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# APPLICATION OF SNAKE VENOM COMPONENTS IN BIOMEDICINES

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**ABSTRACT**

Envenomation by snakes is a significant socio-medical issue. More than 100,000 people die from snake bites each year, which affect over 2.5 million people. Although snake bruises may be fatal, snake venom is a naturally occurring an organic resource that includes a number of elements that may have medicinal utility. Ayurveda, homoeopathy, and folk medicine all use venom to treat a variety of pathophysiological diseases. With the development of biotechnology, the effectiveness of such treatments has been demonstrated by isolating the medicinal characteristics of venom components. This review will concentrate on specific elements of snake venom and how they are used to treat illness and prevent it. Numerous helpful substances have been discovered, most notably the disintegrins (eptifibatide and tirofiban), which have been demonstrated to be potent anti-platelet aggregation both in vitro and in vivo. While the original native compounds found in snake venom are typically unsuitable for therapeutic use, advances in pharmaceutical R & D made it possible to use the proteins found in snake venom as therapeutics for a variety of disorders based on the knowledge of their structural and functional properties. With their unique combination of ingredients, snake venoms hold enormous promise as cures for human illnesses. For thousands of years, nature has served as a source for therapeutic substances, and snake venoms are a particularly rich supply of bioactive compounds, including peptides, proteins, and enzymes with significant pharmacological functions. Furthermore, traditional Chinese medicine has made extensive use of the blood and bile duct of snakes. Protein fold structures have made it possible to create a wealth of peptides that interact specifically and very affinitively with human protein. This will aid in understanding the effects of each interaction and pave the way for the creation of potent medications that are specifically targeted at particular protein activities.

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## INTRODUCTION

Through history, people have been fascinated by, terrified of, and created myths about snakes. Ancient Egypt adored the cobra, and a duplicate of it accustomed to adorn the imperial crowns of Rome. In contrast, in the world of ancient Greece,

The image of the deity of the drug was a stick. Wrapped in an ogre, which still in use to symbolize the guilds of pharmacy and medicine. Complex combinations of in organic ions, nucleotides, and proteins make up snake venom. These combinations endow the venom with an impressive variety of poisonous qualities, with the peptides and poly peptides being in charge of various harmful effects.

Around Every year, 2.5 million individuals receive a snake bite. And about 100,000 of them dying a result.
In the tropics, rural regions experience the highest rates of sickness and mortality[1,2]. Wild snake bites do not spare there sidents of temperate western nations, but they happen less frequently. A significant number of people have also been envenomated by exotic captive snakes. The intrinsic toxicity and quantity of injected venom are two parameters that affect the clinical signs of a snake bite.

Many signs and symptoms can result after being bitten by a snake, but the main ones that have clinical relevance is possible. Systemic myolysis, renal damage and failure, coagulopathy, haemorrhage, flaccid, paralysis, cardio toxicity, regional tissue harm while biting site are the different categories. The symptoms indicate the snakes' venom influence a number of systems, including the cardiovascular, muscular, and vascular systems like the brain and central nervous system. The purpose of throughout this review is to draw attention to some of the components of snake venom that can be employed as molecular probes to study human health and disease.[3]

### Snake Venom Neurotoxins Affecting CNS:

Dendro toxins and neurotoxins **(Table 1)** are the major snake venom toxins that impact the the brain and spinal cord. The manifestation of cranial nerve paralysis, which are characterized symptoms is impaired vision, trouble gulping and slurred speech, and paralysis is in the facial muscles, is the main symptom of neuro toxic envenomation. Similar to this, Dendrotoxins are known to shown to block various kinds of voltage-dependent potassium channel sin neurons.[4]

**Table 1. Snake venom neurotoxins in the CNS and their targets:**

| Type of neurotoxin | Functional target | Source |
|---|---|---|
| Quick-acting neurotoxins | post-synaptic toxin having minimal or no affinity for neuronaln AChR-7 but significant affinity for skeletal and Torped on AChR. | Hydrophids and elapids (Kois, cobras, sea snakes, and Australian elapids) |
| Neurotoxins with long chains | post- synaptic toxin with significantly greater affinity for neuronal α7n AChR than skeletal receptors | Hydrophids and elapids(sea snakes, Australian elapids, cobras, kraits) |
| Weak neurotoxins | Poor affinity for both the skeletal and neuronal nAChRs; post-synaptic poison | Elapids (Australian elapids, cobras, kraits) |
| Tai poxin | Presynaptic toxin; mostly binds to neurons plasma membranes at the Neuromuscular junction. | Australian elapid (taipan) |
| β-Bungarotoxins | Presynaptic toxin; Presynaptic voltage dependent K+channel | Elapids (kraits) |
| Muscarinic toxins | Specific to them AChR sub type and have a strong binding force | Elapids (mamba, kraits and cobras) |

### Neurotoxins:

Neurotoxins belong to one of the most numerous classes of proteins having recognize able core structures. Neurotoxins that attach to receptors for nicotinic acetyl choline are among the most thoroughly researched snake neurotoxins (nAChRs). By competitively interacting with then AChR present at the post synaptic membranes of neurons and skeletal muscles, they have the ability to reversibly block nerve transmission. This prevents neuro muscular transmission and results in death asphyxiation. The post-synaptic (α) neurotoxins are classified into four major groups:

a. Short neurotoxin
b. Long neurotoxin
c. κ-neurotoxins
d. other unconventional neurotoxins called the weak neurotoxins.[5]

Understanding the composition and operation of the nervous system has been aided by the great selectivity of neurotoxins for nAChRs. α Neurotoxins in particular have proven essential for the identification and characterization near the motor end plate of then AChR. The composition of neurotoxins securing to their nAChR molecular target. The interaction of 5 neurotoxic with a particular nAChR peptide isolated from *Torpedo californica*, The binding of 5 neurotoxin to the component of the acetylcholine receptor. The function of some elapid neurotoxins is compare able to that of the auto-antibodies or curr are found in myasthenic graze. Together with Tsetlin and Hucho, Siew et al. provide thorough reviews on neurotoxins[6]. In numerous species and pain tests, it has been demonstrated that nicotine and nicotinic agonists activate central cholinergic pathways to produce anti-nociceptive effects. It has been discovered that cobra venom's neurotoxins a considerable analgesic effect in animal models. There have been reports of cobrotoxin is a post-synaptic short-chain neuro toxic, includes the long-chain neurotoxic-cobratoxin., having analgesic properties. In contrast to cobra toxin, which has a strong preference for the neuronal nAChR-7 and provides an anti-nociceptive result that is independent of opiates, cobra toxin is a particular lig and for the nAChR-1 in muscles and causes potent analgesic actions that are centrally mediated. Also, there is growing proof in which cobro toxin can replace morphine and mitigate withdrawal symptoms from morphine. Similar to this, *Ophiophagush annah*, a king cobra neuro toxic, has also been discovered. Shown to have strong analgesic properties. [7] Green mamba venom contains poisons that attach to neurons muscarinic acidimetric receptors (mAChRs). The muscarinic toxins (MT1–7) can be helpful pharmacological instruments for examining the physiological functions of the sub types of muscarinic toxins because of their potency and specificity receptors. It is thought that specific blockage of these receptors may significantly help in restoring normal mobility and these are called muscarinic receptors. In fact, these sub type-specific mamba toxins were used to clarify the role of muscarinic receptors in Alzheimer's disease and **Table 1**depicted lists the possible origins of nicotinic and muscarinic neurotoxins. On the other hand, the β-neuro toxins influence there lease of acetylcholine via processes to exert their pre synaptic effects. that vary for various β-neurotoxins They result in a poisonous state and eventual respiratory paralysis. They work by stopping the regulated release of acetylcholine, causing acetylcholine-containing vesicles to vanish, and impeding impulse transmission. Pre-synaptic neuro toxins that have been thoroughly investigated to date include Crotoxin (from *Crotalusdur issus terrificus*),-bungaro toxin (from *Bungarus multicinctus*), notexin (from *Note chisscutatus*), and tai poxin (from the Australian tai pan) (*Oxyuranus scutellatus*). In phase 1 clinical studies pre-synaptic neurotoxin with cyto toxic effects called crotoxin, is being employed. For advanced cancer patients, this poison has been tested as an anti-cancer agent, and it is thought to utilize a unique method of action. As tools for examining how potassium channels behave under physiological and pathological settings, and as a result, they have been linked to the creation of introducing fresh medications for the treatment of neurological conditions like alzheimer's illness.[8,9]

**Curaremimetic Toxins (α-Neurotoxins or Postsynaptic Neurotoxins):-**

A toxic condition have extremely high post synaptic nicotinic acetylcholine receptor selectivity, specificity, and affinity. (nAChRs). As a result, they block acetylcholine neuro transmission at the neuro muscular junction of skeletal muscle. Short-chain neurotoxins (60–62 amino acids, four disulfide bridges) and long-chain neurotoxins are the two categories of neurotoxins (66–74 amino acids, five disulfide bridges). The long-chain peptide binds to the neuronal 7 nAChR with greater affinity. The fifth disulfide bond is thought to be the cause of the long-chain peptide's target selectivity. An unprecedented understanding of the exchanges between the toxin and the receptor was provided by the crystal structure of bungaro toxin in complex with nAChR 1. It was discovered that the two crucial residues that block the toxin's finger II, Arg36 and Phe32. [10] It was discovered that the C-terminal arginine of the elapitoxin, which was isolated from *Dendroaspisp. polylepis*, was amidated. The three-finger poisons found in snake venom are rarely subject to this post-translational alteration. The elapitoxin highly inhibits the 7 nAChR, according to assay binding tests, but it has been hypothesized that the C-terminal alteration has no effect on the toxin's selectivity. Three- finger toxin peptides have proven to be a helpful molecular probe in determining the structural and functional characteristics of nAChR since the discovery of the famous peptide bungaro toxin from the venom of a krait, *Bungarus multicinctus*. Further research in the area was motivated by this discovery, which made it feasible to comprehend a number of medical conditions such my asthenia gravis.[11] Form of bungaro toxin revealed that neuronal nAChR may have a chemical of choice for identifying the underlying processes of numerous neuro logical diseases is still bugarotoxic. In a patient with congenital my asthenia syndrome, amutation of the invariant Cys-loop As presidue in the acetylcholine receptor sub unit was found. The development of Parkinson's disease may be influenced by neuronal nAChR, according to a recent study that used a radioactive version of bungaro toxin. Three-finger neurotoxins are drawing interest as possible analgesics, anti-inflammatory compounds, and immune suppressants in addition to acting as molecular probes in a number of medical conditions. Skin allograft rejection was reduced in rats by a neurotoxin isolated from *Naja n. a* venom that blocked the T-cell-mediated immune logical response. Recently the *Ophiophagus Hannah* snake's venom yielded a brand-new class of three-finger toxins (specifically,-neurotoxins)[12].

**MuscarinicToxins:**

These toxins bind to muscarinic acetylcholine receptors (mAChRs) and operate as antagonists oragonists against distinct muscarinic AChR sub sets.(M1–M5).An intriguing example is MT1 (a muscarinic toxin from *Najaka out hia*th at functions as an agonist at M1 and an antagonist at M4). Muscarinic poisons' selective activity has made the man in valuable tool for various biomedical investigations. Other muscarinic toxins derived from the venom of *Dendroaspis angusticeps* show significant selectivity for M4 and M1 mAChRs, respectively[13].

**k-Neurotoxins:**

These peptides have structures that are similar to long chain neurotoxins. The *Ophiophagus Hannah* snake's venom of the 3FTxs family, they exist as dimers. They only recognize the 32 and 42 nAChR sub types. *O. hannah* yielded an intriguing peptide known as haditoxin. It was discovered to be a homodimer-like kappa-neurotoxin based on its crystal structure. Haditoxin's monomeric sub units, on the other hand, are structurally an alogoustocur are mimetic short-chain-neurotoxins. This peptide has been shown to interact with both neuronal pha7 nAChRs and muscular nAChRs.

Site-specific and chemical mutagenesis investigations have revealed that various forms of neurotoxins use a common set of amino acid residues, as well as some additional residues, such as that located near the tip of loop Iiner abutoxin (Laticauda)[14].

**Cardiotoxins (CTXs):**

These peptides have structures that comparable to long-chain neurotoxins. In contrast to other 3FTxs family members, they exist as dimers. They only recognize the 32 and 42 nAChR sub types, not the 1.A fascinating peptide, cardiotoxins are these most common type of three-finger toxin. Because of their capacity to trigger lysis in a wide range of cells, CTXs are also known as cytotoxins. They are hydrophobic, basic, and, on average, short poly peptides (60–62 amino acids). Their molecular structure is comparable to that of short-chain neurotoxins. Cardio toxins, unlike neurotoxins, have a functional location at the final circle of the three. These are of ten hydrophobic amino acids that give the molecule amphiphilic characteristics. A line of amino acids that are positively charged[15]. Cardio toxins have a well-established history of to disturb the membrane, and the extent to which these peptides can do so is known to be dependent on the presence of Ser 30 or Pro 28 residues in loop II. As a result, cardio toxins are classed as S-type CTXs or P-type CTXs. P-type CTXs bind to membranes more strongly. CTXs insert into anionic lipid-containing membranes and exhibit unique characteristics that distinguish in distinguishable from other membrane – active compounds, summarised by Dubovskii et al. Although there was no convincing proof of whether or how CTXs interact with proteins upto this point, certain indications have been suggested. Hemachatoxin is aP-type CT that was isolated and crystallized from the venom of *Hemacatus hemacatus*. It has been proposed that this toxin's loop II is extremely adaptable[16]. Cytotoxins can with stand heat and have a great resistance to denaturing agents. Another type of cardio toxin known as cardio toxins binds to adrenergic receptors. Unlike CTXs, which increase the heart rate, studies demonstrate that these peptides decrease it. Snake venom cardio toxins are currently the focus of various cancer – inhibiting investigations, with promising results already acquired. Some studies classify cyto toxins as necrotic, whereas others classify them as apoptotic. Cytotoxin-1 and cytotoxin-II derived from the venom of *Najaoxiana* shown anti tumor efficacy superior to cisplatin (anti-cancer drug). It was also established that these toxins had no effect on normal cells (e.g., MDCK) while inducing apoptosis in cancer cell lines(e.g.,MCF-7, Hep G2, HL-60, and DU-145) via the lysosomal pathway and cytosolic catheps in release. Cardiotoxins are also recognised to have anti bacterial properties. The tip and strand of cardiotoxin-1's first finger were used as a template to create 20 amino acid residue peptides.[17,18]

**Acetylcholine sterase Inhibitors:**

These toxins, which are known as fasciculins, are structurally related to short-chain neurotoxins and block the enzyme acetylcholine steraseat the neuro muscular junction, causing fasciculation of the muscle. They prevent the enzyme from degrading its substrate (acetylcholine) by blocking the enzyme's peripheral site. Previous research has demonstrated that the first and second loops of the toxin's amino acid residues have a role in the suppression of enzyme activity[19].

**Non-Conventional 3 FTxs:**

These polypeptides feature a fifth disulfide bond in either loop I or loop II. Kini and Doley classed these peptides as non-conventional 3 FTxs, where as they we repreviously classified as "weak" neurotoxins. WTX from Naja Kauthia NMR (nuclear magnetic resonance) investigations demonstrated that the toxin's loop II is crucial for binding to mAChRs. Candoxin, a B-dimer, was isolated. candidus, has a nano molar affinity for both muscle and neuronal AChR. Muscle AChR binding is easily reversible. When compared to mammals, denmotoxin and irditoxin from colubrid venom have a significantly high binding affinity for the avian neuromuscular junction. Mambaglins derived from the venom of the eastern green mamba were found to have analgesic effects. Furthermore, these peptides have the ability to block.[20,21].

**I on Channel Blockers/Modulators:**

Calciseptine and FS2 are L-type calcium channel blockers identified from black mamba venom. They attach to the 1, 4-dihydropyridine binding site of the L-type calcium channel and prevent calcium from passing through. They are structurally similar to short –chain neurotoxins. Some studies anticipate that the functional location of these peptides is positioned on the III loop, between residues 42 and 47 [22].

Mambalgins (I-III) are non- traditional 3 FTxs that particularly inhibit acid- sensing ion channels (ASICs), producing analgesic effects comparable to morphine but with fewer side effects. Loop II contains their functional domain, and it has been postulated that mamba lgins inhibit ASICs via apHsensor – trapping mechanism. Calliotoxin, a short-chain neurotoxin obtained from the venom of a coral snake, Calliophisbivirgatus, was recently identified. It shares 53% of its sequence with Rho-elapitoxin -Da1b. (UniProt ID: P86419). It has been demonstrated that it modulates the voltage-gated sodium channel. Further research into this novel class of 3FTxs may shed light on the physiology and pharmacology of voltage- gated sodium channels.

Another recent study discovered a novel toxin from *Dendroaspis augusticeps*, Tx7335, that activates the bacterial potassium channel KcsA. This newly discovered toxin has a strong despite having a similar sequence to long chain neurotoxins, the amount and distribution of cysteine differs significantly [23].

**Platelet Aggregation Inhibitor:**

Dendroaspinis a well-known platelet aggregation inhibitor. It contains the tripeptide sequence RGD, which is responsible for some proteins' sticky action. It exerts its inhibitory function by blocking fibrinogen and its receptor glycol protein from interacting. Dendro aspin's functional location is at the tip of Loop III [24].

**Toxins affecting the cardiovascular system:**

The first oral angio tens in-converting enzyme (ACE) inhibitor was created in 1975 with the venom-based medication captopril. This success story began with the discovery of the poisonous effects of a Brazilian viper's venom (*Bothrops jararaca*), which led to a sharp, significant reduction in blood pressure Sir John Vane, recipient of the Nobel Prize, was intrigued by this and discovered that the viper venom was a strong ACE inhibitor. Vanetook David Cushman and other scientist soft he pharmaceutical company Squibb made this finding. And Miguel Ondetti, created captopril, the first oral ACE inhibitor. With the success of captopril, snake venoms have been explored for potential applications pertaining to the cardio vascular system. The binding of the anti-hypertensive drug captopril to its substrate ACE. Cardiotoxin is the name given to a toxin that was discovered in the venom of an Indian cobra in the late 1940s and caused cardiac collapse in test animals. Cardiotoxins, also known as cytotoxins are found exclusively in the venom of cobras and ringhals and are membrane-active polypeptides and directly tic factors, respectively. They are single-chain, highly hydrophobic, basic, short polypeptides closely related to the α-neurotoxin that binds to nAChR, but cardiotoxins do not show any significant affinity for the receptors. The main targets of cardio toxins are on excitable cells. They caused depolarization and contracture of cardiac, skeletal and smooth muscles, as well as depolarization and decreased neuronal excitability [25,26]. These toxins are pore-forming substances that cause the plasma membrane of skeletal muscle cells to depolarize and break down. The mechanism of action of degeneration is most probably calcium dependent. It results in the direct activation of calcium-dependent proteases and the eventual failure of mitochondrial respiration as a result of an excess of calcium. In several cellular processes, such as lipid metabolism and calcium ion control in both skeletal and cardiac muscle, cobra cardiotoxins may be helpful probes. Cardio toxins have also been shown to be membrane-active proteins that recognize the proteoglycans of the membrane. Their cardiotoxicity results from their distinct binding to glycosaminoglycans, the sulphated carbohydrate moieties that occur abundantly in cells of cardio vascular tissues. Cardio toxin's interaction with the heparan sulphate moiety. Cardio toxin is currently being used in a phase 1 clinical trial for cancer treatment along with crotoxin (a pre-synaptic neurotoxin) in a combined therapy. Cardio toxin expression at higher levels (60% of the venom dry weigh) has been attributed to the difference in promoter activity [27] A24 nucleotide (nt) silencer in the 5′-flanking region of the -neurotoxin from Naja sputatrix's promoter reduced its activity. These findings indicated that snakes produce venoms that contain highly lethal and specific toxins at lower levels than the multi-functional toxins like cardio toxins. A study by Cher et al demonstrated that the synergistic effects of all the other components, including neurotoxins and phospholipase A2 (PLA2) and the spreading factor, come into play after the first impacts of cardio toxins on a victim's molecular level and physiological states after cobra envenomation, hyaluronidase [28].

**Toxins affecting the muscular system:**

Skeletal muscle cycles of degeneration and regeneration are started by three basic types of venom components:

(a) myotoxins, which are small polypeptides that can be isolated from the venoms of the New World viper subfamily Crotalinae, and which specifically act on skeletal muscles

(b) cardio toxins, poly peptides of 60–65 amino acids that can be isolated from venoms of cobras and which act on smooth muscles (see above) and PLA2, which isolable from the venoms of several snake groups, such as the Viperidae, Elapidae, and Hydrophiidae. The activities of the PLA2s can be myotoxic, cardio toxic, orneurotoxic [29,30].

**Myotoxins:**

Myotoxins are found in venoms and are also known as my one crotictoxins from rattle snakes and other pitvipers. Myotoxin-a, which was discovered in the venom of a Prairie rattle snake, is one of the most well-known myotoxins. It is a small (4600Da), basic protein devoid of enzymatic activity. Mytotoxin-a binds specifically to the sarcoplasmic reticulum of muscles, causing the sarcoplasmic reticulum's ion perme ability to change (an important calcium regulatory system) leading to swelling and disintegration of both the sarcoplasmic reticulum and muscle fibrils. Hence antibody to myotoxin-a has been used to treat my one cros is resulting from Prairie rattle snake venom poisoning.[31,32]

**DISCOVERY OF DENDROTOXINS:**

Only in Africa are mambas (Dendroasp is species) to be found., despite being Elapidae family members, such as Kraits and cobras. early research on drugs to check if mamba contains acetylcholine receptor-blocking poisons venoms was found to cause a flaccid neuromuscular paralysis. The venom of the mamba in green was significantly less harmful than that of other mambas, and it doesn't seem to contain many poisons that block receptors. Nevertheless, it was discovered that the venom of green mambas contained a range of proteins with various functions sequences of amino acids and unidentified pharmacological effects [33].

Acetylcholine's effects have been claimed to be potentiated by the Eastern green mamba snake's venom (*Dendroaspis angusticeps)*, the venom of a the green mamba caused severe muscle fibrillations. Later, it was found that when Motor neurons in isolated skeletal muscle preparation sexcite them. The peculiar pharmacological activity of green mamba venom causes the twitch height to increase. This outcome results from a pre junctional action that makes acetylcholine release easier. The tiny protein known as dendrotoxin, which was isolated from the venom, is what has the facilitative action. Further studies by numerous groups demonstrated that dendrotoxin is a powerful and selective inhibitor of certain K+ currents in neurons [34] The order of the "protease inhibitor homologue" C13S2C3, which was the same as green mamba venom's dendro toxin, occurred concurrently with that finding. Following the identification and sequencing of protease inhibitor homologues from mamba venom, it was soon determined that identical dendrotoxins were present in other mamba venoms [35].

**Snake venom disintegrins:**

Research on tri gramin, the first report on a disintegrin from snake venom, began more than 25 years ago. Many scientists were motivated by this RGD-containing disintegrin by looking for related molecules, new protein classes are discovered. Disintegrins in snake venom can now be categorized into subfamilies based on both their structure and function. In terms of structure, disintegrins are homodimeric and heterodimeric dimers and monomers, respectively. Monomeric disintegrins are classified based based on the length of the polypeptide chain and the amount of cysteines: 12 medium – sized disintegrins, short.14 long cysteines, and 8 cysteines are present. Each subunit of dimeric disintegrin has ten cysteines. The functional classification was based on a tri-peptide pattern observed in the active site of snake
venom disintegrins. Disintegrins are now classified into three functional groups based on the presence of RGD-, MLD-, and KTS sequences [36].

**Structure of snake venom disintegrins:**

Even though different genes for numerous hetero dimeric disintegrins have been discovered, generalized disintegrin-related structures in snake venom originated from metal lo protein ase-containing precursor molecules. Moreover, examination of the cDNA library of viper venom glands that The lack of the metal loproteinase domain was discovered by express KTS-disintegrins. Where as PIII class disintegrins are processed along side acysteine-rich domain, traditional snake venom disintegrins are single domain molecules that are released proteolytically from the a component of the tPII class of metal loproteinases' venom. Moreover, the PIII disintegrins feature an additional cysteine close to the sequence that corresponds to the PII disintegrins' active principle. The extremely preserved disulfide bond structural structure of each family of disintegrins demonstrates particular evolutionary links [36]. The composition of the amino acids around the MLD motifal so controls which integrins—41, 47, or 91—interact with it. KTS – disintegrins are structurally brief monomeric proteins. Compounds that strongly and specifically bind to the 11 integrin collagen receptor. The way the "integrin-binding loop" is organised, however, greatly differs across them. When compared to RGD or MLD - disintegrins, the KTS loop is two residues shorter. Some disintegrins, which primarily express as partic acid, donot, it also lacks any acidic residues. Seldom do KTS- disintegrins exist in viper species. Lebestatin and obtustatin are found Viperistatin is Viperistatin is contained in the venom of the *Vipera lebetina obtusa* but not in the venom of the *Vipera palestinae*. The fourth member of this family is jerdostatin., expresses an RTS motif and has lysine replaced for arginine. Leucine (obtustatin) is converted to arginine (viperistatin), which amplifies the inhibitory action on integrin 11 by almost a two-order difference. In comparison to obtustat in, lebestatin has a more flexible C-terminal tail and more solvent accessibility in the integrin binding loop., according to a recent analysis of their structure/ function relationships. These characteristics show greater biological activity of lebestatin. Acysteine- rich domain is included in PIII class proteins to complement the disintegrin domain. From a small number of venoms, they were identified as a distinct non enzymatic molecule. They often comprise bigger molecules along with metal loproteinase domain. These disintegrins exhibit extremely little anti-integrin activity as compared to PII class. According to reports, the disintegrin-like domain's sequence RSECD serves as the active site for this interaction with the collagen receptor 21 integrin. Recent research with leberagin-Crevealed that it blocks the v3 integrin, a typical lRGD – dependent integrin [37].The initial cells studied in relation to disintegrins in snake venom were platelets. They produce the IIb3 integrin, which utilises an RGD motif to bind fibrinogen. The majority of snakes found these thrombocytes' activity is potently blocked by venom disintegrins, which have an RGD or closely comparable motif in their active site. Tri gramin, the first disintegrin to be discovered, directly bound to the IIb3 integrin to prevent ADP-induced platelet aggregation. Snake venom's capacity to disintegrate to bind IIb3 integrin determines how well they can prevent platelet aggregation. To map the binding epitopes of particular disintegrins on this integrin heterodimer, numerous investigations were conducted. Echistatin and eristostatin, two short monomeric disintegrins, for instance, bind to distinct but over lapping locations on the receptor for fibrinogen. Strangely, neither of these two disintegrins affects rats agglomeration of platelets. The structural variations between the rat IIb integrin subunit and human IIb integrin sub unit are implicated in this occurrence. Kistrin and elegantin, two medium monomeric disintegrins, similarly bind to various but closely related epitopes on IIb3 integrin. The intensity and selectivity of disintegrin's fibrinogen receptor blockade appear to be greatly impacted by the tryptophan residue that is present in the RGD loop. The RGDD motif expressed by echistatin, binds resting platelets around ten times weaker than eristostat in, which contains RGDW motif. It's interesting to note that most disintegrins have a similar affinity for both activated and inactive platelets. The production of alterations in the integrin's tertiary and quaternary structures may provide an explanation for this action of disintegrins structure that alters integrin equilibrium from a thermodynamically unstable oligomeric form tooneth at is active, resting, and clustering [38]. Although it reduces its selectivity, the natural substitution of This hetero dimeric disintegrin is the most effective blocker of the fibrinogen receptor due to the RGD sequence with the WGD in CC8.

Another intriguing characteristic of dimeric disintegrins is that they prevent platelet aggregates from dissociating. Disintegrins also regulate the cytoplasmic proteins of platelets' tyrosine phosphorylation in an aggregation-dependent manner (Table 1). Contrarily, homodimeric disintegrin, contortrostatin, display edstimulatory action on phosphorylation of Syk, but monomeric disintegrin, saxatilin, blocked collagen- induced activation of this protein inplatelets. Saxatilin also prevented the phosphorylation of MAPKErk ½ in this situation, but it had no impact on FAK activation. Contrarily, according to contortrost at in prevented thrombin-stimulated FAK phosphorylation is utilized insoluble or solid (immobilised) form, the effects of echistatin on the signal transduction in platelets were opposing Syk and FAK were activated by platelets after adhering to this disintegr in, whereas echistatin prevented their phosphorylation after adhering to fibrinogen. Similar ability of blocking vs. activation of FAK was observed for other disintegrins used insoluble and solid phase, respectively. FAK's agonist-activated phosphorylation was inhibited by recombinant soluble RGD- disintegr in, Dis Ba-01, however when platelets were placed on GST-rhodostom in, this protein's phosphorylation was increased even further than when it had previously bound to the immobilized fibrinogen. The phenomenon of opposite effects of disintegrinsused in solid or soluble form on platelet signaling may be C [39].

**Use of Neuro toxic Snake Venom Proteins/ Peptides in Biomedicine:**

Purified fractions containing these components, which are Numerous snake species, especially those in the Elapidae family, have venom that is neurologically active and has a number of potential biological applications. Activities could be used. This section will go through some of the potential biomedical uses for these cleaned-up fractions of snake venom. In the section of this chapter titled "Uses of Snake Venom Proteins/ Peptides in Cardio vascular Disease, "it will be discussed how venom fractions, Stroke can be treated with fibrinolytic metal loproteinases found in snake venom and serine proteinases that deplete fibrinogen.

**Pain Relief Peptides:**

Hannalges in is a fascinating neurotoxic peptide that was discovered in a king cobra's (*Ophiophagus hannah*) poison. This drug is currently undergoing preclinical and early clinical creation of a method to manage severe pain. Handled by a French business. The 11- amino acid peptide, which is water- soluble and non-opioid and is produced from hannalges in, is given sublingually. The drug has been proved to be safe and to have analgesic qualities inpreclinical experiments. Preclinical research have also indicated that the drug has a far stronger analgesic impact than morphine, despite the fact that the exact mechanism of action is unknown. It is thought to work by activating the endogenous enkephal in system through a neuronalnitric oxide synthetase- dependent mechanism. There are numerous additional promising candidates for brand-new medicines made from venom. Two peptides from the black mamba's poison (*Dendroaspis polylepis*) have been found by French researchers, and they ion channels that sense acid (ASICs) can be inhibited. ASICs play a significant part in the human pain pathway and both the peripheral and central nervous systems exhibit them. The two peptides, known as mambalgins, are identical save for one amino acid residue and each contain 8 cysteine residues and57 amino acids. These are a subgroup of then on enzymatic proteins known as three-finger toxins (TFTs), which are found in the venom of all species of snakes but are more frequently found in the Elapidae family of snakes. Three beta- stranded loops that extend like three out stretched fingers from a tiny members of the TFT family have globular central cores with four conserved disulfide bridges that cross-link them. The mambalgins had analgesic effects in mice that were as strong as morphine while exhibiting no toxicity. The peptides also caused no respiratory discomfort and a lower to repeated drug administration than morphine. These peptides may contribute to our understanding of pain and may be used to create new, strong, naturally occurring peptides have potential for use as medicinal analgesics. They have strong action against many ASIC channel subtypes, potentially presenting new potential sites for therapeutic action. The same French pharmaceutical company that is working on the peptide produced from hannalgesin is also developing mambalgins as a treatment for human pain [40,41].

**Detoxified Cobra toxin for Multiple Sclerosis:**

The modified (detoxified) cobra toxin from the Thailand cobra venom is being developed for the treatment of a drenomyelo neuropathy (AMN) and multiple sclerosis (MS). A uncommon peroxisomal metabolic disease called AMN results in inadequate - long-chain fatty acid oxidation. It is distinguished by the absence of myelin layer on nerve fibres (Cerebral Demyelination) in the brain as well as the gradual adrenal gland deterioration (adrenal atrophy). Because of the disease's resemblance to MS the neurological problems in AMN emerge gradually overseveral decades. The use of snake venom to treat MS has along and contentious history, according to F.S. Markland and S.D. Swenson 396. Nonetheless, the sporadic accounts on with the studies on the cobra from Thailand that is neuro toxic, the usefulness of snake venom in the treatment of MS may now have some scientific backing. Cobratoxin has a number of pharmacological features that support its usage as a treatment for MS It binds to nicotinic acetylcholine receptors in the brain's neuronal synapses and at neuromuscular junctions. Cobra toxin may now be used to treat MS in a clinical environment with only possibly moderate side effects because to the capacity to detoxify the toxin through a chemical detoxification process. Viral infection may have caused or exacerbated the painful immune-mediated condition known as MS. The fatty coating that surrounds and shields the nerve fibres in the central nervous system is called myelin.) and the nerve fibres themselves are both injured as a result of the immunological attack on the central nervous system, leading to the symptoms of MS. Experimental auto immune encephalitis is a recognised murine model for MS; nevertheless, there has been little consistency between experimental research in this model and the treatment response in humans. It is interesting to note that cobra venom has long been used to treat rheumatoid arthritis in China arthritis and cancer after being partially denatured by heating.

Considering anecdotal evidence that Thai detoxified cobra toxin is effective. A more recent experiment was carriedout in a small number of individuals with AMN about the use of cobra venomin MS. Yet this research was unable to confirm the promising out comes that had been previously reported. Although the trial period was too brief or there were not enough patients enrolled, the short-term medication utilized in this investigation seemed to be safe and well tolerated. The authors advised additional investigation of detoxified cobra toxin in trials involving more patients or lasting longer with the considerable side effects of the majority of the current treatments for MS and preclinical evidence that detoxified cobra toxin exhibits anti viral, neuro modulatory (analgesic) [42].

**Cobra toxin for Mesothelioma:**

Intriguingly, mesothelioma has been treated in animal model systems using the active –cobra toxin (undetoxified) from the monocled cobra's poison, *Naja kaouthia*. The Mesothelioma is an uncommon kind of cancer. that most usually develops from the cells that line the pleural or peritoneal cavities. The most prevalent type, pleural mesothelioma, frequently exhibits signs and symptoms in the chest. Most sufferers of malignant mesothelioma were exposed to asbestos while working- Cobra toxin is a high-affinity antagonist of the 7-nicotinic receptor and a powerful inhibitor of mesothelioma growth. acetylcholine receptor (7-nAChR). The cobra toxin treatment started in this tumour model investigation, however, 48 hours after transplanting mesothelioma cells, maybe without vascular support and before the cells were transplanted. As a result, it's possible that following implantation, resistant cells will be chosen. This includes 397 uses for snake toxins in medicine 19that additional research must be done to assess –cobra toxin's anticancer effects in a model with well-documented pleural implantation. Also, more research is required to comprehend the intricate 7-nAChR adversarial system found inside tumour cells and to assess the potential of 7-nAChR as a target for cancer treatment. Moreover, considering that an active neurotoxic is being employed as a therapy, any off-target adverse effects and they prepare for potential clinical use a same so the lioma treatment, preclinical study on the venom peptide's immunogenicity is required [43].

**A Preliminary Investigation on the Possibility of Developing Cancer Vaccine Using Snake Venom Components:-**

According to the WHO, there will be 10 million cancer-related deaths globally in 2020, with lung cancer accounting for the majority of them. One in five people, or 20%, will develop cancer in developed nations. Additionally, the incidence of new cases of cancer is rising globally, making it a serious issue that is affecting human society's health, particularly in the West. Proliferation is a crucial biological mechanism for cells to live during proper self-renewal and is necessary for cellular up keep. According to the World Health Organization, proliferation is a crucial physiological process for cells to survive and is necessary for maintaining cellular multi potency. Cancer is a significant cause of death globally. However, if the process of repair is not carried out, the unpaired DNA may result in carcinogenesis, or the production of cancer cells, which can be found in all body parts and result in many cancer types like lung, breast, colon and leukaemia. Damaged DNA is typically repaired. In general, the forms of cancer differ between men and women, as well as different age groups. a physiological process that is typical. Apoptosis control is crucial for preserving homeostasis, and a cell's loss of the ability to undergo apoptosis is linked to a wide range of human disorders. This is crucial in many disease processes because it is started by a wide variety of intrinsic or extrinsic cues. In general, malignancies, especially those mentioned above, can be benign, meaning they stay in their original location and do not infiltrate nearby tissues or migrate to other parts of the body. Parallel to this, tumours can also be malignant, in which case the tumour can move through out the body via the lymphatic or circulatory systems and infect nearby tissue, a condition known as metastasis. This results in unchecked cell cycle progression and the deactivation of apoptotic mechanisms and is caused by the activation of oncogenes and/or the deactivation of tumour suppress or genes (TSG) **Table 1** [44]. Two kinds of genes play a role in the emergence of cancer: oncogenes and tumour suppressors. Once activated, these genes aid in the growth of cancer cells by promoting unchecked cell division and the cancer cells' ability to survive even after treatment. On cogenes can have tens or thousands of mutations, but only a small number of these can cause cancer. The seal alterations might be point mutations, inversions, amplifications, deletions, ora combination of these, however point mutations are the most frequent. Numerous factors, such as hereditary mutations, diet, smoking, and infectious organisms, are responsible for these mutations. Despite the seal alterations, cancer cells have the capacity to elude the immune system, which allows the body's immune system to identify and kill these cancer cells before they spread. The cancer cells must there forebere moved by treatment. A worldwide search for several therapeutic approaches, such as chemotherapy radiation, and surgical methods, has been prompted by the rising incidence of cancer. The type of treatment, such as surgery, radiation, or chemotherapy, is determined by the disease's stage. Numerous of these techniques concentrate on the signal ling networks that control cell growth and survival. For instance, the majority of therapeutically used cytotoxic anti cancer medicines, such as doxorubicin, 5 - fluorouracil, and cisplatin, can cause ferroptos is, an alternate form of cell death, in cancer cells that are susceptible to it. The combination of all these moderate therapy techniques improves therapeutic effectiveness but may also increase the risk of medication toxicity. Although cancer is treated with surgery, chemotherapy, and radio therapy, many patients are beginning to look for other options, which includes using complementary and alternative medicine (CAM). Because many cancer patients think CAM can help them treat their illness, lessen the side effects of cancer treatments, and develop immunity to cancer, CAM is practised in many nations, including Europe, the USA, and Asia. In addition, a lot of patients combine complementary and alternative medicine (CAM) with traditional therapies in the hopes of improving their chances of healing. Acupuncture, diets, prayers, massages, and dietary supplements containing pre biotics, vitamins, animal extracts, and herbal items are examples of CAM practises that are not included in traditional medicine. Young to middle-aged women who have a good education make up the majority of CAM users.

This is due to a number of factors, including the fact that they place less trust in conventional treatments than in their CAM provider, prefer natural products with few side effects, or have friends and family who have used CAM and reported improved health and wellbeing. Contrary to conventional medicine, which has been studied, tested, and put through clinical trials before being approved to treat patients, complementary and alternative medicine (CAM) lacks evidence regarding how effective it is in treating cancer, despite the fact that it appears promising. The effectiveness of CAM in the treatment of cancer requires further research. Immunotherapy is an additional, cancer-specific treatment option that is firmly supported by research. The field of immunotherapy is expanding and receiving a lot of attention for its potential to treat cancer. Utilising the patient's innate and adaptive immune system to eradicate cancer cells is known as immunotherapy. This entails giving the immune system the ability to identify, hunt down, and destroy cancer cells within the body, which requires identifying specific antigens expressed on cancer cells. There are two ways to administer immunotherapy: passively and actively. The we provided discusses two main approaches to cancer immunotherapy: the active approach and passive approach. The active approach involves triggering the patients immune responses to develop specific antibodies and T cells to eliminate cancer cells. In contrast, the passive approach involves administering ex vivo immune elements, such as immune cells or antibodies, without initiating an immune response.

There are five types of cancer immunotherapy treatments:

i. Oncolytic Immunotherapy
ii. Cytokine based Immunotherapy
iii. Immune checkpoint Inhibitors
iv. Cancer vaccines
v. Adoptive Cell Therapy

In addition to these conventional approaches, researchers are exploring the use of natural products, including dietary supplements from both plant and animal sources, as potential substitutes for cancer treatment. Specifically, animal and insect products such as venom or milk are being investigated. Bee venom is highlighted as an example of an insect product with potential anti cancer properties. Bee venom contains various components, including peptides like melittin, adolapin, and apamin, enzymes such as phospholipase A2 and hyaluronidase, as well as non-peptides like norepinephrine and dopamine.

Bee venom can be utilized as a treatment for conditions like neurological disease, cardio vascular disease, and rheumatoid arthritis thanks to these components' anti oxidant, anti-apoptosis, and anti-inflammatory effects. Additionally, research has demonstrated that melittin can inhibit phosphorylation that is induced by ligands [47]. Bee venom is an illustration of an insect product. The anti cancer properties of bee venom are drawing attention, as it contains a combination of peptides including melittin, adolapin, and apamin, enzymes like phospholipase A2 and hyaluronidase, and non-peptides like norepinephrine and dopamine. Bee venom can be utilized as a treatment for conditions like neurological disease, cardio vascular disease, and rheumatoid arthritis thanks to these components' anti oxidant, anti-apoptosis, and anti-inflammatory effects [20]. Additionally, research has demonstrated that melittin can inhibit phosphorylation that is induced by ligands. In breast cancer cells of the human epidermal growth factor receptor 2 and the epidermal growth factor receptor. However, because melittin is broken down in the body before acting as an anticancer agent, bee venom has not been approved for the treatment of cancer. Further research is required before conducting clinical trials because injecting bee venom can also result in hemolys is. Snake venom is another type of venom that has been researched as a cancer treatment. Through their fangs, venom ous snakes inject venom into their prey, and according to the WHO, snake bites are a neglected tropical disease that claims the lives of more than 100,000 people annually. Despite this, it has been discovered that snake venom is a biological source that could be used to create medicinal medications. A complex mixture of peptides, proteins, enzymes, carbohydrates, and other bio active compounds can be found in snake venom. Either enzymatic or non-enzymatic activity is expressed by these proteins. Snake venom metalloproteinase (SVMP), snake venom serine proteinase (SVSP), phospholipase A2 (PLA2), hyaluronidase, L-amino-acid-oxidase, or acetylcholinesterase are examples of proteins with enzyme activity, where as three – finger toxins and C-typelectins are examples of proteins without enzyme activity. These component scan also cause many. Additionally, it is well-known that the anticancer properties of snake venom can combat cancer cells. Studies have demonstrated that the venom of *Bungarus fasciatus* can have cytotoxic effects on human lung adenocarcinoma A549 and human breast cancer MCF7 cells. An enzyme called PLA2 with a molecular mass of 13–15k Dahydrolyzes the glycerol phospholipid membrane to liberately so phospholipids and arachidonic acid. This demonstrates that snake venom may be used to cure cancer. Integrins are yet another target for snake venom [47,48]. The non-covalent interaction of the – and – sub units results in the heterodimeric trans membrane proteins known as integrins. Integrins influence the invasion, migration, proliferation, and survival of cancer cells, which contributes to tumour development, metastas is, and angiogenes is. Disintegrins are cysteine-rich, non-enzymatic proteins that are present in the venom of snakes belonging to the Elapidae, Viperidae, Crotalidae, and Atract aspididae families. Research has shown that disintegrins have anti tumor effects that affect angiogenes is and metastas is spread. Leucurogin, adisintegrin that was cloned from the *Bothrop sleucurus*, was discovered to suppress the tumor's angiogenesis, which prevents Ehrlich tumours from growing when implanted in mice. Additionally discovered that platelet aggregation and angiogenesis were inhibited in ECV304 cells by the disintegrin, admonitor, from *Agkistrodonhalys brevicaudus* teenager. For a while now, the impact of snake venom on cancer cells has been well investigated. However, none have ever entered clinical trials because of how toxic it is to humans. The components of snake venom may contain the key to healing cancer, according to the literature [49,50]. This study will examine whether elements of snake venom may be utilised in cancer vaccines and whether they could elicit an immune response and produce memory cells that could target cancerous cells while they were forming.

The stated health benefits of such anti-cancer candidates have never been sufficiently examined in vivo, despite the

fact that enough studies on snake venom have been conducted in vitro [51]. Based on a review of the scientific literature on the potential of snake venom as an anti-cancer agent and (2) a preliminary finding that the two distribution maps of cancer and snake bite in the world show a sufficient overlap, it can be seen that while developed countries have low rates of snakebite, they also have high rates of cancer, as opposed to developing countries, which have high rates of snakebite but low rates of cancer [52]. The present study, therefore, aimed to address this theoretically using bio informatics tools and elicit the possibility that

I. People who have been bitten by venomous snakes will be developing natural immunity to cancer and hence gain prophylaxis

II. If that can be proven then components of snake venom could hold a future promise to be used as a vaccine against cancer [53].

**CONCLUSION**

The incorporation of snake venom components into biomedicines has enormous therapeutic promise. Snake venoms are great sources of pharmacologically active substances because they are complex combinations of bioactive chemicals that have evolved over millions of years. Drug development using components of snake venom has showed promise, especially for the treatment of diseases like cancer, cardio vascular disease, neurological disorders, and pain management. They have shown anticoagulant and anti platelet characteristics, which makes them useful for creating anti thrombotic medications. As an alternative to conventional medications, snake venom toxins also have analgesic qualities and can target particular ion channels and receptors involved in pain feeling. Peptides from snake venom have significant anti bacterial capabilities and can treat germs that are resist ant to anti biotics, which may help in the creation of new medications. By utilizing their distinct binding capabilities to find and track disorders like cancer, venom components can also be employed in the development of diagnostic instruments. To completely comprehend the mechanisms of action, maximize efficacy, and guarantee safety for clinical application, additional research is necessary. To assess effectiveness, dose, and potential side effects, thorough testing, preclinical research, and clinical trials are required. In order to successfully create biomedicines derived from snake venom, strict adherence to scientific and ethical criteria is essential. In conclusion, using components of snake venom in biomedicines is a possible route to treating difficult medical conditions and enhancing human health. These venom-derived chemicals could have a big influence on medicine with more research and development.

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