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Research Article
Potential Analgesic Effect of *Panax ginseng* in Reducing Acute Pain in Mice

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Abstract

Background and Objective: Ginseng (*Panax ginseng* Meyer) is a well-known traditional herbal medicine that has been widely used for several centuries. The goal of this study was to evaluate the effect of *Panax ginseng* in the treatment of acute transient pain. **Materials and Methods:** Thirty male mice (age: 12-13 weeks, weight: 25-34 g) were divided into five groups (n = 6 per group). The animals in the control group received a single-dose injection of sterile water. The diclofenac group received 5 mg kg^{-1} diclofenac. Each of the remaining three animal groups received different doses of *Panax ginseng* (150, 250 and 350 mg kg^{-1}) by intraperitoneal (i.p.) injection. The animals were observed for 2 days to record the experimental findings and mortality. **Results:** Hot-plate and writhing tests showed that treatment with *Panax ginseng* and diclofenac had an analgesic effect compared to the control treatment. Furthermore, the analgesic effect was significant in the diclofenac and *Panax ginseng* groups after 3 hours ($p<0.05$) but not in the first 3 hrs of the treatments. The result did not affect the survival rate of the animals during the experiments. **Conclusion:** *Panax ginseng* treatment had an analgesic effect in male mice, as found in the hot plate and writhing tests, which suggested that it is a potential analgesic treatment.

Key words: *Panax ginseng*, diclofenac, pain, analgesic effect, hot plate, writhing test

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Panax ginseng, also called Asian ginseng, has been used as a medicine for thousands of years and is one of the most widely used traditional herbal medicines[1]. Ginseng is derived from the roots of Korean or Asian ginseng (*P. ginseng*), Siberian ginseng (*Eleutherococcus senticosus*), American ginseng (*Panax quinquefolius*)[2] and several other species of plants from the Araliaceae family[3]. Ginseng products are commonly called "tonics," but they are termed "adaptogens" in most alternative medicine studies[4]. An adaptogen is defined as an agent that improves the body's resistance mechanisms in response to physical, chemical and biological stresses and improves overall vitality[5]. Some of the currently available over-the-counter *P. ginseng* supplements are Celestial Seasonings Ginseng, Centrum Herbals Ginseng, Korean Ginseng extract from Nature's Way, Nature Made's Chinese Red *Panax Ginseng*, Pharmaton's Ginsana and PhytoPharmica's Ginseng Phytosome[6].

Panax ginseng is a highly popular ginseng species that has received the attention of researchers[7]. It is native to China, Korea and Russia and has been used in traditional Chinese medicine for the treatment of weakness and fatigue, among other conditions[8]. Its main active agents are ginsenosides, which are triterpene saponins and therefore, most published studies on this species have been conducted on ginsenosides[9]. Research reviews postulate that *Panax ginseng* extracts affect the hypothalamus-pituitary-adrenal (HPA) axis, which plays a major role in regulating many endocrine hormones associated with the central nervous system and affects the immune system[10]. Ginseng has been reported to regulate the HPA axis in several diseases and disorders such as depression, osteoporosis, vascular disease, arthritis, erectile dysfunction and diabetes mellitus[11-14]. In particular, in individuals with diabetes, *P. ginseng* can improve psychological, physical, immune and other functions[12]. Its effects in these conditions are attributable to different mechanisms such as suppression of stress through cortisol or estrogen modulations or inhibition of the excessive proinflammatory cytokine secretion induced by persistent stress[15,16]. Animal and *in vitro* cellular experiments have demonstrated that *P. ginseng* improves phagocytosis, the function of natural killer cells and interferon production, as well as enhance physical and mental function in mouse and rat models. In addition, *P. ginseng* has been found to induce vasodilation[17], increase resistance to external stressors[18] and exert glycemic control[19-21].

Diclofenac sodium or 2-[(2,6-dichlorophenyl) amino] benzene acetic acid, belongs to the category of non-steroidal anti-inflammatory drugs[22], which can decrease peripheral and central prostaglandin production via their inhibitory effects on cyclo-oxygenase enzymes[23]. The decrease in prostaglandin production induced by these drugs results in a reduction in the peripheral and central nervous mechanisms against noxious stimuli and subsequently, alleviates the associated pain[24,25]. This study aimed to comparatively evaluate the analgesic effects of *Panax ginseng* and diclofenac in a mouse model of acute transient pain, to determine whether *Panax ginseng* could be a potential treatment for pain and its management.

MATERIALS AND METHODS

Study area: This research project was carried out between February, 2023 and March, 2023 at the Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Kingdom of Saudi Arabia.

Drugs and chemicals: *Panax ginseng* (Ginsana 115 capsule 100 mg) was obtained from Ginsana SA, Bioggio, Switzerland. Diclofenac sodium (Voltaren ampoule 75 mg) was obtained from Novartis Pharmaceuticals UK Ltd., London, UK. Acetic acid was obtained from Loba Chemie Company, Mumbai, India.

Experimental animals: Thirty adult male albino mice (weight: 25-35 g) were housed under standardized conditions (natural light-dark cycle, temperature of 25±1°C) and free access to water and food. The mice were randomly divided into five experimental groups. Group 1 (control group) received an intraperitoneal injection (i.p.) of distilled water. Group 2 (diclofenac-pretreated group) was injected with diclofenac sodium 5 mg kg^{-1} i.p. Group 3 (low-dose *Panax ginseng*) was injected with *Panax ginseng* 150 mg kg^{-1} IP. Group 4 (medium-dose *Panax ginseng*) was injected with *Panax ginseng* 250 mg kg^{-1} i.p. Finally, Group 5 (high-dose *Panax ginseng*) was injected with *Panax ginseng* 350 mg kg^{-1} i.p. All tests were performed between 0800 and 1500 hrs and each animal were used once. The animals were monitored throughout the study. The experimental protocol was approved by the Ethics Committee of the Deanship for Scientific Research, Qassim University, Saudi Arabia.

Hot-plate test: The hot-plate test was performed to measure latency time response by using an electronically controlled hot-plate, Eddy's hot plate analgesiometer (G.T Scientific Industry, Ambala Cantt, India) (Synthetic analgesics. II. Dithienylbutenyl- and dithienylbutylamines). The plate was heated to 55±0.1°C. Then, each mouse was placed

unrestrained on the hot plate until either paw licking or jumping occurred. The cut-off time latency for the experiment was 15 sec. Animals from all the groups were individually placed on the hot plate at different time intervals, starting from 1, 2, 3, 4, 5 and 6 hrs following the administration of distilled water in the control group, standard drug (diclofenac) and the test drug (*Panax ginseng*). All the results were compared to those obtained for the untreated control group. The animals' reactions (paw licking or jump response) were recorded and analyzed statistically[26].

Acetic acid-induced writhing test: In this method, animals were divided into five groups and animals in the first group were administered sterile water (control group). The second group received diclofenac injections (5 mg kg^{-1}, positive control group). The third, fourth and fifth groups received *Panax ginseng* injections (150, 250 and 350 mg kg^{-1}, respectively). All injections were administered intraperitoneally (i.p.). Thirty minutes after treatment, the mice received intraperitoneal (i.p.) injections of 0.6% v/v acetic acid at a dose of 10 mL kg^{-1} to induce the characteristic writhing. The animals were video-recorded for 15 min and the number of writhing motions during the 15 min period was counted for further analyses[27].

Ethical approval: The study was approved by the Institutional Animal Care and Use Committee in the Deanship for Scientific Research at Qassim University (approval number 23-24-16).

Statement of animal rights: Animal research used in this study is based on the acceptable morality of experiments offered in specified conditions. The importance of research ethics ensures proper treatment of laboratory animals and prevents excessive animal suffering. It is essential to provide the best human cover for these animals from ethical and scientific points of view. Poor animal care or abuse can affect the experimental outcomes, scientific knowledge and findings from experiments that can make it difficult to be reproduced. Currently, most ethical guidelines are based on the assumption that animal testing is justified because of the potentially significant benefits to humans.

Statistical analysis: All results from all groups were analyzed using GraphPad Prism 5.04 software (GraphPad Software Inc., San Diego, California, USA). Data were analyzed by two-way ANOVA followed by Bonferroni Test to compare all variables and $p<0.05$ was considered statistically significant.

RESULTS

Effects of *Panax ginseng* (150, 250 and 350 mg kg^{-1}) and diclofenac (5 mg kg^{-1}) on survival rate: Pretreatment of the mice with *Panax ginseng* (150, 250 and 350 mg kg^{-1}) and diclofenac (5 mg kg^{-1}) did not affect the survival rate (Fig. 1). Six mice were included in each group in this study.

Comparison of the effects of *Panax ginseng* (150, 250 and 350 mg kg^{-1}) and diclofenac (5 mg kg^{-1}) on acute thermal nociception in mice: In comparison with the control and diclofenac groups, mice treated with *Panax ginseng* extracts showed a significant increase in the time of thermal nociception after 3 hrs with the corresponding values in the control group. Moreover, the treatment with *Panax ginseng* had a significant analgesic effect after 3 or 4 hrs. However, the values measured after 1, 2 and 3 hrs in the diclofenac and *Panax ginseng* groups were not significantly different from those in the control group (Fig. 2).

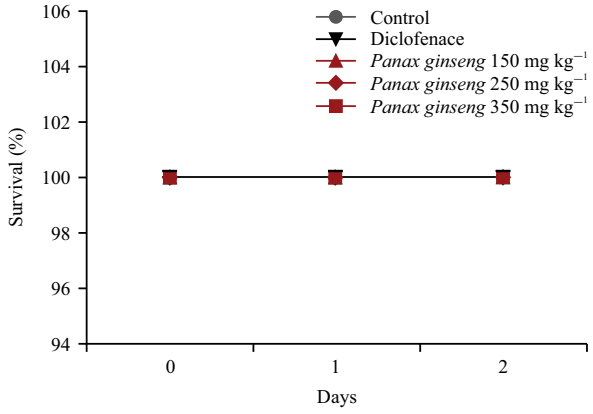

Fig. 1: Illustrative figure demonstrating that *Panax ginseng* and diclofenac did not cause any deaths during the treatments

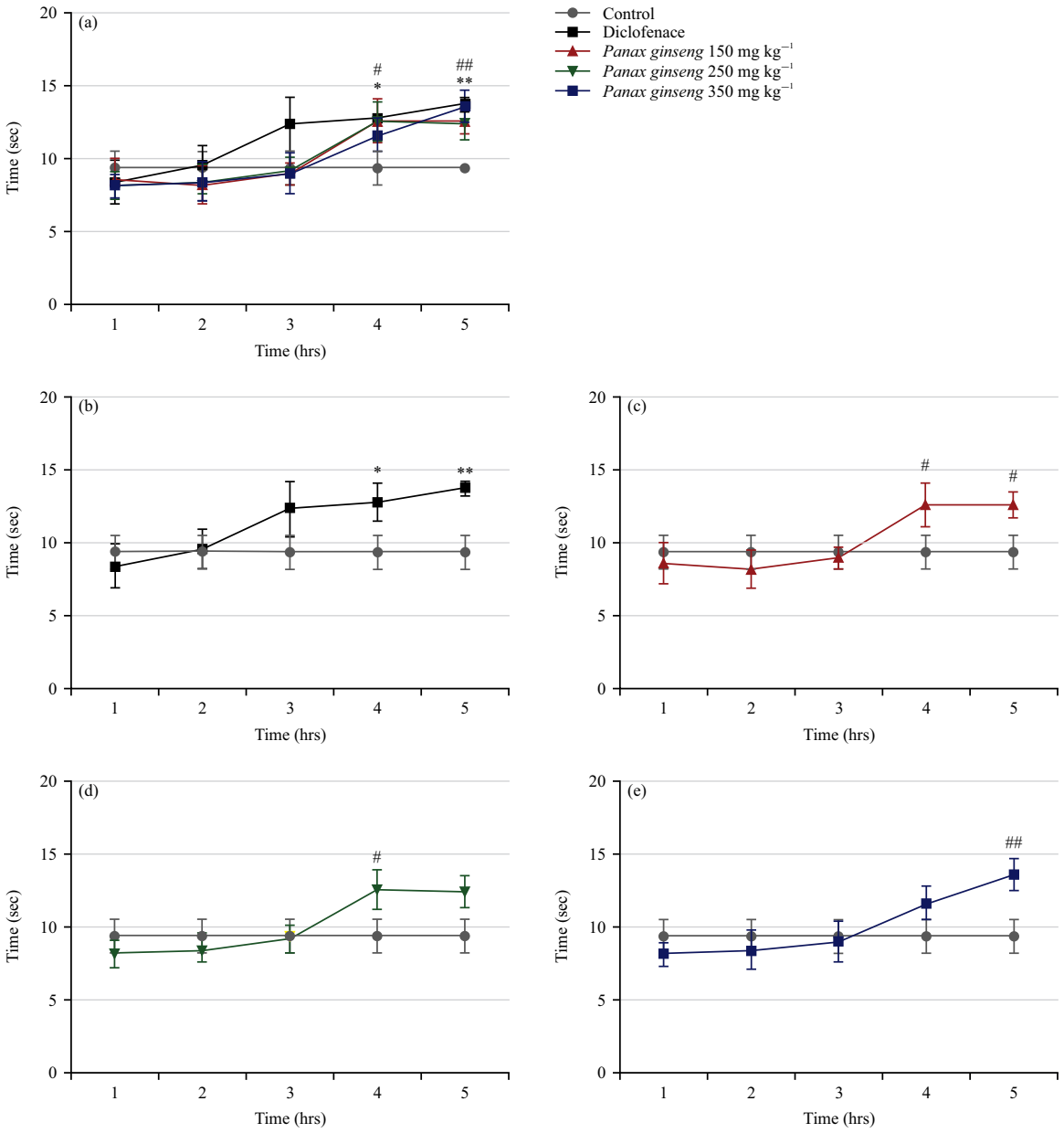

Fig. 2(a-e): Comparison of the effect of *Panax ginseng* (150, 250 and 350 mg kg^{-1}) and diclofenac (5 mg kg^{-1}) on acute thermal nociception in mice. Diclofenac and *Panax ginseng*-treated rats showed analgesic effects, (a) Schematic representation of all groups (diclofenac and *Panax ginseng* at 150, 250 and 350 mg kg^{-1}) in comparison with the control groups, (b) Diclofenac-treated rats displayed statistically significant analgesic effects 3 hrs after treatment, (c) *Panax ginseng* 150 mg kg^{-1}-treated rats showed analgesic effects after 3 hrs which persisted to 4 and 5 hrs, (d) *Panax ginseng* 250 mg kg^{-1}-treated rats showed analgesic effects after 4 hrs, which reduced after 5 hrs and (e) *Panax ginseng* 350 mg kg^{-1}-treated rats showed analgesic effects after 4 hrs

Bars represent mean SEM, *p or $^{\#}$p<0.05, **p or $^{\#\#}$p<0.01 and Number of animals in each group was 6

Comparison of the effects of *Panax ginseng* (150, 250 and 350 mg kg^{-1}) and diclofenac (5 mg kg^{-1}) on acetic acid-induced writhing in rats: In comparison with the control and diclofenac groups, the rats administered *Panax ginseng* extracts exhibited significantly fewer writhing motions during the 15 min observation period. However, the time of the writhes in the *Panax ginseng* groups decreased compared to the control although it was not significant statistically (Fig. 3).

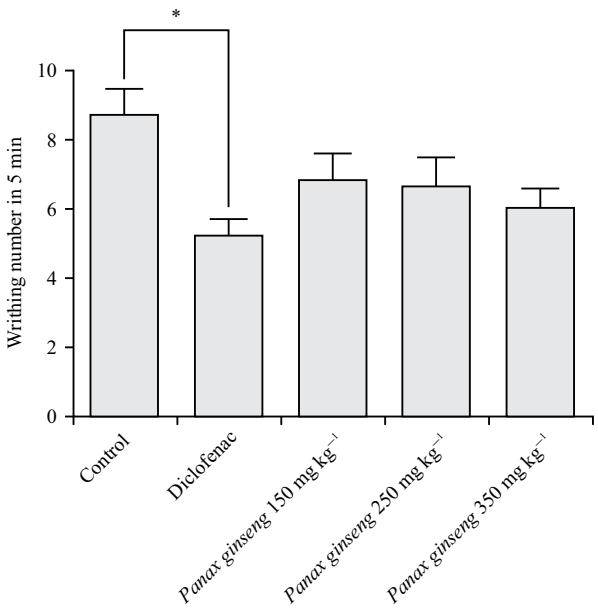

Fig. 3: Comparison of the effects of *Panax ginseng* (150, 250, 350 mg kg^{-1}) and diclofenac (5 mg kg^{-1}) on acetic acid-induced writhing in rats
*Means the p-value is less than 0.05

DISCUSSION

In the current study, the analgesic effect of *P. ginseng* was investigated by inducing acute transient pain (with the hot-plate method) and tonic pain (with the acetic acid-induced writhing method) in mice that were administered ginseng. The hypothesis that *P. ginseng* can improve pain by acting as an antinociceptive drug was investigated by using diclofenac as a positive control. The findings indicated that *P. ginseng* treatment at all the concentrations used (that is, 150, 259 and 350 mg kg^{-1}) did have analgesic effects that were similar to those of diclofenac. However, the time points at which these effects were observed, that is, 1, 2, 3, 4 and 5 hrs, were different from the time points at which the effects of diclofenac were observed. Despite these differences in the time point of the effects, the results demonstrate that ginseng has a similar analgesic effect to diclofenac.

In accordance with the present findings on the analgesic effect of *P. ginseng*, a previous study reported that the ginsenoside Rh2, which is one of the main active components of *P. ginseng*, reduced mechanical allodynia and thermal hyperalgesia in mouse models. In a rat model of toothache induced by intra-pulpal injection of 2 M KCl, *P. ginseng* provided protection against toothache by modulation of the non-opioid system[28]. In addition, a recent study revealed that the ginsenoside Rg3 present in *P. ginseng* could prevent oxaliplatin-induced neuropathic pain in mice[29]. Accordingly, Rg3 and another metabolite, compound K, were found to have analgesic and anti-inflammatory effects in a mouse model of chemically induced colitis and abdominal pain[30,31]. These analgesic effects on abdominal pain have also been reported in the group of patients from Brazil with irritable bowel syndrome[32]. These previous findings, along with those of the present study, provide strong evidence for the analgesic effects of *P. ginseng* and its potential clinical application. Human trials on large patient cohorts are required in the future to confirm these effects and evaluate the clinical potential.

The results of the present study revealed that high doses of *P. ginseng* extracts, that is, 150, 250 and 350 mg kg^{-1}, can induce analgesia and hypothermia in model mice. Further, none of the mice receiving *P. ginseng* died as a result of the treatment. These findings implied that these doses were safe and effective. Similarly, a study on rats that were administered 300 mg kg^{-1} *P. ginseng* extract over a 12 months period confirmed that this dose was effective and safe over the long term[33]. This result was also consistent with the findings of a review on randomized clinical trials on the effects of *P. ginseng* on a range of conditions, including obesity, diabetes mellitus, fibromyalgia and chronic fatigue[34]. This systematic review reported mild and temporary symptoms that included hot flushes, insomnia and dyspepsia but did not result in any adverse events[34]. However, the dosage ranged

from 200 mg to 60,000 mg per day and it was taken in various forms, such as the fermented extract and cultured extract[34]. In addition, the treatment period varied widely from 1 week to 3 years[34]. Therefore, more clinical trials are required in the future to determine the optimal dosage that is safe for specific conditions and the optimum treatment period. Further, the bioactive components and their concentrations in extracts that are currently available may vary widely due to a lack of standard procedures and guidelines for the manufacture of these herbal drugs[35]. This may also affect the efficacy and safety of ginseng products. Thus, it is important to lay emphasis on appropriate cultivation practices by farmers, as well as efficient manufacturing processes. With regard to potential harmful effects, ginseng may inhibit or induce the expression of certain enzymes that are involved in metabolism. For example, it can inhibit CYP2C9 and CYP3A4, which mediate some metabolic reactions in the human liver and can interfere with the metabolism of some drugs, such as imatinib, or induce the expression of CYP3A4, which has been shown to increase luciferase activity in the human liver cancer cell line[36]. Contradictory to this finding, another study reported that *P. ginseng* had strong protective effects against liver damage induced by cyclophosphamide in mice[37]. Therefore, the hepatic effects of *P. ginseng* may be a topic that requires further investigation.

The analgesic and hypothermic effects of *P. ginseng* have previously been reported to involve the non-opiate system[38]. Further, according to a recent review on the analgesic effects of *P. ginseng*, its mechanisms involve changes in the function of neurons and neurotransmitters in the peripheral and central nervous systems, inhibition of proinflammatory cytokines (such as TNF-α and IL-1β), alterations in the activity of sodium and calcium channels in DRG and spinal cord neurons, effects on the TLR4/NF-κB axis and other anti-inflammatory effects.

The mechanisms underlying the analgesic effect of *P. ginseng* could not be examined in the present study. In the future, further studies are needed to evaluate in more depth the molecular mechanisms underlying the analgesic effects of *P. ginseng* extracts, as well as the potential anti-inflammatory mechanisms that may be associated with its analgesic effects. Another limitation of this study was that the compounds that were potentially responsible for the analgesic effects were not isolated or identified. Further studies also are needed to extract and purify the *P. ginseng* compounds that are responsible for these analgesic effects. Despite this, the current findings do point to the potential clinical application of *P. ginseng* for the treatment of pain in the clinic.

CONCLUSION

The present results provide evidence for the antinociceptive effects of *P. ginseng* in mice. Further studies are necessary to confirm the effectiveness of ginseng extract in modulating pain sensation and to demonstrate the molecular mechanisms underlying these effects, as well as to identify the active components of ginseng that are responsible for the effects. In addition, the appropriate dosages and types of extracts that have optimal effects and are safe for use in humans need to be determined.

SIGNIFICANCE STATEMENT

This study evaluated the analgesic effect of *Panax ginseng* by investigating its antinociceptive effects in mice. Acetic acid was used to induce writhing and different concentrations of *Panax ginseng* (150, 250 and 350 mg kg^{-1}) were compared with diclofenac. These findings will assist researchers in developing new alternatives for pain management.

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