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Original Article

Phytochemical Analysis, Antinociceptive and Anti-Inflammatory Effects of *Pycnocycla Bashgardiana* Aerial Parts Essential Oil in Experimental Animals

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ABSTRACT

Pycnocycla bashgardiana is used in Iranian traditional medicine for the relief and treatment of pain and inflammatory disorder. This study investigates the anti-inflammatory and anti-nociceptive activities of *P.bashgardiana* essential oil (PBEO).The anti-inflammatory effect of PBEO (50, 100, and 200 mg/kg, i.p.) were determined using carrageenan test in rat. The analgesic activity of PBEO (20, 50, 100, and 200 mg/kg, i.p.) was studied by formalin test in mice. PBEO (50, 100, and 200 mg/kg) significantly ($p<0.05$) inhibited the carrageenan-induced paw edema which was observed at the 3rd hour of the experiment by 43, 64 and 58%, respectively. PBEO showed significant anti-nociceptive effects in the first phase (200 mg/kg, 40% pain inhibition) and the second phase (100 mg/kg, 37% pain inhibition) of formalin test. According to the GC-Mass spectrometry findings, myristicin (21.1%), cis-isomyristicin (17.2%), E-β-ocimene (11.1%), and Z-β-ocimene (6.2%) were characterized as the main components. The results suggest that PBEO could be a potential candidate as an anti-inflammatory and anti-nociceptive agent in the management of inflammation-based disorders. These effects might be partially due to possible inhibition of or interference with the production of some inflammatory mediators.

INTRODUCTION

Pycnocycla bashgardiana Mozaff. (Apiaceae) is an endemic species found only in southern Iran, in Jask County, Hormozgan Province [1]. The aerial parts of *P. bashgardiana* are popularly used in Iranian traditional medicine in forms of a tincture, decoction and infusion to relieve rheumatoid arthritis, stomachache, headache, cold and snake bite. The decoction made from the aerial parts is also used in folk medicine as wounds and burning wounds cleanser. Because of the common use of *P. bashgardiana* in Iranian traditional medicine for relief and treatment of pain and inflammatory disorders and regarding the high content of the essential oil in the aerial parts, the present study was conducted to assess the antinociceptive and anti-inflammatory activities of the essential oil of the aerial parts. Apiaceae is one of the most important endemic medicinal plants in the south of Iran. The aerial parts of *P. bashgardiana* contain a high amount of essential oil (1.1% based on the fresh weight) and possess a fragrant smell. To detect the potentially responsible compounds for the observed activities, the essential oil content in the aerial parts of *P. bashgardiana* was analyzed by GC and GC-MS. Inflammatory response, as a protective reaction of the microcirculation, is a highly organized sequence of events initiated after injury or infection that involves

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cellular, molecular, and physiological changes. It begins with the production of various mediators such as cytokines, chemokines, eicosanoids, and free radicals by different immune cells including lymphocytes, dendritic cells, endothelial cells, tissue macrophages, fibroblasts, and mast cells in the injured or infected tissues. This well-characterized phase of the inflammatory response is typically targeted by drugs such as pro-inflammatory cytokines antibodies that inhibit the action of the mediators and non-steroidal anti-inflammatory drugs (NSAIDs) [2]. It is well known that therapy with NSAIDs (COX inhibitors) is associated with some side effects including gastrointestinal erosions and renal and hepatic insufficiency [3]. Therefore, finding new drugs derived from natural sources has become a critical issue.

Several biological activities of *Pycnocycla* species such as anti-spasmodic [4,5] and anti-diarrheal [6], anti-microbial [7], relaxant [8], antioxidant [9,10], and cardiovascular activities [11] have been previously confirmed. The *in vitro* strong antimicrobial activities of PBEO have been shown against pathogens such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, and *Candida albicans* [7]. *P. Spinosa* essential oil and its hydro-alcoholic extract act as a relaxant of rat isolated ileum and anti-diarrheal effect [4, 12]. In this regard, our previous study indicated that the essential oil of *P. bashgardiana* fruit has significant anti-inflammatory effects on experimental animals [13].

This study investigates the anti-inflammatory and anti-nociception effects of *P. bashgardiana* aerial-essential oil by systemic uses on improving and treating the symptoms of inflammatory diseases.

MATERIAL AND METHODS

Chemicals

Morphine sulfate, Mefenamic acid, Carrageenan andalmond oilwere purchased from Temad Pharmaceutical Co. (Iran), Merck (Germany), Barij Essence Co. (Iran), respectively.

PLANT MATRIAL

The aerial parts of *P. bashgardiana* including the stems, fruits and spines were collected in September 2016 from Bashagard village, Jask County, Hormozgan Province, Iran (25°38′38″N, 57°46′28″E, 900 m). Specimens were identified by N. Kazemivash and the voucher was deposited in the Herbarium of the Department of Pharmacognosy, Faculty of Pharmacy and Pharmaceutical Sciences, Islamic Azad University, Tehran, Iran, under code number 5067-AUPF.

PREPARATION OF THE ESSENSIAL OIL

The ground dried aerial parts of the plant were subjected to hydrodistillation in a Clevenger-type apparatus for 3 h. At the end of distillation, the oil was collected, dried with anhydrous Na_2SO_4, measured, and transferred to a clean glass vial and kept at appropriate temperature until biological and analytical tests. In the present study, three doses of PBEO (50, 100, and 200 mg/kg) were selected based on previous study [13].

GC-MASS SPECTROMETRY METHOD

Essential oil analysis

Analysis of ZMEO was performed on a HP-6890 gas chromatograph (GC) equipped with a FID and a DB-5 capillary column, 30 m × 0.25 mm, 0.25μm film thickness, temperature-programmed as follows: 60° to 240°C at 4°C/min. The carrier gas N_2 was at a flow of 2.0 mL/min; the temperatures of injector port and detector were 250°C and 300 °C, respectively. The sample was injected by splitting and the split ratio was 1:10. The analysis of GC/MS was performed on a Hewlett-Packard 6890/5972 system with a DB-5 capillary column (30 m × 0.25 mm; 0.25μm film thickness. The operating conditions were the same as described above but the carrier gas was He. Mass spectra were taken at 70 eV. The range of scan mass was from 40-400 m/z at a sampling rate of 1.0 scan/s. Quantitative data were obtained from the electronic integration of the FID peak areas. The components of the oil were identified by their retention time, retention indices, relative to C9-C28 n-alkanes, computer matching with the WILEY275.L library and as well as by comparison of their mass spectra with data already available in the literature [14]. The percentage of composition of the identified compounds was computed from the GC peaks areas without any correction factors and was calculated relatively.

Experimental animals

The present experimental study was conducted on 30 male Wistar rats weighing 200-250 g and 42 male NMRI mice weighing 20-25 g. All animals were kept

under controlled conditions (22-24 °C and 12 h light/dark cycles) and were provided with standard rat food and water *ad libitum*. All procedures were carried out following the Law 11,794, of October 8, 2008, by the National Council of Animal Experimentation Control (CONCEA).

Anti-inflammatory activity against carrageenan-induced rat paws edema

Carrageenan-induced paw edema in male Wistar rats was used to evaluate the anti-inflammatory effect of *P. bashgardiana*[15, 16]. To investigate the acute anti-inflammatory effect of the essence, the rats were divided into three groups of six: 1) standard group, which received mefenamic acid (30 mg/kg; i.p.); 2) vehicle (control) group, which received almond oil (10 ml/kg; i.p.); and 3) three test groups, which received PBEO (50, 100, and 200 mg/kg; i.p.) 30 minute before the injection of carrageenan (0.1 ml 2%) into the sub-plantar region of the right hind paw. The paw volume was measured using a Plethysmometer (model PM 4500, BorjSanat Co., Iran) before and 0.5, 1, 2, 3, 4, and 5 h after the carrageenan administration. Anti-inflammatory activity was identified as the inhibition percentage of edema, compared to the control group. The inhibition of edema was calculated by the following equation:

% Inhibition of edema = 100 (1-Vt/Vc)

Where Vc is the edema volume in the control group and Vt is the edema volume in test groups.

Anti-nociception activity against formalin-induced pain behavior in mice

The antinociceptive effects of *P. bashgardiana* were investigated by the formalin test. About 30 min after separate injection of different doses of the essential oil (20, 50, 100, and 200 mg/kg; i.p.), morphine (5mg/kg, as positive control; i.p.), mefenamic acid (30mg/kg, other positive control; i.p.), vehicle (almond oil, 10 mL/kg; i.p.), and formalin (50µL of 2.5%) were injected into the hind paw of the mice. The nociceptive behaviours were scored immediately after formalin injection and continued for 60 min. A nociceptive score was recorded for each 5 min time block by measuring the amount of time spent in each of the following behavioural types: 3, the injected paw was licked, bitten, or shaken; 2, the injected paw was elevated; 1, the injected paw had a slight or no weight placed on it; and 0, the injected paw was not favoured. Pain rating ranging from 0 to 3 was calculated (Rangriz *et al*., 2016). Individual time course determinations in the formalin test were changed to area-under-the-curve values, 0 to 10 min after formalin injection (AUC phase I) and 10-60 min after formalin injection (AUC phase II) [15].

Statistical analysis

The data at each time point were expressed as the mean ± standard error of the mean (SEM) and analyzed using Graph Pad Prism Program, Version 6.0 (Graph Pad Software, Inc., La Jolla, USA). Comparisons between groups were made by one-way ANOVA and repeated measures analysis of variance (ANOVA) followed by the *post hoc* Tukey's test. Also, $p< 0.05$ was considered a significant difference of means.

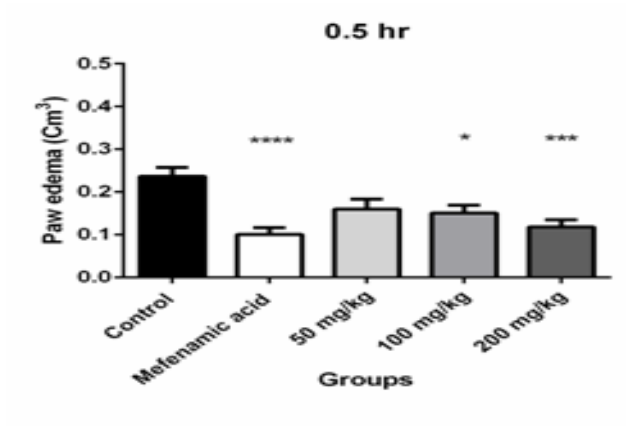
Results and Discussion

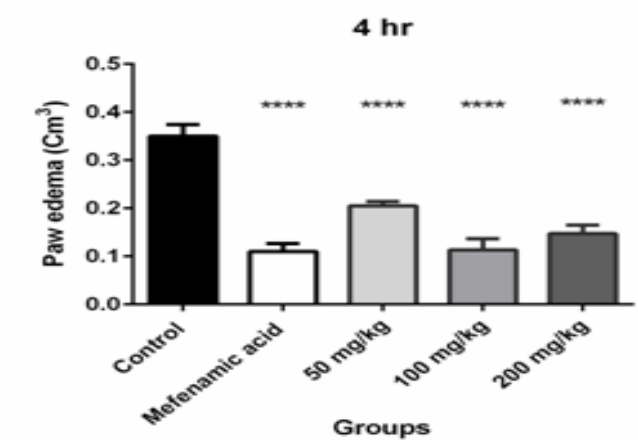
As the Table 1, the phytochemical screening of *P. bashgardiana* aerial parts essential oil revealed myristicin (21.1%), cis-isomyristicin (17.2%), E-β-ocimene (11.1%), and Z-β-ocimene (6.2%) as the major components of the oil.

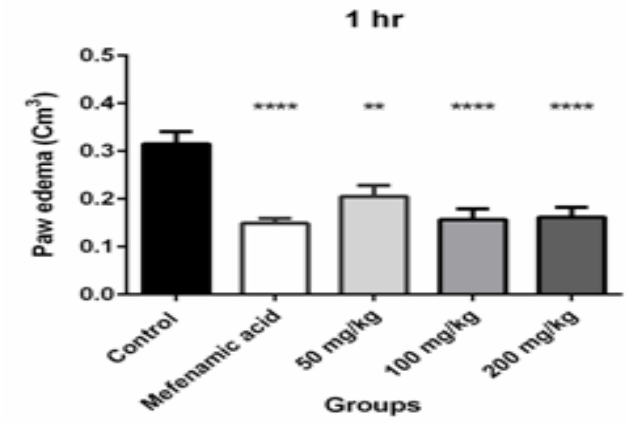
Repeated measures ANOVA showed a statistically significant difference in the interaction between time and paw edema and so interaction between time and groups. PBEO (50, 100 and 200 mg/kg) showed anti-inflammatory activity in the carrageenan-induced paw edema of the rats at different times. The anti-inflammatory activity of essential oil was comparable with that of Mefenamic acid (30mg/kg) (Fig. 1).

The control (Vehicle; 10 mL/kgi.p.), mefenamic acid (30 mg/kg; i.p.), and PBEO (50, 100, and 200 mg/kg, i.p.) were administered 30 min before the carrageenan test. After that, the paw edema was measured at 0.5, 1, 2, 3, 4, and 5 h after the administration of carrageenan. The data represent the mean ± SEM of 6-8 animals in each group (*P<0.05, **P< 0.01, ***P< 0.001, ****P< 0.0001) compared to the control group. Repeated measures ANOVA with Tukey's test was applied for post hoc comparison versus control group rats.

The percentages of rat paw edema in the carrageenan test were also compared at different times and doses (Table 1). PBEO (100 and 200 mg/kg) and Mefenamic acid (30 mg/kg) significantly ($p< 0.05$) inhibited the carrageenan-induced paw edema formation in the rats.







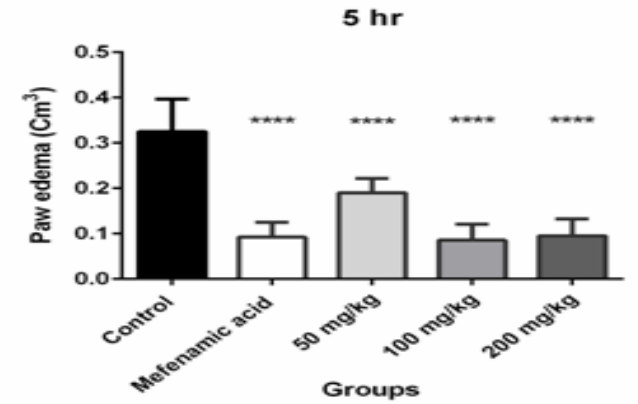
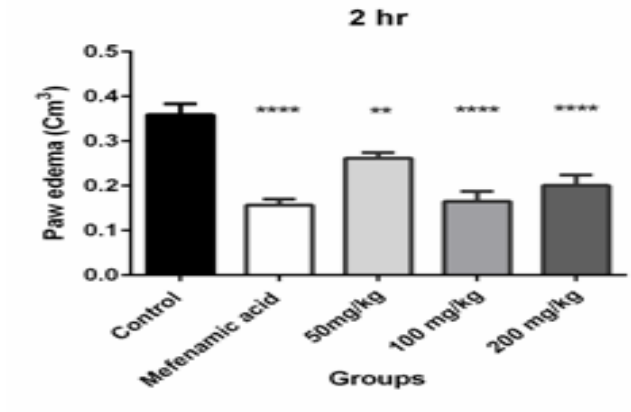
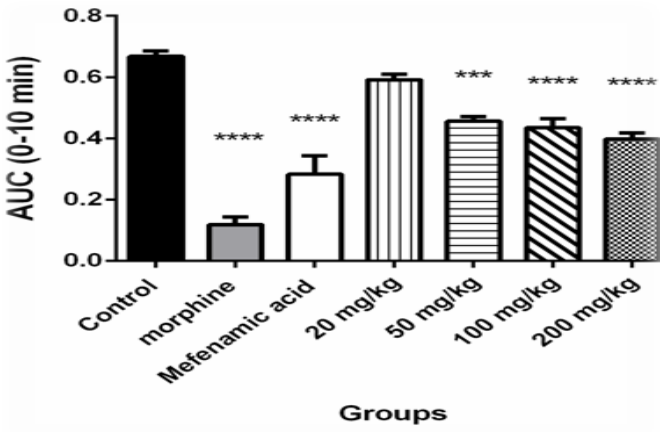
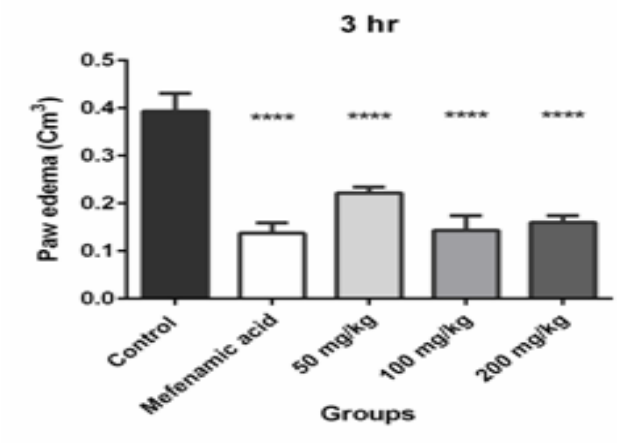


Fig. 1 Anti-inflammatory activity of *P. bashgardiana* essential oil (PBEO) in male rats using the carrageenan test







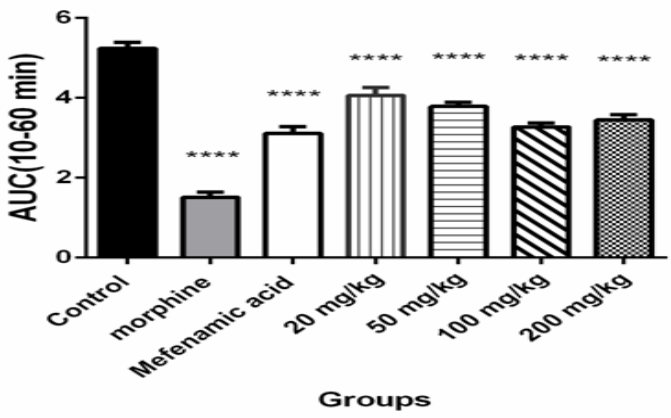


Fig. 2 Effects of PBEO on the nociceptive response in phases I (0-10 min) and phase II (10-60 min) of the formalin test.

The edema peak appeared at the third hour of the experiment as 63.58, 64.10, and 58.97%, respectively, for these injects. At the fifth hour of the experiment, this edema inhibition reached 40.62, 75.00, and 71.87 %, respectively (Table 2).

The anti-inflammatory activity of i.p. administration of *P. bashgardiana* was comparable to that of mefenamic acid at doses 100 and 200 mg/kg and all examined times (0.5, 1, 2, 3, 4 and 5 h).

In the Formalin test, the effect of systemic intraperitoneal administration of different doses of PBEO (20, 50,100, and 200 mg/kg) on the behavioural responses was calculated during the first (phase I) and the second phases (phase II). PBEO revealed anti-nociceptive effects in both phases I and phase II of the formalin test (Fig. 2) compared with the control group.

Table 1 GC-MS analysis of *P. bashgardiana* aerial parts essential oil

Compound [a]	KI [b]	KI [c]	Percentage
1. α-Thujene	929	931	1.1
2. α-Pinene	940	939	0.9
3. Camphene	951	954	0.1
4. Sabinene	977	975	4.2
5. β-Pinene	979	980	0.8
6. β-Myrcene	994	991	0.6
7. α-Phellandrene	1008	1005	0.5
8. α-Terpinene	1023	1018	0.7
9. ρ-Cymene	1028	1026	1.0
10. *cis*-β-Ocimene	1047	1040	6.2
11. *trans*-β-Ocimene	1053	1050	11.1
12. γ-Terpinene	1059	1062	0.8
13. *cis*-Sabinene hydrate	1072	1070	0.6
14. α-Terpinolene	1091	1088	0.2
15. Rosefuran	1097	1093	1.2
16. α-Terpineol	1186	1189	3.1
17. γ-Terpineol	1197	1199	0.1
18. α-Copaene	1380	1377	0.3
19. Methyl eugenol	1408	1401	1.1
20. *trans*-Caryophyllene	1422	1418	0.3
21. α-Guaiene	1444	1439	2.8
22. α-Humulene	1461	1455	0.9
23. β-Selinene	1489	1485	0.2
24. δ-Selinene	1496	1493	1.6
25. α-Selinene	1501	1498	1.4
26. δ-Guaiene	1507	1503	2.1
27. Myristicin	1526	1520	21.1
28. Caryophyllene oxide	1579	1583	0.6
29. *cis*-Isomyristicin	1631	1624	17.2
30. β-Eudesmol	1652	1651	2.1
31. α-Eudesmol	1657	1654	1.4
32. Intermedeol	1669	1667	4.6
Total	-	-	90.9

[a]Compounds listed in order of elution.
[b]KI (Kovats index) measured relative to n-alkanes (C9-C28) on the non-polar DB-5 column under condition listed in the Materials and Methods section.
[c] KI, (Kovats index) from literature.

Table 2 Paw edema inhibition (%) effect of i.p. PBEO injection on the inflammation induced by carrageenan in rats.

Groups/time	0.5 h	1 h	2 h	3 h	4 h	5 h
Mefenamic acid (30 mg/kg)	58.33%	54.83%	57.14%	66.66%	68.57%	71.87%
PBEO (50mg/kg)	33.33%	35.48%	25.71%	43.58%	42.85%	40.62%
PBEO (100mg/kg)	37.50%	51.61%	54.28%	64.10%	68.57%	75.00%
PBEO(200mg/kg)	62.50%	48.38%	42.85%	58.97%	60.00%	71.87%

Table 3 Comparison of the percentage of the area under curve in the phases 1 (0-10) and 2 (10-60) of the formalin test in the study groups and the control group.

Groups	AUC (0 – 10)	AUC (10 – 60)
Morphine (5mg/kg)	83.33%	71.31%
Mefenamic acid (30mg/kg)	57.57%	40.72%
P. bashgardiana (20mg/kg)	10.60%	22.37%
P. bashgardiana (50mg/kg)	31.81%	27.72%
P. bashgardiana (100mg/kg)	34.84%	37.66%
P. bashgardiana (200mg/kg)	40.9%	34.22%

The data expressed as mean ± SEM (n=6-8). ***P< 0.001, ****P< 0.0001; the results show significant differences between the test and the control group.

The percentage of the area under a curve in phases 1 (0-10) and 2 (10-60) of the formalin test was shown in the study groups and the control groups (Table. 3). The carrageenan-induced paw edema has been usually proposed as an acute inflammation model in the experimental animals which is regarded as a biphasic episode that involves inflammatory mediators.

Since the carrageenan-induced inflammation model is a significant predictive test for anti-inflammatory agents acting by the mediators of acute inflammation [16], the results of this study suggest that PBEO can be effective in acute inflammatory disorders. It effectively suppressed the edema produced by carrageenan and, thus, was found to be effective in acute inflammatory conditions. This result shows the essential inhibitory role of this compound in the synthesis, release, and function of inflammatory mediators. The pharmacological effects of NSAIDs are related to the inhibition of the conversion of arachidonic acid (AA) and prostaglandins, which are mediators of the inflammatory process. The anti-inflammatory effect of mefenamic acid is mediated mainly through inhibition of cyclooxygenase and prostaglandin production [17].

The formalin-induced pain models were used to assess the anti-nociceptive effect of PBEO in mice. The formalin test consists of two phases. The first phase (neurogenic pain) is caused by direct chemical stimulation of nociceptive afferent fibers, predominantly C fibers, which can be suppressed by morphine [18]. The second phase (inflammatory pain) results from the action of such inflammatory mediators like prostaglandins, serotonin, and bradykinin in peripheral tissues and also from functional changes in the spinal dorsal horn [19]. The associated effects observed after using different doses of PBEO showed a significant anti-nociception property in both phases compared to the control group. This effect of essence was more predominant in the inflammatory phase of the formalin test. Furthermore, in agreement with the results of the carrageenan test, the essential oil displayed an anti-inflammatory effect followed by decreased behavioural of pain in the formalin test. Thus, it could be concluded that the essential oil generally has anti-inflammatory properties.

The phytochemical results indicated that the anti-inflammatory and anti-nociception effects of *P. bashgardiana* oil may be due to its myristicin and osimene contents. Myristicin is the first major constituent of *P. bashgardiana* essential oil, found in both fruit (76.1%) and aerial parts (21.1%) in varying amounts. The anti-inflammatory activity of myristicin has been previously reported that related to suppression of NO, IL-6, IL-10, GM-CSF, MIP-

1α, MIP-1β, LIF in PIC-stimulated macrophages via the calcium pathway [18].

The second common component of *P. bashgardiana* essential oil is osimene that found in fruit and aerial parts. Ocimene is one of the most common monoterpenes found in nature. In the field of botanical medicine, there is an association of β-ocimene in EOs with anti-convulsant activity, anti-fungal activity, anti-tumor activity, and pest resistance [20-22].

In our previous study, it was shown that the fruit oil of *P. bashgardiana* had high anti-inflammatory activity in carrageenan test, although in formalin test did not show any significant anti-nociceptive properties. Despite lack of any investigation on the analgesic activity of ocimene, it was conjectured that the higher content of total ocimene (17.3%) in the *P. bashgardiana* aerial parts essential oil compared with that of the fruits oil (7.9%) [13] could be a reason for the observed analgesic activity from aerial parts oil compared to the fruit's oil which needs further studies to clarify this hypothesis. This dissimilarity in *P. bashgardiana* pharmacological properties of aerial parts and fruits could be due to the difference in the type and components of the essential oil.

In general, the active components of phytochemicals used in ethnomedicine are mostly unknown and the plant oil is considered as an active ingredient. The plant essential oil is a combination of active compounds and their combined action can mediate therapeutic activity. Nevertheless, the isolation of active compounds should be the next step in order to explain the phytochemical basis of the effects observed in the current study.

The results of the present study suggest that *P. bashgardiana* aerial part essential oil in the studied doses has significant anti-inflammatory and anti-nociceptive effects. In this regard, studying the active ingredients of this essential oil also is of great importance for understanding the mechanism of its anti-inflammatory effect.

Data Availability

Conflicts of Interest

The authors declare that they have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Declaration of interest

The authors report no declarations of interest.

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