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Hydroalcoholic extracts of three *Artemisia* species attenuate dental pulp pain and pain-related abnormal feeding behavior of rats

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ABSTRACT

This study evaluated the therapeutic efficacy of three different *Artemisia* species extracts on capsaicin-induced dental pulp pain and pain-associated changes in feeding behaviors in adult male Wistar rats. The animals were alienated into five groups (n=6), namely sham, capsaicin, and capsaicin groups pre-treated with hydroalcoholic extracts of A. *sieberi*, A. *persica*, and A. *biennis*. Pulpitis was evoked by the intradental administration of capsaicin (100 µg). The plant extracts (200 mg/kg intraperitoneal) were administered 10 min before capsaicin. Pain scores were recorded for 40 min. Afterward, feeding behavior was evaluated within 6 h. All extracts could suppress capsaicin-related dental pulp pain. Furthermore, capsaicin decreased the number of visits to the food and water ports of the feeding behavior evaluation device which led to a reduced amount and duration of meals consumed. These harmful effects of capsaicin on meal duration and frequency were attenuated by A. *persica*. Moreover, the inhibitory effect of capsaicin on food intake and water consumption was suppressed by all the extracts. Overall, the present study showed that *Artemisia* species extracts were useful in suppressing the capsaicin-induced pulpal pain and pain-induced feeding abnormalities.

Keywords

Pulpitis, Capsaicin, Food intake, Artemisia, Rats

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Abbreviations

ANOVA: Analysis of variance
ROS: Reactive oxygen species
CGRP: Calcitonin gene-related peptide
IL: Interleukin
LPS: Lipopolysaccharide
IP: intraperitoneal

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Introduction

Pulpitis is a common primary healthcare problem [1] that rises in response to the stimulation of afferent pulpal nerves by different chemical or mechanical stimuli [2, 3]. In particular, capsaicin has been shown to induce nociceptive behaviors by the activation of polymodal nociceptors. Capsaicin-sensitive fibers constitute the majority of tooth afferent neurons [4]. In addition to the sensory features, the experience of pain correlates with neurophysiological dysfunctions, including altered mood and emotional responses. It may also disrupt metabolic processes [5-7]. In particular, noxious stimuli could alter food intake and food reward/behaviors [8, 9]. There is an inherent and complex relationship between the biochemical mediators, such as histamine, prostaglandins, CGRP, and neuropeptide Y, that contribute to controlling pain and feeding responses [10-13]. Trigeminal nerve dysfunctions have been associated with feeding behavior anomalies in both clinical and preclinical studies [14-16].

Pulpalgia is usually treated with a combination of clinical procedures and chemical medications. However, such treatments have not been sufficient because of various economic, physiological, and psychological difficulties [17, 18]. In this regard, medicinal plants have been frequently used as potential therapeutic compounds for pain originating from the trigeminal nerve [19, 20]. The plant-derived phytochemicals or secondary metabolites, including alkaloids, steroids, tannins, and flavonoids are effective in managing pain and inflammation.

The genus *Artemisia* consists of diverse species that grow in several ecological zones in Asia. In Iran, a number of *Artemisia* species, such as A. *sieberi,* A. *persica*, A. *dracunculus*, and A. *annua*, have been recognized at different altitudes [21]. Artemisia produced analgesia and anti-inflammatory effects. The IP administration of A. sieberi fruits essential oil in mice decreased formalin and carrageenan-induced inflammation [22]. Karimi et al. demonstrated that the methanolic extract of A. *deserti* Krasch could suppress nociception and inflammation in formalin and xylene tests in rats [23]. A. *sieberi* was also shown to be able to inhibit inflammatory and neurogenic pain in mice [24]. In addition, the alleviation of acetic acid-induced writhing pain and thermal nociception has been observed following the oral administration of the essential oil and aqueous extract of absinthium, a species of *Artemisia* [25].

In traditional medicine, *Artemisia* extracts are used to regulate food intake and energy balance [26, 27]. Daily oral treatment with A. annua water extract inhibited adipogenesis in 3T3-L1 adipocytes with no considerable changes in food consumption in a diet-induced obesity mice model [26]. Moreover, A. capillaris extracts could prevent weight gain in obese rats by enhancing lipid metabolism [27]. Whereas, it has been reported that systemic administration of A. absinthium hydroalcoholic extract could not alter food intake and appetite in male rats [28].

It has been indicated that terpenes are the most bioactive chemical compositions of the Artemisia genus [29, 30]. However, there are some differences in the main active compounds among different Artemisia species. The major constituents of A. sieberi have been identified as 1,8-cineole, camphor, α-thujone, p-cymene, terpineol, and camphene [31]. However, the main components in oils obtained from the aerial parts of A. persica Boiss are cis-sabinene hydrate and terpinolene [32]. Furthermore, α- pinene, 1,8-cineole, and camphor have been measured in the oil of A. biennis as the main components [33].

Although previous data have supported the value of Artemisia species against pain and inflammation, their therapeutic value in pulpal pain remains poorly understood maybe due to the unique characteristics of pulpalgia compared to other painful situations. The extracts of Artemisia species contain many bioactive compounds with considerable anti-inflammatory importance. Assessing the efficiency of Artemisia species in dental pulp therapy will help develop cost-effective medicine. The present study used a rat model of capsaicin-induced pulpal pain to assess the effects of the hydroalcoholic extracts of three different Artemisia species, including A. *sieberi*, A. *persica*, and A. *biennis* on pulpalgia. Furthermore, we explored the pain-related changes in the feeding behavior of rats.

Results

Pain assessment

Capsaicin induced significant nociceptive responses compared to the sham-treated group ($p < 0.001$). However, pretreatment of rats with A. sieberi, A. biennis, and A. persica significantly decreased the pain scores at 5, 10, 20, 25, 35, and 40 min intervals after capsaicin administration. In addition, the mean pain scores significantly altered during the 40-min test period among different groups (Chi-Square=21.814, $p = 0.0001$). The post-hoc Mann-Whitney U analysis showed that the nociceptive scores rose in the capsaicin group compared to the sham group ($p =0.02$). However, pretreatment with each of the extracts significantly diminished capsaicin-induced nociceptive responses in rats (Figure 1B).

Food intake

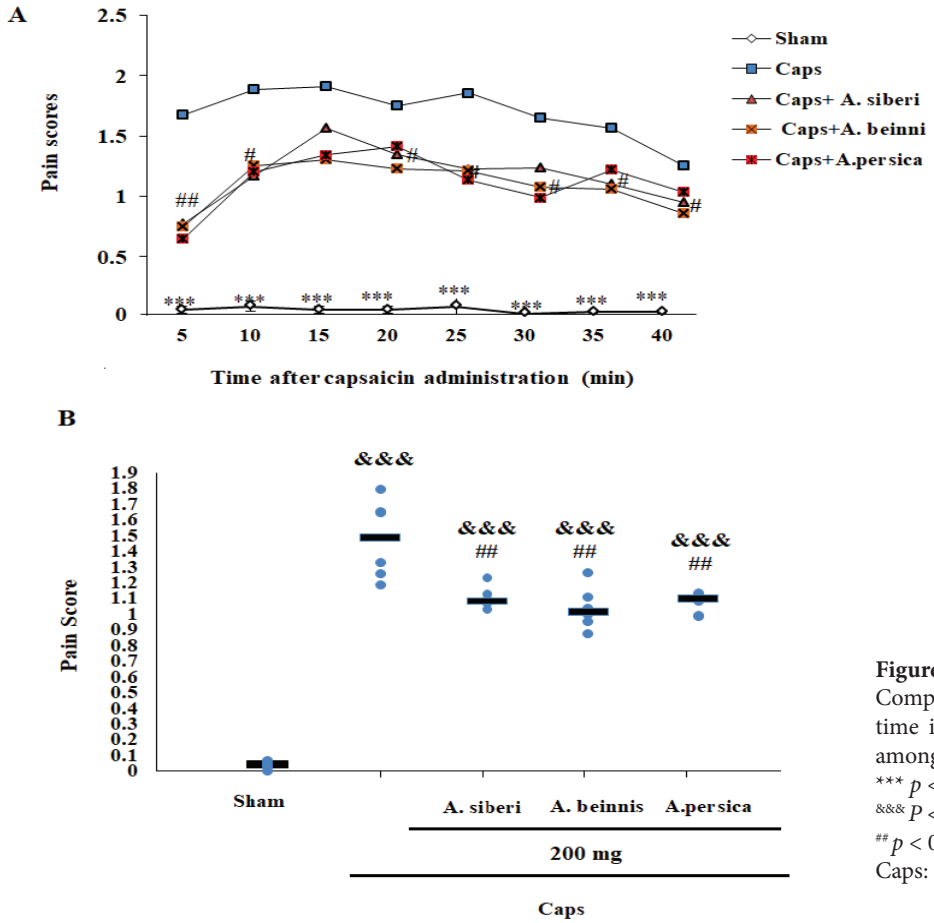

Figure 1.
Comparison of pain scores at different time intervals (A) and total pain scores among experimental groups (B).
*** $p < 0.001$ vs. the other groups;
&&& $P < 0.001$ vs. the sham group;
$p < 0.01$, # $p < 0.05$ vs. the Caps group;
Caps: capsaicin.

The groups showed significant alterations in meal frequency (*Chi*-Square = 20. 266, $p = 0.0001$) and meal duration (*Chi*-Square = 20.839, $p = 0.0001$). As shown in Figure 2, compared to the vehicle group, rats treated with capsaicin presented a decreased number of visits to the meal, along with a shorter time spent there ($p = 0.004$). Capsaicin impact on meal frequency was suppressed by pretreatment with *A. persica* ($p = 0.02$), *A. biennis* ($p = 0.01$), and *A. sieberi* ($p = 0.026$) (Figure 2A). Moreover, meal duration significantly declined in rats treated with *A. persica* ($p = 0.004$), *A. biennis* ($p = 0.01$), and *A. sieberi* ($p = 0.055$) (Figure 2B).

During the 6 h test period, the duration (*Chi*-Square=21.337, $p = 0.0001$) and frequency (*Chi*-Square=22.736, $p = 0.0001$) of water consumption were significantly different between the groups. Capsaicin significantly reduced the duration and frequency of water consumption ($p = 0.004$). In groups of rats treated with capsaicin plus each of the three *Artemisia* extracts, the frequency of water consumption was higher than in the capsaicin group ($p = 0.004$) (Figure 3A). In addition, the time of water consumption, which had decreased due to capsaicin, significantly increased in the groups of rats post-treated with *A. sieberi* ($p = 0.06$), *A. biennis* ($p = 0.02$), and *A. persica* ($p = 0.004$) (Figure 3B).

Significant differences in food intake (*Chi*-Square=17.956, $p = 0.0001$) and water consumption (*Chi*-Square=19.263, $p = 0.0001$) were observed between the groups. As shown in Figure 4, food intake and water consumption rates decreased in rats treated with capsaicin in comparison with the sham group ($p = 0.04$). However, the IP administrations of all three extracts raised food intake in capsaicin-treated rats ($p = 0.03$ and $p = 0.04$) (Figure 4A). Furthermore, water consumption significantly increased in capsaicin plus *A. sieberi* ($p = 0.06$) and *A. persica* ($p = 0.024$) groups in comparison with the animals in the capsaicin group (Figure 4B).

Discussion

Different species of Artemisia have been shown to have analgesic and dietary potentials [22, 26]. In the present study, the IP administration of the hydroalcoholic extracts of A. *sieberi*, A. *persica*, and *A. biennis* decreased capsaicin-induced pulpal pain in rats. In addition, capsaicin application altered the typical pattern of food and water consumption. However, capsaicin-induced reduction in meal duration and frequency were attenuated by pretreatment with *A. persica*. Moreover, all the extracts could improve the reduction in food intake and the time of water con-

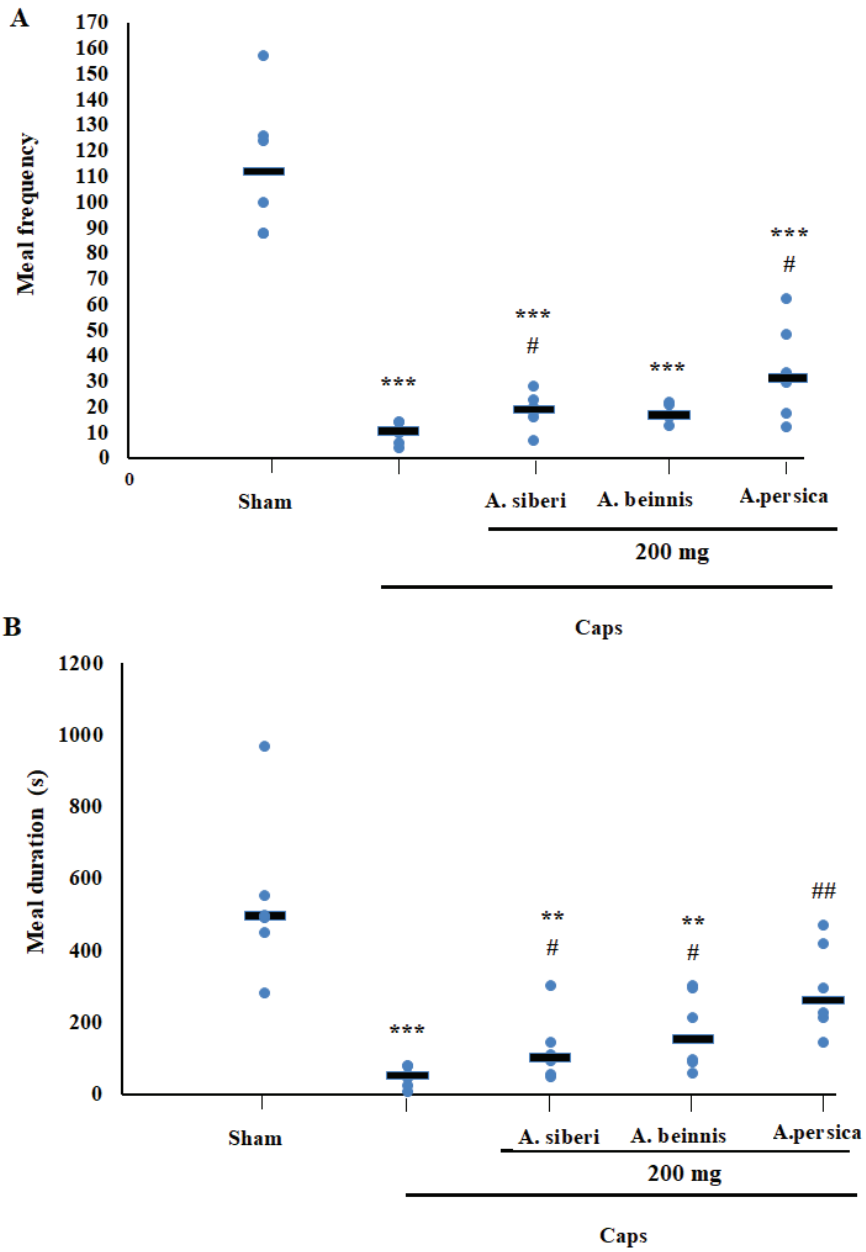

Figure 2.
Comparison of meal frequency (A) and meal duration (B) between capsaicin and capsaicin groups pre-treated with *Artemisia* extracts. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$ vs. the sham group; ##$p < 0.01$, #$p < 0.05$ vs. the Caps group; Caps: capsaicin.

sumption caused by capsaicin.

In the present research, all the extracts of tested *Artemisia* species efficiently suppressed capsaicin-induced inflammatory pulpal pain. This study evaluated for the first time the efficiency of the Artemisia genus for the relief of pulpal pain. Therefore, it was not easy to compare our results with findings from previous and similar studies. However, many previous investigations have supported the anti-inflammatory effects of *Artemisia* species. Furthermore, the IP infusion of *A. sieberi* essential oil was able to decrease anti-inflammatory activities comparable to the standard indomethacin in formalin and carrageenan-induced rat paw edema models [22]. Moreover, *A.* persica essential oil significantly diminished the nociceptive behaviors in the formalin and the tail immersion tests in mice [34].

Capsaicin evokes nociceptive behaviors through the tonic activation of polymodal nociceptors in the pulp [4]. It induces proinflammatory mediators in trigeminal afferents which results in pain sensitization and neurogenic inflammation [35]. However, capsaicin-induced nociception and inflammation have been suppressed by anti-inflammatory agents [36]. It has been indicated that *Artemisia* genus extract consists of potent anti-inflammatory compounds, including 1,8-cineole, Limonene, α-Pinene, and α-Terpineol [37]. Therefore, the modulation of capsaicin-induced pulpal pain in the current study may be at least partially attributed to the anti-inflammatory activity of *Artemisia* extracts.

Moreover, pulpal injury stimulates oxidative stress responses by inducing ROS within the impaired cells, resulting in damage to DNA, proteins, and lipids [38, 39]. Elevated ROS levels negatively affect antioxidant enzyme activity and induce cellular toxicity. Mean-

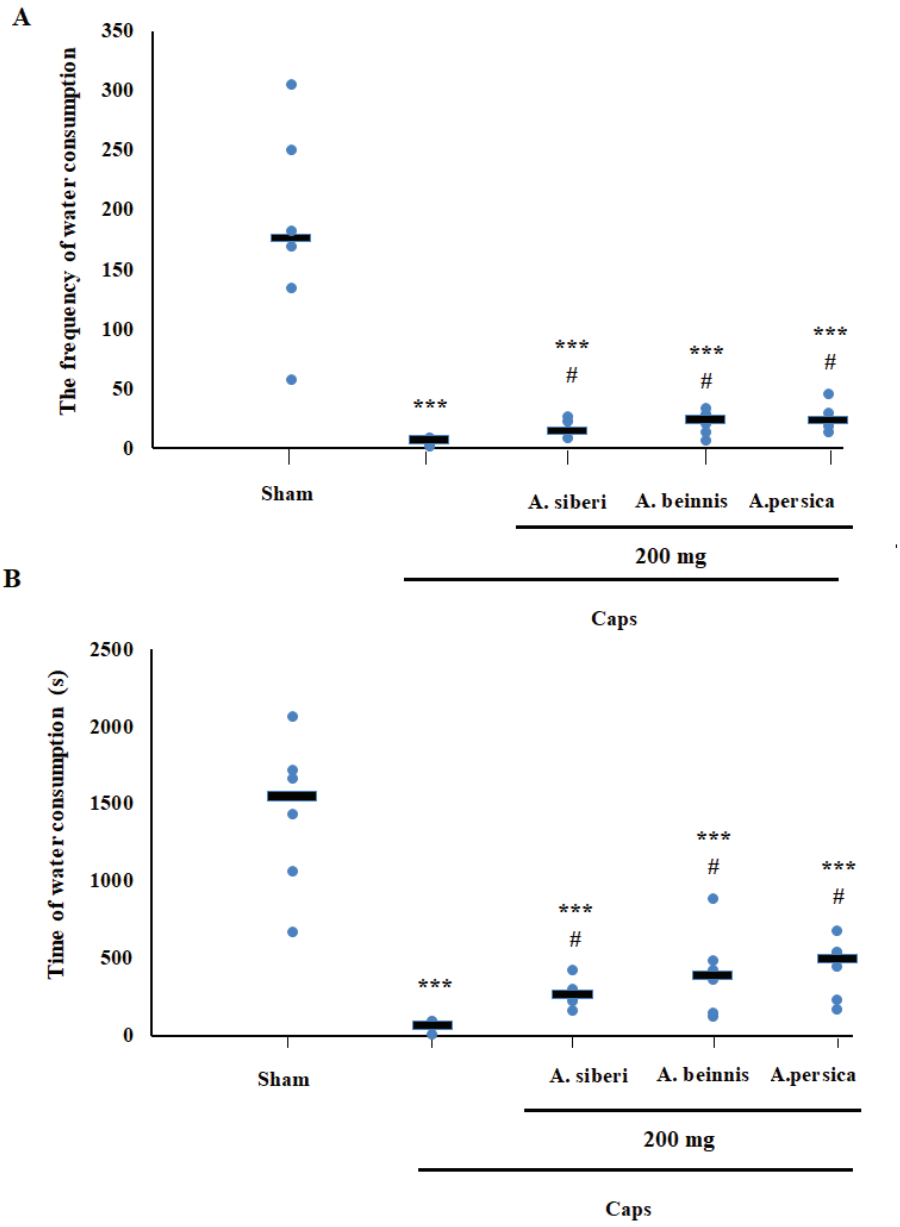

Figure 3.
Comparison of the frequency (A) and duration (B) of water consumption between capsaicin and capsaicin groups pre-treated with *Artemisia* extracts.
***$p < 0.001$ vs. the sham group; #$p < 0.05$ vs. the Caps group; Caps: capsaicin.

while, natural products with potential ROS scavengers are recognized to suppress tissue damage in pulpitis [40, 41]. In this regard, Artemisia species are well characterized as a source of natural antioxidants. It has been indicated that pre-treatment with the extracts of the aerial parts of *A. biennis* could increase the activity of superoxide dismutase and mitochondrial membrane potential, and suppress intracellular levels of ROS in the PC12 cells [42]. In addition, the in vitro administration of A. annua extract has been shown to reduce the levels of oxidative enzymes, malondialdehyde, and 8-OH-dG. On the other hand, it increases the activity of the antioxidant enzyme NQO1 in D-galactose-treated mice [43]. Moreover, *A. vulgaris* extract led to lower nitric oxide scavenging activity, enhanced levels of blood glutathione, and higher superoxide dismutase activity in rats [44]. Therefore, in the current study, the potential antioxidant activity of *Artemisia* extracts might contribute to capsaicin-induced pulpal pain attenuation.

Based on the data, capsaicin-induced pulpalgia was associated with food and water intake abnormalities in rats. In support, previous studies raised a similar argument related to the destructive effects of pain on normal feeding patterns in rodents. It has been indicated that temporomandibular joint pain reduces food intake in rats [45]. Martin et al. reported that upper abdominal surgery disrupts feeding behavior in rats [46]. There are complex associations between brain regions and neurochemical substances involved in controlling feeding and pain processing. Pain experience has been found to disrupt the balance of neurochemicals involved in feeding behaviors [47]. Interestingly, sucrose increased neural

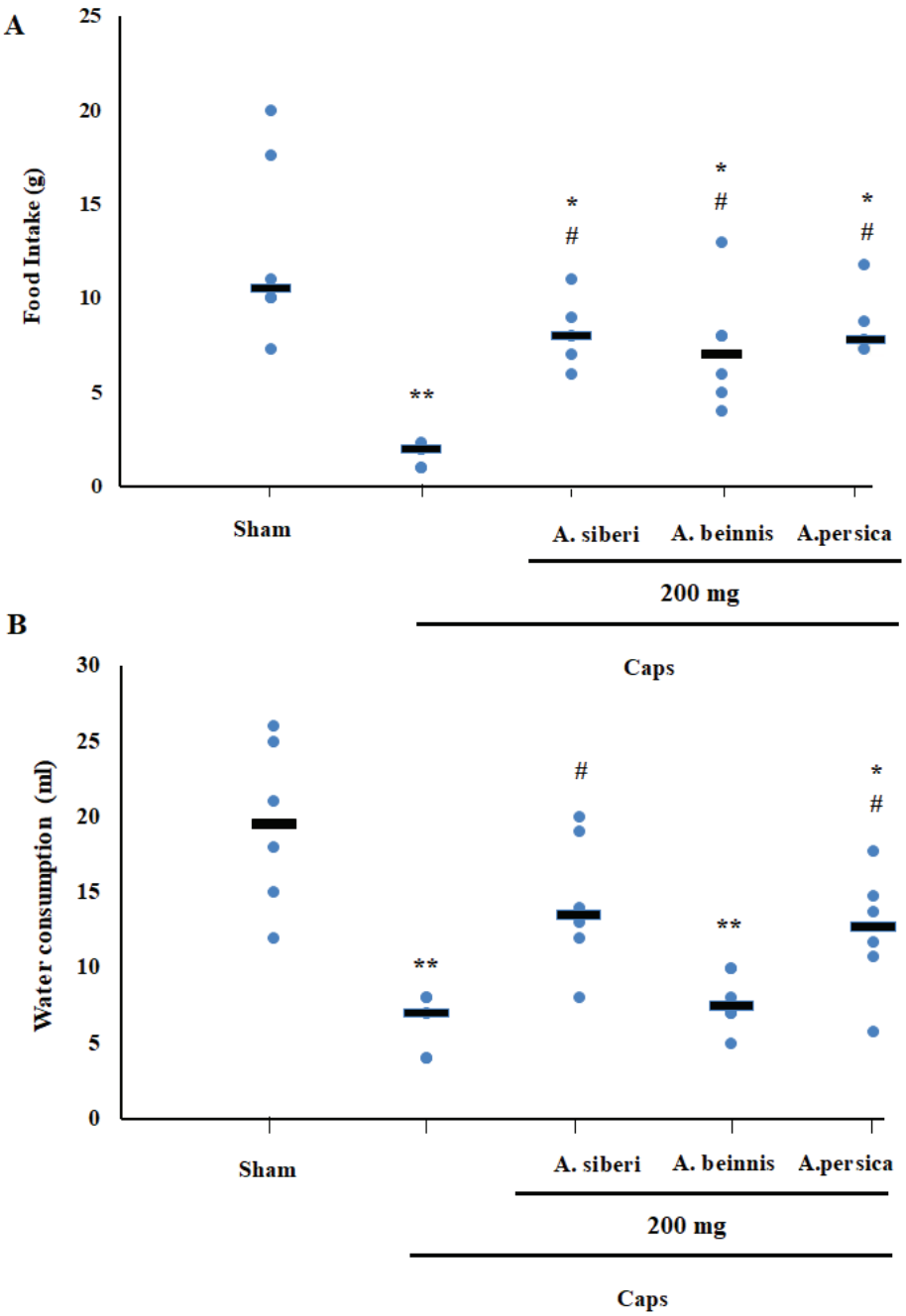

Figure 4.
Comparison of food intake (A) and water consumption (B) between capsaicin and capsaicin groups pre-treated with *Artemisia* extracts.
$^{**}p < 0.01$, $^{*}p < 0.05$ vs. the sham group; $\#p < 0.05$ vs. the Caps group; Caps: capsaicin.

activity within the nucleus raphe magnus and periaqueductal grey matter as critical supraspinal pain modulation regions [48].

Here, abnormalities in food and water intake associated with dental pulp pain were suppressed in rats treated with *Artemisia* extracts. Previous studies have also suggested an important role for the Artemisia genus in regulating metabolic processes and energy expenditure [27]. In addition, daily oral administration of *A. annua* increased lipid peroxidation in a diet-induced obesity mice model [26].

It has been indicated that anti-inflammatory compounds can regulate feeding behaviors. Central administration of IL-10 decreased the peripheral LPS-induced diminished food consumption in rats [49]. Furthermore, the intra-ventromedial hypothalamus infusion of an IL-1 receptor antagonist could disrupt food intake in tumor-bearing anorexic rats [50]. Moreover, the systemic administration of CGRP reduced food consumption and plasma metabolic hormones in rats [51]. As a result, the ability of *Artemisia* species extracts to decrease pain-evoked abnormal feeding behavior may be due to anti-inflammatory compositions, such as sesquiterpenes, scoparone, and flavonols.

In this study, *Artemisia* extracts augmented water intake in capsaicin-treated rats, which may be secondary to increased food consumption. Moreover, this effect may be somewhat related to high locomotor activity. Overall, our results provided a shred of evidence for the efficiency of A. *sieberi*, A. *persica*, and

A. biennis extracts in reducing dental pulp pain and pain-induced food intake anomaly in rats. It indicates an impending value of *Artemisia* extracts in the treatment of dental pain and eating disruption in pulpal inflammation.

Materials & Methods

Animals

This study was conducted in adult male Wistar rats (230-250 g). The animals were maintained in a room with a constant temperature (22 °C ± 1 °C) under a 12:12 h light-dark cycle. There was ad libitum access to food and water. All the procedures were certified by the relevant Ethical Committee of Shahid Bahonar University of Kerman, Kerman, Iran (98.9).

Nociceptive induction

The rats were anesthetized with a low concentration of carbon dioxide. A cavity (2 mm^3) was arranged in the left mandibular incisor using a small fissure bur in a high-speed handpiece. The hole was restored with a small cotton pellet saturated with capsaicin solution. Next, the animals were individually located in a box (30 cm^3) with a mirror set at a 45° angle under the floor to show the responses of the rats. Pain scores were assessed as follows: score 0: normal grooming of body and facial behavior, score 1: mild shaking of the inferior jaw, score 2: continuous grooming of injected zone with the forelimbs, and score 3: extensive rubbing of the mouth. The nociceptive behavior was evaluated in a 40-min test. The nociception scores were calculated using the following formula:

$$\text{Pain score} = \frac{\text{score 0(s)* 0+ score 1(s)* 1+ score 2(s)*2+ score 3(s)*3}}{300}$$

Plant material

Fresh leaves and twigs of *A. persica* and *A. biennis* were collected from the Hezar mountains (Kuh-e Hazaran), and *A. siberia* was collected from the Bidkhoon area, Kerman province, central part of Iran. The samples were evaluated by Dr. Mansour Mirtadzadini. The coupon varieties were placed at the Herbarium of Shahid Bahonar University of Kerman, with the Herbarium codes 3386, 3385, and 3384 for *A. persica, A. biennis,* and *A. Siberia,* respectively. The leaves and twigs were dried at room temperature, cut into small pieces, and distilled. The powder form of *A. persica, A. biennis,* and *A. siberia* (each 50 g) was extracted with methanol (200 ml) three times at room temperature. The methanol extracts were mixed and vaporized by a vacuum rotary evaporator at 45 °C to the dried compound form (yield 2.6% w/w). The provided extracts were then lyophilized and kept in the dark desiccators at +4 °C until tested. They were powdered and extracted with methanol. Afterwards, the solvent was separated, and the extract was determined on a water bath to achieve a dry deposit.

Experimental procedures

The study groups, each with six subjects, included the sham group which received IP normal saline and intradermal capsaicin vehicle, the capsaicin group which received intradermal capsaicin (100 µg), and three groups that received the IP injections of *A. persica, A. sieberi,* and *A. biennis* extracts at a concentration of 200 mg/kg 10 min before capsaicin administration. To evaluate the food intake behavior of animals, 1 h after capsaicin administration and nociceptive assessment, the rats were placed in the middle of an open field-like sealed black plexiglas box (60 cm × 60 cm × 30 cm). A load sensor was mounted underneath the apparatus for recording the behavior of rats, and software processed the location, as well as food and water consumption of animals. There was a port in one of the interval walls that was opened at the middle square allowing access to food and water. The frequency and duration of consuming the meals and the time spent near the food and water port were recorded for 6 h.

Statistical analysis

Statistical analysis was performed using the SPSS software (IBM, USA). The data are summarized as median and range. The statistical differences between the study groups were analyzed by the non-parametric Kruskal-Wallis H test. Moreover, the Mann-Whitney U test was used to compare differences between two independent groups. p-value < 0.05 was considered statistically significant.

Authors' Contributions

J.H. designed the experiments. F.H., A.S., and M.K.H. performed the experiments. R.K. supervised the study and analyzed the data. M.R. and M.A. drafted the manuscript. All authors have read and endorsed the final draft of the manuscript.

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Competing Interests

No competing interests to declare.

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