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KILLER CONE SNAILS: DEADLY PREDATORS OR THE FUTURE OF MEDICINE?

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YOUNG REVIEWERS:

BRISA
AGE: 12

TIBERIUS
AGE: 13

What is your first thought if I say "venom"? Is it something bad or good? As we will discuss in this article, it all depends on the dose. We will examine the beauty of nature and science through an amazing animal: cone snails. These apparently harmless marine molluscs harbor a deadly secret—their powerful venom. Scientists have been studying cone snail venom since the 1980s, when its potential as medicines was discovered. In this article, we will talk about these venomous animals and how scientists investigate whether substances in their venom can actually benefit humans.

DISCOVERING THE AMAZING WORLD OF VENOMS

Since the dawn of life on Earth, living things have faced a crucial challenge for survival: eat and do not get eaten. Predators and prey have been co-existing since the very first steps of evolution. This fact has led all life forms to undergo changes through all the history of evolution: anatomical (e.g., prickles in hedgehogs or sea urchins), behavioral (speed, alarm signals) or biochemical (bad taste). Production of toxic substances by living things appeared early in evolution, hundreds of millions of years ago. Among these substances, **venoms** are one of the most widespread and fascinating **adaptations**.

Venoms are powerful chemical cocktails that are used by venomous organisms to catch their prey and/or for defense. Venoms are normally composed of a mixture of proteins like enzymes, peptides (small proteins), and sometimes other kinds of molecules. Depending on their mode of action we can classify venoms into four types: cytotoxins that kill cells, mycotoxins that lead to muscle necrosis, neurotoxins that target the nervous system, and hemotoxins that disrupt blood clotting.

Although snakes and spiders might be the most well-known venomous animals, toxins can be found across a wide variety of organisms, including lizards, platypuses, some fish, and the main topic of this article: cone snails.

CONE SNAILS ARE AMAZING ANIMALS

Cone snails are **gastropods** that can be found in a variety of marine environments across tropical waters worldwide. Despite their beautiful shell patterns (Figure 1) these animals harbor a sophisticated venom apparatus (Figure 2). Like any other snail they are very slow, so they have overcome this drawback with an incredibly powerful venom that immediately paralyzes their prey. Cone snail venom consists mostly of a mixture of peptides called **conotoxins**, as well as other proteins and small molecules. Conotoxins act on the **central nervous system**, interfering with the function of nerve cells and paralyzing the prey [1]. The venom, which is contained in a duct, is injected into the prey by a muscular bulb that pumps the venom, similar to the way a syringe works.

Like many snails, cone snails also have a tooth, called the **radular tooth**, which is used to eat the plants they feed on. However, in cone snails, the radular tooth has been modified throughout evolution into a sophisticated device similar to a harpoon, which it injects into its prey.

VENOM

Toxic secretions that are delivered into a living organism and manipulate its normal physiological functioning to the benefit of the venomous organism.

ADAPTATION

A heritable change in a species that improves its ability to survive and reproduce in a particular environment.

GASTROPODS

A vast and diverse group of more than 6,500 species of molluscs that include slugs and snails.

CONOTOXINS

Small proteins present in the venom of cone snail which are responsible for the activity and toxicity of the venom.

CENTRAL NERVOUS SYSTEM

The body's main processing center, consisting of the brain and the spinal cord.

RADULAR TOOTH

Anatomical structure found in most molluscs used as feeding tool. Cone snails have efficiently developed it to hunt on their prey.

Figure 1

Figure 1

Cone snails have beautiful patterns on their shells.

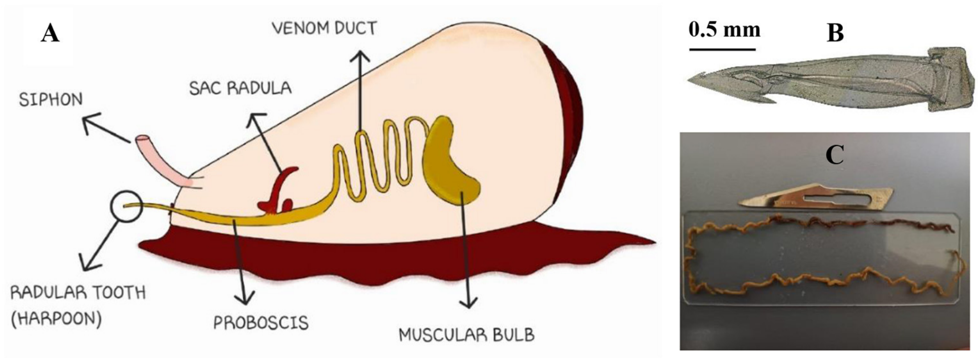

Figure 2

Figure 2

(A) Illustration of the anatomy of a cone snail. The venom is produced in the venom duct, pumped by the muscular bulb and injected into the prey through the radular tooth. The siphon is used to detect their prey. **(B)** Radular tooth of the cone snail *Rhombiconus imperialis* that is efficiently developed to hunt on worms. **(C)** Venom duct of the cone snail *Rhombiconus imperialis*. For scale, the blade at the top is 5 cm long.

Cone snails can be classified into three types depending on their feeding habits: vermivorous, which eat worms; molluscivorous, which eat molluscs; and piscivorous, which prey on fishes. Fish-hunting cone snails are the most dangerous for human beings. Why? Because the human nervous system is more like the nervous system of fishes than it is to worms or molluscs, so the venom of fish-hunting cone snails is more likely to act on the human body. There have been some cases of cone snails attacking human beings in self-defense.

SCIENTIFIC POTENTIAL OF CONE SNAILS' VENOM

If cone snails are that dangerous, how could they be useful for humans? Conotoxins have interested scientists for a long time, as potential models for developing medicines. Conotoxins have several properties that could make them good medicines. First, they are natural products created through evolution, so they have been refined for many years by nature. Second, conotoxins are not easily broken down in the body. Finally, conotoxins interact very potently and specifically with their molecular targets, which means they do not act on other molecular target so eventually they would be good candidates for developing medicines with no side effects.

In summary, hidden within cone snails, Mother Nature has created a great database of chemical weapons that specifically target the actions of nerve cells. What would happen if we could turn this to our advantage, using these toxins to treat diseases in which nerve signals are not transmitted properly? If we find the correct dose, we might be able to change the activity of nerve cells and therefore treat these diseases.

At this time, there is only one approved drug developed from conotoxins. This drug, called ziconotide, was developed from a conotoxin isolated from the venom of the cone snail *Pionoconus magus* (Figure 3). The painkilling effect of ziconotide is 1,000 times more potent than even morphine, without the dangerous side effect of addiction that morphine has [2]. Ziconotide blocks specific “tunnels” through the cell membrane, called calcium ion channels, that are involved in nerve cell function. By reducing the signals nerves send, ziconotide causes patients to feel less pain.

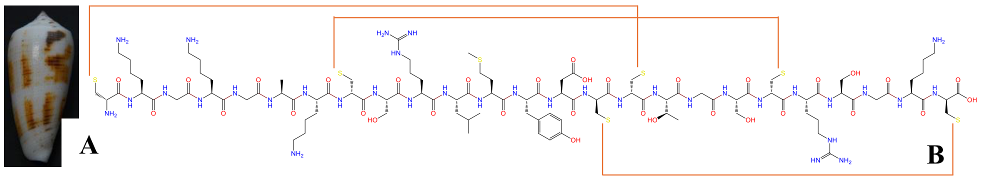

Figure 3

Figure 3

(A) *Pionoconus magus* (magician’s cone)—the source of the toxin used to develop the medicine ziconotide. **(B)** Chemical structure of ziconotide.

Some drugs derived from the components of venoms are used to treat some very common diseases, like high blood pressure. A drug called captopril, one of the top-selling blood pressure medicines, was developed from a peptide found in the venom of the snake *Bothrops jararaca*.

Exenatide is another good example of the successful use of venoms to develop drugs. Exenatide is used to treat diabetes and was developed from a peptide identified in the venom of the Gila monster lizard, *Heloderma suspectum*. It is likely that many other potential drugs are waiting hidden in the libraries that Mother Nature has built over the course of evolution.

FROM A MIXTURE OF COMPOUNDS TO A DRUG

Venoms are complex cocktails of components that need to be characterized to figure out if they can be used as drugs. The classical characterization of natural products consists of the extraction of all components from the venom and then isolate each one from the mixture. Once isolated, scientists use laboratory methods to determine the chemical structure of each compound. This way of unraveling the complex mixtures of components present in the venom of cone snails would be extremely time consuming and require hundreds of animals. Taking that many snails from the wild would damage ecosystems. For this reason, scientists now study cone snail venom using a modern approach called **integrated venomics** [3], which combines several cutting-each techniques, called genomics, transcriptomics, and proteomics, to characterize conotoxins present in venom using less time and resources.

INTEGRATED VENOMICS

Scientific discipline which includes genomics, transcriptomics, proteomics and metabolomics to efficiently study the composition of venoms.

Genomics

Living organisms have a set of DNA instructions, called the genome, that controls their structure and function. Genomics studies the genome of organisms to see what genes they have, how those genes are organized, and what kinds of molecules they can produce. This information is useful because it helps scientists to understand which genes are responsible for making the different toxins in cone snail venom.

Transcriptomics

Imagine the genome as a library containing all the information needed to create an organism. Not all genes (books) are needed all the time, and the organism can choose which books (genes) it needs for each specific moment and make copies of those instructions. These copies are molecules called RNA. All the molecules of RNA present at a single moment are called the transcriptome, which is what transcriptomics studies. Transcriptomics can tell us which genes are being used at that moment and how much of each toxin the snail is producing.

Proteomics

RNA molecules are "read" by cellular machinery to create proteins. Proteins are the molecules that carry out the functions that must happen within each organism. In the case of cone snails' venom, the proteins are the conotoxins the snail uses for predation or defense. All the protein molecules present at a given moment form what is known as proteome. Studying the proteome tells us which toxins are actually made by the snail and released in its venom. This is useful because it helps scientists focus on the toxins that really matter for hunting or defense.

Thanks to integrated venomics, we can untangle the complex mixtures that make up cone snails' venom—but how do we test whether each compound might be useful as a potential drug? According to the most conservative estimates, there are between 100 and 200 conotoxins in each snail. There are close to 1,000 cone snail species, which means there are up to one million conotoxins! It would be almost impossible to test the activity of every one of these compounds. Therefore, we must rely on modern technologies such as artificial intelligence (AI). We can model the 3D structures of all the conotoxins present in the venom within a few minutes, thanks to an amazing new AI system called AlphaFold [4]. This and other advanced laboratory tools allow us to study the potential mode of action of each toxin in the virtual world. That way, we can screen all conotoxins present in the venom and choose those more likely to be useful for developing new drugs.

Once we choose likely drug candidates based on what we learn from AI, we can create those molecules in the lab and experiment with them, to prove what we predicted with the computer. We can even modify the molecules by adding or removing various chemical groups, to try to improve the properties that would make them good potential medicines. If they look promising, all new drugs must be approved by regulatory agencies, like the European Medicines Agency or the U.S. Food and Drug Administration, before they can be used for the betterment of humankind.

WHAT HAVE WE LEARNED FROM VENOM?

This article has shown how science can turn something apparently harmful, such as venom, into something beneficial for humans. That should be one of the great objectives of science: to learn from the world around us to improve our quality of life. To do this, we must protect the amazing treasure we have—nature—taking all possible measures to conserve the biodiversity that surrounds us. What would have happened if *Pionoconus magus* would have become extinct before being studied? It would have been impossible for scientists to study its venom, and we never would have known that it contains a life-saving drug!

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AI TOOL STATEMENT

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Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

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CONFLICT OF INTEREST: The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

BRISA, AGE: 12

Hello, my name is Brisa. I am a girl, currently 12 years old. This year, I am starting my first year of middle school, and when I grow up, I plan to study to become a pharmacist and a writer! I like books, anime, stuffed animals, music, and spending time with my family, my two dogs, and my three best friends.

TIBERIUS, AGE: 13

Hi my name is Tiberius. I am 13 years old and am going to be a 9th grader next year. Something you should know about me is that I really like music. I am in a choir and play many instruments such as the piano, cello and the pipe organ. Other than music, I also like to swim. I am on a swim team during the summer. I also enjoy photography and watching Formula 1.

AUTHORS

ANTONIO CABALLERO FONCUBIERTA

Antonio is a PhD student at the University of Cadiz. His research focuses on the study of the venoms of amphinomid-eaters cone snails. He has presented his final degree and master thesis on the proteo-transcriptomics study of *Rhombiconus imperialis* and *Rhombiconus fuscatus*, both feed on amphinomids. As a chemist, he is interested in the study of conotoxins and dreams of developing a drug inspired on them. With this purpose, he has started studying solid-phase peptide synthesis and would like to carry out bioactivity assays with the synthetic conotoxins.

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JUAN CARLOS GARCÍA GALINDO

Juan Carlos G. Galindo is an associate professor at the University of Cadiz. His research interests involve the biochemical interactions among living organisms, with special emphasis on allelopathic studies and, more recently, venomics studies. In this area, he has focused on proteotranscriptomics studies on cone snails, addressing also other venomous animals like spiders and, more recently, lizards. His areas of interest cover the structural elucidation of natural products using classical techniques (NMR, MS/MS, etc.) and more modern ones (proteotranscriptomics, 3D protein NMR), chemical synthesis and modification, and Structure-Activity Relationship (SAR) studies. He is also passionate about Nature conservation and biodiversity.

MANUEL JIMÉNEZ TENORIO

Manuel Jiménez Tenorio is a full professor in the Department of Materials Science, Metallurgical Engineering, and Inorganic Chemistry. He has been studying cone snails for over 30 years and has published several books and more than 30 scientific articles on the topic. He has been the first to describe many new species and, like his two colleagues, he has conducted scientific campaigns all over the world to study cone snails. He is recognized as one of the world's authorities on this subject.

TERESA-G. SIBON-MACARRO

Teresa is a professor at the University of Cadiz. Her research focuses on education, language, communication, digital literacy and attention to diversity. With the team at the Writing Center of the University of Cádiz, she collaborates with the spreading of scientific knowledge by organizing workshops at Science Fairs and in schools, and by creating stories with activities and games to spark curiosity among kids or teenagers and their families.