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Snake venom-a review

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SUMMARY

Snakes belong to class reptiles; only venomous snakes have venom in special gland and transferred through fangs. Venom mainly consists of proteins. Chemicals that have been identified in venom of the snakes are as; hyluronidases, phosphomonoesterase, thrombin acetylcholinesterase, arginine ester hydrolase, proteolytic enzymes, proteases, collagenase, phosphodiesterase, RNase, hyaluronidase, DNase, lactate dehydrogenase, phospholipase B, C, ADPase, cholinesterase, amino acid oxidase, adenosine triphosphatase, phospholipase A2 (A) 5'-Nucleotidase, peptide bradykinin potentiators, L-Amino acid oxidase, glycoproteins, biogenic amines, deoxyribonucleases, ribonucleases nucleotidases, lactate dehydrogenases, acidic, basic phosphatases, polypeptide toxins, phospholipases, nerve growth factor, phospholipase A2 (PLA2), fibrinogenolytic proteases and metalloproteases. Toxins in venom are different in species and even different in same species due to food and ecology. The venoms are mainly neurotoxic and haemotoxic. Snakes utilize venom to predigest, neutralize and weaken prey. According to WHO approximately 0.1 million people expire each year from venom of snake and 0.4 million wounded per year survive with eternal injuries. And, there is an increasing attention about snake venoms for medication. Parts of animals (i.e. musk gland, bone, scale, meat, musk gland, scale, fat) and plants (i.e. leaves, juice, methanolic extracts, extracts, seed extract, aqueous crude extracts essential oils and ethanolic extracts) species (i.e. *Moschus chrysogaster*, *Tinamus tao Suncus murinus*, *Moschus moschiferus*, snakes (serpentes), *Nothura boraquira*, *Laudakia agrorensis*, *Suncus murinus*, *Fagonia cretica, Planatus orientalis*, *Vitis vinifera*, *Morus alba*, *Mucuna pruriens*, *Dipteryx alata*, *Hibiscus aethiopicus Nectandra angustifolia*) in different countries (i.e. Nepal, Brazil, India, Bhutan, Ethiopia, Brazil, Pakistan, Nigeria, Yemen and Argentina) used to treat snake venom effects viz. hemorrhage, venom activities, myonecrosis, hemorrhaging edema, caseinolytic, edematogenic, procoagulant, hyaluronolytic, cytoprotective, coagulant and hemolytic.

Keywords: Venom, Snake, Enzyme, Protein, Ethnomedicine

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INTRODUCTION

Snake venom is produced in unique glands in the head and usually transferred through fangs (Mackessy, 2010). Venom of snake consists chiefly proteins (i.e. 70 to 90 percent, non-enzymatic and enzymes proteins) with little quantity of amino acids, biogenic amines, carbohydrates, metals, nucleotides, lipids as well as

peptides (Tu, 1977). Venom composition is different in each species and even different among the same species of snakes, while in common; the domination of protein families in venoms usually follows a wide classification tendency and is therefore partly predictable. The broad diversity of toxins of snake venom is because of their evolution mode, where food has played the main character in the snakes divergence (Daltry *et al.*, 1996).

Snakes utilize their venom to predigest and neutralize, and weaken prey. Many kinds of methods present (Fry *et al.*, 2006) like, effect the muscles by block the synapse that are present between nerve fiber and muscle cell, changes of function of the cardiovascular to cause circulatory collapse or tissue ischemia, predigestion of tissue through necrosis of cell. In fact snakebite envenoming reason of a ruthless human health problem in whole world, and also with a range of harsh medical emergencies, with highly deadly end.

Approximately 0.1 million people expire each year from venom of snake and 0.4 million wounded per year survive with eternal injuries (Gutiérrez *et al.*, 2017). While, there is an increasing attention in researching venoms of snake for medicinal uses. Snake venom is a combination of proteins (i.e. non-enzymatic and enzymes) comprising almost 95 percent of dry weight. And also consist of carbohydrates, lipids, inorganic anions and metal ions, These proteins have either non-enzymatic properties like proteinase inhibitors, natriuretic peptides, C-types lectins, three-finger toxins, and bradykinin-potentiating peptides or enzymatic activities for example metalloproteinase, phospholipase A2 (PLA2), serine proteinase, acetylcholinesterase (ACHE), L-amino-acidoxidase (LAAO), (Mackessy, 2010; Utkin, 2015). Venom of snake chemical composition is variable, basis on various aspects like snake stress, ontogeny, geographical distribution, diet and environmental circumstances (Amazonas *et al.*, 2019). Different researches have revealed that venom of snake component can cause a variety of biological effects on the systemic and local level. The local effect is shown by bursting, burning, or sore pain caused by cell death and local swelling. In worldwide, the venom can cause different effects such as cardiotoxicity, circulatory shock, coagulopathy, myotoxicity, nephrotoxicity and neurotoxicity (Mehta and Sashindran, 2002).

FANGS

Venomous snakes are present on all continents except Antarctica, and vary from few centimeters to nearly 6.1 meter long. All species of snakes have one of out of the following fang structure: Solenoglyphous snakes are present in viper family; this species consists of “true vipers” such as Gaboon vipers and pit vipers such as rattlesnakes. This fang is joined to the upper jaw, so they can be bent with the upper part of the jaw when not in use. This bending procedures permit vipers contain the longest fangs of all venomous snakes, with some attain size of two inches elongate. Proteroglyphous snakes are present in the elapid family that contains coral snakes, mambas, cobras and sea snakes. This kind of fang is attached to the upper jaw and cannot bent. Vipers’ fangs must be larger than elapid fangs. Opisthoglyphous snakes belong to the colubrid family that consists of various venomous and non-venomous species. Opisthoglyphous fangs are

situated at the back of the mouth comparatively the front, making envenomation an additional difficult charge. Many snakes are harmless to humans, but some like the boomslang, can be lethal (Stoneley, 2003; Shuter, 2015).

Snakes that contain venom in fact have the capability to control their venom, this mean they can a "dry bite" if these species want to. They use venom especially for food not for harm to other. While snakelets, they may have less accuracy in control of venom. Venom is basically a composite and distinctive mixture of saliva that comes from salivary glands in the head. Venom transfers through fangs to paralysis and eat prey (Pettit, 2019).

CHEMICAL COMPOSITION OF SNAKE

The elapines snakes have short front fangs and they are coral snakes, cobra, and mamba as well as they are neurotoxic (i.e. impact the respiratory system). Viperine have hollow, long and hinged fangs; they are true viper, strike and inject venom. Many bites by elapines apparently do not consequence in injection of considerable venom quantities. Viperines are necrotising (i.e. death of tissue), haemotoxic (i.e. blood toxins) and anticoagulant (i.e. stopping the blood clotting), while neurotoxic chemicals are also present in the some species venom like "Mojave rattlesnake". There are various types of enzymes present in venom of snake in whole the world, while each species has almost 6 to 12 types of enzymes in their venom. Chemicals that have been identified in venom of the snakes are following; hyluronidases, phosphomonoesterase, thrombin acetylcholinesterase, arginine ester hydrolase, proteolytic enzymes, proteases, collagenase, phosphodiesterase, RNase, hyaluronidase, DNase, lactate dehydrogenase, phospholipase B, Phospholipase C, L-Amino acid oxidase, ADPase., cholinesterase, amino acid oxidase, adenosine triphosphatase, phospholipase A2 (A) 5'-Nucleotidase, peptide bradykinin potentiators, glycoproteins, biogenic amines, deoxyribonucleases, ribonucleases nucleotidases, lactate dehydrogenases, acidic, basic phosphatases, polypeptide toxins, phospholipases, nerve growth factor, phospholipase A2 (PLA2), fibrinogenolytic proteases and metalloproteases (Stoneley, 2003).

Table 1: Venomous snakes in Pakistan.

Name of Species and family	**Distribution in Pakistan**	**Distribution in world**	**LD_{50}**	**References**
Russell's Viper (*Daboia russelii*) Viperidae	Punjab, Sindh and AJK	Southern Asia	2.3 mg/kg mice	(Khan, 2006; Thakur *et al.*, 2015)
Himalayan Pit Viper (*Gloydius himalayanus*) Viperidae	KPK, GB and AJK	Himalayan region of Pakistan, India and Nepal.	----	(Khan, 2006)
Saw Scaled Viper (*Echis Carinatus*) Viperidae	Punjab, KPK, Sindh, Balochistan	India, Pakistan, Afghanistan, Iran, Bangladesh, Sri Lanka, Oman, Turkmenistan,	8.3-0.9 (µg/18g mouse)	(Latifi, 1984; Khan, 2006)

		UAE, Uzbekistan and Tajikistan.		
Asian sand viper (*Eristicophis macmahoni*) Viperidae	Balochistan	Iran, Afghanistan and Pakistan border.	7.5 (mg/kg) mouse	(Khan, 2006; Rebmann, 2007; Masroor *et al.*, 2020)
Levant blunt-nosed viper (*Vipera lebetina obtusa*) Viperidae	Chitral, Waziristan, and Quetta	Turkey, Lebanon, Iraq, Syria, northern Jordan, Dagestan, Georgia, Iran, Azerbaijan, Afghanistan, and Pakistan.	12–18 (µg/18g mouse)	(Mallow *et al.*, 2003) (Latifi, 1984; Khan, 2004, 2006; Coşkun *et al.*, 2011; Kurtović *et al.*, 2014)
Persian horned viper (*Pseudocerastes persicus*) Viperidae	KPK	Iran, Pakistan, the United Arab Emirates, Afghanistan, Oman and Jordan	16.2-2.7 (µg/18g mouse)	(Latifi, 1984; Khan, 2006; Thomas, 2019)
Indian Krait (*Bungarus caeruleus*) Elapidae	Punjab, Sindh, KPK, Balochistan, AJK	Pakistan, India, Bangladesh, Sri Lanka, Afghanistan and Nepal	0.04 mg/kg of mice	(Khan, 2006; Al-Mamun *et al.*, 2015)
Indian or black cobra (*Naja naja*) Elapidae	Lower and upper and Indus Valley	India, Bangladesh, Pakistan, Nepal, Sri Lanka, and Bhutan	0.05 µg/g of mice	(Khan, 2006; Parveen *et al.*, 2017)
Central Asian or brown cobra (*Naja oxiana*) Elapidae	Balochistan, KPK, Punjab and Kashmir.	Uzbekistan, Kyrgyzstan, Tajikistan, Turkmenistan, Afghanistan, Pakistan, India, Iran, and Tajikistan	8.3-0.9 (µg/18g mouse)	(Latifi, 1984; Khan, 2006)

VENOMOUS SNAKE IN PAKISTAN

Russell's viper (*Daboia russelii*)

D. russelii is a vital species and generally scattered in whole Asia (Table 1). *Daboia russelii* venom contains combination of a variety of nontoxic and toxic components that obstruct with essential physiological processes such as fibrinolysis and coagulation. Most of these compounds are "metallo- or serine proteinases". Russell's viper venom highly consists of proteinases which is responsible for tissue hemorrhagic impacts, while, till date, not many proteinases have been documented from venom of *D. russelii*. Most significantly, new *D. russelii* venom proteinases can also be documented for their value in the development of therapeutic agents to study with life-threatening ailments (Thakur and Mukherjee, 2017).

Himalayan Pit Viper (*Gloydius himalayanus*)
G. himalayanus bit consequences in inflammation and pain which subsides within three days, leaving no hazardous effect on the wounded with not real need for cure (Wall, 1913, 1921; Acton, 1921). This snake is not documented as harmful and in Himalayan region it enjoys awe of the native societies (Dattatri, 1985; Gopalkrishnakone and Chou, 1990).

Saw Scaled Viper (*Echis Carinatus*)
In *Echis carinatus,* snaclecs and metalloproteases the most profuse "enzymatic" and "non-enzymatic" proteins are present in venom, while aspartic protease, aminopeptidase, defibrinogenation, glutaminyl cyclase, nerve growth factor, phospholipase B, and vascular endothelial growth factor are also documented (Patra *et al.*, 2017).

Asian sand viper (*Eristicophis macmahoni*)
Eristicophis macmahoni venom has been documented (Ali *et al.*, 1999; Alam and Ali, 2001) and consists of "disintegrin eristostatin". It attached to the platelet fibrinogen-receptor therefore a strong inhibitor of platelet aggregation. This little molecular weight amino acid has capability to reduce murine and human melanoma metastases in mouse model systems (Morris *et al.*, 1995; McLane *et al.*, 2001). Neurotoxicity is generally related with elapid bites, but is identified in various other viper species too (Beer and Putorti, 1998; Kularatne, 2003). Little studies are present about the most advantageous healing of bites of this species (Erwin and Emmanuel, 2005).

Levant blunt-nosed viper (*Vipera lebetina obtusa*)
This species venom has high potential (Warrell, 2010). Dry venom yield of "48 mg per snake" and intravenous LD_{50} of "12–18 μg per 18 g murine" weight of body have been documented (Latifi, 1984; Kurtović *et al.*, 2014). Envenomings of human by *Vipera lebetina obtusa* impact on function of kidneys, hemodynamic impacts, and ischemia (i.e. disturbance of blood supply) at the bite site (Sharma *et al.*, 2008). Acute kidney damage is not usual and if occurs, is cause of high tension, and addition of myoglobin, fibrin and hemoglobin in renal tubules causing "acute tubular necrosis" (Burdmann *et al.*, 1993). Though knowledge on the epidemiology of envenoming by Levant blunt-nosed viper across its supply is limited (Dehghani *et al.*, 2014; Zamani *et al.*, 2016; Pla *et al.*, 2020).

Persian horned viper (*Pseudocerastes persicus*)
The venoms impact was mainly restricted to the top of proteins contain molecular weight nearly 15,000. This peak also exposed phospholipase A_2 activity in venoms regarding 800 units/mg protein for Persian horned viper (Simon *et al.*, 1980). Persian horned viper showed strong hemorrhagic action (Ovadia, 1978), with the "hemorrhagic action" in the high molecular weight fraction. As predictable, the venom of Persian horned viper had acid oxidase and L-amino activity (Shaham and Bdolah, 1973; Bdolah, 1986).

Indian Krait (*Bungarus caeruleus*)

B. caeruleus is widely distributed in South Asia (Oh *et al.*, 2017). The three finger toxins and phospholipase, β-bungarotoxin and presynaptic neurotoxin were documented. The venom proteome compounds are linked with its "enzymatic activities", documented clinical manifestations and pharmacological characteristics of *B. caeruleus* envenomation (Patra *et al.*, 2019).

Indian cobra (*Naja naja*) and central Asian cobra (*Naja oxiana*)

Genus *Naja* (i.e. *Naja oxiana* and *Naja naja*) has Pakistani origin. The comparative assessment of the two venoms reported that Indian or black cobra contain highly complex venom proteome than central Asian cobra venom. Data showed the following proteins are present in venom, e.g. ankyrin, cobra serum albumin, deoxyribonuclease-2-alpha, N-terminal acetylation, insulin, leucine repeats, Ras-GTpase and zinc finger. The data can support the manufacture of definite anti-venoms and permit a good knowing of the envenomation of toxins supply (Manuwar *et al.*, 2020).

USES OF PARTS OF PLANTS AND ANIMALS TO TREAT VENOM EFFECT

Parts of animals (i.e. musk gland, bone, scale, meat, musk gland, scale, fat) and plants (i.e. leaves, juice, methanolic extracts, extracts, seed extract, aqueous crude extracts essential oils and ethanolic extracts) species (i.e. *Moschus chrysogaster*, *Tinamus tao Suncus murinus*, *Moschus moschiferus*, Snakes (Serpentes), *Nothura boraquira*, *Laudakia agrorensis*, *Suncus murinus*, *Fagonia cretica, Planatus orientalis*, *Vitis vinifera*, *Morus alba*, *Mucuna pruriens*, *Dipteryx alata*, *Hibiscus aethiopicus Nectandra angustifolia*) in different countries (i.e. Nepal, Brazil, India, Bhutan, Ethiopia, Brazil, Pakistan, Nigeria, Yemen and Argentina) used to treat snake venom effects viz. hemorrhage, venom activities, myonecrosis, hemorrhaging edema, caseinolytic, edematogenic, procoagulant, hyaluronolytic, cytoprotective, coagulant and hemolytic (Table 2).

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Table 2: Ethnomedicinal applications to treat venom.

Sr.	Species	Country	Part used	Snake venom	Treatment (s) of snake bite	References
1	Musk deer *Moschus chrysogaster*	Nepal	Musk gland, bone	All	Venom activities	(Lohani, 2011)
2	Grey Tinamou *Tinamus tao*	Brazil	Scale	All	Venom activities	(Barros *et al.*, 2012)
3	Asian house shrew *Suncus murinus*	India	Meat	All	Venom activities	(Vijayakumar *et al.*, 2015)
4	Siberian Musk Deer *Moschus moschiferus*	Bhutan	Musk gland	All	Venom activities	(Yeshi *et al.*, 2017)
5	Snakes (Serpentes)	Ethiopia	Scale	All	Venom activities	(Haileselasie, 2012)
6	White-bellied nothura *Nothura boraquira*	Brazil	------	All	Venom activities	(Bezerra *et al.*, 2013; dos Santos Soares *et al.*, 2018)
7	Black cobra *Naja naja*	Pakistan	Fat	All	Venom activities	(Altaf *et al.*, 2018)
8	Agror agama *Laudakia agrorensis*	Pakistan	Fat	All	Venom activities	(Altaf *et al.*, 2020)
9	House shrew *Suncus murinus*	Pakistan	Fat	All	Venom activities	(Altaf, 2016; Altaf *et al.*, 2017)
10	Khorasan thorn *Fagonia cretica*	Pakistan	Leaves	*Naja naja*	Hemorrhage	(Tahir Razi *et al.*, 2011)
11	Oriental plane tree *Planatus orientalis*	Pakistan	Juice	All	Venom activities	(Farooq *et al.*, 2019)
12	European wine grape *Vitis vinifera*	India	Methanolic extracts	*Daboia russelli*	Myonecrosis, Hemorrhaging and edema	(Mahadeswaraswamy *et al.*, 2009)
13	White mulberry *Morus alba*	India	Extracts	*Daboia russelli*	Caseinolytic, edematogenic, hemorrhagic, procoagulant and hyaluronolytic	(Chandrashekara *et al.*, 2009)

14	Cowitch *Mucuna pruriens*	Nigeria	Seed extract	*Naja* spp. and *Calloselasma rhodostoma*	Venom activities	(Fung *et al.*, 2009; Tan *et al.*, 2009; Scirè *et al.*, 2011)
15	Pea *Dipteryx alata*	Brazil	Extracts	*Bothrops jararacussu* and *Crotalus durissus*	Venom activities	(Nazato *et al.*, 2010; Puebla *et al.*, 2010)
16	Dwarf yellow hibiscus *Hibiscus aethiopicus*	Yemen	Aqueous crude extracts	*Naja n. nigricollis*	Cytoprotective and anti-hemorrhagic	(Hasson *et al.*, 2010)
17	Nectandra *Nectandra angustifolia*	Argentina	Essential oils and ethanolic extracts	*Bothrops neuwiedi*	Coagulant and hemolytic	(Torres *et al.*, 2011)

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