Indian Journal of Geo Marine Sciences
Vol. 47 (04), April 2018, pp. 773-778

Review Article

Scorpion venom: A poison or a medicine-mini review

Pir Tariq Shah[1], Farooq Ali[1], Noor-Ul-Huda[1], Sadia Qayyum[1], Shehzad Ahmed[1], Kashif Syed Haleem[1], Isfahan Tauseef[1], Mujaddad-ur-Rehman[2], Azam Hayat[2], Attiya Abdul Malik[2], Rahdia Ramzan[2] & Ibrar Khan[1,2*]

[1]Department of Microbiology, Hazara University, 21300 Mansehra, Pakistan

[2]Department of Microbiology, Abbottabad University of Science & Technology, 2250 Havelian, Pakistan

*[E-mail: abrar@aust.edu.pk]

Received 16 June 2016 ; revised 27 July 2016

The Scorpion's venom considered to be highly complex mixture of nucleotides, enzymes, mucoproteins, biogenic amines, salts, as well as peptides and proteins, which have been used in traditional medicine for thousands of years mainly in Asia and Africa. With the significant discoveries in the number of valuable biologically active components of scorpion venom, numerous drug candidates have been found with the potential to encounter many of the emerging global health crisis. This mini-review sheds light on the application of scorpion venoms and toxins as potential novel antibacterial, antifungal and antiviral, especially as anticancer therapeutics.

[Keywords: Scorpion venom, Antibacterial, Antifungal, Antiviraland Anticancer Potential.]

Introduction

Venomous animals are famous only for their adverse effects caused after interaction with humans accidently. These creatures transmit variety of detrimental toxins with diverse physiological activities that may either lead to minor symptoms like dermatitis and allergic responses or highly severe symptoms such as coagulation ailments, disseminated intravascular coagulation and haemorrhage. Other complications like respiratory arrest and necrosis may also occur. Although envenomation effects usually lead to harmful characters, but these venomous creatures are pharmacologically rich source of treasured principles for many scientists. Scientists are still exploring these toxins, aiming to develop new useful molecules to diagnose, treat and cure some types of diseases[1]. Researchers and scientists always continue their efforts to explore and discover new techniques and approaches for the welfare of human beings. In ancient era, the venoms and natural toxin of plants, animals, fungi and marine organisms had played a great divesting role in the mortality and morbidity of human population. Researchers continue their efforts to identify the nature of these toxins. As the chemical composition of these toxins is defined by different researchers, these risky toxins are now used directly or indirectly in the drugs for number of diseases treatments (Table I).

Scorpion

Scorpions are the predatory arachnids and members of the order scorpiones. They have eight legs, a narrow, segmented tail curved over the body, with a poisonous stinger at the end. Size ranges from 9 mm to 20 cm (*Typhlochactas mitchelli* and *Hadogenes troglodytes* respectively)[2]. Scorpion's evolutionary history goes back to the Silurian period 430 million years ago. Taxonomy of all known scorpions recorded from 1758 to 31st December 1998 contain *16 families*, *16 subfamilies*, *155 genera*, *31 subgenera* (including 10 nominotypical), *1259 species* and *356 subspecies* (including 114 nominotypical)[3]. Scorpions belongs to; Kingdom *Animalia*, Phylum *Arthropoda*, Subphylum *Chelicerata*, Class *Arachnida*, Subclass *Dromopoda* and Order *Scorpiones*[4]. Super families; *Buthoidea, Chaeriloidea, Chactoidea, Luroidea, Pseudochactoidea, Scorpionoidea*[4].

Scorpion's venom is one of the most dangerous and life threatening agents causing high number of human

Table 1 — Comparative antibiotic activity of different venoms

Venomous Animal	Antibacterial activity	Antiviral activity	Antifungal activity	Anticancer activity
Scorpion	+ + + [16, 19]	+ + + [28, 30, 32, 33]	+ + + [16]	+ + + [13, 36]
Snake	+ + + [37, 38]	+ + + [39]	+ + + [40]	+ + + [36]
Spider	+ + + [41]	- - -	+ + + [42]	+ + + [43]
Frog and Toad	+ + + [44, 45]	+ + + [46]	+ + + [46]	+ + + [36]

deaths. According to the current studies, seven regions of the world are considered at high risk containing; North-Saharan Africa, Near and Middle-East, South Africa, Sahelian Africa, South-India, East of the Andes, Mexico and South Latin America[5], comprising 2.3 billion population at risk. . Annually more than 1.2 million peoples are stung by scorpions causing more than 3250 deaths[5].

Scorpion's venom is a complex mixture of salt, proteins, small molecules and peptides[6]. It also contains neurotoxic peptides which cause massive damage to the nervous system of both vertebrates and invertebrates[7]. Moreover, it has hyaluronidase, histamine, mucopolysaccharides, phospholipase, enzyme inhibitors and serotonin[8]. Like other predators, scorpion use these toxins or venoms to attack and capture the prey as well as for the protection against other invaders[9]. Taken together, these peptides and toxins extracted from scorpions and other venomous animals are used as therapeutic agents[10], especially with effective inhibitory effect on multiple steps of HSV-1 life cycle and therefore are good candidate for development as virucides (Figure 1).

Scorpion's venoms and toxins contain variety of peptides and other useful molecules which can be used for the treatment of various diseases. Scorpion venom is used for antibodies production in animals like horse and sheep, which are used for the neutralisation of the venom hazardous effects on the humans[11].

Brain tumor (glioma) is considered to be the most common and severe tumor in humans. Since it arises from the glial cells, so called glioma. Its most common site is brain, but it may also start progression from spine. According to recent study, about 30% of glioma starts progression from brain and spine, while 80% leads to malignant brain tumor[12]. Glioma is highly vascular tumor having the ability to infiltrate, which leads to wide areas necrosis, hypoxia and may cause breakdown of blood-brain barrier (BBB) around the tumor. As scorpion venom is concerned, *Chlorotoxin* is considered to its component which specifically binds to the cell surface of the glioma and impairs the invading ability of glioma cell. The chlorotoxin bind specifically to matrix metalloproteinase-2 (MMP-2) receptor which is usually not expressed in normal brain cells, but is upregulated in glioma and cancer. The MMP-2 plays an important role in degradation and remodelling of the extracellular matrix, thereby helping the normal tumor cells to penetrate through tissue barriers. While, the *Chlorotoxin* interacts with MMP-2 receptor and inhibits its enzymatic activity, as well as reduce its expression[13].

Fig. 1 — Collection of scorpion venoms[34].

The endless battle between humans and microorganisms especially bacteria, fungal, parasites, and viruses is going on from very past. On one side, humans design antibiotics against these microbes and its infections. While, on the other side, microorganisms resist these antibiotics and fight back.

The successful use of any therapeutic agent is compromised by the potential development of tolerance or resistance to that compound from the time it is first employed. This is true for agents used in the treatment of bacterial, fungal, parasitic, and viral infections and for treatment of chronic diseases such as cancer and diabetes; it applies to ailments caused or suffered by any living organisms, including humans, animals, fish, plants, insects, etc. A wide range of biochemical and physiological mechanisms may be responsible for resistance. In the specific case of antimicrobial agents, the complexity of the processes that contribute to emergence and dissemination of resistance cannot be overemphasized, and the lack of basic knowledge on these topics is one of the primary reasons that there has been so little significant achievement in the effective prevention and control of resistance development[14]. However, the gradual emergence of populations of antimicrobial-resistant pathogenic bacteria resulting from use, misuse, and abuse of antimicrobials has today become a major global health concern. Thus, urgent measures are required not only to minimize the use of antimicrobials for

prophylactic and therapeutic purposes but also to look for alternative strategies for the control of bacterial infections, in sense of discovering new antimicrobial agents[15].

Venom of the *Opistophtalmus carinatus*, a South African scorpion contain two unique pore-forming peptides known as opistoporin 1 and 2. Similarly, the venom of another South African scorpion species *Parabuthus schlechteri* also contain a pore-forming peptide known as parabutoporin. During an experiment, these two peptides and two other well-known cytolytic peptides, melittin and mastoparan were examined against several Gram positive and Gram negative bacteria and it was found that Opistoporin 1 and parabutoporin are effective against Gram negative bacteria including *E. coli ATCC, E. coli DH5α, P. aeruginosa, H. influenza* and *K. pneumoniae*. Melittin and mastoparan are active against Gram positive bacteria including *B. subtilus ATCC, B. subtilus IP, S. aureus, S, pneumoniae, N. asteroids* and *E. faecalis*[16].

Over dose and long duration of treatment with antibiotics during infections can lead to bacterial resistance. *Staphylococcus aureus* resistance against *Methicillin* and *Vancomycin* is a new emerging problem. MRSA is main causative agent of nosocomial infections[17]. *Staphylococcus aureus* is normal flora of skin, it can colonize on skin or in the nose of healthy persons. It is an opportunistic pathogen, because it may causes infection if reaches to the deeper tissues through wounds or surgical incision. Furthermore, it may also enters into the blood and lungs, which leads to bacteraemia and pneumonia[18]. According to recent report on MRSA, indicates high prevalence rate in Australia, Japan, USA, South-America, Southern-Europe[17].

In recent studies, it is explored that the venom of scorpion *Isometrus maculates* contains a polypeptide called imcroporin, which shows effectiveness against antibiotic sensitive as well as resistant bacteria. During another experiment on mouse, it is found potent against gram-positive antibiotic-resistant bacteria, including Methicillin Resistant *Staphylococcus aureus* (MRSA) [19].

Fungal pathogens influence the plant and animal life to a great extent which leads to food insecurity, species extinctions and disturbance of the ecosystem[20]. Fungi also cause number of human's infection including athlete's foot[21], superficial infections of the skin and nails, mucosal infections of the oral and genital tract[22], oral thrush[23], nosocomial infections[24] etc. According to recent studies, one and half million people die every year due to the invasive fungal infections, out of them, 90% deaths are caused by species belong to the four genera: *Candida*, *Aspergillus*, *Cryptococcus* and *Pneumocystis*[25]. Furthermore, many of the fungal pathogens are also shows resistance against multiple antibiotic[26], so it is needed to develop highly potent and effective drugs against these life-threatening fungal pathogens.

On the other hand, two pore-forming cationic peptides known as *opistoporin* 1 and 2, isolated from venom of most dangerous species of scorpion *Opistophtalmus carinatus* found in South Africa, were found highly active against number of pathogenic fungal strains. Furthermore, O*pistoporin* 1 was found more active in inhibiting growth of *Neurosporacrassa*, *Fusarium culmorum*and *Saccharomyces cereviciae*. It inhibits about 50% growth of *Neurosporacrassa*, *Fusarium culmorum*at a concentration of 0.8μM and *Saccharomyces cereviciae*at a concentration of 0.9μM. Additionally, *Fusarium culmorum* is supposed to be most sensitive fungi for all peptides components of scorpion's venom[16].

According to a report by UNAIDS, approximately 34 million people throughout the world were infected with human immunodeficiency virus[27]. Because of no availability of proper vaccine, HIV/AIDS is wreaking massive destruction to the world for last 30 years. In recent studies, a new peptide derivative of scorpion venom is identified known as Kn2-7which interacts with HIV-1 viral particle and inhibits HIV-1[28], however further research is needed to develop a potent antiviral therapeutic agent using this scorpion venom peptide.

Hepatitis B virus (HBV) is a life threatening viral pathogen of liver, infecting 4 million people currently and approximately 400 million patients have chronic liver infection, who are at risk to develop cirrhosis or Hepatocellular Carcinoma (HCC) or both. Most of the patients with HBV are unaware of the disease, therefore minority of them are receiving treatment which is leading cause of severe HBV infection[29].

The Mucroporin-M1, a derivative of scorpion venom peptide activates mitogen-activated protein kinases (MAPKs) pathway which reduces the expression of hepatocyte nuclear factor 4α (HNF4α) which stimulates the replication of HBV genome even in non-hepatic cell lines. Thus Controlling the HNF4α

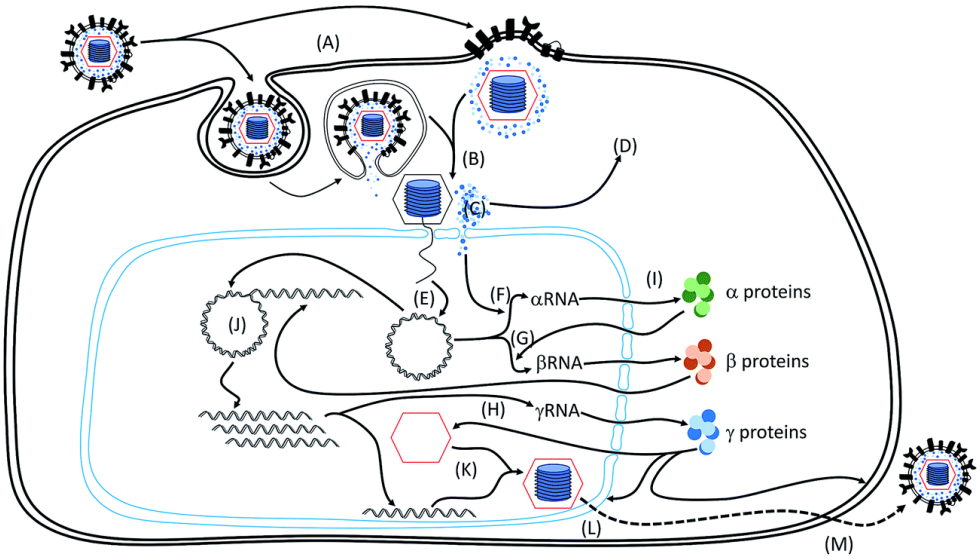

Fig. 2 — Multiple steps of Herpes Simplex Virus Lifecycle [35].

results in the inhibition of HBV replication *in vivo* and *in vitro*[30].

Hepatocellular carcinoma (HCC) is considered to be the fifth most common cancer, third most common cause for cancer death in the world, a major cause of death in patients with chronic hepatitis C virus infection, and responsible for approximately one million deaths each year[31]. A hepatitis C vaccine would be a great victory for preventive medicine and public health, and despite the technical problems involved, scientists are working and making good progress toward developing an effective and affordable vaccine. In fact, one vaccine currently being tested in people in a trial set to end in 2016 has shown promise. The vaccine in development deploys the body's own immune system to ward off infection with HCV using a two-tier approach that first triggers then enhances the immune response. Depending on whether initial testing shows the vaccine is effective in preventing chronic hepatitis C with a reasonable safety profile, it may graduate to test in a larger trial. Therefore, public access to the vaccine is likely years away. Therefore, development of anti-HCV agents are needed for the proper treatment of HCV infections[32].

Recently, a new α-helical peptide is identified from the venom of the scorpion *Heterometrus petersii* known as Hp1090. This Hp1090 show virucidal activity. The Hp1090 peptide acted as a viricide against HCV particles in vitro and prevented the initiation of HCV infection. Furthermore, Hp1090 is virocidal for HCV in vitro, directly interacting with the viral membrane and decreasing the virus infectivity. Thus, these findings put forward that Hp1090 could be used to develop a potential anti-HCV therapeutic compound[32].

Herpes simplex virus type 1 (HSV-1) is one of the prevalent pathogen causing severe diseases that involve mucocutaneous surfaces, the central nervous system and, occasionally, visceral organs such as the lung, but till now, no effective drug is developed against it except acyclovir (ACV) and related nucleoside compounds. Recently, two venom peptides purified from scorpion *Heterometrus petersii* venom, Hp1030 and Hp1239, having α-helical structure were found to be more active against HSV-1 and show effectively inhibit multiple steps in life cycle of HSV-1 (Figure 2), with unknown mechanism. Thus, these peptides could be used to develop effective drug against HSV-1[33].

Conclusion

Venomous animals are well-known only for their adverse effects they cause after interaction with humans accidently. In ancient era, the venoms and natural toxin of plants, animals, fungi and marine organisms had played a great devastating role in the mortality and morbidity of human population. On the other hand, it contains variety of peptides and other useful molecules like chlorotoxin having anticancer activity (anti glioma), Opistoporin 1, 2 (antibacterial and antifungal), Mucroporin-M1, Peptide Kn2-7, Hp1090, Hp1030 and Hp1239, are proved to be effective against HIV, HBV, HCV and HSV-1 viruses, respectively. With the passage of time, the

microbial resistance is increasing worldwide causing the treatment of several infections difficult and expensive. Thus, these molecules and peptides from the scorpion venom can be used to develop highly potent antimicrobial, anticancer and many other effective drugs.

References

1 Veiga, A., Berger, M., Guimarães, J., Lonomia obliqua venom: pharmaco-toxicological effects and biotechnological perspectives. *Animal toxins: the state of the art. perspectives on health and biotechnology, 1st edn. UFMG, Belo Horizonte* **2009**, pp. 371-390.

2 Ruppert, E., Fox, R., Barnes, R., Invertebrate Zoology . Brooks/Cole. *CA, USA* **2004**.

3 Fet, V., Sissom, W. D., Lowe, G., Braunwalder, M. E., *Catalog of the scorpions of the world (1758-1998)*. New York Entomological Society: 2000.

4 Lourenco, W., The scorpion families and their geographical distribution. *Journal of Venomous Animals and Toxins.*, 7 (1)**(2001)** 03-23.

5 Chippaux, J.P., Goyffon, M., Epidemiology of scorpionism: a global appraisal. *Acta tropica.*,107 (2) (**2008)**71-79.

6 Gomes, A., Bhattacharjee, P., Mishra, R., Biswas, A. K., Dasgupta, S. C., Giri, B., Debnath, A., Gupta, S. D., Das, T., Gomes, A., Anticancer potential of animal venoms and toxins.**2010**.

7 Mebs, D., Scorpions and snakes, such as cobras, mambas and vipers made the African continent famous for venomous animals. *Bulletin de la Société de pathologie exotique (1990).*, 95 (3)(**2002)**131.

8 Gwee, M. C., Nirthanan, S., Khoo, H. E., Gopalakrishnakone, P., Kini, R. M., Cheah, L. S., Autonomic effects of some scorpion venoms and toxins. *Clinical and Experimental Pharmacology and Physiology.*, 29 (9) (**2002)** 795-801.

9 Lester, D., Lazarovici, P., Pelhate, M., Zlotkin, E., Purification, characterization and action of two insect toxins from the venom of the scorpion Buthotus judaicus. *Biochimica et Biophysica Acta (BBA)-Protein Structure and Molecular Enzymology.*,701 (3) (**1982)** 370-381.

10 Bücherl, W., Buckley, E. E., Deulofeu, V., *Venomous Animals and Their Venoms: Venomous Vertebrates*., Elsevier: 2013; Vol. 1.

11 Petricevich, V. L., Navarro, L. B., Possani, L. D., Therapeutic use of scorpion venom. *Mol. Aspects Inflamm.*,**2013**, pp. 209-231.

12 Goodenberger, M. L., Jenkins, R. B., Genetics of adult glioma. *Cancer genetics.*,205 (12) (**2012)** 613-621.

13 Deshane, J., Garner, C. C., Sontheimer, H., Chlorotoxin inhibits glioma cell invasion via matrix metalloproteinase-2. *Journal of Biological Chemistry.*,278 (6) (**2003)** 4135-4144.

14 Burmeister, A. R., Smith, J. J., Evolution across the Curriculum: Microbiology. *Journal of microbiology & biology education.*,17 (2) (**2016)** 252-60.

15 Cantas, L., Shah, S. Q. A., Cavaco, L. M., Manaia, C., Walsh, F., Popowska, M., Garelick, H., Bürgmann, H., Sørum, H., A brief multi-disciplinary review on antimicrobial resistance in medicine and its linkage to the global environmental microbiota. *Frontiers in Microbiology.*,(**2013)** 4.

16 Moerman, L., Bosteels, S., Noppe, W., Willems, J., Clynen, E., Schoofs, L., Thevissen, K., Tytgat, J., Van Eldere, J., Van Der Walt, J., Antibacterial and antifungal properties of α-helical, cationic peptides in the venom of scorpions from southern Africa. *European Journal of Biochemistry.*,269 (19) (**2002)** 4799-4810.

17 Bukharie, H. A., A review of community-acquired methicillin-resistant Staphylococcus aureus for primary care physicians. *Journal of Family and Community Medicine.*, 17 (3) (**2010)** 117.

18 JoanneM.Willey, L. M. S., Christopher J.Woolverton, *Prescott's MICROBIOLOGY*, Normal Microbiota of the Human Body, (McGraw-Hill: New York., America) 2011., Vol. 8th, pp. 732-734.

19 Zhao, Z., Ma, Y., Dai, C., Zhao, R., Li, S., Wu, Y., Cao, Z., Li, W., Imcroporin, a new cationic antimicrobial peptide from the venom of the scorpion Isometrus maculates. *Antimicrobial agents and chemotherapy.*,53 (8) (**2009)** 3472-3477.

20 Fisher, M. C., Henk, D. A., Briggs, C. J., Brownstein, J. S., Madoff, L. C., McCraw, S. L., Gurr, S. J., Emerging fungal threats to animal, plant and ecosystem health. *Nature.*, 484 (7393) (**2012)** 186-194.

21 Havlickova, B., Czaika, V. A., Friedrich, M., Epidemiological trends in skin mycoses worldwide. *Mycoses.*, 51 (s4) (**2008)** 2-15.

22 Sobel, J. D., Vulvovaginal candidosis. *The Lancet.*, 369 (9577) (**2007)** 1961-1971.

23 Takakura, N., Sato, Y., Ishibashi, H., Oshima, H., Uchida, K., Yamaguchi, H., Abe, S., A novel murine model of oral candidiasis with local symptoms characteristic of oral thrush. *Microbiology and immunology.*,47 (5) (**2003)** 321-326.

24 Fridkin, S. K., Jarvis, W. R., Epidemiology of nosocomial fungal infections. *Clinical microbiology reviews.*,9 (4) (**1996)** 499-511.

25 Brown, G. D., Denning, D. W., Gow, N. A., Levitz, S. M., Netea, M. G., White, T. C., Hidden killers: human fungal infections. *Science translational medicine.*,4 (165) (**2012)** 165rv13-165rv13.

26 Chandra, J., Kuhn, D. M., Mukherjee, P. K., Hoyer, L. L., McCormick, T., Ghannoum, M. A., Biofilm formation by the fungal pathogenCandida albicans: development, architecture, and drug resistance. *Journal of bacteriology.*,183 (18) (**2001)** 5385-5394.

27 HIV/AIDS, J. U. N. P. o., *Global report: UNAIDS report on the global AIDS epidemic. 2010*., UNAIDS: **2010**.

28 Chen, Y., Cao, L., Zhong, M., Zhang, Y., Han, C., Li, Q., Yang, J., Zhou, D., Shi, W., He, B., Anti-HIV-1 activity of a new scorpion venom peptide derivative Kn2-7. *PLoS One.*, 7 (4) (**2012)** e34947.

29 McMahon, B. J. In *Epidemiology and natural history of hepatitis B*, Seminars in Liver Disease, **(2004)** pp 3-8.

30 Zhao, Z., Hong, W., Zeng, Z., Wu, Y., Hu, K., Tian, X., Li, W., Cao, Z., Mucroporin-M1 inhibits hepatitis B virus replication by activating the MAPK pathway and down-regulating HNF4α in vitro and in vivo. *Journal of Biological Chemistry.*,(**2012)**, jbc. M112. 370312.

31 El-Serag, H. B., Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology.*, 142 (6) (2012) 1264-1273.e1.

32 Yan, R., Zhao, Z., He, Y., Wu, L., Cai, D., Hong, W., Wu, Y., Cao, Z., Zheng, C., Li, W., A new natural α-helical

peptide from the venom of the scorpion Heterometrus petersii kills HCV. *Peptides.*, 32 (1) (2011) 11-19.

33 Hong, W., Li, T., Song, Y., Zhang, R., Zeng, Z., Han, S., Zhang, X., Wu, Y., Li, W., Cao, Z., Inhibitory activity and mechanism of two scorpion venom peptides against herpes simplex virus type 1. *Antiviral research.*, 102 (2014) 1-10.

34 Zlotkin, E., Shulov, A. S., A simple device for collecting scorpion venom. *Toxicon.*,7 (4) (1969) 331-332.

35 Salameh, S., Sheth, U., Shukla, D., Early events in herpes simplex virus lifecycle with implications for an infection of lifetime. *The open virology journal.*,6 (**2012)** 1-6.

36 Gomes, A., Bhattacharjee, P., Mishra, R., Biswas, A. K., Dasgupta, S. C., Giri, B., Debnath, A., Gupta, S. D., Das, T., Anticancer potential of animal venoms and toxins. *Indian J Exp Biol.*, 48 (2) (2010) 93-103.

37 (a) Perumal Samy, R., Gopalakrishnakone, P., Thwin, M., Chow, T., Bow, H., Yap, E., Thong, T., Antibacterial activity of snake, scorpion and bee venoms: a comparison with purified venom phospholipase A2 enzymes. *Journal of applied microbiology.*, 102 (3) (2007) 650-659;(b) Stiles, B. G., Sexton, F. W., Weinstein, S. A., Antibacterial effects of different snake venoms: purification and characterization of antibacterial proteins from Pseudechis australis (Australian king brown or mulga snake) venom. *Toxicon.*, 29 (9) (1991) 1129-1141.

38 Zhang, Y. J., Wang, J. H., Lee, W. H., Wang, Q., Liu, H., Zheng, Y. T., Zhang, Y., Molecular characterization of Trimeresurus stejnegeri venom L-amino acid oxidase with potential anti-HIV activity. *Biochemical and biophysical research communications.*,309 (3) (2003) 598-604.

39 Gomes, V., Carvalho, A., Da Cunha, M., Keller, M., Bloch, C., Deolindo, P., Alves, E., Purification and characterization of a novel peptide with antifungal activity from Bothrops jararaca venom. *Toxicon.*,45 (7) (2005) 817-827.

40 Haeberli, S., Kuhn-Nentwig, L., Schaller, J., Nentwig, W., Characterisation of antibacterial activity of peptides isolated from the venom of the spider Cupiennius salei (Araneae: Ctenidae). *Toxicon.*,38 (3) (2000) 373-380.

41 Saez, N. J., Senff, S., Jensen, J. E., Er, S. Y., Herzig, V., Rash, L. D., King, G. F., Spider-venom peptides as therapeutics. *Toxins.*,2 (12) (2010) 2851-2871.

42 Heinen, T. E., da Veiga, A. B. G., Arthropod venoms and cancer. *Toxicon.*, 57 (4) (2011) 497-511.

43 (a) Cunha Filho, G. A., Schwartz, C. A., Resck, I. S., Murta, M. M., Lemos, S. S., Castro, M. S., Kyaw, C., Pires, O. R., Leite, J. R. S., Bloch, C., Antimicrobial activity of the bufadienolides marinobufagin and telocinobufagin isolated as major components from skin secretion of the toad Bufo rubescens. *Toxicon.*,45 (6) (2005) 777-782;(b) Goraya, J., Wang, Y., Li, Z., O'Flaherty, M., Knoop, F. C., Platz, J. E., Conlon, J. M., Peptides with antimicrobial activity from four different families isolated from the skins of the North American frogs Rana luteiventris, Rana berlandieri and Rana pipiens. *European Journal of Biochemistry.*, 267 (3) (2000) 894-900.

44 Gomes, A., Giri, B., Saha, A., Mishra, R., Dasgupta, S. C., Debnath, A., Gomes, A., Bioactive molecules from amphibian skin: Their biological activities with reference to therapeutic potentials for possible drug development. *Indian journal of experimental biology.*,45 (7) (2007) 579.