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Pistacia atlantica gum and ulcerative colitis: From hypothesis to reality

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Executive Summary

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) characterized by secretory and motility dysfunctions of the intestinal tract. Conventional pharmacological therapies are often associated with significant side effects and impose high costs on patients. In recent years, natural compounds have gained attention as complementary treatments. The present study aimed to investigate the therapeutic effects of *Pistacia atlantica* gum extract on histopathological and immunological markers in an experimental model of UC. The results demonstrated that *Pistacia atlantica* gum extract, administered either before or after disease induction, significantly reduced the levels of inflammatory mediators and cytokines compared to the positive control group. Overall, our findings suggest that *Pistacia atlantica* gum extract alleviates the symptoms of ulcerative colitis in this experimental model. It may serve as a promising complementary treatment option for UC patients; however, further molecular investigations are required to elucidate its mechanisms of action.

Keywords: *Pistacia atlantica*, Ulcerative Colitis, Inflammation, Cytokines, Herbal Therapy

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Introduction

Inflammatory bowel diseases (IBD), particularly ulcerative colitis (UC), are chronic, relapsing conditions that have been increasingly diagnosed in pediatric and adolescent populations.[1] UC most commonly manifests during the second decade of life, although a secondary peak may occur later in adulthood. The disease significantly impairs quality of life due to persistent symptoms and potential complications, such as growth retardation and anemia in young patients, and often imposes a considerable socioeconomic burden.[2] Despite advancements in therapeutic options and understanding of IBD pathogenesis, a definitive cure for UC remains elusive.[3] Current treatments, including corticosteroids, immunomodulators, and biologics, aim to reduce inflammation and manage symptoms but are often accompanied by serious adverse effects and limited efficacy in some patients.[4,5] The overarching goals of UC therapy are to induce and maintain remission, prevent complications such as colectomy, and minimize drug-related toxicity.[6] However, the long-term use of immunosuppressive agents, particularly biologics like anti-TNF therapies, has been associated with heightened risks of infections and malignancies, including colorectal cancer.[7,8] These limitations have spurred interest in the development of safer, more effective alternative or adjunctive therapies, particularly from natural sources with anti-inflammatory and antioxidant properties.[9] Histopathologically, UC is characterized by infiltration of neutrophils and macrophages into the colonic mucosa. Activated neutrophils generate reactive oxygen species (ROS), including superoxide anion, hydroxyl radicals, and hydrogen peroxide, leading to lipid peroxidation, increased vascular permeability, further leukocyte recruitment, and tissue damage.[10] These oxidative insults upregulate

inflammatory gene expression and contribute to ulceration, hemorrhage, and diarrhea. Oxidative stress is also associated with depletion of endogenous antioxidant defenses, aggravating disease severity.[11] Therefore, antioxidants are proposed as supportive agents to mitigate inflammation and reduce relapse risk. One such potential agent is Artemisia dracunculus(Tarragon), a medicinal herb long used in Iranian and East Asian traditional medicine for various ailments, including gastrointestinal disorders.[12] Phytochemical analyses have identified compounds such as flavonoids, tannins, and terpenoid saponins, which contribute to its antioxidant and anti-inflammatory effects.[13,14] Recent experimental studies suggest that tarragon extract can reduce colon carcinogenesis and ameliorate colitis in animal models by modulating oxidative stress and apoptotic pathways, highlighting its potential as a complementary therapy in UC management.[15]

Materials and Methods

Male BALB/c mice weighing 20–30 g and aged 6–8 weeks were obtained from the animal facility. For LD50 determination, six groups of six mice each received increasing logarithmic oral doses (µg/mL) of *Pistacia atlantica* gum extract daily, and mortality rates were recorded to calculate LD50 using GraphPad Prism version 8. For the main study, a total of 40 mice were randomly divided into four equal groups: Control group: UC was induced but no treatment was administered, Pre-treatment group: Received the extract orally for 40 days, starting 10 days before UC induction, Post-treatment group: Received the extract orally for 30 days after UC induction, Positive control group: Received mesalazine orally after UC induction. All animals were housed under standard laboratory conditions (temperature, humidity, light/dark cycle) with free access to food and water. Prior to disease induction, mice were fasted for 36 hours with water available ad libitum. Ulcerative colitis was induced via rectal administration of 4% acetic acid under light ether anesthesia using a polyethylene catheter. For histopathological assessment, mice were euthanized, and colonic tissues were harvested and fixed in 10% formalin. Paraffin-embedded sections were stained with hematoxylin and eosin (H&E), and microscopic evaluation was performed by a blinded pathologist for parameters such as focal and generalized hyperemia, mucosal ulceration, crypt destruction, hemorrhage, and inflammatory cell infiltration.

Results

The GC-MS analysis revealed that α-pinene was the predominant component of *Pistacia atlantica* gum extract. The LD50 value of the extract was approximately calculated, and a dose that caused no mortality was selected for further experimentation. The Disease Activity Index (DAI) significantly decreased in all treatment groups compared to the control group. However, there was no statistically significant difference between the pre-treatment and post-treatment groups. Myeloperoxidase (MPO) levels also showed a significant reduction in all treatment groups compared to the control group. Notably, MPO reduction was greater in the pre-treatment group than in the post-treatment group, and no significant difference was observed between the pre-treatment and mesalazine-treated groups. Nitric oxide (NO) production was significantly decreased in all treatment groups compared to the control group, with no significant difference between the pre- and post-treatment groups. However, both treatment groups (pre- and post-induction) showed statistically significant differences when compared to the mesalazine group. Inflammatory cytokine levels were also significantly reduced in all treatment groups compared to the control group. No significant difference was observed between the pre- and post-treatment groups, but both groups differed significantly from the mesalazine group. Histopathological analysis showed a significant reduction in tissue damage in all treatment groups compared to the control group. There was no significant difference between the pre- and post-treatment groups, nor between the pre-treatment and mesalazine groups. However, a statistically significant difference was observed between the post-treatment group and the mesalazine group.

Discussion and Conclusion

In recent years, there has been a growing interest in the use of medicinal plants for managing chronic inflammatory diseases, driven by their therapeutic potential and minimal side effects. Among these, *Pistacia atlantica* (Beneh), a wild pistachio species native to Iran, has drawn attention due to its diverse pharmacological properties. Its gum, traditionally used for gastrointestinal and respiratory disorders, contains bioactive compounds such as α-pinene and β-pinene, which have demonstrated antioxidant, anti-inflammatory, and antimicrobial activities.[16] This plant's prevalence in the Zagros region and deep roots in Iranian traditional medicine underscore its relevance as a promising natural remedy. The present study investigated the therapeutic effects of *Pistacia atlantica* gum extract in a rat model of ulcerative colitis (UC). The results revealed a significant reduction in Disease Activity Index (DAI), myeloperoxidase (MPO), nitric oxide (NO), and key inflammatory cytokines (IL-1, IL-6, and TNF-α) following both prophylactic and therapeutic administration of the extract. These findings indicate that the extract can modulate the inflammatory response and improve histopathological outcomes in UC, likely through its immunomodulatory and antioxidant mechanisms. These outcomes align with previous studies that have

demonstrated similar anti-inflammatory and tissue-protective effects of *Pistacia atlantica* gum and essential oil in experimental models of colitis and other inflammatory conditions. For instance, Shohan et al. demonstrated that P. atlantica gum reduced inflammation and improved periodontal infections and skin wound healing in rats.[17] The anti-inflammatory effects of other constituents found in *Pistacia atlantica* gum, such as carvacrol, were demonstrated in a study by Feng et al., where carvacrol significantly reduced TNF-α, IL-6, and IL-1β levels and ameliorated LPS-induced acute lung inflammation in a murine model.[18] Esmaeili et al. and Shahkarami et al. reported immunomodulatory effects of aqueous gum extract on humoral and cellular immunity, as well as asthma models.[19,20] Tanideh et al. and Farokhi et al. confirmed reductions in inflammatory markers and tissue damage[21,22], while Bahrami et al. identified optimal dosing for therapeutic efficacy.[23] Additional studies on α-pinene, carvacrol, and related phytochemicals have reinforced the anti-inflammatory and antimicrobial capacity of this plant, supporting its potential use in inflammatory bowel disease. In conclusion, *Pistacia atlantica* gum extract exerts meaningful anti-inflammatory and tissue-regenerative effects in experimental UC. Its natural origin, favorable safety profile, and biological activity suggest it may serve as an effective adjunctive therapy alongside standard medications for ulcerative colitis. Further studies, particularly clinical trials, are warranted to validate its therapeutic potential and determine its optimal formulation and dosing in humans.

Conflicts of Interest Disclosures

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent For Publication

Not applicable

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