WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 14, 493-508. Review Article ISSN 2277– 7105

SNAKE BITE AND SNAKE VENOM – AN OVERVIEW

[1]*Megha K. S. and [2]Dr. Gopikrishna S.

[1]*Final Year PG Scholar, Department of Agad Tantra, VPSV Ayurveda College Kottakkal.

[2]Assosicate Professor, Department of Agad Tantra, VPSV Ayurveda College Kottakkal.

Article Received on
02 September 2022,
Revised on 23 Sept. 2022,
Accepted on 13 Oct. 2022
DOI: 10.20959/wjpr202214-25947

***Corresponding Author**
Megha K. S.
Final year PG Scholar,
Department of Agad Tantra,
VPSV Ayurveda College
Kottakkal.

ABSTRACT

WHO recognizes snake bite as top priority neglected tropical disease. Snake bite envenomation is an important public health issue mostly affecting those who live in rural area, in developing countries. India is estimated to have highest number of snakebite mortality in the world according to WHO with a frequency of 83,000 bites per annum with 11,000 deaths. The most of the envenomation was by Russell's Viper followed by Kraits and Cobras. The snake venom is highly modified saliva produced from specialized oral glands. It contains a complex mixture of several pharmacologically active biochemical substances.

KEYWORDS: snake venom, visha guna, Agad Tantra.

INTRODUCTION

Prevalence of Snake bite

WHO recognizes snake bite as top priority neglected tropical disease. Snake bite envenomation is an important public health issue mostly affecting those who live in rural area, in developing countries. The available records estimates that about 4.5 – 5.4 million peoples are bitten by snakes worldwide and among these 1.8 – 2.7 million peoples develop envenomation symptoms clinically owing to snakebite. The mortality rate accounts upto 81,000- 138,000.[1] Lowest mortality rate are seen in Europe, Australia and North America, and it is highest in sub-Saharan Africa, South Asia and South-East Asia. These are the places where most of the world's population lives, bringing them into direct conflict with snakes.[2] India is estimated to have highest number of snakebite mortality in the world according to WHO with a frequency of 83,000 bites per annum with 11,000 deaths. India recorded 1.2 million snakebite deaths in the 20 year period from 2000- 2019 with an average of 58,000 deaths caused annually. About 70% occurred in rural areas.[3]

The most of the envenomation was by Russell's Viper followed by Kraits and Cobras. Deaths mostly occurred in rural areas (97%) were males (59%) females (41%) and peak age group being 15 – 29 years. The highest rate in Uttar Pradesh (8700) followed by Andhra Pradesh and Bihar.[4] Thus, the average risk of an Indian dying from snakebite before age 70 is approximately 1 in 250, but in some areas, this risk approaches 1 in 100.

Snake bites are considered as a major health problem in North Kerala, among bites, Hump nosed pit viper cases are relatively more and the in effectiveness of the antivenom against its bite worsen the problem. In last 5 years, 24,186 snakebite incidents were recorded with 55 deaths according to data from the directorate of health services. Highest number of cases was reported from Kozhikode (1,125) followed by Kannur and Palakkad and least number of cases in Idukki. The cross sectional study conducted by Abin chandrakumar et, al showed incidence of Russel's viper being the highest in Malappuram district with higher cases noted among male gender working without protective measures in monsoon season.[5]

Snake Venom

The snake venom is highly modified saliva produced from specialized oral glands. It contains a complex mixture of several pharmacologically active biochemical substances, like enzymes, growth factors, activators as well as inhibitors which are mainly used to breakdown the food particles into soluble components. Venom stored in specialized venom glands delivered to target organism through modified teeth called fangs. The major function of venom is to immobilize the prey for capturing, to assist in digestion and to act as a defense mechanism against predators. Snake venom enzymes are also catalytically more active than their counterparts. In general they are more heat stable and more resistant to proteolysis due to the presence of additional disulfide bridges.[10] The normal temperature of human is the optimum temperature at which most of the snake venom enzymes are most active and therefore devastating.

The venom glands in Elapids and Viperids are present behind the eye and are surrounded by compressor muscles. Although sometimes considered as homologous to the parotid salivary glands of mammals, they have a different nerve supply and embryonic origin. According to species, these glands are of pear shaped, almond shaped or triangular. In vipers a special muscle, the compressor glandulae, helps squeeze the secretion from the glands. In case of elapids, the superficialis muscle has this function. Ducts carry the venom to the fangs. The connection between duct and fang is necessary which is somewhat loose and fangs are

regularly shed off and replaced. In case of elapid a glandular tissue encases the duct for most of its length and it comprises the accessory gland. Eventhough its function is not clear venom taken directly from main venom gland has reported to be less toxic than that normally expelled through accessory gland. They inject venom into the prey by fangs which are modified teeth. While in Elapids, the short fangs are mounted on a relatively fixed maxilla in front of the mouth, in Viperids the long fangs are mounted on a rotatable maxilla, facilitating flat folding against the roof of the mouth. A subfamily of vipers called the Crotalinae comprises of pit vipers. They have a special sense organ situated between the nostril and the eye to detect their warm-blooded prey. In humans, snakes usually inject venom subcutaneously or intramuscularly and the average dry weight of venom injected at a strike is approximately 60 mg (N. naja), 13 mg (E. carinatus) and 63 mg (D. russelii) respectively. Snake venom is a highly complex cocktail of proteins, peptides, non protein toxins, carbohydrates, lipids, amines and other molecules. The chemical composition of venom varies at all taxonomic levels. Further, composition can vary considerably between snakes in different geographical locations and individuals within those populations. The composition is also subject to change based on diet, age, season and environment. The widely differing manifestations of snake bite could be attributed to complexity of venom to some extent. The snake venom mainly contains proteins (>90%, dry weight). Among these protein, polypeptides and non - protein comprises of about approximately 90-95% of dry weight venom and at least 25 enzymes.[11] Besides bioactive substances, venom contains several inorganic cations such as sodium, calcium, potassium, magnesium, and small amounts of zinc, cobalt, nickel, manganese.[12] There is no single venom which contains all these compounds. Proteins and polypeptides are further classified into.

1) Enzymatic compounds (PLA2, SVMP,SVSP and L- aminoacid oxidases)
2) Non – enzymatic compounds (3FTXs,Kunitz peptides and Disintegrin)

Based on compositional importance the protein families were classified into five groups.

1) Dominant protein families : PLA2,SVMP,SVSP and 3FTx
2) Secondary protein families : KUN, CRiSP, LAAO, CTL,DIS and NP which make upto 11% and 22% of venom proteome of elapid and viper
3) Minor protein families: acetylcholinesterase, hyaluronidase, 5'nucleotidas, phosphodiesterase, phospholipase B, nerve growth factor, vascular endothelial growth factor and snake venom metalloprotease inhibitor
4) Rare protein families

5) Unique protein families: Defensins (crotalus), Walgerin (tropidolaemus), Maticotoxin (calliophis) and Cystatins (Bitis).these make upto 38% of the whole venom of a single.[13]

Table no: 1: List of common enzymatic contents found in Elapidae and Viperidae families.[14]

Enzymatic components	Mechanism of action	Examples of biological effects	Snake families
Phospholipase A_2 (PLA_2)	Hydrolyses the ester bond of phospholipids producing free fattyacid and lysophospholipid	Myotoxicity, pre snaptic neurotoxicity Edema formation Hypotension Anticoagulation	Elapidae Viperidae
Snake venom metalloproteases (SVMP)	Proteolysis	Contribute to haemorrhagic effects, inflammation and tissue necrosis	Major protein in viper family less abundant in elapid family
Serine proteases (SVSP)	Hydrolyses peptide bonds in pro- enzymes in the coagulation cascade, have kallikrein – like activity leading to release of bradykinin	Hypotension Haemostasis disruption	Almost all Viperidae uncommon in elapidae
L- aminoacid oxidases (LAAO)	Catalyses oxidative deamination of l-aminoacid	Platelet aggregation Induces cellular apoptosis	Elapidae and Viperidae
5- Nucleotidases	Hydrolyses phosphate monoester linked to 5'-position of DNA and RNA	Platelet aggregration inhibition	Elapidae and Viperidae
Acetylcholinesterases	Hydrolyses acetylcholine to choline	Termination of neurotransmission by acetylcholine	Elapidae
Hyaluronidase	Hydrolyse hyaluronan into oligosaccharides and N-acetylglucosamine	Spreading factor alters the structural and chemical properties of the extracellular matrix	Both elapidae and Viperidae

Table no. 2: List of common Non – enzymatic venom components of snakes of Elapidae and Viperidae families.[14]

Three – finger toxin (3FTx)	Inhibit postsynaptic nictonic acetylcholine receptors in neuromuscular junction and interfere with neuromuscular transmission. Cardiotoxins, L-type calcium channel blockage, inhibition of platelet aggregation	Post – synaptic neurotoxicity	Elapidae very rare in Viperidae
Kunitz peptides (KUN)	Inhibit serine protease, interfering with blood coagulation and fibrinolysis, ion channel blockade and inflammation	Haemostasis disruption	Elapidae and Viperidae
Cysteine rich secretory proteins (CRiSP)	Calcium channel blockade	Inhibit smooth muscle contraction	More abundant in Viperidae
C – type Lectins (CTL)	Inhibit / activate specific platelet membrane receptors or blood coagulation factors	Anticoagulation,promote or inhibit platelet aggregation	More abundant in Viperidae
Disintegrins (DIS)	Bind to glycoprotein 11b/11a activated platelet to prevent interaction with fibrinogen	Inhibit platelet aggregation	Viperidae, absent in Elapidae
Natriuretic peptides (NP)	Interaction between NPs and guanylyl cyclase receptors leads to an increase in cGMP levels and subsequent signaling cascade. NPs can also affect renin – angiotensin system by inhibiting angiotensin – converting system	Vasodilation, diuresis and natriuresis leading to hypotension and promote sodium and water excretion	Both Elapidae and more common and abundant in Viperidae

Pharmacokinetics

All venom components from injection sites will not be absorbed. The unabsorbed components of snake venom remains in the injection site and causes local tissue damage.

Phospholipases A2 (PLA 2)

They make upto 95 % of the total venom and were present in 98% of all species. Imparts neurotoxic and myotoxic effects of snake bite. These are classified into I & II and are major components in venom of Elapidae and Viperidae respectively. Although they both contain similar enzymatic properties they have undergone extensive gene duplication facilitating the evolution of new toxic functions. This compound have both local and systemic effect on vascular and nerve endings. It is a strong anticoagulant. Inhibits activation of FX into FXa. It also inhibits activation of prothrombin into thrombin by Prothrombinase complex. The anticoagulant activity of certain PLA2 enzymes is due to their interaction with blood coagulation proteins and not phospholipid hydrolysis. It is a presynaptic neurotoxin, damages the terminal axon, which prevents the release of acetylcholine causing paralysis. PLA2s exert myotoxic effects which often leads to severe necrosis and promote inflammation, cytokine

production and leucocyte recruitment, hyperalgesia, paralysis through block of neuromuscular transmission and produces hemorrhage by inhibiting coagulation. They produce neurotoxic effect via modulating pre synaptic terminals and nerve endings. The pre synaptic effects are produced due to β –neurotoxins and target the motor nerve terminals at neuromuscular junction promoting muscular paralysis.[15]

Snake Venom Metalloproteinases (SVMPs)

Major protein family in viper venoms, present in all of the viper species. The maximum amounts present were 72% for viperines (Echis ocellatus)and 85% for crotalines (Bothrops atrox). They are of lesser importance in elapids although they were present in 88% of species, they make upto smaller proportion of the venom. Zinc dependent proteinases which are major components of viper venom. Most of them are fibrinogenasis and they release peptides from C – terminal fibrinogen and causes physical destruction of fibrin clots by cleaving A alpha chain of fibrinogen since truncated fibrinogen does not form a strong fibrin clot (weakens soft clot formation) as natural fibrinogen does.[18] They extensively causes coagulopathy by synergistic action on multiple steps of the blood clotting cascade. They first cleave the basement membrane and adhesion proteins of endothelial cells to weaken the capillary. In second stage the endothelial detach from the basement membrane and became extremely thin making capillary extremely fragile. It produces depletion of pro coagulation factors, platelet aggregation inhibition and inflammatory activities. It also induces inflammation, including edema and pain by triggering hyperalgesia.[16]

Snake venom Serine proteinases (SVSP)

Least quantitatively important dominant protein group. They present in almost all viper venoms and only 29 % in elapids. It is well known for their ability to rupture capillary vessels, execute their primary toxicity by altering the hemostatic system of their victims by inducing edema and hyperalgesia. Among them only protein C activator exhibit direct anticoagulant effects. Causes inactivation of co factors FVa & FVIIIa degradation and directly activate protein C. Another one thrombin like enzymes which causes fibrinogen depletion in plasma. Type II TLE – thrombin like enzymes deplete the fibrinogen which is commonly seen in pit viper, true viper, colubrid families. They act on blood plasma and induce friable and translucent clots, presumably due to cross linking of fibrin by F XIII a and degrades it. Flavoxobin, a TLE seen in Habu snake activates complement C3 protein and act as C3 convertase which is a defibrinogenating agent.[17] Hemotoxic effects include

fibrinolysis, platelet aggregation and blood pressure. it activate multiple coagulation factors, including prothrombin and factors V VII and X. Platelet – aggregating SVSPs will activate the platelet – receptors to promote binding to fibrinogen and clot formation. These pro coagulant and platelet – aggregating activities will lead to the rapid consumption of key factors in the coagulation cascade and clot formation. Fibrinolytic SVSPs play an important role in the elimination of blood clots by acting as thrombin – like enzymes or plasminogen activators, which eliminates the fibrin in the clots and contribute significantly to the establishment of the coagulopathy.

Three – Finger Toxins

Non – enzymatic neurotoxins present only in venom of elapid and colubrid snakes They make upto 95% of the by binding post synaptically at the neuromuscular junctions to induce flaccid paralysis in snakebite victim.[18]

Hyaluronidase

Primarily causes local tissue destruction which can lead to localized edema, blistering and tissue necrosis. Hyaluronic acid prime function is to resist foreign matter penetration and this resistance is broken down by the enzyme under the influence of hyaluronidase. It helps preparing the ground for the spreading of toxic factors.

Nucleases

Deoxyribonuclease and Ribonuclease in snake venoms are capable of hydrolyzing phosphor diester bonds in DNA and RNA. The Indian cobra has the highest RNA – ase activity and they are a rich source of phosphodiesterase. The activity of these enzymes supplements the hydrolyzing activity of other enzymes in the venom.[19]

Ophio – Amino acid Oxidase

It can activate proteases and peptides bound up in cells. It hastens autolysis and putrification in Viper venom.[19]

Secondary proteins[20]

Kunitz peptide

This protein family is entirely absent in crotalines and in viperines it is commonly found among Bitis, Macrovipera and Daboia genera.

L- Aminoacid oxidases

They were of relatively equal importance in elapids and viperines. Catalyses oxidative deamination of number of L- Aminoacids and generates H_2O_2. Affects the intrinsic pathway by selectively inhibiting F IX activity.

Cysteine – rich secretory proteins

Widespread across all families, but more common in viper than elapids.

Non – enzymatic Anticoagulant Proteins

C- type lectins

These were only a minor component of elapid venom but present in 100% of viperine venoms. They are integral part of pro – coagulant proteins, FX activator. Inhibits the formation of coagulation complexes. It interfers the binding of FIX & FX to phospholipids.

Bothrojaracin & Bothroalternin

Inhibits thrombin – induced platelet aggregation

3FTX s acting on extrinsic pathway of clotting cascade mechanism also belongs to non – enzymatic anticoagulant proteins.

Major inter – family differences

3FTXs and PLA2 is predominant in Elapid snakes while PLA2, SVMP, SVSP are most common in Viper and 3FTX is absent in Viper. More than 90% of venoms of elapid and viper family contents 10 protein families. Four of them of dominant families (PLA2, SVMP, SVSP & 3FTX) six of them are secondary protein families (cysteine rich secretory proteins, LAAO, KUN, DIS, C-type lectins and natriuretic peptides).

The major differences between elapid and viper venom is the presence of 3FTx in elapid venoms and its absence in viper venom. Viper venoms are dominated by SVMP, SVSP and PLA2. These proteins makes upto an average of 83% and 67% of the venom proteome of elapids and vipers. Elapid venoms were also less diverse in the range or number of protein families, largely consisting of PLA2 and 3FTx. But in case of viper venom variability in the amount of different protein families between different groups of vipers was less than for elapids. Kraits are dominated by PLA2 making upto almost half the venom with less 3FTxs, however they contain larger amounts of secondary protein families – KUNs, LAAOs and CRiSPs compared to other elapid groups. The venom of cobra species are dominated by 3

FTxs with less PLA2 , a similar dichotomy between cobra and krait in proportion of PLA2s and 3FTxs. Cobra lack many of the secondary protein families, except for CRiSPs, which are present in relatively large amounts. Viperine and crotaline venoms were similar being composed mainly of 3 dominant protein families: PLA2s, SVMPs and SVSPs. The major difference between the subfamilies is that KUNs were absent in crotalines and present in viperines. Crotalines possess glutaminyl cyclases and defensins wheras cystatins were only found in viperine genus.[21]

Common Krait[22]

Bungarus caerulus is one among the big four group, causing 10,000 fatalities per year in India alone. The mortality rate will reach upto 70 – 80% when proper treatment is unavailable. This comes in Elapidae family having 13 species and 5 subspecies. Envenomation results in severe abdominal cramps, progressive descending flaccid paralysis due to involvement of diaphragm leading to death. Systemic symptoms and abdominal pain are distinctive features, along with hypokalemia. Death usually occurs within 4 – 8 hours after the bite. The bite usually occurs at night hours and they are painless. So many cases remain unnoticed, continues sleep and delays the medical treatment.[3] Death is due to respiratory failure and suffocation. This effect is produced by potent pre synaptic neurotoxin β – Bungarotoxin with PLA_2 which affects the nerve endings near the synaptic cleft inducing muscular paralysis by preventing release of acetylcholine at neuromuscular junctions.[1] Pre synaptic action cannot be reversed and hence developed paralysis is irreversible with antivenom treatment Krait venom contains both pre synaptic (β -Bungarotoxin) and post synaptic neurotoxins (α - Bungarotoxin). Pre synaptic neurotoxins are more important in human envenomation. They causes destruction of motor nerve endings by depleting synaptic vesicles. A group of toxins β 1 - β 5 – caerulotoxins, similar to β - Bungarotoxin, responsible for paralysis in common krait bites. Krait venom has fatal dose of 6 mg with an average deliverable dose of 20 mg.

Cobra venom

The venom mainly consist of three types of proteins: cardiotoxin, neurotoxin and phospholipase A2. Members of cardiotoxin and neurotoxin groups are homologus (50% aminoacid in their aminoacid sequences) but exhibit divergent pharmacological effect. Venom contains post synaptic neurotoxins that spread rapidly in its victim's blood stream, causing respiratory failure and death. It prohibit the interaction of acetylcholine molecules but cardiotoxins show no defined cellular targets. Its effects include lethal toxicity,

hemolysis, muscle contracture and activation of tissue phospholipase C. cardiotoxins are considered as direct lytic factors since it causes membrane depolarization and cytolysis in many tissues. They also prevent platelet aggregation and inhibition of Na+ and K+ ATP ase and protein kinase C. Cardiotoxin induced Ca2+ influx causes cell injury resulting in ischemia and releases large amount of catecholamines.[23] Venom disrupts the neuromuscular junctions involved in human respiration by reacting with receptor sites in the place of the acetylcholine molecules, thus blocking the receptor sites. Unlike Ach molecule venom molecule will not immediately react with alcohol group of receptor site and therefore it will not break down and site will be open draining out the electrical impulses. When the impulse is drained out, muscle fiber does not receive sufficient stimulation. Only 1/3 rd of the receptor site in the diaphragm need to be blocked for cessation of muscle function. In such cases victim usually dies within 30 minutes.[24]

PLA2 catalyses the hydrolysis of phospholipids and produces free fatty acid and lysophospholipid causing severe inflammation and necrosis of affected tissue. This is due to the synergistic action of cardiotoxin and PLA2. Selective interaction of cardiotoxins and PLA2 with glycosaminoglycans results in cardiotoxicity and inflammatory changes. Cobra can deliver 60 mg of venom in single bite, which is five times that of fatal dose.[1] Besides these cardiotoxins and neurotoxins hemotoxic contents are also identified in cobra venom.

Venom of king cobra is almost similar to that of cobra. A unique protein toxin found in venom has cardiotoxic and hemorrhagic characteristic with a fatal dose of about 12 mg.[23]

Viper venom

Viper and crotaline venom are similar being composed mainly of three dominant protein families. PLA_2s, SVMPs and SVSPs. The major difference between the two subfamilies was that KUNs were present in viperines and absent in crotalines. Crotalines possess glutaminyl cyclases which were absent in viperine venom.[25]

Russell's viper: venom causes local and hemotoxic manifestation with distinctive blister formation on the affected limb. Hematuria, renal failure, hyper edema, hemorrhage and anemia are other typical features in Russell's viper envenomation.[26] This snake has a fatal dose of 15 mg and the average delivering dose of about 63mg.[23]

Saw scaled viper: constitutes 80% of total venomous bites in some geographical areas. Ecchymosis, rise in CT/BT, hematological complications, local pain and edema are symptoms.[27] The average bite may yield about 40 mg of venom.[23]

Bamboo pit viper: it has fatal dose of 100mg but bites are never alarmingly toxic and no mortality ever reported. However $PLA_2$is one of the major component and shows moderate anti- platelet activities, edema, mild anti coagulating and myotoxicity resulting in local swelling, dizziness and morbidity.[28]

Ayurvedic view: *Visha*

The word *visha* is originated from the *dhatu* '*visl*' meaning '*vyapane'* (spreading) and '*viprayoge*' (separating). It denotes that *visha* spreads in the body easily. The word *visha* is defined as that which causing depression – '*vishadam janayatha ithi'* this is stated in mythological origin of *visha.*

Visha gunas

Acharya Susrutha, has mentioned 10 *gunas* instead of mentioning taste he included *apaki guna* whereas *Acharya Charaka* has included *anirdesya rasa* instead of *apaki guna*. *Acharya Vagbhata* enumerated 11 *gunas* included *apaki guna* and considered taste as *avyakata rasa*. *Sarangdahara Acharya* mentioned 8 *gunas* of *visha* as: *Chedi, Agneya, Madavaham, Jeevithaharam, Yogavahi, Sukshma, Vyavayi and Vikasi.*

Table. 3*:Visha guna* – an overview as per different *Acharyas.*

Visha guna	*Charaka*[29]	*Susrutha*[30]	*Vagbhata*[31]
Ruksha	√	√	√
Teekshna	√	√	√
Ushna	√	√	√
Sukshma	√	√	√
Aasukari	√	√	√
Vyavayi	√	√	√
Vikasi	√	√	√
Visada	√	√	√
Laghu	√	√	√
Apaki	*X*	*X*	√
Anirdesya rasa	√	*X*	*Avyakta rasa*

Among these 10 qualities *laghu, sookshma, vyavayi, asu* denotes immediate and easiest spreading of venom into tissues. the *gunas* like *ruksha, teekshna, vikasi, ushna* shows the physical action of *visha*. Venom having all these 10 *gunas* and considered as aggravating and deranging all the *doshas* of the body. The distinct qualities of *visha* are opposite to that of ojus which leads to sudden death. Among the 3 types of *ojovyapath* explained by *Susrutha Acharya* in case of *visha ojokshaya* will occur first then affecting *doshas* and *dhatus*.

Pharmacokinetic action of *visha*

Table 4: Action of *visha* with respect to *gunas* described in various texts.

Visha guna	*Susrutha samhita*[30]	*Charaka samhita*[29]	*Astanga sangraha*[31]
Ruksha	*Vayu prakopa*	*Vatha kopa*	*Vatha kopa*
Ushna	*Pitha rakta kopa*	*Pitha prakopa*	*Pitharakta prakopa*
Teekshna	*Mathim mohayati Sandhi bandhan chinathi*	*Marmaghna*	*Pitharakta prakopa*
Sukshma	*Sareeravayava pravishya vikaroti*	*Asrik prakopayathi*	*Dosha dhatu malam and sareeravayava anupravishyati*
Aasukari	*Asu hanti*	*Seeghram vyapnoti*	*Asu vyaptheyati*
Vyavayi	*Prakrithim bhajathi*	*Kevalam deham vyapnoti*	*Sareera avayavan vyapnoti*
Vikasi	*Dosha dhatu malam kshapayathi*	*Pranagham*	*Marma chedena mathim mohayati*
Visada	*Athiricheda*	*Asakthagathi dosham*	*Asaktha vegan prasarathi*
Laghu	*Duschikitsam*	*durupakramam*	*Durniharam*
Apaki	*Durharam, chiram klasayathi*	*Jara no yathi*	
Anirdesya rasa/ avyaktha rasa		*Kapham prakopayathi*	*Sleshamakopana annarasam sarvan anuvarthethe*

By the *ruksha guna* it provokes *vata dosha* and *ushna guna* provokes the *pitha dosha*. Vitiation of *pitha rakta kopa* causes bleeding and is due to specific anticoagulant non enzymatic and enzymatic components found in venom. *Sookshma guna* responsible for passage of *visha* through minute channels in the body. Disruption of cellular permeability by PLA_{2s} and several cytotoxins actions are implicated in this *guna*.By this *guna visha* reaches the intercellular spaces suddenly and act upon them. By its *anirdesya rasa/ avyakta rasa* it provokes *kapha dosha* and spreads quickly in the body's nutrient fluid. *Vyavayi guna* enables the quick spreading in the entire body. This quality which helps the spreading of the venom can be equated to specific component Hyaluronidases by which cellular selective

permeability is disrupted and allows anything to cross through it. *Teekshna guna* causes injures the vital organs and by *vikasi guna* it destroys life. It becomes difficult to treat owing to *laghu guna* and spreading cannot be stopped due to *visada guna*. Thus *rakta* undergoes vitiation due to *teekshna guna* of *visha* and occludes the circulatory channels and kills the man. Thus by giving description about *visha guna Acharya* have explained the pharmacokinetic action played by each *guna* inside the body.

Samprapti

Visha first affects *rakta dhatu* , After entering into blood *visha* spreads all over the body and reaches heart. Then vitiates *kapha pitta* and *vata dosha* along with its *asaya* and reaches *hridaya* and causes death. Here the fatality is mainly due to heart failure and respiratory failure. It is due to the obstruction of various *srotas* especially *pranavaha srotas* leading to respiratory difficulties and *samnjavaha srotas* leading to unconsciousness.

Variations in poison

Composition of venom depends upon emotions of snake (severity of venom / converting factors) *ksheena, ratipluta nakulanirjaritha* etc indicates physical and mental health status of snake and studies have proven highest concentration of venom in summer season but in *Ayurvedic t*exts it is said to be higher in *varsha rtu* since snakes are easily disturbed during this time and also influences the venom delivery system and components of venom. In *vimukta visha kanjuka* it is said poison is reduced and number of bites is very low. But while examining concentration of venom will be very high but avoids the situation for biting. Studies suggested evidences for geographical variations is content of venom. Hybrid varieties (*vaikranja*) descriptions are also seen extensively in all texts. Symptoms of such snakebite will be mixed up according to *dosha* predominance.

Reasons for Biting

A snake bites, while in search of food, when frightened for self protection, trodded upon, due to increased poison, anger, *papavrithi, devarishi yama chodana* etc. that means snake itself determines how much quantity of venom should be possibly injected in these conditions.

Envenomation occurring in *shmasana, devalaya* etc are considered as difficult to treat since snake in rigid or constrained places if there are no chances for escaping it will use whole of its strength to bite and other contributing factor is that it takes more time to get a medical aid from these places. *Nakshathra* and *tidhi* based prognosis are explained in detail and

observational studies have concluded morbidity rate, severity of envenomation and number of vials required for treatment increases on particular *desha, nakshatara, vaara, tidhi and paksha.*[32]

The detailed descriptions of snakes, their habitat, mental status etc in ayurvedic classics were found to be highly relevant in quantifying the venom in emergency room.

REFERENCES

1. Kasturbine Kasturiratne A, Wickremasinghe AR, de Silva N, Gunawardena NK, Pathmeswaran A, Premaratna R, Savioli L, Lalloo DG, de Silva HJ. Estimation of the global burden of snakebite. PLoS Med, 2008; 5: e218.
2. Chippaux JP. Estimate of the burden of snakebites in sub- Saharan Africa: a meta- analytic approach. Toxicon, 2011; 57: 586–99.
3. Suraweera W, Warrell D, Whitaker R, Menon G, et, al. Trends in snakebite deaths in India from 2000 to 2019 in a nationally representative mortality study. eLife 2020 Jul 7; doi 10.7554/eLife.54076.
4. Mohanpatra B, Warrell DA, Suraweera W, et, al Snakebite mortality in India: a nationally representative mortality survey. PLoS Negl Trop Dis, 2011 Apr 12; 5(4): e1018.
5. Chandrakumar A, Suriyaprakash TN, mohan PL, Thomas L, Vikas PV. Evaluation of demographicand clinical profile of snakebite casualities presented at a tertiary care hospital in Kerala. Clnical epidemiology and global health, 2016 Sep 1; 4(3): 140-5.
6. Gupta YK, Peshin SS (2014) Snake Bite in India: Current Scenario of an Old Problem. J Clin Toxicol 4: 1000182. doi: 10.4172/2161-0495.1000182 Page 2 of 9 J Clin Toxicol ISSN:2161-0495.
7. Cribari chris, Management of Poisonous snake bites. American college of Surgeons committee on Trauma subcommittee on publications, 2004 Jun; 1-4.
8. Williams SS, Wijesinghe CA, Jayamanne SF, Buckley NA, Dawson AH, Lalloo DG, de Silva HJ. Delayed psychological morbidity associated with snakebite envenoming. PLoS Negl Trop Dis, 2011; 5: e1255.
9. Bhattacharya Saptarshi, K rishnamurthy Aiswaraya, Gopalakrishnan Maya, et, al. Endocrine and metabolic manifestations of snakebite envenoming. The American Journal of Tropical Medicine and Hygiene, 2020 Oct 7; 103: 1388-1396.
10. Gutiérrez JM, Theakston RD, Warrell DA. Confronting the neglected problem of snake bite envenoming: the need for a global partnership. PLoS Med, 2006; 3: e150.

11. Chippaux JP. Estimating the global burden of snakebite can help to improve management. PLoS Med, 2008; 5: e221.
12. Hazra A. Poisonous snake bites in India. Community Dev. Med. Unit Ration. Drug. Bull, 2003; 30: 1-12.
13. Ferraz RC, Arrahman A, Chunfangxie et,al. Multifunctional toxins in snake venom and therapeutic implications : from pain to hemorrhage and necrosis. Frontiers in Ecology and chemical evolution ecology, 2019; Jun 1.
14. Sanhajariya S, Duffull SB, Isbister GK. Pharmacokinetics of snake venom. Toxins, 2018 feb; 10(2): 73.
15. Chakraborty AK, Hall RH, Ghose AC. Purification and characterization of potent hemolytic toxin with phosphilapse A2 activity from the venom of Indian Russell's viper *MOL.cell. biochem*, 2002; 237: 95–102.
16. Arias A.S, Rucavado A, Gutierrez J.M. Peptidomimetic hydroxamate metalloproteinase inhibitors abrogate local and systemic toxicity induced by Echis ocellatus snake veno. Toxicon, 132: 40-49.
17. Juliana L, Bernardoni, Leijiane F, et, al. Functional variability of snake venom metalloproteases: Adaptive advantages in targeting different prey and implications for human envenomation. PLOS ONE. 2014; 9(10): e109651.
18. Susanta Pahari, David Bickford, R manjunatha Kini et, al. Expression of three finger toxin and phospholipase A2 genes in the venom glands of two sea snakes, Lapemis curtus and Acalyptophis peronei: comparison of evolution of these toxins in land snakes, sea kraits and sea snakes. BMC Evolutionary Biology, 2007; sep 27 175.
19. Sreekrishnan C.M. Dr. et. Al- (1985), A clinical and experimental study on Darweekara visha with special reference to Swetarka (Calotropis procera).
20. Barber CM, Isbister GK, Hodgon WC. Alpha neurotoxins. Toxicon, 2013 Jan 1 47-58.
21. Joshua L, Bottrall, Frank Madras, et, al. Proteolytic activity of Elapid and Viperid snake venoms and its implications in digestion. Journal of venom Research, 2010; sep 30 1: 18- 28.
22. AL- Mamun MA, Rahman MA, Hasan R, Rahmann Z, Haque KMF. Histopathological alterations induced by Common Krait Bungarus caeruleus venom on hepatic, renal and cardiac tissues of albino mice. International journal of Pharmacy and Pharmaceutical Sciences, 2015 Nov; 18(7).
23. Gomes A, DE P, Dasgupta SC. Occurrence of a unique protein toxin from the Indian King Cobra (Ophiophagus hannanh) venom. Toxicon, 2001; 39: 363–70.

24. Dubovskii PV, Utkin YN. Cobra cytotoxins: Structural organization and antibacterial activity. Actanaturae, 2014 Jul-sep; 6(3): 11-18.
25. Seneviratne U, Dissanayake S neurological manifestation of snakebite in Srilanka journal of post graduate medicines, 2002; 48(4): 275-8.
26. World health organization. Regional office for South – East Asia. Management of snake bites in South East Asia. The clinical management of snake bites in the southeast Region Asia (serial online), 2003; (cited 2005 may 04).
27. Lakhotia M, Kothari D, Chaudary DR, Sharma S, Jain P. A case of saw scale viper snakebite presenting as pleuro- pericardial haemorrage. *J. indian. Acad. Clin. Med*, 2002; 3: 392-4.
28. Tsai IH, Wang YM, Chen YH, Tsai TS., TU MC. Venom phospholipases A2 of bamboo viper: molecular characterization, geographic variations and evidence of multiple ancestries. *Biochem. J*., 2004; 377: 215-23.
29. Charaka – (2004), Charaka Samhita, English translation by R.K.Sharma and Bhagwan Dash, published by – Chowkhamba Sanskrit series, Varanasi.
30. Susrutha (2005), Susrutha Samhita with English translation of text and dalhana commentary – vol III, 3rd edition, Chaukambha Visvabharati, Oriental Publishers and Distributors.
31. Vagbhata (1991) Astanga Samgraha – Comm. Indu Sasilekha vyakhya, pub. Central Council for Research in Ayurveda and Siddha, New Delhi.
32. Manjusha menon et, al (2008) An analytical study on mortality in snake bite with reference to *Damsha sthana, Desha, Vaara, Tithi, Nakshatra and Paksha.*