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Biology, ecology and therapeutic possibilities of scorpion venom (Arachnida: Scorpiones).

Carlos Henrique Marchiori[1]

1 Instituto Federal Goiano

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Marco Vinícios de Oliveira Santana and Klebert de Paula Malheiros

Department of Medicine and Biological Sciences, Instituto Marco Santana, Goiânia, Goiás, Brazil.

1. Introduction

Scorpions are small invertebrates from the Phylum Arthropoda, class Arachnida and order Scorpiones and group Chelicerata, such as spiders (Araneae), mites (Acari), harvestmen (Opiliones), and seven other less popularly known groups. The name chelicerates (Chelicerata) comes from the Greek (chele: nail, cerata: horns) and refers to the shape of the first pair of appendages in the form of a stinger or chela, which they all have. The Greek word scorpions gave rise to the word scorpion and the Latin term that designates the Order to which these animals belong: Order Scorpiones (Figure 1) [1-3].

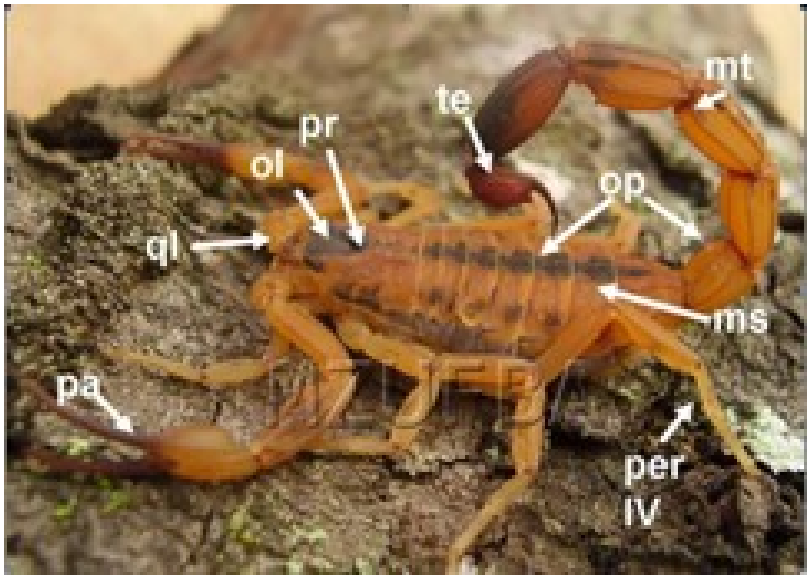

Figure 1. External morphology of a scorpion *Tityus stigmurus* (Thorell 1876) (Scorpiones: Buthidae): op, opisthosoma; pr, prosoma; pa, pedipalp; ql, chelicera; ol, eyes; te, telson; per IV, leg IV. Source: Photo: Tiago Jordão Porto.

Scorpions are carnivores and predators of insects, spiders, birds, snakes, and spiders. Many animals like to feed on

scorpions, such as earwigs, praying mantises, monkeys, spiders, frogs, lizards, meerkats, owls, hawks, coatis, chickens, mice, and some species of ants. Due to their inefficient vision, this animal has developed sensory bristles throughout its evolution that help identify movements and vibrations around it. Furthermore, it can chemically detect the presence of other animals. They can spend months fasting, digestion is almost external, as they deposit digestive enzymes in the prey, then cut the pieces, but do not ingest anything solid, just the liquid part (Figure 2) [3-5].

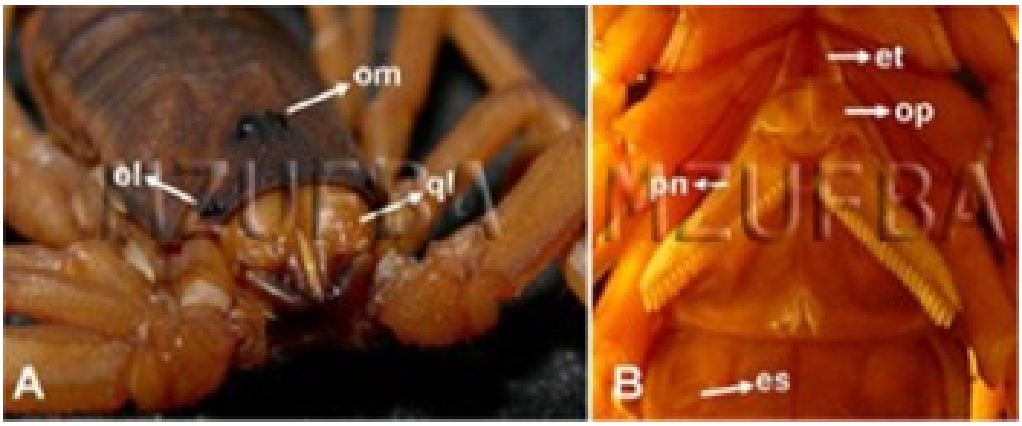

Figure 2. Frontal (A) and ventral (B) view of the scorpion*Tityus serrulatus* Lutz & Mello, 1922 (Scorpiones: Buthidae): es, stigma, or respiratory spiracle; et, sternum; pn, combs; ol, side eyes; om, medium eyes; op, genital operculum; ql, chelicerae. Source: Photos: Tiago Jordão Porto.

Their body is divided into a cephalothorax prosoma and an abdomen opisthosoma. This, in turn, is divided into trunk mesosome and tail metasome: Prosoma: short and covered by a carapace, it has six articulated ends: a pair of chelicerae, a pair of pedipalps, and four pairs of legs. It does not have jaws or antennae; it has simple eyes, one of the pairs being in the central region of the dorsal surface. Mesosome: where the genital operculum, sensory appendages, and spiracles are found: metasome: has a structure called a telson, which has a pair of venom-producing glands. These glands open into two orifices located at the tip of a stinger, through which scorpions inject venom into their prey (Figure 3) [4-6].

Figure 3. Sting on a scorpion's telson showing a drop of venom coming out. Sources: Photo: Eduardo D.V. and available at http://www.flickr.com/photos/eduardo-dv/3298038594/.

During reproduction, there is a kind of mating dance, in which males and females are joined by rotating pincers. After copulation, cannibalism is common, the female eats the male. Most species are ovoviviparous, the offspring develop inside the mother, in eggs that hatch there, but some are viviparous and have a type of membrane equivalent to a placenta. After birth, the puppies walk on their mother's back until their first skin change, when they can feed themselves (Figure 4) [5-7].

Figure 4. Some arachnids demonstrate parental care. Scorpions like this one with a striped shell carry their newborn babies on their backs. Source: https://www.activewild.com/arachnids/.

They spend the day hiding in dark places, between cracks, under rocks, leaves, and logs, or buried in the sand in the desert. They are common in places with rubble, which have wood and construction materials, and are more active at night when they forage and eat. Longevity depends on the species, around 5 years of age, but there are records of more than 20 years in some species. Sexual maturity occurs after the first year. The interesting thing is that some species perform parthenogenesis [8-10].

The scorpion's venom is produced by a pair of glands located in the telson, the last segment of the metasoma. The telson ends in a very sharp sting that has two holes through which the toxins are inoculated. When capturing prey such as termites, cockroaches, crickets, spiders, and small vertebrates, the scorpion makes quick strikes with the telson on the victim. Scorpions only feed on live prey. Thus, the function of the venom is to immobilize the prey and be able to hold it with the pincers and start the meal [9-11].

Scorpion venom is a mixture of several substances whose toxins are low molecular weight proteins and act mainly on the peripheral nervous system. These neurotoxins cause intense release of neurotransmitters from the autonomic nervous system, affecting the cardiocirculatory and pulmonary systems and the digestive tract [10-11].

2. Taxonomy

A. Species of scorpions:

2.1. Scientific name: *Tityus serrulatus* Lutz & Mello, 1922 (Scorpiones: Buthidae).

Measures approximately up to 7cm in length. It has a dark trunk, legs, pedipalps, and a yellow tail, which is serrated on the dorsal side. Considered the most poisonous in South America, it is the scorpion that causes serious accidents, mainly in the State of Minas Gerais.

2.2. Scientific name: *Tityus bahiensis* (Perty, 1833) Scorpiones: Buthidae).

It has a dark brown, sometimes reddish brown color, and yellowish legs with dark spots. Femurs and tibias of pedipalps with dark stains. The male's hand is well enlarged. This species is the cause of the most frequent accidents in São Paulo.

2.3. Scientific name: *Tityus stigmurus* (Thorell, 1876) Scorpiones: Buthidae).

It is light yellow with a black triangle on the head and a median longitudinal stripe and lateral spots on the trunk.

2.4. Scientific name: *Tityus cambridgei* Pocock, 1897 (Scorpiones: Buthidae).

It has a general reddish-brown color, with light-colored spots. The male has a longer tail than the female.

2.5. Scientific name: *Tityus trivittatus* Kraepelin, 1898 (Scorpiones: Buthidae).

It is dark yellow, with three almost black longitudinal bands, although there may be small color variations. Reaches approximately 7cm in size.

2.6. Scientific name: *Pandinus imperator* (Koch, 1841) (Scorpiones: Scorpionidae).

Common name: Emperor scorpion: The emperor scorpion is a nocturnal species native to the west of the African continent. Black in color, when placed under a black light it displays green reflections reminiscent of a metallic tone. Emperor scorpions are almost blind, but they have sensory hairs along their bodies that make up for this deficiency [10-15].

In Brazil, the two most common species in accidents are the yellow scorpion*T. serrulatus* and the black scorpion *T. bahiensis*. A scorpion sting causes a lot of local pain, fever, sweating, and dyspnea and can lead to death, especially in children and the elderly. In case of a bite, wash with soap and water, keep the area at rest, and seek a health center urgently so that you can receive the serum that will neutralize the toxin. Depending on the amount of poison injected, the case becomes more serious [14-15].

3. Prevention measures And Researchers study scorpion venom to treat diseases.

Check clothes and footwear before putting them on; Use gloves when handling yards and gardens; Scorpions also shelter in the sewage system, so it is important to use screens in bathroom drains, sinks, and tanks; Keep cribs and beds at least 20 centimeters away from walls, as scorpions can climb materials such as wood and rough walls; Prevent curtains,

mosquito nets, and bedding from touching the floor, as scorpions can climb through these areas; Pack household waste in plastic bags and keep it in closed places, with a lid; Combat insect infestation and Preserve lizards, frogs, and opossums because they are natural predators of scorpions (Figure 5) [15-18].

Figure 5. The potential therapeutic applications of scorpion venom compounds. Scorpion venom is a rich source of bioactive compounds and as such its toxins are of interest to the pharmaceutical and biotechnology industries. However, although substantial research efforts are underway and the prospects for scorpion-derived therapeutic peptides are very promising, chlorotoxin is the only toxin from scorpion venom that has been included in clinical trials. Furthermore, no scorpion toxin-based medicine is currently available on the market. Potential applications of scorpion venom compounds are presented. Sources:https://www.mdpi.com/2227-9059/8/5/118 and https://doi.org/10.3390/biomedicines8050118.

4. Scorpion venom is used to combat cancer cells.

The venom of the brown scorpion *T. bahiensis*, a species that causes moderate to severe poisonings is found in Bahia and the Central-West, Southeast, and South regions of Brazil. Published in the Journal of Proteomics, the work makes it possible to study proteins isolated from the venom, which can help to understand the secondary effects of poisoning and even identify molecules with therapeutic action (Figure 6) [19-20].

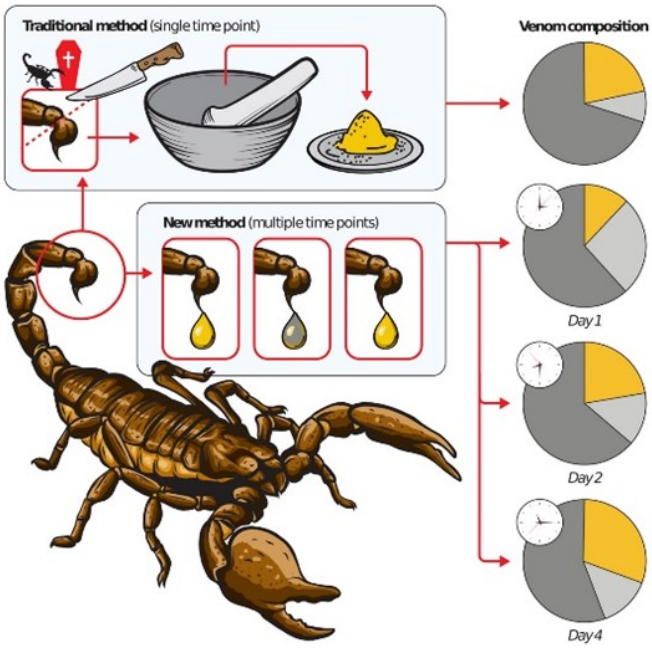

Figure 6. A comparison of techniques used to study venom. The traditional method involves removing the telson to obtain the venom, whereas, in the new method, venom is extracted using electrostimulation and can be repeated at various time points without sacrificing the scorpion. Source: Credit: Vonk et al. PLOS ONE. 2021;16(11):e0258712.

The analysis of the isolated proteins led to the discovery of a peptide with neuroprotective activity, capable of increasing the number of neurons in cell culture and animals. The next step will be to test it in animal models of neurodegenerative diseases, such as Alzheimer's and Huntington's disease. “As scorpion venom is neurotoxic, we tested the toxins in nervous system cells. And so, we identified this peptide that, instead of killing neurons, increased their cell viability (Figure 7) [20-21].

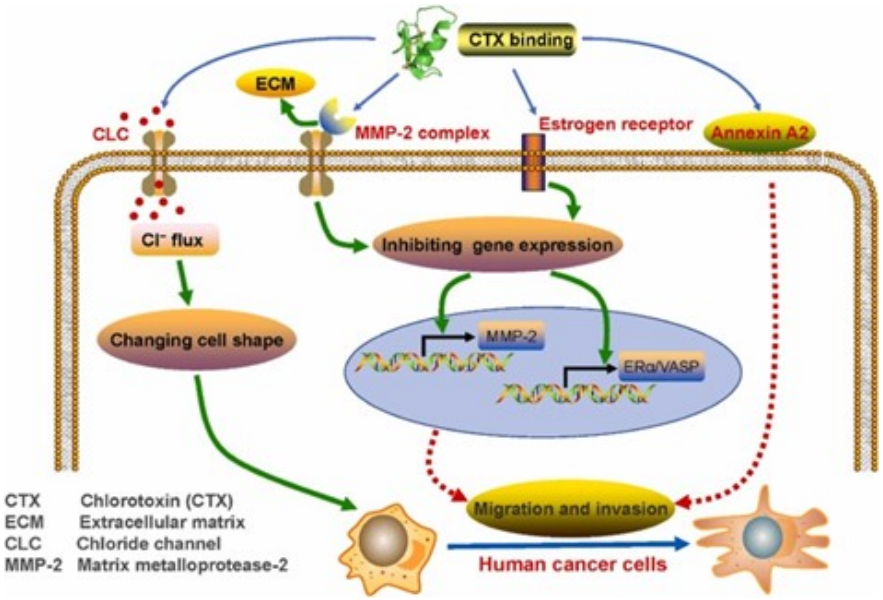

Figure 7. In the model, CTX regulates the migration and invasion of multiple human cancer cells by binding to four different receptors. Normally, CTX blocks the flow of chloride ions and limits the extent of changes in the shape of glioma cells. Meanwhile, CTX can also prevent the invasiveness of glioma cells by inhibiting the expression of tumor-related genes, including MMP-2 or ERα/VASP. Furthermore, CTX can regulate tumor progression by binding to annexin A2 due to its role in cell migration and invasion. The mechanism of action of CTX targeting each receptor needs refinement, especially the interpretation of the downstream pathway after receptor binding (red arrow). Source: https://doi.org/10.1016/j.phrs.2023.106978 and https://www.sciencedirect.com/science/article/pii/S1043661823003341.

Another unprecedented finding was the presence of the ACE enzyme in the venom, a molecule never found in scorpions. In mammals, this enzyme has the function of regulating blood pressure. One of the scientists' hypotheses is that ACE, together with hypotension in the venom, could contribute to the cases of blood pressure variations that are described in poisonings. They characterize molecules that were previously not so well known, and which can give rise to new biotechnological tools pharmacological properties [20-21].

The scorpion *Leiurus quinquestriatus* (Ehrenberg, 1828) (Scorpions: Buthidae) has different neurotoxins in its venom, including chlorotoxin. According to scientists, the component has potential uses in several medical advances, including the treatment of some types of cancer. Chlorotoxin is used to identify the size and location of cancerous tumors. Another experiment with the component used on mosquitoes was able to eliminate malaria, and there are hopes that similar results will be produced in humans [22-23].

5. Brazilian researchers have identified a toxin from yellow scorpion venom that penetrates cells and modified it to fight cancer.

Tityus serrulatus, the most poisonous in Latin America, can penetrate the cell nucleus and carry medicines to combat cancer cells. Called CPP-Ts, the toxin is related to the cardiac effect of a scorpion sting. It increases contraction in heart muscle cells, one of the main causes of death in victims, according to research. CPP-Ts cross the cell membrane, which highlights this peptide as a promising and specific tool for intranuclear administration to cancer cells (Figure 8) [24-25].

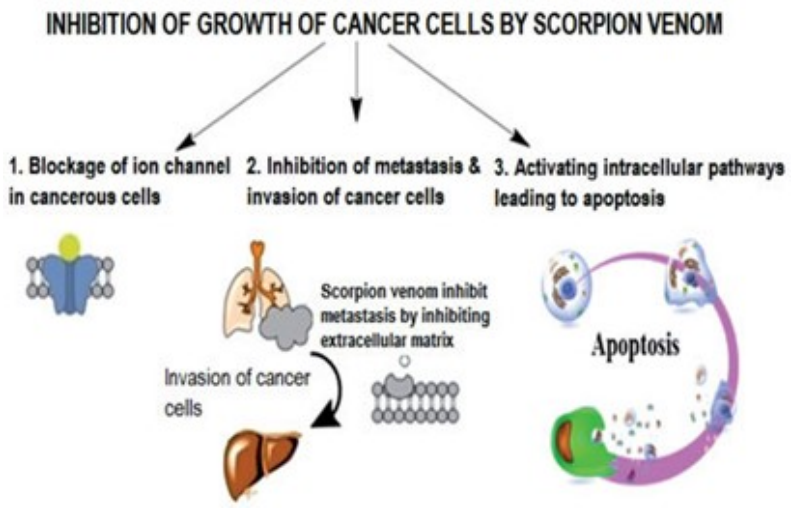

Figure 8. Mechanism of inhibition of growth of cancer cells by scorpion venom Source: https://www.researchgate.net/figure/Mechanism-of-inhibition-of-growth-of-cancer-cells-by-scorpion-venom_fig4_329811057.

After identifying this toxin, researchers modified its structure so that it no longer caused cell contraction but maintained the ability to communicate with cells. Research shows that the modified toxin penetrates exclusively tumor cells, sparing healthy cells. The objective is to link CPP-Ts to medicines used to treat cancer. This should reduce the side effects of chemotherapy and make the treatment more effective [Dr. Evan Guedes Kalapothakis, professor at the Department of General Biology at the Federal University of Minas Gerais] (25-26].

the venom contains low molecular weight basic proteins with damaging action on the nervous system (neurotoxic activity) in addition to enzymes such as hyaluronidase and other constituents in smaller quantities such as histamine and serotonin, the latter involved in the process of pain and inflammation. Hyaluronidases are produced by a variety of disease-causing organisms, including bacteria. These enzymes are also found in leeches, snake and insect venoms, and malignant tissues. “The presence of these enzymes in animal venoms has the function of facilitating the diffusion of toxins into tissues more quickly, contributing to systemic poisoning and restricting the effectiveness of antivenoms, if they are not injected as soon as the accident occurs”, explained Andrea [25-27].

According to her, these enzymes have been used therapeutically because they facilitate the diffusion of injectable liquids, “acting to temporarily reduce the viscosity of the connective tissue, making it more permeable to the diffusion of liquids” [Dr. Andréa Carla Pessini - Faculdade de Ciências Farmacêuticas da Universidade de São Paulo in Ribeirão Preto].

6. Researchers study scorpion venom to treat diseases.

One of the most feared arachnids due to its sting, which can kill, the scorpion is also the source of a promising substance in the treatment of two diseases that are still challenging due to the lack of targeted therapies. In the publication of the journal Science Translational Medicine, two articles from different research centers showed the effectiveness of a small protein from this animal's venom to eliminate the symptoms of rheumatoid arthritis without the toxic effects of current medications and to kill cancer cells of the type of rheumatoid tumor deadliest brain, glioblastoma [25-27].

In rheumatoid arthritis, the body's immune system attacks its tissues, including joints. In severe cases, it attacks internal organs. Rheumatoid arthritis affects the lining of the joints, causing painful swellings. Over time, the inflammation caused by rheumatoid arthritis can lead to bone erosion and joint deformity. Although there is no cure for rheumatoid arthritis. Malignant tumor affecting the brain or spine. This glioblastoma type of tumor grows and spreads quickly, often creating pressure. Symptoms include headache, nausea, drowsiness, blurred vision, personality changes, and seizures (Figure 9) [25-27].

Figure 9. Metabolic arthritis is caused by an increase in glancing biosynthesis, excessive production of uric acid, or poor excretion of uric acid, resulting in an increase in uric acid in the blood and thus causing gout, which is characterized by hyperuricemia and recurrent episodes of gouty acute arthritis, commonly occurring in the joints of the big toe but also in the hands, knees, elbows, and others. Sources: https://certificure.co/products/scorpion-venom-gel and UNPREE™ Scorpion Venom Professional Care Gel.

Toxic substance produced by animals has promising effects in research aimed at two challenging diseases. The protein kills brain cancer cells and relieves symptoms of rheumatoid arthritis, in addition to reducing the side effects of treatment. These products of the defense mechanism of many species are peptides, biomolecules that, like those found in plants, can give rise to medicines. A small protein in scorpion venom that quickly accumulates in joint cartilage. When they linked steroid medications to these peptides, the result was that the medicine concentrated only on the joints, avoiding the toxic effects of the anti-inflammatory corticosteroid on the body as a whole [25-27].

A mini protein in the Palestinian yellow scorpion*L. quinquestriatu* has shown promise for testing. Tests with a steroid called Triamcinolone acetonide, or TAA. Tests on mice showed that the substance was as effective in treating inflammation as dexamethasone, a more powerful corticosteroid used for arthritis. However, when TAA enters the bloodstream, it becomes inactive. Therefore, it does not cause detectable side effects [Oslo and other Fred Hutch scientists] [25-27].

7. Acetylcholinesterase inhibitory potential of scorpion venom in *Aedes aegypti* (Diptera: Culicidae).

Scorpion venom, due to its specific toxins against insects, has become a notable candidate to produce biopesticides. Scorpions contain distinct bioactive neurotoxins. Many neurotoxins in the venom target the insects' nervous system, disrupting their ion channels and neural activity. Insect excitatory toxins can help design new insect-selective biopesticides due to their special modes of action, as they only target the insect nervous system. The neurotoxins present in scorpion venom are also involved in the disturbance of neurotransmitters released at the synaptic junctions of nerves (Figure 10) [25-27].

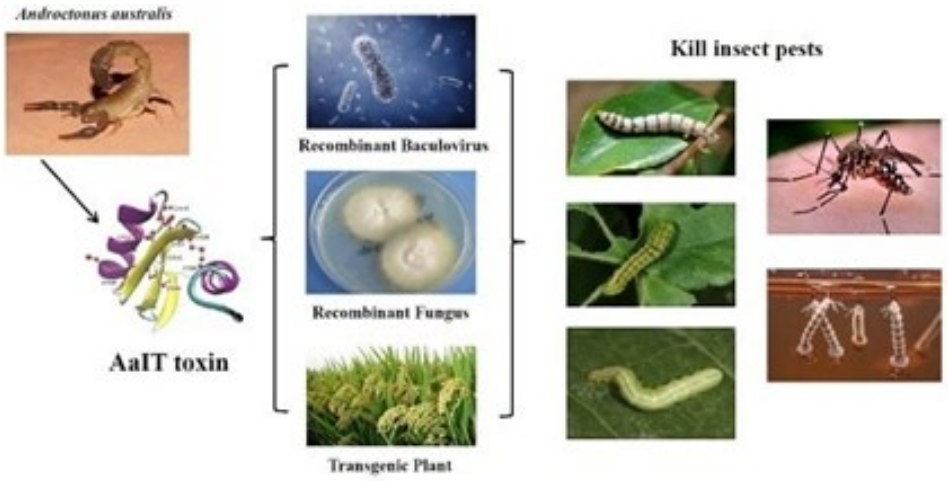

Figure 10. The exclusive and specific target of the toxin is the voltage-gated sodium channels of the insect, resulting in rapid excitatory paralysis and even death. Because of its strict toxic selectivity and high bioactivity, AaIT has been widely used in experiments exploring pest bio-control. Recombinant expression of AaIT in a baculovirus or a fungus can increase their virulence to insect pests and disease vectors. Sources: Int. J. Mol. Sci. 2019, 20(14), 3467 and https://doi.org/10.3390/ijms20143467.

8. The leishmanicidal activity of the venoms of the scorpions*Brotheas amazonicus* Lourenço, 1988 and *Tityus metuendus* Pocock, 1897.

Tegumentary leishmaniasis causes skin lesions, most commonly ulcerations, and, in more serious cases mucosal leishmaniasis, attacks the mucous membranes of the nose and mouth. Visceral leishmaniasis, as the name suggests, affects the viscera or internal organs, especially the liver, spleen, lymph nodes, and bone marrow, and can lead to death. Symptoms include fever, weight loss, anemia, enlarged liver and spleen, bleeding, and immunodeficiency. Leishmaniasis is a public health problem worsened by a series of limitations regarding treatment. In the search for new therapeutic alternatives, scorpion venoms are a source of multifunctional molecules that act against the natural resistance of pathogens. Crude venom from both scorpion species showed similar or superior leishmanicidal effects to standard N-methylglucamine antimoniate (Figure 11) [25-27].

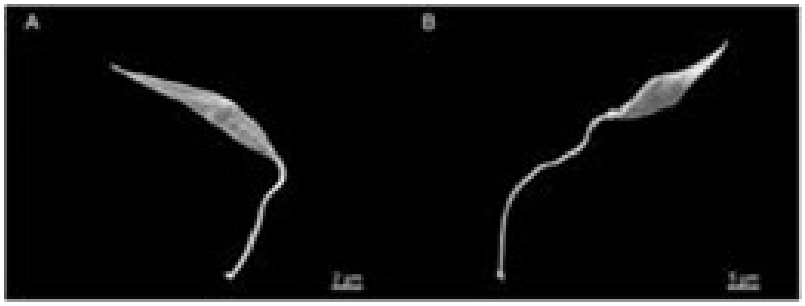

Figure 11. Promastigote forms of *Leishmania amazonensis* Linson & Shaw, 1972 (Kinetoplastida: Trypanosomatidae) (A) and *Leishmania guyanensis* Floch, 1954 (Kinetoplastida: Trypanosomatidae) (B). Source: Brazilian Journal of Biology, 2023; 83: e276872.

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