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Partial Purification and Characterization of Antimicrobial Effects from Snake (*Echis carinatus*), Scorpion (*Mesosobuthus epues*) and Bee (*Apis mellifera*) venoms

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ABSTRACT

Background: Some venoms and their isolated compounds have been shown to have antibacterial properties. Snake, scorpion and bee venoms are a complex mixture of proteins such as phospholipase and melittin, which have an effect on bacterial growth inhibition. This study aimed to investigate of antibacterial effect of three different venoms against selected bacterial strains.

Materials & Methods: Crude venoms obtained from snake (*Echis carinatus*), scorpion (*Mesosobuthus epues*) and bee (*Apis mellifera*) were selected. The crude venoms from these species was purified by using gel filtration chromatography and the molecular weights of the compounds in these venoms estimated by using SDS-PAGE. The approximate lethal dose values of venoms were determined. Antibacterial activity of venoms against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli* were evaluated. Venoms and its isolated fractions and standard antibiotic were tested by using the disc diffusion method.

Results: *E. carinatus* crude venom and fraction 2 were effective against *S. aureus* and *E. coli*. *M. eupeus* crude venom and fraction 1 and 4 were effective against *B. subtilis*. *A. mellifera* crude venom demonstrated antibacterial activity against *E. coli*, *S. aureus* and Fraction 3 of this venom has an inhibition effect for *E. coli* and *S. aureus*.

Conclusion: Snake, scorpion and bee venoms inhibit the growth and survival of bacterial strains and that these venoms can be used as a complementary antimicrobial agent against pathogenic bacteria.

Keywords: *Echis carinatus*, *Mesosobuthus epues*, *Apis mellifera*, antibacterial activity, chromatography, LD_{50}

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Introduction

Infectious diseases have increased in recent years. These diseases are caused by pathogens such as bacteria, viruses, etc. Due to the lack of useful and effective drugs for the treatment of infectious diseases, they have spread worldwide **(1)**. Antibiotic treatment is currently used for bacterial infections. But nowadays, it has been found that the effectiveness of many antibiotics has diminished due to their overuse. This phenomenon is known as antibiotic resistance. Antibiotic resistance is a serious public health problem and this resistance is increasing in today's world. In 2014, the World Health Organization described drug resistance to antibiotics as a "major global threat." **(2)**.

As antimicrobial resistance is spreading throughout the world, the discovery of new substances is mandatory to fight against it. This will cause researchers to conduct more studies on various natural resources in order to discover newer and more effective antibiotics **(3)**. In fact, the vast diversity of bioactive molecules in nature has long inspired scientists in their search for potential therapeutic agents **(4)**.

More recently, there has been a resurge in the use of antimicrobial peptides due to the decrease in the efficiency of common treatments. Antimicrobial peptides are able to target a broad spectrum of microbes with little resistance and can have a synergistic effect with antibiotics. Animal venom is thus a particularly promising source in this search for new antimicrobial compounds. Many antimicrobial peptides from the venom have shown high efficacy in vitro and in vivo, but challenges to overcome their host toxicity **(5, 6)**, hemolytic activity **(7-11)**, as well as the bioavailability and stability of these peptides are still present.

With more than 100,000 venomous animals, naturally occurring antimicrobial agents present in venomous species, thus hold promises for the development of novel therapeutic agents. Currently, only few antimicrobial agents are present on the market for tropical use **(12)**.

Venoms from some animals, including snakes, scorpions, spiders, bees, etc. can be interesting and powerful alternatives to antibiotics **(13)**. In venoms of these animals, bioactive proteins and peptides are found that have various useful pharmacological properties and are stored in large quantities **(14)**.

One of the important reasons for the effectiveness or ineffectiveness of different animal venoms on various bacterial species is their mechanisms of action on the bacterial cell envelope. Bacterial cytoplasmic membrane is the primary target of the antibacterial peptides in venoms. Antibacterial peptides form channels in the bacterial cell membrane or disrupt phospholipid bilayers of bacterial membrane, thereby influencing its numerous functions that are necessary for the survival of the bacteria and thus cause bacterial cell death. As pointed out in some of these studies, some of the differences in the effects of these peptides stem from the differences in bacterial cell envelopes. Since these envelopes in Gram-positive bacteria consist of fewer layers compared to Gram-negative bacteria, antibacterial peptides must be more powerful in order to affect Gram-negative bacteria **(15)**.

Today, many studies have been conducted using molecular methods on a variety of antimicrobial peptides and how they work **(16-18)**.

The findings indicate that some of peptides present in the venom of these animals have antimicrobial properties and prevent the growth of pathogens. Antimicrobial peptides have been shown to inhibit the growth of many resistant pathogens. However, many antibiotics do not show such efficacy **(19)**. They can be useful and valuable as pharmacological tools in drug research, as potential drug design templates, and as therapeutic agents **(20)**.

Here we have characterized and investigated antimicrobial effect from Snake (*Echis carinatus*), scorpion (*Mesosobuthus epues*) and bee (*Apis mellifera*) venoms.

Materials and Methods

Bacterial Strains

Four clinical isolates of bacteria, including *Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* O157:H7 (ATCC 25923), *Bacillus subtilis* (ATCC: 6633) were purchased from the China Center of Type Culture Collection (CCTCC).

Experimental Animals

Animal studies were performed in compliance with the regulations of Razi vaccine and serum research institute (RVSRI), and with generally accepted guidelines governing such works. For this aim, normal male mice, weighing between 25 and 30 g were injected with venoms and investigated.

Other Materials and Equipment

The following Equipment and materials were used for laboratory work; Millipore filter (Biofil 0.45µm, China), Centrifuge (Hermle Z513K, Germany), Freeze dryer (Christ alpha 1-4 lsc, Germany), UV spectrophotometer (UNICO SQ2800, USA), Electric heater (Electrothermal M105, England), Electrophoresis and protein markers (Bio-Rad, USA), Incubator (Memmert, Germany), Sephadex G-50 (Pharmacia, Sweden), and the Standard antibiotic gentamicin (Liofilchem S.r.1, Italy). Other reagents and chemicals were of analytical grade from Merck and Fluka.

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Venoms Preparation

Lyophilized crude venom of *Echis carinatus* (Lot No. V8250) and *Apis mellifera* (Lot No. V3375) were purchased (Sigma Aldrich, Germany). Crude venom of *Mesobuthus eupeus* scorpion was obtained by the electrical stimulation at the end of the tail (128 Hz, 20 V). After lyophilization, it was stored at -20°C. The freeze-dried venoms were dissolved in distilled water or a suitable buffer and then venom solutions were centrifuged at 12000 g for 4 mins and the supernatant was collected.

Venoms Purification

Lyophilized crude venoms (200 mg) were dissolved in 4 mL of 0.1 M ammonium acetate buffer (pH 8.6) and the insoluble material was removed by centrifugation (12000 g, 4 min) and filtration. Supernatant was applied to a column of sephadex G-50 (2.5×150 cm) equilibrated with 0.1 M ammonium acetate buffer (pH 8.6). The elution was carried out with the same buffer at a flow rate of 60 mL/h. Volumes of 10 mL were collected and each fraction was identified by UV spectrophotometer (280 nm), mixed and lyophilized **(5)**.

Venoms protein concentration

Protein content in the crude venom was determined by Lowry **(6)** and Kjeldahl method with some modifications **(21)**. Fourteen mL of distilled water and 2 mL of trichloroacetic acid (100% w/v) was added to 5 mL of protein solution. The solution was mixed and allowed to stand for 5 min and then centrifuged for 10 min at 2000 g. The supernatant liquid was discarded and the residue was dissolved in 0.5 mL of 10 N NaOH. Dissolved residue was adjusted to 25 mL with distilled water. About 0.9 g of K_2SO_4, 0.1 g of $CuSO_4$ and then 10 mL of dissolved residue was added to Kjeldahl flask. Then 7 mL of sulfuric acid 98% and 1 mL of H_2O_2 30% was added. The flask was heated to about 80°C for 48 h using an electric heater. After 48 h, the digested solution was cooled and about 10 mL of distilled water was added to the flask. The contents of the flask were poured into the Kjeldahl machine. Subsequently, 25-30 mL of NaOH 10 N was added and distillation was started. The reagent (10 mL of boric acid 4% with four drops of methyl red and methylene blue mixture) was placed under the outlet of the Kjeldahl distiller. One hundred mL of the output solution was titrated with 0.01 N sulfuric acid. The following formula was used to calculate the protein content (mg/mL).

$$\text{Protein volume} = \frac{\text{Titration volume} \times 0.14 \times 25 \times 6.25}{50}$$

Venoms Electrophoresis

Electrophoresis was performed to check the protein profile of the venoms and its quality. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was performed according to the method of Laemmli with modifications **(22)**. 12% Separating gels and 4% stacking gels were used (the total volume was enough for two gels with 0.75 mm spacer). Glass plates were cleaned with ethanol and casting stand was assembled by following manufacturer's instructions (BioRad, USA). 12% separating gels was prepared by adding the solution (3 mL, 30% Acrylamide/Bis; 1.9 mL 1.5 M Tris-HCl (pH 8.8); 75 µL 10% SDS; 2.5 mL ddH_2O; 37.5 µL 10% ammonium persulfate; 10 µL TEMED). The solution mixed well and quickly transferred by using pipette to the casting chamber between the glass plates and filled up to about 1.5 cm below the top of longer plate. A layer of distilled ddH_2O was added over the top of the resolving gel to prevent polymerization. After 20 min, once the separating gel has polymerized, the ddH_2O layer was removed by using filter paper. 4% separating gel was prepared by adding the solution (1 mL, 30% Acrylamide/Bis; 1.9 mL 0.5 M Tris-HCl (pH 6.8); 75 µL 10% SDS; 4.5 mL ddH_2O; 37.5 µL 10% ammonium persulfate; 10 µL TEMED). The solution mixed well and quickly transferred by using a pipette until the space was full, and then the comb was inserted to the top of the spacers. After 20 min, once the separating gel has polymerized, the comb carefully removed. The gel cassette from the casting stand was removed and the clamping frame was put into the electrophoresis tank (the short plate was placed on the inside). Running buffer 1X (3 g Tris-Base; 14.4 g Glycine; 1 g SDS; 990 mL ddH_2O) was poured into the electrophoresis tank. 25 µL of the sample buffer (10 mL 0.5 M Tris-HCl (pH 6.8); 5 mL glycerol; 1 g SDS, 2 mL 2-mercaptoethanol; 1 mL 1% bromophenol blue; 1 mL ddH_2O) was added to 75 µL protein samples (0.5-1.5 mg/mL). Protein samples heated for 10 min in a boiling water bath and then centrifuged at 13000 rpm for 60 S. 15 µL of each protein samples were then loaded onto each gel well as well as load 10 µL of protein MW marker and electrophoresis was carried out at a constant voltage (100 V, 2 h). The gel was fixed with 5% acetic acid overnight and stained for 2 h in 0.25% Coomassie blue R-250 in 25% acetic acid solution. Distaining was carried out in a solution containing 30% methanol and 10% acetic acid, until the background became clear.

Lethal Dose of Venoms

Lethal dose (LD_{50}) of venoms, which is equivalent to death in 50% of mice within 24 h after venom injection, was determined by Spearman-Karber Finney methods **(23)**. One mg/mL stock of each venom was prepared and centrifuged for 5 min at 10000 g and then filtered. Thirty NIH mice (25-30 g) were selected. The mice were maintained at an appropriate temperature (23±2°C) with free access to water and food. Five groups of mice were treated with different doses of venom (1, 1.5, 2, 2.5, 3 mg/kg) and normal saline was injected into a control group.

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Antibacterial Effects of Venoms

Lyophilized crude venoms (25, 50, 75, 100 µg) and its fractions dissolved in 1 mL of 50 mM Tris-HCl buffer (pH 7.4), were filtered using 0.22 µm syringe filter and stored at 4°C for the assay. Antibacterial susceptibility tests were performed by the disc diffusion assays (19). First, to prepare the disks, different concentrations of venoms were poured onto blank discs and it took 3 h for the discs to dry completely. Then plates containing Mueller Hinton Agar were cultured with a swab soaked in a bacterial suspension equivalent to half a McFarland and the prepared discs were placed on the surface of the plate. The plates were incubated for 24 h at 37°C. Then, the effects of different concentrations of venoms on bacteria were investigated. In this experiment, gentamicin antibiotic disc (10 µg/disk) was used as a positive control.

Statistical Analysis

Means and standard deviations of the zone inhibition data were collected and calculated using Microsoft Excel. Student's t-test was used to determine statistical significance. *P*-value<0.05 was considered statistically significant.

Results

The protein content was improved in the antibacterial active crude venoms of *E. carinatus* (1.7 mg/mL), *M. eupeus* (1.2 mg/mL), *A. mellifera* (0.4 mg/mL), respectively. Electrophoresis revealed that the range of *E. carinatus* proteins was distributed in the light, medium and heavy molecular weight; However, most *M. eupeus* venom proteins were in the average molecular weight range and proteins of *A. mellifera* venom was in the light molecular range (Figure 1).

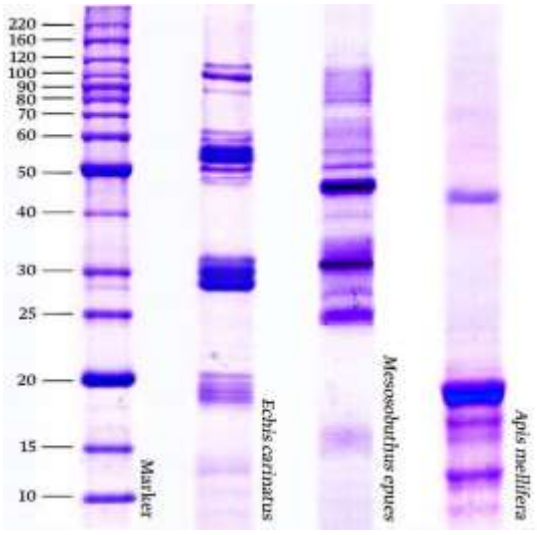

Figure 1. SDS-PAGE profile of *E. carinatus*, *M. eupeus* and *A. mellifera* crude venoms

Chromatography showed that *E. carinatus* and *A. mellifera* had three fractions (Figures 2 and 4) and *M. eupeus* had four fractions (Figure 3).

The numbers of dead mice within 24 h were recorded for each venom. After the registration of deaths, the LD_{50} of each venom was determined, which are as follows:

E. carinatus > *M. eupeus* > *A. mellifera*
11.1 > 46 > 177.8 µg/mouse

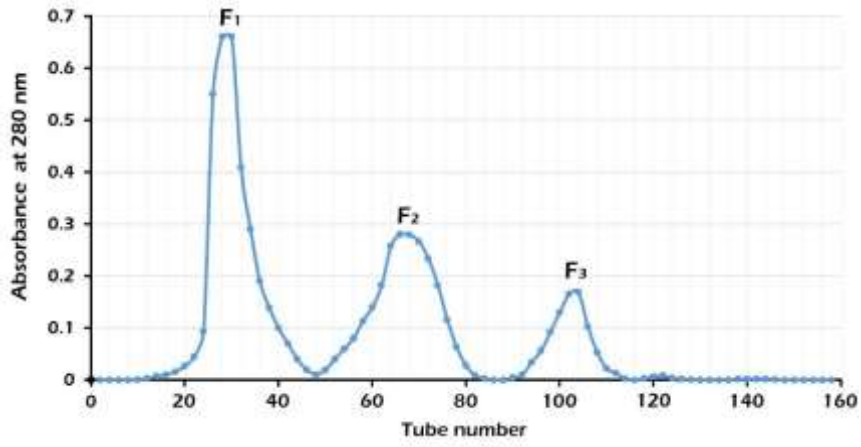

Figure 2. *E. carinatus* venom chromatogram

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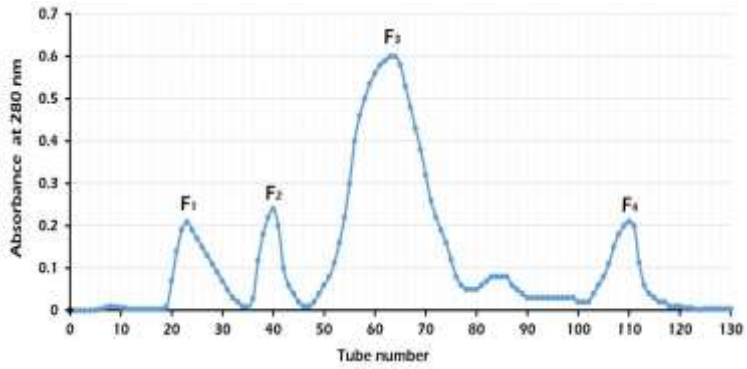

Figure 3. *M. eupeus* venom chromatogram

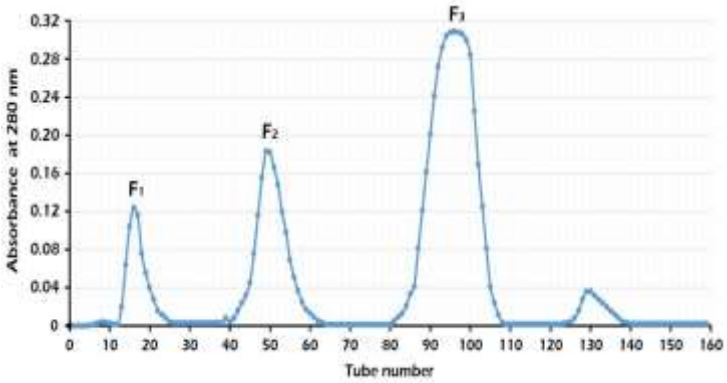

Figure 4. *A. mellifera* venom chromatogram

E. carinatus crude venom and its fractions has shown no antibacterial effects against *P. aeruginosa* and *B. subtilis.* In contrast, the crude venom was effective against *S. aureus* (50, 75 and 100 µg/mL) and *E. coli* (75 and 100 µg/mL). In addition, F_2 was effective against *S. aureus* and *E. coli.* However, standard antibiotics were shown to be effective against all bacteria (Figure 5 and Table 1). The examination showed that the antibacterial activity of F_2 against *E. coli* was more significant than it was for the gentamicin at 10 µg/mL (Figure 5).

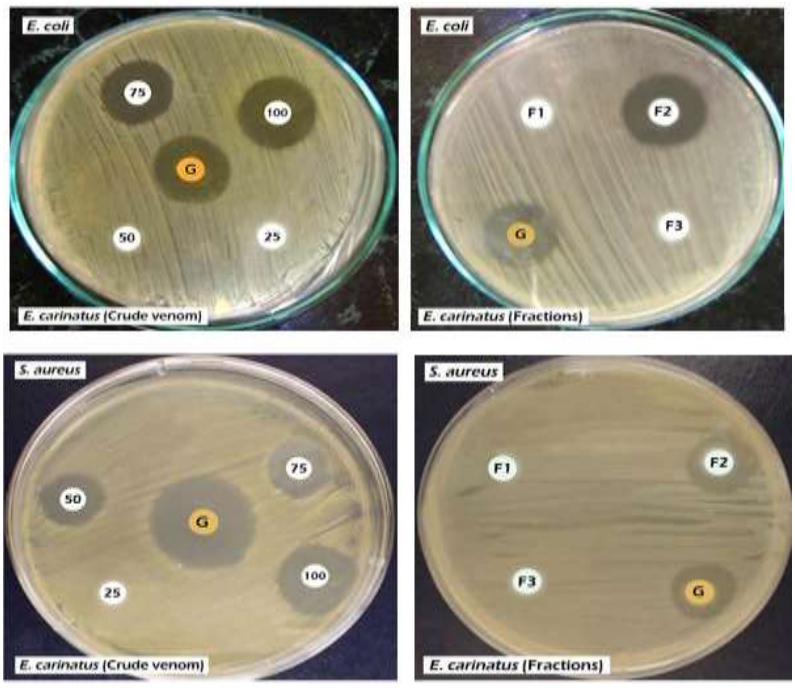

Figure 5. Antibacterial effect of *E. carinatus* crude venoms and fractions against *E. coli* and *S. aureus*

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M. eupeus crude venom and its fractions has shown no antibacterial effects against *P. aeruginosa*, *S. aureus* and *E. coli.* In contrast, *M. eupeus* crude venom was effective against *B. subtilis* (50, 75 and 100 µg/mL). In addition, F_1 and F_4 was effective against *B. subtilis.* However, the standard antibiotic gentamicin was effective against those bacteria (Figure 6 and Table 1). The examination showed that the antibacterial activity of *M. eupeus* crude venom (at the 75 and 100 µg/mL concentrations) and F_1 and F_4 against *B. subtilis* were more significant than it was for the standard antibiotic gentamicin at 10 µg/mL (Figure 6).

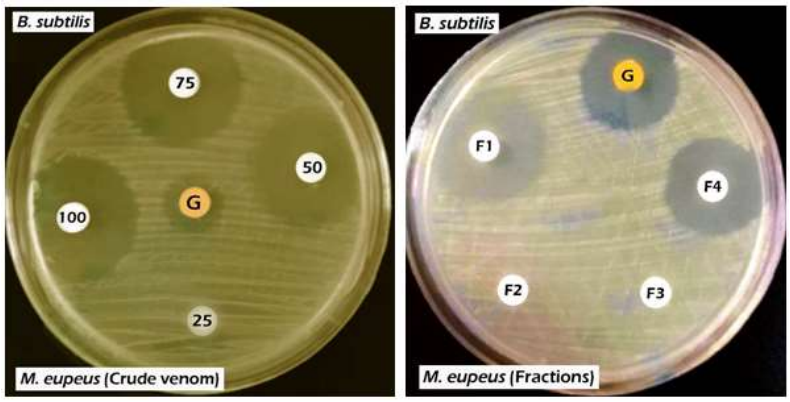

Figure 6. Antibacterial effect of *M. eupeus* crude venoms and fractions against *B. subtilis*

A. mellifera venom demonstrated antibacterial activity against *Escherichia coli*, *S. aureus* at all four concentrations. Moreover, with increasing *A. mellifera* venom concentration, the inhibition zone increased. Fraction 3 (F_3) of *A. mellifera* crude venom have inhibition effect for *E. coli* and *S. aureus* (Figure 7).

The venom concentration of 100 µg/mL showed the highest inhibition zone against *E. coli* (29.06±1.31 mm) and *S. aureus* (17.51±1.07 mm) (Table 1). *A. mellifera* crude venom and F_3 had a more significant antibacterial activity against *E. coli* in the medium than it did against either of the three other strains of bacteria.

The present examination also showed that the antibacterial activity of *A. mellifera* crude venom at the 100 µg/mL concentrations against *E. coli* and *S. aureus* was more significant than it was for the standard antibiotic gentamicin at 10 µg/mL (Figure 7). However, the antibacterial activities of *A. mellifera* crude venom against *S. aureus* (25 and 75 µg/mL) and *E. coli* (25 and 50 µg/mL) were less than the effect of the standard antibiotic gentamicin at 10 µg/mL (Figure 7). Furthermore, *A. mellifera* crude venom and its fractions was found to have no observable effect on the *P. aeruginosa* and *B. subtilis* whereas the standard antibiotic gentamicin was effective against those bacteria (Table 1).

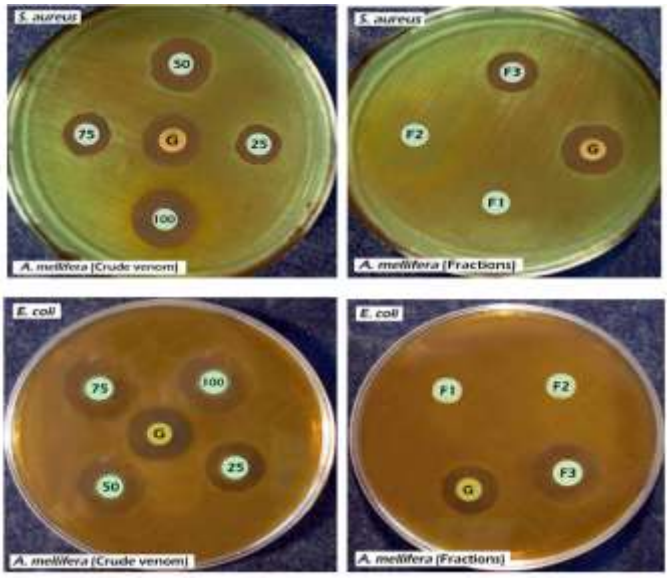

Figure 7. Antibacterial effect of *A. mellifera* crude venoms and fractions against *E. coli* and *S. aureus*

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Table 1. Values of growth inhibition zones due to crude venom and their fractions of *E. carinatus*, *M. eupeus* and *A. mellifera* for bacterial strains

Venoms \ Bacterial strains			*S. aureus*	*P. aeruginosa*	*E. coli*	*B. subtilis*
Echis carinatus	Crude venom µg/mL	25	----	----	----	----
		50	12.92 ± 1.03	----	----	----
		75	15.21 ± 1.56	----	21.08 ± 0.13	----
		100	22.65 ± 2.1	----	23.91 ± 0.13	----
	Gentamicin		25.65 ± 1.64	21.08 ± 1.08	22.11 ± 0.22	19.21 ± 0.97
	Fractions	F_1	----	----	----	----
		F_2	17.2 ± 1.42	----	24.11 ± 0.98	----
		F_3	----	----	----	----
	Gentamicin		16.1 ± 0.98	19.11 ± 1.06	22.54 ± 1.04	18.83 ± 1.17
Mesobuthus eupeus	Crude venom µg/mL	25	----	----	----	----
		50	----	----	----	29.20 ± 0.88
		75	----	----	----	29.41 ± 0.81
		100	----	----	----	30.83 ± 1.04
	Gentamicin		17.03 ± 0.81	11 ± 0.44	20 ± 0.22	4.22 ± 0.83
	Fractions	**F_1**	----	----	----	29.3 ± 0.96
		F_2	----	----	----	----
		F_3	----	----	----	----
		F_4	----	----	----	26.4 ± 0.49
	Gentamicin		20.4 ± 0.19	31.1 ± 1.07	16.5 ± 0.39	25.8 ± 1.02
Apis mellifera	Crude venom µg/mL	25	8.1 ± 0.76	----	20.06 ± 1.50	----
		50	13.2 ± 0.87	----	25.30 ± 1.02	----
		75	9.2 ± 0.98	----	28.31 ± 0.67	----
		100	17.51 ± 1.07	----	29.06 ± 1.31	----
	Gentamicin		11.3 ± 0.47	19.17 ± 0.21	26.11 ± 0.74	9.19 ± 0.08
	Fractions	F_1	----	----	----	----
		F_2	----	----	----	----
		F_3	8.91 ± 1.12	----	29.51 ± 1.41	----
	Gentamicin		13.7 ± 0.89	16.5 ± 0.47	24.36 ± 1.09	9.8 ± 0.29

Discussion

The venom of animals such as scorpions, snakes and bees can prevent the growth of microorganisms. For example, scorpions spray their venom on own bodies to prevent the growth of bacteria and fungi **(24)**. In general, the venom of these animals is a good source for pharmaceutical compounds **(25)**. Although some of venoms and compounds derived from them have antibacterial properties, most of them have not been studied for such activities.

The present study provides evidence that venoms of different animals have antibacterial effects against bacteria. Among the venoms examined, those from snake (*E. carinatus*), scorpion (*M. epues*) and bee (*A. mellifera*) showed strong antimicrobial effects. These venoms exhibited greater zones of inhibition, equivalent to that shown by the gentamicin.

With respect to venoms in current study, *A. mellifera* was the most effective against the two microorganisms, among the venoms examined. All

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concentrations of *A. mellifera* venom showed strong antimicrobial effects against *S. aureus* and *E. coli.* Venoms of *E. carinatus* and *M. eupeus* have got medium effects, presenting only three significant venom concentrations.

Compared with the *M. eupeus* venom, which was more specific against *B. subtilis*, the *A. mellifera* and *E. carinatus* venoms, on the other hand, exhibited a broader spectrum of antibacterial activity.

A strong activity was shown against *B. subtilis* by the *M. eupeus* venom, while venoms of *A. mellifera* (25 and 75 µg/mL) and *E. carinatus* (50 and 75 µg/mL) exhibited only a weaker activity against *S. aureus*. With respect to microorganism susceptibility, The Gram-positive cocci *S. aureus* bacterium appeared to be the most sensitive to venoms. In contrast, the venoms had no effect on *P. aeruginosa*. The results were consistent with Perumal Samy *et al.* **(26)**. Previously, snake venoms were reported to exhibit a strong inhibitory effect against *P. aeruginosa* **(27, 28)**.

The antibacterial effect of the venom derived from scorpions has been demonstrated in various studies. In a study by Zhao *et al.* in 2009 on antibacterial effect of the Chinese scorpion *Isometrus maculates,* it was found that the venom of this scorpion had an inhibitory effect on the growth of Gram-positive bacteria but no effect on Gram-negative bacteria *P. aeruginosa* and *E. coli*. A comparison of the results of this study with those of the present one suggests that the mechanism of the antibacterial effect of the Chinese scorpion venom is similar to that of the Iranian scorpion venom **(29)**.

In this study, *M. eupeus* crude venom was effective against *B. subtilis* showed zone of inhibition 30 mm. These results are similar to spider venom activity reported by Benli and Yigit **(30)** and Ahmad *et al.* **(31)**.

In 2009, in a study on different sources of animal venoms, various species of snakes including *Bothrops jararaca, Bothrops moojeni* and *Bothrops jararacussu* were studied for their antibacterial effects. *B. jararaca* had the strongest antibacterial effect on *S. aureus* **(32)**.

Jami al ahmadi reported that, *E. carinatus* venom has not a wide spectrum antibacterial effect against the mentioned bacteria, although a significant activity against *S. aureus* in comparison with the standard antibiotics has been observed **(33)**.

A study of antibacterial effect of honey bee venom on several bacteria species in 2016 reported that it had a considerable inhibitory effect on *P. aeruginosa* and *E. coli* **(19)**. In the present study, bee venom was exhibited a strong inhibitory effect against *E. coli.* While in the present study, no antimicrobial activity of bee venom against *P. aeruginosa* was observed.

Conclusion

Finally, it should be noted that comparison of the antibacterial effects of the venoms with gentamicin suggested that these venoms had stronger inhibitory effects. However, this comparison was a laboratory estimation carried out without a formulation. Therefore, the results obtained in the preliminary stage seem to be valuable. The results of this study indicate that the use of these venoms, especially associated proteins and peptides has promising results. Further research in the future on other bacterial species and on animal models may allow industrial introduction of these venoms into the pharmaceutical market and help solve the drug resistance problem when treating bacterial infections.

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Conflict of Interest

Authors declared no conflict of interests.

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