



Protective Effect of Nanoparticles of Oleoresin of *Pistacia atlantica* var. *mutica* against Acetic Acid-Induced Ulcerative Colitis in Rats

Maryam Naseri¹, Hanieh Delfani¹, Shahla Mirzaeei¹, Gholamreza Bahrami¹,
Mohammad Hosein Farzaei^{1*}, Pardis Mohammadi Pour²

¹Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, 6734667149, Iran

²Department of Pharmacognosy, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, 8174673461, Isfahan, Iran

Received: 6 Jul 2021

Revised: 9 Oct 2021

Accepted: 12 Oct 2021

Abstract

Dying Various therapeutic activities of *Pistacia atlantica* var. *mutica* such as hypoglycemic, antioxidant and anti-inflammatory activity were shown by several studies. Regarding these therapeutic activities, and due to advantages of nanoparticles for drug delivery systems, the anti-colitic effects of *P. atlantica* var. *mutica* oleoresin nanoparticles were studied in acetic acid-induced ulcerative colitis in rats. Nanoparticles were synthesized by using ethanol and acetone as solvent. Nano precipitation method was also used for nanoparticles synthesis. *P. atlantica* oleoresin was orally administered to acetic acid-induced colitis rats at the doses of 50, 100 and 200 mg/kg. Then rats were killed and their colons were dissected away for histopathological and macroscopic tests. Statistical results showed homogeneity and uniformity in size and size distribution of fabricated nanoparticles. Proposed models for size and size distribution of nanoparticles were also adequate (P value < 0.05). All doses of nanoparticles of *P. atlantica* oleoresin significantly reduced macroscopic damage score. The microscopic study also showed anti-colitic activities of *P. atlantica* oleoresin nanoparticles. Administration of 200 mg/kg of fabricated nanoparticles showed better anti-inflammatory and healing effects compared to other doses. Our results showed that nanoparticles of *P. atlantica* var. *mutica* oleoresin might be an effective agent to treat ulcerative colitis disease, due to the therapeutic activities of the plant and desirable properties of fabricated nanoparticles. Therefore, nanoparticles of *P. atlantica* var. *mutica* oleoresin might provide an alternative drug for colonic inflammation.

Keywords: *Pistacia atlantica*; Ulcerative colitis; Nanoparticle; Rat; Persian medicine

Introduction

Inflammatory bowel disease (IBD) is one of the most important chronic inflammatory disorders of the gastrointestinal tract, which includes Crohn's disease (CD) and ulcerative colitis (UC) [1]. World Gastroenterology Organization has declared that occurrence of IBD is more common in cities than villages. Also,

people in the third decade of their life have the highest incidence of IBD than any other decades [2]. The exact etiology of IBD still remains far from clear; nonetheless genetic, environmental, multiple immune and oxidative stress were reported as effective factors in the pathogenesis of IBD [3-5].

CD is distinguished from UC by the location and na-

Citation: Naseri M, Delfani H, Mirzaeei S, Bahrami G, Farzaei MH, Mohammadi Pour P. **Protective Effect of Nanoparticles of Oleoresin of *Pistacia atlantica* var. *mutica* against Acetic Acid-Induced Ulcerative Colitis in Rats.** Trad Integr Med 2022;7(2):161-170.

*Corresponding Author: Mohammad Hosein Farzaei

Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, 6734667149, Iran

Tel: +98-8334266780

E-mail: mh.farzaei@gmail.com

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face charge (Zeta potential) of fabricated nanoparticles were all measured by using Zetasizer analyzer (Zetasizer Nano ZS, Malvern, UK), in water and ambient temperature.

Transmission electron microscopy (TEM)

Synthesized nanoparticles were examined in a Philips CM120 transmission electron microscope to determine their morphology on the optimum conditions.

Fourier transformation infrared (FT-IR)

The FT-IR spectrum of fabricated nanoparticles were carried out using infrared spectrometer (IRPrestige-21, Shimadzu, Japan) conducted to identify and study functional groups of synthesized nanoparticles of *P. atlantica*.

Experimental Animals

Experiments were done using matured Wistar strain female albino rats (170-200 g), which were gifted from Razi Vaccine and Serum Research Institute. The animals were maintained for a week under standard controlled laboratory condition (12 h light/dark photo-cycle, temperature (23 ± 2) °C) with ad libitum access to food and water. The study was done in compliance with the ethical principles about using laboratory animal guidelines and all the protocols were approved by the Institutional Ethics Committee of Kermanshah University of medical sciences (ethical approval code: IR.KUMS.REC.1397.290).

Acetic acid-induced ulcerative colitis

Forty healthy female Wistar rats were used to investigate the anti-ulcer effects of fabricated nanoparticles. These rats randomly divided into eight groups, each include five rats. Group 1 served as normal control group and received distilled water and Group 2 (Sulfasalazine group) was administered by standard sulfasalazine at dose of 500 mg/kg body weight. Groups 3-5 were treated by *P. atlantica* oleoresin nanoparticles at doses of 50, 100 and 200 mg/kg body weight, respectively. Groups 6-8 were treated by *P. atlantica* oleoresin at doses of 50, 100 and 200 mg/kg body weight, respectively. Oral gavage treatments were given 7 days. For 24 h prior to the induction of UC, the animals were fasted with access to water ad libitum. Rats were anesthetized by ketamine (10%) following a 24-h fasting and received enemas of 4 mL acetic acid (4%) in water. The rats were maintained in head-down position to avoid expelling the solution. All acetic acid-administered rats were sacrificed 72 h later and their colons were removed. Colons were used for macroscopic scoring and microscopic evaluations [25].

Macroscopic Evaluation of colitis

Distal 7 cm of colon was excised and opened by a

longitudinal incision. The colons were immediately examined under a stereomicroscope and scored according to Morris et al. method [26] by two independent observers without previous knowledge of the treatments, as follow:

0 = damage, 1 = Localized hyperemia, but no ulceration, 2 = Linear ulcers with no significant inflammation, 3 = Linear ulcer with significant inflammation at one site, 4 = Two or more sites of ulceration and/or inflammation, 5 = Two or more major sites of ulceration and inflammation or one major site of inflammation and ulcer extending > 1 cm along the length of the colon. "Inflammation" was defined as regions of hyperemia and bowel wall thickening.

Histopathological studies of colitis

Freshly excised colon tissues of rats were fixed and then embedded in 10% formalin solution for histopathological studies. Colon sections were stained with H & E and reviewed by a blinded pathologist (Dr Khodabakhsh Rashidi) by using optical microscope.

Statistical analysis

Data were analyzed by Design Expert software (Version 8.0.7.1, statEase, Inc., USA). The differences between groups were carried out by one-way analysis of variance (ANOVA) and Tukey test on InStat software (Graphpad InStat 3 Software, Inc., USA). The values were expressed as mean \pm SD and P values < 0.05 were considered as significant.

Results

Results of fabricated nanoparticles

The size of nanoparticles ranged from 155.1 to 288.4 nm and size dispersion index of nanoparticles (nPDI) ranged from 0.064 to 0.315, which showed nanoparticle fabricated with desirable size and size distribution for pharmaceutical purposes. By introducing the response variables (size and nPDI) for Design Expert software, equations for size and PDI of nanoparticles were modeled and P values for these modeled equations were investigated. Finally, the results showed that the quadratic regression model was statistically appropriate at 95% confidence level, $P < 0.0001$ and insignificant values of "Prob. > F" and lack-of-fit, which showed this model was significant and adequate.

Optimization was applied after correlating the size and nPDI to experimental variables and ensuring the accuracy and validity of model. Eventually, results showed insignificant difference between optimum values obtained experimentally and those predicted by model (P value < 0.05). As a result, the optimum size of nanoparticles and nPDI of *P. atlantica* var. *mutica* oleoresin were 173.6 nm and 0.06, respectively, by

using ethanol as solvent at the concentration of plant oleoresin of 3.18% (w/v) and aqueous/organic volume ratio of 1/14.85. The results showed that predicted amounts of size and PDI of nanoparticles from software greatly corresponded with the actual amounts for the size and PDI of nanoparticles [24].

The size distribution of fabricated nanoparticles (Figure 1) showed that nanoparticles were fabricated with uniform size. Zeta potential results also represented nanoparticles with high stability in the circulatory system (Figure 2). Morphology of fabricated

nanoparticles (TEM results) showed the appropriate surface properties of nanoparticles (Figure 3) and Fourier transform infrared (FT-IR) peaks (Figure 4) represented the functional groups of phenolic compounds and infrared peaks were also observed as follows: 2926 cm^{-1} (C-H stretching), 2858 cm^{-1} (N-H stretching vibration of amide II), 1510 cm^{-1} (amide II), 1462 cm^{-1} (amine I bands), 1130 cm^{-1} (C-N of amines), 833 cm^{-1} (N-H out of plane bending), and 615 cm^{-1} (N-C=O bending) [27,28]. All the peaks represented the functional groups of terpenoids in

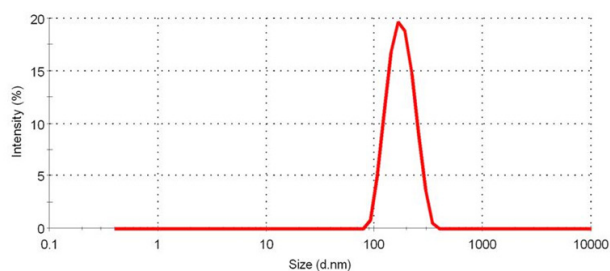


Figure 1. Size distribution of *Pistacia atlantica* oleoresin nanoparticles at optimal conditions

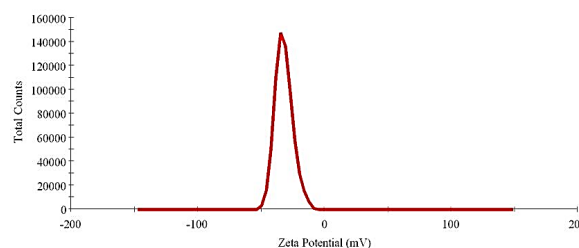


Figure 2. Zeta potential distribution of *Pistacia atlantica* oleoresin nanoparticles at optimal conditions

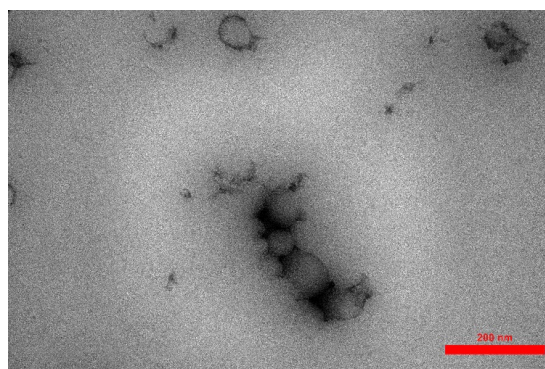
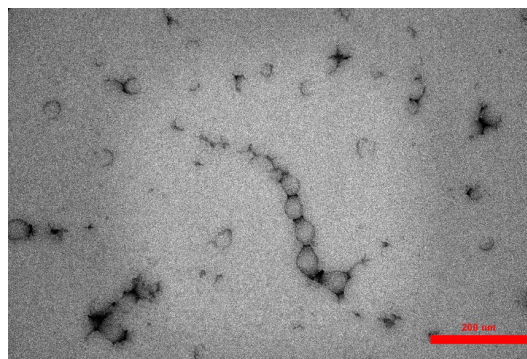
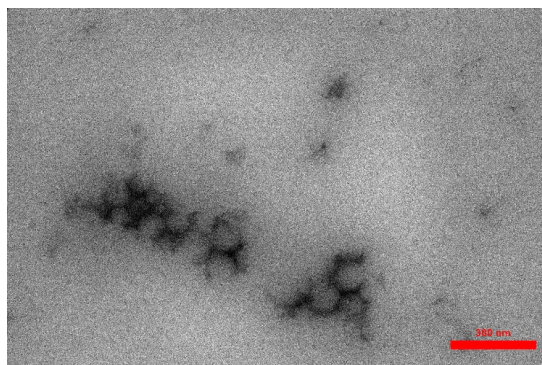


Figure 3. TEM results of *Pistacia atlantica* oleoresin nanoparticles at optimal conditions

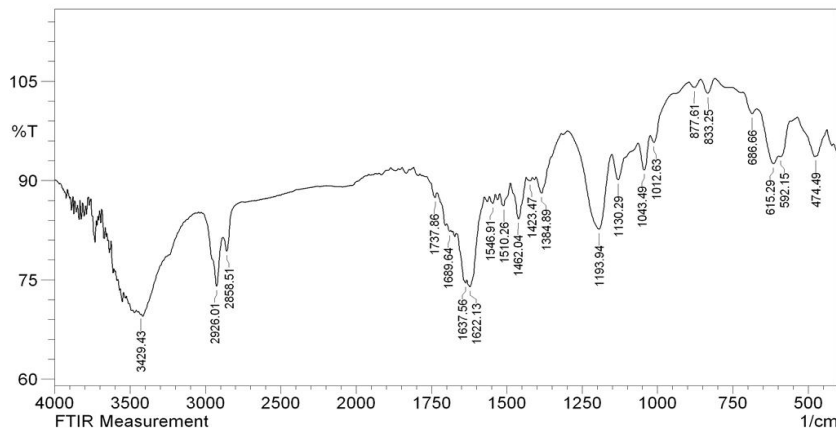


Figure 4. FT-IR analysis of *Pistacia atlantica* oleoresin nano particles at optimal conditions

the nanoparticles from plant oleoresin [24].

Anti-colitic activity of the nanoparticles of P. atlantica var. mutica oleoresin

Macroscopic evaluation

The photographs of distal colon and macroscopic evaluation of colitis in different groups of rats after acetic acid administration are shown in figures 5 and 6, respectively. Normal colon mucosa was visible in normal rat (A); while in control group rat (I) bleeding, bowel wall thickening and inflammation were observed (Figure 5). The mean macroscopic score of acetic acid control group (4 ± 0.82) was found to be significantly ($P < 0.05$) increased as compared to sulfasalazine group (0.8125 ± 0.24). In rats treated with *P. atlantica* oleoresin and oleoresin nanoparticles (50, 100 and 200 mg/kg) the colonic macroscopic score significantly decreased in comparison with control group. Treatment with nanoparticles of *P. atlantica* oleoresin compared to treatment with *P. atlantica* oleoresin caused reduction of macroscopic damage score. Administration of nanoparticles (100, 200 mg/kg) led to reduction of macroscopic score of colon (0.375 ± 0.25 and 0.25 ± 0.29 resp.) significantly ($P < 0.05$) as compared to sulfasalazine group (Figure 6). As it can be seen in figure 6, administration of 200 mg/kg of nanoparticles of *P. atlantica* oleoresin showed the highest pharmacological effect (the least damage score) than other doses of nanoparticles as compared to sulfasalazine group and control group, then 100 mg/kg of nanoparticles showed higher pharmacological effect (less damage score) than 50 mg/kg of nanoparticles as compared to sulfasalazine group and control group. On the other hand, 50 mg/kg of nanoparticles only showed a significant difference compared to the control group.

Microscopic evaluation

Microscopic findings of the different groups of rat studied by the histopathological analysis is presented in figure 7. The normal group did not have any histopathological damage; while massive necrotic destruction of the epithelium, disruption of the structure of folds, short and abnormal crypts, bleeding and severe inflammation with white blood cells accumulation were observed in control group rats. Treatment with Sulfasalazine significantly decreased the extent and severity of lesion and inflammation, normal crypt in colonic mucosa when compared with control group. The 50 and 100 mg/kg of oleoresin nanoparticle group showed mild and moderate protection against necrotic destruction of epithelium, respectively. While 200 mg/kg of oleoresin nanoparticle reduced the histological signs of colon injury and showed most protection activity in colitis rat. Thus recovery of mucosa from colon damage were observed in *P. atlantica var. mutica* oleoresin nanoparticles treatment dose-dependently.

Discussion

IBD as a gastrointestinal disease includes Crohn's disease and UC. The exact etiology of these diseases is unknown. Variable pathophysiological mechanisms were characterized by clinical manifestations have been reported as possible causes of these diseases, which involved weight loss, diarrhea, abdominal pain and blood in the stool [29]. Treatment of these diseases is difficult, costly, and is associated with serious adverse effects and uncertain response to the treatments [20].

Therefore, several studies on herbal medicines as suitable and important positions for IBD treatments, have

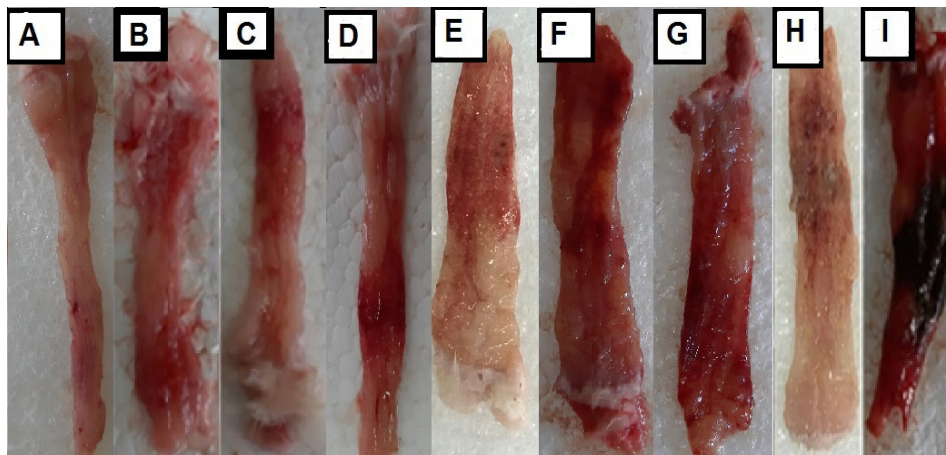


Figure 5. The distal colon appearance, A: normal group; B: sulfasalazine group; C-E: The synthesized *P. atlantica* oleoresin nanoparticles treated group by 200, 100 and 50 mg/kg body weight, respectively; F-H: The *P. atlantica* oleoresin treated group by 200, 100 and 50 mg/kg body weight, respectively; I: control group

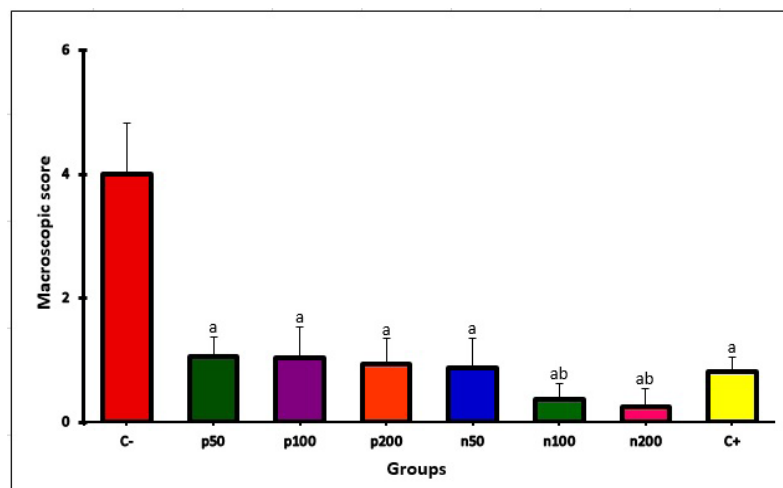


Figure 6. The effect of administration of different dose of oleoresin and nanoparticle of *P. atlantica* oleoresin Control group: administration of distilled water; P50, 100 and 200: The *P. atlantica* oleoresin treated group by 50, 100 and 200 mg/kg body weight, respectively; N50, 100 and 200: The synthesized *P. atlantica* oleoresin nanoparticles treated group by 50, 100 and 200 mg/kg body weight, respectively; sulfasalazine group: 500 mg/kg, values represent mean \pm standard error of the mean of protection rate. Means with different superscripts differ statistically (One-way ANOVA analysis of variance followed Tukey test). a: $P < 0.05$, significant difference compared with control group; b: $P < 0.05$, significant difference with sulfasalazine group

been conducted to control and prevention of UC [30-32]. Nonetheless, issues associated with the biocompatibility, toxicity and large sized materials of natural compounds face appreciable limitations for using these herbal medicines including instability, poor bioavailability, low solubility and absorption in the body [33]. Thus, introducing nanoparticles as drug delivery systems for targeting drugs to specific body parts can improve the therapeutic value of various water soluble/insoluble medicinal drugs [33,34]. Polymeric drug carriers of nanoscale size range have attracted significant attention of pharmaceutical scientists in recent years [35-37] due to high drug carrying capacity, high stability, high specificity, enhancing the solubility, absorption into a selected tissue, bioavailability, ability for controlled drug release and delivery with immense

success, subcellular size, capability to deliver both hydrophilic and hydrophobic drug molecules [33,38,39]. Therefore, targetable drug carriers based on nanoparticles derived from herbal plants lead to formation of attractive treatment strategy for improving IBD. Wang et al. suggested the grapefruit derived nanovesicles (GDNs) as immunomodulators in the intestine. They demonstrated that intestinal macrophages ameliorate dextran sulfate sodium (DSS)-induced mouse colitis took up GDNs. They also studied the effect of adding methotrexate (MTX) as an anti-inflammatory drug to GDNs and delivering effect of the MTX-GDNs to mice. The reduction of MTX toxicity and enhancement of therapeutic effects were noticeable compared to free MTX [40].

In this study, we focused on the fabrication of poly-

H&E

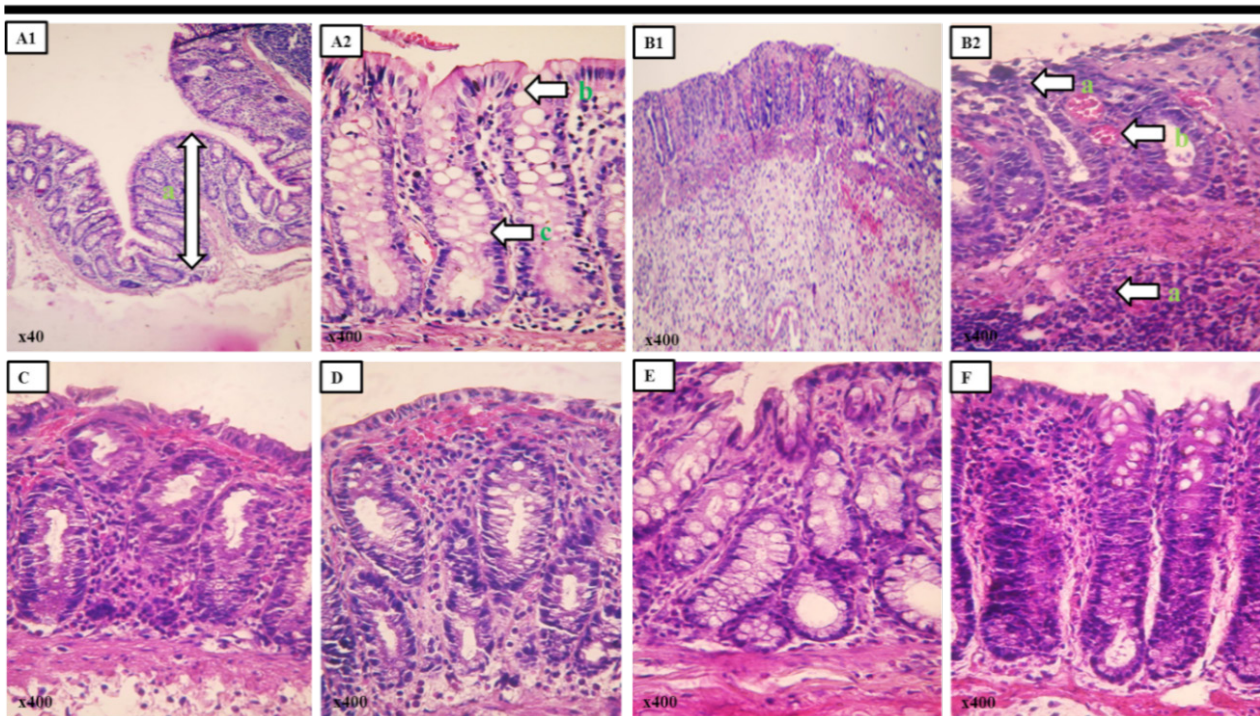


Figure 7. Representative histological slides of rat colonic mucosa. A: Normal control group ($A_1 \times 40$, $A_2 \times 400$); B: Control group ($B_1 \times 40$, $B_2 \times 400$); C-E: *P. atlantica* oleoresin nanoparticles treated group by 50, 100 and 200 mg/kg body weight ($\times 40$); F: Sulfasalazine group ($\times 40$), Arrow a of A_1 : Mucosal folds; arrow b of A_2 : epithelium; arrow c of A_2 : gland; arrow a of B_2 : Inflammatory cells; arrow b of B_2 : blood penetration

meric nanoparticles as drug delivery systems due to appropriate nanoparticles size and distribution range. The particle size and size distributions are especially important features that determine drug loading and release, targeting ability, toxicity and stability. Therefore, narrow size distribution leads to uniformity of system conditions, controlled release and also predictable absorption kinetics, which are desirable for delivery system.

P. atlantica oleoresin is traditionally used for treatment of IBD, but high viscosity and adhesive properties of oleoresin lead to consumption problems for patients and hard delivery of this oleoresin to colon. Therefore, nano-formulation of *P. atlantica* oleoresin by reducing viscosity of oleoresin and improving drug delivery to the target organ might be useful for treatment of UC.

This study was aimed to evaluate the protective effects of different doses of *P. atlantica* var. *mutica* oleoresin nanoparticles in a dose dependent manner on acetic acid-induced colitis in rats at single doses of 50, 100 and 200 mg/kg of rate weight dose.

Oxidative stress in colon tissue as main contributing factor associated with UC leads to product free radicals which release inflammatory mediators and damage intestinal mucosa [19,41].

Tanideh and coworkers suggested *P. atlantica* fruit oil extract as a novel drug for treatment of UC. It was proposed that oral and rectal administration of *P. atlantica* could improve induced colitis physiologically and pathologically in rats and reduce colonic injury by suppressing oxidative damage. This antioxidant activity of *P. atlantica* was attributed to the presence of tocopherols and tocotrienols [19]. It was also evidenced that *P. atlantica* was an effective agent to reduce colon oxidative stress markers in 2,4,6-trinitrobenzene sulphonic acid (TNBS)-induced rat colitis model [42]. The antioxidant activity of *P. atlantica* has been also reported by various investigations [43-45]. Wound healing activity of *P. atlantica* was also reported [46]. These effects might be responsible for possible treatment mechanisms of *P. atlantica* in treatment of colitis.

This study aimed to evaluate the protective effects of different doses of *P. atlantica* var. *mutica* oleoresin nanoparticles for reducing the inflammation in the intestinal mucosa and intestinal tissue repair on acetic acid-induced colitis in rats at single doses of 50, 100 and 200 mg/kg of rate weight. The results demonstrated that nanoparticles of *P. atlantica* oleoresin could reduce colon injury due to its antioxidant and anti-inflammatory activities.

The pathogenesis of colitis was assessed by evaluating the macroscopic and microscopic parameters. Sulfasalazine was used as the standard drug. The macroscopic and microscopic results revealed that synthesized nanoparticles were effective in attenuating inflammation, hyperemia, gastrointestinal mucosal injuries and infiltration of inflammatory cells in rats by intracolonic administration of acetic acid in a dose-dependent manner. The results also showed more reduction of intestinal inflammation severity and intestinal tissue damage following treatment with *P. atlantica* oleoresin nanoparticles, compared with *P. atlantica* oleoresin. The best therapeutic effect was observed at 200 mg/kg of *P. atlantica* oleoresin nanoparticles.

In the present study, we used *P. atlantica* based nano-formulations. It has been proposed that novel drug delivery systems for herbal medicines reduced the repeated administration to overcome non-compliance and increased the therapeutic effects of herbs resulting in reduction of toxicity and enhancement of the bio-availability [47]. The effect of using nanoparticles for treatment of IBD were studied by several researchers. Abdelmegid et al. investigated the therapeutic effect of gold nanoparticles on DSS-induced ulcerative colitis, these nanoparticles could target the colonic tissue and improve injuries induced by DSS [21]. Unique physico-chemical properties of nanoparticles have been reported. Memariani et al. identified *P. atlantica* essential oil of components and reported α -pinene as main responsible component for anti-ulcer activity of *P. atlantica* [15]. Delazar and coworkers analyzed the essential oil of oleoresin of *P. atlantica* to specify oleoresin components. They reported 70% of α -pinene in essential oil of distilled oleoresin of *P. atlantica* [48]. α -pinene was also reported as main component of essential oil of *P. atlantica* by several studies [45,49,50]. Other terpenoids like β -pinene, oleanolic acid, ursonic acid, masticadienonic acid, masticadienolic acid, morolic acid, and 3-O-acetyl-3-epiisomasticadienolic acid were observed in oleoresin of *P. atlantica* [46]. Sivedoroudi et al. performed GC-MS analysis of genuine *P. atlantica* oleoresin and reported 10 components, including α -pinene (95.3 %), α -terpinolene (1.8 %) and β -pinene (1.3 %) [46]. Therefore, terpenoids especially α -pinene are main components of oleoresin of *P. atlantica*. Terpenoids also exhibited by FT-IR spectroscopy analysis of fabricated nanoparticle of oleoresin of *P. atlantica*. However, lack of phytochemical analysis of nanoparticles of *P. atlantica* oleoresin is one of the limitations of this study, which is suggested to be performed in future studies. Antioxidant activity of α -pinene was reported in several works. High reducing power activity, good radical scavenging activity and metal chelating effect of α -pinene indicated high antioxidant activity

of this component [51-53]. Reactive oxygen species (ROS) are associated with UC [54]. On the other hand, α -pinene as antioxidant agent lead to decreased generation of ROS and compensate the harmful effects of excessive ROS by improving endogenous antioxidant defense systems [53], which results in protective effects of α -pinene against UC.

α -Pinene also showed anti-inflammatory properties, which can explain pharmacological activity of α -pinene against UC as an inflammatory bowel disease. This component could suppress the protein expression of the inflammatory mediators, resulting in decreased inflammatory responses [55]. Thus α -pinene, as a main component of *P. atlantica* oleoresin, can be introduced as a therapeutic agent to treat UC. Furthermore, fabricated nanoparticles represented specific kinetics and the ability to distinguish between diseased and healthy sites and reduced doses of drugs, proteins, or siRNA to specific cell types and tissues and the systemic side effects of medications in treatment of IBD [22]. Nanoparticles also showed nontoxic delivery system which targeted inflamed intestinal mucosa, blocked damaging agents and improved healing mechanisms [22,56]. Zhang et al. characterized the effects of nanoparticles derived from edible ginger (GDNPs 2) for prevention and treatment of IBD. They demonstrated that oral administration of GDNPs 2 has the potential to increase the survival and proliferation of intestinal epithelial cells and attenuate the pro-inflammatory cytokines (TNF- α , IL-6 and IL-1b) and increase the anti-inflammatory cytokines (IL-10 and IL-22) in rats with UC [56]. The presence of anti-inflammatory cytokines and anti-inflammatory transduction cascades, reducing oxidative agents and enhancing antioxidant enzymes has been also reported for herbal-based nanostructures [38]. Thus, high ability of nanoparticle structure as a good delivery system and pharmacological activity *P. atlantica* oleoresins as mentioned Persian medicine might be responsible for anti-ulcer activity of fabricated nanoparticles. Therefore, nanoparticles of *P. atlantica* var. *mutica* oleoresin can be suggested as alternative medicines to treat UC.

Investigation of mechanism of anti-ulcer activity of *P. atlantica* oleoresin nanoparticles and investigation of the effects of fabricated nanoparticles on chronic UC model can be suggestions for future studies.

Conclusion

This study demonstrated that oral administration of *P. atlantica* var. *mutica* oleoresin nanoparticles can relieve the UC induced by acetic acid in the colon of rat. Thus, fabricated nanoparticles of *P. atlantica* open up a new chapter for the treatment of UC. These nanoparticles were uniform in terms of size and distribution, which are important and influential factors

of drug delivery systems. *P. atlantica* oleoresin nanoparticles are more effective in relieving inflammation and intestinal tissue injuries compared to *P. atlantica* oleoresin. The anti-ulcer effect of fabricated nanoparticles was dose-dependent and the highest dose of 200 mg/kg of body weight given orally, showed the most effectiveness ones. Future studies are needed to confirm the safety and efficacy of this novel formulation in human.

Funding

This work was supported by Kermanshah University of Medical Sciences (project name: Evaluation of protective effect of *Pistacia atlantica* gum nanoparticles in animal model of colitis, [grant number 97266])

Conflict of Interests

The author certify that no actual or potential conflict of interest in relation to this article exists.

Acknowledgments

None.

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