Indian Journal of Pharmacology

ISSN 0253-7613

Official Publication of the Indian Pharmacological Society
December 2007 Vol 39 Issue 6

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Review Article

Therapeutic alternatives from venoms and toxins

Shivaji P. Gawade

SVERI's College of Pharmacy, Gopalpur-Ranjani Rd, P.B. 54, Pandharpur - 413 304, Solapur, MS, India

Received: 22.01.2007
Revised: 10.11.2007
Accepted: 08.01.2008

Correspondence to:
Dr. Shivaji P. Gawade
E-mail: shivaji.gawade@gmail.com

ABSTRACT

The medicinal value of venoms has been known from ancient times. The active principles in venoms have been extensively investigated for their target specificity. Affinity for the primary sites responsible for lethality and efficacy at extremely low concentrations made these agents valuable tools or surrogates for basic biomedical research. The therapeutic effects of these agents are usually achieved by mechanisms that are different from that of conventional therapeutic agents. In the present paper, nonherbal natural therapeutic alternatives approved by the FDA, those that have undergone extensive clinical evaluation and shown promise in preclinical evaluation, or those that are isolated in pure form or subjected for the treatment to venoms are reviewed. These agents are suggested for the treatment of various diseases, including inflammatory, hematological, autoimmune, infectious, cardiovascular, malignant, neuromuscular, and psychotic diseases.

KEY WORDS: Nonherbal natural therapeutic alternatives, snake venomoid

The planet Earth has been blessed with a vast variety of flora and fauna. Most of these still remain uninvestigated in the search for biomolecules with specialized structures and target specificity. Natural nonherbal therapeutic alternatives (NNTA) with proven therapeutic actions would be of immense value for the treatment of age-old diseases. These therapeutic alternatives are atypical therapeutic agents that originate from natural sources and are used for the treatment of diseases when the patient is found to be refractory to the conventional therapies. These agents are effective at extremely low doses and the therapeutic properties exhibited by them are achieved by mechanisms other than that of the known therapies. *Venom* is a complex mixture of a number of constituents proteins, peptides, enzymes and trace amounts of nonprotein inclusions, which exist in a specialized reservoir, i.e., the venom glands of arthropods and reptiles. These specialized secretions are employed by these creatures to paralyze their prey and its subsequent catabolism. On the other hand, *toxin* is a homogenous structure that is isolated, extracted, or derived from plant, animal, or microbial sources and has a specific locus of action.

The NNTA, currently under extensive evaluation, come from diverse natural sources, such as marine snail, sea anemone, leech, frog skin, snake venoms, and microbes such as *Clostridium botulinum* type A. These substances are being evaluated for use in various disease conditions, including inflammatory, hematological, autoimmune, infectious, cardiovascular, malignant, neuromuscular, and psychotic diseases. Table 1 summarizes the various NNTA that are under extensive evaluation.

Inflammatory Diseases

The NNTA used for inflammatory pain include, ziconotide, Xen 2174, hannalgesin, epibatidine, Keluoqu tablets, etc.

Ziconotide (Prialt)

Ziconotide (2699 Da, 25 aa) is a nonopioid nonsteriodal alternative for pain relief. It is a synthetic analogue derived from omega conotoxin MVII A, which is isolated from the marine snail, *Conus magnus*. The analgesic action of ziconotide is by blockade of the presynaptic N-type of Ca^{2+} channel present on sensory neurons. Ziconotide is used as an intrathecal analgesic in patients refractory to intrathecal opioid or oral opioid therapy. The data from a phase III clinical trial on 1250 patients revealed that ziconotide is devoid of adverse effects such as respiratory depression, tolerance, and the withdrawal syndrome.[1]

Xen 2174

It is an analogue of MrIA X conapeptide isolated from the venom of the marine snail *Conus marmoreus*. Xen 2174 is more potent, selective and stable than X conapeptide. Xen 2174 has been proved to be safe in phase I clinical trials. It is recommended intrathecally to treat severe and unmanageable pain in cancer patients.[2] In a phase III clinical trial on 322 patients for 6.5 months, Xen 2174 decreased sweat production in 50% to 80% patients. It is suggested for the treatment of underarm hyperhidrosis (USFDA, July 2004). Intrathecal X conopeptide, Xen 2174 dose dependently alleviated mechanical allodynia in rats with neuropathic and intractable pain.[3]

Hannalgesin

It is isolated from the venom of *Ophiophagus hannah*.[4]

Table 1

The therapeutic alternatives from venoms and toxins

Disease conditions	*Category*	*Nonherbal natural therapeutic alternatives*
Inflammatory disease	Analgesic	Ziconotide, Xen 2174, hannagesin, epibatidine, Keluoqu tablet
Hematological disease	Fibrinolytic	Batroxobin, ancrod
	Anticoagulant	Lepirudin
	Antithrombotic	Bothrojaracin, fibrolase
	Platelet aggregation inhibitor	Lebecetin
	Diagnostic hematological	Ecarin, RVV X and V enzymes, pseutarin C
Autoimmune disease	Immunomodulator	Sh K (L 5)-amide, α-bungarotoxin
Infectious disease	Antibacterial (Gram +ve), *E. coli*, *S. aureus*, Aeromonas	L-amino oxidase peptide Pandinins Pim 1, Pim 2
Cardiovascular disease	Cardiotonic	Bufodienolides
	Antihypertensive	BPP9a Teprotide (Captopril)
Malignant disease	Potent anticancer activity in preclinical evaluation	Salmosin, contortrostatin, eristostatin, rhodostamin, contortrostatin, toxin CM -28, BM-T 2, Dr-CT1
Neuromuscular disease	Muscle relaxant	BOTOX
Psychotic disease	Snake venomoids	POVRVP, POECVP, POESVP

The analgesic action of hannalgesin is by binding to the SS1 or SS2 subunit of the sodium channel, similar to tetrodotoxin and saxitoxin.[5] In the dose of 16-32 ng/gm by i.p. injection, hannalgesin induced analgesia is without causing neurological and muscular defects. The analgesic action is blocked by naloxone and L-NG-nitro methyl ester. Additionally, hannalgesin produced sedation and muscle relaxation and also induced locomotor activity.[4]

Epibatidine

Epibatidine ($C_{11}H_{13}N_2C1$)[6] is an alkaloid extracted from the skin of the frog, *Epipedobatus tricolor*. Epibatidine binds to nicotinic ACh receptors and receptors at the neuromuscular junction. It produced a typical arched tail in mice when injected parenterally. Epibatidine is 200 times more potent than morphine in the relief of pain.[7,8]

Keluoqu tablet

Keluoqu tablet is prepared by the incorporation of neurotoxin from the venom of the Chinese cobra. The duration of its analgesic effect is longer lasting (24 h) than that of tramadol (2.5 h). In a clinical trial on 200 patients, the effective rate of analgesia of keluoqu tablet in comparison with tramadol is 88: 72.2%. The side effects of Keluoqu tablet and tramadol recorded during the clinical trial included muscle weakness and constipation, respectively.[9]

Hematological Diseases

The venom of viperidae and crotalidae primarily exert their lethal action by interference with blood coagulation, either by accelerating the process or by specific delineation of a vital factor that prevents or inhibits the coagulation process. NNTA approved by the FDA, and those undergoing extensive clinical evaluation for the treatment of various hematological diseases, include fibrinolytics, anticoagulants, thrombin inhibitors, platelet aggregation inhibitor and hematological diagnostics etc.

Fibrinolytics

Batroxobin: Batroxobin (43 kDa, 231 aa, 12 cysteines) is a serine protease from *Bothrops atrox moojeni* venom. It is a thrombin-like enzyme (factor IIa), which inhibits the conversion of fibrinogen to fibrin. Botroxobin is used to study coagulation on patient's blood in the presence of heparin and prothrombin time in the absence of thrombin.[10] It is used to treat vascular thrombosis. It is also used to monitor fibrinogen levels in patients on heparin therapy.[10]

Ancrod (Viprinex): Ancrod is a directly-acting defibrinogenating enzyme. The drug prevents clot formation (by cleavage of fibrinogen), reduces blood viscosity, and increases blood flow to ischemic regions. Ancrod is a promising reperfusion agent for the treatment of acute ischemic stroke. Phase 3 clinical trials are underway to confirm its efficacy when used within 6 h of onset of stroke.[12]

Anticoagulant alternatives

Lepuridin: Lepuridin is a thrombin inhibitor derived by recombinant DNA technology from hirudin, which is isolated from the medicinal leech, *Hirudo medicinalis*. The antithrombic action of lepuridin is independent of antithrombin. Lepuridin inactivates fibrin-bound thrombin in thrombi. It is used in thromboembolic disease of arterial and venous origin and in thrombosis due to heparin-induced thrombocytopenia.[13]

Antithrombotics

Bothrojaracin: Bothrojaracin (27 kDa) is an c-type lectin-like protein from *Bothrops jararaca*. Bothrojaracin, at a concentration of 1 mg/kg (i.v.), decreased thrombus weight by 95% in rats with venom thrombosis and exhibited 100% protection in mice with thrombin-induced thromboembolism.[14] The antithrombic action of bothrojaracin is by binding to the two-thrombin anion-binding exosites, exosite I at fibrinogen and exosite II at antithrombin.[15]

Fibrolase: Fibrolase is a directly-acting plasminogen activator isolated from *Agkistrodon*, copperhead snake venom. Fibrolase rapidly lyses clot. It was also able to lyse a carotid artery thrombus rapidly when administered locally in an anesthetized dog. Fibrolase, in combination with known antiplatelet drug is suggested to be more effective thrombolytic

alternative.[16] Fibrolase, a metalloproteinase fibrinolytic agent, which was patented (US patent 7134114) as a novel-acting thrombolytic, is useful for lysis of blood clots *in vivo*. Unlike streptokinase, fibrolase causes degradation of fibrin and fibrinogen by direct action.[17]

Platelet aggregation inhibitors

Lebecetin: Lebecetin (29779 Da) is a basic protein (pH 9.9) comprising two alpha and beta subunits. Lebecetin dose dependently inhibited thrombin-induced platelet aggregation. However thromobxane A_2, U46619, or acachidonic acid-induced platelet aggregation was not inhibited by lebecetin. Lebecetin, by binding to the platelet GPIb/IX receptor system, inhibited ristocetin-induced platelet aggregation in human platelet-rich plasma.[18]

Hematological dignostics

Ecarin: Ecarin is a metalloproteinase isolated from the venom of *Echis carinatus*. It is a prothrombin-independent group 1A prothrombin activator. Prothrombin is converted into meizothrombin ecarin. Ecarin is used to facilitate detection of von Willebrand disease.[19]

RVV X and RVV V enzymes: RVV X and V enzymes are isolated from the venom of *Vipera russelli*. These enzymes are used to detect von Willbrand disease by determining factors X and V and prothrombin in blood.[20,21]

Pseutarin C: Pseutarin C is a group C prothrombin activator isolated from the venom of *Pseudonaja textiles*. Pseutarin C converts prothrombin to thrombin by activation of prothombin. The action of pseutarin C is similar to the mammalian factor Xa-Va complex.[22]

Autoimmune Diseases

The NNTA to treat autoimmune diseases include Sh K (L5)-amide, cobra drug and basic short chain snake venom neurotoxins like α-bungarotoxin are used as autoimmune diagnostics.[23]

Sh K (L 5)-amide

Sh K (L5)-amide is a peptide analogue of Sh K toxin generated from the sea anemone, *Stichodactyla helianthus*. Sh K (L5)-amide selectively blocked the potassium channel Kv 1.3 at very low concentrations. It is a novel immunomodulator, useful to selectively suppress memory T lymphocytes in patients of multiple sclerosis, type I diabetes mellitus, and rheumatoid arthritis.[23]

Cobra drug (immunokine)

Immunokine nontoxic peptide derived from cobra venom, termed as polypeptide O3 (PPO3) or peptide E (PEP-E), inhibited 90% of HIV infection tropism independently by blocking the chemokine receptors, CCR 5 and CXCR 4. The cobra drug, immunokine peptide, was found safe in clinical trials on HIV patients subjected to different applications.[24]

α-bungarotoxin

Neurotoxins, like α-bungarotoxin, with a strong affinity for muscle acetylcholine receptors have been used to generate acetylcholine receptor antibodies and diagnostically, in the autoimmune disease, myasthenia gravis, which is characterized by the presence of pathogenic antibodies to acetylcholine receptors.[25]

Infectious Diseases

The NNTA for infectious diseases include, L-amino oxidase, cobra peptide and pandinins.

L-amino oxidase

L-amino oxidase enzyme from the venom of *Crotalus adamenteus* showed antibacterial activity against Gram-positive bacteria. The venom of *Agkistron halys pallus*, *Bothorops alternatus*, and *Trimeresurus jerdoni* showed antibacterial activity against *E. coli* and *S. aureus*. The antibacterial activity of the venom of *Pseudechis australis* against aeromonas was 70-fold higher than that of tetracycline.[26,27]

Peptide

Peptides from the venom of *Naja atra* have been shown to possess antitubercular activity against *Mycobacterium tuberculosis*.[26]

Pandinins

Pim 1 (4799.5 Da) and Pim 2 (2612.9) from the venom of *Pandinin imperator* showed antibacterial activity against *B. subtilus* and *E. coli*. The antibacterial activity of pandinins was higher against Gram-positive bacteria than against Gram-negative bacteria.[28]

Cardiovascular Diseases

The NNTA to treat cardiac failure and hypertension are the bufodienolides and BPP9a, respectively.

Bufodienolides

Bufodienolides are glycosides isolated from the venom of the Central Asian green toad, *Bufo viridis* laur. There are six different glycosides, namely, gamabufotulin, arenobufugin, telcocinobufagin, marinobufagin, bufaregonin and bufalin. The cardiotonic action of the bufodienolides is probably by the inhibition of endogenous myocardial Na^+-K^+-ATPase. Bufodienolides increased the force of contraction and to some extent, the heart rate. Frog atrial trabecular contractions are also increased with the rise in the slow calcium current. The yield of bufodienolide is 30% of the total venom, i.e., 70 mg/toad. The bufodienolides are NNTA to stropanthin K, celanidum, and digitoxinum.[29]

BPP9a

BPP9a, a nanopeptide bradykinin potentiator with angiotensin converting enzyme-inhibiting action, was isolated from the venom of *Bothrops jararaca*.[30] BPP9a was synthesised at Squibb Corporation as Teprotide®, a parenteral product. BPP9a was further developed as an oral ACE inhibitor, captopril—an antihypertensive alternative for the treatment of renovascular hypertension.[31]

Malignant Diseases

The NNTA for the treatment of malignant diseases include salmosin, rhodostamin, contortrostatin, toxin-28, and dr-CT-1.

Salmosin

Salmosin is a disintegrin comprising a Arg-Gly-Asp sequence, isolated from the venom of the Korean snake *Agkistrodon halys brevicaudus*. Salmosin acts by blocking the function of α2β3 integrin.[32] Salmosin suppressed tumor

progression by strongly inhibiting tumor-derived angiogenesis, adherence and proliferation of tumor cells. Maintenance of drug levels in antiangiogenic cancer therapy through liposome delivery of the salmosin gene for *in vivo* expression has been investigated.[33]

Rhodostomin

Rhodostomin is a disintegrin from the venom of *Calloselasma rhodostoma*. Rhodostomin inhibited angiogenesis induced by basic fibroblast growth factor and suppressed murine melanoma B16-F10 tumor growth.[34] The antiangiogenic effect of rhodostomin is related to integrin $\alpha_v \beta_3$ blockade.

Contorstrostatin

Contorstrostatin, a disintegrin isolated from *Agkistrodon contortrix contortrix*, strongly inhibited the adhesion of human metastatic melanoma (M-24 met) to extracellular matrix and *in vivo*, lung colonization by M-24 met cells.[35] Contorstrostatin inhibited tumor growth and angiogenesis and prolonged the survival of mice with glioma.[36] Intravenous liposomal delivery of contorstrostatin was shown to be promising for human breast cancer therapy as it has a longer half life. It gets accumulated in the tumor cells and is devoid of platelet reactivity. Liposomal delivery of contorstrostatin does not respond to the immune system.[37]

Toxin CM-28

Toxin CM-28, a protein toxin from the venom of *Vipera russelli* and BM-T2, a nonprotein toxin from the skin of *Bufo melanostictus*, showed pronounced reduction in proliferation of the cancer cell cultures U937 and K562. In microscopical observations, both the toxins revealed membrane blebbing and nuclear fragmentation. BM-T2 decreased PCNA expression and exhibited cytotoxicity by MTT assay.[38,39]

dr-CT-1

dr-CT-1 (7.2 KDa), a heat-stable protein from *Daboia russelli russelli* venom, showed significant decrease in EAC cells *in vivo* and on human leukemic cell lines (U937 and K 562) *in vitro*; there was also significant prolongation of survival in mice. The antiproliferative action of the drug is evident from the reduction in MTT values. The apoptic effects of the drug is confirmed by observations of membrane blebbing, perforations, nuclear fragmentation, and cell cycle arrest in G_1 phase.[40]

Neuromuscular Diseases

Botulinum toxin type A (Botox)

Botox is injected locally in the limbs to treat generalized spastic disorders like cerebral palsy and can produce prolonged and persistent improvement, lasting several weeks.[41] Intramuscular injection of Botulinum toxin type A is used to treat involuntary muscle contractions (FDA approval, 1989). A cosmetic product of Botulinum toxin A, BOTOX®, is used to treat moderate to severe frown lines between the brows (FDA approval, 2002).[42]

Psychotic Diseases

The NNTA snake venomoids POVRVP, POECVP, and POESVP are central nervous system depressants, antidepressants, and stimulants with a wide spectrum of neuro- and psychopharmacological properties.

Snake venomoids[43]

POVRVP: A photooxidised product, POVRVP was generated by exposure of *Vipera russelli* venom to UV radiation (37°C, 15 min) in the presence of methylene blue. In preclinical evaluation in experimental animal models, POVRVP showed sedative, analgesic, and anti-inflammatory actions and decreased locomotor activity.[44] POVRVP also showed cardiac stimulant properties on isolated rat heart perfusion and shortened human plasma clotting time (unpublished observation, 2004-2005). Stability and subacute toxicity studies have shown that POVRVP is viable for 3 months. It is a NNTA for the treatment of chronic psychotic hyperactive disorders. POECVP (UVR, 37°C, 90 min), from *Echis carinatus* venom, showed antidepressant and nootropic properties,[45,46] and POESVP (UVR, 37°C, 30 min) from *Enhydrina schistosa* venom showed central nervous system stimulant, analgesic, anticoagulant nootropic and properties.[47] POECVP and POESVP are NNTA for chronic psychotic depressive disorders.

Remedies from snake venoms have been reported for the treatment of illnesses in the ancient literature of Charaka, Sushruta, and Vagbhata. However, extensive investigation on these natural leads for the generation of valuable pharmaceutical product is realized only in the last four decades, after a bradykinin-potentiating nanopeptide from *Bothrops jararaca* venom, with ACE-inhibitory action, was introduced as a natural alternative for the treatment of renovascular hypertension. The area of NNTAs is scanty, largely unattended and extremely expensive. However, these natural substances can offer cure for the disease conditions of tomorrow, which may not respond to currently available therapy.

Acknowledgments

The paper was presented in the poster session of 39th Annual Conference of Indian Pharmacological Society, Department of Pharmacology, SMS Medical College, Jaipur, Dec.21-23, 2006. The support and encouragement of Prof. B.P. Ronge, Secretary, Shri Vittal Education and Research Institute, and Principal, College of Engineering, Pandharpur is gratefully acknowledged.

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