

Scorpion Venom as Therapeutic Agent - Current Perspective

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ABSTRACT

Scorpions and their venoms have been employed in medication since thousands of years in Asia. The scorpion venom is an extremely advanced mixture of salts, nucleotides, biogenic amines, enzymes, mucoproteins, peptides and proteins (e.g. Neurotoxins). Scorpion venoms contain peptides that block or modify ion-channel function and present some doable applications to regulate cell excitability. Specific literature regarding the results of scorpion venom elements on T-cell differentiation, autoimmunity as well as on cardiac, haematological, neoplastic and infectious diseases has been revised in this article. Several investigations highlighted their potent effects against microbes and showed their potential to modulate varied biological mechanisms that are concerned in immune, nervous, cardiovascular and neoplastic diseases. As a result of their necessary structural and purposeful diversity, it's projected that scorpion-derived peptides might be accustomed to develop new specific medicine. This review is focused on the therapeutic potential of scorpion venoms and toxins and also the doable mechanisms for their anticancer, anti-inflammatory, antimicrobial activities and for the treatment of autoimmune, cardiac, hematological, infectious, osteoporosis, homeostasis and neurological diseases.

Keywords: Scorpion venom, therapeutic agent

INTRODUCTION

Envenomation by scorpion stings cause a heavy pathological state in certain regions of the globe¹. The most important components involved during this pathological state are polypeptides that modify or block Na⁺, K⁺ and Ca⁺² channels^{2,3}. Additionally a number of the peptides and enzymes from Scorpion venom like proteases, hyaluronidase and phospholipase-A2 that have antimicrobial, hemolytic, bradykinin-potential and immune-modulating activities⁴. However, a variety of components are present in these venoms, some of which have shown potential applications as therapeutic agents. The advancements in biotechnology have made it feasible to synthesize new natural products like parts of venom refined with therapeutic properties. The therapeutic effects of those agents are typically achieved by mechanisms that are completely different from that of typical therapeutic agents. Scorpion and its organs are known to cure brain disorder, rheumatism and male impotency since medieval times. This review is focused at particular scorpion venom parts and their potential applications for the treatment of some diseases such as cardiovascular reaction, infectious, inflammatory, autoimmune and malignant diseases. Scorpion venom is a mixture of polypeptides, nucleotides, lipids, mucoproteins, biogenic amines, and unknown substances. The amounts of these compounds might vary depending upon animal specimen and number of stings (and eventually of extractions). Noticeably, scorpion derivatives with protein activities are less portrayed⁵. The total amide contained within the venom did not exceed five-hitter of its dried weight⁶. This fraction contains polypeptides in relevance to their structures, targeted sites,

medical specialty connectedness and toxicities for mammals and/or insects and crustaceans^{7,8}. A broad array of bioactive peptides are already purified and characterized from scorpion venoms, with a complete variety accounting

to 1 lakh completely different ones, among which just one is usually better-known⁹. These peptides bunch remains debated. However, regular families are nevertheless into consideration. In conjunction with their targeted particle channels, four completely different families are considered: peptides modulating sodium, potassium, chloride, or calcium-gated channels. These neurotoxins are likely originating from a typical ancestral native amide¹⁰. Alternative compounds consist virtually of short peptides exhibiting antimicrobial (amps) and bradykinin potentiating (bpps) activities. These later are characterized by free amino acid residues¹¹. Fewer scorpion peptidic derivatives have shown protein activities almost like phospholipase A2^{12,13}, muramidase C¹⁴ and enzyme¹⁵. Scorpion neurotoxins have a tightly stabilized tridimensional-shaped backbone by 3 or four disulfide bridges. This property decreases their in-vivo degradation; and expectedly increases their effective binding-time and action^{16,17}. The appearance of latest tools for molecular engineering intensively prompted the formulation of assorted peptides chimera and lots of recombinant scorpion peptides have been generated. When they need divergent targeted sites, scorpion bioactive compounds exhibit allosteric interference activities, in a manner to intensify their biological effects¹⁸. Mainly, neurotoxins bind to surface membrane receptors (sites), however several peptides penetrate the cytomembrane and activate

parts at its cytosolic interface; for instance, maurocalcine and imperatoxin-A penetrate the membrane bilayers and activate the intracellular ryanodine receptor to electrify the calcium release¹⁹. The large structural and medical diversity of scorpion peptides encourages varied approaches for its use in new drugs-development. Herein, we have tried to gather some featured clinical potential of those peptides.

Scorpion venoms

Scorpion body is split into 3 parts: the pinnacle (cephalothorax), the abdomen (mesosoma) and the tail (metasoma). Scorpions are venomous arthropods, members of class Arachnida category and order Scorpiones. These animals are found all continents except Antarctica and cause problems in tropical and climatic zone regions. The scorpion species that possess medical importance belong to the family Buthidae and the genera *Androctonus*, *Buthus*, *Buthotus*, *Mesobuthus*, *Parabuthus* and *Leiurus* placed in geographic areas like Asia and the middle East. *Centruroides spp* are found in Southwest of USA, Mexico and Central America, whereas *Tityus spp* are found in Central and South America and Caribbean. In these totally different regions of the planet the scorpionism is taken into account as a public health issue. The signs of the scorpion envenomation are determined by the: a) scorpion species; b) venom composition and c) the victim's response to the venom. The symptoms begin within few minutes after the sting and frequently become more severe within five hours. At this point the massive release of neurotransmitters ends up in sweating, nausea and vomiting^{20,21}. The victims might exhibit signs and symptoms involving the central nervous system, stimulation of the autonomous nervous system, and sometimes, respiratory and heart disease, and even death. The victims of scorpion envenoming that bestowed multi-system-organ failure characterized by changes in hormonal environment with an enormous release of counter-regulatory hormones like internal secretion, glucagon, cortisol, angiotensin-II and with diminished levels of hormone and a rise of glucose level. The grading of those scorpions envenomation rely on local signs and whether or not neurological signs prevail. Central nervous system signs are: sympathetic, parasympathetic, somatic, cytotoxic and peripheral nervous system. Scorpions use their venoms for assassination or paralyzing their prey. The venom helps the capture and digestion of prey, however can also serve to protect them against predators. The venom is constituted by phospholipase, mucopolysaccharides, serotonin, hyaluronidase, histamine, enzyme inhibitors and proteins commonly named neurotoxins^{22,23,169}. Scorpion toxins are classified with respect to their structural properties, mode of action and binding sites on different channels or channel sub types²⁴⁻²⁶. The long-chain toxins affecting sodium channels are divided primarily into 2 major sub-types, α and β -toxins^{27,28}. Whereas the α -toxins bind to receptor site 3 of the voltage-gated Na^+ channels of vertebrates in a membrane-dependent manner and induce a prolongation of the impulse of muscles and nerves²⁹, the β -toxins present in American scorpions bind to receptor site 4 of vertebrate

Na^+ channels developed a shift to a negative membrane potential³⁰⁻³⁹. The β -scorpion poisonous substance is believed to bind, to just one of the four voltage sensors of the ion channel³⁸⁻⁴². In accordance to the classical models of ion channel gating, the voltage sensors of the ion channel activate separately. At least a minimum of 3 of them have to be compelled to be in an activated position for the channel to open^{43,44}. However, if one of them is activated by the β -toxin, the brink of activation is unlikely to shift considerably since different voltage sensors stay unaffected. As earlier mentioned scorpion venom consists of various peptides that interfere with the activity of particle channels and modulate their useful properties. Varied studies have shown that scorpion toxins have totally different physiological and pharmaceutical activities with potential therapeutic uses.

Scorpion venoms are reported to contain peptides such as: a) Cysteine-free antimicrobial peptides (AMP) are capable of self-integrating into class and microorganism membranes to create transmembrane pores, that make the membranes leaky^{45,46}.

b) Cysteine-free non-antimicrobial peptides (NAMPs) showed the power of potentiating bradykinin activity⁴⁷⁻⁴⁹. Venoms and toxins have found a distinct segment within the pharmaceutical market. Many isolated toxins with known mode of action have sensible applications as therapeutic agents¹⁶⁹.

Therapeutic use of scorpion venom

Autoimmune diseases

Immuno-regulatory abnormalities are shown to exist in an exceedingly large wide variety of autoimmune and chronic inflammatory diseases as well as in general lupus erythematosus, chronic rheumatism, diabetes type I and II, inflammatory bowel disease, cirrhosis billar, uveitis, degenerative disorder and different disorders like Crohn's malady, inflammatory bowel disease, psoriasis, inherited disorder and Graves ophthalmopathy. Though the underlying pathologic process of each of those conditions is completely different, they need in common a range of auto antibodies and self-reactive lymphocytes. Such self-reactivity is also due, partially to a loss of the homeostatic controls beneath that the normal immune system operates. Anti-inflammatory agents act primarily by obstructing the impact or secretion of those mediators while not modifying the immunological basis of the problem. The method of inhibition of potassium channels has been delineated by immunological disorder response. Potassium channels will modulate variety of cellular events like muscular contraction, neuro-endocrine secretion, frequency and interval of action potentials, electrolyte equilibrium, and resting membrane potential. The course of inhibition of potassium channels has been delineated by immunosuppressive response. Scorpion venoms are recognized as a source of peptidyl inhibitors of varied sorts of potassium-channels. A number of these peptides area unit capable of depolarizing human T cells, and preventing inflammatory and proliferative responses, and therefore may play a potent treatment of autoimmune diseases, within the bar of rejection of foreign organ transplants and/or connected afflictions diseases and sickness. The

recently delineated Vm23 and Vm24 are capable of decreasing considerably the delay type hypersensitive (DTH) in rats, applied at terribly low amounts (10 micrograms per rat)^{50,169}.

Anti venom production

Scorpion anti venom treatment, ab initio introduced in 1909, continues to be the sole technique used for the medical aid against scorpion stings^{51,52}. The primary application of the venom of scorpions is that the preparation of heterologous antibodies capable of been used as anti-venoms. Normally, homogenates of telsons are used to prepare a raw extract that's injected in little doses to horses and/or sheep with increasing amounts throughout several months⁵³. After a protracted amount of immunization, the blood of the hyper-immunized animal is obtained and also the immunoglobulins are sublimated to be used as anti-venoms. Some special anti venoms are offered, that are constant horse antibodies treated with enzymes to produce F(ab)'2 fragments that are used for therapy⁵⁴. Recently smaller recombinant fragments, like classic monovalent protein fragments (FAB, scFv and designed variants: diabodies, triabodies, minibodies and single-domain antibodies) are currently being engineered as credible alternatives. These fragments maintain the targeting specificity of whole antibody and might be used for therapeutic applications⁵⁵. Single-chain Fvs are a preferred format during which the VH and VL domains are joined with a versatile peptide linker preventing dissociation. Antibody Fab and scFv fragments, comprising both VH and VL domains, sometimes retain the particular, monovalent, antigen binding affinity of the parent immunoglobulin, whereas showing improved pharmacology for tissue penetration (55). During this context, recently single chain antibodies of human origin were developed and shown to be effective for neutralization of scorpion envenomation⁵⁶⁻⁵⁸.

Cardiac diseases

Cardiac diseases square measure legitimate by coronary heart and cerebro-vascular diseases. Peptides from animal venoms, active as bradykinin-potentiating factors are of explicit interest attributable to their robust impact as hypotensive agent. These factors are found in *Leiurus quinquestriatus*, *Tityus serrulatus*, *Buthus martensii* and *B. occitanus* scorpions. Pharmacologically, these peptides obtained from scorpions venoms act as bradykinin-potentiating peptides and might be used as hypotensive agents for the treatment of cardiovascular disease. Moraes et al., 2011⁵⁹ represented that metal channel gating from *Tityus bahiensis* scorpion venom possessed different effects on isoforms of sodium channel.

Hematological diseases

The scorpion venom exerts its deadly action by interference with coagulation of blood, either by accelerating the method or inhibits the coagulation processes. A polyamide with anti-thrombotic action was found to be present within the venom from the scorpion *Buthus martensii karsch*⁶⁰. This same peptide is said to be resistant against blood platelet aggregation and causes increase in the concentration of prostaglandin I2 in plasma⁶⁰. *Tityus discrepans* scorpion venom modifies

natural clotting times in humans. Brazon et al., 2008⁶¹ represented the impact of *T. discrepans* venom on a partial thromboplastin time prothrombin time and its direct clotting action. This venom contains anticoagulants that prolong clotting factor time and partial thromboplastic time.

Infectious diseases

Cationic host defense peptides are formed by several organisms as a part of their host defense system⁶²⁻⁶⁴. These peptides are thought of as antimicrobial agents against microorganisms such as: bacteria, fungi, parasites and viruses^{65,66}. Numerous studies have shown that the targets of cationic host defense peptides varied from the outer membrane to the signal pathway^{67,68}. These peptides are sometimes legitimate of 10-50 amino acids⁶². The variety of scorpion venoms is standard to contain around 400 such polypeptides with or without disulfide bonds. Within the literature numerous studies represented the presence of cationic host defense peptides in hemolymph and venoms from completely different species of scorpions. The vaccination with SARS-coV, contagion A (H5N1, H1N1) and rubella virus have incontestable variable effectively. The cationic host defense peptides from scorpion venom will be changed for antiviral activity, particularly against SARS-coV, contagion A and rubella virus. Another study represented by Li et al., 2011⁶⁹, showed the microporin, a cationic host defense amide from scorpion venom, which might effectively inhibit microorganism growth. The optimized microporin-M1 will inhibit grow of gram-positive microorganism at low concentrations and antibiotic-resistant pathogens¹⁶⁹.

Inflammatory response

The inflammatory response is triggered by a cascade of events that includes: systems, cell elements and release of mediators⁷⁰. Scorpion venoms will stimulate the discharge of immunological mediator cytokines. There's currently accumulating proof to counsel a causative relationship between over production of certain cytokines like IL-1 and IL-6 and morbidity and mortality related to critically sick patients. Sofer 1995⁷¹ was the first that reported the involvement of the inflammatory systems after scorpion envenomation in humans, this work is documented the increment of IL-6 levels in body fluid of children severely envenomed by the scorpions *L. Quinquestriatus* and *B. Judaicus*. The elevated levels of IL-6 were discovered at 1 to 3 hours after the sting. The IL-6 levels step by step came back to normal values at 12 and 24 four hours measurements, however remained higher than managing levels altogether measurements. These results were quite similar like those found by others authors that describe the protein production once sting caused by *Tityus serrulatus* scorpion in humans^{72,73}. With respect the experimental animal high levels of cytokines were found in body fluid from mice injected with *Centruroides noxius* and *T. Serrulatus* venom^{74,75}. Altogether in these works the authors concluded that the activation and release of cytokines might play a very important role within the pathophysiology of envenomation after stings and will be responsible for some systemic inflammatory manifestations with cytokine release and organ failure⁷⁶.

Cytokines are shown that in native action of cytokines promote enlisting of inflammatory cells to inflammation sites, whereas their general impact to induce fever and increase symptoms. Throughout both responses local and systemic are discovered the ejection of pro-inflammatory cytokines, arachidonic acid metabolites proteins of the contact phase, complement factors; it's outlined as systemic inflammatory response. Experimental models are described that following the injection of scorpion venoms and their fractions, a range of cytokines are released, and therefore the outcome of an inflammatory response is set by a range of factors, that include the duration of stimulus, and therefore the balance between the pro-inflammatory and anti-inflammatory response. The imbalance determines the degree and extent of inflammation, and so will cause dysfunctions in multiple organ⁷⁹. With relevance to the tissue injury most of them are associated with the acute involuntary disturbances triggered by the venom, which may provoke both the activation and delayed inactivation of neurotic sodium channels, where they modulate the discharge of neurotransmitters, that results in a range of adverse effects that include respiratory failure, lung edema, arrhythmias, arrhythmia followed by bradycardia, striated muscle stimulation, lacrimation, convulsions, and enlarged pupils, among others⁷⁸⁻⁸⁵. However, the role of different members of IL-family in envenomation is progressively appreciated, and within the present work are summarized all presently offered information from human and experimental studies. With respect the scorpion envenomation the immunologic response is also triggered by cascade, including the release of mediators like nitric oxide and complement system^{86,169}. Multiple sclerosis is an inflammatory disease of the central nervous system characterized by localized areas with degenerative disorder. It's an autoimmune disorder mediated by activated immune cells like T- and B-lymphocytes and macrophages/microglia. Within the venom of the Moroccan scorpion *Androctonus mauretanicus* a polyamide was found and characterized, that showed several toxins cross-reaction with fatal α -toxins found in north african scorpion venoms and are thought to be as potent toxins for treatment of the inflammatory diseases⁸⁷.

Cancer

Cytotoxic compounds that kill cells or repress their growth are needed attribute for cancer and malignant diseases therapy⁹¹. The power of natural toxins to bind specifically to numerous cellular domains upholds new hope for antineoplastic drug development, like bombesin and bombesin-like toxins that are used as drug motifs carriers with high specificity against tumoral cells⁹². This property is an attribute of chlorotoxin, a peptide extracted from the venom of *Leiurus quinquestratus hebraeus*, that specifically binds to chloride-gated channels⁹³⁻⁹⁵ that are firmly concerned in cancer cells mobility mechanism⁹⁶; and impairs the in vitro glioma invasion⁹⁷⁻⁹⁹. Veiseh and her colleagues¹⁰⁰⁻¹⁰² examined the utility of the chlorotoxin as a nanovector carrier for gene transfection into each C6 brain glioma and DAOY medulloblastoma cells and improved its effectiveness as a honest tool for clinical

use^{101,102}. Now, the chlorotoxin-like repertoire contains alternative peptides like the recombinant BmkTa, isolated from area unit *Buthus martensii Karsch*, that abolishes tumoral cells growth, however not traditional ones¹⁰³. The list of scorpion peptides exhibiting anti-proliferative and cytotoxic effects on tumour and malignant cells is growing, and new substances area unit being frequently value-added^{104,170}. Various kinds of potassium current, like those of the human ether-a-go-go-related K⁺ channels¹⁰⁵ and Kv11.1¹⁰⁶ and Kir4.2 channels¹⁰⁷ are concerned in metastasis and tumour growth¹⁰⁸. For instance, outward current of potassium through the voltage-gated pore rectifier (Kir4.2) enhances the integri mediate cellular migration and dissemination¹⁰⁹. Since that, hampering these gated pores peptides, like Ammtx3 (*Androctonus mauretanicus mauretanicus* poison 3), Bm Tx3 (*Mesobuthus martensii* poison 3), Bekm-1 (*Mesobuthus eupeus* toxin 1), and lots of alternative potassium scorpion toxins, may convey a promising field in counteracting the evolution of metastasis. Recently, it had been approved that voltage-gated Na channels are functionally overexpressed in varied kinds of human cancers, and correlate with metastatic progression¹¹⁰. Seemingly, they're concerned within the metastatic process through their interactions with completely different sorts of cytoplasmatic proteins and enzymes, like the adenylate cyclase and phosphokinases which mediate signals transduction regulation cellular motility¹¹⁰. Targeting these channels by specific scorpion derived blockers may probably suppress cancer cells functionalities. Phase I trials are advanced using Pertussis toxin as "adjuvant" before radical cystectomy in bladder malignant {neoplastic disease} and had promising effects against micrometastasi and neoplastic regeneration¹¹¹. Hyaluronidases, endogenous enzymes (endoglycosidases), are scattered with battery of numerous effects regulating cells activities and growth. They're concerned in cell cycle progression, aging processes, and caspase-mediated cell death. At some extent, they're additionally used for varied objectives in cancer treatments. For instance, they did facilitate drug penetration and biodistribution¹¹². Such enzyme, known as BmHYA1, had been extracted and sublimate from the venom of the Chinese scorpion *Buthus martensii*. The BmHYA1 impairs the animate thing matrix receptor III (CD44) surface marker that's over expressed in cancer cells and promotes the matrix adhesion¹¹³. Wei-Dong and colleagues from the Institute of Basic Medicine (Shandong University, China) spare nice effort to explore the utility of scorpion polypeptides in combating cancer diseases. They provided proof for the potent inhibition of tumour development and metastasis processes in prostate, W256 sarcoma, liver, pancreas, DU-145, H-22 viscus, S-180 sarcoma, BT474 breast, and SKOV-3 ovarian cancerous cell lines, in in vitro and in vivo transplantation mice models, by scorpion derivatives. The mode of action of the used polypeptides continues to be mentioned and appears to conduit completely different pathways. In 2010, Xu and her coauthors had mentioned that a PESV fraction from a scorpion venom exhibited potential antitumoral activity against Lewis carcinoma cells that were inoculated

in mice. PESV appears to act through the immune sentinel stimulation by decreasing VEGF, TGF-beta1, and IL-10 expressions in tumor setting and enhancing the over expression of co stimulatory molecules CD80 and CD86 in nerve fiber cells infiltrating the tumour¹¹⁴. Such findings can in all probability prompt the breaking down of immune tolerance to cancerous cells and improve cellular therapeutic ways. Alternative peptides enhance the expression of P21 and caspases-3 proteins, members of the programmed death, or inhibit the expression or the activity of matrix metalloproteinase-2 and alter the β -catenin localization¹¹⁵. Relative to the proteolytic enzyme inhibitor-based treatments against invasive cancer cells¹¹⁶, a monomeric conjugated protein with a 120 KDa, sublimate from *Heterometrus bengalensis*, may contribute during this anti neoplastic treatment¹¹⁷. Similarly, BmAPI can do thus, the analogue of serine protease inhibitor that was extracted from *B. Martensii Karsch* venom^{118,170}.

Osteoporosis

Heterometrus bengalensis scorpion venom exerts anti osteoporotic effects on ovariectomized female albino rats treated with methylprednisolone. The impact of the scorpion venom is thought to be directed on osteoclasts. It seems that it did increase the bone mineral deposit in conjunction with the modulation of concerned restrictive factors (hormones, enzymes, and cytokines)¹¹⁹. Earlier report of Valverde et al. Characterization and testing bioactivities. The connotation of such arranges is to predict the “desirable” scorpion and also the substance in need. For instance, to isolate a malignant neoplasm cytotoxic peptide, it'd be prejudicially to use animals from the Chactidae family because of the familiar lytic and cytotoxic effects of their venoms. Once the venom (or its derivative) fits the wanted clinical objectives, through the first series of bioassays, serial biochemical, pharmacologic, and toxicological experiments can isolate and characterize the substance in need and improve its efficacy and safety. As a consequence, objectives are fine-tuned to create call for continuation. To optimize the pharmaceutical pattern of the extract, additional biochemical and genetic intervention are needed, before running clinical trials. The art of this arrange is that the distillation of the tremendous researches in scorpology toward clinical applications. Systematically, enormous and sparse plethora of scorpion venoms and hemolymph analysis is current however remains specializing in the isolation, purification, and characterization of sequences. We have a tendency to ponder for extra experimental straightforward tests, like toxicity against tumoral cells or pathogens throughout the characterization steps that ought to be allotted to accurately conceit these peptides for basic researches for drug development¹⁷⁰.

Antimicrobial Activities

Antimicrobial peptides (AMPs) are isolated from a large type of animals and plants. They are cationic and amphipathic peptides, basically inside 50 acid residues, and were gathered into completely different groups. Some AMPs function by disrupting the semi-permeable membrane, whereas others use completely different mechanism of action. Three intended mechanistic models

are planned to clarify the cell membrane disruption: the “barrel stave,” “micellar mixture,” and “carpet” ones. Several scorpion-derived AMPs will be set as α -helical free-cysteine peptides that alter the cellular membrane structure¹²⁰. Androctonin, a 25-residue disulphide-bridged polypeptide originating from *Androctonus australis* venom, exhibited potent antigrowth impact on each gram-positive and negative microorganism. This antibiotic activity is accomplished by membrane disruption and leakage of infective cells. Curiously, in ex vivo experiments, this peptide didn't have an effect on mammalian erythrocytes, a predictable attribute for clinical application. Further, androctonin evoked a major decrease in oxygen consumption and adenosine triphosphate generation and thereby can get rid of the microorganism energetic machinery^{121,122}. Modulating the calcium intracellular signaling is another mechanism to inhibit microorganism growth. Consequently, parabutopporin and opistoporins, severally, isolated from *Parabuthus schlechteri* and *Opisththalmus carinatus* scorpions, interact with coupled G proteins and consequently modulate intracellular calcium signaling and exert their anti-bacterial effects¹²³. These findings purpose toward two completely different targeted sites for these peptides: an intra cytoplasmic site implying an intracellular elements such a DNA, RNA, and enzymes; and aberrant action on outer membrane sites^{124,170}. In addition to direct membrane disruption, the external impact of scorpion toxins may well be mediated through their binding to definite gated ions channels, like calcium dependant potassium pores concerned in microbiology¹²⁵. The repertoire of scorpion peptides contains lots of those channel blockers that might be used as antibiotics. Other scorpion-derived AMPs inhibited microbial growth through their phospholipase activity¹²⁶. Guillaume and her colleagues¹²⁷ reported that a three disulfidebridged amide, the Imperatoxin-I (a 75 amino acid stranded peptide from the venom of *Pandinus imperator* scorpion), exhibited a Phospholipase A2 activity that inhibits the intra erythrocytic development of *Plasmodium falciparum* that causes the foremost severe sorts of human protozoal infection. It's seemingly that this peptide interacts with the infected erythrocytes membrane lipids¹²⁷ or plasma-free fatty acids and liberates lipid product (peroxides) resulting in infection ending. The Imperatoxin I fully reserved each fecundation and ookinete formation inside in vitro micromolar concentrations¹²⁸. A pioneer assay to combat malaria at its biological cycle was advanced by Possani and her collaborators (2002). They had made a resistant transgenic vector to protozoal infection transfecting genes encoding the imperatoxin that abolished the parasite biological cycle^{129,170}. The poor sensitivity of scorpions AMPs to pathogens could be a major challenge for his clinical application. With the allowance of molecular engineering tools, Lee et al. had synthesized a pool of analogous for isCT that is a 13 amino acids-residue refined from *Opisthacanthus madagascariensis*, exhibiting high sensitivity to microorganism membranes and keeping soft mammalian cells. They found that substitution of the pro for Gly8 and Lys for Glu7 and Ser11 improved the cationic

charge of the native isCT molecule and permitted it to expeditiously bind to negatively charged phospholipids of microorganism¹³⁰. Varied AMPs are frequently isolated from scorpion transcriptomes¹³¹ that might alleviate pathogens resistance to standard medication.

Homeostasis and Rheology

Among pharmacology patterns of scorpion envenoming is that the alteration of the hemodynamic and cardiovascular functions that are mediated through either direct or indirect effects of neurotoxins. Apparently, many elements of the venom are wanted as potential remedies for many blood and rheology injuries. The principally spectacular is that the use of scorpion venom in Chinese ethnopharmacy to enhance blood homeostasis and physiological condition¹³². A common challenge in cardiovascular and occlusion disorders is to surpass the medicine efficiencies limitation by patient's resistance and unfavorable facet outcomes¹³³. Since coagulation and/or its regulator factors perturbations are determined after scorpion stings¹³⁴, it's planned that the entire scorpion venom or its elements may intervene in prevailing thrombocyte aggregation. The SVAP, a lively peptide isolated from the scorpion *Buthus martensii karsch*, improves the peritoneum microcirculation and blood rheology by decreasing the blood viscosity¹³². Later, it absolutely was well-tried that it inhibits the thrombosis formation parameters (inhibition of thrombocyte aggregation and prolongation of the occlusion occlusion time) in ex vivo and in vitro experiments, in an exceedingly dose-dependent manner¹³⁵. It was concluded that SVAP will increase the generation of prostaglandin i2 which may be a necessary thrombosis regulator¹³⁵. Any clinical and experimental findings accounted for the perturbation of the balance between pro- and anti-inflammatory cytokines and prostanoids production, after scorpion envenomation, implying that such endogenous compounds can mandate the scorpion venom antithrombotic impact¹³³. To some extent, thrombosis management might be operated through direct inhibition/activation of the platelet membrane permeation to potassium ions through voltage-operated and Ca²⁺-activated channels¹³⁶. Such formulation instigated Wolfs et al. to analyze the impact of charybdotoxin, a scorpion peptide obstructing the calcium-activated potassium channels with intermediate conductance, on thrombocyte function¹³⁷. Charybdotoxin acts by decreasing the prothrombinase activity and also the exposition of phosphatidylserine that is an outer surface membrane aggregating factor¹³⁸. Borges et al. showed that the entire venom of the Brazilian scorpion *Tityus serrulatus* modulates the blood clot formation via platelet-activating factor receptor (PAFR) function alteration^{139,170}. Another alternate use of scorpion peptides in cardiovascular therapy is to manage blood vasomotion via the reninangiotensin system inhibition. For that reason, Hodgson and Isbister have reviewed the potential application of a range of venomous animal extracts to cardiovascular drug discovery. They mentioned that a pool of bradykinin potentiating peptides (BPPs), extracted from a variety of snakes and scorpions, inhibit the down breaking of the endogenous bradykinin and therefore the

synthesis of the angiotensin (vasoconstrictor). Such effects cause the reduction of the systemic blood pressure. Furthermore, hypotensins, extracted from the *Tityus serrulatus* scorpion venom induce hypotension however while not intervening within the angiotensin converting enzymes activity. Their mechanism of action is believed to be mediated via nitric oxide release and offers a second stratagem for the wound healing¹⁴⁰.

Immune Diseases

In 1980, Brahmi and Cooper showed that the native *Androctonus australis* hemolymph and its partial fraction 1 (eluted by natural process in G-200 Sephadex column at most of 280–340 nm, with 0.01 M and an extraction hydrogen ion concentration of 8.05) excited the human, rabbit, and mouse lymphocytes mitogenesis in in-vitro studies. Also, they did show that it triggered the lymphocytes erythrocytes agglutination which is inverted by sugar derivatives¹⁴¹. Twenty years later, approval of such immune cells perform improvement by *Tityus serrulatus* was provided. This leukocytosis was assumed to conclusion in great part from the release of neutrophils from the bone marrow to blood vessels bed. The mechanism of this mobilization did involve the platelet-activating issue (PAF) receptor communication¹³⁹. Since it seems that scorpion venom is capable of modulating lymphoid cell lines proliferation and activities. Recently, 5 totally different fractions from above mentioned venom (*T. Serrulatus* venom) obtained by gel filtration chromatography were assayed for his potential to modulate immune peritoneal macrophages secretions. These later contributed to a differential modulation of macrophages function and will most likely act with one another in an exceedingly synergistic manner¹⁴². Among them an isolated γ -Ts poisonous substance accomplishes its immune restrictive impact through pro- and anti-inflammatory factors release. In view of the actual fact that a very important role was attributed for shaker potassium channels within the regulation of immune cells, Beeton and her colleagues had well-tried that a peptide (ShK (L5)) isolated from the ocean anemone (*Stichodactyla helianthus*) suppresses the proliferation of human and rat TEM cells and inhibits the IL-2 production at terribly low doses. Such effects are after the voltage-sensitive potassium channels (Kv1.3) inhibition. This peptide is in a position to stop by experimentally induced autoimmune encephalomyelitis and suppress the hypersensitivity in rats¹⁴³. In an exceedingly similar manner, charybdotoxin isolated from *Leiurus quinquestriatus* venom blocked the voltage-gated K⁺ channels in human and murine T lymphocytes and suppressed their proliferation¹⁴⁴. The inhibition of each voltage-sensitive (Kv1.3) and Ca²⁺-activated (with intermediate conductance) potassium channels modulates the membrane potential of the T lymphocyte, in manner to sustain an elevated level of intracellular-free calcium which is essential for the primary steps of their activation. Since that, more than twelve scorpion toxins which can block K⁺ channels in T cells with K_d starting from picomolar to micromolar values were prompt to counteract immune diseases progression^{145,170}. Moreover, parabutoprin an isolated

AMP from *Parabuthus schlechteri* scorpion venom can activate the exocytosis and chemotaxis and inhibit superoxide production in human poly morphonuclear granulocytes, at sub-micromolar concentrations¹⁴⁶. Chemotaxis was exploitation using *Tityus serrulatus* scorpion venom that activates the complement system that takes a part of wide-ranging immune sentinel¹⁴⁷. The mechanism of such impact is mediated by the Rac receptor, concerned in chemotaxis and exocytosis stimulation, most likely through the activation of G proteins. The α -helical amphipathic sheet of the scorpion AMP permits its insertion into the membrane to trigger the G proteins activation and therefore prevents the NADPH enzyme function¹⁴⁸. NADPH enzyme inhibition may even be triggered via the parabutoporin-p4 7phox interaction resulting in PKC pathway stimulation¹⁴⁹. Recently, Remijns et al. showed that the most activity may be a consequence of an indirect stimulation of Akt following lipid rafting¹⁵⁰. Recent investigations showed that a lot of AMPs, originating from scorpions, and their unnaturally generated analogues exhibit potent antiviral activities against contagious disease, SARS-Cov, H5N1¹⁵¹, hepatitis B¹⁵² and C¹⁵³, and HIV-1¹⁵⁴ viruses. Chiefly, these peptides operate through a direct disruption of the viral envelope and consequently decrease the infectivity of the pathogens. Exceptionally, peptides directed against HIV-1 adopted another pathway. In fact, a structurally changed scyllatoxin, a derived scorpion peptide, with efficiency suppressed the binding of gp120 to CD4 in a competitive manner and therefore suppressed the infection of CD4+ lymphocytes by human immunodeficiency viruses^{155,156}. Similarly, the Kn2-7 and mucroporin-S1 scorpion derived peptides are shown to exert potent anti-HIV actions via the inhibition of chemokine receptors CCR5- and CXCR4-mediated activities and replication of the viruses^{154,170}. These findings would possibly improve the anti-AIDS therapy.

Neurological Diseases

Nervous system activities are mainly governed by gated ion channel frameworks. These later modulate ion traffic through the cellular membrane and regulate the firing and propagation of action potentials which are responsible for signal transmission. Any aberrant pores components expression and/or perform would result neurological diseases. Attributable to their incontestable high specificity and affinity to numerous elements of ions-gated channels, scorpion neurotoxins are featured as a possible candidate for neurological drug development¹⁵⁷. In this topic, the “magic” *Buthus martensii Karsch* scorpion is widely used in Chinese ethnomedicine to treat some neuronal diseases like epilepsy, apoplexy and cerebral palsy¹⁵⁸. Recently, proof upon the antinociceptive effect of a number of its constituents was provided¹⁵⁷. The necessary role of voltage-sensitive sodium channels in pain physiopathology and its treatment impressed the utilization of those channels blockers as remedies (reviewed by Dib-Hajj et al.)¹⁵⁹. During this sense, it had been shown that Bmk AS isolated from *Buthus martensii Karsch* induced a gigantic antinociceptive result via the inhibition of the voltage tetrodotoxin-sensitive sodium

current in sensory nerves¹⁶⁰. Anti-nociception was conjointly induced by alpha-anatoxin Amm VIII, a weak modulator of Na(v)1.2 channel, and also the depressant insect-selective beta-toxin LqqIT2, in a mechanistic theme involving opioid receptors activities^{161,170}. Presumably, the reinstatement of the hyperexcitability of sensory nerves may be a meeting purpose for wound healing varied neuronal diseases like allodynia and hyperalgesia. Since that, toxins working on particle permeableness of nerves membranes are sought-after to be within the high focus for neurological drug discovery. In sclerosis, that is an inflammatory disease of the central nervous system, there's destruction of sheath of the nerves that is related to a relative nerve fiber stinting. Such structural disorganization leads to conductivity deficits. To stop medicine signs and symptoms elicited in pathology, potassium effluxes blockers are recruited. Multiple K+ channels blockers with completely different affinities and specificities are extracted and sublimate from scorpion venoms and would possibly improve treatment of the symptomatic table developed by multiple sclerosis patients¹⁶². Earlier reports showed that scorpion venoms network with neurotransmitter receptors like dopaminergic^{163,164} and G protein coupled like adrenergic and cholinergic receptors¹⁶⁵. They most likely did block them or influence their release¹⁶⁶. Recently, Sudandiradoss and her colleagues well-tried the arrival interaction of 10 different scorpion neurotoxins with the D2 Dopastat receptor and their antagonizing effects¹⁶⁷. These neurotoxin interactions may be prompt dopamine receptors targeting for treating schizophrenic disorder and Parkinson's disease^{168,170}.

CONCLUSION

Nature has been a supply of medicative merchandise for thousands of years, among those; scorpion venom is a rich supply of bioactive molecules, like peptides, proteins and enzymes with necessary medicine activities. Moreover, blood and duct from scorpions are wide utilized in Chinese ancient medication. With the appearance of macromolecule fold structures, a rich supply of peptides that act specifically and with high affinity with human macromolecule may be developed. This may facilitate not solely in understanding the implications of every interaction however also will result in the event of effective medication targeted to specific macromolecule functions. Except for the assembly of specific anti-venoms to save lots of lifetime of individuals evenenomated by scorpion stings, several potential application of scorpion venom elements are foreseen. Future analysis within the next decade with venoms and toxins will certainly adjoin data to be used as ion-channels inhibitors for management of cell excitability, immune-modulation of T-cells, antibiotics against microorganisms, parasites and additionally for management of neoplastic cells. Whereas the initial native scorpion venom compounds are typically unsuitable as medical specialty, interventions by medicative chemists moreover as scientists and clinicians in pharmaceutical R & D have created its potential to use the scorpion venom proteins as medical specialty for

multiple disorders supported on the their structural and functional information. Scorpion venoms, with their cocktail of individual elements, have excellent potential as therapeutic agents for human diseases.

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