Natural toxins and their therapeutic potential

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Plants have been extensively investigated for exploring their therapeutic potentials, but there are comparatively scanty reports on drugs derived from animal kingdom, except for hormones. During last decade, the toxins that are used for defense by the animals, have been isolated and found useful tools for physiological and pharmacological studies, besides giving valuable leads to drug development. Toxins with interesting results have been isolated from the venoms of snakes, scorpions, spiders, snails, lizards, frogs and fish. The present review describe about some toxins as drugs and their biological activities. Some fungal, bacterial and marine toxins have also been covered in this article.

Keywords: Animal toxin, Fungal toxin, Natural toxin, Therapeutic use, Venom

Natural toxins, whether derived from plants, fungi, marine organism, snails or animals have played a significant role directly or indirectly in drug development. The first of the angiotensin converting enzyme (ACE) inhibitor captopril owes its discovery to venom of the poisonous Brazilian viper, Bothrops juraraca. Bakhle1 has reported that peptides from the Brazilian viper venom inhibit the activity of ACE present in cell-free extracts of dog lung. Captopril emerges2,3 as a drug used in the management of hypertension, and in heart failure after myocardial infarction. Exendin-4, a peptide isolated from the venom of gila monster, Heloderma suspectum, a species of poisonous lizard from North America exhibits a significant amino acid homology with glucagon-like peptide1 (GLP-1) secreted from intestinal L-cells. Extendins are carboxy-amidated peptides containing 39 amino acid residues. Extendin-4 stimulated insulin secretion in vitro and is a potent agonist of the GLP receptor4. Studies in diabetic mice have shown long-lasting reduction of blood glucose concentration following once daily injection. Synthetic extendin-4 (exenatide) was licensed in 2005 for the treatment of type-2 diabetes in combination with metformin and/or sulphophy lureas when either drug, alone or in combination, is inadequate5. Palytoxin6,7, one of the most complicated natural product with sixty four chiral centres and seven double bonds allowing a large number of stereoisomers, is the most active coronary vasoconstrictor acting through interaction with calcium channels. Palytoxin is the most poisonous non-proteinaceous substance has been isolated from zoanthid coral Palythoa toxica. It is used as a physiological tool to evaluate anti-anginal chemotherapeutic agent. Toxins like betrachotoxins, tetrodotoxin, saxitoxin, have not only given new leads, but have given impetus to neurophysiology and pharmacology by acting as pharmacological tools. Molecular aspects of electrical excitability in nerve, skeletal muscle and cardiac cell can be elucidated with the help of natural toxins. The present communication presents an account of recent advances made in natural toxins and their role in drug development.

Plant toxins

Fungal toxins—Among the toxins obtained from different fungi aflatoxins are the most documented of all mycotoxins. Aflatoxins are closely related group of secondary metabolites produced by Aspergillus flavus and A. parasiticus. Improper storage of crop products often results in their contamination by these toxicogenic moulds. Thus, aflotoxins have been reported to naturally occur in plants, corns, cotton seed, groundnuts and peppers, etc. There are four naturally occurring aflotoxins (B1, B2, G1 and G2). Chemically, aflatoxins are fluorescent compounds characterized by a dihydrofuran or tetrahydrofuran moieties fused to a substituted coumarin heterocycle. The aflatoxins are listed as known human carcinogens8, aflatoxin B1 (I) being one of the most potent environmental mutagens and carcinogens known.
Mycotoxins produced by *Fusarium* species, represented by trichothecenes, zearalenones and fumonisins also affect animal and human health and possess divergent biological activities. Zearalenone, a β-resorcylic acid lactone, is reported to have hyperestrogenic activity in mice. Ochratoxin A, roquefortine and citrinin are some of the toxicants of genus *Penicillium* associated with human and animal disease. Griseofulvin (2), a toxicant from *P. griseofulvum* is used as an antifungal drug. Panigrahi has reviewed the mycotoxins of the genus *Alternaria* and discussed their toxic activities.

A mention may be made of amanitin and phalloidin, the cyclopeptide toxins from the poisonous mushroom *Amanita phalloides*. Amanitin is a mixture of α-, β-, γ-amanitin and amanin. α-Amanitin, which is the major constituent, is 10-20 times more toxic than phalloidin. Development of cyclosporin A (ciclosporin A) as an immunosuppressive drug has been traced back to the stimulus derived from the first highly-active cyclopeptides from *Amanita* mushrooms.

**Algal toxins**—Anatoxins represent first neurotoxins present in fresh-water blue-green alga *Anabaena flos-aquae*. Anatoxin-a is the strongest agonist known for the nicotinic acetylcholine receptor. Despite its apparent structural dissimilarity to the natural transmitter acetylcholine, the physiological effects of the toxin are identical with those of acetylcholine. Anatoxin-a is about 30 times more potent than carbachol (carbamylcholine).

**Bacterial toxins**—The anaerobic bacterium *Clostridium botulinum* produces a family of potent neurotoxins collectively called as botulin toxins. Seven serologically distinct types are known designated as botulin A, B, C, D, E, F and G. Botulinum toxin has long been known as one of the deadliest nerve poisons known throughout history. It is estimated that an oral dose of 70 µg or inhalation of a hundredth of that amount is enough to lethally poison an average adult and most dreaded as biological weapon. The toxin blocks the release of acetylcholine from presynaptic nerve terminals causing a generalized paralysis of the muscle resulting in death. Its name is derived from “botulus”, Greek for sausage, the food linked to many outbreaks of botulism. Botulin toxin has been used as an investigational agent for the study of synaptic neurotransmission. Besides, it has proven to be an extremely useful therapeutic agent for clinicians to treat various gastrointestinal smooth muscle disorders. Its use in the treatment of achalasia is well documented. Botulin A and B have been approved for clinical use. Recently, use of botulinum toxin in the treatment of chronic anal fissures has been reviewed. Relief of post-radiotherapy masticatory spasms, and inducement of cervicospinal excitability changes in a population of patients with limb spasticity.

**Marine toxins**—A mention has already been made of palytoxin, a highly poisonous toxin from zoanthid coral *Palythoa toxica* used as a physiological tool. Other marine toxins of medicinal interest are didemnins which are depsipeptides extracted in 1978 from a Caribbean tunicate (sea squirt) of the genus *Trididemnum*. Although more than nine didemnins (A-E, G, X and Y) have been isolated from the extract of *Trididemnum solidum*, it is didemnin B that possesses the most important biological activities. Didemnin B is a strong antiviral agent active against both DNA and RNA viruses like *Herpes simplex* virus type 1, and a strong immunosuppressant that shows some potential in skin grafting. It shows strong activity against murine leukemia cells. It has undergone phase
II human clinical trials against adrenocarcinoma of kidney, advanced epithelial ovarian cancer and metastatic breast cancer. Unfortunately, it has shown high toxicity and anaphylactic reactions in patients resulting in terminating the trials.

**Animal toxins**

Venomous animals possess a wide range of toxins for predation and defense. It is difficult to comprehend the exact number of venomous species or the number of toxins they produce. A number of venomous animals and their toxins have been investigated to explore their biological activities and therapeutic potential. Among the animal, toxins of snake, scorpion, spider, snail, lizard, frog, fish and insect have been described as follows.

**Snake toxins**—Snake venom is a mixture of both proteinaceous and non-proteinaceous components. Protein components comprise enzymes, polypeptides and proteins. These toxins are reported to exhibit a variety of pharmacological activities such as myotoxic, neurotoxic, hypotensive, haemolytic, platelet-aggregation inhibition, anticoagulant, inflammatory, analgesic and bactericidal. Use of snake venom in different pathophysiological conditions has been mentioned in Ayurveda, homoeopathy and folk medicine. Snake venom contains several neurotoxic, cardiotoxic, cytotoxic, nerve growth factor, lectins, disintegrins, haemorrhagins and many enzymes.

Venom of Southeast Asian banded snake, *Bungarus multicinctus* yields several proteinaceous factions of which α-bungarotoxin and β-bungarotoxin are the important ones. α-Bungarotoxin is a single polypeptide chain of molecular weight of about 8,000 kDa containing 74 amino acid residues with 5 disulphide bridges. It is a post-synaptic neuron toxin with curare-like action that binds selectively and irreversibly to acetylcholine receptor sites, producing neuromuscular blockade resulting in skeletal muscle paralysis. α-Bungarotoxin is used as a most reliable pharmacological tool to study neuromuscular blockade. Its slow rate of dissociation makes it an excellent ligand for labeling, for affinity purification, and for pharmacological analysis of acetylcholine receptor. It is also a selective antagonist of the α-7 nicotinic acetylcholine receptor in the brain, and as such has applications in neuroscience research. A monoclonal antibody specific for α-bungarotoxin has been prepared. β-Bungarotoxin, the main presynaptic phospholipase A₂ neurotoxin, consists of two dissimilar polypeptide chains (chains A and B) cross-linked by an interchain disulphide bond. The larger chain contains 120 amino acid residues, the smaller chain contains 60 residues. It has been suggested that both A and B chains are indispensable parts of β-bungarotoxin for inducing the facilitation of spontaneous synaptic currents frequency with *Xenopus* nerve-muscle cultures. Recently, it has been indicated that both A and B chains possess the capability to induce vesicle leakage, and reduction of interchain disulphide bond markedly releases this ability from intact β-bungarotoxin molecule.

The venom of *Vipera russelli* produces alterations in general behavioral pattern, reduction in spontaneous motility, hypothermia, potentiation of hypnosis, analgesia, and muscle relaxation.

Cobrotoxin isolated from the venom of Taiwan cobra, *Naja naja atra*, has been first reported to have anti-nociceptive effect which has been, in a later study, attributed to one of the six neurotoxins. Four cardiotoxins have been isolated from *Naja naja atra* venom and their amino acid sequences have been determined. The cardiotoxins have been found to be comprise 60 amino acid residues. King cobra, *Ophiophagus hannah*, found in India, Myanmar, Thailand, Malaysia, China, Japan and the Philippines is the largest venomous snake in the world. At least six α-neurotoxins have been isolated from king cobra venom, of which four have been sequenced. They have been reported to act post-synaptically with similar biological properties to

**Fig. 2**—Structure formula of compound (3)
cabrotoxin. Hannalgesin, a long-chain α-neurotoxin from the venom of king cobra, exhibits analgesic activity in mice. It produces analgesia at a dose of 16-32 ng/g (ip) without causing any neurological or muscular deficits. The analgesic effect was blocked by both naloxone and L-NG-nitroarginine methyl ester (inhibitor of NO synthase) suggesting the possible involvement of opioid and nitric oxide systems, respectively, in anti-nociceptive pathway.

From Indian king cobra venom a lethal neurotoxin protein (Toxin CM36) has been isolated. It exhibits Ca²⁺ dependent neurotoxicity and produced irreversible blockade of isolated chick biventer cervicis and nerve phrenic nerve diaphragm. A novel short toxin (composed of 60-62 amino acid residue) has been isolated from the venom of monocellate cobra Naja kaouthia found in Yunnan province of South-West China.

The venom of South American rattle snake, Crotalus durissus terrificus, has been investigated. A neurotoxin crotamine which a single polypeptide chain of 42 amino acids with three disulphide bridges has been shown to induce myonecrosis, and has been used as a tool to study sodium channel distribution in the muscle fiber membrane. Crotamine is also reported to produce analgesic effect at lower doses without any apparent in vivo toxicity. The anti-nociceptive effect of crotamine is about 30-fold higher than that of morphine and has been demonstrated to involve both central and peripheral mechanisms. A review on crotamine giving additional information on the biological activity of crotamine has appeared. Another study reveals that the factors with an apparent molecular weight less than 3000 daltons from the venom of Crotalus durissus terrificus causes an anti-nociceptive effect in mice which is possibly mediated by opioid receptors. Subsequently, it has been shown that the anti-nociceptive effect of venom involves, at least partially, a cascade of molecular events involving δ- and κ-opioid receptors.

Batroxobin, an enzyme derived from the venom of Bothrops atrox (a pit viper found in Southern and Central America), has thrombin-like properties. It produces analgesia at a dose of 16-32 ng/g (ip) without causing any neurological or muscular deficits. The analgesic effect was blocked by both naloxone and L-NG-nitroarginine methyl ester (inhibitor of NO synthase) suggesting the possible involvement of opioid and nitric oxide systems, respectively, in anti-nociceptive pathway.

Recently, isolated perfused rat kidney method has been described to evaluate the renal effects of B. jararacussu myotoxin I and II. Myotoxins I and II have antibacterial effect against Xanthomonas axonopodis pv. passiflorae, a gram negative bacteria. The venom of Chinese pit viper, Zhaemia mangshanensis, exhibits coagulant activity on bovine and human fibrinogen and human plasma, high phosphodiesterase and arginine esterase hydrolytic activity, and moderate to low L-amino acid oxidase, kallikrein, caseinolytic, phospholipase A₂, haemorrhagic acid myotoxic activities. The major toxin from the venom named zhasermiatoksin has been isolated and found to be a homodienia with momemeric mass of 13,972 kDa, and consists of 121 amino acids residues cross-linked by seven disulphide bridges.

Envenomation by snake poisonous snake bite causes a variety of symptoms which depend on the family to which the snake belongs. For example, snakes of viperidae family usually cause oedema, haemorrhage and myonecrosis; in severe cases permanent tissue loss, disability or amputation may result. Natural resistance (immunity) against snake venom has been reported in hedgehog, mongoose and opossum. In most cases, the resistance of several animals to snake venom can be explained by the presence of protein factors in the blood which inhibit the activity of important toxic compounds. These proteins are either metalloproteinase inhibitors (antihemorrhagic factors) or PLÁ₂ inhibitors (antineurotoxic and/or antimyotoxic factors). A current state of art of protein inhibitors of toxic PLÁ₂s derived from snake and mammalian blood and plants has been discussed. A special mention is made on a newly described glycoprotein PLÁ₂ inhibitor from Withania somnifera, which exhibits anti-myotoxic and anti-oedema properties against a multi-toxic PLÁ₂ from Indian cobra. These proteins have therapeutic potential in the snake envenomations. Recently, Chatterjee and co-workers have reported that whole seed extract of Strychnos nux vomica effectively neutralizes Daboia russelli venom induced lethal, haemorrhage, defibrinogenating, PLÁ₂ enzyme activity and Naja kaouthia venom induced lethal, cardiotoxic, neurotoxic, PLÁ₂ enzyme activity. The seed extract also potentiated polyvalent snake venom antiserum action in experimental animals. An active compound (SNVNF) has been isolated.

Scorpion toxins—Scorpions have been used in Chinese system of medicine for amelioration of a number of diseases. Whole scorpions, scorpion sting
or their extracts have been found to be effective in treating some neural diseases such as apoplexy, epilepsy, facial paralysis, hemiplegia besides being used to soothe the nerves and relieve pains caused by meningitis, cerebral palsy and rheumatism.\textsuperscript{53,54}

Scorpion venom contains a large number of biologically active substances such as peptide toxins with different in-channel specificities, enzymes, nucleotides, lipids, mucoproteins, biogenic amines, glycosaminoglycans and histamine.\textsuperscript{55} Injection of scorpion venom can induce the secretion of inflammatory mediators such as bradykinin, platelet activating factor, prostaglandins, leucotriens, cytokines and 5-hydroxytryptamine that contribute to pain response.\textsuperscript{56}

Anti-nociceptive activity has been demonstrated by scorpion venoms and their peptide toxins.\textsuperscript{53,57-59} An antitumour-analgetic peptide from \textit{Bothus martense} venom shows strong inhibitory effect on both visceral and somatic pain and also antitumour activity on \textit{E. ascites} tumour and S-180 fibrosarcoma cells.\textsuperscript{54} Scorpion \(\beta\)-toxins have also been used as pharmacological tools in the study of voltage-activated \(Na^+\) channels.\textsuperscript{50,61}

Indian red scorpion, \textit{Mesobuthus tamulus}, venom causes cardiac abnormalities like acute myocarditis, cardiac dysrhythmia (achy arrhythmias, bradyarrhythmias) and various degrees of heart block. Recently, it has been shown that the venom induces activation of muscarinic receptors by enhanced cholinergic activity via Gi-guanylyl cyclase mediated cell-signaling pathways in producing atrial rate changes. Vaso-sensory responses elicited by Indian scorpion venom have been compared with capsaicin (which also evokes vaso-sensory refluxes)-induced responses. It has been shown that intraarterial injection of scorpion venom produces prolonged cardiorespiratory alterations as compared to capsaicin-induced responses.\textsuperscript{63}

\textit{Spider toxins}—Spider toxins comprise polypeptides with molecular weights ranging from 4 to 10 kDa, which function as neurotoxins. The pharmacology and biochemistry have been reviewed by Rash and Hodgson\textsuperscript{64}, who have classified toxins from spider venom affecting: glutamatergic neurotransmission; voltage-sensitive calcium channel; voltage dependent \(Na^+\) channel; \(K^+\) channel; and chloride channel. Also classified are toxins which stimulate transmitter release and toxins blocking post-synaptic cholinergic receptors. It has been reported that co-agatoxin IVA from the venom of funnel web spider, \textit{Agelenopsis aspera}, enhances the agonist-induced tail flick anti-nociception when co-administered spinally with both morphine and clonidine suggesting use of the toxin in opioid dependent/tolerant patients.\textsuperscript{65} Psalmotoxin isolated from South American tarantula \textit{Psalmopoeus cambridgei} selectively blocks acid-sensitive ion channels or \(H^+\)-gated cationic channels. The channels have been reported to play an important role in pathological conditions such as brain ischemia or epilepsy.

\textit{Snail toxins}—Among the numerous marine animals cone snails (Family Cnidae; genus \textit{Conus}) have been investigated extensively to explore their therapeutic potential. Cone snails are predators that live in tropical and sub-tropical waters. Cone snail toxins named conotoxins are primarily used to stun, immobilize and kill prey, although they could be used for defensive purposes also. The toxins derived from cone snails are currently being investigated for the treatment of chronic pain, epilepsy, cardiovascular diseases, psychiatric and movement disorders.\textsuperscript{67}

A 25 amino acid peptide co-conotoxin MVIIA isolated from venom of \textit{Conus magus} has been shown to inhibit neuropathic pain responses and induces less tolerance than morphine.\textsuperscript{68} A synthetic co-conotoxin MVII, ziconotide (PRIAL), has been approved by FDA of US for the treatment of severe pain.\textsuperscript{69} Conantokintokin G, a 17 amino acid peptide from \textit{C. geographus}, has been reported to be a novel therapeutic agent for the treatment of pain.\textsuperscript{70} Co-conotoxin GVIA\textsuperscript{71}, Contulakin-G\textsuperscript{72} from \textit{C. geographus}; and co-conotoxin from \textit{C. catus}\textsuperscript{73} have also been reported to have promising anti-nociceptive activity. Biologically active T-1-conotoxin\textsuperscript{74}, and a V-conotoxin-like peptide\textsuperscript{75} from venoms of \textit{C. spurious} and \textit{C. austini}, respectively, have also been reported. Sodium channel modulating activity in S-conotoxin isolated from \textit{C. amadis}, an Indian marine snail, has been reported.\textsuperscript{76}

\textit{Lizard toxins}—Mention has already been made of the gila monster, \textit{Heloderma suspectum}, native to the South-Western United States and North-Western Mexico. From the venom of the lizard \textit{Goke et al.}\textsuperscript{5} have reported exendin-4, a glucagon-like peptide. The lizard hormone is almost half identical to a similar hormone in the human digestive tract, called glucagon-like peptide-1 (GLP-I), that increases the production of insulin when blood sugar levels are
high. Insulin helps to move sugar from the blood into other body tissues where it is used for energy. Exendin-4 remains effective much longer than human hormone. A synthetic exendin-4 named exenatide has been prepared and marketed as Byetta which has been approved by the Food and Drug Administration of US in April 2005 to treat type-2 diabetes in patients who are not able to control their high blood sugar with three other medications, metformin, sulphonylurea or thiazolidenedione. Another long-acting GLP-1 mimic braglutide is in advanced clinical development.

From Heloderma horridum, a Mexican headed lizard, exendin-3 has been isolated with interesting biological activity. Structurally related peptides known as helospectin and helodermin have also been isolated from venom of these species.

**Frog toxins**—Number of potent bioactive compounds of interesting structures have been isolated from frog skin. More than hundred toxins have been identified from the skin secretions of frogs of genus *Dendrobates* and *Phyllobates*. From the latter genus, toxins like batrachotoxins and histrionicotoxins with novel structure have been isolated which have given impetus to neurophysiology and pharmacology besides giving new leads in synthetic organic chemistry.

Batrachotoxins (4) are potent cardiotoxic and neurotoxic steroidal alkaloids found in certain species of South American poison-dart frogs of genus *Phyllobates*. The name has been derived from the Greek word “betrachas” meaning frog. Batrachotoxin, generally classified as a neurotoxin, has marked effects on cardiac muscles which are similar to cardiotoxic effects of digitalis. Acting on peripheral nervous system, it causes activation of Na⁺ channels. Batrochotoxin kills by permanently blocking nerve signal transmission. It is used as a biochemical tool for the study of Na⁺ channel. Batrachotoxin R, bathachotoxinin A and homobatrachotoxinin are the other members of the family. Histrionicotoxin is a piperidine alkaloid isolated from the skin of poisonous arrow frog *Dentrobates histrionicus*. It causes non-competitive inhibition of nicotine receptors. It is used as biochemical probe for neuromuscular transmission.

A special mention is made of dermorphine and related peptides isolated from the South American frog skin of *Phyllomedusa* species. Dermorphine (5) which is a heptapeptide chain shows high affinity for re-opioid receptors. Several peptides related to dermorphin have also been reported. Like µ-opiates agonists, dermorphins produce anti-nociception, catalepsy, rigidity and sedation. Intrathecal administration of dermorphins in humans has shown 100 times greater potency than morphine. Deltorphins and related peptides isolated from the frog skin have also been found to exhibit high selectively for δ-opiate receptors and produce analgesia in laboratory and humans.

A comprehensive review on the bioactive molecules such as peptides, proteins, steroids, alkaloids and opioids isolated from various amphibian skins has appeared. Potent therapeutic activities like antibacterial, antifungal, antiprotozoal, antidiabetic, antineoplastic, analgesic and sleep inducing properties have been discussed which provide potential clue towards new drug development.

**Fish and mollusc toxins**—The two toxins which are probably the most widely used tools both by electrophysiologists and by biochemists to study Na⁺ channel are tetrodotoxin (6) and saxitoxin.

Tetrodotoxin is obtained from ovary and liver of many species of fish of family Tetradontidae, specially the globe fish, *Spheroides rubripes*. According to Ishikawa Health Service Association, Japan, tetrodotoxin is nearly 100 times more toxic than curare. The structure of tetrodotoxin (6) is shown in the following figure.
poisonous than cyanide. Saxitoxin is a neurotoxin produced by certain species of marine dinoflagellates *Gonyaulax catenella* or *G. tamarensis*. The toxins are used in biochemical research.

A mention may be made of urotensin, a straight-chain peptide of 38 amino acids isolated from many fish. It is reported to produce a sustained hypotension in most mammalian species. A myotoxin (TmC4-47.2) from the toadfish *Thalassophyzone maculosa* has been reported to depolarize skeletal muscle fibres.

A sting of the fish, *Scatophagus argus*, an Indian venomous edible spotted butterfish produces tremendous local pain, severe swelling, rise of body temperature, throbbing sensation, etc. From the spine extract of the fish a haemorrhagic protein toxin (SA-HT) has been isolated with molecular weight of 18.1 kDa. The toxin produces severe haemorrhage on stomach wall, but is devoid of cutaneous haemorrhage. SA-HT significantly increases plasma plasmin, serum MDA level and decreases SOD level indicating the possible involvement of cyclooxygenase and lipoxygenase pathway. Detailed pharmacological studies on the sting extract of the butterfish have also been carried out.

**Honey bee toxins**—From the venom (opitoxin) of honey bee *Apis mellifera*, a 18 amino acid polypeptide neurotoxin apamin has been isolated. It is used primarily in biomedical research to study the electrical properties of small conductance Ca$^{2+}$ activated K$^+$ channels (SK channels). Apamin binds to these channels in the brain and spinal cord and inhibits them. Apamin as a SK channel blocker has therapeutic applications on the peripheral cells (e.g. the insulin releasing cells of the pancreas) and on the central nervous system where there is evidence for a role of SK channels in memory processes.

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