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The Effect of Latrodectus Venom and its Proteomic Functional Analyses

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Abstract:-Only a small number of spiders worldwide have fangs that penetrate human skin. Their venom is strong enough to harm humans. Among them, Latrodectus has 30 species and Sicariidae has more than 140 species worldwide. The bite of Latrodectus also called red back spider contains a neurotoxin that causes a condition called latrodectism. The bite of this type of spider causes a condition called loxoscelism, in which local necrosis of the surrounding skin and extensive breakdown of red blood cells may occur. While there is antivenom for Latrodectus venom, the bite of this spider is similar to a state of anaphylaxis and thus it is not commonly used. In many reports of spider bites, it is unclear whether a spider bite really occurred. Historically, a number of conditions were attributed to spider bites. Although necrosis has been attributed to the bites of a number of spiders, good evidence supports this only for Sicariidae. This review provides an overview of the development of spider venom research, focusing on the structure and function of venom components and analysis techniques.

Keywords*: Neurotoxins, Proteomics, Toxins, Proteomics, Spiders*

Introduction

Spider venom is a mixture of many chemicals. Some of them are neurotoxins evolved to kill or immobilize arthropods such as insects by attacking their nervous systems and some others are cytotoxins that help break down tissue so the spider can eat a liquid meal. Unfortunately, only a limited number of these chemicals can be seriously toxic to humans. Venoms are chemicals of biological origin (i.e., made by an animal) that are used for attacking or defending. Venoms are made by specialized organs such as modified salivary glands and enter the body through specialized systems such as grooved or hollow fangs. Most venoms are a complex mixture of chemicals including proteins, peptides, sugars, and other substances. Venoms can affect many body systems. Common effects of the venoms include paralysis, interference with blood clotting, muscle breakdown, pain, tissue breakdown, and effects on the cardiorespiratory system. The primary groups of venom components are low molecular mass compounds, antimicrobial (also called cytolytic or cationic) peptides (only in some spider families), cysteine-rich (neurotoxic) peptides, enzymes, and proteins. Cysteine-rich peptides are examined based on their various structural motifs, their targets (ion channels, membrane receptors), and molecular binding. We further describe the latest findings on the maturation of cysteine-rich antimicrobial peptides, expressed as propeptide-containing precursors in most cases known. Spiders are the most abundant poisonous animals on the planet. The number of their species is predicted to be150000. It is thought that their number is higher than any other poisonous creatures. Almost all spiders, except for some cases, produce venom whose primary purpose is to immobilize their prey. However, the content of this venom can vary from species to species. The majority of them are not harmful to humans. In addition to snakes and some marine animals, common poisonous animals especially include arthropods such as scorpions, various insects, and spiders.

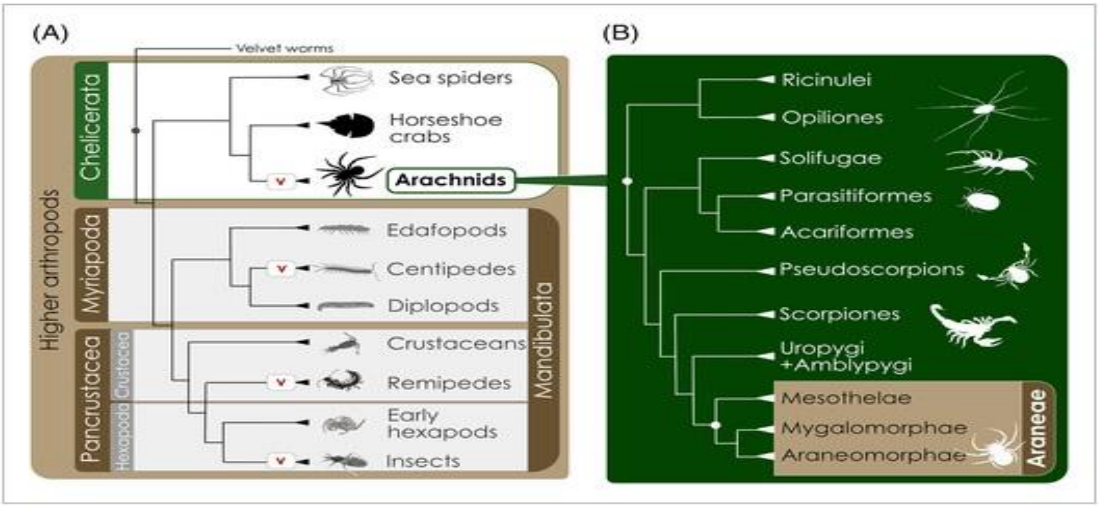

Figure 1: The structure of the arthropods and their subgroups

After insects, spiders are the largest taxonomic group of terrestrial creatures and occupy most of the ecological niches of our planet. Spider venom has received little attention owing to its limited effects on human health. Studies paid attention to it after realizing the enormous medicinal potential of spider venom peptides. This graphic looks at some of the different possible components and their roles in venom. However, only about 200 species of spiders are medically significant and cause public health problems or even death. Two spider families, Theridiidae Sundevall, 1833, and Sicariidae Keyserling, 1880, are dangerous for humans in Iran. Theridiid Latrodectus Walckenaer, 1805 is known as the Latrodectus and is one of the most poisonous species of spiders in the world and in Iran. This genus has 32 species in the world and 5 species in Iran. L. tredecimguttatus Rossi, 1790 is one of the significant medical spider species, which is known as the Mediterranean widow spider or "Dolmak".

History:

The classification of the Latrodectus genus was uncertain before the DNA analysis. Changes in the number of species indicate the difficulty of using morphology to determine sub-classifications within this genus. Considerable interest in their systematics was most likely due to the medical significance of these venomous spiders. Tamerlan Thorell, a Swedish arachnologist, described the Latrodectus in 1870. He named it Latrodectus hasseltii in honor of fellow A.W.M. Van Hasselt. In the same paper, he referred to a substance from Cape York with an all-black belly of L. scelio, which is now considered the same species. These specimens are in the Naturhistoriska Riksmuseet in Stockholm. The German archaeologist Friedrich Dahl revised this genus in 1902 and named it L. ancorifer from New Guinea, which was later considered a subspecies of the Latrodectus. Another subspecies, L. h. aruensis was described by the Norwegian entomologist, Embrik Strand in 1911.

The subspecies indica (from L. scelio) was described by Eugene Simon in 1897, while its origin is unclear. Frederick Octavius Picard-Cambridge questioned Dahl's separating species on minor anatomical details. However, Dahl rejected Picard-Cambridge as "ignorant". Pickard-Cambridge was unsure whether L. hasselti ensured species status, although he confirmed scelio and hasselti as a single species. The Latrodectus was also considered by some to be consistent with the katipō (L. katipo), which is native to New Zealand, although Koch considered them distinct. After examining the genus Latrodectus in 1959, entomologist Herbert Walter Levy concluded that color changes were highly consistent throughout the world and were not suitable for distinguishing individual species. Instead, he focused on differences in the morphology of the female genitalia and revised the number of known species from 22 to 6. It included reclassifying the Latrodectus and several other species as subspecies of the most known member of the group, the black spider. He did not consider the Latrodectus mactans, found in North America and other regions. Anchorifer stated that L. h. aruensis and L. h.

indicus is sufficiently distinct to be recognized. Subsequently, more reliable genetic studies have divided the genus into about 30 species, and the Latrodectus has no recognized subspecies in modern classifications.

Types of spiders:

The current spiders are divided into three suborders: Mesothelae, Mygalomorphae, and Araneomorphae. The oldest of them is the Mesothelae, a monotypic suborder containing a single family of Liphistidae, segmented trapdoor spiders comprising 140 species from Asia (World Spider Catalogue, 2021). In contrast, Mygalomorphae is globally distributed, although about 3,000 described species are found in the tropics and subtropics. Several prominent spider families belong to this lineage, including Theraphosidae), Ctenizidae, and Atracidae. Finally, the Araneomorphae is the most diverse spider suborder. Spiders share a conserved body plan with two tagmata (grouping of segments) defined as prosoma and opisthosoma. The anterior prosoma is used for movement, sensing, and feeding. It includes the brain, walking legs, and versatile pedipalps. It also has a pair of chelicerae that covers the oral cavity. They have evolved into venom-injecting apparatus in spiders but not in most chelicerates. The posterior opisthosoma is used for reproduction, digestion, excretion, and respiration. It includes organs such as book lungs, vascular system, and digestive system. The abdominal part of the opisthosoma is where the spinnerets, as the primary components of the silk-spinning apparatus found in all spiders, are located. Spiders are characterized by a predatory lifestyle. They prey mostly on other arthropods, although some species sometimes prey on vertebrates. Several groups have evolved feeding specializations, such as feeding on other spiders (araneophagy, e.g. Portia spp.), ants (myrmecophagy, e.g. Zodarion spp.), woodlice (oniscophagy), and even occasional vegetarianism. However, most spiders feed primarily on insects and thus occupy a significant ecological niche that maintains the balance of insect populations (Foulix, 1983). The evolution of spiders is closely associated with the evolution of their insect prey, which is confirmed by observing that the evolutionary innovations of spiders follow earlier innovations in insects. For example, the evolution of aerial search webs coincided with the evolution of insect flight and some of the most specific radiations of spiders with similar radiations of insects. The close associations between spiders and insects with the negative impacts of the global decline of insects, which also threaten spiders, are becoming more apparent.

Architecture and development of the venom system:

The venom system of spiders is organized around chelicerae, which vary in organization based on lineage. Mesothelae and Mygalomorphae have chelicerae that are orthogonal (chelae in parallel orientation), as shown in the figure below.

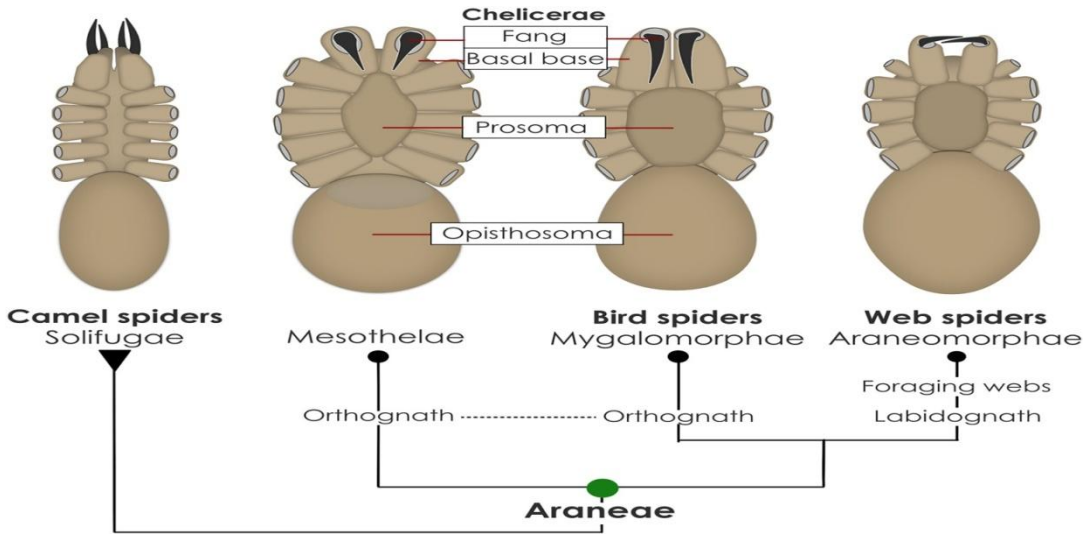

Figure 2: The venom system of all types of spiders is shown in detail regarding the organization of the body structure and the structure of its bite.

Chelicerae in spiders have two functional units that move in a jack-knife manner. The first unit, a base segment, is attached to the prosoma and forms a movable base for the second unit, a sting. Chelicerae from three major lineages in Araneae shows abstract ventral sides of different configurations of chelicerae and main characters are plotted in the phylogram

Solifugas are added as an older chelicerate group that still has chelicerae (plesiomorphic) state and was originally three-segmented and scissor-like. The venom system of each chelicera includes a venom gland that is connected to a narrow opening at the tip of the bite through a thin venom duct. Each venom gland is embedded in muscles and nerves and allows precise control of venom release. The localization of venom glands is different between Orthognathous and Labidognathous species. The venom gland of the former is located in the basal part of the chelicerae, while it can extend into the prosoma in the latter one. Venom glands in spiders are more functionally divided and their subsections produce and modify different venom components. Spider venom glands are very complex despite their simple appearance and ancient origin and they produce and secrete various venom mixtures. A similar specialization has been described in more recent evolutionary organisms, such as killer insects and cone snails, which produce defensive and predatory venoms in different glands or different parts of the same gland. The venom glands (Vg) and the venom duct (Vd) ending in the venom pore (Vp) on the outer side of the sting tip are shown in red. The muscle layer around the gland is shown in white. There is little information about the development of the venom system in spiders. Generally, the development of spiders is divided into four primary stages. The oldest of them is the pre-larva, which is followed by the larva. These stages are embryonic and these animals are hardly similar to their adult counterparts. After that, the spiders enter the first stage of full development, which is called the nymph stage. They already mirror adults. They are fully developed and mobile, yet very small. A spider goes through several nymph stages until it reaches maturity, the final stage of the growth process. It was first proposed that the pre-larva and larva stages have only undifferentiated chelicerae, venom glands, and venom ducts and that these structures exist only as distinct structures in nymphs and adults. However, recent studies on the Brazilian Phoneutria nigriventer showed that venom glands are already present in pre-larva stages, and the larva venom system already includes chelicerae, ducts, and glands. The larva venom glands are located between the chelicerae and the prosoma but subsequently migrate to the prosoma. Venom biosynthesis starts from the embryonic stage in this species. Early activation of the genetic machinery that produces venom components is also highlighted by the presence of venom-encoding messenger RNA (mRNA) in eggs of Latrodectus species.

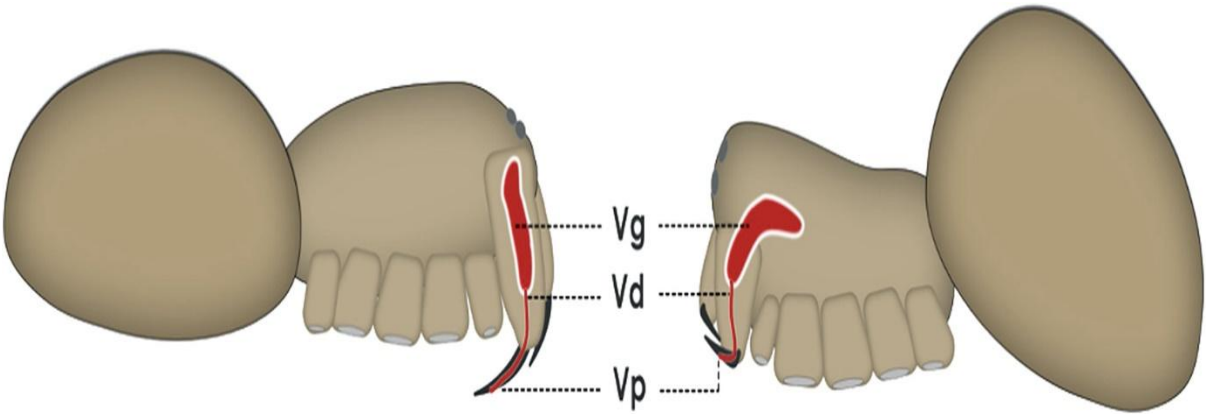

Figure 3: The structure of the spider's bite in the structural part of the spider's body.

Spider venom:

The venom is produced by holocrine glands in the spider's chelicerae. The venom accumulates in the ducts of the glands and passes through paired ducts to the spider's two hollow fangs. It includes a complex combination of cellular components, enzymes, and a number of high molecular weight venoms, such as insect venoms and a vertebrate neurotoxin called α-latrotoxin, which causes severe pain in humans. In vertebrates, α-latrotoxin

applies its effect through cell membrane destabilization and degranulation of nerve terminals, leading to excessive release of neurotransmitters, namely acetylcholine, norepinephrine, and GABA. Neurotransmitters' excessive activity results in clinical manifestations of toxicity, although the exact mechanisms have not been yet clarified.

The release of acetylcholine is responsible for neuromuscular manifestations and the release of norepinephrine is responsible for cardiovascular manifestations. Female spiders include an average of 0.08-0.10 mg of venom. Experiments indicate that the mean lethal dose (LD50) for mice at room temperature is 10-20% of this amount (0.27-0.91 mg/kg based on the mass of mice used). However, it is much more lethal to mice kept at lower or higher temperatures. Pure α-latrotoxin has an LD50 in mice of 20-40 µg/kg. A specific type of vertebrate venom found in redback spiders was cloned and sequenced in 2012 and was found to be a sequence of 1,180 amino acids and it is highly similar to the equivalent molecule in the Latrodectus mactans clade. The syndromes caused by the bite of any Latrodectus spider have similarities with each other. Evidence suggests that sweating and local and radiating pain are more common with redback, while Latrodectus envenomation leads to more pain in the back and abdomen, and abdominal stiffness is a common feature with spider bites. A crustacean-specific neurotoxin and two insect-specific venoms recovered from the L. tredecimguttatus and small peptides that inhibit angiotensin-converting enzyme-1 probably have similar effects.

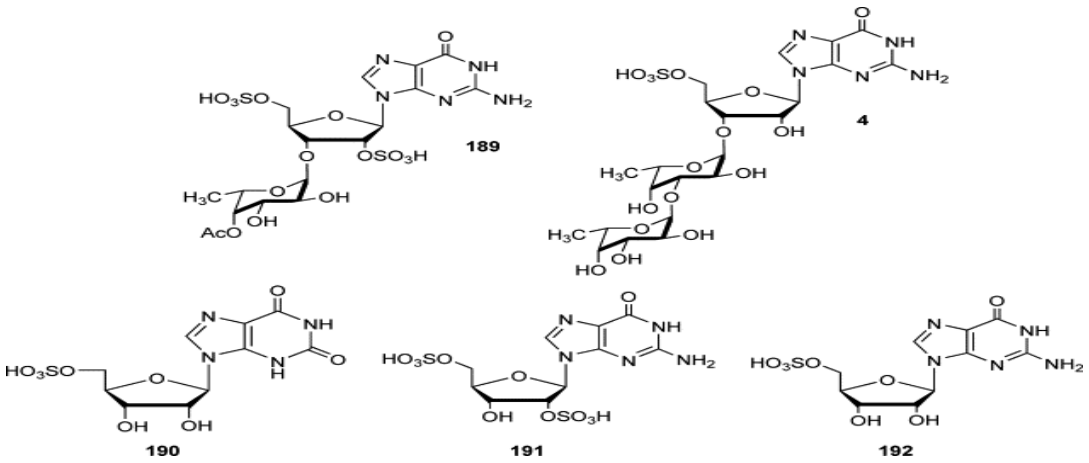

Figure 4: The chemical anatomical structure of spider venom is shown using its elements.

Spider venom in the human body:

Venoms are chemicals of biological origin (i.e., made by an animal) used for attacking or defending. They are made by specialized organs such as modified salivary glands and enter the body through specialized systems such as grooved or hollow fangs. Most of them include a complex mixture of chemicals including proteins, peptides, sugars, and other substances. They may affect many body systems. Common effects of them include paralysis, interference with blood clotting, muscle breakdown, pain, tissue breakdown, and effects on the cardiorespiratory system (heart and lungs). There are basically two types of venoms that affect humans: neurotoxins and cytotoxic (or necrotic). Neurotoxic venoms directly affect the nervous system.

The best-known example is the venom of Latrodectus species. Necrotic venoms cause tissue damage such as blisters and lesions. There are no confirmed cases of spider bites in Australia causing necrotic lesions, although it has been proven that bites from recluse spiders native to the Americas cause tissue necrosis. Generally, neurotoxins are eliminated more quickly than cytotoxic venoms. The primary effect of the neurotoxic venom is to block nerve impulses to the muscles, which causes cramps and stiffness and also disrupts many body functions. It also over-stimulates the production of neurotransmitters, acetylcholine, and norepinephrine, and paralyzes the entire nervous system.

The combined effect causes sudden and intense stress in the entire human body. In severe cases, it can cause death due to respiratory or circulatory failure. The venom of the funnel web spider, known as delta atracotoxin, directly affects the nervous system. Necrotic venoms cause blistering of the skin around the bite site, which may cause scar and tissue death or necrosis. Recent studies of confirmed spider bites indicated that in Australia, these bites do not cause tissue necrosis. These types of symptoms are most likely due to other types of clinical conditions. Spider venom antivenom is produced by injecting spider venom into horses, goats, or rabbits. It does not harm these animals since either they are only given small doses of the venom or they naturally have a mild reaction to it. Antibody molecules are produced due to the reaction of the animal's immune system to foreign venom molecules. These are used to make life-saving antivenoms for humans. Molecular studies are being conducted to make synthetic antivenoms.

The structure of spider venom:

Spider venom can be divided into two general categories: necrotic and neurotoxic. Necrotic or cytotoxic venoms cause cell and tissue damage. It can lead to the appearance of inflammation, lesions, and blisters. Neurotoxic venoms apply their effects on the nervous system and disrupt the signaling between neurons. In severe cases, it can lead to respiratory and cardiac arrest. Some spider venoms can contain necrotic and neurogenic components.

Regarding the venom components, they are often classified based on their molecular weight: low molecular weight compounds (less than 1000), peptides (1000-10000), and proteins (+10000). For different spider species, one of these classes may contain the primary component of the venom. Despite the large number of different spider species, the components of a small percentage of spider venoms have been identified. However, they generally contain a large number of compounds from all three groups. Low molecular weight compounds include salts, carbohydrates, and small organic compounds such as amines, acids, and acyl polyamines. It is thought that the potassium ions in the salts may help the toxic parts of the venom reach their molecular targets in the victims. High concentrations of potassium ions can also affect signaling between neurons in the insect nervous system. Moreover, amines can include neurotransmitters such as serotonin and noradrenaline. These can interact with the insect's nervous system and help release the venom through the insect's body. Acyl polyamines are significant low molecular weight toxins in the venom of some spiders, and more than 100 of them have now been identified.

Spider venom mostly contains several different acyl polyamines, not just one. It is thought that their primary goal in venoms is to paralyze insects by blocking glutamate receptors. Peptides are the primary component of most spider venoms. They are thought to contain about 25% polypeptide by weight. Analysis has shown that some individual venoms can contain up to 1000 different peptides. Some contain linear cytolytic peptides that have necrotic effects. The action of these cytolytic peptides is relatively non-specific and can also act synergistically with neurotoxic components. They can be effective in the external digestion of spider prey. However, disulfide-containing peptides are the key players in spider venom. They are the primary toxic component in most venoms, apart from a few exceptions. They are more potent than cytolytic peptides and are more selective in terms of targets. These are primarily ion channels on neurons.

Moreover, it has been suggested that some of them may have evolved for repelling predators rather than insecticidal activity owing to the nature of some of the other purposes of these compounds. Finally, higher molecular weight components include larger enzymes and proteins. Enzymes play a key role in the external digestion of spider prey after envenomation. Various types of enzymes have been identified in spider venom. Also, they enable the release of venom by breaking the extracellular structures. One of the enzymes, namely hyaluronidase, is thought to be for self-defending since its target, hyaluronan, is found in vertebrates but not in invertebrates. High molecular weight proteins are relatively uncommon as toxic components of the venom. However, there is one considerable exception in this regard, widow spiders, which include Latrodectus. Their venom contains a toxin called latrotoxin, which has been the subject of many studies. One of them is α-latrotoxin, which binds to nerve terminals and causes a massive release of neurotransmitters at synapses, and

blocks signal transmission. The effects of a Latrodectus bite can last up to 5 days, although it is rarely lethal. You may wonder why scientists have spent so much time researching spider venom. The demand for better insecticides, which can target specific insects without damaging other wildlife, means that we are looking to spider venoms.

Spider venom components and their biochemistry:

Spider venoms are very complex mixtures made up of thousands of different components. Many of them interact with ion channels and other receptors in the prey. Thus, spider venoms are primarily neurotoxic. The components fall into four primary categories, small molecules, larger proteins, cysteine-rich peptides, and antimicrobial peptides.

A) Small molecules: there are several classes of abundant small molecule components in spider venom. A significant group described as neurotransmitters in other animals includes serotonin, octopamine, 5-hydroxytryptamine, 5-methoxy tryptamine, Histamine, tyramine, γ-aminobutyric acid, aspartic acid, and glutamic acid. Another recently-discovered group includes sulfated nucleosides, such as sulfated guanosine isolated from Loxosceles reclusa, and non-sulfated nucleosides, such as adenosine, guanosine, inosine, and 2, 4, 6-trihydroxy purine in Latrodectus menavodi, and inosine, bianata in Parawia. Neurotoxic alkaloids are uncommon in venom systems and are commonly found in venoms, particularly those produced by amphibians. However, β-carboline alkaloids have been identified in P. bistriata venom. Ph. nigriventer venom also contains the dioxopiperidine compound. Spider venom is also rich in citrate, mineral ions, and salts. For example, high concentrations of minerals, including iron, zinc, lead, copper, calcium, magnesium, sodium, phosphorus, and S, are found in the venom produced by Nephila species. They probably act as factors that facilitate the folding and activity of toxins. Acylpolyamines are the most extensively studied small molecule venom components, discovered in the 1980s in the Nephila and Argiope. However, it has been proven that they are found in many different species. These polyamines are insecticidal neurotoxins that act as open-channel blockers of glutamatergic and/or nicotinergic receptors. Acyl polyamines consist of an aromatic acyl group and polyamine chain. Some of them have additional amino acids in the polyamine chain, often with a terminal arginine residue. The length of the polyamine chain can vary from seven atoms, such as pseudoargiopinin III, to more than 40, such as nephylatoxin-6.

B) Larger proteins: The significance and abundance of large proteins in spider venom are currently discussed. However, in some species, they constitute key components of the venom. For example, the toxicity of Latrodectus spp. venom in humans reflects the presence of α-latrotoxin (αLTX) that forms homotetramer pores in the presynaptic neuron membrane of vertebrates. This leads to an uncontrolled influx of Ca2+ and neurotransmitters, leading to pain, convulsions, and even death. Similarly, venoms produced by the Sicariidae family contain phospholipase D (PLD), a highly cytotoxic sphingomyelin-hydrolysis enzyme. It is shown in Figure 4. Finally, a cytotoxic hyaluronidase-like enzyme has recently been shown to enhance the uptake of co-administered neurotoxins, thus acting as a release agent.

Except for these examples, the role of larger proteins in spider venom is unclear. Details are presented in the caption below. Figure 4 shows the protein and peptide classes identified in spider venom. Top panel: Large proteins expressed by phospholipase D. Bottom two panels: Short spider venom peptides are divided into two main classes. The middle panel depicts ICK (cysteine knot inhibitor) neurotoxic toxins (verotoxin, robotoxin, and Hemotoxins-I). The bottom panel shows the antimicrobial peptides (Latarcin-II and Oxyopinin). The names of the species of spiders from which the parts were isolated are indicated below the combined names. Secondary structures are indicated by color (alpha helices in blue, β-sheets in red and change to purple). For example, many spider venoms contain metalloprotease neprilysin and members of the CAP (cysteine-rich secreted protein, pathogenicity-associated antigen 5 and 1) family. However, their molecular roles are unclear. Many spider venoms also contain disulfide isomerases and carboxypeptidases. Many spider venoms contain metalloprotease neprilysin and members of the cysteine-rich secretory protein family, antigens associated with pathogenesis, but their molecular roles are unclear. Many spider venoms also contain disulfide

isomerases, carboxypeptidases, and serine proteases, which may facilitate post-translation modification and maturation of venoms. There is evidence that the chymotrypsin-like activity of a serine protease facilitates venom maturation, but more studies are needed to confirm the role of other enzymes.

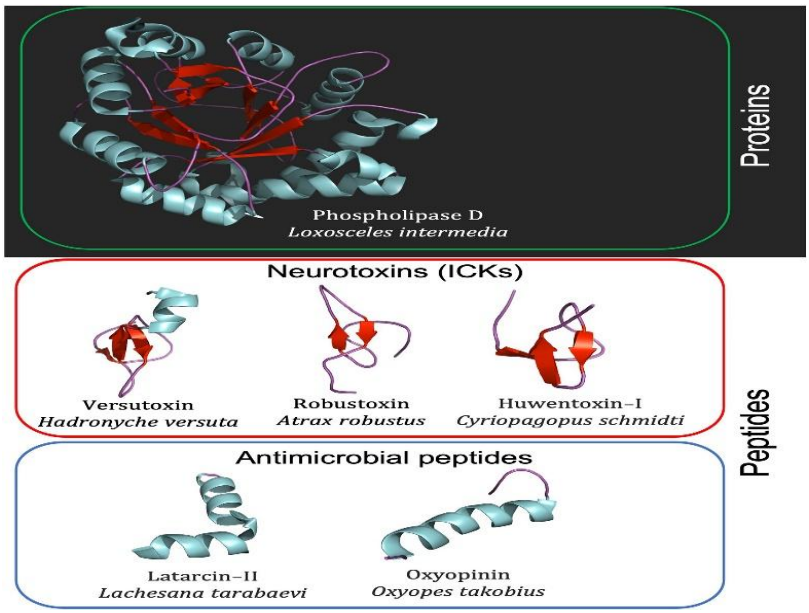

Figure 5: The protein structure of the effect of spider venom and its chromosomes

C) Cysteine-rich peptides: They are the most significant group of spider venom components. They usually have a molecular mass of less than 10 kDa, which is rich in disulfide bonds. Many peptides interact with ion channels and other receptors. Thus, they represent the primary neurotoxic components of spider venom. Cysteine-rich peptides can be assigned to different families, such as Kunitz-type serine protease inhibitors, neuropeptide-derived peptides, Helicobacter pylori (HAND), colipase fold peptides (MIT-1), disulfide-directed β-hairpin fold peptides (DDH), and most importantly, peptides with an inhibitor cysteine knot scaffold (ICK). Although many of these components have not been examined in detail, studies have focused on the ICK family, which is the most diverse, abundant, and characterized secondary structure component of spider venom systems. ICK peptides are a three-stranded antiparallel β-sheet, and their tertiary structure is determined by at least six cysteine residues oxidized to form disulfide bonds that form the characteristic pseudoknot motif. Most ICK peptides have six cysteine residues, thus they have three disulfide bridges. However, others have extended cysteine scaffolds and/or double ICK (dICK) motifs. ICK peptides form stable complexes with prey receptors and disrupt their natural mode of action. Key targets include sodium, Potassium, and calcium channels having voltage. However, acid-sensitive ion channels, glutamate receptors, and transient receptor potential channels are essential for signal transduction and cellular communication in the prey. Thus, their dysfunction disrupts the physiological homeostasis of the poisoned organism. The binding of a neurotoxic ICK polypeptide is mostly facilitated by partial penetration of the cell membrane and subsequent lateral migration to the target and then binding with high affinity and specificity. The physicochemical properties of ICK peptides reflect their pharmacodynamic behavior. Since the molecular size is negatively correlated with distribution time, small ICKs apply their physiological effects rapidly after injection, and the exceptional stability of these molecules resists proteolytic degradation. Thus, their efficacy is maximized.

D) Antimicrobial Peptides: Most spider venom AMPs are linear and alpha-helical peptides without disulfide bonds. They show antimicrobial activity and endanger eukaryotic cells by disrupting the integrity of their membranes. For this reason, they are called lytic peptides. Therefore, these short peptides may have a dual function in venom systems by defending the venom gland against microbial colonization while facilitating prey

paralysis and potential digestion. Although AMPs are found in many spider venoms, most of those identified so far have been found in the venoms of hunting spiders (Lycosidae) and tarantulas (Theraphosidae). They are very diverse in hunting spiders, so more than 50 such peptides discovered in Lycosa sinensis venom. The synergistic molecular interactions increase the versatility of spider venoms.

Antivenom:

It was produced by the Commonwealth Serum Laboratories, a government agency involved in the discovery of antivenoms for many Australian venomous organisms at that time. Production involves milking Latrodectus venom and frequently inoculating horses with non-lethal doses. The horse's immune system produces polyclonal antibodies. Blood plasma, containing antibodies, is extracted by plasmapheresis. The plasma is treated with pepsin and the active F (ab)2 fragments are isolated and purified. Each vial contains 500 units of red antivenom in 1.5 mL, which is enough to inactivate 5 mg of Latrodectus venom in a test tube. This antivenom was safely injected into women at various stages of pregnancy. Redback antivenom has been extensively used in Australia since 1956 until now, although controlled studies have not provided any evidence about its effectiveness. Recent trials suggest that antivenom has a lower response rate than placebo, and any effect is less than that obtained with optimal use of standard pain relievers. More studies are required to prove or disapprove of its effectiveness. It appears to be clinically active against spiders caused by Steatoda spiders. However, this treatment is not recommended since these cases are often mild and there is limited evidence about its effectiveness. Similarly, antivenom has been reported to be effective against L. katipo and L. tredecimguttatus bites. Animal studies also support its use against detoxification from other Latrodectus venoms.

Spider venom in medical service:

Thanks to the presence of latrotoxin in their venom, Latrodectus bites are potentially dangerous and may cause systemic effects (latrodectism), including severe muscle pain, abdominal cramps, hyperhidrosis, tachycardia, and muscle spasms. Symptoms usually last 3 to 7 days but may persist for several weeks. In 1933, one of the University of Alabama Medical School students, namely Alan Blair, conducted an experiment on himself to record the symptoms of a Latrodectus bite, and to test whether a person could develop immunity after being bitten. The effects of the bite were so painful and intense that Blair was unable to complete the test and did not continue the bite a second time. About 2,200 people in the United States report being bitten by a Latrodectus each year. However, most of them do not require medical treatment. Some bites do not inject any venom (dry bite). In the United States, no deaths have been reported from Latrodectus to the American Association of Venom Control Centers since 1983. Latrodectus is not a particularly aggressive spider and rarely bites humans unless it is threatened. Unlike popular belief, most people who are bitten are not seriously injured. Lethal bites in the early 20th century were mostly reported for Latrodectus tredecimguttatus. Antivenoms are used to relieve pain and not to save lives since venom is usually not life-threatening. However, one study revealed that standard pain relievers, when combined with antivenom or a placebo, produced similar improvements in pain and symptom relief. Researchers have reported weakened sexual power and fertilization in men bitten by a Chilean black widow. Studies have shown that the venom of this species of spider has a kind of sperm-neutralizing substance that is not found in similar species of this spider in other regions. Researchers now decide to take steps to create new ways to prevent pregnancy by using the special property of this spider's venom. They argue that it requires having sufficient knowledge about the side effects of sperm neutralization.

Behavior therapy:

Treatment is based on the severity of envenomation. Most cases do not require medical care, and patients with local pain, swelling, and redness usually require only topical application of ice and simple oral pain relievers such as paracetamol. Pressure stabilization of the wound site is not recommended. Keeping the affected person calm is helpful. A hospital evaluation is recommended when simple pain relief does not resolve local pain or systemic symptoms occur. Opioid pain relievers may be needed for pain relief. Antivenom has been given to adults who suffer from severe local pain or systemic symptoms consistent with Latrodectus, which include pain and swelling that spreads from the area near the site, annoying local or systemic pain, chest pain, abdominal

pain, and diaphoresis. A significant number of bites do not lead to envenomation or cause symptoms. About 2 to 20 percent of the affected people are treated with antivenom. In an Australian study on 750 people hospitalized in the emergency departments, among the spider bites where the spider was definitively identified, 56 belonged to Latrodectuss. Among them, 37 had significant pain that lasted more than 24 hours. Only six people were treated with this antivenom. The manufacturer's product information recommends one vial of antivenom, although more were used. Previous guidelines indicated two vials, with two additional vials if symptoms did not resolve within two hours. However, recent guidelines state that antivenom is sometimes prescribed if there is a history, signs, and symptoms consistent with systemic envenomation, and severe pain unresponsive to mouth. However, recent trials show that antivenom has a slightly lower response rate than placebo, and the manufacturer recommends intravenous (IV) administration of antivenom for life-threatening cases. In January 2008, a toxicologist, Geoffrey Isbister, suggested that IM antivenom is not as effective as IV antivenom since IM antivenom takes longer to reach blood serum. Then, Isbister found that the differences between the IV and IM routes of administration were at best small and are not justified. These concerns led to two guidelines for recommending IV rather than IM administration in Australian practice. Isbister et al. (2014) conducted a randomized controlled trial of intravenous administration of antivenom versus placebo for redback envenomation. The results showed that adding antivenom did not significantly improve pain or systemic effects, while antivenom resulted in acute allergic reactions (3.6 percent) in those who received it. The issue of abandoning antivenom according to these results and previous studies was raised in the Annals of Emergency Medicine in 2015. White and Weinstein argued that the recommendations of Isbister et al. (2014) were followed and it led to the abandoning of antivenom as a therapeutic option, an outcome that White and Weinstein consider undesirable. Isbister et al. (2014) reported that there is enough evidence that it is no better than a placebo and given the risk of anaphylaxis and serum sickness, a routine use of antivenom is not recommended.

Benzodiazepines and intravenous calcium gluconate were used to relieve symptoms of pain and discomfort before the introduction of the antivenom, although calcium is not recommended since its benefit has not been demonstrated in clinical trials. Safety studies support the antivenom with a 5% chance of an acute reaction, a 1-2% chance of anaphylaxis, and a 10% chance of a delayed reaction due to serum sickness. However, if treatment of a severe anaphylactic reaction is required for more than 30 minutes, it is recommended to have an adrenaline injection ready and available and a diluted vial of antivenom in a 100 mL bag of intravenous solution for infusion. While it is rare for patients to report symptoms of envenomation several weeks or months after the bite, there are case reports from the 1990s that antivenom was reported effective in relieving chronic symptoms when administered weeks or months after the bite. However, in most cases, this medication is prescribed within 24 hours. Based on NSW Health, Latrodectus bites are not considered life-threatening but can cause severe pain and systemic symptoms

Conclusion

Although spider venom proteomes have been primarily qualitatively evaluated over the last years, few studies are more extensive among the analysis of other animals. Quantitative approaches have also recently been applied to top-down proteomics. Nowadays, top-down approaches are in their infancy and are more challenging to implement than bottom-up approaches. It is primarily due to less expertise, the need for protocols for samples before separation and high-resolution spectra, and more sophisticated data analysis tools. Despite its many advantages, including obtaining information on changes after translation and qualitative discrimination between closely related proteoforms, using top-down approaches along with transcriptional or genomic analysis predicts a bright future in this regard. This result suggests that Latrodectus raw venom is a suitable combination of substances with useful biological properties for the possible isolation of new antimicrobial molecules to deal with bacteria resistant to existing antibiotics.

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