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Research Paper

Enhancing Venom Lethality: The Incompatibility of *Cannabis sativa* Extract in Snakebite Management

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ABSTRACT

Introduction: Snakebite envenoming is recognized by the World Health Organization (WHO) as a neglected public health issue, particularly in tropical and subtropical regions. Since some victims of snake bites have been reported to use *Cannabis sativa* to fight snakebite envenoming, the objective of this study was to examine the impact of this herb on the lethal effects of *Naja naja oxiana* cobra venom in mice.

Materials & Methods: This study utilized four protocols and 80 mice, divided into ten equal groups. The intraperitoneal (IP) route was used for injection. In protocol I (control), group A received 2 mg/kg of venom. Groups B1, B2, and B3 received *C. sativa* extract at doses of 80, 120, and 160 mg/kg, respectively. In protocol II, groups C1 and C2 received simultaneous administration of 80 and 120 mg/kg of the extract together with 2 mg/kg of venom. In protocol III, groups D1 and D2 were injected with 2 mg/kg of venom, followed by administration of 80 and 120 mg/kg of the extract after a 20-minute interval. In protocol IV, groups E1 and E2 received the pre-incubated (20 minutes) of venom-extract at the similar doses.

Results: On average, animals succumbed to death 35 minutes after being injected with venom. The extract significantly reduced this time in groups C1, C2, D2, E1 ($P<0.01$), and E2 ($P<0.001$) compared with group A.

Conclusion: The *C. sativa* was not only unable to neutralize the lethal effect of *N. n. oxiana* venom, but it also potentiates its effect, significantly decreasing the time of the animal's death.

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1. Introduction

For centuries, medicinal plants have been utilized to treat snakebites, particularly in areas with limited access to healthcare. In such cases, traditional herbal remedies may represent the sole option for providing care to victims and preserving their lives [1]. Snakebite envenoming is recognized by the World Health Organization (WHO) as a neglected public health issue, particularly in tropical and subtropical regions. According to the WHO, over 5000,000 victims are bitten by venomous snakes annually, resulting in more than 135,000 deaths and leaving more than three times this number disabled [2].

Iran is a temperate region that is home to 81 species of snakes, 25 of which are venomous and medically significant due to their potential to cause mortality and morbidity [3]. A ten-year survey conducted between 2002 and 2011 in Iran documented 53,787 cases of snakebite, with 67 resulting in fatalities [4].

The Iranian snake *Naja naja oxiana*, (Figure 1), belongs to the Elapidae family and mainly inhabits the northeastern region of Iran [5]. *N. n. oxiana* is highly venomous and possesses a potent neurotoxin with one of the lowest level of median lethal dose (LD_{50}), making it deadlier than other venomous cobras. It's LD_{50} has been reported to be approximately 10 µg/mouse when injected intravenously, verified after 24 hours [6]. Its neurotoxic venom exhibits both pre- and post-synaptic blocking properties, paralyzing the neuromuscular junction and ultimately killing its prey [7].

The clinical symptoms resulting from a bite by *N. n. oxiana* include intense localized effects like pain, redness, swelling, bleeding, blistering, and tissue necrosis at the site of the bite. Additionally, neurological complications can arise, including weakness, ataxia, peripheral nerve paralysis, ptosis of eyelids with mydriasis, shock, excessive salivation (sorrhea), and ultimately respiratory arrest (asphyxia) because of paralysis of the respiratory muscles. These complications have the potential to be fatal [8]. Thus, treatment of patients bitten by this cobra requires urgent medical attention.

For over a century, the conventional and effective treatment for envenomation has been the administration of antivenoms soon after a bite. Currently available antivenoms consist of heterologous allergenic proteins, which pose a risk of acute adverse effects, including potentially life-threatening anaphylactic or pyrogenic reactions. These reactions are usually noticed during the first hour following administration. Additionally, delayed reactions of the serum sickness type have also been reported [9].

In clinical practice, certain patients may encounter early side effects following antivenom therapy, including urticaria, itching, rapid heartbeat, abdominal cramps, nausea, vomiting, bronchospasm, low blood pressure, and angioedema after receiving antivenom therapy [10].

In general, there are several disadvantages associated with antivenoms, including limitated accessibility, costly production, difficulties in affordability, variation in efficacy, possible low quality, and the need for high and potentially unsafe doses [11]. Therefore, it is crucial to continue scientific investigations to develop new neutralizing agents with lower side effects than current antivenoms.

Herbal medicines represent a valuable source of numerous pharmacologically active materials and have been utilized for years to treat many medical problems and diseases. Pharmacological studies have demonstrated that a significant number of herbal compounds can counteract the effects of various venoms and toxins [12].

One such herbal extract is *Cannabis sativa*, also known as marijuana, hemp, or ganja, from the Cannabinaceae family. It is an important psychoactive substance that originated in Central Asia [13]. *C. sativa* has been used for more than 5,000 years to treat various diseases, including hysteria, psychosis, insomnia, nausea, glaucoma, pain, convulsion, inflammation, depression, and even as an insect repellent [14]. *C. sativa* contains over 538 chemically active compounds, including cannabinoids, terpenoids, flavonoids, ketones, esters, alkaloids, and other phenolic compounds. Also, research suggests that in certain inflammatory conditions, cannabidiol derivatives may act as an anti-inflammatory agent similar to dexamethasone [15].

Additionally, it consists of over 140 phytocannabinoids, which exhibit diverse biological and pharmacological activities and act on multiple targets [16]. Among these phytocannabinoids, the most active component to produce psychoactive effect is trans-delta-9-tetrahydrocannabinol (D9-THC) [17].

Cannabinoids interact with two receptors, namely the type-1 and type-2 (CB1 & CB2) cannabinoid receptors, and have two endogenous ligands: Arachidonoylethanolamine and 2-arachidonylglycerol [18]. These can-

nabinoids have the ability to penetrate the blood-brain barrier (BBB) and attach to their receptors in the central nervous system, leading to psychoactive effects.

This interaction could potentially neutralize or reduce the lethality of the venom, as well as moderate the clinical symptoms and shock caused by a snake bite. Given the impact of *C. sativa* on the nervous system, we hypothesized that its components might interact with the neurotoxic venom of *N. n. oxiana*, which also targets the nervous system. This interaction could potentially neutralize or reduce the lethality of the venom and moderate the clinical symptoms and shock caused by a snake bite.

Furthermore, our research revealed that individuals may use *C. sativa* for various purposes, including pain relief, stress management, and treatment of venomous animals' stings or bites, due to its anti-inflammatory and analgesic properties. Therefore, this study aimed to assess the potential antagonistic effects of *C. sativa* on the lethal activity of cobra snake (*Naja n. oxiana*) venom in mice, addressing the lack of systematic research into the plant's properties as an antivenom.

2. Materials and Methods

2.1. Venom

The lyophilized crude venom of *N. n. oxiana* was kindly supplied by the Razi Vaccine and Serum Research Institute, Karaj, Iran. It was stored at 4 ˚C and freshly reconstituted in sterile saline solution just before administration via intraperitoneal (IP) injection into the mice.

2.2. Plant material and extraction of *C. sativa*

Fresh female *C. sativa* plants were harvested from an agricultural field in the South Khorasan region of Iran, specifically in Se Ghale City (33° 40′ E and 58° 23′ N). The plant specimen was identified as *C. sativa* at the Ferdowsi University of Mashhad Herbarium (13613-FUMH). The collected plant materials were thoroughly washed and suspended upside down in a dark environment at 28±4 ˚C two weeks to facilitate air-drying. Following this, the flowers were then detached, chopped into small pieces, and ground into a fine powder. The extraction process for *C. sativa* was conducted at the Department of Pharmacognosy, Ferdowsi University of Mashhad, Pharmacy College. A total of 20 grams of the powder was mixed with 200 mL of 70% ethanol. The mixture was stirred for one hour at room temperature, repeated three times over the course of 48 hours, and filtered three times using Whatman filter paper No. 1. The resulting solution was stored in an aluminum-covered glass container to protect it from light. Ethanol was subsequently removed using a vacuum rotary evaporator set at 50 ˚C (IKARV 10, Germany). The obtained solution was then covered and left under the hood until it became highly viscous solution.

2.3. Preparation of injectable extract solution

A very thin layer of the extract was spread onto aluminum foil, carefully weighed, and placed in an oven at 60 ˚C to dry completely. Once its weight remained constant, it was considered a dry extract. The injectable solution was prepared by dissolving a proper quantity of *C. sativa* extract in ethanol. Then, Tween 20 (Sigma-Aldrich) solvent was added, the mixture vortexed and allowed to evaporate the ethanol. Finally, normal saline was added to the solution at a ratio of 1:1:8, and the mixture was vortexed until the extract completely dissolved [19].

2.4. Animals

A total of eighty (80) albino mice of both sexes, each weighing between 25-40 g and aged 8-10 weeks, were obtained from the Animal House at Mashhad University of Medical Sciences for this research. The mice were kept in the animal facility of the Faculty of Veterinary Medicine under standard conditions, including temperature 24±2 ˚C, relative humidity 55±10%, and a 12-hour light/dark cycle, in standard rodent cages.

They were given mouse pellets for nourishment and had access to water at all times. The experimental procedures adhered to the guidelines established by the Animal Ethics Committee at the Faculty of Veterinary Medicine, Ferdowsi University of Mashhad.

2.5. Experimental protocols

The study examined the efficacy of *C. sativa* extract in counteracting the lethal effects of *N. n. oxiana* venom through four distinct protocols (I, II, III, and IV), as detailed in Table 1. The animals were divided into ten equal groups: A, B1, B2, B3, C1, C2, D1, D2, E1, and E2. In protocol I, group A, served as the control and received 2 mg/kg of *N. n. oxiana* venom. Groups B1, B2 and B3, received *C. sativa* extract at doses of 80 and, 120 and 160 mg/kg, respectively. In protocol II, groups C1 and C2 received simultaneous administration of venom (2 mg/kg) and *C. sativa* extract at 80 and, 120 mg/kg, respectively.

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Figure 1. Iranian snake *N. n. oxiana* (2017-Khorasan)

In protocol III, groups D1 and D2 were administered *N. n. oxiana* venom (2 mg/kg), followed 20 minutes later with 80 and 120 mg/kg of *C. sativa* extract, respectively. In protocol IV, venom was mixed with *C. sativa* extract and pre-incubated for 20 minutes at room temperature (26±2 ˚C) prior to injection into animals. Groups E1 and E2 were received this mixture at 2 mg/kg of venom and 80 and 120 mg/kg of *C. sativa* extract, respectively. The route of administration was IP injection. The duration of survival (in minutes) for each animal following the injection of venom, extract, and venom/extract was documented and statistically analyzed against control groups.

2.6. Statistical analysis

Data are expressed as Mean±SEM, and all results were analyzed using SPSS Software, version 22 (SPSS Inc., Chicago, Illinois). A one-way analysis of variance (ANOVA) was conducted, followed by post-hoc analyses using the Tukey test. A significance level of $P<0.05$ was considered statistically significant.

3. Results

3.1. Evaluation the antivenom activity of *C. sativa* extract

3.1.1. Protocol I, study the acute toxicity

The *N. n. oxiana* venom and *C. sativa* extract were tested in vivo to evaluate their toxic effects. All mice in group A were administered 2 mg/kg of venom alone. This group exhibited a 100% mortality rate, with an average time to death of 35 minutes (Figures 2 and 3). In contrast, all mice in groups B1, B2, and B3, which received only the *Cannabis* extract at doses of 80, 120, and 160 mg/kg, respectively, survived. This demonstrated that the extract had no toxic effects at the concentrations tested (Table 1).

3.1.2. Protocol II, effect of simultaneous injection of *C. sativa* extract and *N. n. oxiana* venom

All mice in groups C1 and C2 were treated with 80 and 120 mg/kg of *C. sativa* extract, respectively, along with 2

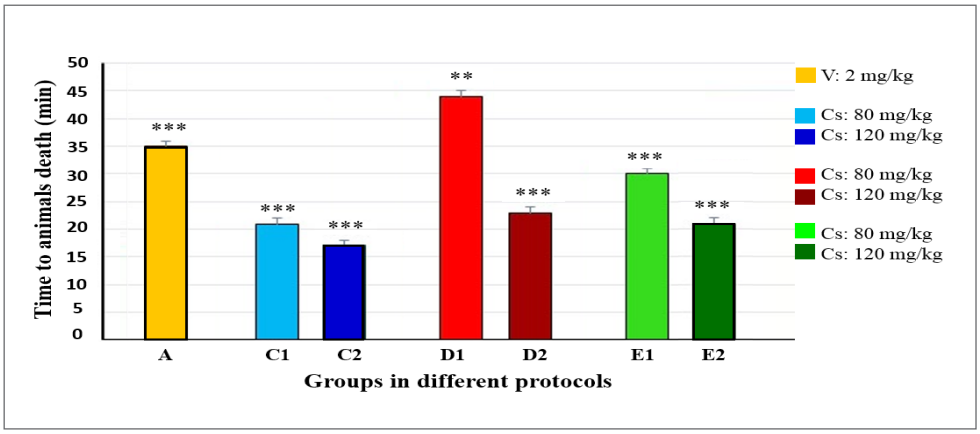

Figure 2. Time to death of mice after application of venom (V) and *C. sativa* (Cs) extract in different experimental protocols

Note: Protocols: I (groups A), the only venom was injected at 2 mg/kg (control). Protocols: II (group C1 & C2), venom and plant extract have been injected simultaneously at 80 and 120 mg/kg respectively. Protocols: III (groups D1 & D2), the plant extract has been injected 20 min after to venom injection at pervious doses. Protocols: IV (groups E1 & E2), venom and plant extract have been incubated for 20 min prior to being injected at pervious doses. The level of significance considered was P<0.05.

mg/kg of venom simultaneously. These groups exhibited a 100% mortality rate, with an average time to death of 21 and 17 minutes, respectively.

The time to death in animals from group A showed a significant difference compared to these values (P<0.001) (Figures 2 and 3) (Table 1).

3.1.3. Protocol III, effect of *C. sativa* extract injected 20 minutes after *N. n. oxiana* venom

Animals in groups D1 and D2 treated with 80 and 120 mg/kg of *C. sativa* extract, respectively, 20 minutes after receiving 2 mg/kg of venom.

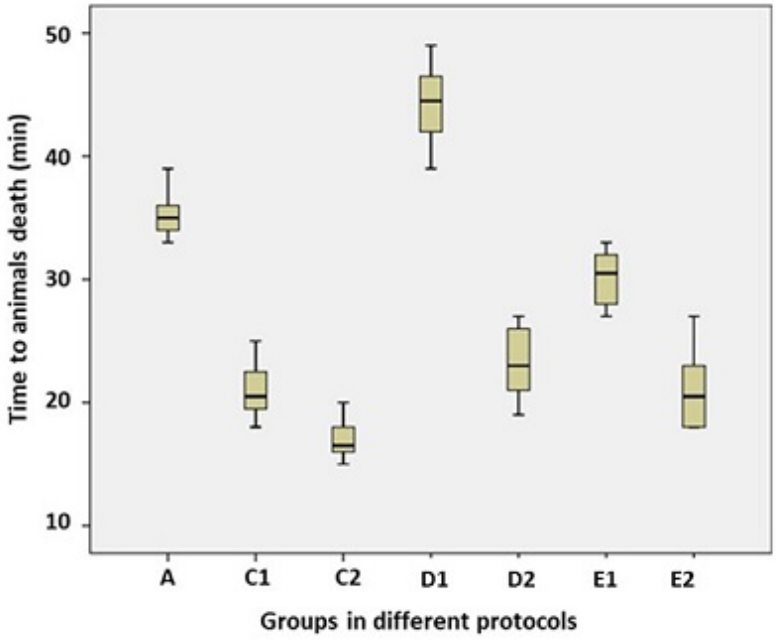

Figure 3. The comparison chart of death distribution time of animals using a Box Whisker graph in different groups

Note: The bold line in the middle shows the median.

Table 1. Summary of experimental protocols

Protocols	Groups	Number of Mice/Group	Doses of Venom & Plant Extract		Average time to Death (min)
			N. n. Oxiana venom (mg/kg)	*C. sativa* (mg/kg)	
I	A	8	2	-	35
I	B1	8	-	80	Live
I	B2	8	-	120	Live
I	B3	8	-	160	Live
II	C1	8	2	80	21
II	C2	8	2	120	17
III	D1	8	2	80	44
III	D2	8	2	120	23
IV	E1	8	2	80	30
IV	E2	8	2	120	21

Note: Protocol I, (groups A, B1, B2 & B3), the only venom and *C. sativa* extract have been injected (control) respectively. Protocols II, (groups C1 & C2), venom and plant extract have been injected simultaneously, Protocols III, (groups D1 & D2), the plant extract has been injected 20 min after to venom injection, Protocols IV, (groups E1 & E2), venom and plant extract have been incubated for 20 min prior to being injected.

In group D1, the average time to death was 44 minutes, while in group D2, it was reduced to 23 minutes, showing a significant difference compared to group A's time to death (P<0.001) (Figures 2 and 3) (Table 1).

3.1.4. Protocol IV, effect of mixture of *C. sativa* extract with *N. n. oxiana* venom

Group E1 received a mixture of 2 mg/kg of venom and 80 mg/kg of *C. sativa* extract, while group E2 was administered the same dose of venom with 120 mg/kg of *C. sativa* extract. In group E1, the average time until death was 30 minutes, whereas in group E2 this time decreased to 21 minutes. This difference was statistically significant compared to the time to death for animals in group A (P<0.01 and P<0.001), respectively (Figures 2 and 3) (Table 1).

4. Discussion

According to the available literature, this is the first assessment of the effects of *C. sativa* extract on the fatality effects of snake venom. Although a dose of 2 mg/kg of *N. n. oxiana* venom resulted in the death of all the mice tested, administration of the extract by itself at doses of 80, 120, and 160 mg/kg showed no toxic effects on the mice. The study revealed that the *C. sativa* extract not only failed to prevent the death of envenomed mice but also accelerated their time of death. Therefore, the *C. sativa* extract appeared to enhance the fatality effect of the venom of *N. n. oxiana*. The potentiation effect of the extract seemed to be dose-dependent, with the higher dose (120 mg/kg) exhibiting a stronger effect than the lower dose (80 mg/kg).

The average time of death for animals in all three protocols was 20 minutes at 120 mg/kg, compared to 32 minutes at 80 mg/kg. The shortest time to death (17 min) was observed in protocol II, where the extract was injected at higher doses of 120 mg/kg simultaneously with the venom (Figures 2 and 3). On the other hand, the longest time until animal death was 44 minutes in protocol III at a dose of 80 mg/kg, which was significantly different (P<0.001). The survival time of animals at higher doses of *C. sativa* extract (120 mg/kg) in protocols III and IV was 23 and 21 minutes, respectively, which is not significantly different. In protocol III, the extract was injected 20 minutes after venom administration, while in protocol IV, the venom was pre-incubated with *C. sativa* extract for 20 minutes prior to administration to the animals.

Therefore, these findings suggest that *C. sativa* extract does not physically interact with the venom.

Earlier research has demonstrated that *C. sativa* can penetrate the BBB, possiblly assisting *N. n. oxiana* neurotoxin molecules in passing through cell membranes and reaching their targets faster when injected simultaneously with the venom. In contrast, animals subjected to protocol III exhibited the longest time to death (44 minutes), where *C. sativa* extract was injected 20 minutes after venom injection at a lower dose of 80 mg/kg. This time delay may reduce the opportunity for the extract to exert its potentiating effect. However, no direct evidence is currently available for these hypotheses, and further investigations are needed to examine them. While the current study does not provide direct evidence for the mechanisms that explain the significant effects of *C. sativa*, several hypotheses can be proposed based on the existing literature. It has been shown that components of *Naja n. oxiana* venom, including presynaptic and postsynaptic neurotoxins can block neuromuscular junctions in different parts of the body.

This occurs either by preventing the release of acetylcholine (Ach) from the nerve terminal or by attaching to the nicotinic acetylcholine receptor (nAChR), particularly in respiratory muscles, preventing them from twitching and ultimately leading to a lethal effect [20]. It has been shown that Cannabidiol (CBD) exerts pharmacological effects through various specific molecular targets, including nAChR

Therefore, the blocking of nAChR may contribute to the blocking action of *Naja n. oxiana* venom, consistent with the findings of this study. Furthermore, several non-psychoactive phytocannabinoids found in *C. sativa*, including CBD, cannabidivarin (CBDV), cannabigerol (CBG), and Δ9-tetrahydrocannabivarin (THCV) have reduced acetylcholine-induced bladder contractions by directly activating smooth muscles in mouse bladders (by blocking muscarinic receptors) [21]. Moreover, CBD and CBG have induced the same effect on the human bladder, but not through the cannabinoid CB1 or CB2 receptor mechanisms [22]. Additionally, under similar experimental settings, Cannabichromene (CBC) has also been able to inhibit intestinal contractility by reducing electrically-evoked contractions rather than ACh-induced contractions [23]. Therefore, it can be hypothesized that the *C. sativa* effects are mediated by its ability to block neuromuscular junctions in mice, potentially enhancing the blocking effect of *N. n. oxiana* venom [21]. Further studies, such as using the chick biventer cervicis nerve-muscle preparation during the application of venom and *C. sativa* extract may provide a more accurate measure to explain the mechanism of action of this plant.

Another hypothesis is that phytocannabinoids and other molecules present in *C. sativa*, especially cannabidiol, potently inhibit many CYP450 enzymes, altering the metabolism of other drugs and cause their toxicity [24]. Therefore, we can assume that *C. sativa* may reduce venom metabolism and elimination by inhibiting CYP or other enzymes responsible for the metabolism of *N. n. oxiana* venom, thereby increasing its bioavailability in the target sites and potentially increasing its toxicity.

However, a lack of basic investigations on the pharmacokinetics of *N. n. oxiana* venom renders these hypotheses unproven, requiring detailed investigation. Additionally, it has been reported that cannabinoids have various short-term effects, including antispasmodic properties and muscle relaxation effects in both human patients with multiple sclerosis [25] and animal models These effects may also facilitate the paralysis induced by *N. n. oxiana* venom and accelerate the time of animal death, aligning with the results of the present study.

5. Conclusion

In conclusion, the extract of *C. sativa* does not exhibit any protective or inhibitory effects against the lethality of *Naja n. oxiana* venom in mice. Although the tested concentrations of *C. sativa* extract did not show any toxic effects, they did enhance the lethal effect of *Naja n. oxiana* venom or somehow increase the susceptibility of animals to this venom. Therefore, *C. sativa* cannot be considered an alternative to conventional antivenoms for treating cobra envenomation, nor can it be used to manage severe pain, intense fear, shock, and anxiety associated with snakebites. In fact, due to its potential to increase the lethality of venom, it is advisable to avoid using this remedy to create a sense of comfort after a snakebite.

Further studies are required to extend these findings to bites from other venomous animals, isolate the potentiating components, and understand their mechanisms of action.

Ethical Considerations

Compliance with ethical guidelines

This study was performed according to international ethical standards and was approved by the Animal Ethics Committee at the Faculty of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran (Code: IR.UM.REC.1401.171).

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Authors' contributions

Study design and writing: Behrooz Fathi; Data collection: Behrooz Fathi and Tayebeh Zeinali; Experiments: Tayebeh Zeinali and Fatemeh Salami; Statistical analysis: Fatemeh Salami.

Conflict of interest

The authors declared no conflict of interest.

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