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Antinociceptive effect of hydroalcoholic extract of *Passiflora incarnata L.* in an animal model of hyperalgesia induced by acute and chronic immobilization stress

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Abstract

Background: Stress and pain are overlapping processes and exert bidirectional influences. Passiflora incarnata (Passionflower) is a perennial plant that has long been used for its therapeutic effects. The primary objective of this study was to investigate the hypothesis that *Passiflora incarnata L.* extract exerts a protective effect against stress-induced hyperalgesia.

Methods: Adult male Wistar rats were randomly assigned to 9 groups (n=6): the control group (No stress, no treatment), 2 PFE-only groups that received PFE (100 or 200 mg/kg) for 21 days without stress, an acute stress group (6 h restraint), a chronic stress group (6 h/day for 21 days), and stress groups orally pretreated with PFE (100 or 200 mg/kg) 1 hour before each stress session (1-day treatment for the acute protocol and 21 days for the chronic protocol). The thermal pain threshold was evaluated using the hot-plate test (52±0.5°C), and chemical nociception was assessed using the formalin test. All behavioral tests were conducted 24 h after the final stress session.

Results: Stress (Acute/Chronic) elevated chemical ($p<0.01$-$p<0.001$) and thermal ($p<0.001$) nociception versus controls. PFE (Both doses) reversed chemical hyperalgesia at 0-7 min ($p<0.01$/$p<0.001$) and 15-60 min ($p<0.001$) versus acute stress; only the high dose was effective during the 60-90 min phase versus chronic stress ($p<0.01$). In addition, PFE (100 mg/kg) reversed thermal hyperalgesia versus acute stress, and both doses alleviated hyperalgesia versus chronic stress ($p<0.001$).

Conclusion: This research evaluates the potential modulatory role of Passiflora incarnata extract in pain perception under stress conditions, which may have implications for the management of stress-related pain disorders.

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Highlights

What is current knowledge?

Passiflora incarnata is well documented for its anxiolytic, sedative, and antinociceptive properties, acting primarily via GABAergic and opioidergic pathways. Its efficacy has been demonstrated in neuropathic pain, inflammatory pain, and chemical-induced nociception.

What is new here?

This is the first study to specifically evaluate the modulatory effect of P. incarnata on stress-induced hyperalgesia (Rather than pain resulting from direct tissue injury or neuropathy).

Introduction

Stress is consistently associated with adverse effects on physical and mental health (1). Stress and pain are two interrelated phenomena that frequently co-occur and exert reciprocal influences on one another (2). Stress is a homeostatic adjustment process in response to demanding events, whereas pain is a multidimensional experience generated by nociceptive signaling associated with tissue damage. Evidence indicates that stress plays a major role in modulating both normal and pathological pain regulation (3). Exposure to persistent stress can induce hyperalgesia, meaning a reduction in an individual's pain threshold (4). It has been noted that stress-induced hyperalgesia is mediated by sensitization of primary nociceptors (5). In addition, recent studies identify the amygdala as a central region involved in stress-related pain (6). Immobilization stress provides a well-established model for inducing psychological and physical stress in mammals (7,8). Studies in rodents have previously demonstrated that prolonged immobilization stress reduces the threshold for mechanical pain (9). Herbal medicine has been used for centuries for pain management. Plant extracts are inherently complex mixtures of numerous bioactive compounds, and synergistic interactions among these compounds may provide substantial therapeutic advantages (10). *Passiflora incarnata L.*, also known as passionflower, is a perennial plant native to South America, Australia, and Southeast Asia. *Passiflora incarnata L.* is rich in alkaloids, phenolic compounds, and cyanogenic glycosides that have been used for pharmaceutical purposes; accordingly, the European Medicines Agency has recognized it as a medicinal product (11). *Passiflora incarnata L.* has also been used therapeutically for neurotic disorders, insomnia, morphine dependence, convulsions, anxiety, and neuralgia (12). The anti-stress effect of *Passiflora incarnata L.* has been demonstrated by reduced stress levels and increased motivation in an in vivo study (13). It has been well documented that the anti-stress effects of *Passiflora incarnata L.* are linked to modulation of the gamma-aminobutyric acid (GABA) system, the major inhibitory neurotransmitter system (14). *Passiflora incarnata L.* extracts (PFE) from aerial parts of the plant, including leaves, fruits, and seeds, prepared using different extraction methods such as hydroalcoholic and methanolic extraction, have consistently demonstrated a variety of neurological effects in both preclinical animal models and clinical trials (15). PFE has demonstrated significant anti-inflammatory, analgesic, and anti-stress effects in animal models, including carrageenan-induced paw edema and alloxan-induced diabetic neuropathy in rats (16-18). The analgesic effects of PFE have been attributed to its phytoconstituents, including oleamide, chrysin, vitexin, isovitexin, orientin, isoorientin, apigenin and kampferol (16,19). Nonetheless, its specific antihyperalgesic potential in stress-induced pain models remains unexplored. Given that stress activates pain pathways via the amygdala and nociceptor sensitization, and that PFE modulates GABAergic neurotransmission, we hypothesized that PFE would exert dose-dependent analgesic effects against immobilization stress-induced hyperalgesia. Specifically, we predicted that both acute and chronic stress would reduce pain thresholds and that PFE treatment would reverse these effects, with the higher dose demonstrating superior efficacy. Therefore, the present study aimed to investigate the antinociceptive effects of PFE in acute and chronic immobilization stress models.

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Methods

Drug administration

The hydroalcoholic extract of Passiflora incarnata was obtained from Iran Darouk Company and stored according to the manufacturer's instructions until administration.

Experimental protocol

54 adult male Wistar rats (Weighing 250-270 g) were purchased from the Pasteur Institute in Amol, Mazandaran province, and then randomly assigned to 9 experimental groups (n=6 per group). All experiments were conducted in accordance with the ethical guidelines established by Golestan University of Medical Sciences under ethical code IR.GOUMS.AEC.1404.002. The animals were maintained under standard laboratory conditions (12-h light/dark cycle,22 ± 2°C), with ad libitum access to food and water. The experimental groups were as follows:

1) the Control group (No stress exposure, no treatment).
2) PFE 100 (Without stress): received daily administration of 100 mg/kg PFE via gavage for 21 days.
3) PFE 200 (Without stress): received daily administration of 200 mg/kg PFE via gavage for 21 days.
4) Acute stress group: exposed to a 1-day immobilization stress paradigm without treatment.
5) Chronic stress group: exposed to a 21-day immobilization stress paradigm without treatment
6) Acute stress + PFE 100: received 100 mg/kg of PFE orally and was then exposed to a 1-day immobilization stress.
7) Chronic stress +PFE 100: received 100 mg/kg of PFE orally for 21 days and was then exposed to a 21-day immobilization stress.
8) Acute stress + PFE200: received 200 mg/kg of PFE orally and was then exposed to a 1-day immobilization stress.
9) Chronic stress +PFE 200: received 200 mg/kg of PFE orally for 21 days and was then exposed to a 21-day immobilization stress.

PFE was administered orally to the rats by gavage 1 hour before each stress session. The treatment was administered once before the acute stress session and daily for 21 days in the chronic stress protocol. Behavioral assessments were performed on the day following the final immobilization session. Pain thresholds were measured using the hot plate test (For thermal nociception) and the formalin test (For chemical nociception) in all groups.

Stress induction protocol

Immobilization stress was induced using two protocols, acute and chronic (1-day and 21-day), with polyethylene restrainers for a period of 6 hours (From 8:00 AM to 2:00 PM). The restrainers were designed with perforated sides and detachable caps on both ends so that only the animals' tails remained outside. In addition, the animals were deprived of food and water throughout the immobilization period (20,21).

Pain assessment tests

Hot plate test

The hot plate test was conducted in accordance with the method described by Eddy and Leimbach after immobilization stress induction. Rats were individually placed on a heated surface maintained at 52 ± 0.5°C, and the latency to nociceptive responses, including paw licking, paw withdrawal, or jumping, was recorded using a 20-second cut-off latency (22).

Formalin test

The formalin test was conducted to assess tonic pain resulting from chemical nociception. Animals were placed individually in a transparent plexiglass chamber (30 × 30 × 30 cm) with a flat floor and a mirror placed beneath it to permit clear visualization of the hind paw. Then, 50-µL of formalin (2%) was injected subcutaneously into the left hind paw. Finally, nociceptive behaviors were scored (0-3) as follows: 0 = paw flat on floor; 1 = paw slightly touching floor; 2 = paw lifted; 3 = paw licking/biting (23). Pain-related behaviors were assessed during the early phase (0-7 min, neurogenic pain) and late phase (15-60 min, inflammatory pain), with the 60-90 min interval evaluated for prolonged inflammatory responses.

Statistics

The data were presented as means ± S.D., and statistical analysis was performed using two-way ANOVA followed by Tukey's multiple-comparison tests. Data were analyzed using two-way repeated-measures ANOVA, with Stress (No stress, acute and chronic) and Treatment (PFE 0, 100 and 200) as between-subjects factors, and Time (0-7, 15-60, and 60-90 min) as the within-subjects (Repeated-measures) factor. The significance level was set at $p<0.05$. All graphs were generated using GraphPad Prism 9.0.0 software.

Results

Effect of PFE treatment on chemical pain induced by acute immobilization stress in the formalin test

Two-way ANOVA revealed a significant main effect of stress ($F(2, 90) = 31.27$, $P<0.0001$), a main effect of PFE doses ($F(5, 90) = 26.13$, $P<0.0001$), and a significant interaction between stress and PFE ($F(10, 90) = 3.434$, $P=0.0008$). Figure 1 shows that acute immobilization stress significantly increased pain-related behaviors in phases 0-7 and 15-60 compared with the control group ($p<0.01$), whereas PFE treatment at both doses reduced pain sensitization in phase 0-7 ($p<0.01$, $p<0.001$, respectively) and phase 15-60 ($p<0.001$) compared with the acute stress group. In addition, PFE at the higher dosage was more effective in reducing pain-related behavior in phase 0-7 ($p<0.05$). During the 60-90 min phase, pain sensitization was significantly increased in the acute stress group compared with controls. Although PFE treatment at both doses reduced pain sensitization, the differences between groups were not statistically significant.

Effect of PFE treatment on chemical pain induced by chronic immobilization stress in the formalin test

Two-way ANOVA revealed a significant main effect of stress ($F(2, 90) = 30.77$, $P<0.0001$), a main effect of PFE doses ($F(5, 90) = 43.26$, $P<0.0001$), and a significant interaction between stress and PFE ($F(10, 90) = 2.285$, $P=0.0195$). Figure 2 shows that chronic immobilization stress significantly increased pain-related behaviors in the 3 phases compared with the control group ($p<0.001$), whereas PFE treatment at both doses reduced pain sensitization in phases 0-7 and 15 ($p<0.001$) compared with the chronic stress group. In addition, PFE at the dose of 200 mg/kg reduced pain-related behavior in phase 60-90 ($p<0.01$) compared with the chronic stress group.

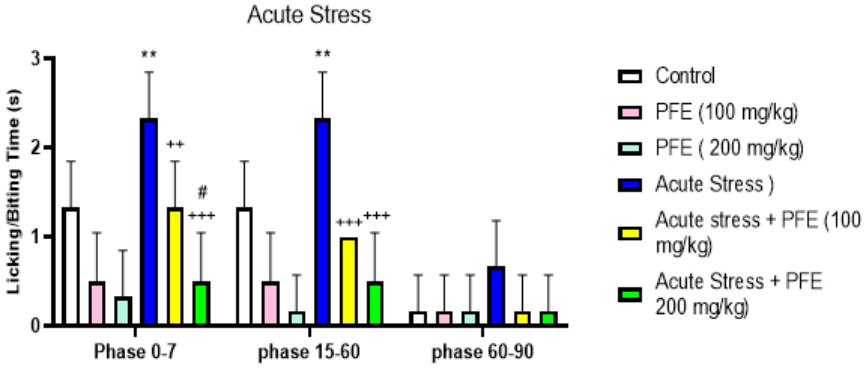

Figure 1. Effect of PFE treatment on chemical pain induced by acute immobilization stress in the formalin test. Data are presented as Mean ± SD. **p<0.01 compared with the control group, ++p<0.01, +++p<0.001 compared with the Acute Stress group. #p<0.05 significant difference between the PFE 100 mg/kg and PFE 200 mg/kg groups.

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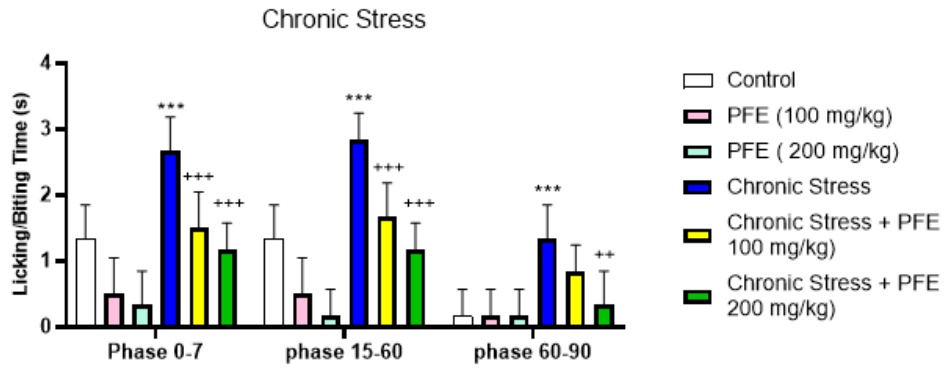

Figure 2. Effect of PFE treatment on chemical pain induced by chronic immobilization stress in the formalin test. Data are presented as Mean ± SD. ***p<0.001 compared with the control group, ++p<0.01, +++p<0.001 compared with the Chronic Stress group.

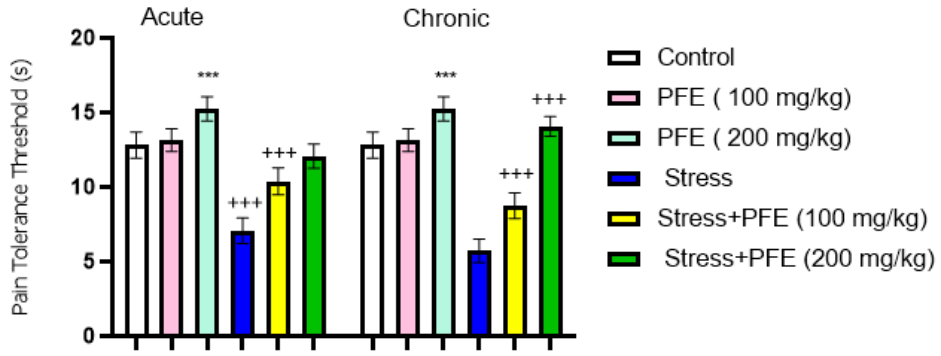

Figure 3. Effect of PFE treatment on thermal pain induced by Acute and chronic immobilization stress in the hot plate test. Data are presented as Mean ± SD. ***p<0.001 compared with the control group, +++p<0.001 compared with the Acute Stress and chronic Stress groups.

Effect of PFE treatment on thermal pain induced by acute and chronic immobilization stress in hot plate test

Two-way ANOVA revealed a significant main effect of stress ($F(1, 60) = 0.7297$, $P=0.3964$), a main effect of PFE doses ($F(5, 60) = 183.1$, $P<0.0001$), and a significant interaction between stress and PFE ($F(5, 60) = 7.543$, $P<0.0001$). Figure 3 shows that acute and chronic immobilization stress significantly decreased the pain tolerance threshold compared with the control group ($p<0.001$). PFE (100 mg/kg) treatment increased the pain tolerance threshold compared with the acute group, and both PFE doses significantly reduced hyperalgesia compared with the chronic stress group, suggesting an analgesic effect of PFE ($p<0.001$).

Discussion

Our results showed that PFE reduced hyperalgesia induced by acute and chronic stress, as evidenced by increased pain tolerance in the hot-plate test and reduced pain-related behaviors in the formalin test. Evidence suggests that stress can enhance pain sensitivity in rodents. A variety of animal models have been used to study stress-induced hyperalgesia. These include vibration, air stress, and immobilization, which may have significant clinical validity (24). In the present study, the immobilization paradigm was employed to induce acute (1-day) and chronic (21-day) stress. These paradigms are known to produce distinct physiological and behavioral outcomes. The formalin test and hot plate test were used for pain assessment. The hot plate test evaluates thermal nociception by measuring latency to heat stimuli, whereas the formalin test assesses persistent chemical pain (25,26). Behavioral analyses showed that the pain threshold in the acute and chronic stress groups was significantly reduced, suggesting an increase in thermal nociception induced by stress. A recent study demonstrated that chronic restraint stress (6 hours of immobilization/day for 4 weeks) induced significant hyperalgesia in mice (9). It has also been noted that restraint stress induces mechanical allodynia in female rats (27). On the other hand, treatment with PFE at both doses ameliorated pain-related behaviors by increasing the thermal pain threshold in the hot plate test. The formalin test produces a biphasic pain response: an early neurogenic phase (0-5 min) and a late inflammatory phase (15-60 min), with the 60-90 min interval evaluated for prolonged inflammatory responses (28). Our findings showed that PFE attenuated both phases (05 and 15-60), suggesting that its antihyperalgesic effects are probably mediated through anti-inflammatory and antioxidant activities (29). GC-MS analysis in a previous study confirmed abundant flavonoids (Chrysin, vitexin, apigenin, quercetin) in PFE. Specifically, flavonoids such as chrysin and apigenin act as positive modulators of the GABAergic system, whereas vitexin has demonstrated anxiolytic and neuroprotective effects (19). In agreement with the present data, a recent paper demonstrated the antihyperalgesic activities (Thermal and mechanical hyperalgesia) of PFE in a rat model of diabetic neuropathy (18). Additionally, another in vivo study suggested that PFE at doses of 100, 200, and 400 mg/kg increased the pain threshold in the hot plate test. It also decreased paw licking time in both phases of the formalin test, supporting its potential analgesic effects (30). Moreover, PFE improved stress, anxiety, cognitive disorders, and neural damage caused by chronic immobilization stress in rats (16). However, the dose-dependent effects, differences in efficacy across formalin phases and stress models, and established opioidergic/GABAergic mechanisms support genuine antinociception (19). Nonetheless, the absence of motor coordination tests is a limitation. Future studies should include motor coordination tests to determine whether the observed effects are independent of sedation or motor impairment.

Conclusion

In conclusion, the present study demonstrates that PFE effectively attenuates hyperalgesia induced by both acute and chronic immobilization stress in rats. These results support the potential therapeutic utility of Passiflora incarnata extract as an antihyperalgesic agent. Nevertheless, some limitations should be acknowledged. Our study primarily focused on behavioral assessments, and future investigations incorporating molecular markers would further strengthen the mechanistic conclusions. The absence of pharmacokinetic data and a positive control group do not undermine our findings, as the observed effects were robust and dose-dependent across multiple behavioral paradigms. However, these considerations provide valuable directions for future research.

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Ethical Statement

All animal experiments were conducted in full accordance with the National Research Council's Guide for the Care and Use of Laboratory Animals and the ethical guidelines established by Golestan University of Medical Sciences (Approval Code: IR.GOUMS.AEC.1404.002).

Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

Soghra Hesam: Study design, Writing and Editing of manuscript, Project administration. Fatemeh Piri: Project administration, Data collection, Project administration, Data collection. Hamid Sepehri: Data Analysis, Methodology.

Data Availability Statement

The authors do not have permission to share data.

Use of Artificial Intelligence

An AI tool was used only for minor language editing purposes and not for data analysis, scientific writing, or the generation of any part of the research content. The scientific content, interpretation, and conclusions were fully developed by the authors.

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