.0 ¹ ±0.0	2.83 ⁵ ±0.40	1.33 ^{2,3} ±0.51	2 ⁴ ±0.0	1.67 ^{3,4} ±0.51	<0.01 (HS)
Crypt loss Score (0-4)	0.0 ¹ ±0.0	4.0 ⁴ ±0.0	0.67 ² ±1.03	2.0 ³ ±0.0	0.67 ^{2,3} ±0.51	<0.01 (HS)

Data are expressed as mean $\pm$ SD. Different superscript numbers within the same row indicate statistically significant differences among groups according to Duncan's multiple range post hoc test. P<0.01 was considered highly significant at the 95% confidence level.

Discussion.

Ulcerative colitis is no longer viewed as a disease from one pathogenic pathway but rather an interconnected weave of multiple inflammatory, oxidative, and epithelial injury circuits [4,39]. In the current work, DSS administration resulted in a significant experimental colitis phenotype characterised by a significant increase in disease activity scores and colon shortening and splenic enlargement, along with dysregulation of pro- and anti-inflammatory cytokines, oxidative stress, and severe histopathological injury. This pattern is characteristic of the DSS-induced colitis model, one of the most used models for human ulcerative colitis, as it replicates several key hallmarks of human disease, such as epithelial barrier disturbance, mucosal erosions, innate immune activation, and inflammatory cell infiltration [11,40,41]. Clinical and tissue-level changes in the DSS group corroborate that this model is appropriate for assessing acebrophylline monotherapy potential.

A major result of this study is that acebrophylline has inhibited DSS-induced colitis in a clearly dose-dependent manner. In comparison to 5 mg/kg/day, higher doses (10 mg/kg/day) of acebrophylline exhibited significant amelioration of DAI, colon length, colon weight, spleen weight, and general morphology score. This graded response is significant, as it indicates a pharmacological rather than nonspecific disease-suppressive effect. In models of experimental colitis such as DSS, improvements in DAI and restoration of colon length are considered composite surrogate markers for lower inflammatory burden and mucosal integrity [30,41,42]. Herein,

the simultaneous clinical and macroscopic improvements observed further endorse the idea that acebrophylline alters disease behaviour in terms of both function and structure.

One of the mechanistic insights from this study is the capacity of acebrophylline to alter the colonic cytokine milieu towards a less inflammatory profile. DSS significantly increased TNF- α , IL-1 β , and IL-6 levels and decreased IL-10. This pattern of cytokines corresponds to a common inflammatory signature in the experimental model of colitis, characterised by recruitment and activation of pro-inflammatory mediators that enhance the recruitment rate of leukocytes into both epithelial injury and damage inside the mucosa [34,43-45]. Cytokine imbalance in this model was successfully reversed with acebrophylline, where stronger inhibition of TNF- α , IL-1 β , and IL-6 was observed at the 10 mg/kg dose than at the 5 mg/kg dose. It suggests that acebrophylline not only ameliorates clinical signs but also controls relevant upstream pro-inflammatory mediators of colitis progression.

Decreased IL-1 β is particularly pertinent since IL-1 β has been increasingly promoted as a central amplifier of intestinal inflammation. It participates in causing epithelial barrier dysfunction, activation of inflammatory cells, and maintenance of mucosal damage [43,46-48]. IL-6, in a parallel mechanism, drives persistence of inflammation through downstream pathways leading to immune-cell survival and amplification of inflammation; TNF- α is also an important therapeutic target in the treatment of ulcerative colitis by its diverse role in leukocyte recruitment, epithelial apoptosis, and cytokine induction [48].

Thus, this simultaneous decline in three cytokines indicates that acebrophylline may have a more generalised immunomodulatory effect rather than just one isolated inflammatory mediator.

Restoring IL-10 also complements the immunological interpretation. IL-10 is an essential anti-inflammatory cytokine for intestinal immune tolerance and limiting excessive mucosal inflammation. In this study, DSS markedly depleted IL-10, whereas acebrophylline increased IL-10 in a dose-dependent pattern. This is important because therapeutic control of ulcerative colitis depends not only on suppression of inflammatory mediators but also on restoration of regulatory immune balance [49-52]. Thus, acebrophylline appears to promote a bidirectional immunoregulatory shift: downregulation of pro-inflammatory cytokines and partial restoration of anti-inflammatory signalling.

This cytokine profile may be explained, at least partly, by the pharmacology of acebrophylline as a xanthine-derived compound. Acebrophylline has been reported to possess anti-inflammatory activity through inhibition of phosphodiesterase activity and modulation of inflammatory mediator release, including TNF- α and leukotrienes [21,53]. Phosphodiesterase inhibition increases intracellular cyclic adenosine monophosphate (cAMP), which can suppress inflammatory cell activation and reduce cytokine production. Increased cAMP signalling is similarly functionally associated with diminished NF- κ B-dependent transcriptional activity, a key pathway regulating TNF- α , IL-1 β , and IL-6 expression in intestinal inflammation [54]. Though NF- κ B was not directly measured in this study, the changes seen are consistent with a reduction in transcriptional output of inflammatory cytokines.

A further important result was that acebrophylline normalised redox balance in DSS-induced colitis. DSS also elevated MDA and MPO while reducing SOD and GSH, suggesting lipid peroxidation, neutrophil-mediated oxidative damage, and decreased antioxidant defence. Taken together, these observations align with ongoing evidence implicating oxidative stress as a key pathogenetic determinant of inflammatory bowel disease marked by excessive reactive oxygen and nitrogen species inducing damage to lipids, proteins, DNA, and epithelial barrier structures [11,55,56]. These oxidative changes were reversed by acebrophylline to a dose-responsive extent, with the high dose of 10 mg/kg being more effective at reducing both MDA and MPO and restoring SOD and GSH.

Although diminished MDA implies a decrease in lipid peroxidation, the decreased MPO indicates either limited neutrophil infiltration or less oxidising activity of neutrophil-derived oxidants. In colitis, both measures are clinically relevant because lipid peroxidation damages epithelial membranes while MPO reflects neutrophil-driven inflammatory injury. The increased SOD and GSH indicate the restoration of endogenous antioxidant defences. Previous literature highlights that markers of oxidative stress are closely related to inflammatory bowel disease activity and could be used as a determinant of the degree of severity and therapeutic response [57,58]. Thus, the redox-modulating action of acebrophylline further consolidates its multi-target potential in colitis.

Notably, it is important to highlight that the inflammatory and oxidative findings should not be interpreted as independent biological phenomena. In ulcerative colitis, inflammation and

oxidative stress are a continuously amplifying cycle: recruited immune cells produce ROS, which itself activates inflammatory signalling pathways that exacerbate epithelial damage. Acebrophylline seems to break this inflammatory-oxidative feedback loop by reducing pro-inflammatory cytokines, MDA, and MPO simultaneously while restoring IL-10, SOD, and GSH [56]. This is the central mechanistic distinction of the present study. Rather than describing acebrophylline as simply anti-inflammatory or antioxidant, the data suggest coordinated immuno-redox reprogramming.

Histopathological results confirm this interpretation on a structural level. Intestinal lesions associated with DSS were characterised by epithelial disruption, ulceration, inflammatory infiltration (submucosal lymphocytes and macrophages), goblet cell depletion, oedema, crypt shortening, and crypt loss. These lesions are characteristic of DSS-induced colonic damage and indicate concurrent impairment of the epithelial barrier, immune activation, and impaired mucosal repair [41,59-61]. Acebrophylline ameliorated these pathological features in a dose-dependent manner. While the 5 mg/kg dose provided partial protection, the 10 mg/kg dose resulted in more clearly maintained epithelial integrity and crypt architecture with reduced inflammatory infiltration and reduced goblet cell depletion. The histological recovery correlates with the biochemical findings that acebrophylline modifies major pathogenic processes and is not merely symptomatic.

This study is among the most comprehensive in terms of the wide range of outcome domains investigated, particularly with respect to that dose-dependent pattern across multiple domains. When comparing 10 mg/kg vs. 5 mg/kg, it was found that the 10 mg/kg dose was consistently superior with regard to clinical, macroscopic, inflammatory, oxidative, and histological endpoints. This stability lends support for an actual dose-response association and reinforces the internal validity of the results. This point is especially relevant because evidence of improvement of a therapeutic candidate across independently assessed but biologically correlated disease domains strengthens the case for efficacy [30,62]. Also, the same graded pattern appeared in DAI, morphology, cytokines, redox markers, and histopathology, which indicated that acebrophylline had a concerted disease-modifying action.

The present study findings position acebrophylline as a repurposed candidate for an immunomodulatory and redox-regulating approach in experimental ulcerative colitis. Drug repurposing is a highly appealing approach in inflammatory bowel disease, as it holds the potential to accelerate translational pipelines and find agents with established pharmacological and safety profiles [63-65]. Thus, the present findings support further mechanistic and translational studies of acebrophylline in a variety of diseases beyond respiratory conditions.

This study uses sulfasalazine as the reference standard to establish a pharmacological basis for the protective effects of acebrophylline. This research does not aim to verify that the latter test drug has superior efficacy; instead, it assesses its dose-dependent improvements across clinical, biochemical, oxidative, and histopathological metrics. The core focus of this study consistently remains the dose-response activity of acebrophylline, while sulfasalazine only serves as a baseline control.

While the integrated dose-response pattern is strong, a few limitations need to be acknowledged. First, the study utilised an acute DSS-induced colitis model, which does not establish the chronic relapsing-remitting characteristic of human ulcerative colitis. Second, while the cytokine and oxidative profiles indicated that cAMP/NF- κ B and redox-sensitive pathways were affected, examination of such processes through Western blotting, RT-qPCR, immunohistochemistry, or pathway-specific assays was not performed directly. Third, epithelial barrier proteins, apoptosis markers, Nrf2/HO-1 signalling, MAPK signalling, and gut microbiota composition were not assessed despite these mechanisms defining an important component of DSS colitis and mucosal healing [41,66].

Future studies should directly explore differences in NF- κ B, Nrf2/HO-1, MAPK, PI3K/Akt, and JAK/STAT signalling pathways to delineate the underlying molecular basis of acebrophylline-mediated protection. Studies using chronic and relapsing DSS models should be performed to ascertain whether acebrophylline provides long-lasting mucosal protection after resolution of the acute inflammatory response. Moreover, wider dose ranges and pharmacokinetics, as well as longer-duration safety trials, have to be carried out to define the dosage and translational potential of acebrophylline in ulcerative colitis. The small sample size and short duration of disease induction or therapy are limitations that require future studies with larger samples for longer periods to mimic the chronic nature of the disease or therapy.

Conclusion.

Acebrophylline showed a dose-dependent protective effect against DSS-induced ulcerative colitis. The results of this study show that acebrophylline alleviates clinical disease severity, ameliorates macroscopic and histopathological damage as well as the oxidative stress response, and modulates several key pro-inflammatory pathways. In particular, acebrophylline led to decreased levels of pro-inflammatory cytokines (TNF- α , IL-1 β , and IL-6); restored anti-inflammatory interleukin (IL-10) values to control levels; reduced oxidative marker factors (MDA and MPO); and increased redox defences (SOD and GSH). The effects were always stronger for the high dose (10 mg/kg), demonstrating a clear dose-response effect.

Importantly, the integrated amelioration seen in clinical, biochemical, and histological parameters indicates coordination of immuno-redox modulation by acebrophylline rather than inhibition of isolated pathways. This multi-targeted profile supports the potential of acebrophylline as an independent therapeutic candidate able to alter key pathogenic mechanisms involved in ulcerative colitis, with sulfasalazine providing reference pharmacological context. In conclusion, the current results validate acebrophylline repositioning to deliver it as an attractive immunomodulator and antioxidant in preclinical experimental ulcerative colitis.

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