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Case Study

DIVERSITY OF *CONUS* SPECIES AND IMPORTANCE OF CONOTOXINS

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ABSTRACT
The genus *Conus* belongs to the group Conidae which is one of the largest groups of gastropods. These species are widely distributed all over the world but scantily reported. Species specific identification is mainly based upon the radular structure. Predacious gastropod cone shells have a diverse mechanism of prey capture and divided into three major feeding types namely; vermivorous, piscivorous and molluscivorous. Piscivorous species are very dangerous, can kill and swallow the prey of similar size. Toxins from this genus are referred as conotoxins. There are 5 (α-conotoxins, δ-conotoxins, κ-conotoxins, μ-conotoxins and ω-conotoxins) different conotoxins based upon the binding site. Conotoxins have a valuable probe in physiological and pharmacological studies. The studies on the conotoxin is still at infancy stage, so far only 100 out of a potentially identified 50,000 toxins have been extracted and analyzed from *Conus*. A single species of *Conus* can yield 100-200 peptides with potential therapeutic uses but attention on this conotoxin research has to be initiated. Since India is blessed with hundreds of *Conus* species, the potential bioactive property of these toxins has to be established for their effective utilization.

KEYWORDS: *Conus*, Molluscan diversity, radular structure, conotoxin, bioactive properties.

INTRODUCTION
Molluscs are highly diversified group differ in size, shape, as well as in habit and habitats. The history of Malacological study is immense and interesting in India. Studies on Indian molluscs were initiated by the Asiatic Society of Bengal (1784). Benson (1830) was the first to publish a systematic paper on Mollusca. During the recent years, the contribution from Zoological Survey of India, Central Marine Fisheries Research Institute and other several maritime universities enhanced the knowledge of the mollusc and fauna of India. Nearly 5,070 species have been recorded in India till today, of which 3,370 species have been reported to be from marine habitats (Subba Rao, 1991), belonging to 220 families and 591 genera. Bivalves are considered to be the most diverse (1100 species) group followed by cephalopods (210 species), gastropods (190 species), polyplacophore (41 species) and scaphopods (20 species). India has extensive molluscan resources along the coast. These resources have been exploited since time immemorial in the numerous bays, brackish waters, estuaries and seas around the sub-continent for the food, pearls and shells. Rich molluscan diversity has been described from Andaman & Nicobar Islands, which includes over 1000 species from the marine region (Subba Rao, 1991), while Gulf of Mannar and Lakshadweep were found to be represented with 428 and 424 species respectively (Venkatraman *et al.,* 2004). Gastropods occupy significant place in the commercial shell-craft manufacturing industry. The marine gastropod resources in India comprise a variety of species and are exploited regularly for various purposes (Ramadoss, 2003). Predacious gastropod cone shells have a diverse mechanism of prey capture and divided into three major feeding types namely; vermivorous, piscivorous and molluscivorous (Kohn, 1978). Among the various feeding types, piscivorous species are very dangerous. They can kill and swallow the prey of similar size (Kohn, 1956). When in contact with the prey, few *Conus* spp. use single radular teeth for injection of the venom and others use more than one radular teeth. The venom of each species of *Conus* has estimated to comprise between 100-200 peptide components (Myers *et al.,* 1993). Olivera and Teichert (2007) indicated that the conotoxins have proved to be a valuable probe in physiological and pharmacological studies of ion channels and other receptors. So far only 100 out of a potential 50,000 toxins have been extracted and analyzed from *Conus*. Since a species of *Conus* can yield 100-200 peptides with potential therapeutic uses, it is hoped that discovery of new species of cone snails would add to the knowledge of extant species as well as to the chemical diversity of pharmacologically active peptides.

A unique feature of conotoxins is due to their high degree of post-translational modification which is up to 75% of the amino acids in a single conotoxin found to be modified (Jimenez *et al.,* 1997 and Olivera, 1997). McIntosh *et al*., (2001) have reported the presence of serotonin, a smooth muscle relaxation compound in the venom of the Cone snail, *C. imperialis*. Studies on conotoxin are very much limited in India, especially in the south east coast of India. The present review discusses about the diversity of the *Conus* species in India and World with main emphasis on the toxin types and their importance.

Taxonomy and diversity of *Conus* species
Conidae is one of the largest groups of gastropods, belongs to the super-family Toxoglossa, which are

characterized by possession of venom apparatus. This group comprises about 500 species in the family Conidae, most of them are members of the single genus *Conus*, with a few exceptions. Nearly, all taxonomists agree that large and worldwide extensive dispersal of this genus should be split into smaller groups, but scheme has been generally accepted for dividing the several hundred *Conus* species into compact generic groups (Olivera *et al*., 1990). Cone snails are the inhabitants of shallow water and are found in variety of microhabitats (Kohn, 1978). These species are known to attach to the algae of coral reefs, crawl under the coral heads, and prefer sandy or coral rubble substrate (Halstead, 1965).

Conus species are highly diversified group of organisms documented by different authors from different localities. Kohn (2001) revealed the geographical variation of species diversity of *Conus* species along the North-East coast of Papua New Guinea. Kohn (1978) reported 70 *Conus* species from Sri Lanka and 64 species whereas in Maldives and Chagos. Richmond (1999) documented 198 species of Conidae from Western Indian Ocean. The Conidae documented from the Philippines was 287 species (Poppe, 2008) while in Vietnamese waters, 122 species have been recognized (Nguyen**,** 2005). Few studies indicated limited number of *Conus* species in the Krusadai Island (Satyamurti, 1952). Rockel *et al.* (1995) gave a detailed note on world living *Conus* and documented 316 valid species along with several subspecies and forms from the tropical Indo-Pacific region. In recent years, their taxonomic identification was felt to be very important due to the use of *Conus* venom in neurological research and drug discovery (Kohn *et al.*, 1999).

SubbaRao (1991) reviewed the Conids of Andaman and Nicobar Islands, recorded about 45 *Conus* species. *Conus* are common in Gulf of Mannar, Andaman and Nicobar Islands and Gulf of Kutch and Lakshadweep where coral rocks are found. The study on Indian *Conus* species started way back 1860's. The taxonomy and distribution of Indian Conidae was studied by Winckworth (1949). A total of 14 *Conus* species was reported from Krusadai Island of Gulf of Mannar (Satyamurti, 1952). Among the various *Conus* species, *C. milneedwadsi* is the only species protected in India (WPA, 1972). A recent study on *Conus* diversity of Tamil Nadu indicated the existence of 60 species (Franklin *et al.,* 2009), indicated that the richness of *Conus* in Gulf of Mannar is far better than other parts of Tamil Nadu. Adult specimens of two species *viz*; *C. virgo* (Linnaeus, 1758) and *C. bayani* (Jousseaume, 1872), recorded from the Pondicherry Coast, southeast coast of India were described by Satheesh Kumar and Khan, 2010. From the reports available, it has been understood that there is only sporadic sampling along the Tamil Nadu coast and necessitates systemic studies.

Structure of poisonous gland

Toxoglossan gastropods are among the most highly populous groups of marine invertebrates, due to use of their venom while capturing their prey. These include cone snails (Conidae), auger snails (Terebridae), and augur snails (Turridae) (Taylor *et al.,* 1993). They are most diverse and rich group of predatory snails in number of species of Toxoglossate molluscs (Kohn, 1998). In most of the molluscan taxonomy, cone snails are generally brought under the single large genus *Conus*. While other groups such as augers are assigned by the most taxonomists to several different genera like *Terebra, Hastula, Duplicaria* in the family Terebridae (Bouchet and Rocroi, 2005). A venom apparatus made up of a muscular venom bulb and a tubular venom gland generally characterizes these marine molluscs.

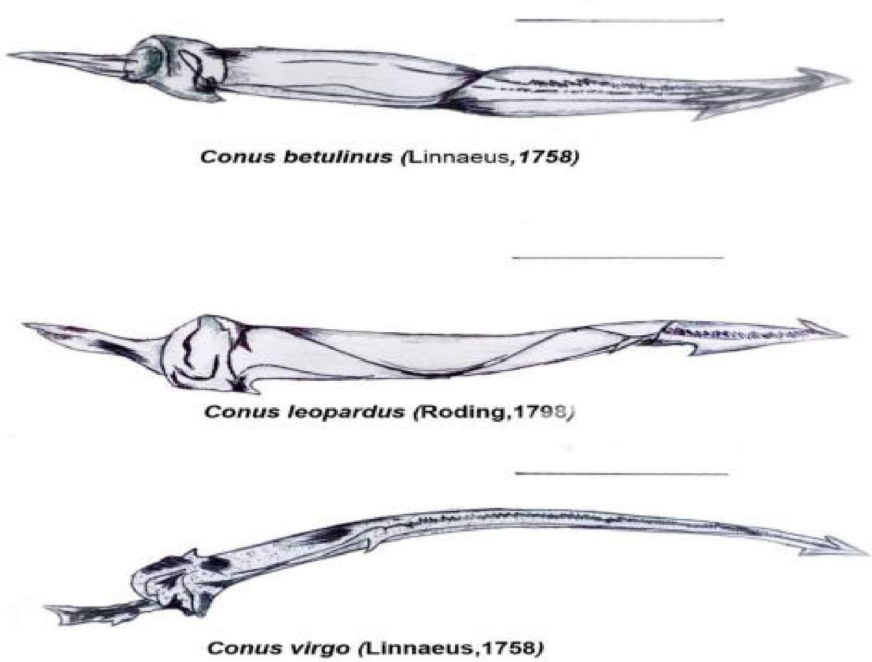

FIGURE 1. Radular tooth structure of *Conus* species

In general, the anatomical studies of venom apparatus are limited (Hinegardner, 1958, Halstead, 1988). There are only few reports on the venom apparatus like the anatomical structure of venom apparatus of *C. imperialis*

*(*Kohn *et al*., 1975*).* Toxins are injected into target animals *via* hollow disposable needle like radular tooth and act to immobilize prey or defend against predators (Olivera, 2002). The radular teeth have to perform three functions namely, pierce the body, firmly lodge and inject venom into the prey (Endean and Rudkin, 1965).

Radular structure of *Conus* species

The identification of *Conus* species is mostly based on the morphology and colour of the shell (Kohn *et al.,* 1999). The venom components are not highly species-specific, changes with the geographic location and age (Nybakken, 1970).To avoid these imprecision in species identification, reliable non-shell characters are needed. The molluscan radular teeth are often unique to species and genus corresponding to shape, structure and the most widely used source of data in molluscan systematic traditionally. In order to this some features of the radula were studied for higher level taxonomic relationships. The radular teeth of cones are unattached and resemble barbed hypodermic needles that are used to inject venom into prey. Thus, there should not be any minor imprecision in species identification and may have superfluous consequences. The *Conus* species are found to have a remarkable range of structures in their radular tooth morphology (Nybakken, 1970; Kohn, 1959; Massilia, 2001; Nishi and Kohn 1999). *Conus* species have been classified into different feeding modes and groups by studying radula structures (Azuma, 1964; Nybakken, 1990). Nishi and Kohn (1999) recognized three distinct groups of radular structures and indicated that teeth characters are potentially useful in differentiating species by using qualitative and quantitative characters.

In India, only few reports are available on the radular teeth of *Conus* species (Azuma, 1964; Ramu *et al.,* 1996; Nishi and Kohn 1999). Franklin *et al.* (2009) reviewed radular morphology of Indian *Conus* and established that the morphology and morphometry of radular teeth help to identify accurately. They studied systematically radular tooth of 25 of the available species and classified according to their feeding habits such as piscivorous (*C. achatinus*) and molluscivorous (*C. Amadis* and *C. araneosus*), and vermivorous (*C. inscriptus, C. loroisii* and *C. hyaena hyaena*).

Action of Conotoxin

Presence of multiple toxins in *Conus* venoms is evident from the physiological studies of Endean *et al*. (1963). The venom was found to paralyze the skeletal musculature of representatives in all vertebrate classes, but there was no noticeable effect produced in a variety of invertebrate tests (Endean and Rudkin, 1963). The investigations using crude venoms from several species, found a rather complex pharmacological picture revealed the presence of more than one active compound. Pharmacological study of the venom of *C. magus* revealed that the posterior duct venom increased the strength of contraction of the musculature of the ventricle of the toad heart, but decreased its rate of contraction. *C. striatus* venom was tested on a range of nerve and muscle preparations with a view to facilitate a comparative action of the venom with those of the venoms of *C. geographus* and *C. magus* (Endean *et al.,* 1974). Preliminary study on *Conus* venom protein revealed that effective purification methods are needed for separating individual toxic compounds. The recent researches mainly concentrate on purifying and characterizing the toxins from the venom gland of *Conus* and demonstrating its multiple toxin property, mostly small peptides that targets specific receptors or channels (Craig, 2000, Terlau and Olivera, 2004 and Olivera, 1997).

Types of conotoxins

Conotoxins of *Conus* species contain tremendously diverse, natural pharmacology compounds consisting of about 10 to 30 amino acid residues with one or more disulfide bonds (Joseph *et al.,* 2010). Conotoxin family comprises around thousands different peptides, most have a corresponding ion channel family target such as ω-conotoxins and Ca channels, α-conotoxins and nicotinic receptors and different conotoxins have different binding sites on the same ion channel target *i.e*., µ-conotoxin and δ-conotoxin to sites (Myers *et al*., 1993 and Olivera, 2002). Only a small fraction of the entire conopeptide diversity has been analysed and reviewed (Rojas, *et al.,* 2008). Currently, conotoxins are a valuable tool of scientific research, due to the intense pharmacological activity presented by the peptides. Five conotoxin activities have been determined so far like α- (alpha) conotoxins, δ-(delta) conotoxins, κ- (kappa) conotoxins, µ- (mu) conotoxins and ω- (omega) conotoxins

α-conotoxins

α- conotoxins completely blocks the post synaptic acetylcholine receptor of vertebrate skeletal muscle, which results in paralysis and death (Gray*et al.,* 1981). It contains two cysteine bonds and thirteen to fifteen residues. Majority of the α-conotoxins were extracted from the fish eating species (Joseph *et al.,* 2010). These are reported from *C. striatus* (Jones and McIntosh, 2001). It has been observed that alterations in sodium channel gating produced by the venom of the marine snail *C. striatus* (Hahin *et al.,* 1991). The action was studied using the voltage-clamp technique on militated nerve and produced repetitive firing of action potential when the Ranvier node was depolarized under current clamp conditions.

δ-conotoxins

It is relatively less toxic towards vertebrates. The delta- conotoxins such as conotoxin SVIA from *C. striatus* bind with high affinity to voltage- independent sodium channels. The venom of *C. purpurascens* contains a delta- conotoxin (PVIA) termed the 'lock- jaw' peptide, which specifically targets the voltage sensitive sodium channels.

κ-conotoxins

These toxins can obstruct the potassium channel and have a knotting or inhibitor cysteine knot scaffold. The knotting scaffold is a very special disulfide- through- disulfide knot, peptide toxins. The small size, multiple disulfide bonding and ingenious variations make conotoxins to have tremendous natural pharmacological value.

µ-conotoxins

It blocks muscle voltage sensitive sodium channel with only minimal binding to neuronal sodium channel. This is unlike tetrodotoxin and saxitoxin which bind to both muscle and nerve sodium channels with equal affinity and independent of voltage. These are conotoxin GIII isoforms from *C. geographus* venom (Jones and McIntosh, 2001). These toxins are similar to tetrodotoxin in the selective blocking of skeletal muscle sodium channels, as well as competitively inhibiting saxitoxin binding to receptor site 1 of voltage- sensitive sodium channels.

ω-conotoxins

These toxins are no less restrained in activity or diverse in sequence than the other classes of conotoxins. The effect of ω- conotoxin M VII A is 100 to 1000 times that of morphine18. Therefore a synthetic version of ω- conotoxin M VII A has found application as an analgesic drug Ziconotide (Prialt).

Conotoxin Research in India

Oceans are the potential source of bio-medically important substances, while considering the pharmacologically active compounds from marine resources in relation to drugs and medical agents, *Conus* toxins (conotoxin) have a great attention because of their thousands of different pharmacologically active peptides (Olivera *et al*., 1997). The conotoxins are a group of neuroactive polypeptides found in the venom of all marine gastropod snail of the genus *Conus.* These potent bioactive products play an important role in the explosive growth of biomedical science and its highly active neurotoxin substances act as molecular probes in neurophysiological research and offer fascinating possibilities in elucidating the nature of both nervous and muscular functions. It modulates the activity of ion channels like potassium, sodium and others (Terlau and Olivera, 2004). Gowd *et al.* (2005) indicated that the works of Baldomero Oliver on Preliminary studies on conotoxin from Indian waters were initiated as early as 1960 (Kohn *et al.,* 1959). Limited studies on the toxic property of *C. amadis* and *C. Aulicus* revealed that it is necessary to strengthen the studies on effect of conotoxin on invertebrates and vertebrates (Kasinathan *et al.,* 1989a, b). Pharmaceutical property was partially studied in *C. amadis* (Ramu, 1994) and in *C. loroisii* (Saminathan, 1997). The identification and characterization of peptides from *Conus* snails were taken by Gowd *et al.* (2005) in Indian region. Sarma *et al.* (2005) elucidated the structure of conotoxin *C. amadis* Joseph *et al.* (2010) reviewed the potential of conotoxins for relieving the pain.

Several *Conus* peptides are widely used as research tools in neuroscience, such as ω-conotoxin and some are potential therapeutic agents, such as Ziconotide (Gowd *et al.,* 2005). Sudarslal *et al.* (2003) investigated the modulatory activity of sodium channels in a δ-conotoxin from an Indian marine snail (*C. amadis*). The isolated novel conotoxins from Indian marine cone snails revealed different novel peptides targeting on Na and Ca channels (Gowd *et al.,* 2005). The research on conotoxin is still in an infancy stage in India and much remains to be found. It is high time that concentrated and organized research on marine bioactive compounds has to be taken up. However, till date, there has not been a demonstrable growth in *Conus* toxin research. Since India is blessed with hundreds of *Conus* species, the potential bioactive property of these toxins has to be established for their effective utilization.

Conotoxin research in the World:

Kohn (1956) was the pioneer in the study of hunter or prey relationship of cone snails and they recognized that the venom of cone snails may possess therapeutic components. Salivary gland secretion of *Conus* species is one of the important venoms possessing analgesic property and also the most extensively studied (Sakthivel, 1999). Endean *et al*. (1963, 1974 and 1977) studied the venom of different species of cone snails in Australia and reported that venom contains a diversity of biologically active components. Their pharmacological studies could help to establish the venom caused paralysis of the skeletal musculature of representatives in all vertebrate classes but in invertebrates, their investigation also revealed that crude venoms of several conids had a complex pharmacological picture which suggested the presence of more than one active compound (Endean and Rudkin, 1963). Olivera (1990) was the primary innovator of the successful laboratory techniques in the study of venom components extracted from cone snails. They developed a new intracranial bioassay technique to study the property toxin in mice. The first *Conus* peptide extracted is a13 amino acid peptide with two disulphide bonds from *C. geographus* confirmed by chemical synthesis of α-conotoxin (Cruz *et al.,* 1978; Gray *et al.,* 1981). Clark *et al.* (2001) injected the venom fraction directly into the central nervous system of mammals, instead of using the intraperitoneal injection which resulted in better observation. However, when the same fractions were injected intracranially or intra-cerebrally, the true pharmacological diversity of *Conus* venoms was revealed by the amazing array of different behavioural phenotypes elicited in the mice (Olivera *et al.,* 1990). The conotoxin inhibit calcium currents and synaptic transmission at the frog neuromuscular junction (Kerr and Yoshikami, 1984). Sleeper peptide a sleep inducing peptide, γ-carboxyglutamate has been isolated from fish-hunting cone snail, *C. geographus* (Mclntosh *et al*., 1984).

Now-a-days, shaker peptides are known as ω-conotoxins (GVIA and MVIIA), ω-conotoxin GVIA is the most widely used toxin in neuroscience followed by tetraodotoxin (Olivera *et al.,* 1990). In Brazil, three *Conus* species of large diameter are potentially dangerous, all are piscivores*viz*; *C. regius*, *C. centurio* and *C. ermineus* were identified from Fernando de Noronha Islands. Alonso *et al.* (2003) reported that conotoxin leads to the neuropathic pain and other neurological conditions. Ziconotide, a derivative of conotoxin helps to manage the severe chronic pain (Oren Bogin, 2005; Joseph *et al.,* 2010). Terlau and Olivera (2004) reviewed the conotoxin and its impact on ion channels. Recently, efforts have been made to obtain the pharmaceutically valuable extracts from venom ducts of Toxoglossate gastropod genus *Conus* in the Gulf of Mexico.

CONCLUSION

The conotoxins have proved to be a valuable probe in physiological and pharmacological, and it has significant application in neurobiology and other biomedical sciences. Since a species of *Conus* can yield 100-200 peptides with potential therapeutic uses but research on conotoxin is still in an infancy stage in India and more and more research has needed to be done in future days to make use of bioactive properties of conotoxins. In view of the fact that India is blessed with hundreds of *Conus* species, the potential bioactive property of these toxins has to be established for their effective utilization.

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