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A perspective on toxicology of *Conus* venom peptides

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ABSTRACT

The evolutionarily unique and ecologically diverse family Conidae presents fundamental opportunities for marine pharmacology research and drug discovery. The focus of this investigation is to summarize the worldwide distribution of *Conus* and their species diversity with special reference to the Indian coast. In addition, this study will contribute to understanding the structural properties of conotoxin and therapeutic application of *Conus* venom peptides. Cone snails can inject a mix of various conotoxins and these venoms are their major weapon for prey capture, and may also have other biological purposes, and some of these conotoxins fatal to humans. *Conus* venoms contain a remarkable diversity of pharmacologically active small peptides; their targets are an iron channel and receptors in the neuromuscular system. Interspecific divergence is pronounced in venom peptide genes, which is generally attributed to their species specific biotic interactions. There is a notable interspecific divergence observed in venom peptide genes, which can be justified as of biotic interactions that stipulate species peculiar habitat and ecology of cone snails. There are several conopeptides used in clinical trials and one peptide (Ziconotide) has received FDA approval for treatment of pain. This perspective provides a comprehensive overview of the distribution of cone shells and focus on the molecular approach in documenting their taxonomy and diversity with special reference to geographic distribution of Indian cone snails, structure and properties of conopeptide and their pharmacological targets and future directions.

1. Introduction

Many marine organisms produce a variety of chemicals for defense purposes; often serve as the basis for chemecological studies and also as a valuable source offering a vast choice of bioactive molecules for the development of novel pharmaceutical materials. This highly divergent genus, with >700 species worldwide, contribute differently to the chemical diversity of bioactive peptides with a peptide library of the order of 70 000 sequences generated from them[1]. These products exhibit exquisite selectivity of ion channels and receptor isoforms for being increasingly important in research and medicine[2,3]. A large proportion of natural compounds are extracted from marine invertebrates and many of them are under clinical trials[4].

The physiological action and pharmacological potential of conopeptides in vertebrate and invertebrate nervous systems are presently being studied in many research laboratories of the world. Conotoxins represent extremely specific biological probes that offer researchers a tool to understand and discriminate between closely related receptors[5]. The simplicity of conotoxins has made them valuable natural source in the advancement of neuroscience research and consequent drug development[6]. Active research in the field of conotoxins involves to isolating, identify structural properties, and assessment of biological activity of individual peptides that possess the potential to be made into potent and selective therapeutic drugs. Scientists either use a small amount of purified native conotoxin or they use automated synthesis techniques to prepare milligram quantities of material for their investigations. Currently, only about 0.2% of the conotoxin peptide library has been cataloged[7,8].

This present work represents the geographical distribution of cone shells and diversity with special reference to Indian cone snails,

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evolution of phylogeny, structural diversity of conopeptide chemistry and biochemistry, conopeptide sequences and their physiological applications of specific Conus peptides, pharmacological targets and future commissions.Additionally, this work presents an overview of conotoxins reported from Indian cone snails.

2. Distribution and ecology of cone shells

Conus are the most diverse genus of marine invertebrates and contribute substantially to the great biodiversity in the tropical Indo–Pacific reef environments[9]. Speciation and rich endemism are evidenced by the morphology and toxicology of the genus *Conus*[1]. *Conus* is widely distributed throughout all tropical oceans comprising one-fourth the earth's ocean area[10], yet roughly 60% of their habitation occur in the Indo-Pacific region. Over 20 species have been observed to co-occur on reef platforms, at the maximum of 27 species observed in Indonesia[11,12]. In more recent reports Kohn reported 36 species of *Conus* on the reef platform fringing Laing Island and 32 species on four small reefs of Near Madang of Northeast Papua Guinea[13]. The species *Conus anemone* and *Conus victoriae* is the dominant species in intertidal habitats in the inner region of the Dampier Archipelago. In favorable habitats their estimated densities were recorded 0.2–2.6 and 0.1–0.3 individuals/10 m^2, respectively. Both the species occurred predominantly under rocks, on sand or limestone substrate[14].

The Indian coasts inter- and subtidal regions contain nearly 100 species, but due to the lack of sufficient information, sixteen of the identified species found off the coast of India are still currently placed on the list of unverified species[15]. *Conus generalis* and *Conus litoglyphus* were considered as unverified species but have been confirmed as a species native to Indian Coastal waters[1,13,14]. According to the 1996 IUCN study, *Conus africanus, Conus cepasi*, *Conus nobrei*, and *Conus zebroides* are vulnerable and *Conus kohni* remains data deficient[16].

2.1. Biology of Conus

The cone snail's venom has secured its survival with its value in foraging and defensive strategies[5]. Cone snails are effective venomous predators of worms, other molluscs, and small fish by using a deadly combination of paralyzing neuronic peptide toxins. The singular preferential prey choice, discovered from the gut content and fecal analyses[11,17], of all the species, but a few have become a way to categorize the numerous species into three important groups that provide in general the projected threat level of their venom toward humans. The piscivorous class contains the smallest number of species, but is assessed as deadly to humans. A larger number of species belong to the molluscivorous class that is dangerous by means of their aggressive behavior (although some members have been implicated in unconfirmed fatalities). The largest vermivorous class contains about 80% of the genus and is found to be timorous and nonthreatening. Although diet diversity is a genus level examination, individual species tend to be specialized particularly where large numbers of congeners co-occur[15,17], and most *Conus* species hunt prey of only one of the three types listed above.

However, the diets of a few species span more than one prey category. *Conus californicus* is the most notable exception with the broadest diet known of all *Conus* species; its diet includes fish, molluscs (including bivalves as well as gastropods), polychaetes and crustaceans[18]. *Conus bullatus* (*C. bullatus*) have been observed to feed on both fish and molluscs[19] as cited by Rockel *et al*[1]. Also, several vermivorous species, including *Conus arenatus, Conus eburneus* (*C. eburneus*), *Conus miliaris*, *Conus lividus* and *Conus sponsalis*, have been reported to prey on sedentary polychaetes, errant polychaetes and hemichordates in different geographic locations; *C. eburneus* and *Conus tessulatus* occasionally prey on fishes as well[11,20]. Geometric morphometric techniques allow for the direct quantification and analysis of variation in biological shapeand have been used in studies in systematic biology. Geometric morphometric analysis of shell shape variations in *Conus* sp, the results of this study established the utility of geometric morphometric methods in capturing the interspecific differences in shell form in the genus *Conus* sp[21].

Human envenomation [principally by piscivorous *Conus geographus (C. geographus)*] has caused around 30 recorded fatalities. The first recorded death by envenomation in 1705 has lately been attributed to molluscivore C*onus textile*[22], and since cone shell popularity ornamentally has grown internationally, subsequent envenomations (including casualties) has likely gone unreported. Therefore, it must be emphasized that collecting live cone snails from the field is a perilous undertaking and requires assiduousness, experience with species identification and ethology[23].

2.2. Molecular taxonomy and phylogeny of Conus species

Most taxonomists place all of the venomous neogastropod taxa in the single superfamily, Conoidea[24,25]. Though the efforts to subdivide the genus conus has found little support, the recently proposed alternative classification based on shell and radula[26], recognizing 4 families and 80 genera has found some acceptance. The difficulty in *Conus* taxonomy involves multiple examples of species complexes[27,28]. Distinctive species taxonomical confirmation has been challenging, descriptions and identification has entirely depend on shell characters, primarily color patterns, and these habituallylook to integrate among putative species.

Pigmentation pattern of cone shells is complex phenotypes, itvary significantlymore with closely related species, but the complexity of the color patterns makes it difficult to characterize their similarities and differences. Gong *et al*[29] studied an attempt to resolve this problem by combining phylogenetic methods with a realistic developmental model that can generate pigmentation patterns in the diverse cone shells. He found phylogenetic signals are of the primary neural network and in the presence or absence of hidden network, suggests that the model reasonably approximates the developmental processes underlying pigmentation patterns in the *Conus* species. In contrast, various features of the pigmentation patterns, such as the presence of dots and stripes, do not have a significant phylogenetic signal.

DNA barcoding has been proposed as a technique that will make confirmation of species identification faster and more accessible using a small fragment of DNA sequence, peculiarly in species with complex morphologycharacteristic[30]. Species identification using DNA Barcoding should be kept clear and distinct from other proposed uses of DNA sequence information in taxonomy and biodiversity studies, such as ''DNA taxonomy'' using DNA sequences[31,32]. This recent usage, and its subsequent successes, have induced criticism and taxonomic debate.

One method is grounded on the degree of sequence variation between species, and the alternative technique involves the recovery of species as discrete clades (monophyly) on a phylogenetic tree. Yet, few issues make difficulties the use of both methods. In recent times, the character-based DNA Barcodingtechnique, characterizes species through a unique combination of diagnostic characters[33]. He concluded that both COI and 16S rDNA genes well suited as character-based barcode markers for the neogastropod discrimination throughout the genus and species taxa. However, an evolutionary framework for the 700 species in the genus is not yet available, and the relationship of *Conus* to the other predatory snails belonging to the superfamily Conoidea is poorly understood. Employing molecular sequence data sets are suggested for delimiting species of this group, particularly in cases where morphological differences are obscure[34]. Partial sequences of mitochondrial CO Ⅰ, 16S rRNA, 12S rRNA, nuclear ITS2, and Calmodulin genes are appropriately studied to understand the diversity of Gastropods at various levels such as population, varieties and species. Till recently the efforts on molecular taxonomy of the group was focused more on the higher taxonomic categories above species.

Conus species were studied rather more for their pharmacological potential than phylogenetic understanding. The understanding of genetic variation as indicative of the origins of feeding divergences, that in turn is associated with the class of conopeptides in the venom, with the use of DNA sequence data from mitochondrial and nuclear loci provided a phylogenetic perspective for screening species for venom conopeptides[35]. Distinctive clustering of the species with similar diets was observed while mapping the known diets to the phylogeny of the 72 species of the genus based on mitochondrial 16S rRNA and nuclear calmodulin gene sequences.An attempt to date the evolution of this different feeding modes and speciation of a few species was also made. The phylogenies of *Conus* species have been incompletely resolved as the employed 'standard genes' are less reliable for resolving relationships among recently diverged species[36]. They employed ITS2 sequences of 26 molluscivorous species to elucidate their evolutionary relationships and found three well supported clades among them. They suggested the inclusion of the region in future studies considering the better resolution and support observed throughout the phylogenetic tree.Duda and Kohn[27] were studied species-level phylogenetic hypotheses based on nucleotide sequences of the nuclear calmodulin and mitochondrial 16S rRNA genes of 138 *Conus* species. These results indicated that extant species from two major divergent lineages. Their geographic distributions suggest that one clade originated in the Indo-Pacific and the other in the eastern Pacific + Western Atlantic lineages of *Conus*[27].

Duda *et al*[34] has provided a phylogenetic basis for evaluating morphological criteria and characterizing the genetic discontinuity to distinguish members of the *Conus sponsalis* species with use of molecular sequence data from two mitochondrial gene regions (16S rRNA and cytochrome oxidase subunit Ⅰ) and one nuclear locus (a four-loop conotoxin gene). The genetic variation was hypothesized to indicate the origins of feeding divergences by using DNA sequence data from mitochondrial and nuclear loci 76[35]. The generated species-level genetic comparisons and known diets assisted the surveyed species phylogenic origins.The phylogeny of 22 speciesof *Conus*, particularly the *Conus pennaceus* (*C. pennaceus*) complex, collected along the coasts of Mozambique and southern Angola and observed a clear genetic differentiation in both 16S and 12S rRNA genes between northern and southern Mozambican populations of the *C. pennaceus* species complex[37]. The study also pointed to a close genetic relationship between *Conus lohri* and *Conus bazarutensis*, as well as between *Conus praelatus* and *C. pennaceus* (forms of Pemba and Nacala). Phylogenetic analyses are essential to determine patterns of speciation and divergence. The monophyly of the Conoidea, characterized by a venom apparatus, is not questioned[38], but subdivisions within Conoidea, and relationships between them are controversial, mostly because the extensive morphological and anatomical variation encountered is itself not well understood. In this context, molecular perspective can aid in the phylogenetic classification of Conoidea.

3. Research on neurotoxic *Conus* peptides

Unquestionably, the lethality of cone snail stings motivated the investigation of *Conus* venoms. Pioneering work was done in Australia by Alan Kohn, who first discovered that cone snails hunted fish, and later the work of Robert Endean and co. documented pharmacological relevance of crude venoms in the 1970's. Their explorations demonstrated that different cone snail venoms contain different biologically active components[39–41]. An early attempt to purify the bioactive components from cone snail venoms, carried out by an Australian group[42], resulted to validate a peptide composition by its amino acid composition; the component is known as a μ-conotoxin.

Chemical synthesis began on *Conus* peptide, α-conotoxin GI, (from *C. geographus* venom) which confirmed its native amino acid sequence of 13-amino acids and two disulfide bonds[43]. Following the first venture securing milked venom's peptide composition, a second attempt at finding bioactive peptides from *C. geographus* milk venom discovered the μ-conotoxins, that were characterized similarly[44]. The presence of these two functional peptides in the venom of *C. geographus* also evoked how the venom of cone snail was effective. Containing both a potent nicotinic receptor antagonist (α-conotoxin) and sodium channel blocker (μ-conotoxin)[45], these molecules act synergistically to bind and inhibit different receptors of multiple molecular pathways responsible for the prey's normal evasion behaviors. Ultimately, the work to establish the activity of different toxins on different receptors expressed the need for categorizing the paralytic peptides on the basis of their pharmacological targets.

4. *Conus*–rich source of pharmacologically active peptides

Although cone snail venoms have been intensively investigated over the final few decades, know that little information on whole conopeptide and protein content in venom ducts, particularly at the transcriptomic level[46]. *Conus* represents a large number of venomous marine snails containing valuable neuro-active peptides for developing pharmaceutical therapeutics and phyla-selective pesticides. Conotoxins are small peptides (usually 10–35 amino acids) that exhibit an extraordinary variability and selectivity over the range of pharmacological targets. Mass spectrometry techniques have revealed that the species of cone snail produces from 200 to 1 100++ distincttoxins[46–50]. In addition to the pharmacological families of *Conus* peptides, there are structured classesthat can be definedby characteristic patterns of arrangement of either theCys residues, or the post-translationally modifiedamino acid, γ-carboxyglutamate[48,51]. The conopeptide mass range has classified according to their cysteine number; each conopeptideclass/ cysteine framework,considered masses were limitedto the mass range were reported in Table 1. Recently a number of cases have shown that the traditional identification method based on the shell color patterns was inadequate in distinguishing between species clearly identified at the genetic level[34]. These observations indicate that the number of conopeptides per species might exceed 1 000 and suggest that conopeptide diversity may be greater than expected[47]. These diverse mixtures of potential pharmacological agents make them hot targets for biomedical applications. A great number of research studies and large amount of data on conopeptides made way topool the database, ConoServer (http://www.conoserver.org), to help catalog the growing literature on conopeptide sequences and three-dimensional structures[7]. This database has now grown substantially and provides a valuable resource for analyzing the sequence and structural features of conopeptides.

Conus venom peptides arise from genes that are translated as pre-pro-peptide precursors. The pharmacological active peptide is generated by post-translational modification of enzymatic cleavage at the end of the pre-pro-region. Mature conopeptides are extremely variable in their primary sequences, yet interestingly, the signal sequences of the precursor peptides are highly conserved within the super families[52,53]. This factor can be used to aid the identification of new peptides to substantiating super families.

Regarding the primary (amino acid) sequence, conopeptides are associated namely as the disulfide-rich (generally termed conotoxins) and the non-disulfide rich peptides[50,54], although by convention, the conopeptides have been categorized according to three dimensional structure motifs (superfamily) and the selectivity of their pharmacological targets (family)[55]. Three large super families of conotoxins are well characterized: the O-superfamily including ω-, -, κ-, and μ-conotoxins[56], the A-superfamily, of which the -conotoxins belong[57], and the M-superfamily, containing the μ-conotoxins[58]. Eight different T-superfamily conotoxins identified from five *Conus* species; they are among the smallest of the disulfide rich conotoxins[59]. The venom of cone snails has been the subject of intense studies because it contains small neuroactive peptides of therapeutic value. Yet, a little known about their larger protein counterparts and their role in prey envenomation. Moller *et al*[60] were analyzed the proteolytic enzymes in the injected venom of *Conus purpurascens (C. purpurascens)* and Conus ermineus (piscivorous), and the dissected venom of *C. purpurascens*, *Conus marmoreus (C. marmoreus)* (molluscivorous) and *Conus virgo (C. virgo)* (vermivorous). However, the electrophoresis patterns and sizes of the proteases varied considerably among these 4 species. The distribution of varied dramatically between the injected and dissected venom of *C. purpurascens.* Consequently, different conoproteases play major roles in venom processing and prey envenomation[60].

5. Structural and functional aspects of conotoxin

5.1. Conotoxins

Conotoxins are obtained from the venom ducts of predatory snails of the genus *Conus* represent a unique arsenal of neuro-pharmacologically active peptides that have been used as research tools to target voltage-gated and ligand gated ion channels and

Table 1
Superfamilies of neurotoxic conotoxins.

Superfamily	Class of cysteine arrangement		Pharmacological family	
	Designation	Pattern	Designation	Action
A	Ⅰ	CC-C-C		Competitive antagonist of ACh receptor
	Ⅳ	CC-C-C-C-C	A	Competitive antagonist of ACh receptor
	Ⅳ	CC-C-C-C-C	κ A	Inhibits K^+ channels (VSPC)
M	Ⅲ	CC-C-C-CC	μ	Blocks Na^+ channels (VSSC) at site Ⅰ
	Ⅲ	CC-C-C-CC	ψ	Noncompetitive antagonist of ACh receptor
O	Ⅵ	C-C-CC-C-C	ω	Blocks Ca^{2+} channels (VSCC)
	Ⅶ	C-C-CC-C-C	ω	Blocks Ca^{2+} channels (VSCC)
	Ⅶ	C-C-CC-C-C	κ	Inhibits K^+ channel
	Ⅵ	C-C-CC-C-C		Delays inactivation of VSSC by binding to site Ⅵ
	Ⅵ	C-C-CC-C-C	μ	Blocks VSCC; does not compete with TTX and STX
P	Ⅸ	-C-C-C-C-C-C-		Unknown
S	Ⅷ	C-C-C-C-C-C-C-C-C-C		5-HT_3 receptor
T	Ⅴ	-CC-CC-		Unknown

receptors[61-64]. Figure 1 shows the basic scheme workflow for the isolation of conopeptide and screening of bioactive compounds from *Conus* sp. The toxicity of the venom is considerably more potent due to additive or synergistic effects of several toxins acting at different sites rather than from the considerable toxicity of each of the peptides individually[65].

The major paralytic peptides of fish hunting cone venoms were the first to be identified[51]. In *C. geographus* venom, three of the pharmacological classes were primarily discovered. These conotoxins were of the -class that target acetylcholine receptors[66], then μ-class that target skeletal muscle Na^+ channels[44] and the ω –class that target presynaptic neuronal Ca^{2+} channels[51].

α –Conotoxins: Alpha Conotoxins are the first toxins isolated from *Conus* venom and were designated after the α-toxins from snake venom because they inhibit the same receptor category, the muscle-type nicotinic receptor[67,68]. Three alpha-conotoxins, G Ⅰ G Ⅰ A, and G Ⅱ (from *C. geographus*) and M Ⅰ [from *Conus magus* (*C. magus*)] are homologous peptides of target selectivity possessing 13 and 15 amino acids respectively. Each contains two disulfide bridges in the 3:5 loop configurations and contains a highly basic region in the sequence. These alpha conotoxins cause postsynaptic inhibition at the neuromuscular junction; the paralytic symptoms eventually develop into respiratory failure[69].

ω – Conotoxins: Omega conotoxins are peptides, composed of 24-30 amino acids and three disulfide bonds[70]. The most characterized omega conotoxins are G Ⅵ A from *C. geographus* and omega conotoxins M Ⅶ A, M Ⅶ C and M Ⅶ D from *C. magus* venom. They are also known as 'shaker peptides' since they induce persistent tremors in mice intracerebrally. Conotoxins G Ⅵ A, G Ⅵ B and G Ⅵ C inhibit at the neuromuscular junction of skeletal muscle by blocking Ca^{2+} channels without interfering directly with the ion channels in the mechanism of intracellular action potentials. However, different effects are observed upon the three types of Ca^{2+} channels (L, N and P) during the application of G Ⅵ A. The peptide will block L and N types of neurons, but in muscle, only the N type is affected, while M Ⅶ A, specifically targets N-type Ca^{2+} channels ($Ca_v2.2$) with little affinity to other Ca^{2+} channel sub types[51,71]. Also known as Ziconotide, M Ⅶ A has successfully completed phase Ⅲ clinical trials for two therapeutic applications of alleviating pain relatedto malignant disease and for non-malignant neuropathic pain; it is an alternative when widely used opioids become ineffective[72].

μ-Conotoxins: μ-Conotoxins G Ⅲ A, G Ⅲ B and G Ⅲ C are hydroxyproline-rich basic peptides having 22 amino acids. These peptides contain three hydroxyprolines and six cysteines. The presence of several basic Lys and Arg residues confers a high positive charge of +6 on G Ⅲ A and +7 on G Ⅲ B and G Ⅲ C[73,74]. The μ-conotoxins act upon sodium channels in muscle, and limitedly in neurons. There, they bind to a site designated at the mouth of the Na^+ channel and hinder the influx of sodium ions into the cell. Notably, μ-conopeptides from species in the *Conus* clades were previously shown to target neuronal Na channel subtypes[75]. Recent comparative operational studiesof the structure-activity link of M-4 μ-conotoxin G Ⅲ A[76] and M-5 μ-conotoxin K Ⅲ A[77] have led to the identification of specific residues involved in high affinity interactions with $Na_v1.4$. Recently, three new μ-conotoxins, Bu Ⅲ A, Bu Ⅲ B, Bu Ⅲ C, encoded by the fish hunting species *C. bullatus*[78]. Bu Ⅲ A, Bu Ⅲ B and Bu Ⅲ C are strikingly divergent in their amino acid composition compared to previous m-conotoxins known to target the voltage gated Na channel skeletal muscle subtype $Na_v1.4$. The activities of the three *C. bullatus* peptides were assessed on $Na_v1.4$ expressed in *Xenopus* oocytes[78] and compared to the activities of a representative set of μ-conotoxins, P Ⅲ A, G Ⅲ A, and K Ⅲ A[77].

δ-Conotoxins: δ–Conotoxins are one of the most intriguing families of conotoxins. These peptides target Na^+ channels and do not compete with the well-known agents of competitive displacement such as tetrodotoxin and the μ-conotoxins[79]. Structurally, they stand alone with an internalized core of disulfides that restricts

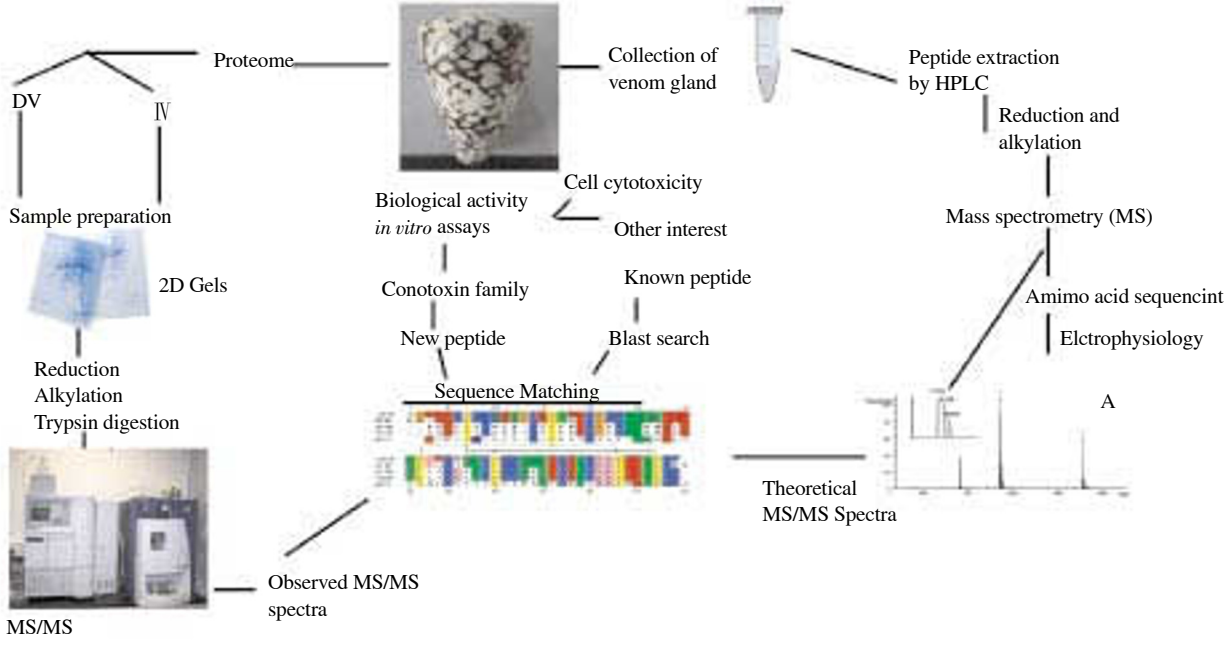

Figure 1. Basic scheme showing the workflow for the Isolation of peptide and screening of bioactive compounds from *Conus* sp.

the hydrophobic amino acids from the interior and out into the surrounding solvent. The hydrophobic exterior of the δ-conotoxins may permit them to dissolve in the lipid membrane to interfere with Na^+ channels through lateral binding within the lipid membrane. δ-conotoxins are suspected to be essential for the rapid immobilization of quickly moving prey[80,81]. Barbier *et al*[82] reported that δ-EVIA, of *Conus ermineus* venom, selectively acts on neuronal voltage-dependent Na^+ channels, implicating it in the excitotoxic shock and tetanic paralysis produced in fish. In terms of prey immobilization the piscivore *Conus purpurascens (C. purpurascens)* has shown that δ-conotoxins PVIA and the κ-conotoxin PVIIA work together in rapid prey paralysis by inhibiting multiple targets during envenomation.

κ-Conotoxins: κ-PVIIA was the first *Conus* peptide identified to target K^+ channels. PVIIA, a 27-amino acid peptide from *C. purpurascens* venom inhibits the Shaker K^+ channel and has been chemically synthesized in the biologically active native form[83,84]; the disulfide connectivity of the peptide has been determined. Generallyclosing down of this κ-conotoxin is similar to that of the *Conus* Ca^{2+} blocking κ–conotoxins, nevertheless vary from the known K^+ channel-blocking toxins from sea anemones, scorpions and snakes[85].

5.2. Conantokins

The conantokins are conopeptides that target the principal excitatory receptors in the vertebrate central nervous system, the glutamate receptors[86]. The conantokins selectively inhibit a subtype of glutamate receptor, the N-methyl-daspartate (NMDA) receptors, which are ligand-gated Ca^{2+} channels involved in seizures in intractable epilepsy[87]. The conantokins have no disulfide bonds, but derive their crucial structural stability from post-translationally modified glutamic residues existing as γ-carboxy glutamate (Gla). It remains unclear whether the functional role of γ- carboxy glutamatic acid in other vitamin K-dependent protein is as a calcium-binding amino acid[88]. To address this potential role for γ-carboxy glutamatic acid[51,89,90] studied the role for γ-carboxy glutamatic acid and discovered γ-carboxy glutamatic acid were found higher amount in crude conotoxins of marine snail *Conus*. Conantokin G is a 17-residue conotoxin from the venom of *C. geographus*, a fish-hunting cone snail whose venom has been known to cause human fatalities. Conantokin G contains five γ-carboxyglutamic acid residues; Gla 3 and Gla 4 are critical to the neurotoxin function[91].

5.3. Contulakins, contryphans and other conotoxins

A few conopeptides are being developed as pro-drugs for treatment of neurological conditions. These include contulakin-G a glycosylated 15 amino acid conopeptide from the venom of *C. geographus*, which is being developed for acute management of post-operative pain[92]. The contryphans from *Conus ventricosus* (*C. ventricosus*) and *Conus regius* are the smallest bioactive conopeptides containing eight or nine amino acids and just one disulfide bond; they are distinguishable by their numerous post-translational modifications[93]. Although the disease target for the contryphans is not yet known, the peptides have been shown to elicit body tremor and mucous secretion when injected into fish, implying they may have biological activity related to endocrine or neuronal function[65]. The ρ-conotoxin TIA acts as a non-competitive inhibitor of α-1 adrenergic receptors[94] and the χ-conopeptides (Mr. IA/B) from *Conus marmoreal*, that act as non-competitive inhibitors of the neuronal noradrenaline transporter are being developed for treatment of neuropathic pain[94].

Contryphan-Vn is the first *Conus* peptide described from a vermivorous species and the first purified from the venom of the single Mediteranean *Conus* species[95]. The intramuscular injection of Contryphan –Vn in freshwater fishes (*Poecelia pinnata*) caused the secretion of mucous substances, a reaction was already observed in fish with other contryphan[96]. Massilia *et al*[97] were reported the use of dorsal unpaired median neuron cells from cockroach nerve cord to demonstrate that contryphan-Vn from *C. ventricosus* blocks the Ca^{2+}-dependent K^+ current. These authors also demonstrated the effect of the peptide on the global outward K^+ current in the rat fetal chromaffin cells. A novel conotoxin, called Vn2, was recently identified in *C. ventricosus*, the primary structure wasdetermined[98], revealing a cysteine framework common to I1, I3, M, O1 and O3 gene superfamilies. Conotoxin Vn2 displays quite a high degree of sequence similarity with some conotoxins targeting calcium channels, in particular PnVIB from *C. pennaceus*[99] and an O1 superfamily ω-conotoxin. GST-conotoxin has been purified and their neurotoxic activities were assayed on the larvae of the moth *Galleria mellonella*. Results obtained indicate that indeed conotoxin Vn2 has strong insecticidal properties at a dose of 100 pmol/g of body weight; it can be used for environmental friendly crop protection applications[100]. It is noted from this review study O-superfamily conotoxins are not well represented from vermivorus species[101]. The elucidated cDNAs of these newly found vermivorus toxins would facilitate a better understanding of basic research and drug discovery and potential pharmacological applications.

6. Recent developments

Marine cone snails have developed sophisticated chemical strategies to capture prey and defend against predators. Recently, a γ-conotoxin-like peptide, de7a, was purified from a vermivorous cone snail *Conus delessertii*[102]. The components of the venoms of *Conus cancellatus*, a vermivorus cone collected in the western Gulf of Mexico, from which 6- and 4-Cys-containing peptideshave beenidentified[103] and similar an O-conotoxin[104] andtwo framework-XIV-conotoxins was purified from *Conus austini*[105]. The intracerebral injection of the peptide as 7a (500 pmol/mouse) in mice didn't cause any behavioral distress compared to control mice. The 23-amino acid peptide, called as 25a, is characterized by the sequence pattern CX1 CX2 CX8 CX1 CCX5, which is, for conotoxins, a new arrangement of six cysteines (framework XXV) that form three disulfide bridges. Ye *et al*[106] reported the isolation and characterization of two novel conotoxins from the venom of *Conus imperialis*. These two toxins contain a novel cysteine

framework, C-C-CCC-C, which has not been found in other conotoxins described to date. He named as XXⅢ and designates the two toxins im23a and im23b; cDNAs of these toxins exhibits a novel signal peptide sequence, which defines a new K-superfamily. The biological effect of conopeptide im23a and im23b and recombinant im23a were tested on 2-week-old (P14) Kunming male mice. Intracranial injection of im23a or im23b into mice induced excitatory symptoms; Though, the biological target of this conopepide has yet to be named. Various conotoxin diversifications revealed by a venomic study of *Conus flavidus*[107], has been identified 69 nonredundant cDNA sequences and 31 conotoxin components with confident MSspectra. A new Q-superfamily was also identified. A novel peptide, RsXXⅣA, was isolated from the venom duct of *Conus regularis*, a worm-hunting species collected in the Sea of Cortez, México[108]. This conotoxin contains 40 amino acids and exhibits a novel arrangement of eight cysteine residues (C-C-C-C-CC-CC), two loops of the novel peptide are highly identical to the amino acid sequence of ω-MⅦA. The toxin shows an anti-nociceptive effect in a formalin chronic pain test. However, the low attraction for CaV2.2 indicates that the main target of peptide could be different from that of ω-MⅦA[108].

The majority of *Conus* venom peptides is encoded by a great number of gene families, and targeted selectively tobind voltage-gated ion channels (Na^+, K^+ and Ca^{2+} channels) and to membranereceptors (nAChR, 5-HT3R, NMDAR). Liu *et al*[109] were constructed cDNA libraries derived from the venom ducts *C. virgo*, *C. eburneus*, *Conus imperialis* and *C. marmoreus* of the South China Sea, to identify novel conotoxin genes and analyze the diversity and evolution of typical conotoxin superfamily genes from different *Conus* species. Bingham *et al*[110] was investigated molecular mass analysis of the milked venom (MV) of *C. geographus*, and reported the first insight into the composition of its deadly cocktail. This study identified the presence of additional highly abundant peptides that illustrate unknown or unassigned compounds (40%) of the observed MV m/z, This indicate that all the same within this well-studied *C. geographus* comprises numerous uncharacterized venom peptides, specifically those observed with a m/z <, similar observations are seen in MV from *C. purpurascens*[111]. Neves *et al*[112] identify disulfide-rich conotoxins in Conus crotchii using MALDI-TOF and mass-matching. All the conopeptides was discovered belongs to the A-, O1-, O2-, O3-, T and D-superfamilies, which can block Ca^{2+} channels, inhibit K^+ channels and act on nicotinic acetylcholine receptors (nAChRs).

7. Research on Indian cone snails

7.1. Geographic distribution of cone snails

The taxonomy and distribution of Conidae in India were studied[15] and the diversity of cone snails in Indian Coastal waters is fairly well documented[1]. The principal important *Conus* species found in Indian coast are present in Figure 2. Several investigations on the taxonomy and distribution of Family; Conidae from the Indian waters carried out during 1835-2009 have recorded 81 species[115]. Within them *Conus milneedwardsi* is enlisted in the schedule Ⅰ of the Indian wildlife (Protection) act. The *Conus* species possess more or less potent venom, which is used primarily in the capture of prey. In Indian waters, there is only little information on the structure and function of the venom apparatus of cones[116,117]. Currently ongoing is a comparative study of the Indian species' radula morphology (based on their feeding habits) and diversity of species composition[118]. Figure 3 provides a summary of species richness in different regions in Indian coast. A total of 84 species of the genus *Conus* was recorded along the Indian coast. The highest number of *Conus* species is found in Tamil Nadu coast, Gulf of Mannar (52 species), followed by northern region (22) species, southern (6) and (5) species from the Palk Bay regions, with inventory numbers such as from Andaman and Nicobar Islands 53 species, Mumbai coast 16 species, 14 species from Gujarat coast, 4 species from Kerala coast, 8 species from Andhra coast, Odisha coast 7 species, Goa and Lakshadweep Islands 6 species, Puducherry coast 5 species, and 3 species were reported from Karnataka and West Bengal coast respectively (numbers represent the exact number of species mentioned in each citation). Geographically *Conus acutangulus*, and *Conus amadis* was the most widespread species, present at almost all stations followed by *Conus arenatus, Conus ineditus, Conus malacanus, Conusterebra, Conustessulatus.*

Kulkarni *et al*[119] were reported four fossil *Conus* species *(Conus marginatus, Conus ineditus* and *Conus litteratus, Conus odengensis)* from the Miocene sediments of Kachchh, Gujarat, India. Satheeshkumar and Khan[120] reported *C. virgo* and *Conus bayani* for the first time out of Pondicherry, located in the southeast coast of India. Recently Dalia susan *et al*[121] were first reported of two cone snails, *Conus cataus* and *Conus ebraeus* in seagrass ecosystem, Minicoy Island, Lakshadweep. A recently, Franklin *et al*[122] reported three *Conus* species' first time in the Andaman Islands from this *Conus coffeae* was reported first time in India. The highest species distribution and diversity of cone snails wasobserved in the Gulf of Mannar (Tamil Nadu) reflects the physical conditions, microhabitats and other all-important resources such as food and shelter that favor the occurrence of the maximum number of *Conus* species[115]. Fifty two species were reported at depths <50 m in the Gulf of Mannar region. In other coral reefs stations such as Andaman and Nicobar Island, Lakshadweep Islands, Netrani regions were reported species very poor with only 3-16 species respectively. Where the biogenic complexity of coral reefs is lacking15, few Conus species co–occur, for example the limestone platform at Okha, the mixed and rocky shores near Mumbai, and the shallow subtidal sand habitats in the Northern region of Tamil Nadu coast. Thus, this discrepancy appears to be a result of very limited knowledge of the natural history of *Conus* in India, (except Gulf of Mannar regions) and fewer sampling efforts, rather than a decrease in *Conus* diversity and low number of species attributable to the limited heterogeneity of the Indian coasts. During 1978, Khon reported seven species as unverified records since no other records or any specimen deposited in the

museum, hence consider them all unverified. Our inventory of 84 described species of Indian *Conus* is certainly incomplete in this perspective, with an estimated that approximately 20 species remain to be discovered and described. Applying molecular approaches may further assist in locating cryptic speciation of a single species. Acute toxicity of the venom of *Conus zeylanicus* was studied to evaluate its risk and toxic factors in view of human safety[123]. The lethal toxicity of crude venom (LD_{50} 60 mg/kg) in mice causes increased heart rate and strong muscular hind limb paralysis, skeletal muscle paralysis, dyspnea, loss of spontaneous activity followed by respiratory failure.

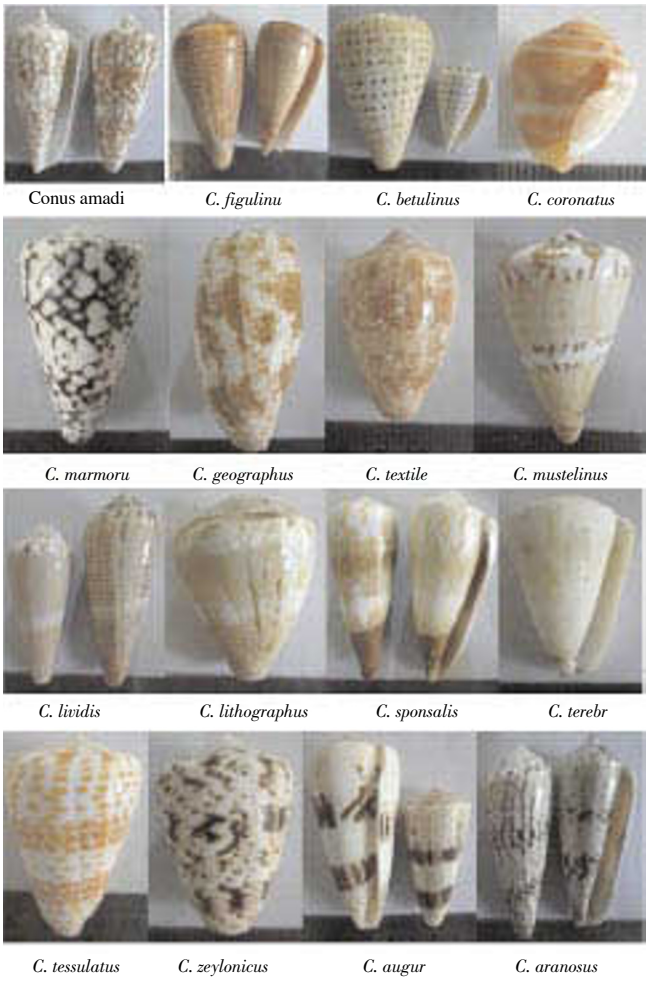

Figure 2. Important *Conus* sp. present in Indian coast.

Figure 3. Cone snails distribution in Indian coast.

Station 1, Dwarka; Station 2, Kachch; Station 3, Veraval; Station 4, Kodinar; Station 5, Okha; Station 6, Kollam; Station 7, Malabar; Station 8, Mumbai; Station 9, Calicut; Station 10, Mandapam; Station 11, Pamban; Station 12, Vedalai; Station 13, Keelakarai; Station 14, Goa; Station 15, Tuticorin; Station 16; Puducherry; Station 17, Cuddalore; Station 18, Chennai; Station 19, Parangipettai; Station 20, Tranquebar; Station 21, Nagapattinam; Station 22, Vishakhapatnam; Station 23, Kanyakumari; Station 24, Andaman and Nicobar Island; Station; Station 25, Netrani-Karanatka; Station 26, Gopalpur-Orissa; Station 27, Kolkatta; Station 28, Minicoy Island-Lakshadweep.

7.2. Diversity of conopeptide in Indian cone snails

This review focuses on some of the pharmacological important peptides from Indian cone snails. India has a diversity of 20%-30% of total cone snail species distributed worldwide. A group of promising Indian scientists has established drug discovery programs from *Conus* peptides[55,124–127]. The summary of novel conotoxin isolated from Indian cone snails are given in Table 2.Mass spectrometry offers a powerful and rapid way of probing the composition of peptide mixtures. A novel 13-residue peptide Mo1659 has been isolated from the venom of a vermivorous cone snail, *Conus monile*[124]. The sequence (FHGGSWYRFPWGY-NH_2), corresponding to a calculated average mass of 1659.8 Daltons were reported. It appears to be the first non-disulfide bonded peptide, which influences K^+ currents in neurons. Mandal *et al*[129] had independently been investing the peptide components of the venom from *C. virgo* and had completed the sequence assignment

Table 2
Novel conotoxin isolated from Indian cone snails.

Species	Name of peptide	Sequence	Target	Reference
C. amadis	Am2766	CKQAGESCDIFSQNC-CVGTCAFICIE-NH_2	Na^+ channel	[126]
C. monile	Mo1659	FHGGSWYRFPWGY-NH_2	K^+ channel	[127]
C. loroisii	Lo959	GCPDWDPWC- NH_2	Ca^{2+} channel	[87]
C. achatinus	Ac 6.1	DECFSPGTFCGIKPGLCCSAWCYSFFCLTLTF	Voltage gated Na^+ channel	[130]
	Ac 6.2	DECYPPGTFCGIKPGLCCSERCFPFVCLSLEF	Voltage gated Na^+ channel	[130]
	Ac 6.3	YECYSTGTFCGVNGGLCCSNLCLFFVCLFS	Voltage gated Na^+ channel	[130]
	Ac 6.4	CKGKGASCSRTMYNCCTGSCNRGKCG		[130]
	Ac 6.5	ATDCIEAGNYCGPTVMKICCGFCSPFSKICMNYPQN	Voltage gated Ca^{2+} channel	[130]
C. virgo	Vi1359	Z*CCITIPECCRI-NH_2	Pyroglutamic acid residue	[129]

of the peptide MALDI Mass spectrometry. Distinctly different effects of two closely related contryphans have been demonstrated on voltage-activated Ca^{2+} channels[87]. The peptides Lo959 and Am975 were isolated from *Conus loroisii*, a vermivorous marine snail and *Conus amadis*, a molluscivore, respectively. The peptide sequences of Lo959 and Am975 were derived by mass spectrometric sequencing (MALDIMS/MS) and confirmed by chemical synthesis. The sequences of Lo959, GCPDWDPWC-NH_2 and Am975, GCODWDPWC-NH_2 (O: 4-trans-hydroxyproline: Hyp), vary only at residue 3; Pro in Lo959, Hyp in Am975, which is identical to contryphan-P, earlier derived from *C. purpurascens*, a piscivore; while Lo959 is a novel peptide. Mandal and Balaram[129] were reported mass spectrometric identification of pyroglutamic acid in peptides following hydrolysis. During the course of fractionating crude venom from *C. virgo* using reverse-phase high-performance liquid chromatography was encountered two closely related peptide components with a mass of 1 359 Da (Vi1359) and 1 361 Da (Vi1361). Gowd *et al*[130] were reported the sequencing of cDNA derived using O-superfamily specific primers yielded five complete conotoxin precursor sequences (Ac 6.1 to Ac 6.5) δ , ω , and ω -like conotoxins. Although he concluded a crude venom analysis should prove powerful in studying both inter-and-intra species variation in peptide libraries.Saravanan *et al*[131] isolated conotoxin from *Conus figulinus*, biological activity studies were performed with the purified toxin containing proteolytic peptides, which inhibit the trypsin and chymotrypsin enzymes. The genus *Conus* presents vast opportunities for research in the fields of biochemistry, natural products, evolution, and clinical medicine. However, there are many fields related to *Conus* venom peptides are least known, and in others the available data should be updated and retooled. Many most conscious species are yet to discover in Indian coast, contributing to our accumulating knowledge of this unique group.

8. Therapeutic application of *Conus* conopeptides

Research into the pharmacological properties of marine natural products has led to the discovery of many potentially active agents considered worthy of clinical application[132], and a variety of biologically active constituents have been isolated from various species of *Conus*[133-136]. The extraordinary pharmacological selectivity of conopeptides has caused a dedication in characterizing them and diversifying their applications. The summary of the therapeutic applications of conopeptides was described in Table 3.

The ω -conotoxins are heavily used in Neuro- and pharmacological research to study the function of Ca^{2+} channel subtypes. Due to their specific binding properties, conopeptides proved useful tools to acquire structural information about their corresponding targets. Interestingly, recent data obtained by solid-state NMR suggest the binding of peptide toxins to their target induce conformational changes of both binding components[137]. These results can infer that some conformational dynamics take place during drug–target interactions. Since voltage-gated and ligand-gated ion channels are involved in a variety of different physiological functions, certain conopeptides function as leads for new drugs. Currently, several conopeptides are currently undergoing clinical trials. However, the application of peptides as drugs is constrained so the actual peptide may be modified or redesigned to mimic its original function; the new chemical structure is designed to have improvements in molecular stability, biological activity, cell permeability, administration, *etc*. Nevertheless, these peptides competently serve in the development of drug candidates from existing natural compounds and further our confidence and reliance upon using natural templates for structural design.

The first conopeptide used as a drug for the treatment of intractable pain is ω -conotoxin M\\[A (Ziconitide, Prialt®) from *C. magus*[138-140] and is currently completing a repeat of Stage [[[clinical trials for the treatment of cancer pain[139]. Ziconotide has also been tested for neuro-protection as its efficacy has been tested against ischemic stroke and in coronary bypass surgery[142]. However, these human neuro-protection trials have been disappointing and abandoned[142]. Recently, other conopeptides with analgesic activity have been identified in the venom of the fish-eating snail, *Conus catus*[70], the molluscivorous *C. marmoreus*[143], and *Conus victoriae*[144]. It

Table 3
Therapeutic applications of conopeptides.

Conopeptide	Sequence	Target	Clinical application		Reference
α -Vc1.1 (ACV1)	GCCSDPRCNYDHPEIC*	nAChR (α 9 α 10)	Pain	Phase I	[141, 176]
χ -MrIA(Xen2174)	NGVCCGYKLCHOC	Norepinephrine transporter	Pain	Phase I	[177]
Contulakin-G (CGX-1160)	ZSEEGGSNATKKPYIL	Neurotensin receptor	Pain	Phase I	[59]
	GE γ γ LQ γ NQ γ LIR γ KSN*	NMDA receptor (NR2B)	Epilepsy	Phase I	[92, 178, 179]
Conantokin-G (CGX-1007)	CKSKGAKCSKLMYDCCSGSCSGTVGRC*	Ca^{2+} channel (CaV2.2)	Pain	Phase I	[70, 143]
Conantokin-G (CGX-1007)	GE γ γ LQ γ NQ γ LIR γ KSN*	NMDA receptor (NR2B)	Pain/ Neuroprotection	Preclinical	[92, 180)]
κ -PVIIA (CGX-1051)	CRIONQKCFQHLDDCCSRKCNRFNKCV	K^+ channel(KV1)	Myocardial infarction	Preclinical	[146]
μ -conotoxins	Various	Na^+ channels	Pain	Preclinical	[145, 181]
ω -MVIIA (Ziconotide,Prialt®)	CKGKGAKCSRLMYDCCTGSCRSGKC*	Ca^{2+} channel (CaV2.2)	Pain	FDA approved	[71,182]

Z, pyroglutamate; O, 4-trans-hydroxyproline; γ , γ -carboxyglutamate; T, O-glycosylated threonine; *, C-terminal amidation; nAChR, nicotinic acetylcholine receptor; NMDAR, N-methyl-D-aspartate receptor. A derivative of χ -MrIA, rather than the native peptide, advanced to human clinical trials.

preliminarily appears that *Conus* has included an analgesic among its lethal components of the venom to pacify its victim as part of the immobilization strategy. The finding that these marine invertebrate neurotoxins and analgesic peptides from *Conus* are effective in humans has opened a treasure chest of potential drugs from the sea for commercial development as clinical pharmaceuticals.

Besides their use as pain killers, conopeptides are useful for other clinical indications. It has been demonstrated that κ-conotoxin PVIIA reduces the size of the myocardial infarct in an ischemia/reperfusion model in rabbits, rats, and dogs *in vivo*[145,146]. Additionally, other conopeptides are also being evaluated for other neurological symptoms[147-149]. Venom studies in *C. bullatus* have already yielded results of exceptional pharmacological interest. The best characterized *C. bullatus* venom component, the alpha conotoxin BuIA is a small peptide antagonist of nicotinic receptors that has become the standard pharmacological tool for differentiating nicotinic receptor subunits, b2 and b4. These receptors are of considerable interest in Parkinson's disease[150]. The recent identification of alpha-5 and alpha-6 subunits contributing to the nAChRs expressed on striatal dopaminergic terminals opens up the possibility of developing selective nAChR ligands active on dopaminergic systems and associated diseases, such as Parkinson's disease[152,153].

Both conantokins and conotoxins have potential applications in Alzheimer's disease. With regards to the conantokins, it has been proposed that over excitation mediated by specific NMDA receptors might contribute to localized brain damage in Alzheimer's disease. Revised conantokins are valuable for identifying the NMDA receptors involved and may have potential as protective agents[153,154]. This increase a possibleness that the 500-700 species of cone snails may supply a maximum of 100 000 compounds of potential biomedical attention, possibly more when all the species of family Conidea are considered[151]. A Further comparison with proteomic and genomic data will lead to a better understanding of conopeptides diversity and the underlying mechanisms involved in conopeptide evolution.

9. Conclusion

Marine pharmacology research on *Conus* conotoxin during 1982-2013 was truly global in nature involving investigators from many countries lead to discover novel therapeutic peptides. The data presented here undoubtedly indicate the great value of marine natural products as well as marine-derived analogs of novel peptide that make them important candidates for further pharmaceutical studies for therapeutic applications of various diseases. The vast array of combinatorial libraries of conopeptides remains pharmacologically uncharacterized, the enormous opportunity remains discovered potential therapeutics from amongst the highly diverse venoms. Based on the present study, 84 species of *Conus* are now recognized as occurring in Indian waters, from the intertidal zone to 200 m depths. The examinations of cone snail's venom components from discovery into novel drug development are scarce in India. Continued preclinical and clinical research with *Conus* peptide demonstrating a broad spectrum of pharmacological activity will probably result in novel therapeutic agents for thetreatment of multiple disease categories. In general, studies on Indian *Conus* are necessary and should be done in terms of monographic works, and scientists there should be encouraged to study other aspects of this animal. In conclusion, we remain convinced that the Indian EEZ still contains valuable "cone snails" waiting to bemined by inquiring medicinal chemists as well as drug discovery.

Conflict of interest statement

We declare that we have no conflict of interest.

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