International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
(A Peer Reviewed, Referred, Indexed and Open Access Journal)
DOI: 10.22192/ijarbs Coden: IJARQG (USA) Volume 9, Issue 7 -2022

Review Article

DOI: http://dx.doi.org/10.22192/ijarbs.2022.09.07.008

Cone snail venom a peptide as Anticiceptive: A Review

Jayshree R. Aate, Sakshi Wairagade, Manisha G. Suryavanshi, Sonali S. Masirkar, Naznin D. Sheikh.
Hi- Tech College of Pharmacy, Morwa, Chandrapur.

Abstract

Cone snails have evolved a specialized venom apparatus to subdue their prey. It is comprised of a venom gland, salivary glands (and accessory salivary glands), a radular sac, a pharynx, a proboscis and a radular A cone snail's radular acts as a delivery system, and is hollowed and barbed to resemble a miniature harpoon up to 10 mm long)19. These harpoons are produced and stored in a specialized organ, the radular sac, which is divided into two arms and connects to the pharynx. Each venom typically comprises 200-1000 bioactive with members belonging to a few to dozen different scaffolds, sometimes with dozens of closely related analogues. However, this restricted number of scaffolds does not limit functional diversity 37. By contrast, these limited categories provide a foundation for a working hypothesis on the basis of a structure, since homology modeling enables construction of a plethora of molecules from a limited set of available data. Indeed, sometimes changing just one or a few amino acids in such a mini protein can drastically change its potency and selectivity towards a pharmacological target without affecting its structural backbone.

Keywords: Cone snails, venom, homology modeling, pharmacological target.

1. Introduction

The knowledge of marine biodiversity is likely underestimated, especially regarding deep water forms of life because access to the resource is very restricted, rendering the sampling effort difficult and expensive. Yet, the remarkable hit rates of marine compounds in screening for drug leads have maintained the interest of pharmaceutical companies Therefore, the major hurdle to the development of an active marine compound into a drug remains the procurement or manufacturing of large quantities in a sustainable way. Many of the marine organisms of interest are difficult to breed or grow in vitro, implying that the only source of the compound is from wild harvest. While it is quite challenging to evaluate the full extent of marine bioprospecting, concerns over the overexploitation of endemic species or small local populations have emerged2. Recently, the approval of the first marine-derived drug for the treatment of intractable pain has further stimulated drug discovery programs from marine organisms, This molecule, a short peptide called

ω-MVIIA or Zinconotide and marketed as Prialt, was originally discovered in the venom of the magician cone snail, Conus magus, as a potent blocker of N-type calcium channels). Several other "Conopeptide" targeting ion channels, transporters and receptors are in various stages of clinical trials for the treatment of pain, but also myocardial infarction, epilepsy and neurodegenerative diseases). As a result, cone snail venoms are regarded as pharmacological treasures2. Historically, cone snails have been harvested from the wild, their venom gland dissected, the venom extracted from the venom duct, and the venom peptides tested in animals, isolated tissue preparations or a range of bioassays.

Figure 1. Species of cone snail

When more material is necessary to allow minor components to be characterized, further snails are collected, with tens to hundreds of cone snails sometimes necessary to obtain a single molecule of interest). This practice has been questioned as to whether it was sustainable and ethically acceptable. Yet, a collective reply from researchers corrected that most world leading groups working with cone snail venoms are limited to 15-20 specimens per species per year. This number is dwarfed by the hundreds of thousands of snails harvested for the shell trade around the globe each year. Research efforts into the discovery of new drugs are certainly more valuable than ornamentation, with outcomes such as drugs that can directly benefit us[3].

A. Biology of cone snail

Source and culture of larvae: A cluster of egg capsules laid on the underside of a limestone boulder in shallow, near shore water off Oahu, Hawaii provided larvae for this study. The location is given as "station 9"in survey of Hawaiian cone snails. Species identification as *C. livid us* HWASS IN BRUGUIÈRE, 1792, was confirmed by amplification of a portion of mitochondrial 16S rRNA extracted from larvae Hatched larvae were cultured at 24–27°C in 1.0 or 2.0l glass beakers of coarse-filtered sea water (Millipore pre-filter) at an initial density not exceeding 0.2 larvae ml−1.After two weeks of culture, density was reduced to not more than 50 larvae in 2l.

B. Habitat

As Generally, the genus Cones occurs throughout all tropical and subtropical oceans but is most diverse in the Indo-West Pacific region .The few species found beyond the 40° N or S parallel are localized in South Africa, Southern Australia, Southern Japan and Mediterranean Sea.

C Behavior

The adult cone snail hides under rocks or buries itself in sand during the day. Cone snails are usually solitary, but some species can be found in great numbers in particular areas, mainly due to their specialized habitats (i.e. a microhabitat) at night. cone snails become active, leave their retreat and search for prey. Cone snails are highly specialized predators with some species feeding exclusively on worms (70%), mollusks (15%) or fishes (15%)

D. Taxonomy

Conus is the type genus of the Conidae, which was validly established as a family by John Fleming in 1822.The Conidae together with the Turridae and Terebridae form the Super family Conidae, also known as the Conceal or Toxoglossa12. As the largest genus of marine invertebrates, Conus arguably presents the most challenging taxonomy and nomenclature, with many new species described every year. Recently, a revised classification of the recent and fossil Conidae gastropods has been published, based on radular morphology as well as other factors such as dietary habits and periostracum morphology[13].

E. Reproductive Biology

Reproduction in cone snails has appears that most have separate sexes and are fertilized internally Eggs are laid once a year and attached to substrate in capsules, with each capsule containing a varying number of eggs13. Typically, egg masses are made of up to 25 egg capsules, and each capsule may contain up to 1,000 eggs. Therefore, each egg mass may contain about 25,000 eggs. Two types of offspring or hatchlings have been described, the villager (free-swimming larvae) and veliconcha (juvenile snails) stages.

F. Venom Apparatus

Cone snails have evolved a specialized venom apparatus to subdue their prey. It is comprised of a venom gland, salivary glands (and accessory salivary glands), a radular sac, a pharynx, a proboscis and a radular A cone snail's radular acts as a delivery system, and is hollowed and barbed to resemble a miniature harpoon up to 10 mm long)19. The total number of radular present in a radular sac is species-dependant, and seems to vary according to the feeding habits (e.g. molluscivorous snails, which can inject venom multiple times into their prey, produce larger number of harpoons,

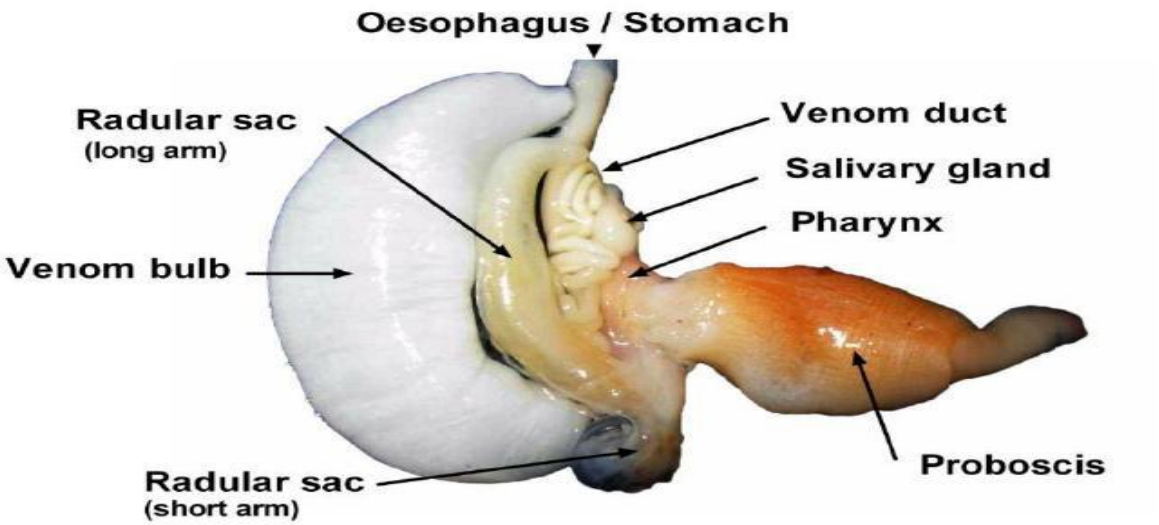

Figure 2: Cone Snail Venom Apparatus

2. Various species of conus snail:

The conidian (cone snails, terabits, and turrids) are a hyper diverse group of marine gastropods that prey on fish, worms, and other mollusks (Figure). Several conidian lineages are characterized by specialized organs referred to as a venom apparatus that is used to subdue prey, Analysis over the last three decades of venom toxins produced by various species in the genus *Conus* (cone snails), the most famous representative of this group.

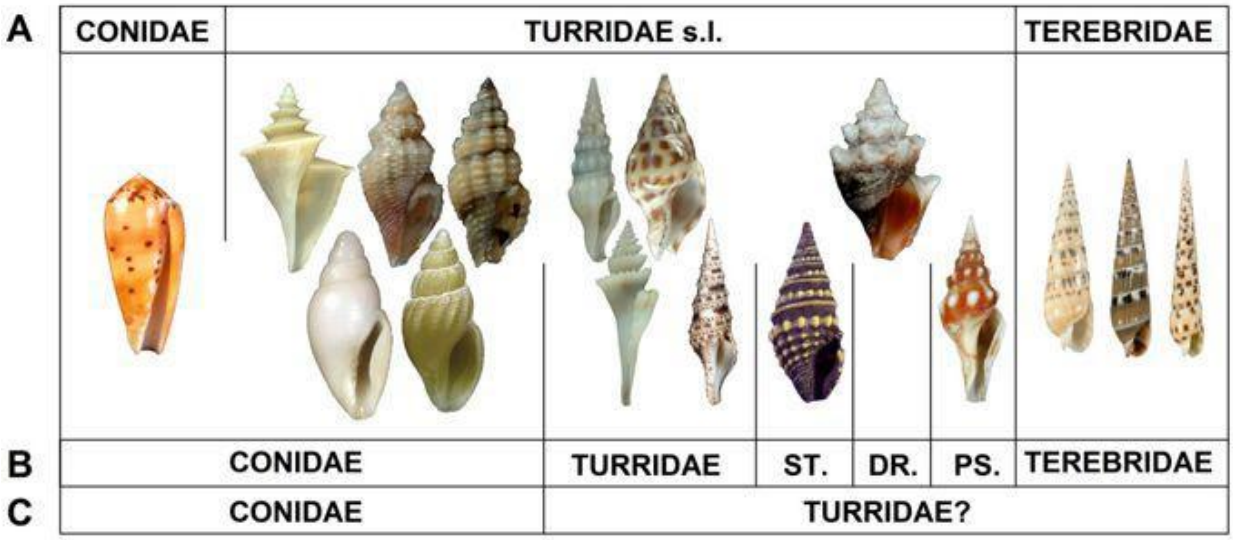

Figure 3: Types of conus snail

a. Magician's cone: (*Conus magus*)

The magician‟s cone, *Conus magus*, is a fish-hunting or piscivorous cone snail found in the Western Pacific. It is so common in some of small Pacific islands, especially in the Philippines, that it is routinely sold in the market as food.

Figure 04: Magician's cone

b. Geography Conus: (*Conus geographus*)

The geographic cone is the most venomous of the 500 known cone snail species, and several human deaths have been attributed to them. Their venom, a complex concoction of hundreds of different toxins, is delivered via a harpoon like tooth propelled from an extendable proboscis.

Figure 05: Geography Conus

c. Barthelme's cone :(*Conus barthelemyi*)

This species occurs off islands throughout the Indian Ocean, ranging from Reunion to the Maldives and Seychelles; it also occurs around Christmas Island. At Christmas Island, this species occupies a unique niche; only seven specimens are known but the species is extant. It is found on coral walls in caves, 30-60 m deep.

Figure 06: Barthelme's cone

d. Glory of the sea cone: (*Conus gloriamaris*)

Although the Glory of the Seas Cone Shell is perhaps the most famous and coveted shell in the history of conchology, it is neither the most attractive nor rarest species of the Cone family. When first described in 1777, however, it enjoyed what could only be described as true „celebrity statuses amongst rich European collectors. Specimens changed hands at auction houses for very large sums of money especially the larger and more impressive examples.

Figure 07: Glory of the sea cone: (*Conus gloriamaris*)

e. Virgin cone:(*Conus virgo*)

This marine species occurs in the Red Sea and in the tropical Indo-West Pacific off Tanzania, Madagascar, Aldabra, Chigoes, the Mascarene Islands; India, the Philippines and Australia (Northern Territory, Queensland, Western Australia[29].

Figure 08: Virgin cone: (*Conus virgo*)

f. *Conus californicus*:

A small but very aggressive species, Conus. Californicus immediately reacts to the presence of a large polychaete worm. Several *C. californicus* simultaneously attack the worm, resulting in many individuals feeding on the larger polychaete[28].

Figure 09: *Conus californicus*

3. Chemistry of cone snail:

a. Pharmacology:

The enormous molecular diversity of the venom components of cone snails ranges from small molecules10 to larger protein toxins. The first active molecular component identified from Conus venom was serotonin in 1972. Although serotonin appears to be involved in the envenomation mechanism of some *Conus* species.[12]

Table no.01. Receptor Class Involve In Venomics Study

Sr. no	CLASS	MODE OF ACTION	EXAMPLE
1	ω-conotoxins	Ca‟‟v 2.2 inhibitor	MVIIA
2	μ- conotoxins	Na‟‟v inhibitor	SIIIA
3	μO- conotoxins	Na‟‟v 1.8 inhibitor	MrVIB
4	Δ- conotoxins	Na‟‟v enhancer	EVIA
5	Ķ- conotoxins	K‟‟v inhibitor	PVIIA
6	χ-Conopeptide	NET inhibitor	Xen2174
7	α- conotoxins	NaChR inhibitor	VC1.1
8	σ- conotoxins	5HT 3 antagonist	GVIIIA
9	ρ-Conopeptide	α-1 adrenoceptar inhibitor	TIA
10	Conantokin	NMDAR antagonist	conotokin-G
11	Conopressin	Vasopressin agonist	Conopressin-G
12	Contulakin	Neurotensin R agonist	Conotulkin-G

protocols along with biochemical and spectrometric determinations28. Extracting the mRNAs from the venom and producing their corresponding cDNA libraries, genes encoding for the venom precursors can be outlined and several „unmodified‟‟ Conopeptide sequences deduced via mRNA-

Figure 09: Conopeptide sequences deduced via mRNA

Zinconotide:

Zinconotide, originally known as SNX-111 and now marketed as Prialt, is a novel 25 amino acid peptide isolated from marine snail venom. It is a highly selective N-type voltage-sensitive calcium channel antagonist; these channels are found at the presynaptic nerve terminals in the spinal dorsal horn. The putative mechanism of Zinconotide induced pain relief is the blockade of neurotransmitter release at the primary afferent nerve termina l32.

The FDA and the European Union have approved the use of Zinconotide as a nonopoid intrathecal analgesic option for patients with neuropathic pain refractory to conventional treatments. Common causes of neuropathic pain include complex regional pain syndrome (CRPS), HIV-associated neuropathy, post herpetic neuralgia, diabetic peripheral neuropathy , and central neuropathic pain syndromes related to multiple , post stroke pain, and spinal cord injury[31].

Statistically significant improvement in pain relief was noted with Zinconotide as compared to placebo in all trials (malignant pain: 53% Zinconotide v. 18% placebo; nonmalignant pain: 31% Zinconotide v. 6% placebo; slow titration study: 14.7% Zinconotide v. 7.2% placebo). In these studies, the mean reduction in neuropathic pain was 15.7%, 31.6%, and 29.1%, respectively[34.]

Side effect:

Zinconotide has a relatively narrow therapeutic window, with a small difference between the dose required for analgesia and the dose required to produce side effects. Reported side effects include dizziness, confusion, gait ataxia, memory impairment, nystagmus, dysmtria, sedation, agitation, hallucinations, nausea, vomiting, urinary retention, somnolence, and coma. Elevated uric acid, lactate dehydrogenize, and creatine kinase levels have also been reported[34.]

Uses:

1. Hyperalgesia & Allodynia:

Hyperalgesia and allodynia are frequent symptoms of disease and may be useful adaptations to protect vulnerable tissues. Enhanced sensitivity for pain may, however, persist long after the initial cause for pain has disappeared, then pain is no longer a symptom but rather a disease in its own right.

2. Referred Hyperalgesia:

Hyperalgesia of a somatic area that is referred from diseased or inflamed viscera pain as the referred Hyperalgesia often continues during the pain-free periods. Patients report the experience of “tenderness” in the referral zone. Referred Hyperalgesia has been quantified in patients with a variety of different visceral pain states and has also been measured in animal models of visceral pain.[20]

3. Calcium Channels Blockers:

Compounds that alter cell membrane hyper excitability by altering Ca2+ ion channel function have analgesic activity. Zinconotide (SNX-111) is a 25 amino acid peptide o-conotoxins, isolated from snail venom, that act as an N-type calcium channel antagonist. It is currently in trials for severe cancer pain, but can be given only *via* the intrathecal route. Gabapentin which is approved for use as an anticonvulsant, is used extensively off-label to treat neuropathic pain due to anecdotal evidence of its effectiveness. Gabapentin was thought to be a selective GABA modulator, but evidence for a direct effect on GABAergic function has not been forthcoming.

4. Peptide from cone snail: snail peptide:

The *Conus* peptides had great majority of biologically active *Conus* venom components are peptides, initially synthesized through ribosomal translation as polypeptide precursors, and

posttranslational processed to yield the mature, biologically active venom peptides. *Conus* venoms are unusually complex; every *Conus* species can express its own repertoire of approximately 100–200 different peptide toxins in the venom duct. Because there is virtually no molecular overlap between the peptides found in the different *Conus* species, there are >50,000 different peptides in living cone snail venoms.

toxins are expressed in the epithelial cells of cone snail venom ducts and initially translated as prepropeptide precursors, with an N-terminal signal sequence, an intervening “pro” region and at the C-terminal end, the mature toxin in single copy. This is highly unusual, because in most gene families encoding secreted polypeptides, the *Conus* peptides are generally disulfide-rich. However, three characteristics differentiate conotoxins from other venom polypeptides. The mature toxins from *Conus* venoms are unusually small, typically 10–30 amino acids[28]

5. Peptide from cone snail venom:

The cone snails from all marine environments (Phylum Mollusks, Class Gastropods, and Order Sorbeoconcha) represent a large genus of approximately 700 carnivorous predator species they are classified into three groups, referred to as molluscivore, vermivore, and piscivore. The vast majority of peptides (several thousands) are expected to be short, highly rigid, disulfide-bridged 10- to 20-mer products. They target enzyme, neurotransmitter transporters (e.g., noradrenalin/nor epinephrine transporter targeted by χ-Conopeptide), G-protein-coupled membrane receptors, voltage-gated ion channels (Na+, Ca2+, and K+ channels) and ligand-activated ion channels (nicotinic acetylcholine receptor of neuronal and neuromuscular subtypes, 5HT3 serotonin receptor, glutamate-type receptor such as *N*-methyl-d-aspartate/NMDA receptor Interestingly, it has been highlighted that several venom components act simultaneously to paralyze the prey and alter neuromuscular transmission. Indeed, these molecules act in concert on targeted presynaptic Ca2+ channels, postsynaptic nicotinic receptors, and voltage-gated Nav channels to maximize‟ venom toxic effects[39].

The precursors are composed of:

(1) A pre-region which is well-conserved among members of the same super family,
(2) A more or less conserved pro-region,
(3) A Conopeptide amino acid sequence itself. The conotoxins formally refer to as cone snail peptide toxins cross-linked by two or more disulfide bridges, and acting on voltage-gated ion channels (K^+, Ca^{2+}, and Na^+ channels).

6. Pain & its mechanism:

Pain is a sensory and emotional experience. The emotional component is variable from person to person and in the same person from time to time. But the most relevant in terms of therapeutic application is into nociceptive and neuropathic. The International Association for Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage[23]

Pain can be continuous and paroxysmal, as in headaches or neuralgia. Considering the durations of symptoms, pain can be divided into groups:

• **Acute pain**: duration < 3 months, acts as a warning defensive (post-operative pain, traumatic, associated with medical procedures).
• **Chronic pain**: duration > 3 months does not fulfill the role of warning and defensive, due to the nature and symptoms of the disease is considered in itself, and requires a multi therapeutic activities • **Survived pain**: most often occurs as a result of improper treatment of acute pain, persists despite the healed tissue, the damage to which resulted in acute pain[34].
Nociceptive Pain Nociceptive pain is the most common type of pain and is caused by the detection of noxious or potentially harmful stimuli by the nociceptors around the body23.
Anticeceptive pain: the action or process of blocking the detection of a painful or injurious stimulus by sensory neurons[24].

Central mechanism of sensitization: Increased responsiveness of the spinal cord after prolonged, intense nociceptive input. This includes the dorsal horn neurons, interneuron‟s, and ventral horn neurons. The thalamus, cortex, and other brain areas also develop relevant changes. As a consequence of the central sensitization.

• There is role of excitatory Amino Acids and tachykinins in the sensitization of dorsal horn neurons.

• Activation of NMDA receptors and increases in intracellular Ca++ level play role in triggering and maintaining neuronal sensitization in the dorsal horns.

• NMDA receptor antagonists (ketamine) potentiate the analgesic effect of opioids and may play a role in preventing central hypersensitive states[27].

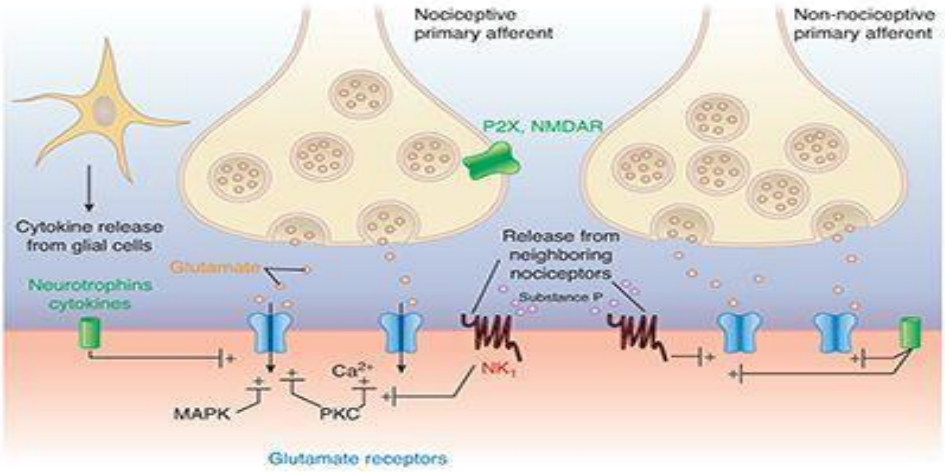

FIGURE 6-5 The synaptic mechanism underlying peripheral nociceptive stimuli-induced persistent heterosynaptic potentiation of dorsal horn neurons. Transmitters and mediators released from primary afferents and surrounding microglial cells, including substance P, neurotrophins, and cytokines, may act at a distance on dorsal horn neurons to produce long-lasting heterosynaptic potentiation of glutamatergic transmission. Note that both inputs from nociceptors and nonnociceptors may be potentiated. MAPK, mitogen-activated protein kinase; P2X, purinoreceptor; PKC, protein kinase C; NK_1, Neurokinin 1 (substance P receptor).

Figure 10: The Synoptic Mechanism underlying peripheral nociceptive stimuli.

7. Mechanism of action of venom:

Defination of venom:

A toxic substance produced by some animals (such as snakes, scorpions, or bees) that is injected into prey or an enemy chiefly by biting or stinging and has an injurious or lethal effect (a substance that is poisonous)[27].

a) Animal venomics: Venoms typically consist of a cocktail of structurally and functionally different bioactive ranging from small molecules up to large proteins. However, most of the compounds fall within the class of well structured medium sized peptides. Each venom typically comprises 200-1‟000 bioactive with members belonging to a few to dozen different scaffolds, sometimes with dozens of closely related analogues. However, this restricted number of scaffolds does not limit functional diversity37

b) Venomics: Venom proteomic, venom gland Transcriptomics and genomic investigations have revealed axon specific trends for the formulation of venom complexity. Moreover, venom peptidomes provided qualitative and quantitative information over time on translation efficiency.[29]

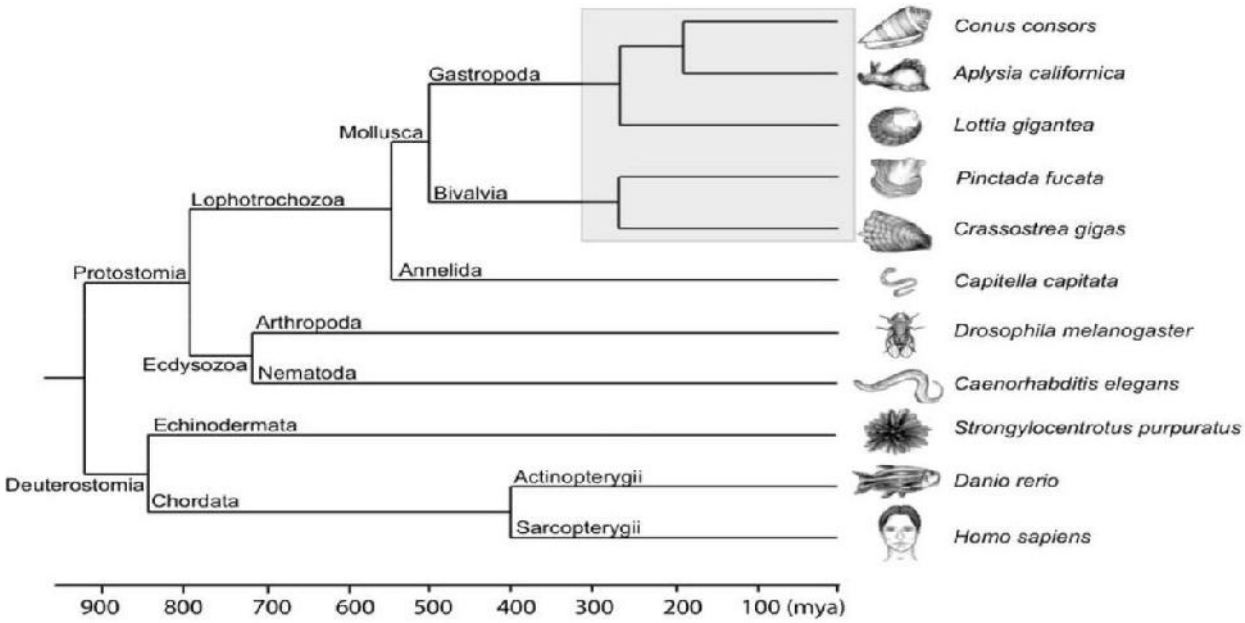

Figure 11: Family representation of venomics

Mechanism:

Within the snail venom, there are various "conotoxins" in combination specific to the species. These toxins have a variety of neuromuscular effects through glutamate, adrenergic (chi conotoxins), serotonin, and cholinergic pathways. Some conotoxins exert their effects on sodium (delta conotoxins), potassium, and calcium ion channels[2]

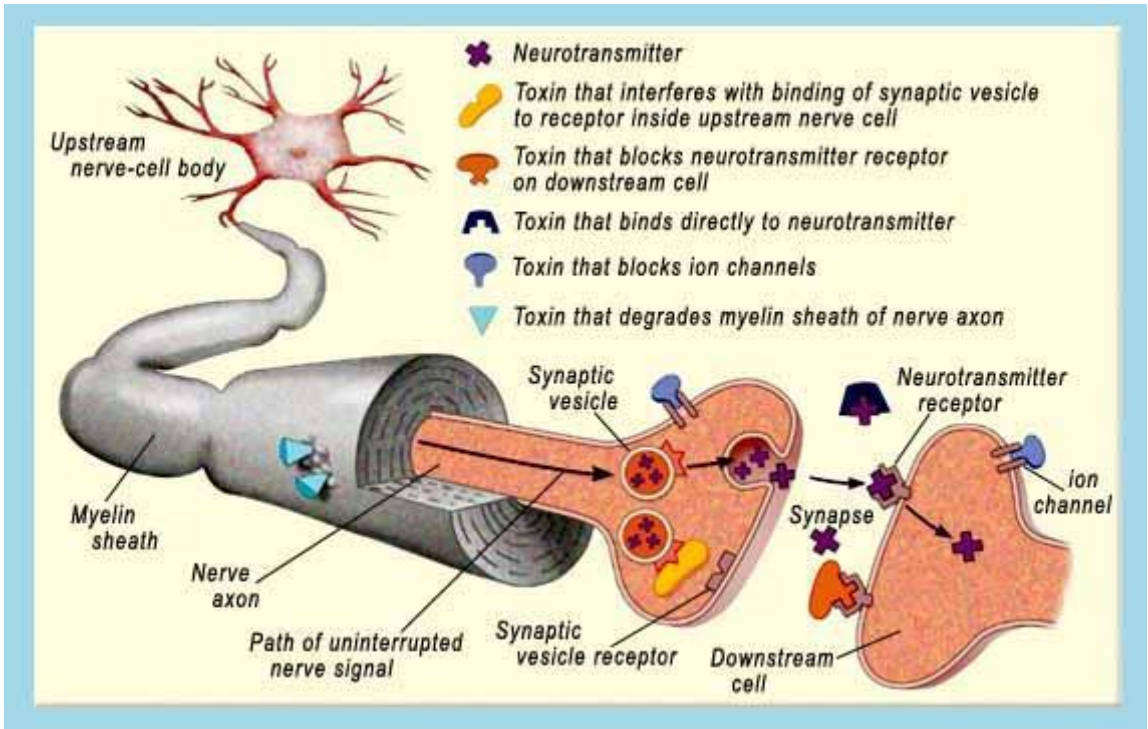

Figure 12: Mechanism of action of venom

8. Benefits over other drugs:

The standard preparation procedures for crude venoms require a pre-fractionation step prior to conducting bioassays to reduce sample complexity and to discard undesired effects that may be induced by cytotoxic components, pore forming toxins, proteases, hyaluronidases, nucleases or lipases. Once bioactive are identified in a primary screen, several rounds of sub fractionation and rescreening can be required19. Furthermore, the deconvolution process, to determine the complete primary structure of a highly potent hit present in a small sample, may require additional material. This represents maybe 1/1000 of the molecular biodiversity offered by these creatures, only a portion of which has undergone functional studies on a limited number of pharmacological targets.

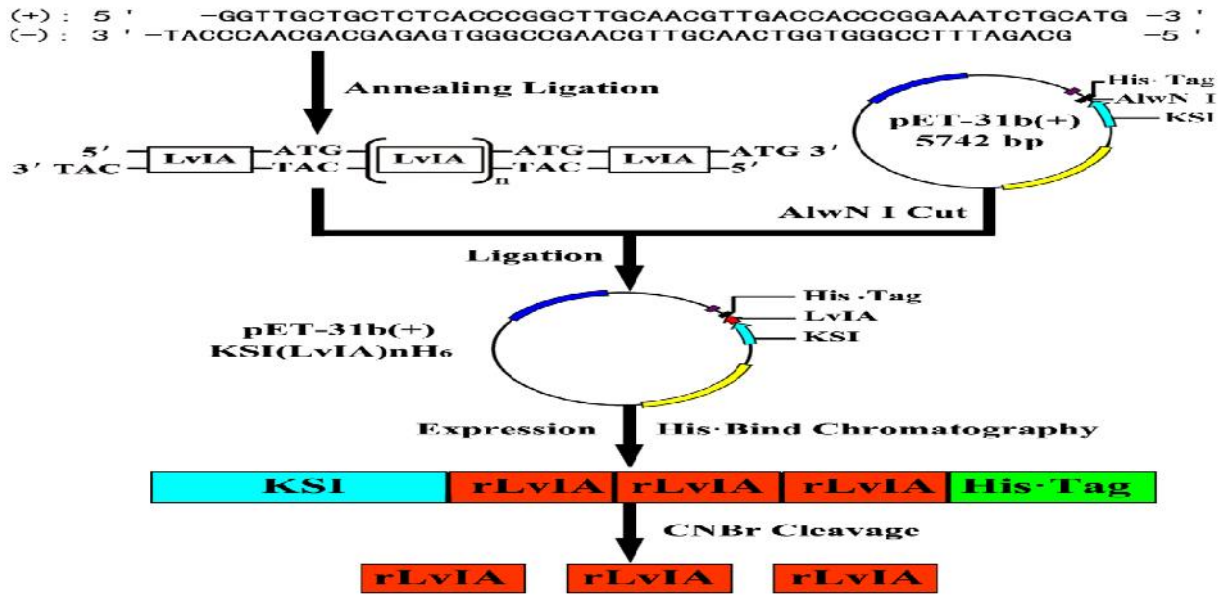

Figure 13: Bioassay from pre fractionation to deconvolution process to show binomial role in venomics study.

9. Bio-prospecting:

Bioprospecting is broadly defined as the exploration of biodiversity for commercial and/or scientific purposes to generate valuable genetic and biochemical resources clearly, the primary goal of such activity is often to find novel molecules to cure human diseases. Plants, microbes and marine invertebrates are currently the main focus of academic and industrial discovery programs Indeed, more than half of our modern medicines are or derived from natural chemical compounds provided by nature.[22]

While a number of traditional medications derived from the venom of snakes, spiders and frogs have shown promise over the years the relative infancy of venom peptide bioprospecting is mainly due to the difficulty in obtaining the material, and to the nature of the active components of venoms, which comprise mainly small proteins and peptides23.Indeed, proteinaceous molecules have long been regarded as poor drug candidates, due to their poor bioavailability and short half-life in biological fluids such as blood and serum. Peptides typically have greater selectivity and affinity compared to small molecules, providing better efficacy and safety, and potentially fewer side effects.

10. Conservation:

Scientific investigations have so far mostly focused on common species of cones snails, and therefore the impact of collecting for scientific purposes has remained limited. By far the most serious threat to cone snail diversity is the destruction of their habitat, which in most cases consists of fragile reef ecosystems Coral reefs around the world are threatened by pollution, destructive fishing practices, coastal developments and mass tourism, not to mention acidification and warming of oceans due to climate change.[41] However, it should also be mentioned here that none of the 700 species of cone snails is listed on CITES (Convention on International Trade in Endangered Species).

11. Assay/testing of venom:

a) High Throughput Screening (HTS) Assays: A range of HTS platforms are already available (such as fluorescence resonance energy transfer or homogeneous time resolved fluorescence), permitting the screening of thousands of samples per day. The miniaturization of HTS assays is an important objective for the pharmaceutical industry as well as for fundamental science (Houston & Banks 1997).

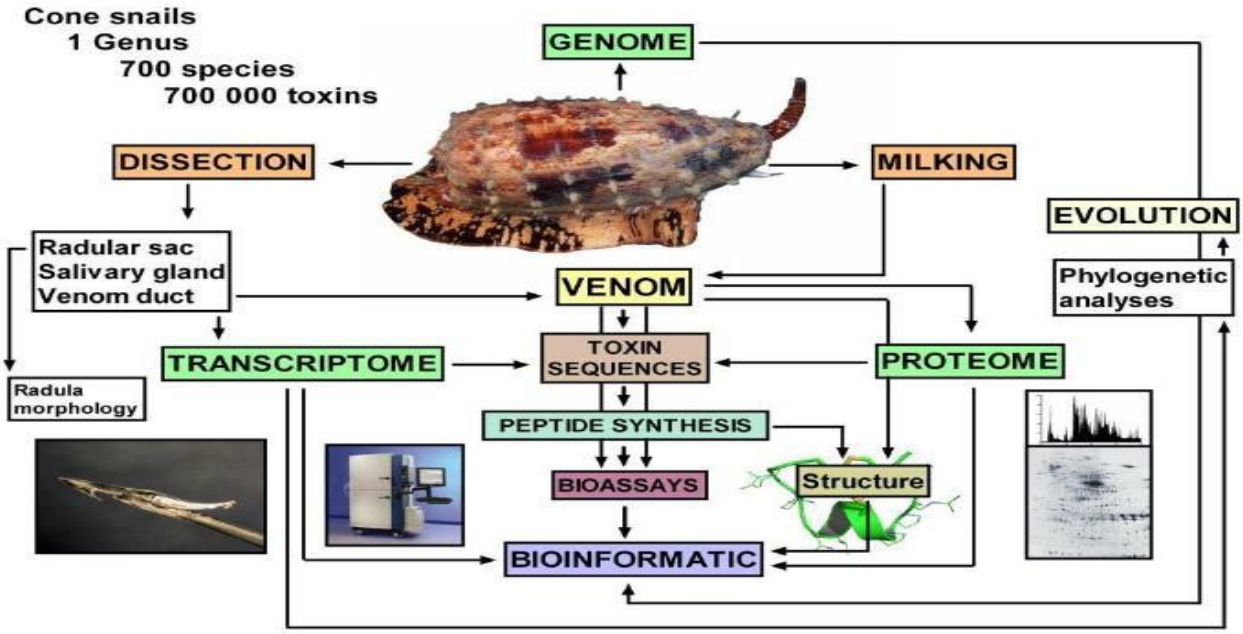

Figure 14: Current strategies to maximize scientific outcomes from a unique specimen.

b) Mass Spectrometry:

Mass spectrometry has become the method of choice to study the complexity of venoms In particular; soft ionization technologies such as matrix-assisted laser desorption-ionization (MALDI) and electrospray (ESI) are heavily utilized to unravel the composition of these proteinaceous mixtures). A liquid chromatography step can be carried out off-line (MALDI) or online (ESI), each method providing high quality yet complementary data

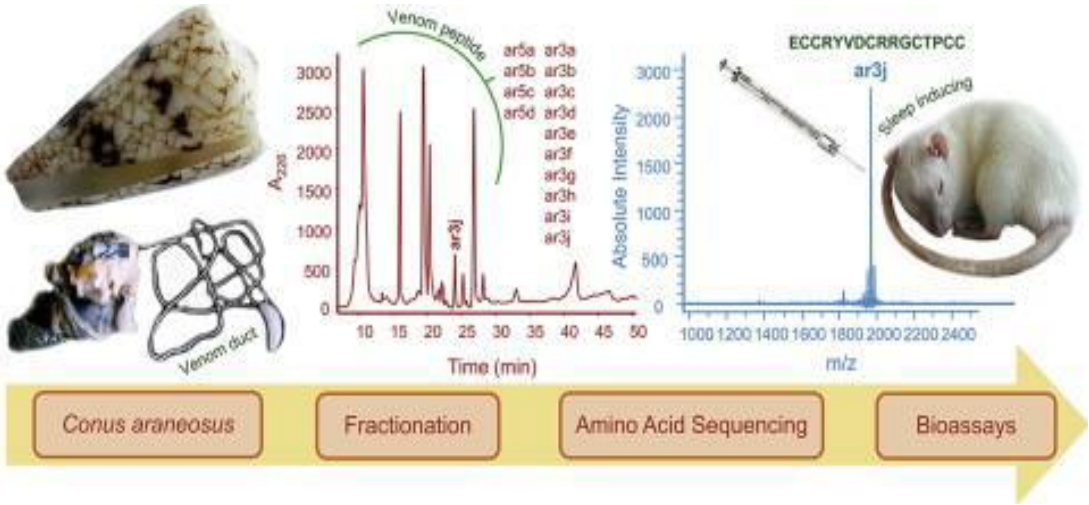

Figure 15: Mass Spectroscopy of venom

c) Transcriptomics :

The Human Genome Project, with the unprecedented throughput requirement for DNA sequencing, has fuelled the development of novel technologies that can benefit many different research projects, including those dealing with non-model organisms such as cone snails. The so-called “next-generation sequencing” technologies, as opposed to the traditional Sanger sequencing.

Future scope:

a. Gene duplication‟ through diverfication of venom gene.
b. Venomous cone snail are specialized insulin to elicit hypoglycemic shocks for glucose homeostasis, highly expressed venom insulin similar to fish insulin had smallest insulin characterized from any source, potentially provide new insights into structure for functions element of insulin action.
c. Venom effect on monoaminergic, (dopamine,epinephrine,histamine,nor-epinephrine,octopamine,seotonine,tyramine) system via. Manipulate cellular mechanism offensive and defensive action on cvs.
d. Find out new peptides linkage in snake, spider, lizards, scorpion venom (similar transcriptinase effect).

Conclusion and Perspectives

In the near future, marine bioprospecting efforts will likely focus not only on natural extracts from ocean plants, animals, and microbes, but also on the genetic information stored in the genomes and Transcriptomics of these organisms. Thanks to the Human Genome Project, the expertise and technology assembled now benefits sequencing of non-human genomes. The genome and venom gland Transcriptomics of one species of Conus has been published already and more can be expected in the future. Coupled to high throughput mass spectrometry and miniaturized bioassays, these integrated approaches will likely increase the rate of discovery from this valuable resource.

References

1. Arico, S. and Salpin, C. (2005) Bioprospecting of genetic Resources in the Deep Seabed: Scientific, Legal and Political Aspects. United Nations University Institute of Advanced Studies, Tokyo, Japan
2. Biass, B., Krizaj, I., Leonardi, A., Dutertre, S., Favreau, P. and Stocklin, R. (2009) Peptidomics and Proteomics of Conus Consors Cone Snail Venom. Biopolymers, 92, 348-348.

3. Biggs, J. S., OliveraB. M. and Kantor, Y. I. (2008) Alpha-conopeptides specifically expressed in the salivary gland of Conus pulicarius. Toxicon, 52, 101-105.
4. Bingham, J. P., Mitsunaga, E. and Bergeron, Z. L. (2009) Drugs from slugs--past, present and future perspectives of omega-conotoxin research. Chem Biol Interact, 183, 1-18.
5. Chivian, E., Roberts, C. M. and Bernstein, A. S. (2003) The threat to cone snails. Science, 302, 391.
6. Clark, R. J., Fischer, H., Dempster, L., Daly, N. L., Rosengren, K. J., Nevin, S. T., Meunier, F. A., Adams, D. J. and Craik, D. J. (2005) Engineering stable peptide toxins by means of backbone cyclization: stabilization of the alpha-conotoxin MII. Proc Natl Acad Sci U S A, 102, 13767-13772
7. Clark, R. J., Jensen, J., Nevin, S. T., Callaghan, B. P., Adams, D. J. and Craik, D. J. (2010) the engineering of an orally active conotoxin for the treatment of neuropathic pain. Angew Chem Int Ed Engl, 49, 6545-6548.
8. Davis, J., Jones, A. and Lewis, R. J. (2009) Remarkable inter- and intra-species complexity of conotoxins revealed by LC/MS. Peptides, 30, 1222-1227.
9. Droege, M. and Hill, B. (2008) The Genome Sequencer FLX System--longer reads, more applications, straight forward bioinformatics and more complete data sets. J Biotechnol, 136, 3-10.
10. Duda, T. F., Jr., Bingham, J. P., Livett, B. G., Kohn, A. J., Massilia, G. R., Schultz, J. R., Down, J., Sandall, D. and Sweedler, J. V. (2004) How much at risk are cone snails? Science, 303, 955-957; author reply 955-957.
11. Dutertre, S., Biass, D., Stocklin, R. and Favreau, P. (2010) Dramatic intraspecimen variations within the injected venom of Conus consors: An unsuspected contribution to venom diversity. Toxicon, 55, 145
12. Dutertre, S. and Lewis, R. J. (2010) Use of Venom Peptides to Probe Ion Channel Structure and Function. Journal of Biological Chemistry, 285, 13315-13320.
13. Escouba P. (2006) Mass spectrometry in toxinology: a 21st-century s technology for the study of biopolymers from venoms. Toxicon, 47, 609-613.
14. Escoubas, P., Quinton, L. and Nicholson, G. M. (2008) Venomics: unravelling the complexity of animal venoms with mass spectrometry. J Mass Spectrom, 43, 279-295
15. Escoubas, P., Sollod, B. and King, G. F. (2006) Venom landscapes: mining the complexity of spider venoms via a combined cDNA and mass spectrometric approach. Toxicon, 47, 650-663.
16. Fegan, D. and Andresen, D. (1997) Conus geographus envenomation. Lancet, 349, 1672.
17. Garrett, J. E., Buczek, O., Watkins, M., Olivera, B. M. and Bulaj, G. (2005) Biochemical and gene expression analyses of conotoxins in Conus textile venom ducts. Biochem Biophys Res Commun, 328, 362-367.
18. Harvey, A. L. (2002) Toxins 'R' Us: more pharmacological tools from nature's superstore. Trends Pharmacol Sci, 23, 201-203.
19. Harvey, A. L. (2007) Natural products as a screening resource. Curr Opin Chem Biol, 11, 480-484.
20. Harvey, A. L. (2008) Natural products in drug discovery. Drug Discov Today, 13, 894-901
21. Hopkins, C., Grilley, M., Miller, C. et al. (1995) A new family of Conus peptides targeted to the nicotinic acetylcholine receptor. J Biol Chem, 270, 22361-22367.
22. M. Castelin, N. Puillandre, Yu.I. Kantor, M.V. Modica, Y. Terryn, C. Cruaud, P. Bouchet and M. Holford, Macroevolution of venom apparatus innovations in auger snails (Gastropoda; Conoidea; Terebridae), *Molecular Phylogenetics and Evolution*, 10.1016/j.ympev.2012.03.001, **64**, 1, (21-44), (2012).

23. Maria VittoriaModica and MandëHolford, The Neogastropoda: Evolutionary Innovations of Predatory Marine Snails with Remarkable Pharmacological Potential, Evolutionary Biology – Concepts, Molecular and Morphological Evolution, 10.1007/978-3-642-12340-5_15, (249-270), (2010).
24. Natural product struacture diversity-II secondary metabolites: source, structure, chemical biology, Frank Marí, Jan Tytgat, in 2010 .
25. Allan Nanney MD, Robert M. Levy MD, PhD, in Essentials of Pain Medicine (Third Edition), 2011.
26. Elizabeth A. Kowaluk, Stephen P. Arneric, in Annual Reports in Medicinal Chemistry, 1998.
27. Venom and poisons from marine oaraganism, Jay W. Fox, in Goldman's Cecil Medicine (Twenty Fourth Edition), 2012.
28. Baldomero M. Olivera, Gisela P. Concepcion, in Handbook of Biologically Active Peptides (Second Edition), 2013.
29. Nicolas Andreotti, Jean-Marc Sabatier, in Comprehensive Natural Products II, 2010.
30. Peptide and protine in organism, E.G. Moczydlowski, in Current Topics in Membranes, 2016.
31. Ariadna Lobo-Ruiz, Judit Tulla-Puche, in Peptide Applications in Biomedicine, Biotechnology and Bioengineering, 2016.
32. Domżał T. Kliniczne podstawy badania i oceny bólu wprowadzenie dotematu. Pol Przegl Neurol. 2007; 3 (4), 211–215.
33. Neural Plasticity and Disorders of the Nervous System. Cambridge University Press. Pain 2006.pp. 149–240.
34. Fields HL, Martin JB. Harrison‟s Principles of Internal Medicine. 16th ed. New York: McGraw-Hill; 2005. p. 71-76.

Access this Article in Online	
Quick Response Code	Website: www.ijarbs.com Subject: Pharmacology
DOI:10.22192/ijarbs.2022.09.07.008	

How to cite this article:
Jayshree R. Aate, Sakshi Wairagade, Manisha G. Suryavanshi, Sonali S. Masirkar, Naznin D. Sheikh. (2022 Cone snail venom a peptide as Anticiceptive: A Review. Int. J. Adv. Res. Biol. Sci. 9(7): 73-88.
DOI: http://dx.doi.org/10.22192/ijarbs.2022.09.07.008