Volume 9, Issue 7, July – 2024 International Journal of Innovative Science and Research Technology
ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL1170

Snake Venom : A Bioactive Cocktail and its Therapautic use

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Abstract:- From ancient time whenever we face any problem, we came to nature for the solution. Our nature is self renewable, she has solution for every problem, but we have to find the right path to respond more quickly. This review is regarding chemical nature of snake venom and about different life saving drugs extracted from snake venom. Venoms were originated from non poisonous proteins, and with subsequent generations under evolution these proteins become mutated and modified multiple times to develop deadly poison. With every modification venom becomes enriched with new diverse group of compounds. Main constituents of venom is hydrolyses, PLA2, phosphodiesterases, serine proteases and metalloproteases. Snakes use their venom to paralyzed their prey and to digest food, but these components can be used to treat various life threatening disease. Cobra, krait and rattle snakes are most poisionous snakes and their venom contains different enzymes, are classified as neurotoxic, haemotoxic and cytotoxic in nature and these have different impact upon exposure to animal. Neurotoxic venom destroy nervous system, haemotoxic venom leads to the destruction of red blood cells and also interfere with blood clotting factors, whereas cytotoxic venom can cause necrosis and apoptosis. With the discovary of modern techniques, isolation of different proteins and peptides and analysis of their nature are become easier. Most widely used drugs extracted from snake venom are Tirofiban, Eptifibatide, Captopril, enalapril, cobratide and batroxobin ete. The source of tirofiban, captopril, enalapril batroxobin is the venom of different viper species. On the other hand, eptifibatide is extracted from rattle snake and cobratide is from Chinese cobra .

I. INTRODUCTION

Snakes, one of the deadliest creation of nature.This limbless reptile contains over 6500 species. They are thought to be evolved in cretaceous period from burrowing lizards. During their course of evolution few order of snake remain non venomous and few acquired venom that undergo tremendous diversification among different snake species. Aspididae, Elapidae, Viperidae and hydrophidae are the family of venomous snake. Venom is produced form the poison gland, which is a modified salivary gland and often associated with various kinds of stings, fangs or spines. Different venoms contain different combinations of proteins, peptides and enzymes depending on snake's habitat, food as well as their age and other biochemical factors. Snakes posses special immune cells in their body to neutralize their own venom, therefore, if a poisonous snake is bitten by another poisonous snake of the same species, there will be no affect. But, if it is bitten by a poisonous snake of different species it could be die. During biting they can control the amount of injected venom on the basis of their aggressiveness. Generally snake uses their venom to immobilize or predigest their prey, but sometimes they use it in defense response also. They inject their venom during bite with the help of their hollow teeth (fangs) although some snake species can also spit venom to the victim. Snake venom can be neurotoxic, hemotoxic and cytotoxic in nature. Many components from snake venom are used in therapy of asthma, heart attack, kidney disease, brain injuries, Parkinson's and Alzheimer's disease including various painful disorders and chemotherapy.

➢ *Objectives:*

- To discus about venomous and non venomous snake.
- To focus on the composition of snake venom.
- To study the mechanism of action of different kinds of snake venom.
- To analyze the role of snake venom in life saving therapy.

➢ *Weapon of Venomous & Nonvenomous Snake* :

Like other animals, snakes are more afraid of us than we do. In most cases they bite for self defense when they feel threatened. Some non venomous snake like python and anacondas use their enormous strength while cobra, krait and viper use deadliest poison as weapon in danger or to immobilize their victim. Sometimes biting a prey can cause injury to them which include breaking of teeth although they can regenerate their teeth including poison gland and duct .The teeth of non venomous snake is long and sharp but venomous snake posses a syringe like fangs that have groove in middle to deliver poison to their biting area. Besides differences in fangs venomous and non venomous snakes differ in their appearance also. Non venomous snakes have narrow, oval shaped head, thin body and a long tail that gradually tappers to a pointed end. On the other hand, venomous snakes have broad, triangular head, fatty body and a tail that suddenly tappers to a blunt end ,in adult stage few posses rattle(rattle snake). Often some non venomous snake uses the coloration of venomous snake as their survival weapon, known as batesian mimicry. By such mimicry they are pretend to be venomous and rejected by their predator. One example of this is the mimicry of harmless scarlet king snakes with the deadly venomous coral snake, The non venomous rat snake inflate its head and

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also make a hissing sound as warning signal like dangerous Indian cobra. By such techniques both types of snakes sometimes kill their victim and sometimes warn them to be aware.

➢ *Composition of Snake Venom :*

Biting of non venomous snake does not causes much injury to the victim but care should be taken to prevent any kind of infections as their teeth may contain several bacteria. On the other hand biting of venomous snake can produce immediate localized pain, swelling, convulsion and even paralysis of the affected part. Snake venom is a cocktail of different types of proteins & polypeptides including amino acids, nucleic acid, carbohydrates, lipids that play a major role in effective toxicity. Different percentage of enzymes present on various types of snake, ranging from 70-95% of viperid to 30-75% of elapid venoms. These include hydrolases phosphodiesterases, that interfere with cardiac system of the victim, thrombin like coagulant, causing clots in the circulatory system, metalloproteinase and serine proteases that causes internal bleeding by vascular endothelial destruction. Some polypeptide toxins include postsynaptic neurotoxins which bind to acetylcholine receptors at neuromuscular junctions and block muscular transmission. Another important constituent of this types of venom is phospholipase A2 (PLA2s) and three –finger toxins (3FTxs) ,although the mode of action and amount of PLA2 and 3FTxs in different species differ despite of their sequence identity. The African black mamba (*Dendroaspis polylepis)* and the Eastern green mamba (*Dendroaspis angusticeps),*show a diversity of venom composition as their venom is devoid of PLA2 and contain mostly Kunitz -type peptides and 3FTxs.

➢ *Types of Snake Venom :*

Depending on the mode of action snake venom can be classified into following categories. These are :

➢ *Neurotoxic Venom :*

Neurotoxic venom affect brain and nervous system by blocking the transmission of nerve impulses to various muscles, that includes the diaphragm muscle, facial muscles etc. Thus, snake bite with neurotoxic venom can cause immediate shortness of breath, diplopia and drooping eyelid, inability to speak or swallow and involuntary tremor of facial muscle .Venom of cobra and krait are neurotoxic in nature and bite with a certain quantity of venom can cause death within 30 minutes due to paralysis of heart and lungs.

➢ *Hemotoxic Venom :*

Hemotoxic venom destroy red blood cells , interact with the blood clotting factors including platelets of blood and causes clotting within 60 seconds. On the other hand, venom composition of some snakes appear to have anticoagulant properties and work by preventing the formation of prothrombinase complex on activated platelets. Haemostatic disruption or a said to be very painful and takes longer time than neurotoxic venom to cause death of the victim. Russell's viper and various pit viper species have haemotoxic venom.

➢ *Cytotoxic Venom :*

Cytotoxicity refers to the toxicity of cell that leads to edema, cell blistering, necrosis and even apoptosis. Cytotoxic venom often kills the cells of the envenomation site but it also toxic to the heart as it can cause heart to beat irregularly or stop beating. Due to limited blood circulations some black spots may appear in the victim's body. Cytotoxic venom is not much deadly than neurotoxic or haemotoxic venom but its severity depends upon the snake species and amount of toxin. Immediate symptoms include pain and swelling which become more severe in next 6-8 hours, after that a certain shock appear, which is often termed as cold fire ,that leads to death of the victim.

All these three types of venom fall into one common category the **proteolytic** venom. Effect of proteolytic venom results from the envenomation with neurotoxic, hemotoxic or cytotoxic venome. Metalloroteinases, serine proteinases, plasminogen activators are the key ingredient for proteolytic activity.

➢ *Blessings of Snake Venom:*

In ancient greek medicine and also in ayurveda, snakes are thought to be the God of medicine. Cobra venom have been used for traditional medicine by Indian and Chinese. From the 20th century pharmacists start to show their interests on different types of zootoxins. With the help of modern biotechnology they isolate different types of snake venom proteins, few of them become FDA approved while few are still in clinical trials. In addition with the medicinal property snake venoms are also used to prepare anti venom that can prevent many death from snake bites.

Snake venoms are mainly of three types. Among them cytotoxins are widely used for their anticancer property. Hemotoxins play worldwide role in treating cardiovascular disease. Due to complexity of drug delivery to human neurological system, medicines from neurotoxins are still slow growing branch for pharmaceutical industries.

Let's focus on some drugs approved by the US Food and Drug Adminstration (FDA) and the European Medicines Agency(EMA).

➢ *Tirofiban and Eptifibatide :*

Tirofiban and Eptifibatide are antiplatelet medication, belongs to a class of glycoprotein IIb/IIIa inhibitors. They are nonpeptide drug and has the same RGD (Arg-Gly-Asp) domain like fibrinogen. Tirofiban and Eptifibatide works by preventing blood clotting by interfering with platelet aggregation. They perform rapid onset and have approximately 2-2.5 hours of plasma half life. Therefore their effect diminishes just after discontinuation. These two drugs have similar functions but they differ in their origin. Tirifiban is extracted from the snake venom of saw-scaled viper *Echis carinatus*, while the source of eptifibatide is pigmy rattlesnake *Sistrurus miliarus barbourin*. These two are very useful drug for the patient with ischemic and coronary heart disease.

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➢ *Bivalirudin :*

Bivalirudin is FDA approved thrombin inhibitor that inhibit both the circulating and platelet bound thrombin. It is a good alternative of thrombin during coronary intervention. According to the evaluation of scientists continuous use of low dose of subcutaneous heparin can cause many vascular complications including hematoma and in some cases hemorrhage, much greater than bivalirudin. Bivilarudin reversibly binds with the active site of thrombin and has a plasma half life of 25minutes.It is a non immunogenic anticoagulant that interfere in the conversion of fibrinogen to fibrin. Due to lower rate of bleeding risk bivalirudin is a good choice for the patients who have serious heart attack and undergo percutaneous coronary intervention.

➢ *Captopril and Enalapril :*

Captopril was the first FDA approved drug which is served as anti hypertensive medicine. It is also used in the treatment of high blood pressure, kidney failure due to prolonged high blood pressure and cardiac damage. Its active ingredients bradykinin was extracted from the venom of Bothrops jararaca, a species of pit viper. Captopril is an angiotensin converting enzyme (ACE) inhibitor. ACE converts angiotensinIto angiotensinII and thus causes arterial vasoconstriction and retention of Na and H2O. By inhibiting ACE captopril causes vasodilation and reduces blood pressure. Like Captopril, Enalapril and Quinapril both are ACE inhibiting drugs but captopril differs from these two on the basis of the presence of sulfhydral group (which is the most important for the development of most of the adverse effect) and its metabolism in plasma.

➢ *Batroxobin :*

Bothrops atrox and *Bothrops moojeni*, are two venomous species of south american pit viper . From their venom a serine protease drug batroxobin is made. Like thrombin it also can convert fibrinogen into fibrin. This property of the drug makes it very useful to treat myocardial infarction, stroke and post surgery bleeding.

➢ *Cobratide :*

This is another drug purified from the venom of Chinese cobra, *Naja naja atra* **.** Generally cobra venom serves as analgesics without causing addiction like morphine. In India and china cobratide drug is used in the treatment of inflammation, arthritis, and pain .Cobra toxin show their action by binding with the post synaptic receptor of neuromuscular junction and thus prevent receptor's ability to bind with neurotransmitters like acetylcholine, serotonin. As a result propagation of nerve impulse through the pre synaptic neurons fail. Thus, nociception (pain sensation) does not reach to the brain and we can't feel the pain.

According to some previous research, acetylcholine receptors show over expression in certain lung cancer. A ligand, Nicotine, by binding with this receptor stimulates the tumor growth. In those cases cobratide may be used as inhibitor of receptor and can cause suppression of tumor.

II. CONCLUSION

Sources of life saving drugs may be synthetic, biosynthetic and natural. In recent few decades research on different animal sources like scorpions, crabs, spiders, snails, lizards, insects, including snakes have emerges as great reservoir of various drugs. Among these Snake venom, being a bioactive cocktail shows high specificity and effectiveness than any other animal venoms. Although, only a fraction of active ingredients become available to scientists for the improvement of mankind. With the increased scientific and industrial interests it will be more likely to uncover the hidden benefits of snake venom .

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ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24JUL1170

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