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Antimicrobial activities of scorpion and honey bee venom against some common selected pathogen

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ABSTRACT
Multidrug resistant pathogens are reported in high numbers in the world. This cause failure of the currently available antibiotics to treat these multidrug resistant pathogens. This lead to the global concern to discover alternative to antibiotics. Various researchers have conducted many studies about the biological activities of bee venom and scorpion venom. In the literature it is reported that the venom of bee and scorpion have some peptide which have antimicrobial activity. Our study was therefore conducted to determine the antimicrobial property of bee venom and scorpion venom against some common selected pathogens. Bee venom and scorpion venom antimicrobial activity was tested against common selected pathogenic bacteria and fungi that includes Staphylococcus aureus, Salmonella typhimurium, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, Trichophyton mentagrophytes and Trichophyton rubrum.Disc diffusion method was used to evaluate the antimicrobial activity of these venom.Standard antibiotics and antifungal that includes Chloramphenicol, streptomycin and penicillin, fluconazole and amphotericin B were used as control for antimicrobial activity. Against all selected common pathogenic bacteria and fungi both of the venom of bee and scorpion shows antibacterial and antifungal activity. The bee venom give zone of inhibition 25mm, 18mm, 21mm 15mm against E. coli, S. aureus, and Salmonella typhyimurium and Pseudomonas aeruginosa respectively while the scorpion venom gives 23mm, 16mm, 21mm and 17mm zone of inhibition against these bacteria respectively. While in case of fungi the zone of inhibition of bee venoms against C. albicans T. mentagrophytes and T. rubrum was 18mm, 20mm and 17mmwhile scorpion venom gives 17mm, 21mm and 15mm zone of inhibition against these fungi respectively. Our study shows that both bee venom and scorpion venom have the ability to inhibit bacteria and fungi which may be used complementary to antibiotics. Therefore, our study might conclude that specific mechanism, which is not well known, is used by bee venom and scorpion venom to inhibit the growth of both bacteria and fungi. Further in vivo and in vitro study based on a chemical, pharmacological, and clinical approach must be conducted to understand the exact mechanism of these venoms.
Key words: *Antibacterial; Antifungal; scorpion venom; honey bee venom; inhibition zone*

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INTRODUCTION
Currently the conventional available antibiotics are not working properly because most of the pathogenic microbes are reported to be antibiotic resistant. 70% of the hospital acquired infection causing bacteria have been reported to be resistant to one or more available antimicrobial agents. However some bacterial

strains are reported to be multi drug resistant while some of the bacterial strains are reported to be resistant to all available conventional antibiotics [1].

Due to drug resistance the global public health is at high risk and the risk is increasing with the time because the drug resistant pathogens are emerging continuously [2, 3].The most threatening pathogenic bacteria for public health is methicillin-resistant *Staphylococcus aureus* (MRSA). This is because of increased death rate and cost in treating this multidrug resistant bacteria [4, 5].Currently there is a need to develop new antimicrobial agents to decrease the threat of drug resistant pathogen to the public health [6].

Pharmaceutical products that are available commercially, mostly are direct or indirect derived product of microbes, animals and plants of both terrestrial and marine origin [7].Generally, it is highly studied and reviewed to use plants for medicinal purposes in previous studies. On the other hand, the same attention has not been paid to the animals to be used for medicinal purposes as insects has the potential to be used for this purpose. By comparing the research per species between plants and insects, it has been observed that plants chemicals have been 7000 time more studied as compared to chemicals present in insects. Currently the attention of the researchers are attracted highly towards insects to contribute in novel discoveries [8, 9].

Evolutionarily Antimicrobial peptides are considered as prehistoric weapons. As the antimicrobial peptides are distributed widely all over the animal kingdom. This distribution suggested their role in complex multicellular organism's evolution successfully [10]. From antimicrobial secretions and venoms numerous antimicrobial peptides have been isolated. Numerous peptides have been derived from the scorpion's venom. These peptides are reported to have antibacterial and antifungal activity in a similar manner like broad spectrum antibiotics [11]. Against a large number of gram-positive bacteria, pandinin 1 and 2 of scorpion venom are reported to have strong antimicrobial activity [12]. Additionally, venom of the scorpion CsTX also shows antimicrobial activity [13]. Other than venom of scorpions of, the bee venom (*Apis mellifera*) also shows antimicrobial activity [14]. Mellitin component of the bee venom shows more potent antimicrobial activity against gram-positive bacteria as compared to gram negative bacteria. Moreover, in addition to wasps venom, honey bees and many snakes have antimicrobial peptides, however no investigation have been done on the functions of these peptides [15].

Bees belonging to the species *Apis mellifera* species of bee have many activities that are similar to human being. Traditionally these includes; pollination, honey production, resins, wax, jelly, pollen, and venom like apitoxin. Compounds synthesized by bees synthesized many compounds that have been widely studied because these compounds have many application therapeutically [16, 17, 18, 19]. Bee produce many substances, among these the most important substance is apitoxin. This complex chemical is synthesized by the gland located in the abdomen of these insects. Apitoxin of bee venom have 88%water content while 12% comprises of many components like phospholipase A2, hyaluronidase, melittin, histamine. Additionally it contains peptides such as apamin, secapin etc. [20]. Regarding the components of apitoxin,the highly studied compound is phospholipase A2. Samel et al. done their study in which they shows that *sn-2* fatty acyl ester bond of *sn-3* phosphoglycerides hydrolysis is catalyzed by phospholipases A2 due to which they give free lysophospholipids and fatty acids [21]. Phospholipases A2 protein have been found in numerous tissues of mammals and arthropods. It has been found in snakes, scorpions and bee venom. This constitute a large family of protein in these [22]. Among these 10 groups are of secretoryphospholipase A2 [23, 24]. Molecular weight of Phospholipase A2 is low. They have high potential of immunogenicity and their catalytic activity is also high.Phospholipase A2 enzyme shows antibacterial and anticoagulant activity and shows vigorousrole in chemical mediator's generation, proliferation of cell, contraction of muscle (25, 26). Vital component of apitoxin is melittin. It contains 26 amino acids having amphipathic character. These amino acid chain let melittin interaction with lipid membranes. This also increase the erythrocytes and other membrane. About 50% of the bee apitoxin belong to species *Apis mellifera* are constituted by these amino acids [20]. Cytotoxic activity has been observed for melittin and it has potential activity of cell lysis and its cell lysis activity has been evidenced in human cell lysis of erythrocytes (27). Moreover, cell membrane is directly acted upon by it (28, 29). Melittin have numerous biological activities that includes activity against microbes like bacteria, fungi, viruses. They also have anti-inflammatory activity, inhibitory effect on cell growth and different cancer cell line apoptosis [30, 31].

Scorpions are considered as one of the utmost prehistoric animals living on earth. They have lived over 400 million years [32].This old evolutionary changes attribute mainly to develop weapon of efficient venom that will support their requirement to prey and their defense. In the whole globe they have wide distribution and they have about 1500 species [33].The venomous glands of the scorpions comprises of large number of biologically active molecules such as lipids, nucleotides, biogenic amines, enzymes and other molecules that are unknown [34, 35]. Beside these it also comprises of numerous peptides having multiple activities biologically. These peptides are considered to be the main component of an innate immune system that give protection to the scorpion against various pathogens [36, 37]. A less abundant group of peptides called non-disulfide bridged peptides, having no disulfide bridges, have currently achieved great interest. They have many biological activities such as anticancer activity, hemolytic activity, activity against inflammation and immune-modulatory effect. Beside these they also have activity against microbes (38, 39, 40).By keeping in mind the various biological activities of bee venom and scorpion venom reported in literature, we piloted our study to evaluate the antibacterial potential of the scorpion and honey bee venom available commercially against common selected pathogenic bacteria and fungi.

MATERIAL AND METHODS

Commercialized sources of venom were collected in lyophilized form in the department of zoology, Kohat University of science and technology, Khyber Pakhtunkhwa, Pakistan. Sterile condition were strictly adopted during collection of venoms and at $4C^0$ they were centrifuged and after six hours of extraction they were frozen and lyophilized. Packing and storage of the venom was taken in the dark at $20C^0$.These information were taken from the leaflet provided with the commercial venom.Standard antibiotics and antifungal that includes Chloramphenicol, streptomycin and penicillin, fluconazole and amphotericin B were used as control for antimicrobial activity. MuellerHinton (MH) agar medium was used to check the antimicrobial activity of both bee and scorpion venom.*Staphylococcusaureus*, *Salmonella typhimurium*, *Escherichia coli, Pseudomonas aeruginosa*, *Candida albicans, Trichophyton mentagrophytes* and *Trichophyton rubrum* were used in our study to determine the antimicrobial activity of the bee and scorpion venom. The bacteria were picked up from the research laboratory in the department of microbiology, Kohat University of science and technology, Khyber Pakhtunkhwa, Pakistan, in which these cultures were preserved at –80°C.The bacteria and fungi with the ATCC number are given in table 1.The Muller Hinton agar prepared and then autoclaved. Then 20ml of it was poured in 90mm plate. 100μg lyophilized crude venoms were dissolved in 1 ml of buffer (Tris-HCl)and then it was filtered with syringe filter having pore size of 0.22μm. After that it was stored for further use at $4C^0$. Disc-diffusion method was used to determine the antimicrobial activity as done by Bauer et al (41).Sterile cotton swab was used to spread inoculums of the bacteria on the MH agar plates. For about three minutes the medium surface was allowed to dry. On the surface of the MH agar 7mm (Diameter) sterile paper discs were placed. Then 20μl samples of both the venom having concentration of 100μg/ml were added in the discs. Then at $37C^0$ the plate incubation was done for 24 hours. Finally the zone of inhibition was measured by using guidelines of NCCLS (2002) (42).To determine the antifungal activity of bee venom and scorpion venom the fungal ATCC cultures collected from microbiology department, Kohat University of science and technology, Khyber Pakhtunkhwa, Pakistan were first cultured on sabouraud dextroseagar plates, and then it was incubated at35°C for 48 hours. To make stock solution amphotericin Band fluconazole were dissolved in 2% dimethyl sulfoxide. Then it was diluted for further use. Mueller-Hinton agarglucose methylene blue medium was used for disk diffusion method to determine the antifungal activity of scorpion and bee venom. Sterile cotton swab was used to spread inoculums of the fungi on the MH-GMB agar plates. For about three minutes the medium surface was allowed to dry. On the surface of the MH agar 7mm (Diameter) sterile paper discs were placed. Then 20μl samples of both the venom having concentration of 100μg/ml were added in the discs. Then at $35C^0$ the plate incubation was done for 24 hours. Finally the zone of inhibition was measured .All the data was analyzed statistically.

Table 1: ATCC number of bacteria and fungi used in our study

Serial NO	Bacteria/ Fungi	ATTC No
1.	*S. aureus*	25923
2.	*Pseudomonasaeruginosa*	27853
3.	*E. coli*	25923
4.	*Salmonella typhimurium*	25923
5.	*Candida albicans*	10231
6.	*T. rubrum*	28188
7.	*T. mentagrophytes*	18748

RESULTS

The antimicrobial activity of honeybee venom and scorpion venom was checked against common pathogenic bacteria including *Staphylococcus aureus* (*S. aureus*), *Salmonella typhimurium*, *Escherichia coli, and Pseudomonas aeruginosa*. The antimicrobial activity of these venoms was also checked against pathogenic fungi *C. albicans, T. mentagrophytes* and *T. rubrum.* Disc diffusion method was used to evaluate

the antimicrobial activity of these venom. Standard antibiotics and antifungal that includes Chloramphenicol, streptomycin and penicillin, fluconazole and amphotericin B were used as control for antimicrobial activity. Against all selected common pathogenic bacteria and fungi both of the venom of bee and scorpion shows antibacterial and antifungal activity. Both bee venom and scorpion venom was observed to have a substantial antibacterial effect against *E. coli*, *S. aureus*, and *Salmonella typhyimurium* and *Pseudomonas aeruginosa.* The bee venom give zone of inhibition 25mm, 18mm, 21mm 15mm against*E. coli*, *S. aureus*, and *Salmonella typhyimurium* and *Pseudomonas aeruginosa* respectively(Table 2)while the scorpion venom gives 23mm, 16mm, 21mm and 17mm zone of inhibition against *E. coli*, *S. aureus*, and *Salmonella typhyimurium* and *Pseudomonas aeruginosa* respectively.(Table 3)
Figure 1 and figure 2 shows zone of inhibition of scorpion and bee venom against bacteria and fungi. While in case of fungi the zone of inhibition of bee venoms against *C. albicans T. mentagrophytes* and *T. rubrum* was 18mm, 20mm and 17mm.(Table 4) while scorpion venom gives 17mm, 21mm and 15mm zone of inhibition against *C. albicans T. mentagrophytes* and *T. rubrum* respectively.(Table 5)Figure 3 shows comparative zone of inhibition between bee venom scorpion venom against selected pathogens.

Table 2: Bee venom zone of inhibition against selected bacteria

Serial No	Common name	Scientific name	Bacteria/Zone of inhibition			
			Salmonella typhimurium	*E.coli*	*S. Aureus*	*Pseudomonas aeruginosa*
1.	Bee venom	*Apis mellifera*	21	25	18	15
2.	Antibiotic					
	Chloramphenicol (CHL)	30 µg/ disc	23	20	20	18
	Streptomycin (STR)	10 µg/ disc	25	22	20	18
	Penicillin (P)	10 µg/ disc	20	18	16	16

Table 3: Scorpion venom zone of inhibition against selected bacteria

Serial No	Common name	Scientific name	Bacteria /Zone of inhibition			
			Salmonella typhimurium	*E.coli*	*S. Aureus*	*Pseudomonas aeruginosa*
1.	Scorpion	Buthotus hottenota	21	23	16	17
2.	Antibiotic					
	Chloramphenicol (CHL)	30 µg/ disc	23	20	20	18
	Streptomycin (STR)	10 µg/ disc	25	22	20	18
	Penicillin (P)	10 µg/ disc	20	18	16	16

Table 4: Bee venom zone of inhibition against selected fungi

Serial No	Common name	Scientific name	Fungi /Zone of inhibition		
			C. albicans	*T. mentagrophytes*	*T. rubrum*
1.	Bee venom	*Apis mellifera*	18	20	17
2.	Antibiotic				
	fluconazole	100mgper disc	20	22	20
	amphotericin B	100mg per disc	23	21	22

Table 5: Scorpion venom zone of inhibition against selected fungi

Serial No	Common name	Scientific name	Fungi /Zone of inhibition		
			C. albicans	*T. mentagrophytes*	*T. rubrum*
1.	Scorpion	*Buthotus hottenota*	17	21	15
2.	Antibiotic		20	22	20
	Fluconazole	100mg per disc	23	21	22
	Amphotericin B	100mg per disc	20	22	20

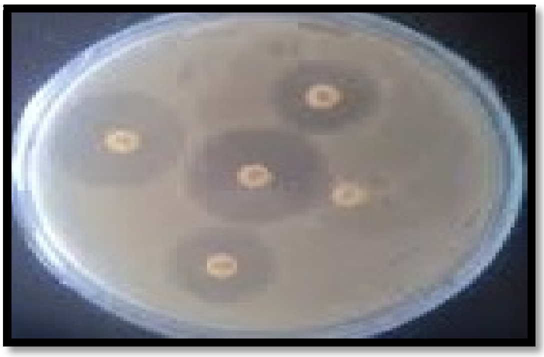

Figure 1: Zone of inhibition against selected pathogen

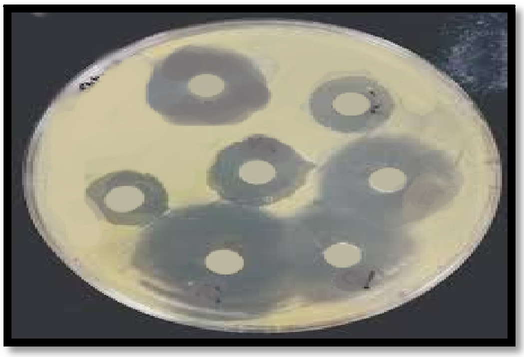

Figure 2: Zone of inhibition against selected pathogen

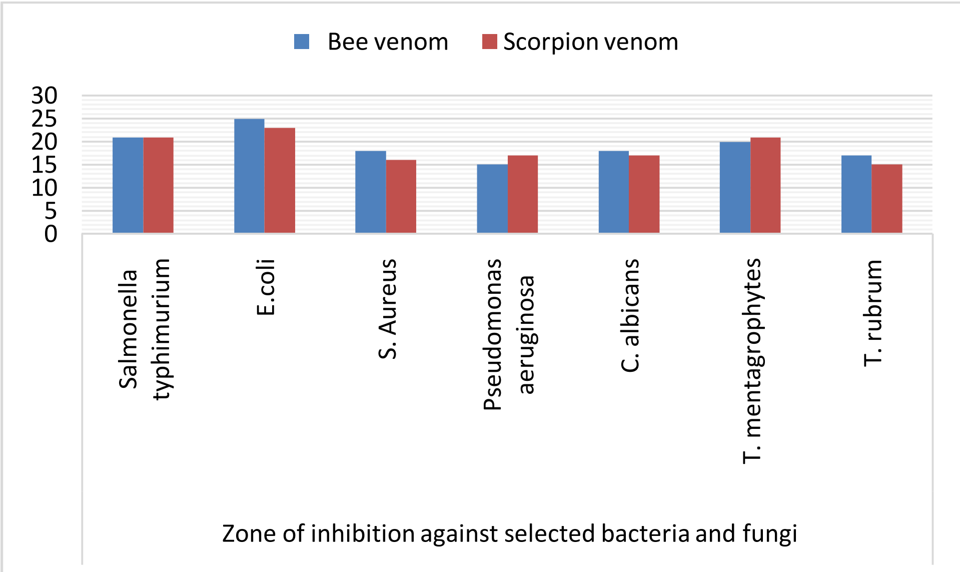

Figure 3: Comparative zone of inhibition of scorpion and bee venom against selected pathogens

DISCUSSION

Multidrug resistant pathogens are reported in high numbers in the world. This cause failure of the currently available antibiotics to treat these multidrug resistant pathogens. This lead to the global concern to discover alternative to antibiotics. Various researchers have conducted many studies about the biological activities of bee venom and scorpion venom. In the literature it is reported that the venom of bee and scorpion have some peptide which have antimicrobial activity. Bee venom and scorpion venom antimicrobial activity was tested against common selected pathogenic bacteria and fungi that includes *Staphylococcus aureus*, *Salmonella typhimurium*, *Escherichiacoli,Pseudomonas aeruginosa*, *Candida albicans, Trichophyton mentagrophytes* and *Trichophyton rubrum.* Disc diffusion method was used to evaluate the antimicrobial activity of these venom. Standard antibiotics and antifungal that includes Chloramphenicol, streptomycin and penicillin, fluconazole and amphotericin B were used as control for antimicrobial activity. Against all selected common pathogenic bacteria and fungi both of the venom of bee and scorpion shows antibacterial and antifungal activity. The bee venom give zone of inhibition 25mm, 18mm, 21mm 15mm against *E. coli*, *S. aureus*, and *Salmonella typhyimurium* and *Pseudomonas aeruginosa* respectively while the scorpion venom gives 23mm, 16mm, 21mm and 17mm zone of inhibition against *E. coli*, *S. aureus*, and *Salmonella typhyimurium* and *Pseudomonas aeruginosa* respectively. While in case of fungi the zone of inhibition of bee venoms against *C. albicans T. mentagrophytes* and *T. rubrum* was 18mm, 20mm and 17mm while scorpion venom gives 17mm, 21mm and 15mm zone of inhibition against *C. albicans T. mentagrophytes* and *T. rubrum* respectively.

In numerous studies effects of bee venom have been studied biochemically, anti-microbiologically and pharmacologically [43, 44]. The bee venom antimicrobial activity might be due to existence of numerous peptides like melittin, adolapin,, apamin, mast-cell-degranulating peptides, various enzymes, amines that are active biologically and various components that are non-peptide [45]. A previous study done by Cujova *et al* [46]shows that melittin is present in bee venom which has more potential against gram positive bacteria as compared to gram negative bacteria. The sensitivity of the bacteria was measured by measuring the inhibitory zone. Another study done by Ortel and Markwardt shows that gram positive bacteria have more sensitivity towards lower concentration of bee venom as compared to gram negative bacteria [47].The bee venom antimicrobial activity might be due to existence of numerous peptides like melittin, adolapin,, apamin, mast-cell-degranulating peptides, various enzymes, amines that are active biologically and various components that are non-peptide [48]. These components might have ability to interact with the molecules of some bacteria while other bacterial molecules may not have interaction. The antibacterial activity of Phospholipase A2 have been reported previously [49, 50]. The melittin in the bee venom have reported to have antibacterial activity. Depending on the antibacterial agents,various researchers have reported that against gram positive and gram negative bacteria the antimicrobial activity might be different [51].Our study results are in accordance with the study done by Kondoand Kanai [52]. A previous study done by Hegazi *et al* is in contrast with our study. They reported that bee venom has less antimicrobial activity against *E.coli* [53]. A study done by Rybak et.al shows that by mixing bee venom and kanamycin, it gives synergetic effect against *S. aureus* that are resistant to kanamycin [54]. Many infections are caused by fungi in the world like superficial skin infections and allergic problems etc.In addition, the major challenge to the public health is that antifungal agents are toxic and many fungus have been reported to be resistant to the available antifungal agents. On the other hand researchers are thinking about natural products likeplant products, marine life, microbes and bee products to be used as antifungal agent because they have less side effect [55]. Currently against many fungal pathogens like *Trichophyton mentagrophytes* and *Trichophyton rubrum*, bee venom has been reported to be effective and can inhibit them [56]. The anti-fungal action of BV on Against 10 clinical isolates of *Candida albican,* bee venom for their antifungal activity has been test and MIC was calculated that ranges from 62.5-125µgm/ml [55]. Previously another study reported the antifungal activity of melittin against numerous fungus and MIC was also determined that ranges between 30-300µgm/ml (57). Furthermore, numerousamino peptides in scorpion venom have been reported that includes hadrurin [58], scorpine (59), opistoporins, parabutoporin [60]. These amino peptides shows cell lysis activity and also cause inhibition of various functions of microbes.

CONCLUSION

Multidrug resistant pathogens are reported in high numbers in the world. This cause failure of the currently available antibiotics to treat these multidrug resistant pathogens. This lead to the global concern to discover alternative to antibiotics. Various researchers have conducted many studies about the biological activities of bee venom and scorpion venom. In the literature it is reported that the venom of bee and scorpion have some peptide which have antimicrobial activity. Our study shows that both bee venom and scorpion venom have the ability to inhibit bacterial and fungi which may be used complementary to antibiotics. Therefore, our study might conclude that specific mechanism, which is not well known, is used by bee venom and scorpion venom to inhibit the growth of both bacteria and fungi. Further in vivo and in vitro study based on a chemical, pharmacological, and clinical approach must be conducted to understand the exact mechanism of these venoms.

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