

Therapeutic Effects of Baneh Gum (*Pistacia atlantica* Desf.) Extract on Immunological and Histopathological Alterations in an Experimental Model of Ulcerative Colitis

Majid Mirzaei Nodoushan¹, Hadi Esmaeili Gouvarchinghaleh¹, Ebrahim Salimi-Sabour^{2*}, Mohammad Amrollahi-Sharifabadi³, Javad Raouf Sarshori⁴, Alireza Shahriary⁵

¹Applied Virology Research Center, Biomedicine Technologies Institute, Baqiyatallah University of Medical sciences, Tehran, Iran.

²Department of Pharmacognosy and Traditional Pharmacy, Faculty of Pharmacy, Baqiyatallah University of Medical Sciences, Tehran, Iran.

³Department of Basic Sciences, Faculty of Veterinary Medicine, Lorestan University, Khorramabad, Iran.

⁴Department of Anatomical Sciences, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran.

⁵Chemical Injuries Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran.

*Corresponding Author: Ebrahim Salimi-Sabour, Pharm.D, PhD., Department of Pharmacognosy and Traditional Pharmacy, Faculty of Pharmacy, Baqiyatallah University of Medical Sciences, Tehran, Iran. Email: E.salimisabour@gmail.com

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Abstract

Introduction: Ulcerative colitis (UC) is a common inflammatory bowel disease that presents significant therapeutic challenges, including adverse drug effects and high treatment costs. Natural-derived agents, such as herbal products, may provide new treatment avenues. This study evaluated the effects of Baneh gum extract (BGE) on immunologic and histopathologic changes in an experimental UC model.

Method: UC was induced using acetic acid in BALB/c mice. Forty mice were randomly divided into four groups (n = 10): the first group served as a control (no treatment); the second and third groups received BGE before (pre-BGE) and after (post-BGE) disease induction, respectively; and the fourth group received mesalazine. After 10 days, the mice were euthanized, and the levels of inflammatory biomarkers, including myeloperoxidase (MPO), nitric oxide, interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α), were measured. In addition, histopathologic examinations were performed according to standard protocols.

Result: Our results showed that BGE significantly reduced the production of mediators and inflammatory cytokines, including myeloperoxidase, nitric oxide, IL-1, IL-6, and TNF- α , in an experimental mouse model of acetic acid-induced UC. Histopathological changes were also significantly alleviated by BGE in this model.

Conclusion : Our findings support the beneficial use of BGE by attenuating the histopathological and immunological perturbations induced by this experimental animal model of UC. The study highlights the therapeutic promise of BGE, a natural product, in reducing inflammation and tissue damage associated with UC. Further research is needed to establish its clinical efficacy and safety in human patients.

Keywords: Baneh gum extract, Ulcerative colitis, Inflammation, Natural antioxidants, Phytotherapy.

Introduction

Ulcerative colitis (UC) is one of the most prevalent inflammatory bowel disorders and can be characterized by inflammation of the gastrointestinal tract ¹. This condition can affect a large population across different ages, ethnicities, and geographical regions, imposing a significant disease burden and costs for hospitalization

and remission therapies ². Despite the advancement of our understanding of the pathogenesis of this disease, its exact etiology remains largely unknown. Genetic predisposition, environmental conditions, immune system dysfunctions, and dietary habits are among the hypothesized factors affecting this condition.

Responses to therapeutic options—including corticosteroid anti-inflammatory drugs, aminosalicylates, antibiotics, immunomodulatory agents, and biological agents—differ among patients^{3,4}. Most of these drugs have severe side effects, such as diarrhea, vomiting, fever, skin problems, growth retardation, anemia, osteopenia, increased risk of infections, liver disorders, kidney disorders, pancreatitis, and gastrointestinal ulcers⁵⁻⁷. In addition, patients respond differently to the mentioned treatments, and some may require surgery and colectomy⁸. Furthermore, patients with UC are at risk of developing colon cancer if inflammation is not controlled⁹. Consequently, preventing disease complications—including colectomy—and controlling inflammation with minimal drug side effects are important aims in the management of UC.

Several studies are being conducted to identify effective drugs with fewer side effects and lower costs for patients and the healthcare system¹⁰. Generally, plant-derived natural products are considered a promising area for discovering appropriate, safer, and less expensive drugs for various diseases.

Inflammatory processes, including the infiltration of neutrophils and macrophages into the colonic mucous tissue, are an essential feature of UC. Activated neutrophils in the intestinal mucosa can trigger oxidative stress by secreting reactive oxygen species such as superoxide anion, hydroxide radical, and hydrogen peroxide¹¹. These events cause lipid peroxidation, increase mucus and blood vessel permeability, enhance neutrophil entry into the mucous tissue, and promote inflammation^{11,12}. By affecting the expression of cytokine genes and enzymes involved in the inflammatory response, reactive oxygen species trigger the destruction of the intestinal wall, causing ulcers, bleeding, and diarrhea¹³. Moreover, oxidative stress can reduce the antioxidant defense mechanism and thus increase the severity of this disease^{14,15}. Therefore, drugs that modulate the above-mentioned mechanisms—including natural antioxidant products—can be investigated to elucidate their beneficial effects in preventing and treating this disease¹⁶.

A recent study reported that *Pistacia atlantica* leaf-bud extract showed beneficial anti-inflammatory effects in a mouse model of inflammation, suggesting the potent biological activities of this plant¹⁷. This finding inspired the current study, which aims to evaluate the beneficial effects of Baneh gum extract (BGE) (*Pistacia atlantica* Desf.) in an animal model of UC.

Methods

Chemicals and Drugs

Mesalazine (5-aminosalicylic acid), also known as mesalamine, was purchased from Sigma-Aldrich (St. Louis, MO, USA). Acetic acid 4% was purchased from Merck (Dusseldorf, Germany). Accredited suppliers provided other chemicals and drugs with high purity.

Plant Material

BGE (*Pistacia atlantica* Desf.) was provided by Van Turpentine Company (Sanandaj, Kurdistan Province, Iran). According to the company's statement and as described previously¹⁸, the extraction was performed using the alcohol/water soaking method. The gum was soaked for 48 hours in an ethanol-water mixture (3:1), filtered, concentrated, and then dried at 40°C. The dried extract was then pulverized, and a very small amount of Tween 80 was added as a solvent. The extract was stored at 4°C until use in the study.

Gas Chromatography-Mass Spectrometry Analysis of BGE

Gas chromatography (GC) analysis of BGE was performed as described in our previous study (18). An Agilent model 7890B, coupled with a TRACE MS detector and an HP-5MS column (30 m × 0.25 mm × 0.25 μm film thickness), was used for analysis. The mass spectrometric detector was operated in electron impact ionization mode with 70 eV ionization energy. The GC temperature program started at 60°C and increased to 280°C at a rate of 5°C/min. The detector and injector temperatures were set at 280°C and 250°C, respectively. The identification of separated peaks was carried out by matching their mass spectra with those in the literature and mass spectral databases of the device library (Wiley Adams and Main Library). A homologous series of n-alkanes (C8–C24) was injected under similar GC/MS conditions. The area under the peaks was used to calculate the approximate quantities of the samples¹⁸.

Range-Finding Study and Determination of LD₅₀

This study was designed based on a previous LD₅₀ calculation experiment¹⁸. In brief, male BALB/c mice weighing 25–30 g were obtained from the Laboratory Animal Breeding Department of Baqiyatallah University of Medical Sciences. One hundred microliters of BGE (µg/mL) were given orally to the mice in each group once daily. Following the initial oral dosages, the animals were observed to record the mortality rate. Based on the range-finding study¹⁸, a dose of 0.1 mg/kg was utilized, and the LD₅₀ was determined after analysis using GraphPad Prism software version 8.0.

Experimental Animal Design

The animal population in this study included 40 BALB/c mice with an average age of 6–8 weeks and a weight range of 25–30 g. Mice were purchased from the Animal Husbandry of Baqiyatallah University of Medical Sciences. After two weeks of acclimatization, the mice were randomly divided into four groups, each containing ten mice:

Group 1 (control group): Ten mice in which UC was induced and underwent no treatment.

Group 2 (pre-BGE): Ten mice that received 0.1 mg/kg of BGE orally daily for 20 days, beginning 10 days before the induction of UC.

Group 3 (post-BGE): Ten mice that received 0.1 mg/kg of BGE orally daily for 10 days after the induction of UC.

Group 4 (positive control): Ten mice that received 30 mg/kg of mesalazine orally daily after disease induction^{19, 20}.

UC Induction and Grading Methods

Mice were kept in separate racks under controlled conditions (standard temperature, humidity, and day-night cycle) with a natural diet and water. Before the induction of disease, the mice were fasted for 36 hours with free access to water. Under mild anesthesia with a mixture of ketamine and xylazine, 100 µL of 4% acetic acid was injected into the rectum through a polyethylene tube to induce disease.

The disease activity index was measured by daily recording of fecal consistency and blood in the stool. Grading was performed as follows:

Stool consistency criteria:

Normal: score 0

Soft: score 1

Very soft: score 2

Diarrhea: score 3

Blood in stool criteria:

Negative occult blood: score 0

Low trace occult blood: score 1

Occult blood positive (+): score 2

Occult blood positive (++) : score 3^{20,21}

Measurement of Myeloperoxidase (MPO) Enzyme Levels

First, colon tissue was homogenized with phosphate buffer (pH 7.4) using a homogenizer. The homogenized tissue was then centrifuged at 1500 rpm for 5 minutes. Enzyme activity in the supernatant of the homogenized colon tissue was measured using the tetramethylbenzidine method^{21,22}.

Measurement of Nitric Oxide Levels

Nitric oxide production was determined using the Griess colorimetric method^{21,23}.

Measurement of IL-1β, IL-6, and TNF-α Cytokine Levels

The enzyme-linked immunosorbent assay (ELISA) method was used to measure TNF-α, IL-1β, and IL-6 levels in spleen supernatant samples from treated and healthy mice using commercial kits manufactured by Karmania Pars Gene (Kerman, Iran), according to the manufacturer's instructions^{21,24}.

Histopathological Study

After the mice were euthanized, the colons were completely dissected and placed in 10% formalin solution. The tissues were embedded in paraffin, sectioned, stained with hematoxylin and eosin (H&E), and examined under light microscopy. A scoring system was used for histopathological evaluation (H&E, 40× magnification):

Score 0: No inflammation observed

Score 1: Inflammatory cells occasionally observed

Score 2: Mild mucosal edema, mild bleeding, or mild lesions

Score 3: Severe wound, severe lesions, edema, and tissue necrosis

Statistical Analysis

Data are presented as mean ± SEM. One-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test was used to compare the studied groups. Statistical analysis and graph illustrations were performed using GraphPad Prism software version 8.0 (GraphPad Software Inc., San Diego, CA, USA).

Results were considered statistically significant at $P < 0.05$.

Results

GC/MS Analysis of BGE

Phytochemical analysis of BGE by gas chromatography-mass spectrometry (GC-MS) identified approximately 36 compounds. Among these, α -pinene, dl-limonene, α -terpineol, and β -pinene were the major constituents, exhibiting various biological activities including antimicrobial, antioxidant, anti-inflammatory, antitumor, and analgesic effects^{18, 24, 25}.

Results of the Range-Finding Study and LD₅₀ Determination

According to the results of the range-finding study, a dose of 145.6 $\mu\text{g/mL}$ was identified as the LD₅₀ dose of BGE in mice. Therefore, in the current study, a dose of 25 $\mu\text{g/mL}$ was selected as a sub-lethal dose with no associated mortality.¹⁸

Results of Confirmation of Disease Induction

Figure 1 shows the results of disease induction in all studied groups. A significant decrease was observed in all groups compared to the control group ($P < 0.001$), with no statistically significant difference between the pre-induction and post-induction and mesalazine treatment groups ($P > 0.05$).

Myeloperoxidase Enzyme Levels

The results showed that myeloperoxidase production decreased significantly in all study groups compared to the control group (Figure 2) ($P < 0.0001$). Statistically significant difference was observed between the pre-induction treatment group and the post-induction treatment group ($P < 0.0001$). The reduction level was greater in the pre-induction treatment group. Additionally, no statistically significant difference was observed between the pre-induction treatment group and the mesalazine group ($P > 0.05$).

Nitric Oxide Levels

The results showed that nitric oxide production decreased significantly in all study groups compared to the control group (Figure 3) ($P < 0.0001$). Statistically significant difference was observed between the pre-induction treatment group and the post-induction treatment group ($P < 0.001$). Also, a statistically significant difference was observed between the two treatment groups (pre-induction and post-induction) and the mesalazine group ($P < 0.0001$).

Levels of Inflammatory Cytokines

Figures 4–6 show the measured levels of inflammatory cytokines. The levels of these factors showed a significant decrease in all studied groups compared to the control group ($P < 0.0001$). No statistically significant difference was observed between the pre-induction treatment group and the post-induction treatment group ($P > 0.05$). Also, a statistically significant difference was observed between the two treatment groups (pre-induction and post-induction) and the mesalazine group ($P < 0.0001$).

Histopathological Results

Figure 7 presents the results of the histopathological study. As observed, histopathological damage to colon samples decreased significantly in all studied groups compared to the control group ($P < 0.0001$). No statistically significant difference was observed between the pre-induction treatment group and the post-induction treatment group. Furthermore, no statistically significant difference was observed between the pre-induction treatment group and the mesalazine group ($P > 0.05$).

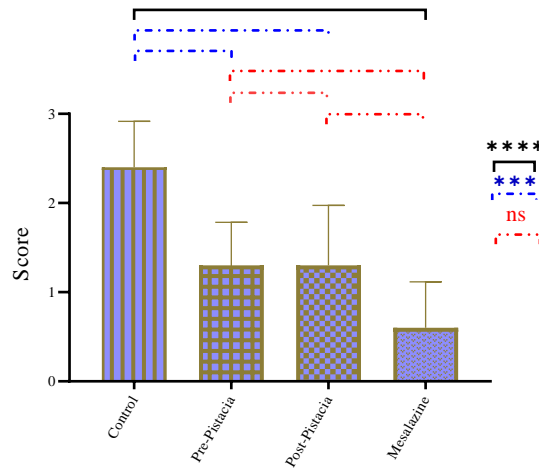


Figure 1. Results of the disease induction in different studied groups (* indicates $P<0.05$, ** indicates $P<0.01$, *** indicates $P<0.001$, **** indicates $P<0.0001$).

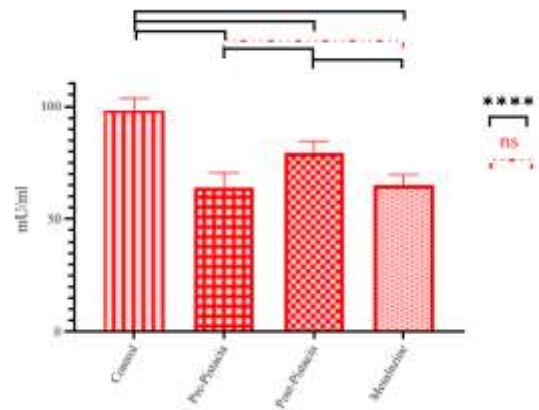


Figure 2. The measured levels of myeloperoxidase (MPO) in different studied groups (* indicates $P<0.05$, ** indicates $P<0.01$, *** indicates $P<0.001$, **** indicates $P<0.0001$).

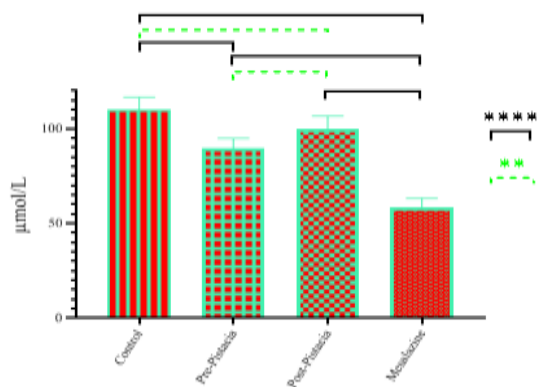


Figure 3. The nitric oxide (NO) levels measured in different studied groups (* indicates $P<0.05$, ** indicates $P<0.01$, *** indicates $P<0.001$, **** indicating $P<0.0001$).

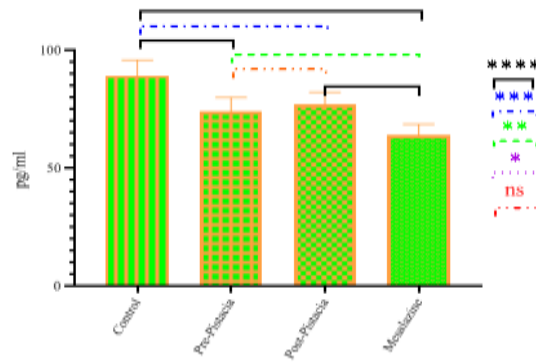


Figure 4. Inflammatory cytokine levels IL-1β in different studied groups (* indicates $P<0.05$, ** indicates $P<0.01$, *** indicates $P<0.001$, **** indicates $P<0.0001$).

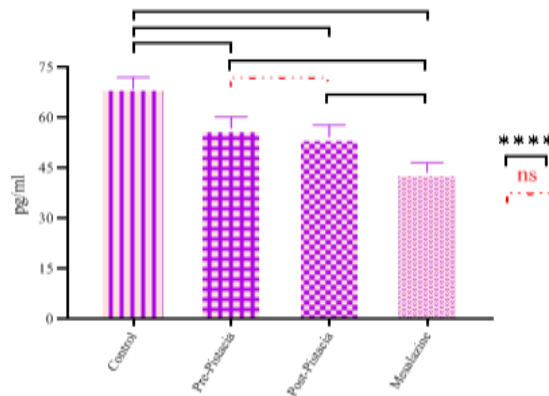


Figure 5. Inflammatory cytokine IL-6 levels in different studied groups (* indicates $P<0.05$, ** indicates $P<0.01$, *** indicates $P<0.001$, **** indicates $P<0.0001$).

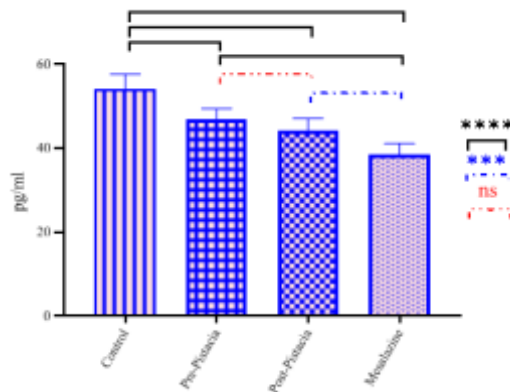


Figure 6. Levels of inflammatory cytokine TNF-α in different study groups (* indicates $P<0.05$, ** indicates $P<0.01$, *** indicates $P<0.001$, **** indicates $P<0.0001$).

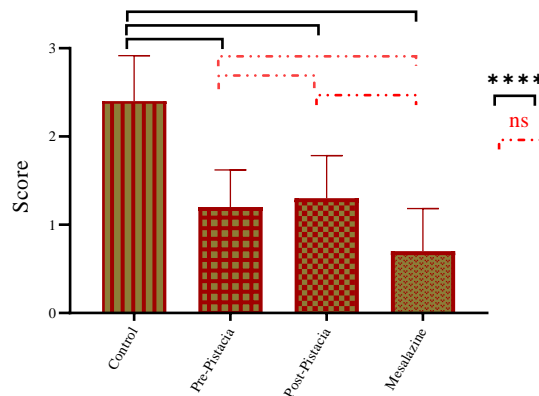


Figure 7. Pathological index based on scoring system in different studied groups (* indicates $P<0.05$, ** indicates $P<0.01$, *** indicates $P<0.001$, **** indicates $P<0.0001$).

Discussion

Natural herbal products have beneficial effects on inflammatory bowel diseases, including UC. Several studies have suggested the therapeutic efficacy of medicinal plants and natural products, including *chamomile* flower extract, *Andrographis paniculata* extract, *myrrh*, *curcumin*, Chinese medicine (Xilei-san), and *Fufangkushen* in patients afflicted with UC^{25,26}. *Pistacia atlantica*, from the Anacardiaceae family, is one of the wild pistachio species in Iran, which includes Mutica, Kurdika, and Kabolica cultivars. Its distribution ranges from the Canary Islands and countries on the Mediterranean coast to Asia Minor, Syria, the Caucasus, Iran, Afghanistan, Pakistan, and African countries²⁷⁻²⁹. Mutica and Kurdika subspecies grow wildly in over 1.2 million hectares of western, central, and eastern Iran, particularly in the Zagros region between Fars and Kurdistan provinces³⁰⁻³³. Baneh gum is a traditional medicinal source used for relieving eczema, abdominal pain, diarrhea, indigestion, stomach ulcers, stomach pain, asthma, throat infection, kidney stones, and as an astringent, anti-fever, anti-viral, and antibacterial agent³¹⁻³³.

Previous studies reported α -pinene as the main chemical constituent of BGE, with β -pinene, sabinene, and trans-verbenol as other chemical constituents^{34,35}. These findings agree with our study, which revealed that the main phytochemical constituent of BGE (*Pistacia atlantica* Desf.) was α -pinene, with other chemicals including dl-limonene, α -terpineol, and β -pinene. These compounds exhibit antimicrobial, antibacterial,

antifungal, antioxidant, and anti-inflammatory properties^{36,37}. Thus, the anti-inflammatory effects of BGE can be attributed to the active compounds investigated in the current study.

We showed that BGE significantly decreased the levels of inflammatory mediators such as myeloperoxidase and nitric oxide, as well as inflammatory cytokines including IL-1, IL-6, and TNF- α . In 2014, Tanideh et al. found relieving effects of oral and rectal administration of *Pistacia atlantica* fruit oil extract on a rat model of UC based on histopathological changes³⁸; however, inflammatory biomarkers were not investigated in their study. Our study demonstrated the ameliorative effects of BGE through both histopathological findings and inflammatory biomarkers. In 2019, Farokhi et al. reported that oleoresin extracted from Baneh gum reduced inflammatory cytokines and showed promising protective effects against tissue damage in an experimental rat model of UC³⁹. Another study reported the beneficial effects of the essential oil of *Pistacia atlantica* in an experimental rat model of acetic acid-induced UC⁴⁰. The authors found that oral administration of Baneh gum essential oil reduced cyclooxygenase-2 levels and alleviated histopathological changes in the animals' colons. In an investigation evaluating the beneficial effects of *Pistacia atlantica* subsp. kurdica gum in an experimental rat periodontitis model, Azeez et al. (2020) showed gingival anti-inflammatory properties of topical application of the extract by lowering IL-1 β levels⁴¹. Shakarami et al. (2019) showed that the aqueous extract

of *Pistacia atlantica* gum modulated the immune system in an animal model of asthma by diminishing inflammatory cytokine levels and histopathological changes in the lungs of BALB/c mice⁴².

Collectively, these findings underscore the broad therapeutic applications of *Pistacia atlantica* and its derivatives, including BGE. Future studies can investigate its long-term efficacy, safety, and potential clinical application in combination with standard treatments for UC and other inflammatory diseases. This could pave the way for novel, cost-effective, and natural therapeutic options in clinical settings.

Limitations

This study provides valuable insights into the therapeutic potential of BGE in managing UC. However, certain limitations should be acknowledged to place the findings in proper context.

First, the study relies exclusively on an animal model, which, while helpful for understanding disease and treatment mechanisms, cannot fully replicate the complexity of UC in human patients. The immune system, microbiota composition, and disease progression in humans differ significantly from those in mice, which may affect the translational relevance of the findings. Additionally, no human clinical trials were conducted to validate the safety, efficacy, or optimal dosing of BGE for treating UC.

Second, the investigation focuses on short-term outcomes by measuring inflammatory markers and histopathological changes over a limited timeframe. The study does not address the long-term effects of BGE, such as its potential to prevent disease recurrence or progression, which is critical for chronic conditions like UC. The absence of longitudinal data limits understanding of whether the observed benefits are sustained over time or if additional treatments would be necessary to maintain remission.

Furthermore, while the study demonstrated BGE's effectiveness in reducing inflammatory cytokines and improving histopathology, it did not explore potential mechanisms in greater detail. For instance, the pathways modulated by BGE—such as specific gene expression changes or its effects on gut microbiota—were not examined. Exploring these mechanisms would provide a deeper understanding of how BGE exerts its therapeutic effects.

The potential interactions between BGE and standard UC treatments, such as mesalazine, were not studied.

Understanding these interactions is vital for determining whether BGE can be safely and effectively used in combination therapies.

Finally, the study does not detail the systemic effects of BGE or its safety profile. While the LD₅₀ was determined, there is limited information on potential side effects, organ toxicity, or pharmacokinetics, which are essential for future clinical applications. Addressing these gaps in future studies would significantly enhance the clinical relevance and applicability of BGE as a therapeutic option for UC.

Conclusion

In the present study, we elucidated the ameliorative properties of BGE in a mouse model of acetic acid-induced UC. BGE demonstrated anti-inflammatory properties by reducing inflammatory mediators and cytokines, including myeloperoxidase, nitric oxide, IL-1 β , IL-6, and TNF- α . These findings suggest that BGE, with its rich composition of bioactive compounds such as α -pinene, β -pinene, and dl-limonene, could serve as a cost-effective and safer alternative or adjunct to conventional treatments for UC. Accordingly, further research to evaluate the efficacy and safety of this natural product in clinical settings is encouraged to assess its potential application as an adjuvant treatment alongside conventional drugs used in patients with UC.

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Conflict of Interest Disclosures

The authors have no relevant financial or non-financial interests to disclose.

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Authors' Contributions

Conceptualization: Ebrahim Salimi-Sabour, Majid

Mirzaei Nodoushan, Mohammad Amrollahi-Sharifabadi, Hadi Esmaeili Gouvarchinghaleh; Methodology, validation, analysis, investigation, and resources: Majid Mirzaei Nodoushan, Mohammad Amrollahi-Sharifabadi, Ebrahim Salimi-Sabour, Alireza Shahriary, Javad Raouf Sarshori, Hadi Esmaeili Gouvarchinghaleh; Data curation, original draft preparation, editing, and reviewing: Majid Mirzaei Nodoushan, Ebrahim Salimi-Sabour, Mohammad Amrollahi-Sharifabadi, Hadi Esmaeili Gouvarchinghaleh, Alireza Shahriary, Javad Raouf Sarshori, Visualization, supervision, and project administration: Ebrahim Salimi-Sabour, Majid Mirzaei Nodoushan, Mohammad Amrollahi-Sharifabadi, Hadi Esmaeili Gouvarchinghaleh. All authors read and approved the final version of the manuscript.

Ethical Statement

All experimental procedures of the current research were approved by the Research Ethics Committee of Baqiyatallah University of Medical Sciences (ethical code IR.BMSU.AEC.1400.016), conforming with the national and international ethical legislations, including ARRIVE guidelines for in vivo animal studies.

Declaration of Generative AI and AI-assisted technologies

Not used.

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