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Research Article

The study of the anti-inflammatory effects of Baneh gum (*Pistacia atlantica* Desf. or mastic resin) in an in vivo mouse model of carrageenan-induced paw edema

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Abstract

Introduction: Although several studies have highlighted the beneficial effects of Baneh gum extract (BGE), characterizing its anti-inflammatory effects remains an unmet need. The present study aimed to investigate the in vivo effects of the BGE on the inflammation induced by carrageenan in an in vivo mouse model.

Methods: Inflammation induced using carrageenan. The animal population included 50 BALB/c mice with an age range of 6-8 weeks and a weight of 25-30 grams. The animals were divided into 5 groups (n=10 in each group) including inflammation control group (no treatment), intraperitoneal injection group before inflammation (25µg/ml BGE injected intraperitoneally), oral administration group before inflammation (25µg/ml BGE orally administered), the group of intraperitoneal injection concurrently with the induction of inflammation (25µg/ml BGE injected intraperitoneally), the group of oral administration concurrently with inflammation (25µg/ml BGE orally administered). Seven hours after the induction of inflammation, animals euthanized and samples harvested to measure biomarkers including pro-inflammatory and anti-inflammatory cytokines, antioxidant enzyme, oxidative stress indices, and liver enzymes.

Results: Our findings showed that the BGE can significantly reduce the amount of inflammatory cytokines and oxidative stress compared to the control group. Moreover, BGE can augment the amount of antioxidant enzymes and anti-inflammatory cytokines.

Conclusions: Based on the results of this study, it is proposed that the BGE can be a beneficial natural product with anti-inflammatory properties requiring further clinical studies to evaluate its potential application in the treatment of diseases with underlying cause of inflammation.

Keywords: Inflammation, Baneh gum, Anti-inflammatory agent, Ethnopharmacology, carrageenan, *Pistacia atlantica* Desf.

Introduction

Inflammation is a natural reaction of the immune system produced in response to the pathogens and is detected in the acute phase through increased blood flow and increased permeability of vessels along with the accumulation of extracellular fluids, leukocytes and body products such as cytokines.[1] Inflammation is a physiological response to various stimuli such as infection, tissue wounds, and temperature fluctuations which develops quickly and can be exacerbated or subsided depending on the healthcare, dietary, or drug

therapy modalities.[2] Triggers of inflammation can be microbiological (e.g. bacteria, viruses, fungi) or chemical (e.g. allergens, toxins), or physical (heat, ionizing radiations) agents. Inflammation can also occur as a result of an autoimmune reaction in the body, especially in rheumatic diseases. The body tries to remove harmful determinants and replenish the damage through inflammation.[3] Cytokines are protein or glycoproteins mediators that play an important role in inflammation and its regulation. These two groups of mediators are proinflammatory cytokines such as IL-1, IL-6, TNF-α, IL-8, INF-α and anti-inflammatory cytokines such as IL-10, IL-13, and receptors antagonists of IL-6 and IL-1 just to name a few. The existence of a dynamic balance between these two groups of mediators is required to maintain the body homeostasis. In autoimmune diseases, it has been found that the balance between these mediators is disturbed shifting to pro-inflammatory cytokines.[4] However, when there is an increase in pro-inflammatory cytokines and a cytokine storm occurs, large amounts of cytokines enter the bloodstream and affect the entire body, which can lead to dangerous and life-threatening consequence such as a significant drop in blood pressure, multiple organ failure including heart, lung, brain, kidney, sepsis, and even death.[5, 6] Wild pistachio (*Pistacia atlantica* Desf.) is one of the Iranian medicinal plants vernacularly named Bene or Baneh with promising therapeutic properties.[7, 8] This plant is a species of pistachio genus belonging to the Anacardiaceae family that included around 11 different species and subspecies.[9] It is widely grown in the mountainous areas in the western and northwest of Iran as well as semiarid central parts of the country.[10] One of the natural products of *Pistacia atlantica* Desf. is its gum or mastic resin which is called traditionally as Saqqez or Baneh gum (BG) and has various applications in food and pharmaceutical industries and recently researched to use as a biopolymer.[8, 11] BG used as a natural chewing gum in Iran.[12] Moreover, BG has been used in a traditional Persian medicine for different illnesses including abdominal pain, indigestion, stomach ulcers, asthma, eczema, respiratory infections, kidney problems and is well-known for its medicinal properties such as anti-diarrheal, astringent, anti-pyretic, and anti-microbial properties.[7, 13] It is evident that the biological and medicinal effects of plants and natural products are related to their active chemical compounds, which are able to react with the components of the body organs at the cellular and molecular levels based on their physicochemical properties. Although the pharmacologically active chemicals of BG have not been fully studied yet, studies on the essential oils of hull, kernel, or fruit of *Pistacia atlantica*, have showed the presence of phytochemicals of polyphenols and flavonoids such as α-pinene, luteolin, gallic acid, and quercetin just to name a few.[7, 10] Also, an interesting recent study introduced the anti-melanogenic properties *Pistacia atlantica* Desf. extract on in vitro murine cell model suggesting the promising dermatological and cosmetic applications of this natural product.[14] However, there is scarcity of data on the phytochemistry and evaluation of biological activities of the BG, the present study aimed to elucidate the anti-inflammatory effects of BGE (*Pistacia atlantica* Desf. or mastic resin) in an in vivo mouse model of carrageenan-induced paw edema.

Materials and methods

Chemicals

Carrageenan, PBS, RPMI, and FBS were purchased from the Sigma-Aldrich company (St. Louis, MO, USA). Solvents for extraction and analysis were provided with analytical grades. All other materials were sourced from reliable research suppliers with commercial grades.

Plant material

The extract used in the present study was prepared from Saghez Sazi Kurdistan (Van) Co. located in Sanandaj city. According to the interview with the CEO of the company, the gum extract of the tuber plant is processed according to the following steps. Extraction is done by the alcoholic-water soaking method. The gum of the tuber plant was soaked in ethanol and water at a ratio of 3:1 for 48 hours. After this time, the extract was filtered and half of the total volume was added to it, and the solvent was removed at 40°C. After removing the remaining solvent, the extract was dried at 40°C. The dried extract was completely powdered and stored in the refrigerator until use. A few drops of Tween 80 were used as a solvent. All experimental protocols in the current study complied with international rules and legislations including the protection and preservations of natural resources and medicinal plants.

GC-MS phytochemical study

Gas chromatograph model 7890B was manufactured by Agilent company and equipped with FID detector. The length of the column was 5-HM meters, the inner diameter of the column was 0.32 mm, and the thickness of the stationary phase layer was 0.25 µm, and the thermal programming was done from 60 to 280 °C with an increase rate of 5 °C per minute. The temperature of the injection part was set at 250 degrees Celsius and the temperature of the detector was set at 280 degrees Celsius. Helium carrier gas with a flow rate of 1.1 ml/min was used as the mobile phase. Termoquest Finnigan gas chromatograph connected to TRACE MS mass spectrometer and HP SMS column with a length of 30 meters and an internal diameter of 0.25 mm and the thickness of the stationary phase was 0.25 micrometers, the ionization energy was equal to 70 electron volts, thermal planning and type and the velocity of the carrier gas and the temperature of the chamber, the injection was set like a GC device, the essential oil compounds were identified by comparing the mass spectrum of each peak with the standard compounds in the device library (Wiley Adams and Main library) and also calculating the inhibition index and matching each compound with the sources through injection normal hydrocarbons (C8-24) were obtained under the same conditions.

Determination of LD50

Male BALB/c mice weighing 20-30 grams were used for this experiment. These mice were obtained from the Department of Laboratory Animal Breeding of Baqiyatallah University of Medical Sciences. Mice in different groups received 100 µl of logarithmic doses (µg/ml) of the gum extract of the tuber plant daily orally. After the first oral administration, the mortality rate was checked. LD_{50} was calculated through GraphPad version 8.0 software and the dose in which there was no mortality was used for the study.

Experimental animal study

The carrageenan-induced paw edema BALB/c mice model was used to induce in vivo experimental animal model of inflammation and appropriate volumes of carrageenan solution was injected subcutaneously to the left paws of animals.[15, 16] The animal population studied in this experiment modeled using a case and control design, included 50 male BALB/c mice with an age range of 6-8 weeks. Animals were obtained from the animal house of Baqiyatallah University of Medical Sciences, Tehran, Iran. The mice were kept under standard conditions of *ad libitum* water and food and appropriate temperature and light standards. All experimental procedures of this research were approved by the Research Ethics Committee of Baqiyatallah University (ethical code: IR.BMSU.REC.1400.164) and was in accordance with national and international ethical standards including the 1964 Declaration of Helsinki and subsequent amendments.[17, 18]

After one week of initial adaptation in experimental laboratory, animals were randomly divided into 5 groups (n=10 in each group) including inflammation control group (no treatment), Before IP group: intraperitoneal injection group before inflammation (25µg/ml BGE injected intraperitoneally), Before G group: oral administration group before inflammation (25µg/ml BGE orally administered), IP group: the group of intraperitoneal injection concurrently with the induction of inflammation (25µg/ml BGE injected intraperitoneally), G group: the group of oral administration concurrently with inflammation (25µg/ml BGE orally administered). We used the sub lethal dose based on the pilot study (LD50 determination as above mentioned). Finally, at seven hours after carrageenan induced inflammation, all animals were euthanized with an intraperitoneal injection of ketamine and xylazine combinations (100 mg/kg ketamine, and 10 mg/kg xylazine), and paw edema scoring performed to evaluate the inflammation.[15, 16] Also, blood samples collected via cardiac puncture and serum prepared after 3000 g centrifuge for 15 min.

Preparation of spleen cell culture to check cytokine levels

After harvesting the blood from animals, their spleens were removed under sterile conditions and weighed. Then, the spleen tissues were cut into pieces and crushed in 5 ml RPMI-1640 culture medium containing 10% FBS. The resultant samples were passed through sterile mesh to prepare a cell suspension. After centrifugation for 10 minutes at 2000 rpm, in order to remove RBCs, lysing buffer was added to the obtained cell sediment and while adding 10 ml of culture medium, it was centrifuged again for ten minutes at 2000 rpm. Then the cell sediment was suspended in RPMI culture medium containing 10% FBS. Next, cell suspensions (2×10^6 cells/ml) were incubated in 24-well plates and pulsed

with 50 µl PHA solution (1 mg/ml) or medium alone for 72 hours, then their supernatants were used to measure levels of IL-1β, IL-6, TNF-α, IL-10, IL-4, IL-17A, TGF-β cytokines by ELISA kits.

Serological and biomarker examinations

The amount of liver enzyme levels AST, ALT, ALP, NO production, PGE2, SOD, MPO, and MDA in serum were investigated according to the instructions of the ELISA kits manufacturers.

Statistical analysis

The values were expressed as mean ± S.D (n=10). Statistical analysis was performed using SPSS 18 (SPSS Inc., Chicago, USA). The significance level was set as P-value<0.05.

Results

Table 1. shows the results of the GC-MS phytochemical analysis of BGE presenting different phytochemicals. As can be noticed, the α-pinene was the highest chemical compounds among other phytochemicals.

Table 1: Results of GC-mass analysis of BGE

No	RT (min)	Area%	Name	Quality	CAS Number
1	5.099	0.38	Tricyclene	96	000508-32-7
2	5.394	65.67	Alpha-Pinene	95	000080-56-8
3	5.716	2.07	Camphene	97	000079-92-5
4	5.799	0.23	Verbenene	87	000000-00-0
5	6.188	0.37	Sabinene	96	003387-41-5
6	6.282	4.35	2-Beta-Pinene	97	000127-91-3
7	6.541	1.18	Beta-Myrcene	93	000123-35-3
8	6.78	0.08	(+)-2-Carene	98	000000-00-0
9	6.868	0.12	l-Phellandrene	81	000099-83-2
10	7.003	0.89	Delta-3 Carene	97	013466-78-9
11	7.148	0.10	Alpha-Terpinene	98	000099-86-5
12	7.33	0.50	P-Cymene	97	000099-87-6
13	7.444	5.99	DL-Limonene	99	000138-86-3
14	7.625	1.39	Trans-Alpha-Ocimene	97	006874-10-8
15	8.134	0.15	Gamma-Terpinene	96	000099-85-4
16	8.45	0.06	Linalool oxide	52	005989-33-3
17	8.85	2.90	Alpha-Terpinolene	98	000586-62-9
18	9.094	0.23	L-Linalool	93	000078-70-6
19	9.452	0.68	D-Fenchyl alcohol	98	001632-73-1
20	9.742	0.18	Alpha-Campholenal	90	004501-58-0
21	9.815	1.83	Alloocimene	97	000673-84-7
22	10.069	0.58	Trans-Pinocarveol	78	000547-61-5
23	10.298	0.31	P-Menth-1,5-dien-8-ol	78	001686-20-0
24	10.635	0.06	Alpha-Pinocarvone	96	016812-40-1
25	10.713	0.54	L-Borneol	94	000464-45-9
26	10.983	0.47	P-Menth-1-en-4-ol	98	000562-74-3
27	11.18	0.71	P -Cymen-8-Ol	91	001197-01-9
28	11.335	5.70	Alpha-Terpineol	91	000098-55-5
29	11.45	0.22	Myrtenol	94	000515-00-4
30	11.74	0.28	Verbenone	98	000080-57-9
31	13.229	0.06	2-Methyl-2-cyclopenten-1-ol	50	000000-00-0
32	13.504	0.36	(-)-Bornyl acetate	99	005655-61-8
33	14.065	0.07	P-menth-1-ene-4,8-diol	64	054649-49-9
34	14.744	0.09	Exo-2-Hydroxycineole acetate	93	057709-95-2
35	18.33	0.14	Phenol, 2,4-di-tert-butyl-	97	000096-76-4
36	34.762	0.97	M-Nitrophthalic acid	91	000603-11-2

According to the Fig. 1, the results showed that the dose of 145.6 µg/ml is the LD50 dose of the BGE. Therefore, for the design of the study, a dose of 25 µg/ml was used, which had no mortality.

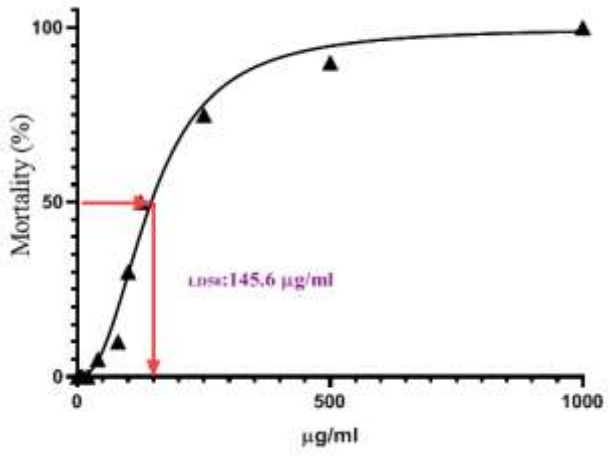

Figure 1: The dose range-finding study standard curve.

The paw edema inflammation results

Fig. 2. compared the percent of paw inflammation in different animal groups. Accordingly, the groups II, III, and IV show a significant reduction in plantar inflammation in comparison with the inflammation control group (group I). Also, group V did not show a significant statistical difference compared to the control group.

Pro-inflammatory cytokines levels

According to Fig 3. the results of measuring pro-inflammatory cytokines showed that BGE significantly decreased the amount of IL-1β (in the group II, III and IV), TNF-α (in the group II, III, IV and V), and IL-17A (in the group II, III, IV and V) cytokines in comparison with the inflammation control group (group I). But it has no effect on the amount of IL-6 cytokine in different groups.

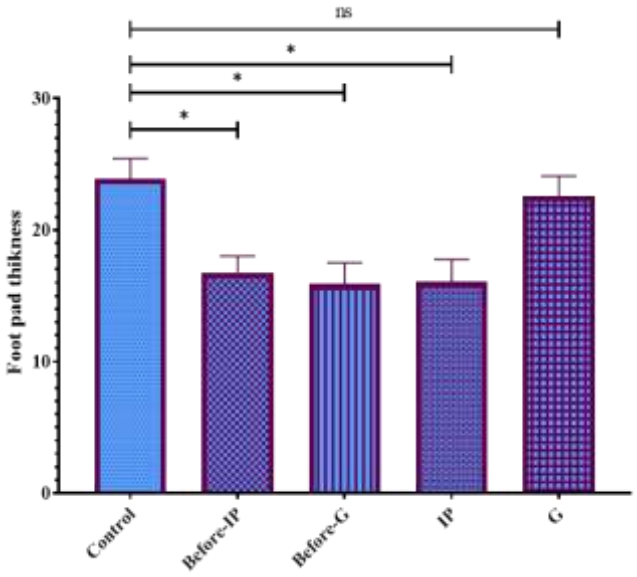

Figure 2: Comparison of the percent of plantar inflammation (paw edema) across different groups in mice. Control: untreated group, Before IP group: intraperitoneal injection group before inflammation, Before G group: oral administration group before inflammation, IP group: the group of intraperitoneal injection concurrently with the induction of inflammation, G group: the group of oral administration concurrently with inflammation; (* indicated significance at the P<0.05 level and ns indicated not significant.

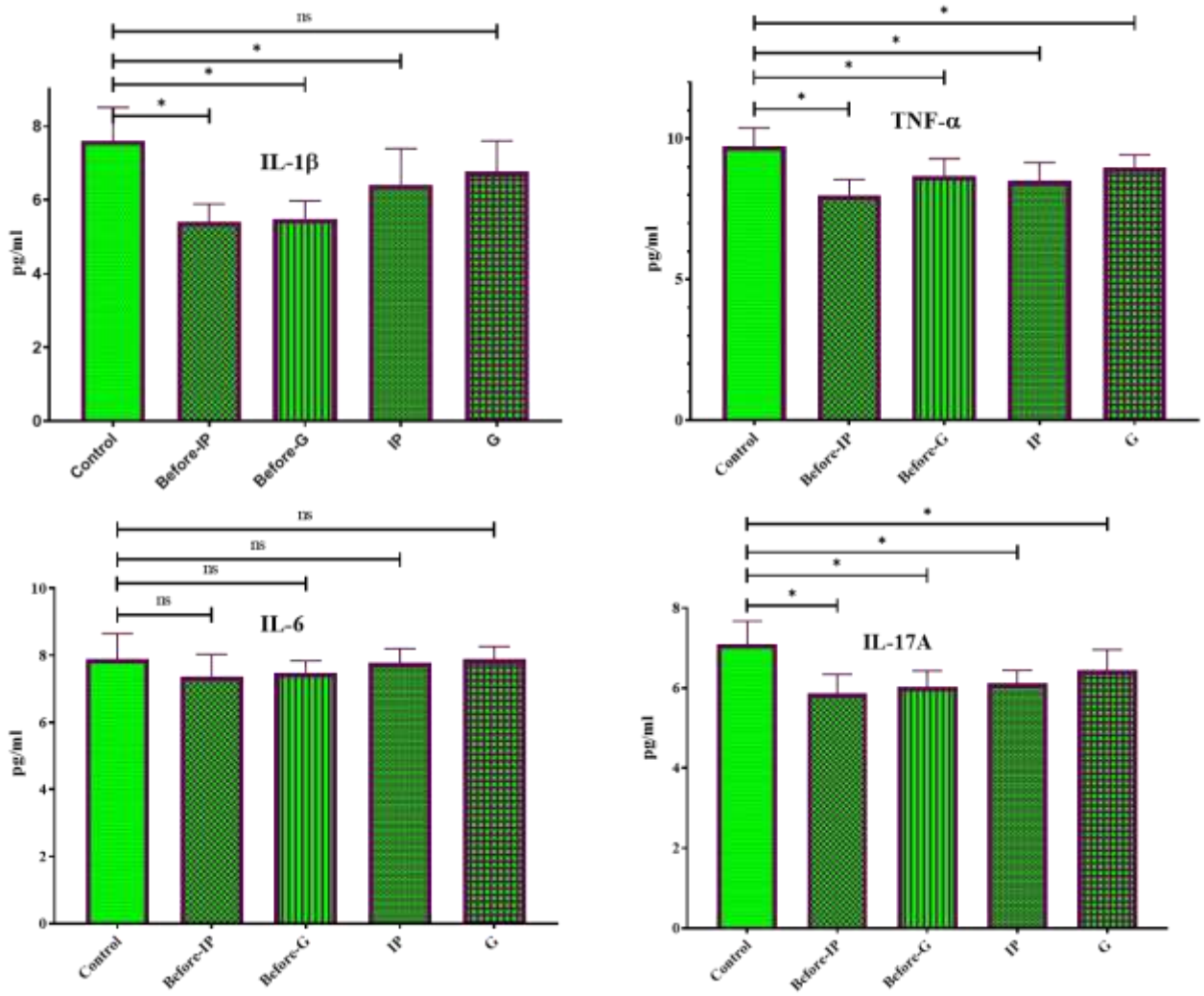

Figure 3: The amount of pro-inflammatory cytokines across different groups in mice. Control: untreated group, Before IP group: intraperitoneal injection group before inflammation, Before G group: oral administration group before inflammation, IP group: the group of intraperitoneal injection concurrently with the induction of inflammation, G group: the group of oral administration concurrently with inflammation; (* indicated significance at the P<0.05 level and ns indicated not significant).

Anti-inflammatory cytokines levels

According to Fig. 4, the results of measuring the levels of anti-inflammatory cytokines showed that the BGE caused a significant increase in the amount of IL-4 (in the group II, III, IV and V), IL-10 (in the group II and III) and TGF-β (in the group III) cytokines in comparison with the inflammation control group (group I).

Oxidative stress biomarkers

According to the Fig 5., the results disclosed that the BGE brought about a significant decrement in the amounts of MDA (in the group II, III, IV and V), MPO (in the group II, III, IV and V), NO (in the group II, III and IV) and PGE2 (in the group II and IV) in comparison with the inflammation control group (group I).

Antioxidant enzymes assessment

Fig 6. showed the of BGE on the levels of antioxidant enzymes. Results show that there is a significant increase in the amount of SOD (in the group II, III and IV) in comparison with the inflammation control group (group I).

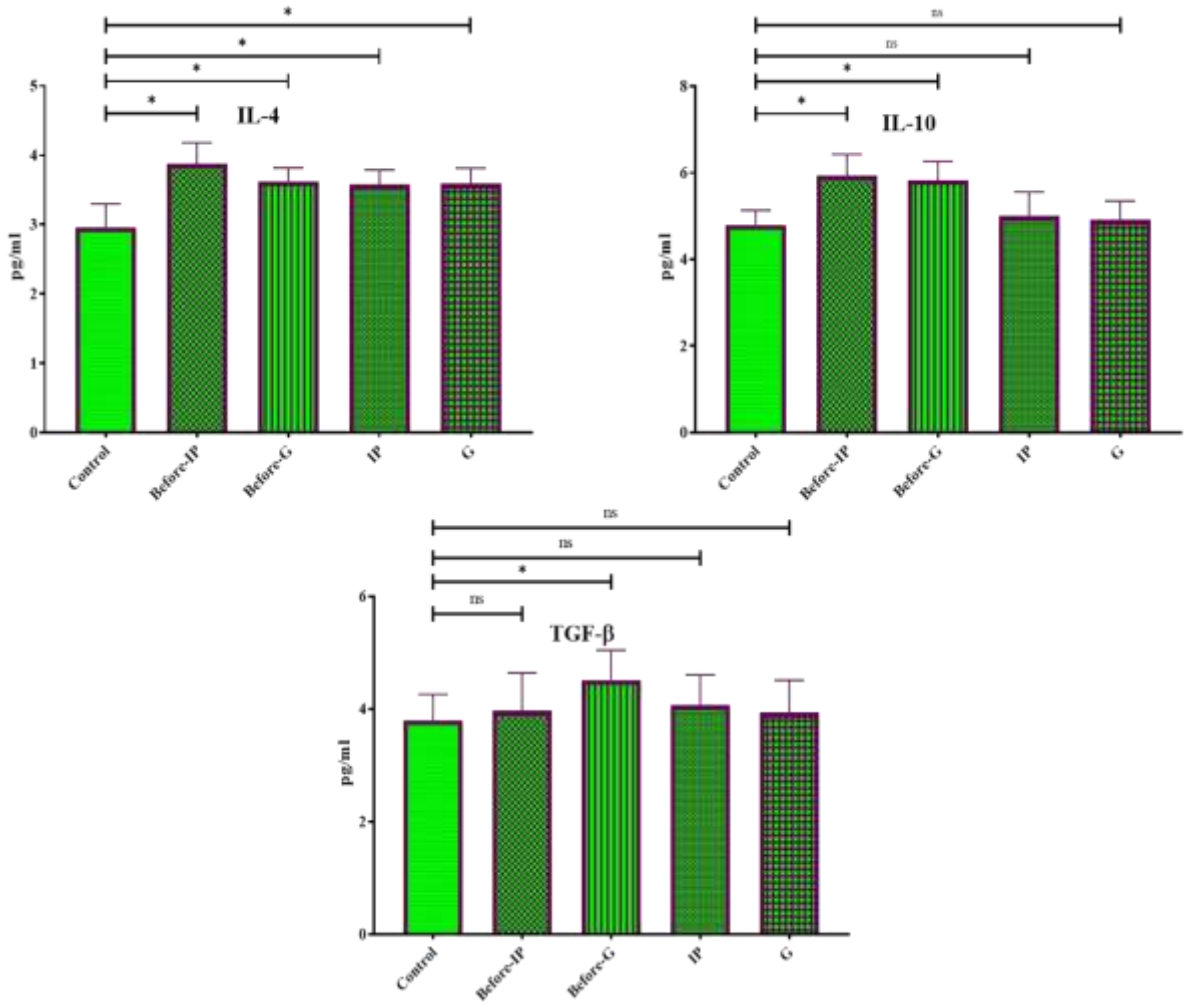

Figure 4: The amount of inflammatory cytokines in different treatment and control groups in mice. Control: untreated group, Before IP group: intraperitoneal injection group before inflammation, Before G group: oral administration group before inflammation, IP group: the group of intraperitoneal injection concurrently with the induction of inflammation, G group: the group of oral administration concurrently with inflammation; (* indicated significance at the P<0.05 level and ns indicated not significant).

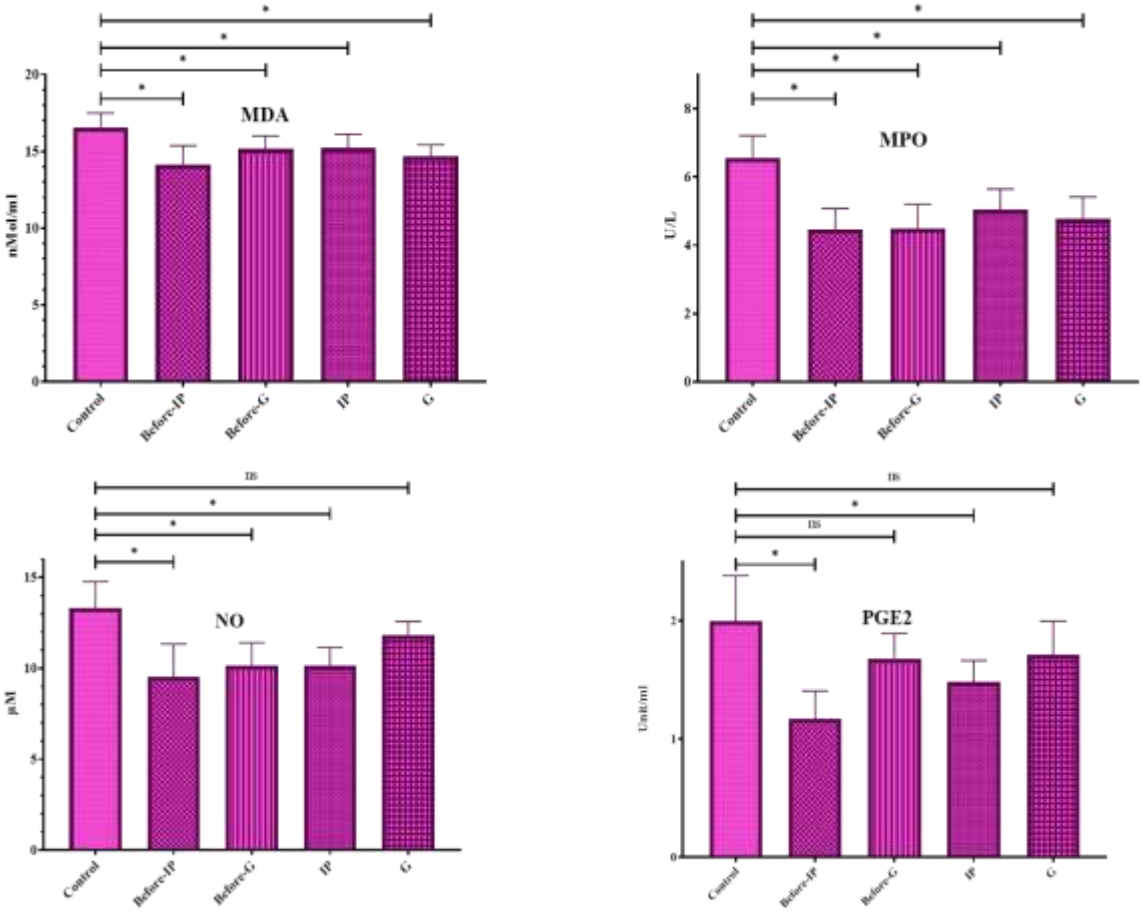

Figure 5: The amount of oxidative stress biomarkers in different treatment and control groups in mice. Control: untreated group, Before IP group: intraperitoneal injection group before inflammation, Before G group: oral administration group before inflammation, IP group: the group of intraperitoneal injection concurrently with the induction of inflammation, G group: the group of oral administration concurrently with inflammation; (* indicated significance at the P<0.05 level and ns indicated not significant).

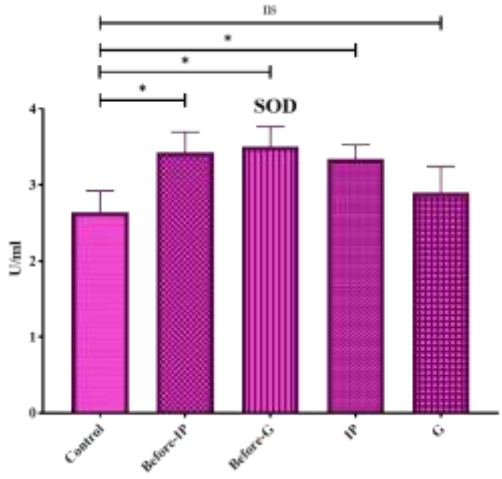

Figure 6: The amount of antioxidant enzyme in different treatment and control groups in mice. Control: untreated group, Before IP group: intraperitoneal injection group before inflammation, Before G group: oral administration group before inflammation, IP group: the group of intraperitoneal injection concurrently with the induction of inflammation, G group: the group of oral administration concurrently with inflammation; (* indicated significance at the P<0.05 level and ns indicated not significant).

Liver damage

As seen in Fig 7, the results showed that the BGE caused a significant increase in ALT (in the group II, III, IV and V) and AST (in the group II and V) levels in comparison with the control group (group I).

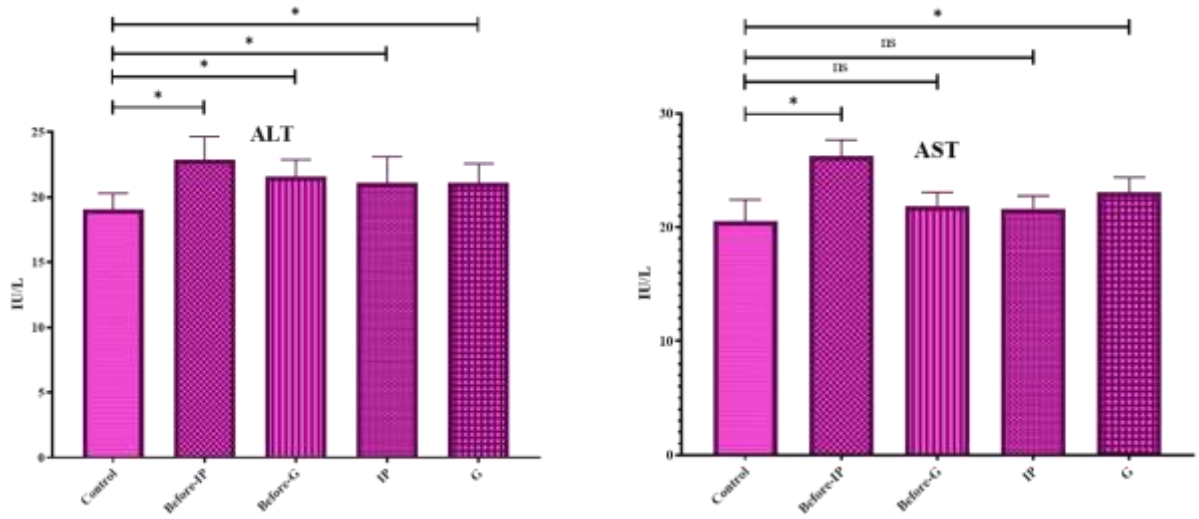

Figure 7: Level of liver enzymes in treatment and control groups in mice. Control: untreated group, Before IP group: intraperitoneal injection group before inflammation, Before G group: oral administration group before inflammation, IP group: the group of intraperitoneal injection concurrently with the induction of inflammation, G group: the group of oral administration concurrently with inflammation; (* indicated significance at the P<0.05 level and ns indicated not significant).

Discussion

Bene or Baneh tree is from the Anacardiaceae family, one of the wild pistachio species in Iran, which has subspecies mutica (*Pistacia atlantica* Desf.) and its distribution starts from the Canary Islands and Cabolica Cordica countries on the coast of the Mediterranean Sea and extends to Syria, Crimea, Armenia, Turkey, Caucasus, Iran, Afghanistan, and Pakistan.[19, 20] Baneh trees of subspecies of mutica and kurdika grow wildly in more than 1,200,000 hectares of the western, central and eastern parts of Iran in the mountainous regions including Lorestan, Sharekord, West Azerbaijan, East Azerbaijan Fars, Ilam, Tehran, Yasouj, Kermanshah, and Kurdistan provinces.[21, 22] Baneh gum or mastic resin is both a traditional medicinal source for relieving different disorders due to beneficial therapeutic properties and recently research as a source of biopolymer and biofuel just to name a few as modern applications with for sustainability purposes.[7, 13, 23, 24] Inflammation is a physiological response to various stimuli such as wounds and infections, temperature changes, microbial agents, toxins and autoimmune diseases that require appropriate care and treatment.[25, 26] Studies have introduced various plant-based agents and natural products as anti-inflammatory agents. However, as there is not enough information on the anti-inflammatory effects of Baneh gum or mastic resin, the present study was performed to investigate the phytochemicals and anti-inflammatory effects of this natural product. In the present study, carrageenan, was used as an inflammatory agent which its subcutaneous injection induces inflammation depending in a time and dose dependent manner. The experimental model of carrageenan induced inflammation is an appropriate method to examine the anti-inflammatory agents.[15, 16] The results of the present study showed that the BGE could significantly reduce inflammatory cytokines and oxidative stress compared with the control group. Furthermore, the results showed that the BGE could increase the amount of antioxidant enzymes and anti-inflammatory cytokines. Tavakoli et al. 2019 evaluated the anti-oxidant properties of Baneh fruit extract via an in vitro DPPH radical-scavenging assay.[27] In a study for examining the activities of aqueous extract of wild pistachio (*Pistacia atlantica* Desf.) leaves on in vitro

assay, the anti-oxidant activity of the mentioned product was comparable with well-known antioxidants ascorbic acid and butylated hydroxyanisole, attributed to the high contents of the flavonoids in the extract such as catechin.[28] Minaiyan et al. 2015 showed that α-pinene, β-pinene, and trans-verbeno were the major constituents of the oil extract of Pistacia atlantica subsp. kurdica.[29] They found that oral administration of the gum extract or volatile oil of this species of wild pistachio could decrease the colitis indicators including ulcer index and total colitis index in acid acetic-induced colitis model in rats. However, the therapeutic effects were not dose dependent. Previous studies on the HPLC analysis of the hull oil of *Pistacia atlantica* Desf. found that it was a rich source tocol isomers including tocol, α-tocopherol, α-tocotrienol, δ-tocopherol, and γ-tocopherol.[30] The anti-oxidant and anti-inflammatory properties of these compounds are well-establish in the literature.[31-33] Another study revealed saturated and unsaturated fatty acids including the palmitic acid, stearic acid, oleic acid, and linoleic acid in the seed oil of *Pistacia atlantica* Desf..[34] Eghbali-Feriz et al. 2018 by exposing B16F10 murine melanoma cells with the extract of P. atlantica subsp. mutica showed that in a dose dependent manner the extract suppressed H2O2-induced oxidative stress.[14]

Conclusion

In conclusion, the findings of the present study proposed that the BGE can be an effective natural product for its anti-inflammatory properties requiring further examination in clinical settings such as randomized controlled trials to evaluate its potential therapeutic and toxicity and thus its appropriateness for the treatment of diseases with underlying cause of inflammation.

Acknowledgments

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Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

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Authors' Contributions

All the authors contributed in designing, collecting, analyzing editing the final manuscript.

Ethical Statement

Conceptualization: Methodology, software, validation, analysis, and investigation: Hadi Esmaeili Gouvarchinghaleh, Mohammad Amrollahi-Sharifabadi, Ebrahim Salimi-Sabour, Bahman Jalali Kondori, Alireza Shahriary, Masoud Ezami, Seyed Morteza Hosseini, Ahmad Reza Sharifi Olounabadi, Majid Mirzaei Nodoushan; **Data curation, original draft preparation, editing, and reviewing:** Hadi Esmaeili Gouvarchinghaleh, Mohammad Amrollahi-Sharifabadi, Ebrahim Salimi-Sabour, Bahman Jalali Kondori, Alireza Shahriary, Masoud Ezami, Seyed Morteza Hosseini, Ahmad Reza Sharifi Olounabadi, Majid Mirzaei Nodoushan; **Visualization, supervision, and project administration**: Hadi Esmaeili Gouvarchinghaleh, Mohammad Amrollahi-Sharifabadi, Majid Mirzaei Nodoushan. The authors read and approved the final version of the manuscript.

Abbreviation list

ALP: Alkaline phosphatase, AST: Aspartate transaminase, ALT: Alanine transaminase, BG: Baneh gum, BGE: Baneh gum extract, CEO: Chief Executive Officer, °C: Degree Celsius, DPPH: 2,2-Diphenyl-1-picrylhydrazyl, ELISA: Enzyme-Linked Immunosorbent Assay, FBS: Fetal bovine serum, FID: Flame ionization detector, GC: Gas chromatograph, GC-MS: gas chromatography-mass spectrometry, HPLC: High-performance liquid chromatography, IL-1β: Interleukin-1β, IL-6: Interleukin-6, IL-8: Interleukin-18, IL-10: Interleukin-10, IL-13: Interleukin-13, LD50: Median lethal dose, MDA: Malondialdehyde, MPO: Myeloperoxidase, NO: Nitrous oxide, PBS: Phosphate buffered saline, PGE2: Prostaglandin E2, RPMI-1640: Roswell Park Memorial Institute-1640, RBC: Red blood cell, SOD: Superoxide dismutase, TNF-α: Tumor necrosis factor- α, TGF-β:

Transforming growth factor-β.

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