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Peganum harmala extract delayed the lethal effect of viper snake Echis carinatus venom in mice

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ABSTRACT

This study investigated the possible antagonistic effects of *Peganum harmala* extract against the lethal toxicity of *Echis. carinatus* venom. A total of 72 adult albino mice were divided into 12 equal groups in 6 experimental protocols. In protocol I (control), Group A only treated with E. carinatus venom (10 mg/kg). They died after 80 min averagely. In protocol II, Groups B1 and B2 were treated simultaneously with 15 and 30 mg/kg of *P. harmala*, respectively, and 10 mg/kg venom. Their survival time increased to 232 and 210 min, respectively. In protocol III, groups C1 and C2 were treated with 10 mg/kg venom followed 15 min later by *P. harmala* at 15 and 30 mg/kg respectively. Their time to death was increased to 246 and 220 min respectively. In protocol IV, groups D1 and D2, treated with pre-incubated of venom with 15 and 30 mg/kg of *P. harmala*. Their survival time increased to 211 and 195 min, respectively. In protocol V groups E1 and E2 received only *P. harmala* extract intraperitoneally (15 and 30 mg/kg). In protocol VI, groups F1, F2, and F3 received only *P. harmala* extract (orally) at 15, 30, and 60 mg/kg. All mice in these groups remained alive. *Peganum harmala* extract significantly ($p < 0.05$) increased animal survival time, has an antagonistic effect against lethal action of Echis carinatus venom.

Keywords

Snakebite, Echis carinatus, Venom, Peganum harmala, Antivenom, Mice

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Abbreviations

PLA2: Phospholipase A2
IV: Intravenously
IP: Intraperitoneal
µl: Microliter
MAO: Monoamine oxidase
WHO: World Health Organization
LD50: Lethal dose 50%
LD100: Lethal dose 100%
FUMH: Ferdowsi University of Mashhad Herbarium
DPPH: 2, 2-diphenyl-1-picrylhydrazyl

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Introduction

Snakebites are a considerable global public health concern that pose a significant threat to both humans and animals. Approximately 5.4 million individuals are bitten by snakes annually, resulting in up to 138,000 deaths . Therefore, it is essential to promptly diagnose and provide appropriate treatment to minimize potential complications of envenomation [1,2].

Iran, located in West Asia, possesses remarkable biodiversity and a land of 81 snake species, of which 25 are venomous and considered medically significant. Among these, the Echis. carinatus, (Figure 1) a member of the Viperidae family, is predominantly found in the southern regions of Iran [3]. *E. carinatus* is infamous for its aggressive behavior and a highly toxic venom, which primarily disrupts blood coagulation and the haemostatic system [4]. Warrell et al. (1977) reported that bites from E. carinatus result in a higher mortality rate than those caused by other venomous snake species in Northern Africa and Asia [5]. Between 2002 to 2011, Iran recorded 53,787 snakebite cases and 67 related deaths [6].

Antivenom therapy remains the important mainstay of snakebites treatment. It can effectively neutralize venom toxins and alleviate their adverse effects. However, several limitations are associated with antivenom use. First, antivenoms often exhibit limited specificity and may not be effective against venom variants. Additionally, their administration can trigger allergic reactions in recipients, ranging from mild skin rashes to severe life-threatening anaphylaxis. Furthermore, antivenoms may not always be readily available, especially in remote areas or low-resource countries, due to high production costs. Administering antivenoms can be complex, as they often require careful dosing and monitoring. In some cases, multiple doses may be needed, factors that increase cost and logistical challenges. Moreover, their effectiveness in addressing localized tissue damage induced by venoms is limited and in severe cases, if left untreated, local effects may lead to disability, permanent tissue necrosis, or amputation [7,8,9].

Given these limitations, the development of improved or adjunctive treatments for snakebite envenomation is essential. Therefore, scientists are searching for safer alternative treatment options that are easier to produce, store, transport, purchase, and administer, in order to overcome these barriers. In regions where snakebite incidents are prevalent and access to medical facilities is limited, plant-based medicine stands as an exceptional reservoir for seeking antivenom. In such regions, herbal remedies may often be the only treatment available [10,11].

It is worth noting that while herbal medicines have their advantages, the efficacy of many of them have not been scientifically investigated, nor have their active components been identified and isolated [13]. In some tribal areas of India, sometimes local populations rely on plant extracts to manage the severe local effects of Daboia russelli russelli (Russell's viper) envenomation, without any scientific validation [14]. However, some plant species have demonstrated scientifically measurable anti-venom properties. For instance, the Withania somnifera (ashwagandha) has been shown to neutralize venom of the speckled cobra [15], and aqueous root extract of Mimosa pudica have inhibited hyaluronidase and protease activities

Figure 1.
Viper snake Echis carinatus, also called saw-scaled viper (prepared by B. Fathi)

from venoms of Indian snake, *Naja naja*, *Vipera russelli* and *E. carinatus*, in dose dependent manner [16]. These compounds have natural PLA2 inhibitors and interact with the active site of PLA2s, proving their efficacy as anti-inflammatory and antidotes [17].

It has been reported that Tabernaemontana alternifolia root extracts neutralize enzymatic activities of *E. Carinatus* and *Naja naja* venom [18]. The compounds such as flavonoids, polyphenols, tannins, sterols, terpenoids, and polysaccharides, found in this plant, neutralize the venom's hydrolytic enzymes, specifically phospholipases, proteases, and hyaluronidase. These compounds effectively interfere with the harmful effects of the venom [13, 19], thereby preventing the release of inflammatory, vasodilatory, and vasoconstrictive mediators that typically occur during envenomation. This, in turn, minimizes damage to local tissue, inflammation, myonecrosis, impairment of vital organs, and modifications in coagulation compo-

nents [13, 20].

Peganum harmala L, (Syrian Rue) is a perennial plant belonging to the family Zygophyllaceae [21,22]. *P. harmala*, particularly in its seed, contains a variety of phytoconstituents mostly bioactive alkaloids [23], including harmine, harmalol, harmaline, harmol, vasicine, vasicinone, deoxyvasicine, deoxyvasicinone, and several β-carboline [24,25]. These compounds contribute to the *P. harmala*'s broad spectrum of therapeutic beneficial properties such as, antidiabetic, anti-asthmatic, anti-arthritis, antihypertension, anticancer, antimicrobial, anti-inflammatory, antiviral, antidiarrheal, antiemetic, antidepressant, anthelmintic, and antioxidant effects[26]. In Iranian folk medicine, burning *P. harmala* seeds and utilizing the resulting smoke is a common practice for air disinfection.

There been unverified reports suggesting the use of *P. harmala* in certain regions of Iran for relieving bites and stings from various animal sources. However, these claims have yet to be supported by scientific evidence and research. The present study, aimed to investigate the potential of *P. harmala* extract as a treatment for snakebites, marking the first examination of its effectiveness against the lethal effects of *E. carinatus* venom.

Table 1.
Application of different protocols and summary of the experiment results

Protocols	Groups	No of mice	venom mg/kg	P. Harmala mg/kg	Average time to death (min)
I	A	6	10	-	80
II	B1	6	10	15	232
II	B2	6	10	30	235
III	C1	6	10	15	246
III	C2	6	10	30	220
IV	D1	6	10	15	211
IV	D2	6	10	30	195
V	E1	6	-	15	Live
V	E2	6	-	30	Live
VI	F1	6	-	15/Po	Live
VI	F2	6	-	30/Po	Live
VI	F3	6	-	60/Po	Live

Protocols: I, Group A, only received venom at dose of 10 mg/kg (control).
Protocols: II, Groups B1& B2, received venom at 10 mg/kg along with P. harmala at 15 and 30 mg/kg (simultaneously).
Protocols: III, Groups C1 & C2, received venom at 10 mg/kg and P. harmala at 15 and 30 mg/kg respectively, after a 15-minute interval.
Protocols: IV, Groups D1 & D2 received venom at 10 mg/kg along with P. harmala at 15 and 30 mg/kg incubated for 30 min prior to injection. The intraperitoneal (IP) route was used for injection.
Protocols: V Groups E1 & E2 received only P. harmala at 15 and 30 mg/kg orally (IP).
Protocols: VI Groups F1, F2 & F3 received only P. harmala at 15, 30 and 60 mg/kg orally(Po).

Result

Protocol I

In Protocol I, group A served as control group and received an intraperitoneal injection of E. carinatus venom at a dose of 10 mg/kg. The mortality rate in this group was 100%, and the average time to death recorded at 80 ± 5 minutes (Figure 2).

Protocol II

In this protocol, mice in groups B1 and B2 were received *P. Harmala* extract at the doses of 15 and 30 mg/kg, respectively, in combination with 10 mg/kg of *E. carinatus* venom administered simultaneously. In this group, the mortality rate was 100%, and the average time to death was 232 minutes in Group B1 and 235 minutes in Group B2. These values were significantly different from the time to death of animals in Group A ($p < 0.01$). (Figure 2) (Table 1).

Protocol III

In this protocol, animals in Groups C1 and C2 received *P. harmala* extract at doses of 15 and 30 mg/kg, respectively, 20 minutes after being injected with 10 mg/kg of E. carinatus venom. The average time to death were 246 minutes for Group C1 and 220 minutes for Group C2. These values were significantly different from the time to death of animals in Group A ($p < 0.01$) (Figure 2) (Table 1).

Protocol IV

In this protocol, groups D1 and D2 received a pre-incubated mixture of *P. harmala* extract at doses of 15 and 30 mg/kg, respectively,

with 10 mg/kg of E. carinatus venom. The extract and venom were incubated together for 20 min prior to injection. The average time to death was 211 minutes in Group D1 and 195 minutes in Group D2. These values were significantly different from the time to death of animals in group A ($p < 0.01$) (Figure 2) (Table 1).

Protocol V

In this protocol, groups E1 and E2 received only *P. Harmala* extract at doses of 15 and 30 mg/kg, respectively, via intraperitoneal injection. All mice in these groups survived, indicating no observable toxic effects at these dosages.

Protocol VI

In this protocol, groups F1, F2, and F3 received *P. Harmala* extract at doses of 15, 30 and 60 mg/kg, respectively, administered orally. All mice in these groups survived (Table 1). This observation indicates no toxic effects of the extract at the tested concentrations.

Discussion

To date, there has been no documented scientific research on the interaction between *P. harmala* and animal venom particularly the venom of *E. carinatus*. The findings of this study provide initial evidence that *P. harmala* extract possesses a notable antagonistic effect against the lethal toxicity of *E. carinatus* venom.

Statistical analysis confirmed that simultaneous administering of *P. harmala* extract at doses of 15 and 30 mg/kg with the venom significantly increased the average survival time compared to the control group. Interestingly, this protective effect did not appear to follow a strict dose-dependent pattern. In fact, increasing the dose from 15 to 30 mg/kg resulted in a decrease in average survival time in some groups (C2 and D2). Although *P. harmala* extract did not fully neutralize the lethality of *E. carinatus* venom, it significantly increased the average survival time of the tested animals. The mechanism underlying this protective effect remains unclear. Previous studies on other plant-derived compounds have suggested different mechanisms, that maybe could also potentially apply to *P. harmala* as well.

Importantly, the extract of *P. harmala* did not exhibit any toxic effects on its own at different dosage levels, whether administered through injection or oral administration. This observation supports its potential safety as a therapeutic agent at these concentrations. Nonetheless, it is important to note that *P. harmala* extract can be toxic at higher orally doses [22]. The antagonistic effect of extract when combined with venom, may suggest it's possible interference with the venom's molecular interactions. The exact mechanism is still unknown.

The venom of *E. carinatus* consists of PLA2, hyaluronidase, and Zn2+ metalloprotease, it's known for potent hemorrhagic and procoagulant effects. [4,16]. PLA2 enzymes are particularly damaging due to their ability to hydrolyze phospholipids in cell membranes, leading to the rupture of erythrocytes and capillaries, and resultant hemorrhage [27]. Beyond bleeding, these enzymes can induce various systemic effects, including cardiotoxicity, myotoxicity, neurotoxicity (both pre or post-synaptic), edema, hemolysis, hypotension, convulsion and platelet aggregation [28].

In addition to PLA2, the zinc-dependent metalloprotease found in viper venom including that of E. carinatus, degrade the endothelial linings of blood vessels, resulting in spontaneous hemorrhage [29]. The synergistic action of metalloprotease and PLA2 is responsible for the release of endogenous inflammatory mediators, promotes local edema, and increased free radical formation at the bite site.

It is possible that the hemorrhagic activity of this venom is interfered by the P. harmala extract components. These com-

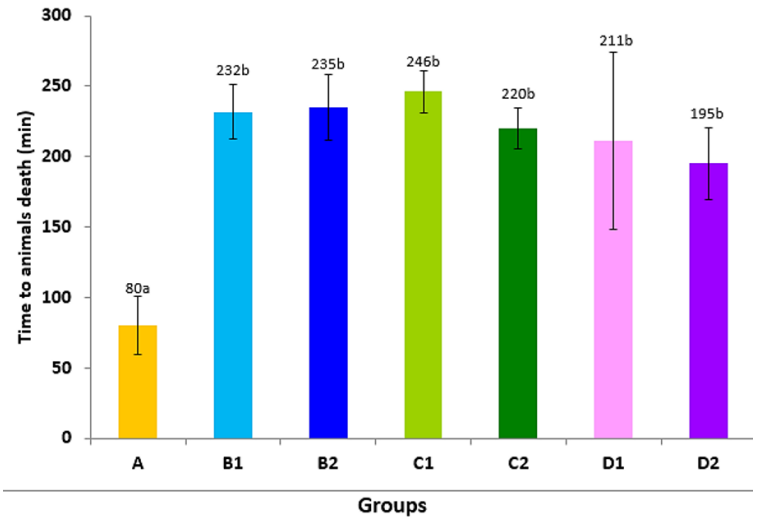

Figure 2.
Display the Mean and standard deviation of the survival time for different treatments groups. Values that are followed by different superscript letters (a, b) indicate a significantly difference at the level of ($p < 0.05$).
Group A, received only venom at 10 mg/kg, Groups B1& B2, received venom at 10 mg/kg along with P. harmala at 15 and 30 mg/kg (simultaneously).
Groups C1 & C2, received venom at 10 mg/kg and P. harmala at 15 and 30 mg/kg respectively, after a 15-minute interval.
Groups D1 & D2 received venom at 10 mg/kg along with P. harmala at 15 and 30 mg/kg incubated for 30 min prior to injection. The intraperitoneal (IP) route was used for injection.

pounds may have antagonistic effects with the metalloprotease and PLA2 activities or chelate metal ions such as Zn2+ or Ca2+; which are essential cofactors for the enzyme's functionality [30,31].

Previous research have been reported with other plant extracts. For example, Andrographis paniculata and Aristolochia indica have demonstrated the ability to block the hemolysis caused by E. carinatus venom in agarose-erythrocyte gels [32]. Likewise , Horsfieldia amygdaline is a plant from which PLA2 inhibitors have also been extracted [33]. Also, it has been reported that Vitis vinifera extracts have shown efficacy in neutralizing venom induced edema [34[. It is plausible that P. harmala extract operates through a comparable mode of action, which contains numerous anti-inflammatory and active chemical constituents These include phenolic compounds, amino acids (such as phenylalanine, valine, histidine, and glutamic acid), flavonoids (such as coumarin, tannins), sterols, and toxic alkaloids known as β-carbolines (which include Harmine, Harmaline, Harmol, and Harmalol) [25,24]. These β-carbolines have an affinity for multiple receptor type, such as serotonin, muscarinic, histamine, and benzodiazepine [35]. We can assume that the extract of *P. harmala* extract interferes with interaction between the specific receptors and their counterpart components present in the venom of *E. carinatus* , thereby potentially diminishing the venom's lethal potency.

In addition to receptor- level effects, several studies suggest that the bioactive alkaloids, harmaline and harmine, possess the capability to interfere with various enzymatic activity. Harmaline and harmine are selective inhibitors of monoamine oxidase (MAO), an enzyme responsible for the degrading crucial neurotransmitters, such as serotonin, dopamine, and norepinephrine [36].

Some snake venoms can block acetylcholine release and inhibit the neuromuscular junction [37]. Interestingly, P. harmala's substances has demonstrated the ability to inhibit acetylcholinesterase and butyrylcholinesterase. Inhibiting acetylcholinesterase can lead to the accumulation of acetylcholine, prolonging muscle stimulation and delaying paralysis [38].

Another critical avenue through which snake venom often exerts its toxicity is through the generation of reactive oxygen species (ROS), leading to oxidative stress, inflammation and tissue damage. P. harmala has been found to possess strong antioxidant properties, known as 2, 2-diphenyl-1-picrylhydrazyl (DPPH). Its β-carbolines have shown considerable anti-inflammatory and antioxidant properties, which can effectively neutralize ROS. This ability to reduce oxidative stress, inflammation, and pain potentially contributes to its antivenom activity against E. carinatus venom" [39].

Conclusion

In conclusion, our study demonstrates that the extract of Peganum Harmala effectively extract possesses significant protective effects and can delay the lethal toxicity of Echis. carinatus venom. Consequently, it can be considered as an adjunctive therapy to complement standard clinical treatments, particularly in remote areas where immediate access to healthcare facilities and anti-venom is limited .

Materials and Methods

Ethical Considerations

Compliance with ethical guidelines: The proposal and experiments were approved by the Animal Ethical Committee of our Faculty of Veterinary Medicine. (Ethics code IR.UM.REC.1401.171).

Venom

The freeze-dried crude venom of *E. carinatus* was kindly provided by the Razi Vaccine and Serum Research Institute (Karaj, Iran). It was stored at 4ºC and freshly prepared by dissolving it in a sterile saline to a final volume of 500 µl prior to administration.

Preparation of Peganum harmala extract

The *P. harmala* plants were harvested from agricultural fields near the city of Sabzevar (36°12'45"N and 57°40'35"E), located in the western region of Razavi Khorasan province in Iran. The species was identified at the Herbarium of Ferdowsi University of Mashhad (13613-FUMH). After drying the plant material in a dark room at 28 ± 4 °C for two weeks, the black seeds were separated and ground into a fine powder. Ethanolic extraction was carried out at Department of Pharmacognosy, Faculty of Pharmacy, Mashhad University. About 100 grams of the powdered seeds were poured into a 500 ml Erlenmeyer flask, and 300 ml of methanol was added until the solvent covered the powder by approximately 2 cm. The mixture was stirred, covered, and kept in a dark location for 48 hours. Then the upper portion of the solution was filtered using Whatman no. 1 filter paper. Additional methanol was added to the sediment portion and stirred for 30 minutes, and this process was repeated multiple times until the upper phase of the solution turned completely colorless. The resulting solution was subjected to a vacuum rotary evaporator (IKARV 10, Germany) set at 45 °C and 60 rpm. The solvent was gradually evaporated, eventually yielding a viscous extract. The extract was then transferred onto a plate and oven-dried to fully remove residual solvent. Finally, the extract was wrapped in aluminum foil and stored in a refrigerator at 4°C. Initial efforts to dissolve the extract using conventional solvents were unsuccessful. Ultimately, it was found that the most effective method involved dissolving the extract in 2 Normal HC followed by pH adjustment to 7.5 using NaOH , resulting in a stable and fully soluble preparation.

Animals

A total of 72 healthy adult albino mice (8-10 weeks and weighing 35±5 grams) were obtained from the Animal House at Mashhad University of Medical Sciences. The mice were housed

in the animal facility at Faculty of Veterinary Medicine, with controlled environmental conditions including a 12:12 light-dark cycle, a temperature of 22 ± 3°C, and a relative humidity of 55 ± 10%. Animals were maintained in standard rodent cages with free access to food and water. All experimental protocols were approved by the Animal Ethics Committee at Ferdowsi University of Mashhad (code: IR.UM.REC.1401.171).

Experimental protocols

The study was designed using six experimental protocols (I-VI) (Table 1). involving 12 equal groups of mice (n = 6 per group): A, B1, B2, C1, C2, D1, D2, E1, E2, F1, F2 and F3.

Protocol I (control): group A received only *E. carinatus* venom at a dose of 10 mg/kg intraperitoneally (IP). Protocol II: groups B1 and B2 were treated with 15 and 30 mg/kg of P. Hermala extract, respectively, simultaneously with 10 mg/kg of venom (IP). Protocol III: group C1 and C2 were treated with 15 and 30 mg/kg of P. Hermala extract, respectively, 20 minutes after receiving venom at 10 mg/kg (IP). Protocol IV: group D1 and D2 received a mixture of venom and P. Hermala extract (15 and 30 mg/kg, respectively), that were pre-incubated at room temperature (26 ± 2°C) for 20 minutes before IP injection. Protocol V: groups E1 and E2 received only P. Hermala extract at doses of 15 mg/kg and 30 mg/kg, respectively, via IP injection. Protocol VI: groups F1 and F2 and F3 received only P. Hermala extract orally at doses of 15, 30 and 60 mg/kg, respectively. The survival time of each animal after the administration of venom, extract or venom-extract combinations was recorded in minutes. These values were statistically compared with the across groups.

Statistical analysis

Data are presented as mean ± SEM. All the results were analyzed using SPSS-19 (SPSS Inc., Chicago, Illinois). One way analysis of variance (ANOVA) was used, followed by a post-hoc analysis using a Tukey test. A p-value of less than 0.05 was considered statistically significant.

Authors' Contributions

FB supervised, design the experiment and wrote the manuscript, revised and corrected it FB. SS performed the experiments, collected data, analyzed and interpreted the results, and prepared the manuscript. All authors read, discussed, commented, and approved the final manuscript.

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Competing Interests

The authors have declared that there is no conflict of interest.

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