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Evaluation of the antinociceptive effect of hydroethanolic extract of *Rhaponticum repens* (L.) hidalgo in Wistar rats

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Abstract

Background: Chemical analgesics often have limitations, including adverse effects and insufficient efficacy. Therefore, novel compounds with greater efficacy and a more favorable adverse-effect profile need to be investigated.

Methods: This experimental study evaluated the analgesic properties of *Rhaponticum repens* (RR) extract, a natural compound, using the formalin test in Wistar rats. Twenty-one male Wistar rats were randomly divided into three groups (n=7): group 1 received normal saline, group 2 received morphine (10 mg/kg), and group 3 received RR (100 mg/kg). Thirty minutes after injection, formalin (2.5%) was injected into the hind paw of each rat to induce pain. Licking time and pain scores were recorded during the acute and chronic phases of the test. Data were analyzed by one-way ANOVA using Prism software, with statistical significance set at $P \leq 0.05$.

Results: RR extract significantly reduced licking time and pain scores compared with the control group ($P \leq 0.01$ in the early phase, $P \leq 0.001$ in the late phase, $P \leq 0.05$and $P \leq 0.001$ in the pain scores). In addition, the extent of hind paw edema was significantly reduced in both the morphine and RR extract groups ($P \leq 0.001$).

Conclusion: These findings suggest that the hydroalcoholic extract of RR exerts analgesic effects on both acute and chronic formalin-induced pain and may represent a potential alternative to chemical analgesics. However, further research is required to fully elucidate its therapeutic potential.

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Introduction

Pain is an unpleasant sensation resulting from damage to various tissues and organs of the body (1). However, it also serves as a warning signal that helps prevent accidents and serious injuries and contributes to the maintenance of homeostasis through protective reflexes (1,2).

Since first becoming aware of pain, humans have sought to identify its causes and develop methods for its alleviation. Understanding pain and its mechanisms is essential for the accurate classification of patients. Throughout history, various treatments have been used to relieve pain, including opioid analgesics, steroidal anti-inflammatory drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and local and general anesthetics (3,4).

Despite advances in pharmaceutical science and the development of synthetic drugs for pain relief, herbal medicines are recommended because they are associated with fewer complications and are more accessible and cost-effective (5,6).

Given the adverse effects associated with synthetic drugs, scientists and researchers have increasingly focused on the therapeutic potential of medicinal plants in recent decades.

Rhaponticum repens (RR) is native to Iran and commonly grows as a weed in fields, gardens, and barren land. It has antiparasitic and antibacterial properties and is used to treat constipation, prevent excessive gallbladder secretions, reduce blood pressure, and prevent hemorrhoidal bleeding and intestinal ulcers (6,7).

Phytochemical analyses of this plant have identified six primary compounds in its various parts: camphor, myrcene, α-cubenene, caryophyllene oxide, and heptadecane (7,8). Camphor plays an important role in pain reduction by activating and subsequently desensitizing the TRPV1 channel (9).

Given the analgesic and anti-inflammatory properties of plants in the *Asteraceae* family and the adverse effects associated with many synthetic drugs, investigation of the analgesic and anti-inflammatory effects of these plants is warranted.

In this study, we investigated the analgesic potential of an alcoholic extract of RR in a Wistar rat model of formalin-induced pain to identify a more effective and potentially safer alternative to conventional chemical analgesics (10,11).

The formalin test is a standard method for assessing the efficacy of chemical and herbal analgesics and was first introduced by Duboyson and Denis in 1977. The injection of diluted formalin induces a two-phase pain response. The first phase is characterized by acute, rapid pain during the first 5 minutes of the test. A relatively painless period begins 10 to 15 minutes after injection following the activation of neurophysiological pathways that inhibit pain. The second phase, characterized by chronic pain, then begins and persists until 60 minutes after injection. Transient pain in the first phase (Acute) results from the direct stimulation of pain receptors by formalin. In contrast, pain in the second phase (Chronic) results from inflammatory reactions following tissue damage and involves the release of inflammatory mediators, such as histamine, prostaglandin, and bradykinin, after formalin injection (12). Given the adverse effects of synthetic analgesics associated with long -term use, including addiction, gastrointestinal complications, and central nervous system disturbances, this study explored the potential of RR extract as a natural alternative with potentially fewer adverse effects. The investigation focused on evaluating the early antinociceptive properties of the extract using the formalin test, which enables the simultaneous assessment of neurogenic and inflammatory pain pathways. This research adds to the growing evidence supporting the use of phytochemicals in pain management and addresses the need for safer analgesic options.

Methods

This experimental study included 21 male Wistar rats weighing 200-250 g, obtained from the Laboratory Animal Center of Bu-Ali Sina University. The animals were housed in polypropylene cages (4 rats per cage) under standard laboratory conditions (12-hour light/dark cycle,

temperature of 22 ± 2°C, and humidity of 50 ± 10%). Throughout the study, the international regulations approved by the Ethics Committee of Bu-Ali Sina University (IR.BASU.REC.1401.008) regarding the treatment of laboratory animals were followed. Male Wistar rats were selected to avoid the hormonal fluctuations associated with the estrous cycle in female rats (13).

The rats were randomly divided into three groups (n=7 per group)

- Group I: Received an intraperitoneal (i.p.) injection of saline (100 µL), followed by a subcutaneous (s.c.) injection of formalin (2.5%,100 µL) into the left hind paw (14).
- Group II: Received a subcutaneous injection of formalin into the left hind paw 30 minutes after an intraperitoneal injection of morphine (10 mg/kg).
- Group III: Received the extract (i.p.) (100 mg/kg), followed 30 minutes later by an injection of formalin (s.c.) into the left hind paw.

The dose of RR extract was selected based on previous studies demonstrating the efficacy of similar sesquiterpene-rich plant extracts in pain models (15).

The formalin test was used to assess the analgesic effects of RR extract. Thirty minutes after the administration of saline, morphine, or RR extract, 100 µL of 2.5% formalin solution was injected subcutaneously into the plantar surface of the left hind paw. The animals were then placed individually in transparent glass observation chambers.

The formalin test comprises two distinct phases

Acute Phase (0-5 minutes): Characterized by an immediate pain response, primarily manifested as licking and flinching behavior.

Chronic Phase (15-60 minutes): Associated with a delayed inflammatory response characterized by persistent licking and biting of the injected paw.

Pain behaviors were scored by an observer using a 4-point scale

0: No response
1: Slight flinching or licking
2: Moderate flinching or licking
3: Severe flinching, biting, or lifting of the paw

The duration of pain-related behaviors (Licking and flinching) and the pain scores were recorded during both phases (14,16). The formalin test was selected because it can evaluate both acute (Neurogenic) and chronic (Inflammatory) phases of pain, thereby providing a more comprehensive assessment than single-mechanism tests such as the hot plate or tail flick test (17).

RR leaves were collected from local agricultural fields and orchards in Hamedan. The leaves were air-dried in a dark, well-ventilated room, ground into a fine powder using a mechanical grinder, and sieved through a 1-mm mesh.

A 100 g portion of the powdered leaves was macerated in 1000 mL of 80% ethanol for 48 hours at room temperature with continuous stirring.

The resulting extract was filtered through Whatman No. 1 filter paper and placed in an incubator at 40 °C for 48 hours to remove the solvent.

The concentrated extract was further dried in a fume hood to obtain a dry powder.

Formalin-induced pain scores were recorded individually for each rat. The mean and standard deviation were calculated for each group of seven rats. One-way ANOVA was used to compare the means among the treatment groups using Prism software. Statistical significance was set at $P \leq 0.05$.

Results

The level of inflammation in the rats' hind paws was measured after RR administration. Inflammation was significantly lower in the groups that received the extract or morphine than in group I, which received saline. These findings indicate that RR exhibited notable anti-inflammatory properties. Figure 1 shows a representative inflamed rat hind paw.

Licking time

Early Phase: Licking time was measured in three groups. The morphine and RR extract groups showed similar pain levels, and both exhibited a significant reduction in licking time compared with group I ($P \leq 0.01$) (Figure 2a).

Late Phase: The results showed that the extract, like morphine, significantly reduced formalin-induced licking time. Thus, the extract effectively alleviated pain compared with group I (Figure 2b).

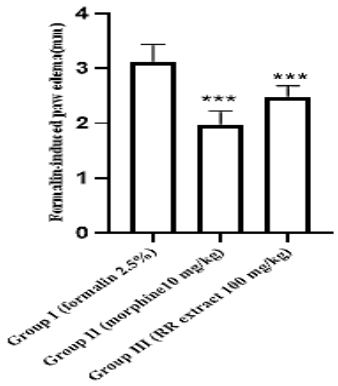

Figure 1. Effects of intraperitoneal administration of RR extract and morphine on formalin-induced paw edema. Significant differences between group I and the other groups are indicated by *** ($P < 0.001$)

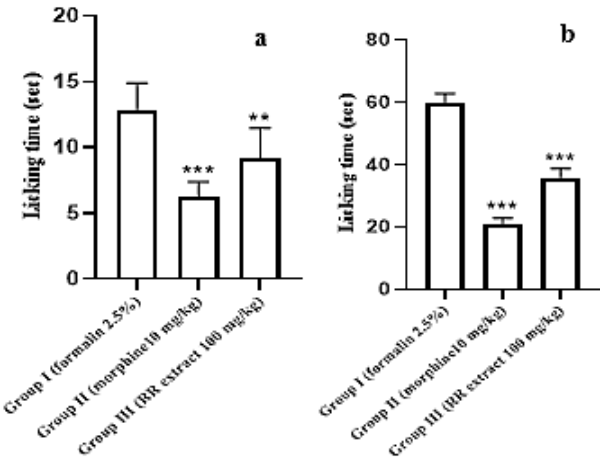

Figure 2. Effects of intraperitoneally administered RR extract and morphine on the early (a) and late (b) phases of formalin-induced paw-licking in rats. Significant differences between groups are indicated by ** ($P < 0.01$), *** ($P < 0.001$)

Pain score

In this study, the total number of reactions exhibited by the rats following formalin injection was evaluated during both the acute and chronic phases. The movements were quantified and assigned as a pain score for each rat.

As shown in Figure 3, the mean pain score in group I was approximately 13.1, which was significantly higher than the scores in the other groups.

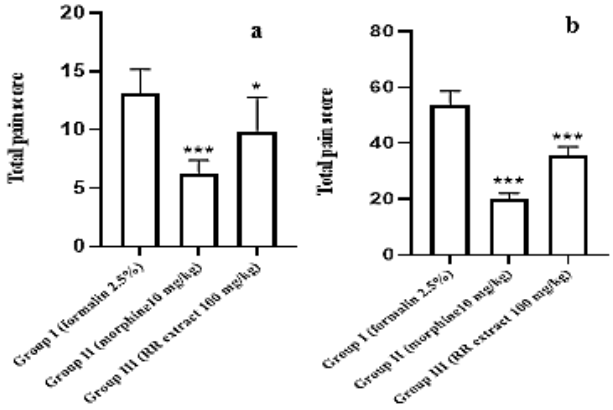

Figure 3. Effects of intraperitoneally administered RR extract and morphine on pain scores during both the early (a) and late (b) phases. Significant differences between groups are indicated by * ($P < 0.05$), *** ($P < 0.001$)

Thus, both morphine and the extract significantly reduced pain scores in their respective groups. The results during the chronic phase were similar to those observed during the acute phase. Both the morphine and RR extract groups had significantly lower pain scores than group I.

Discussion

Pain is among the most widely recognized medical conditions and has attracted considerable research attention. It is a physiological response to harmful physical, chemical, or other stimuli. Pain is experienced by all individuals throughout their lives and is one of the primary reasons people seek medical attention for a specific area of the body (18,19).

Analgesics are commonly used to relieve pain. However, these medications, which are metabolized in the liver, can cause numerous complications, including central nervous system disorders, respiratory and cardiovascular problems, smooth muscle contractions, gastrointestinal disorders, reduced alertness, drowsiness, and addiction (20). In traditional medicine, numerous medicinal plants, including *Matricaria chamomilla*, *Teucrium polium*, *Vitis vinifera* fruits and leaves, *Glycyrrhiza glabra* root, *Valeriana officinalis*, and *lavandula angustifolia*, as well as herbal products such as RR extract, have been used as analgesics and sedatives (10,19). Given the complications associated with synthetic drugs and the ineffectiveness of some treatments, this study investigated the analgesic effect of RR extract as a natural alternative in Wistar rats.

The first factor examined in this study was the degree of inflammation in the hind paws of the rats in the study groups. Inflammation was significantly reduced in the groups receiving the extract or morphine compared with group I. In other words, both RR extract and morphine prevented the recruitment of inflammatory cells to the formalin injection site, thereby inhibiting the inflammatory response.

Research has shown that RR contains isoflavonoid compounds that inhibit cyclooxygenase (COX) activity in human monocytes. By inhibiting the COX enzyme, these compounds reduce the synthesis of prostaglandins, particularly prostaglandin E2 and thromboxane B2. COX inhibition is one of the primary mechanisms underlying the anti-inflammatory effects of these plants (21-23). Flavonoids are natural polyphenolic compounds in plants that reduce inflammation and pain in humans (22).

Similarly, Hoodgar et al. (2011) found that the hydroalcoholic extract of *Securigera securidaca L.* seeds exerted anti-inflammatory effects in mice. They attributed this effect to the flavonoids and tannins in the plant (15).

Other anti-inflammatory compounds identified in RR extract include sesquiterpene lactones. These compounds, which are found in plants of the Salvia L. genus, inhibit tissue inflammation by suppressing the cyclooxygenase pathway (Leading to reduced prostaglandin and thromboxane production) and the lipoxygenase pathway (Leading to reduced leukotriene production) (24,25).

The second objective of this study was to investigate the analgesic effects of RR extract and morphine using the formalin test in rats. First, licking duration was measured in the three groups during the early phase of the test. Pain-related licking time was significantly lower in both group III and morphine-treated group II than in group I ($P \leq 0.05$). Similarly, during the late phase of the test (15-60 minutes post-formalin injection), both RR extract and morphine significantly reduced formalin-induced licking behavior.

Extensive research has examined the analgesic effects of medicinal plant extracts in Iran and worldwide. This growing body of evidence highlights the potential importance of natural compounds in pain management.

Similarly, Eidi (2014) investigated the analgesic effects of sage extract in NMRI mice using the acetic acid, formalin, and hot plate methods. The study found that *Salvia aethiopis* extract, at a concentration of 50 mg/kg, significantly reduced pain in mice during the chronic phase (26). In contrast, the present study demonstrated that RR extract significantly reduced pain in rats during both the primary and secondary phases of the test. This finding suggests that RR extract may have stronger analgesic properties than *Salvia aethiopis* extract.

Mahmoudi et al. (2013) used the tail-flick and writhing tests to investigate the analgesic effects of the hydroalcoholic extract of *Hedera helix* in male rats. Doses of 200 and 300 mg/kg of the extract significantly reduced pain compared with the control group. The authors proposed that this analgesic effect may be mediated by activation of the opioid pathway (27).

Alimohammadi et al. (2015) used the hot plate test to investigate the analgesic effects of the hydroalcoholic extract of *Scrophularia striata* Boiss. They demonstrated that the hydroalcoholic extract of *Scrophularia striata* Boiss has analgesic properties and may be a viable alternative to synthetic analgesics. They attributed the analgesic effects of the hydroalcoholic extract of *Scrophularia striata* Boiss to flavonoid compounds, glycotropenoids, and phenylpropanoid glycosides, which are believed to reduce edema and inhibit cellular inflammation (28).

Dashti et al. (2009) investigated the analgesic effects of cinnamon extract in Wistar rats using the formalin test. Doses of 50 mg/kg and 100 mg/kg of cinnamon extract did not exhibit significant analgesic properties. However, a higher dose of 500 mg/kg significantly reduced pain in the rats (29). The present study demonstrated that RR extract exerted analgesic effects at a lower concentration (100 mg/kg) than cinnamon extract (500 mg/kg). This finding suggests that RR extract may contain higher concentrations of analgesic compounds than cinnamon. Camphor, a major analgesic constituent of RR extract, binds to its numerous receptors on nociceptive neurons, thereby reducing pain sensation (9,30).

In addition, numerous studies of the analgesic mechanisms of medicinal plants have identified compounds such as carotenoids, vitamin C, phytosterol and calcium as potential analgesics (31-33). The dosage of herbal extracts is a critical factor in analgesic testing. In all the studies cited, the dose of the extract was directly correlated with its analgesic properties. In other words, higher doses of the extract were associated with greater pain reduction.

Taheriran et al. (2004) demonstrated a dose-dependent analgesic effect of *Coriandrum sativum* (CS) extract in the formalin test. A dose of 100 mg/kg reduced pain by 82%, whereas a dose of 200 mg/kg reduced pain by 92% in mice (34).

Conclusion

The results of this study demonstrated that RR extract has anti-inflammatory properties and reduces inflammation induced by formalin injection into the rat hind paw. The acute and chronic analgesic effects of RR extract were also investigated using the formalin test. A concentration of 100 mg/kg of the extract significantly reduced pain during both the acute and chronic phases, suggesting that it may be a promising analgesic agent.

However, further pharmacological and toxicological research is required to evaluate the safety and efficacy of RR extract as a therapeutic agent. A comprehensive understanding of its underlying physiological mechanisms of action would contribute to the development of more effective pain management strategies.

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Ethical Statement

The study was approved by the Ethics Committee of Bu-Ali Sina University (IR.BASU.REC.1401.008).

Conflicts of Interest

All authors declare that they have no conflicts of interest.

Author Contributions

M. R: Writing - Original draft, Investigation, Data curation. S.Y: Writing - Review and Editing, Validation, Supervision, Resources, Investigation, Formal analysis, Conceptualization. R. K: Writing - Review and Editing, Validation. A. S: Writing - Original draft, Investigation, Data curation, Formal Analysis.

Data Availability Statement

Data will be made available on request.

Use of Artificial Intelligence

Artificial intelligence has not been used in the preparation of this manuscript.

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