

CHAPTER 16

Natural Toxins as Therapeutic Agents

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ABSTRACT: Natural toxins are bioactive compounds synthesized by animals, plants, fungi, and microorganisms, primarily as defensive or predatory tools. Despite their inherent toxicity, these molecules possess exceptional therapeutic potential, driven by their ability to precisely target and modulate essential biological pathways. Natural toxins interact with ion channels, enzymes, receptors, and cytoskeletal components, enabling highly specific pharmacological effects that can be harnessed for medical use. Over recent decades, these compounds have emerged as promising candidates in the treatment of a wide range of diseases, including diabetes, chronic pain, cancer, and cardiovascular disorders. Many natural toxins also exhibit potent antioxidant, antiviral, anti-parasitic, antibacterial, and anti-inflammatory activities, further expanding their relevance in modern therapeutics. Their structural diversity and target specificity make them invaluable templates for drug discovery and development. This chapter provides an in-depth exploration of the medicinal properties of natural toxins, emphasizing their mechanisms of action and therapeutic applications.

Natural toxins are poisonous substances produced by living organisms, including animals, plants, fungi, and microbes, often as a defense mechanism or for predation. These toxins exhibit diverse biological properties that could be detrimental to human as well as animal health (Bucheli, 2014). These biologically active compounds are produced by organisms for the competitive advantage in the environment and to increase survival chances (Valério et al., 2010). These natural toxins exhibit neurotoxic, coagulant, proteolytic and hemolytic effects. Natural toxins display health benefits for humans and animals because some xenobiotics obtained from these substances are applied in current medical treatments (Kachel et al., 2018). The classification system for natural toxins depends on their biological source as well as their effects on specific organs and their particular way of action (Hodgson, 2012).

Natural toxins develop through biological processes. These toxins are used to defend against predators, maintain colony safety and capture prey (Hardy et al., 2014). The toxins consist of three

main types which include bioactive peptides, cardiac glycosides and cardioactive steroids (Kowalski et al., 2018). Natural toxins operate through various mechanisms, which include angiotensin converting enzyme, inhibiting sodium-potassium ATPase, as well as attaching to ion channels and proteins to render them inactive (Buratti et al., 2017). Toxins exhibit various resistance levels to heat and sunlight because they include heat-sensitive substances that affect their ability to bioaccumulate (Abdallah et al., 2021). The spider venom displays toxicity to numerous animals, yet it remains harmless to lizards, which stands as an example of how toxins affect different species in different ways (Thill et al., 2022). Natural toxin poisoning causes several main symptoms, including gastrointestinal problems, neurological damage, paralysis, cardiac toxicity, liver damage, nausea and pain (Yang et al., 2012; Piontek et al., 2020). Moreover, research is conducted to assess the anticancer and antimicrobial actions of natural toxins (Kachel et al., 2018).

It is a matter of fact that humans as well as animals are exposed to numerous natural toxins present in the environment that exhibit adverse impact on their health (Youthao & Amornsiriphong, 2021). Health conditions caused by zoonotic diseases are an example of toxin induced damages (Zhang et al., 2022). However, these compounds exhibit numerous medicinal benefits and are used as therapeutic agents. The current chapter discusses the medicinal actions of natural toxins in detail.

ANIMALS OR VENOM-DERIVED NATURAL TOXINS:

Biochemical composition:

Animal venoms consist of multiple biologically active substances that include proteins, peptides, lipids, enzymes, small organic compounds and nucleotides (Oliveira et al., 2022). The composition of venom varies significantly across species, reflecting evolutionary adaptations to different ecological niches and prey types (Michálek et al., 2024). The two main categories of venom components consist of enzymatic substances and non-enzymatic substances. Tissue degradation, homeostasis disruption, inflammation and hemorrhage are caused by venom. These conditions

occur because of enzymatic components, including serine proteases, phospholipase A2 enzymes (PLA2s), hyaluronidases, metalloproteinases and L-amino acid oxidases (Kini & Koh, 2016). The non-enzymatic components of venoms, include cytotoxins, cardiotoxins, neurotoxins and ion channel blockers exhibit strong effects on specific cellular receptors as well as channels (AlShammari et al., 2023). Recent transcriptomic and proteomic research has demonstrated that venoms exhibit greater complexity in their composition. It has discovered the low-abundance components that were previously unrecognized, with potent pharmacological properties (Aird et al., 2015).

These components include novel natriuretic peptides, bradykinin-potentiating peptides and disulfide-rich peptides. These components enhance the therapeutic landscape of natural venoms for different health situations i.e., chronic pain and hypertension (Modahl et al., 2018). Table 1 shows different types of venoms and their mode of action.

Therapeutic applications:

Scientists have observed promising results from venom-derived compounds in developing new medicines because these substances demonstrate strong and precise binding to particular molecular

Table 1. Venoms and their mode of action

| Venom | Mode of Action | Reference |
|--------------------------|---|--|
| Snake Venoms | <ul style="list-style-type: none"> Venom in kraits and cobras, i.e., elapid venom, is neurotoxic and dendrotoxic (block or modulate neurotransmitter receptors and ion channels). Viperid venoms are cytotoxic and hemotoxic, which disturb the integrity of extracellular matrix, injure the vasculature and disrupt normal coagulation. | (Kini, 2006; Gutiérrez et al., 2016) |
| Cone Snail Venoms | <ul style="list-style-type: none"> They produce cono-toxins that affect G-protein-coupled receptors, nicotinic acetylcholine receptors and voltage-gated ion channels. | (Lebbe & Tytgat, 2016) |
| Arachnid Venoms | <ul style="list-style-type: none"> They are produced by spiders and scorpions. They contain neuropeptides that modulate calcium, potassium, and sodium channels. They offer potential treatment options against pain as well as neurological disorders. | (King, 2011) |
| Marine Venoms | <ul style="list-style-type: none"> These venoms exhibit novel biologically active proteins and peptides that have neurotoxic, cytolytic and hemolytic properties and are extracted from marine animals, i.e., sea anemones and jellyfish. Research suggests that they may be used for cancer therapy and modulation of ion channels. | (Mariottini, & Pane, 2013; Xie et al., 2017) |
| Bee Venom | <ul style="list-style-type: none"> Bee venom produced by honeybee and other stinging insects, releases enzymes, peptides, proteins and activating mast cells. Bee venom also possesses Hyaluronidase which breaks the connective tissue component, hyaluronic acid and allows venom to penetrate tissues. | (Darwish et al., 2021; Ku et al., 2020) |

targets (Kini & Koh, 2020). Multiple peptide- as well as protein-based medications derived from animal venoms have been permitted for clinical application, while numerous others are in different evaluation stages, i.e., preclinical and clinical trial phases (Sadeghi et al., 2017; Munawar et al., 2018). These medicines are used for various therapeutic applications against various diseases, i.e., diabetes, chronic pain, cancer and cardiovascular diseases.

Captopril stands out as a highly successful drug because it was the first angiotensin-converting enzyme (ACE) inhibitor approved for the treatment of cardiac failure and hypertension. This drug was developed through the isolation of bradykinin-potentiating peptides found in the venom of *Bothrops jararaca* snakes (Smith & Vane, 2003). Lisinopril and enalapril, synthetic analogs of captopril, were later developed by modifying captopril. This shows how venom-based research served as the initiating point for drug design (Bader & Ganten, 2008).

Ziconotide (Prialt®) has become a ground-breaking medical treatment for pain management. Ziconotide is the synthetic analog of ω -conotoxin MVIIA isolated from *Conus magus*, which blocks N-type calcium channels to treat patients with chronic pain who are resistant to opioid medications (McGivern, 2007). Ziconotide functions differently from opioids and does not lead to respiratory problems or addiction, so it serves as a useful alternative for pain medication.

Venoms are also used in the development of antiplatelet agents. Eptifibatid and tirofiban are obtained from viper venoms. They inhibit platelet aggregation via acting as glycoprotein IIb/IIIa inhibitors and are used during percutaneous coronary interventions and to regulate acute coronary syndromes (Estevez et al., 2015). This shows that venoms can be used for cardiovascular therapeutics.

Exenatide (Byetta®) is a synthetic form of exendin-4, which was extracted from the venom of the Gila monster (*Heloderma suspectum*). The medication functions as a GLP-1 receptor agonist, which is used to regulate type 2 diabetes mellitus. It regulates blood sugar levels via delaying the emptying of the stomach, lowering inappropriate glucose release and improving the secretion of glucose-dependent insulin. Moreover, it helps patients lose a little weight because it reduces their

desire to eat which makes it useful for treating type 2 diabetes patients who struggle with excess body weight (DeMarsilis et al., 2022).

Research studies concentrate on venom peptides to develop new cancer therapies that extend beyond their present roles in heart disease and pain treatment. Scientists discovered chlorotoxin from scorpion venom binds to matrix metalloproteinase-2 (MMP-2), which is overexpressed in glioma cells. The unique characteristics of MMP-2 aided in their use in tumor imaging and targeted therapies (Wiranowska, 2024). The main component of bee venom is “melittin” which fights cancer via activating apoptosis, reducing angiogenesis and disturbing the membrane of cancer cells, but its harmful effects on normal cells present a major drawback. The clinical research showed that melittin treatment lowers pain and inflammation (Son et al., 2007).

Recent research has concentrated on studying how venom peptides function as antimicrobial and antiparasitic agents. Spider and scorpion venoms contain defensin-like peptides which show broad-spectrum antifungal and antibacterial effects through their ability to disturb microbial membranes. The peptides derived from cone snail and wasp venoms show potential for blocking protozoan parasites which indicates they could be useful for treating tropical infectious diseases (Vinhote et al., 2017).

The therapeutic applications of venom-derived compounds have reached new heights via synthetic biology and peptidomimetic design that improve their pharmacokinetic properties and specificity (King, 2011). The development of venom-based drug candidates depends on these efforts because they are important for overcoming various challenges related to immunogenicity, peptide stability and delivery. The examples show how venom-derived compounds move from laboratory research to medical practice via their ability to treat cancer, chronic pain, inflammatory diseases, diabetes and hypertension.

PLANT-DERIVED TOXINS WITH BIOMEDICAL APPLICATIONS

Phytotoxins are poisonous substances produced naturally by plants. These phytochemicals from plants serve as environmental xenobiotics which

sometimes produce negative effects on human beings, animals as well as the environment (Kilmer, 2008). People worldwide show growing interest in medicinal plants for health management because conventional drug misuse has led to drug resistance which affects both human and animal medical treatments (Jamil et al., 2022). Besides their health benefits, phytotoxins can still cause various health conditions. Lectins, cyanogen, ricininechaconine, glycosides and alkaloids are the major phytotoxins (Salgar et al., 2018). The composition and the mechanism of action of these toxins vary from one another. Lectins exist as multivalent carbohydrate-binding proteins that are primarily present in legumes, causing cell agglutination or polysaccharide and glycoconjugate precipitation (Gorakshakar & Ghosh, 2016).

Human consumption of lectins may lead to abdominal cramps, pain, joint swelling and nausea (van Buul & Brouns, 2014). In animals, excessive consumption of lectins can lead to poor nutrient absorption and damaged intestinal lining (Pusztai, 1998). However, they are used in the field of biotechnology to detect surface markers of stem cells and red cell antigens as well as to stimulate lymphocytes (Gorakshakar & Ghosh, 2016). Lectins also show antimicrobial properties which make them suitable for developing powerful antimicrobial substances (Dias et al., 2015).

Glycosides exist in fruit pigments and flowers and they can also cause. Onojah & Odin (2015)

reported that hydrogen cyanide is present in many plants in the form of cyanogenic glycoside. If intoxicated, the cells in the body become unable to use oxygen because cyanide blocks oxygen usage, which results in cell death that primarily affects brain and cardiac cells. However, these glycosides function as antibiotics (streptomycin) and they may also be utilized for their potential to treat heart diseases (Kytidou et al., 2020). Some other plant-based toxins and their medical applications are reported in Table 2.

FUNGAL TOXINS WITH THERAPEUTIC POTENTIAL

Mycotoxins pose a global human health risk because they produce toxic effects and contaminate food sources that are consumed by humans and animals (Rong et al., 2019). In addition, they are utilized in agriculture and medicine for their therapeutic applications. The therapeutic properties of mycotoxins are due to the presence of bioactive molecules. Research has proven mycotoxins work effectively as insecticides, antidiabetic, antioxidant and antibacterial agents. Different fungi species produce multiple mycotoxins which demonstrate antitumor effects against various cancers.

Mycotoxin derivatives are used for various medical purposes which make them vital components of contemporary healthcare systems. Research has focused on mycotoxins and their derivatives to understand their potential anticancer

Table 2. Phytotoxins and their medical applications

| Phytotoxin | Medical Application | Reference |
|---------------------------------------|--|--|
| Safrole | Antioxidant, antidiabetic and antibacterial | (Eid & Hawash, 2021) |
| Phytoestrogens | Modulate endocrine disruption and hormonal imbalance in postmenopausal women, with reduced physiological levels of estrogen | (Moreira et al., 2014) |
| Alkaloids | Anti-viral and anti-parasitic | (Aydin et al., 2020) |
| Terpenoids | Bioactive compounds with anti-inflammatory, neuro-protective properties | (Kiyama, 2017) |
| Ribosome inactivating proteins (RIPs) | RIPs inhibit the polypeptide chain elongation and protein synthesis by removing rRNA. It has antiviral property used against Herpes virus. | (Chen et al., 2022) |
| Cyanogenic glycosides | Phytotoxin that produce Hydrogen cyanide, acting as defense mechanisms against herbivores. Antioxidant, anti-inflammatory properties. | (Chen et al., 2022; Cressey & Reeve, 2019) |
| Non-protein amino acids | Antioxidant, anti-inflammatory and antimicrobial activities. Play a role in biochemical and metabolic machinery | (Felicoli et al., 2018; Chen et al., 2022) |

properties which reveal the pharmaceutical importance of these chemicals (Safe & Kasiappan, 2016). It has been revealed that particular mycotoxin derivatives are used for cancer treatments (Harvey et al., 2015) and some of these compounds are also available in the commercial market.

Anicequol is a mycotoxin that exhibits marked anti-tumor properties as it can inhibit the growth of cancer cells (Igarashi et al., 2002). Auranomide B is another fungal toxin that inhibits cancer due to its cytotoxic behavior. In addition to anticancer properties, some mycotoxins also exhibit phytotoxic, antifungal, antibacterial, and cytotoxic effects, such as Chaetoglobosin A (Nicoletti & Trincone, 2016).

Furthermore, *Penicillium aurantiogriseum* is a fungus that produces taxol during the fermentation process (Bouhoudan et al., 2024). Taxol is one of the most commonly used drugs in clinical practice against various tumors. Therefore, besides their toxicity, mycotoxins are also used for their medicinal properties, particularly due to their anticancer activities. Figure 1 demonstrates some mycotoxins that offer medicinal benefits.

MECHANISTIC INSIGHTS INTO TOXIN-BASED THERAPEUTICS

Natural toxins undergo transformation into therapeutic agents through the application of their evolutionary developed structures. Through the process of evolution spanning millions of years, toxins have developed into "privileged scaffolds" which are pre-optimized structures that bind physiological targets with high affinity and selectivity. The therapeutic value of these molecules stems from their ability to modulate ion channels, enzymes, receptors and cytoskeletal networks through specific molecular mechanisms rather than their toxic effects (Kim et al., 2025).

Voltage-gated ion channels function as the main targets that neurotoxins attack in the body. The mechanism of ziconotide (Prialt), derived from the cone snail *Conus magus*, illustrates the clinical application of pore blockade. The drug Ziconotide works by blocking N-type voltage-gated calcium channels (CaV2.2), which exist on the nerve endings of dorsal horn neurons in the spinal cord. By physically occluding the pore of these channels, ziconotide inhibits the calcium influx required for

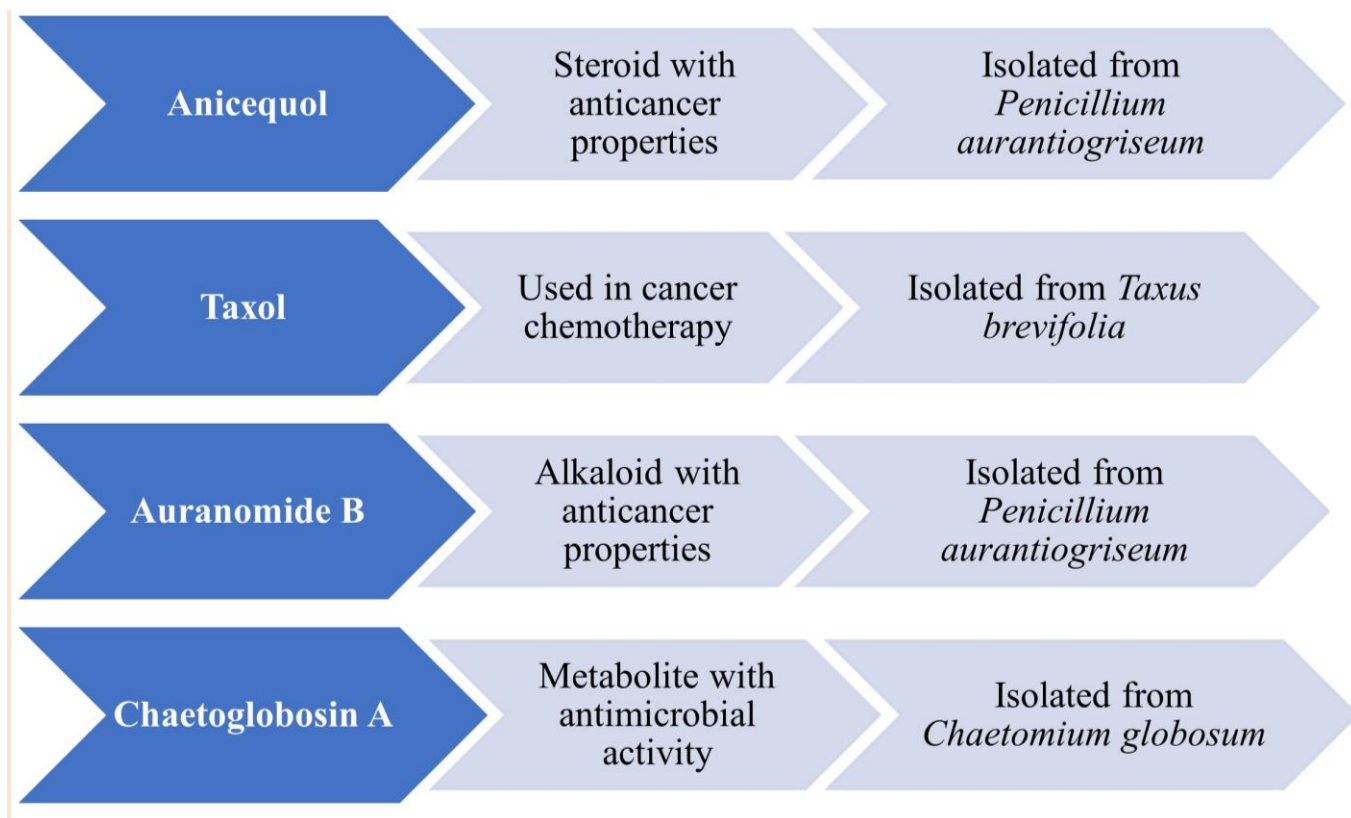


Fig 1. Mycotoxins offering medicinal benefits

the exocytosis of synaptic vesicles. This blockade uncouples the arrival of nociceptive action potentials from the release of pro-nociceptive neurotransmitters (e.g., glutamate, substance P), thereby silencing pain transmission at the spinal level without targeting opioid receptors (McGivern et al., 2007).

Venom-derived peptides have provided critical insights into enzymatic regulation. The development of ACE inhibitors, such as captopril, was based on the mechanism of bradykinin-potentiating peptides (BPPs) from the venom of *Bothrops jararaca*. These peptides competitively inhibit Angiotensin-Converting Enzyme (ACE), preventing the conversion of angiotensin I to the vasoconstrictor angiotensin II while simultaneously inhibiting the degradation of the vasodilator bradykinin (Kim et al., 2025).

Toxins also act as high-potency ligands for G Protein-Coupled Receptors (GPCRs). Exenatide, a synthetic version of exendin-4 from the Gila monster, functions as a GLP-1 receptor agonist. Its therapeutic value stems from a single amino acid substitution (Glycine for Alanine at position 2) compared to human GLP-1, which renders it resistant to degradation by the enzyme DPP-4. This allows for sustained receptor activation and insulin secretion (Huerta et al., 2023).

The medical field uses the extreme power of toxins to treat cancer patients through Antibody-Drug Conjugates (ADCs) and immunotoxins. *Pseudomonas* exotoxin A (PE) belongs to bacterial toxins which enter the cytoplasm to start ADP-ribosylation of Elongation Factor 2 (EF-2). The process creates an unchangeable protein that stops all protein production and this leads to cell death through apoptosis (Alewine et al., 2015). The same way fungal toxins such as α -amanitin serve as payloads in ADCs to attach and block RNA Polymerase II. The system stops gene expression which makes it work against dormant tumor cells that do not respond to conventional antimitotic chemotherapy drugs (Cañas et al., 2022).

CONCLUSION

Although toxins derived from animals, plants or fungi are hazardous for humans and other living organisms, they also provide novel therapeutic options for the treatment of various health

conditions. Natural toxins are useful for their potential anticancer, cytotoxic, immunomodulatory, anti-bacterial, anti-inflammatory and antidiabetic properties. Despite their health benefits, natural toxins should be used cautiously due to the risk of potential toxicity associated with their application. Therefore, further research is indispensable in the field of natural toxins and their safe application for the benefit of living organisms.

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