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Antinociceptive mechanisms of *Bunium persicum* essential oil in the mouse writhing test: role of opioidergic and histaminergic systems

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ABSTRACT: *Bunium persicum* (Boiss.) is an economically important medicinal plant growing wildly in arid regions in Iran. The fruit of *B. persicum* is widely used in traditional Iranian medicine to control colic pain and dysmenorrhoea. The aim of the current study was to determine antinociceptive mechanisms of *B. persicum* essential oil using an acetic acid-induced writhing test as a model of visceral pain and to determine the possible involvement of opioidergic, serotoninergic and histaminergic systems on antinociceptive mechanisms of *B. persicum* in male mice. In experiment 1, *B. persicum* was intraperitoneally (*i.p.*) injected (0.001, 0.01, 0.05, 0.1, 0.5 and 1%; 10 ml/kg) in Tween-80 (0.5%) and a writhing test served as a model of visceral pain. In experiments 2–5, opioidergic receptor antagonist (naloxone, 2 mg/kg), serotonergic receptor antagonist (cyproheptadine, 4 mg/kg), histamine H_1-receptor antagonist (chlorpheniramine, 20 mg/kg) and histamine H_2-receptor antagonist (cimetidine, 12.5mg/kg) injection was followed by *B. persicum* (0.01%; 10 ml/kg) and the writhing test response was measured for 30 min. According to the results, essential oil of *B. persicum,* administered *i.p.* (0.001, 0.01, 0.05, 0.1, 0.5, and 1%; 10 ml/kg) in Tween-80 (0.5%), elicited antinociceptive effects in a dose-dependent manner. Moreover, the antinociceptive effect of *B. persicum* was significantly attenuated by pre-treatment with naloxone, chlorpheniramine and cimetidine ($P < 0.001$). These results suggest that *B. persicum*-induced analgesia may be mediated via opioidergic and histamine H_1 and H_2 receptors.

Keywords: *Bunium persicum*; antinociception; writhing test; mouse

Visceral nociceptors are responsible for the detection of visceral pain e.g. angina, colic, dyspepsia, pancreatitis, appendicitis and dysmenorrhoea (Giamberardino 1999). Pain is a sensorial modality and primarily protective in nature, but often leads to discomfort (Hasan et al. 2009). Currently, available analgesic drugs such as opiates and non-steroidal anti-inflammatory drugs (NSAIDs) are not beneficial in all cases due to their side effects. The search for new analgesic substances has been a priority of pharmacologists and pharmaceutical industries (Mattison et al. 1988). *Bunium persicum* (Boiss.) Fedtsch. seeds (Sofi et al. 2009), locally known as Parsi Zira and/or Zireh kuhi are native medicinal plants of Iran. *Bunium persicum* belongs to the Apiaceae family, and grows in the wild in arid regions of Iran. Its seeds contain high level of essential oils (EOs) (Zargari 1996). According to previous research, the EO of *B. persicum* consists primarily of four-terpine followed by cumin aldehyde and α-methyle-benzenemethanol. Furthermore, smaller amounts of other substances have been found in EOs such as α-pinene, β-pinene, myrcene, α-terpinene, *p*-cymene, limonene, α-terpinolene, β-sinensal, β-selinene, β-Germacrene, and Dillapiole (Sofi et al. 2009). Several therapeutic effects have been de-

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scribed for seeds of *B. persicum* in ancient Iranian medical books, namely on digestive disorders, urinary tract and diuretic disorders, convulsions, asthma and dyspnoea (Boskabady and Talebi 1999). In addition, *B. persicum* has biological and pharmacological properties including antimicrobial (Moghtader et al. 2009), antioxidant (Shahsavari et al. 2008), antifungal (Takayuki et al. 2007), antibacterial (Demirci et al. 2008; Oroojalian et al. 2010), hypoglycaemic (Kochhar 2008), and anti-inflammatory activities (Hajhashemi et al. 2011a). We have previously found that histaminergic and opioidergic systems play a prominent role in the antinociceptive response. The present study was designed to investigate the antinociceptive effects of EO of *B. persicum* in mice using the writhing test as a model of visceral pain. Furthermore, to reveal possible interactions of neural pathways on the antinociceptive mechanisms of *B. persicum*, we examined the effects of opioidergic, serotoninergic and histamine receptor antagonists on *B. persicum*-induced antinociception in adult male albino Naval Medical Research Institute (NMRI) mice.

MATERIAL AND METHODS

Preparation of essential oil. In this study, seeds of *B. persicum*, which grows in the Lalehzar mountains around the city of Kerman, Kerman province (Iran), were collected (about 300 g fresh wild) in June 2012 and subjected to hydro-distillation (4 h) using a Clevenger-type apparatus (Wang et al. 2009). Samples of the plant were identified at the division of Pharmacognosy, Faculty of Pharmacy, Tehran University of Medical Sciences, Iran. The essential oils were dried over anhydrous sodium soleplate to approximately 9% EO (v/w dry weight basis). The dried aerial parts were stored in a dark place at 4 °C until used.

Animals. One hundred and nineteen adult male albino N-MRI mice (Pasteur Institute, Tehran, Iran) weighing 25–30 g were used in the experiments. Animals were kept in groups of 8–10 per cage (45 cm × 30 cm × 15 cm) at a controlled room temperature (23 ± 1 °C), relative humidity of 55–65% and were maintained on a light-controlled regime (12-h light cycle, lights on at 07:00 h) according to European Union recommendations for laboratory animals. During the study, all animals had *ad libitum* access to chow pellets and fresh water. Mice were acclimatised to laboratory conditions for one week prior to experiments; each animal was used only once and killed immediately after the experiment. All experimental procedures were carried out during the light phase (10:00–17:00 h) and executed in accordance with the Guide for the Care and Use of Laboratory Animals to Investigate Experimental Pain in Animals (Zimmermann 1983). Animal handling and experimental procedures were performed according to the Guide for the Care and Use of Laboratory Animals by the National Institutes of Health (USA) and the current laws of the Iranian government. All protocols for animal experiments were approved by the institutional animal Ethical Committee, University of Tehran, Tehran, Iran.

Drugs. Acetic acid, indomethacin, naloxone, cyproheptadine, chlorpheniramine and cimetidine were purchased from Sigma Chemical Co. (St. Louis, MO, USA) and Tween-80 was from Merck (GERBU, Germany). All drugs were dissolved in saline. The different doses (0.001, 0.01, 0.05, 0.1, 0.5, and 1%) of EO were prepared in Tween-80 (0.5%). Tween-80 was dissolved in distilled water to prepare 1% (v/v) and diluted with an equal volume of saline. The control group received vehicle as control. All drugs were prepared just before use.

Antinociceptive activity evaluation of *B. persicum* and pre-treatment with antagonists. The *B. persicum* essential oil (BPEO) was dissolved in saline and Tween-80 (0.5%) and administered *i.p.* at doses of 0.001, 0.01, 0.05, 0.1, 0.5 and 1%; 10 ml/kg. Indomethacin (as NSAID drug) (5 mg/kg) was dissolved in saline and *i.p.* injected for comparison (Kozak et al. 1998; Ahmed et al. 2004). Control group was *i.p.* treated with 10 ml/kg of 5% Tween-80. Antinociceptive activity was expressed as the percentage inhibition of abdominal constrictions using the ratio: (Controlmean – Treatedmean) × 100/Controlmean

Initially, mice were *i.p.* pre-treated with either saline, opioidergic receptor antagonist (naloxone, 2 mg/kg), serotonergic receptor antagonist (cyproheptadine, 4 mg/kg), histamine H_1-receptor antagonist (chlorpheniramine, 20 mg/kg) and histamine H_2-receptor antagonist (cimetidine, 12.5 mg/kg) 15 min before *i.p.* administration of vehicle as a control or ED_{50} of BPEO (0.01%; 10 ml/kg). Then, the writhing test response was determined 30 min after treatment with either vehicle or BPEO. Onset of the first abdominal writhing was recorded as the latency time. The time and dose of antagonists was chosen according to previous

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reports and pilot studies (Van Riezen 1972; Schmitt et al. 1974; Bero and Kuhn 1987; Leza et al. 1990; Gray et al. 1998; Mobarakeh et al. 2000; Hosseinzadeh and Younesi 2002; Choi et al. 2003).

Analgesic activity. The antinociceptive activity of the herbal samples was studied using an acetic acid-induced writhing model in mice (Ahmed et al. 2004). Animals were divided into control, positive control and test groups (n = 7 mice in each group).

This test consists of inducing nociception in mice by an *i.p.* injection of 0.6% acetic acid in a volume of 10 ml/kg (N'gouemo et al. 1996; Sulaiman et al. 2008). The induced nociceptive behaviour is characterised by abdominal contractions known as writhing, described as an exaggerated extension of the abdomen combined with the outstretching of the hind limbs (Koster et al. 1959; Golshani et al. 2004; Santos et al. 2005; De Sousa et al. 2010). The total number of writhing movements following *i.p.* administration of acetic acid was recorded for up to 30 min after acetic acid injection.

Statistical analysis. Data were prepared in excel, analysed with analysis of variance (ANOVA) using SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL, USA) followed by Tukey's post-hoc tests and presented as means ± SEM. P values of < 0.001 were considered to denote significant differences between groups.

RESULTS

Evaluation of antinociceptive effects of *B. persicum* in the writhing test

BPEO (0.001, 0.01, 0.05, 0.1, 0.5, 1%; 10 ml/kg; *i.p.*) induced a significant reduction in the pain response compared to the control group in a dose-dependent manner (P < 0.001). As a reference drug, indomethacin significantly decreased the number of writhing movements (P < 0.001). BPEO at doses of 0.001, 0.01, 0.05, 0.1, 0.5 and 1%; 10 ml/kg inhibited the writhing response by 23.35, 51.42, 61.29, 56.73, 66.23 and 90.7%, respectively. In comparison, indomethacin diminished the writhing response by 38.13% (Table 1).

Effect of naloxone on antinociceptive activity of *B. persicum* in mice

As shown in Table 2, *B. persicum* (0.01%; 10 ml/kg) induced a significant reduction in the pain response (51.42%) compared to the control group (P < 0.001). In this regard, naloxone (2 ml/kg) had no significant effect on the pain response compared to the control group (P > 0.001). The naloxone (2 ml/kg) + *B. persicum* (0.01%; 10 ml/kg)-treated group exhibited a significant decrease in the pain response compared to the control group (31.11%) (P < 0.001). Also, in the same group, pain sensation significantly increased in comparison to the group treated with *B. persicum* alone (0.01%; 10 ml/kg) (P < 0.001). These findings demonstrate that naloxone decreases the antinociceptive effect of BPEO (from 51.42% to 31.11%).

Effect of cyproheptadine on antinociceptive activity of *B. persicum* in mice

The effect of cyproheptadine on the antinociceptive activity of *B. persicum* is presented in Table 3. Injection of cyproheptadine (4 ml/kg) had no significant effect on the pain response compared to

Table 1. Effect of *Bunium persicum* essential oil on acetic acid-induced writhing in mice

Treatment	Dose (mg/kg, *i.p.*)	Writhing count (mean ± SEM)	Inhibition (%)	*P*-value
Tween-80 (0.5%, control)	10 (ml/kg)	75.29 ± 1.78	–	–
*B. persic*um	0.001%	57.71 ± 3.72	23.35	≤ 0.001 vs. control
	0.01%	36.57 ± 3.93	51.42	
	0.05%	29.14 ± 1.03	61.29	
	0.1%	32.57 ± 2.46	56.73	
	0.5%	25.43 ± 2.31	66.23	
	1%	7 ± 1.3	90.7	
Indomethacin	5	46.57 ± 2.67	38.13	< 0.001 vs. control

P < 0.001 vs. control group; n = 7 for each group

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Table 2. Effect of naloxone on *Bunium persicum*-induced antinociception in the acetic acid-induced writhing test in mice

Treatment	Dose (mg/kg, *i.p.*)	Writhing count (mean ± SEM)	Inhibition (%)	*P*-value
Tween-80 (0.5%, control)	10 (ml/kg)	75.29 ± 1.78	–	–
*B. persic*um	0.01%	36.57 ± 3.93	51.42	≤ 0.001 vs. control
Naloxone	2	67.14 ± 1.65	–	< 0.001 vs. control
Naloxone + *B. persicum*	2 + 0.01%	51.86 ± 1.53	31.11	< 0.001 vs. control

$P < 0.001$ vs. control group; $n = 7$ for each group

Table 3. Effect of cyproheptadine on *Bunium persicum*-induced antinociception in the acetic acid-induced writhing test in mice

Treatment	Dose (mg/kg, *i.p.*)	Writhing count (mean ± SEM)	Inhibition (%)	*P*-value
Tween-80 (0.5%, control)	10 (ml/kg)	75.29 ± 1.78	–	–
B. persicum	0.01%	36.57 ± 3.93	51.42	< 0.001 vs. control
Cyproheptadine	4	39.43 ± 1.64	–	–
Cyproheptadine + *B. persicum*	4 + 0.01%	33.57 ± 0.99	55.41	< 0.001 vs. control

$P < 0.001$ vs. control group; $n = 7$ for each group

the control group ($P > 0.001$). The cyproheptadine (4 ml/kg) + *B. persicum*-treated (0.01%; 10 ml/kg) group exhibited a significant reduction in the pain response compared to the control group (55.41%) ($P < 0.001$). Moreover, in the same group there was no significant change in the pain response compared to the group that received *B. persicum* only (0.01%; 10 ml/kg) ($P > 0.001$). These findings reveal that cyproheptadine does not inhibit the antinociceptive effect of *B. persicum* in mice (Table 3).

Effect of chlorpheniramine on antinociceptive activity of *B. persicum* in mice

Injection of chlorpheniramine (20 ml/kg) had no significant effect in pain response compared to control group ($P > 0.001$) (Table 4). A significant decrease in the pain response was observed in the chlorpheniramine (20 ml/kg) + *B. persicum* (0.01%; 10 ml/kg)-treated group in comparison to the control group (28.86%) ($P < 0.001$). Also, in the same group pain sensation significantly increased compared to the *B. persicum* (0.01%; 10 ml/kg)-treated group ($P < 0.001$). These results show that chlorpheniramine decreases the antinociceptive effects of BPEO (from 75.29% to 61.66%).

Effect of cimetidine on antinociceptive activity of *B. persicum* in mice

No significant effect was observed in the pain response after cimetidine (12.5 mg/kg) injection compared to the control group ($P < 0.001$). However, the cimetidine + *B. persicum* (0.01%; 10 ml/kg)-treated group exhibited a significant reduction in the pain response compared to the control group (27.89%) ($P < 0.001$). Also, in the same group, pain

Table 4. Effect of chlorpheniramine on *Bunium persicum*-induced anti-nociception in the acetic acid-induced writhing test in mice

Treatment	Dose (mg/kg, *i.p.*)	Writhing count (mean ± SEM)	Inhibition (%)	*P*-value
Tween-80 (0.5%, control)	10 (ml/kg)	75.29 ± 1.78	–	–
B. persicum	0.01%	36.57 ± 3.93	51.42	< 0.001 vs. control
Chlorpheniramine	20	76.29 ± 1.75	–	–
Chlorpheniramine + *B. persicum*	20 + 0.01%	51 ± 2.47	28.86	< 0.001 vs. control

$P < 0.001$ vs. control group; $n = 7$ for each group

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Table 5. Effect of cimetidine on *Bunium persicum*-induced antinociception in the acetic acid-induced writhing test in mice

Treatment	Dose (ml/kg, *i.p.*)	Writhing count (mean ± SEM)	Inhibition (%)	*P*-value
Tween-80 (0.5%, control)	10 (ml/kg)	78.50 ± 2.766	–	–
B. persicum	0.01%	30.33 ± 1.238	66.4	≤ 0.001 vs. control
Cimetidine	12.5	71.86 ± 2.34	–	–
Cimetidine + *B. persicum*	12.5 + 0.01%	54.29 ± 1.64	27.89	< 0.001 vs. control

$P < 0.001$ vs. control group; $n = 7$ for each group

sensation significantly increased compared to the *B. persicum* (0.01%; 10 ml/kg)-treated group ($P < 0.001$). These results demonstrate that cimetidine decreases the antinociceptive effect of BPEO (from 51.42% to 27.89%), see Table 5.

DISCUSSION

To date, several studies have been performed to investigate possible anti-inflammatory and antinociceptive activities of medicinal plants (Hajhashemi et al. 2011b). In the current study, *i.p.* injection of BPEO revealed a dose-dependent antinociceptive effect on acetic acid-induced visceral nociception in mice. The writhing test has long been used as a screening tool to evaluate antinociceptive and anti-inflammatory properties of new substances (Collier et al. 1968). In the writhing test, acetic acid activates peripheral nociceptors on the sensory nerve fibres by releasing pro-inflammatory substances (Satyanarayana et al. 2004). The nociceptive response in the acetic acid-induced abdominal constriction assay arises from synthesis of prostaglandins by the action of the constitutively expressed enzyme cyclooxygenase-2 (COX-2), which leads to hyperalgesia and pain (Berkenkopf and Weichmann 1988; Ballou et al. 2000). Terpenes, the major constituent of BPEOs, possess numerous pharmacological and therapeutic properties and exert antinociceptive and anti-inflammatory effects (Mendes et al. 2010; Guilhon et al. 2011). Previous studies demonstrated analgesic activity for *p*-cymene (Illouz and Delbarre 1964; Duke et al. 2002) and anti-inflammatory activity for γ-terpinene (Duke et al. 2002; Milde et al. 2004). Cineole is a terpenoid oxide in BPEOs which has anti-inflammatory and antinociceptive effects (Santos and Rao 2000). In this study, indomethacin (a NSAID) was used as a positive control. Indomethacin attenuates pain by inhibition of COX in arachidonic acid pathway(s) (Levine and Taiwo 1994). It seems, therefore, that the antinociceptive effects of BPEO may be mediated by the terpenoid components (*p*-cymene, γ-terpinene and terpenoid oxide). To reveal the antinociceptive mechanisms of *B. persicum*, we examined the possible involvement of opioidergic, serotonergic and histaminergic receptor antagonists on *B. persicum*-induced antinociception. Our findings showed that pre-treatment with naloxone, an opioid receptor antagonist, significantly attenuated the antinociceptive effect of the BPEO. Opioid analgesics are the most broadly used agents to relief moderate-to-severe pains (Inturrisi 2002). The opioid receptors μ, κ and δ are located in the central nervous system (CNS) and throughout peripheral tissues (Trescot et al. 2008). These receptors mediate many physiological effects of the endogenous opioid system including behaviour, pain and analgesia, tolerance and dependence, alcohol and drug abuse, mental illness and mood, seizures and neurological disorders and locomotion (Bodnar 20). Mu opioid receptors (MOR) in the CNS and peripheral nervous system (PNS) are the principal targets of exogenous opioid analgesics (Reisine and Pasternak 1996). The opioid receptor antagonist naloxone is a competitive antagonist of the μ, κ, and δ receptors, with an high affinity for the MOR (Trescot et al. 2008). Naloxone is widely used to investigate the role of the endogenous opioid analgesic system in pain modulation (Zendehdel et al. 2011; Zendehdel et al. 2012). Linalool, a monoterpene compound, is a component of EOs in diverse aromatic *B. persicum* species (Elisabetsky et al. 1995; Shahsavari et al. 2008). Linalool seems to exert its antinociceptive effects via opioidergic neurons, as these effects were antagonised by naloxone (Peana et al. 2003). As the linalool-induced antinociceptive effect can be antagonised by naloxone and as naloxone has a high affinity for the MOR, this may suggest that linalool exerts its analgesic effects via the MOR. Further,

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the activity of BPEO is significantly, but not completely reversed by naloxone which is an indicator for the involvement of further mechanisms in antinociception. In the present study, pre-treatment with chlorpheniramine (H_1 receptor antagonist) and cimetidine (H_2 receptor antagonist) attenuated *B. persicum* induced-antinociception. These results are consistent with our previous reports that H_1 and H_2 blockers antagonise the antinociceptive effect of *Teucrium polium* and *Foeniculum vulgare* in a mouse writhing test (Zendehdel et al. 2011; Zendehdel et al. 2012). Modulation of pain transmission can take place through various neuronal systems such as the histaminergic system (Malmberg-Aiello et al. 1994). The cell bodies of this system are recognised only in the tuberomammillary nucleus (TMN) of the hypothalamus and their nerve fibres innervate all part of the CNS (Schwartz et al. 1991). Several lines of evidence demonstrated that systemic or central injection of histamine or histamine agonists produces antinociception, suggesting the importance of the histaminergic system in pain regulation (Chung et al. 1984). Peripheral histamine activates and sensitises itch-specific nociceptive C fibres (Schmelz et al. 1997; Zendehdel et al. 2012). Also, it is known that central histamine plays a principal role in antinociception (Robertson et al. 1988). Intracerebroventricular (ICV) injection of histamine at low doses induces hyperalgesia by acting on presynaptic receptors (H_3 receptors) whereas at high levels it elicits antinociception by acting on postsynaptic receptors (H_1 and H_2 receptors) (Malmberg-Aiello et al. 1994; Brown et al. 2001). ICV injection of H_1 and H_2 receptor antagonists into the periaqueductal gray has an antinociceptive effect (Thoburn et al. 1994). Previously, Mojtahedin et al. (2008) reported that ICV pre-treatment with mepyramine (H_1-receptor antagonist) and famotidine (H_2-receptor antagonist) prevented histamine-induced antinociception in the formalin test in rats. These differing findings with respect to histamine and its antagonist are possibly associated with the type of experiment performed, species properties, site affected by histamine and behavioural tests. Our results suggest that *B. persicum*-induced antinociceptive effects are mediated by H_1 and H_2 receptors. In the current study, administration of cyproheptadine as nonselective serotonin antagonist had no effect on the *B. persicum*-mediated antinociception. However, previous studies reported that serotonin plays an important role in the modulation of the pain response (Zendehdel and Babapour 2010). In summation, taking into account the new findings of the current study, we conclude that *B. persicum* has an antinociceptive effect which acts, at least at the level of the CNS, via opioidergic, histaminergic H_1 and H_2 receptors.

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