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Scorpio maurus palmatus crude venom: A natural spermicidal agent inducing human spermatozoa membrane disruption

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Abstract

Many spermicide products currently in use incorporate contraceptive detergents as their active ingredients. These substances have been shown to adversely affect normal microbiota and vaginal epithelial cells, as well as raise the risk of vaginal and cervical infections and ulcers. This study investigated the potential impacts of crude venom from the scorpion species *Scorpio maurus palmatus* (Smp) on the motility of human spermatozoa in vitro. Semen samples were provided by 12 healthy fertile men. The crude venom of Smp was diluted in a series and tested for its capacity to immobilize sperm using the Sander-Cramer assay. To assess sperm vitality and membrane integrity, the test for sperm viability and hypo-osmotic swelling were utilized. The results revealed that Smp crude venom at a concentration of 0.8 mg/mL effectively immobilized and killed 100% (10.0 million/mL) of human spermatozoa within 20 s. In summary, this study demonstrates that Smp crude venom possesses spermicidal properties, acting by disrupting the sperm cell plasma membranes.

Keywords: Spermicides; contraceptive; Human spermatozoa; *Scorpio maurus palmatus*; Sperm motility

1. Introduction

By 2050, there will be more than 8 billion people on the planet [1]. Numerous contraceptive techniques are currently available to overcome these effects. Nevertheless, most are either expensive, unpleasant, or hormonal, potentially disrupting the body's homeostasis [2]. Consequently, there is a global effort to develop locally acting, non-hormonal spermicides [3]. To prevent pregnancy, spermicides are birth control agents that, when applied vaginally before sexual intercourse, permanently immobilize or destroy spermatozoa.[4]. Spermicides are categorized as synthetic or natural. Natural spermicides include saponins [5], gossypol [6], desgalactotigonin [7], curcumin [8], and *Carica papaya* seed [9]. Artificial compounds, like substituted imidazoles,

acrylophenones, benzophenones, chlorpromazine [10], and cationic detergents [11], long-term use or a very potent dosage may change vaginal permeability. Nowadays, nonoxynol-9 (N-9) detergents are used as birth control. The primary drawback of using surfactants is how the detergent affects natural vaginal bacteria and epithelial cells [11]. Experts are currently focusing on natural products to identify superior replacements. Naturally occurring substances like *Lactococcus lactis' nisin* [12], magainins from *Xenopus laevis* [13], and synthetic compounds such as benzalkonium chloride [14], antiseptic chlorhexidine [15], and cellulose sulfate [16] have demonstrated spermicidal and antibacterial properties. Furthermore, all chemicals cause cervical-vaginal inflammation, hypersensitivity, acute toxicity, burning and itching, and disruption of the normal vaginal microbiome.

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Venoms from animals are incredibly plentiful sources of bioactive substances found in nature with a variety of therapeutic effects [17]. There are twenty-four species of scorpions in Egypt. *Smp*, a member of the Scorpionidae family, is found in the Western Mediterranean Coastal Desert and the Sinai Peninsula. It is also common in the Middle East, Saudi Arabia, and Jordan. Although each scorpion lives alone in a burrow that is at least 100 cm deep, there may be concentrations of hundreds of burrows in some places. Although *Smp* is not harmful to humans, its venom contains toxins that have been shown to have neurotoxic and cytotoxic effects on insect cells [18]. *Smp* was selected for this investigation due to its distinct venom composition and pharmacological characteristics, which have been documented by multiple studies that have examined the structural and biological features of *Smp* venom [18-20]. This study investigates the potential of *Smp* venom as a safe contraceptive due to its unique composition, pharmacological properties, and reported spermicidal effects on human sperm activity.

2. Materials and methods

2.1. Collection of human sperm cells

Semen samples were provided by 12 healthy fertile men and collected in sterile cups for in vitro testing by masturbation. The Research Committee of Al-Azhar University, Faculty of Medicine in Assiut, Egypt, authorized the study protocol (Code No.: RESEARCH/AZ.AST./PHA006/4/235/1/2025). The contributors provided written informed consent. Samples selected had concentrations of 60-80 million/mL, motility exceeding 70%, viability over 90%, and normal morphology. The examination was according to the WHO Human Semen Laboratory Examination and Processing Standardized Manual [21].

2.2. Isolation and processing of ejaculates

human sperm cells

Sperm were selected using a ZyMot device (microfluidic technology used in IVF labs) based on selecting sperm with the lowest DNA fragmentation rate and the healthiest motile sperm [22]. The device mimics how sperm naturally move through the female reproductive system. Unlike standard density gradient procedures, it does not include centrifugation, which causes oxidative stress and probable DNA damage.

Fresh semen samples were liquefied for 20 min at 37°C. Using the ZyMöt 850 µL device, 850 µL of ejaculate was introduced via the inlet port. Media (750 µL) was layered over the membrane, and 50 µL of media primed the outlet port. After 30 min incubation at 37°C with 6% CO₂, 0.5 mL of the strongest and most motile sperm migrated upward through the pores into the clean medium for collection, extracted from the outlet port [23]. To get a workable suspension of 8–10 × 10⁶ cells/mL, it was finally resuspended in 1.0 mL of sperm wash.

2.3. Collection and preparation of scorpion extract

Approximately 100 adult Egyptian scorpions, specifically *Smp*, were collected from the Western Mediterranean Coastal Desert in the Alexandria Governorate of Egypt. These scorpions were then transported to the animal house of the Zoology Department at the Faculty of Science, Al-Azhar University in Assiut, Egypt, where they were individually housed in plastic containers. Venom extraction was performed on 80 scorpions through electrical stimulation at 12–16 V for 3 ms [24]. The collected venom was placed in Eppendorf tubes, dissolved in Milli-Q water, and then subjected to centrifugation at 14,000 rpm for 10 min at 4°C. The resulting supernatant was combined, freeze-dried, and stored at -20°C until needed. Protein concentration was measured using a NanoDrop 2000c Spectrophotometer (Thermo Fisher Scientific, Wilmington, USA).

2.4. Materials

Phosphate-buffered saline (PBS), pentoxifylline (PTX), non-ionic detergent N-9 (IGEPAL CO-630), and ZyMötTM sperm separation device (Cooper Surgical, Trumbull, United States) were acquired from Sigma (Sigma-Aldrich). FertiPro (Beernem, Belgium) supplied the eosin-nigrosin staining and vitality stain. cGMP-compliant (Grand Island, New York) sold Ham's F-10.

2.5. Human sperm as an in vitro model for cell membrane viability

2.5.1. Assessment of spermicidal activity test

The modified Sander-Cramer technique was used to assess human sperm motility [25-27]. In summary, varying serial concentrations of crude venom of *Smp* (0, 200, 400, 600, 800, and 1000 µg/mL) were used to calculate MIC and IC₅₀.

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The equivalent concentration was 90 μL of physiological saline of sperm suspension ($10^7/\text{mL}$) mixed with a 10 μL aliquot of different concentrations. As a control, untreated sperm was used. Sperm motility was assessed using an inverted Nikon Eclipse microscope Ti2, Japanese (400x), at 20 s, and motile sperm were counted. The positive control was commercial N-9 (100 $\mu\text{L}/\text{mL}$). Both the minimum inhibitory concentration (MIC), representing 100% effective inhibition, and the half-maximal inhibitory concentration (IC₅₀), representing 50% effective inhibition, were evaluated.

2.5.2. Sperm revival test

After being exposed to crude venom of Smp, the sperm that completely lost motility within 20 s was assessed for the possibility of motility revival. The treated sperm underwent two washes with physiological saline and were then incubated again in Ham's F-10 media at 37°C for one hour to detect any signs of motility recovery. If even a single sperm in the 8 to 10 fields examined displayed any movement or signs of life, the dose was not deemed an "effective dose".

2.5.3. Sperm viability test

The eosin-nigrosine method of supravital staining was used to evaluate the vitality of the spermatozoa. Live spermatozoa appeared white, whereas spermatozoa that had died were stained pink or red. Each sample contained a minimum of 200 spermatozoa counted.

2.5.4. Hypo-osmotic swelling test

Human sperm samples were incubated in a hypo-osmotic swelling (HOST) solution (0.735 g sodium citrate dehydrate and 1.351 g fructose in 100 mL deionized water) for at least 30 min at 37°C. Sperm membrane integrity was assessed by counting at least 200 spermatozoa exhibiting characteristic tail curling. Sperm was assessed using an inverted microscope, Nikon Eclipse Ti2, Japan (400x).

2.5.5. PTX supplementation

In a CO₂ incubator set at 5% and 37°C, crude venom of Smp was incubated with sperm for two hours. Throughout this period, PTX at 500 $\mu\text{g}/\text{mL}$ was introduced into the medium at various intervals. In a separate series of experiments, crude venom of Smp combined with PTX was added before sperm was incorporated into the mixture at various intervals. Changes in sperm motility were noted after 20 s and then every 30 min for the duration of the two-hour incubation period.

2.6. Inactivation of crude venom Smp treatment

2.6.1. Digestion by proteinase K

To establish if the crude venom of Smp causes a spermicidal effect is protein-based, Smp at 800.0 $\mu\text{g}/\text{mL}$ was treated with proteinase K at 1.0 mg/mL (Sigma-Aldrich) and heated at 56°C for one hour. Following this treatment, the venom was exposed to human spermatozoa and tested for motility, as previously described.

2.6.2. Heat treatment

The crude venom of Smp at 800.0 $\mu\text{g}/\text{mL}$ was subjected to cooling at 4°C or heating at 95°C for 30 min. Following this treatment, Smp was combined with sperm and analyzed using the motility assay, as previously described.

2.7. Statistical analysis

Data were presented as the mean $\pm$ SEM of three independent experiments. Using Prism (10.0 GraphPad Software), we conducted one-way ANOVA and the Student's test to evaluate different treatments and quantify significance. P-values < 0.05 indicated statistical significance. The visuals were created using R-project and Prism [28-30].

3. Results and discussion

Part 1: Human sperm as an in vitro model for cell membrane viability

3.1. The spermicidal activity test

Human sperm motility was dose-dependently reduced by the crude venom of Smp (Figure 1A). It was revealed that the human spermatozoa treated with Smp crude venom had motility ranging from 0 to 95% of control motility values. Comparing the study of Smp crude venom concentrations (800 $\mu\text{g}/\text{mL}$) to the control sample revealed a decrease in motility. Differences were statistically significant ($P < 0.0001$). The quantity of Smp needed to diminish sperm motility by 50% in 20 s, or the IC₅₀ value, was determined with an optimum or appropriate serial dilution (Table 1). Following a two-hour incubation at 37°C using Ham's F-10 medium, motility did not return, indicating that the IC₅₀ contains immobilizing factors that impair movement.

3.2. The sperm viability test

To determine if Smp crude venom impacts sperm viability, human sperm samples were combined with 800

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$\mu\text{g/mL}$ Smp crude venom, observed after 20 s, and their vital sperm were recorded. Sperm without any treatment served as a negative control. Following mixing with (N-9) 100.0 $\mu\text{g/mL}$ as a positive control, the sperm viability dropped to zero right away and stayed that way throughout the time (Figure 2A).

Sperm death was indicated by the color red or pink, whereas sperm life was indicated by the color white or colorless (Figure 2B). The differences were statistically significant ($P < 0.0001$). These results suggested that Smp crude venom might instantly destroy the sperm membrane at the specified doses.

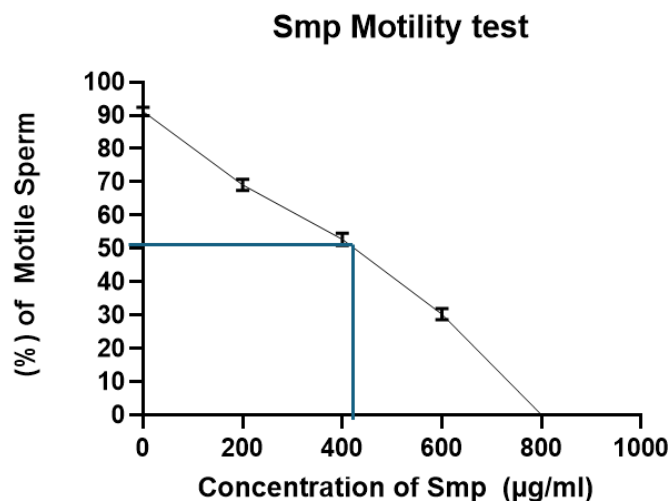


Figure 1. Dose-dependent sperm immobilizing activity of Smp crude venom: the percentage of motile sperm after 20s at different concentrations. The mean $\pm$ SEM of three separate experiments is shown in the data. * $P < 0.05$, *** $P < 0.001$.

Table 1. MIC and IC50 of serial dilution of Smp crude venom.

Treatment	MIC ($\mu\text{g/mL}$)	IC50 ($\mu\text{g/mL}$)
Smp crude venom	800	405

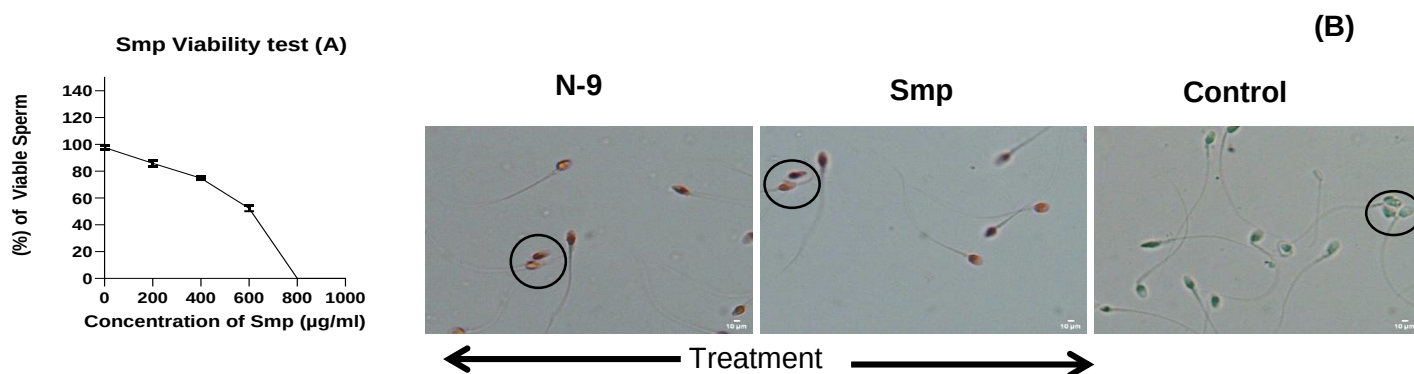


Figure 2. (A) The human spermatozoa were treated with Smp crude venom at 800 $\mu\text{g/mL}$ for 20 s or left untreated as a control; **(B)** Sperm viability tests were assessed by the eosin–nigrosine staining technique, untreated human spermatozoa (control), Smp crude venom and N-9 treated with human spermatozoa. The mean $\pm$ SEM of three separate experiments is shown in the data. * $P < 0.05$, *** $P < 0.001$.

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3.3. Sperm membrane integrity

In a study using phase-contrast microscopy, human spermatozoa that had not been treated were examined, revealing a curled tail region, which indicated an undamaged membrane upon exposure to Smp crude venom at 800 µg/mL and (N-9) 100.0 µg/mL. Every spermatozoon had a straight tail, recommending a non-HOST reaction (Figures 3A and 3B). While all spermatozoa treated with Smp crude venom and (N-9) 100.0 µg/mL were totally non-responsive to HOST, about 94.4% of the control human sperm were receptive to HOST (Figures 3A and 3B). This implies that sperm membrane physiology is significantly lost during HOST treatment, leading to a poor response of human spermatozoa to HOST.

3.4. Sperm PTX supplementation

PTX increases the motility of both normal and asthenozoospermic ejaculated sperm in vitro and in vivo. Its effect in the presence of Smp crude venom was tested by adding it to the sperm/Smp mixture at various intervals (Figure 4). According to the results, PTX did not increase or improve human sperm motility. In the presence of Smp crude venom, thereby confirming its spermicidal effect.

3.5. The spermicidal action of Smp is eliminated by protein digestion

Scorpion venom is a complex mixture of different peptides and proteins [18]. To evaluate if spermicidal activity was due to protein or non-protein compound (s), Smp (800.0 µg/mL) was treated with proteinase K (1.0 mg/mL) at 56°C for one hour. Smp crude venom treated with proteinase K was combined with human sperm for 1 h at 37°C and tested for sperm motility. The results showed that sperm motility was unaffected by proteinase K heated to 56°C. Furthermore, following 1 h of incubation with proteinase K-pretreated Smp crude venom, human sperm showed normal motility, like untreated sperm (control) (Figure 5). These results indicate that removing the protein reduced the spermicidal efficacy of Smp crude venom.

3.6. The Smp spermicidal factor is heat insensitive

Enzyme activity is known to be temperature dependent. We investigated how temperature affected Smp crude venom's ability to kill sperm. Smp (800.0 µg/mL) was heated to 95°C for 30 min and then cooled to 4°C for 30 min. Human spermatozoa were combined with Smp that had been heated to 95°C or cooled to 4°C for 30 min, and the mixture was then incubated for 30 to 60 min. During incubation, neither preheated nor precooled Smp crude venom produced any motile sperm (Figure 6). This implies that Smp crude venom contains a bioactive component that affects human sperm motility and is not heat-sensitive.

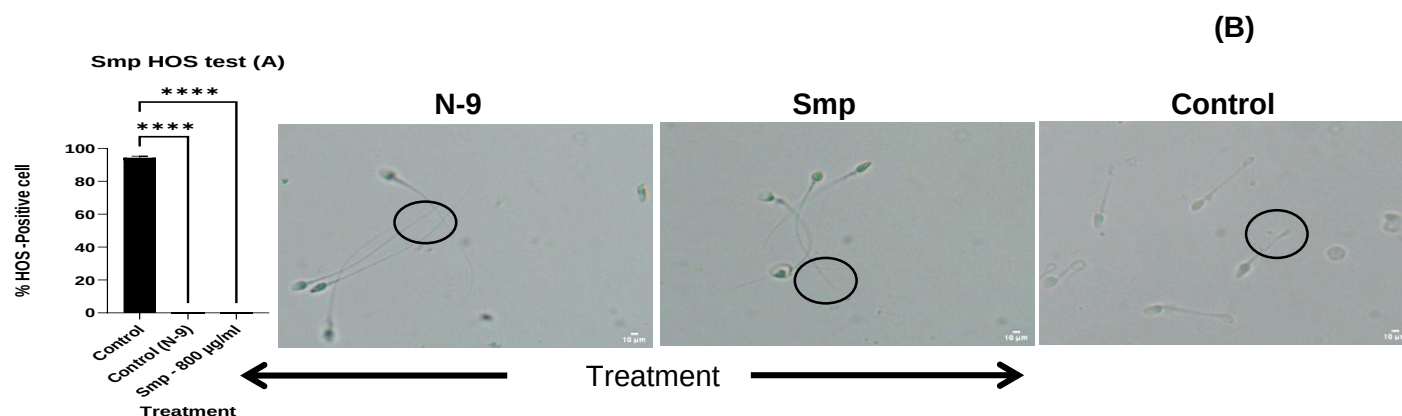


Figure 3. (A) Effect of Smp crude venom and (N-9) on human spermatozoa response to HOST were investigated and (B) untreated human spermatozoa (Control) were exposed to HOST and displayed distinguishing tail curling; however, Smp crude venom and (N-9) -treated human spermatozoa were non-HOST responsive. The data represents the mean $\pm$ SEM of three independent experiments. *** $P < 0.001$, * $P < 0.05$.

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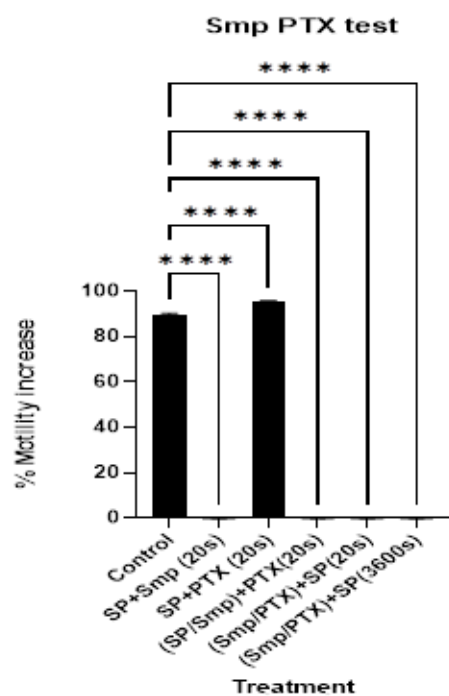


Figure 4. Effects of PTX on the spermicidal properties of Smp crude venom were assessed at 800 $\mu\text{g/mL}$. The mean $\pm$ SEM of three separate experiments is shown in the data. * $P < 0.05$, *** $P < 0.001$.

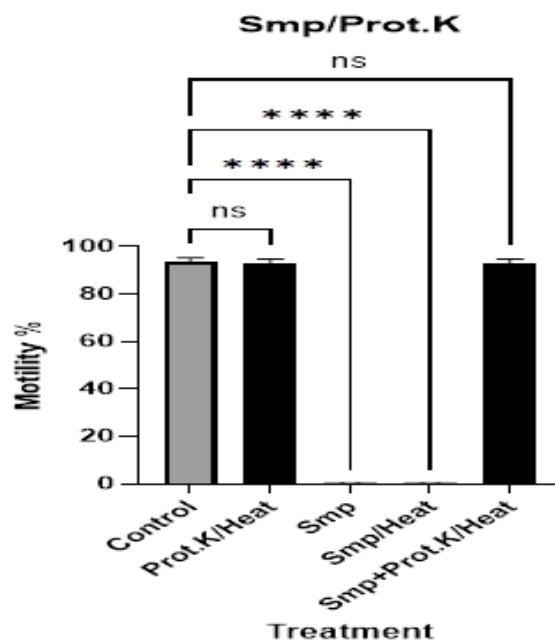


Figure 5. Effects of protein digestion on the spermicidal activity of Smp crude venom. Proteinase K was used to treat Smp (800.0 $\mu\text{g/mL}$). The mean $\pm$ SEM of three separate experiments is shown in the data. * $P < 0.05$, *** $P < 0.001$.

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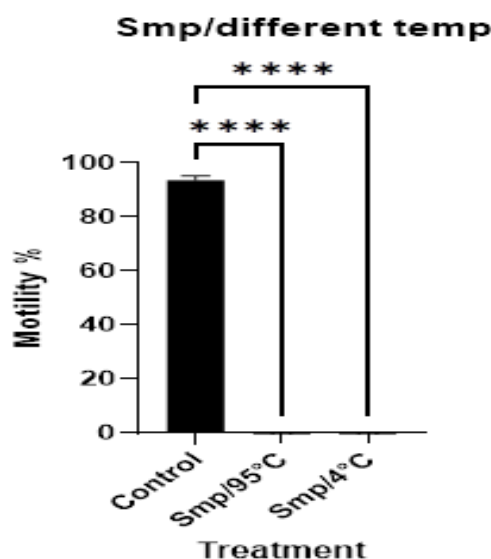


Figure 6. Effects of different temperatures on the spermicidal activity of Smp. 800.0 $\mu\text{g/mL}$ of Smp heated at 95°C for 30 mins or cooled at 4°C for 30 mins. The mean $\pm$ SEM of three separate experiments is shown in the data. * $P < 0.05$, *** $P < 0.001$.

The present study provides the first evidence that crude venom from Smp has potent spermicidal activity against human spermatozoa. Smp crude venom induced rapid and irreversible sperm immobilization, severely decreased sperm viability and compromised the integrity of the plasma membrane. Among the tested venoms, Smp crude venom exhibited spermicidal potency, achieving complete immobilization at a lower concentration (0.8 mg/mL). These results support the hypothesis that membrane-active venom can effectively impair sperm function and may be viable options for the creation of innovative non-hormonal birth control methods. Meeting the increasing need for reliable and safe contraceptive options is a significant global health issue, especially in developing nations. These regions face the dual challenges of fast population growth and restricted access to reproductive health services, which heavily strain healthcare infrastructures [7]. Although numerous contraceptive methods have been developed, their acceptance is frequently hindered by issues such as side effects, potential for failure, irreversibility, and inadequate protection against sexually transmitted infections (STIs) [26, 31]. Significant attempts have been made to identify multifunctional medicines that can reduce microbial transmission and prevent pregnancy simultaneously. Because of their biological diversity and evolutionary significance for survival, animal venoms are among the most potent natural

products. Additionally, they show potent antibacterial qualities against a range of pathogens, including bacteria, viruses, fungi, and parasites. [32, 33]. Without a doubt, animal venoms are likely to include a lot more substances that are beneficial for altering spermatoc activity in vitro and in vivo. Rapid sperm immobilization observed in the present study is consistent with the well-established membrane-disruptive mechanism of crude venoms. Thus, crude venom from Smp can bind to the membrane, insert into lipid bilayers, causing membrane destabilization, pore formation, and increased permeability, ultimately leading to cell death [32]. Since sperm motility depends on plasma membrane integrity and ionic homeostasis, membrane disruption rapidly compromises sperm function and fertilization capacity [34]. Complete loss of motility within seconds following Smp crude venom exposure strongly suggests membrane perturbation is a primary mechanism underlying their spermicidal action. This conclusion is supported by staining with eosin-nigrosin and the hypo-osmotic swelling test (HOST), which demonstrated severe membrane damage in Smp-treated spermatozoa. The sperm plasma membrane plays a crucial role in regulating osmotic balance, capacitation, acrosome reaction, and sperm-oocyte interaction [34]. Therefore, membrane disruption inevitably leads to loss of viability and fertilizing potential. Similar observations have been reported for other naturally

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occurring spermicides. For example, MaximinBk isolated from *Bufo kavirensis* irreversibly disrupted sperm membrane integrity and eliminated sperm viability at high concentrations [35]. Similarly, dermaseptins that were extracted from *Phyllomedusa sauvagei* skin secretions had strong spermicidal activity by rupturing membranes and killing sperm quickly [36].

It has also been demonstrated that melittin and other membrane-active venom peptides cause instantaneous immobilization and irreversible loss of viability in sperm [17]. The PTX recovery experiment provided additional proof of the permanent nature of Smp crude venom-induced sperm destruction. By inhibiting phosphodiesterase and raising intracellular cyclic adenosine monophosphate (AMP) levels, PTX is frequently used to increase sperm motility. PTX did not restore motility after treatment with Smp crude venom in the current investigation, suggesting that irreversible structural damage rather than temporary metabolic suppression caused sperm immobility. Similar results have been reported for other strong spermicidal substances, where administration of motility-enhancing drugs did not prevent recovery due to persistent membrane disruption [27, 37]. Previous studies have also demonstrated that venom-derived molecules can alter intracellular calcium signaling and membrane potential in spermatozoa. For example, arachnotoxin from the Chilean spider *Latrodectus mactans* affects intracellular calcium homeostasis and pH regulation in human sperm cells [38], whereas snake venoms from *Oxyuranus scutellatus* and *Daboia russellii* have been reported to strongly inhibit sperm motility through ion-channel-mediated mechanisms [39, 40]. Although calcium fluxes and mitochondrial membrane potential were not assessed in the present study, these pathways may contribute to the spermicidal activity of Smp crude venom and warrant further investigation.

Nevertheless, several limitations should be acknowledged. The present investigation was conducted exclusively under in vitro conditions and did not evaluate the safety of this crude venom toward vaginal epithelial cells or beneficial vaginal microbiota. Assessments of caspase activation, mitochondrial membrane potential, reactive oxygen species production, Annexin V staining, and the effectiveness of in vivo contraceptives should be included in future research. Such

investigations will be essential to fully characterize the mechanism of action and therapeutic potential of this venom. Overall, the present findings demonstrate that Smp crude venom exerts potent spermicidal effects through irreversible impairment of sperm motility, viability, and membrane integrity. These results expand the known pharmacological activities of venom and identify them as promising lead molecules for the development of next-generation non-hormonal contraceptive agents.

4. Conclusion

In this study, we established that crude venom from Smp at a concentration of 0.8 mg/mL can swiftly and irreversibly immobilize human sperm in vitro by compromising the integrity of the plasma membrane. This finding also reinforces the idea that animal venoms, overall, provide a valuable reservoir of bioactive substances for reproductive pharmacology. Additional studies are required to explore the molecular mechanisms, evaluate safety, and verify contraceptive efficacy in vivo.

Authors' contributions

Mohamed A. El-Hakeem: Writing – original draft, Methodology, Investigation, Formal analysis.

Alhussin M.A. Megaly: Writing – review & editing, Visualization, Software, Conceptualization. **Mohamed A.**

Abdel Rahman: Writing – review & editing. **Mohamed M.**

A. Shahat: Writing – review & editing.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval and consent to participate

The Research Committee at Al-Azhar University's Faculty of Medicine in Assiut, Egypt, accepted this work with code

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number RESEARCH/AZ.AST. PHA006/4/235/1/2025. Every experiment was carried out in compliance with Al-Azhar University's applicable policies and procedures.

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Data availability

Data will be available upon request.

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