



Therapeutic, Pharmacological and Biomedical Uses of Marine and Terrestrial Molluscs: A Review

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Abstract

This review article explains the therapeutic, pharmacological, and biomedical uses of marine and terrestrial molluscs. There are two categories of molluscs: the first one is those that synthesise toxins, and the second is those that inhabit marine algae or protozoans and store. These toxins are used in defence or predation. These toxins pose risks to human health as they impose paralytic (PSP), amnesic (ASP), diarrhetic (DSP), and neurotoxic (NSP) effects. This article sketches out the biological effects of conotoxins, Saxitoxin, Tetrodotoxin, Okadaic acid, Domoic acid (DA) and Brevetoxins (BTXs), Yessotoxin (YTX), Gymnodimine, Neosaxitoxin (NeoSTX), Pectenotoxin (PTX), and dinophysistoxin. These toxins bind to different receptor sites and act in various ways. This article explores the mechanisms of action of marine mollusc toxins, their stability, and their binding to various ion channels. Marine mollusc toxins act more specifically and exhibit anticancer, anti-proliferative, anti-angiogenic, antioxidant, anti-allergic, proteolytic, antidiabetic, antimicrobial, anti-parasitic, and anti-helminthic activities. These are used in cardiovascular diseases and wound healing.

Keywords: Marine Molluscs; Conotoxins; Tetrodotoxins; Proteolytic Activity; Antidiabetic; Antimicrobial; Anti-Parasitic; Anthelmintic Activity

Introduction

Molluscs are invertebrates belonging to the phylum Mollusca, the second-largest animal phylum after Arthropoda and the most diverse in the animal kingdom [1]. This phylum encompasses well-known groups, such as snails, clams, squids, and octopuses, as well as less familiar ones, including chitons and tusk shells. Among the seven classes of molluscs, gastropods, bivalves, and cephalopods are of economic importance globally [1,2]. The phylum comprises a vast diversity of molluscs, with 85,000 species living in marine, freshwater, and terrestrial environments. The majority of molluscs are marine. The representatives are slugs, clams, scallops, and

mussels; squids, octopuses, and nautiluses; chitons, which have a segmented shell; tusk shells; cap-like shells; and shell-less molluscs. Terrestrial molluscs are primarily snails and slugs, typically found in high-humidity environments. Many species have adapted to freshwater environments, including freshwater mussels and snails, but most of them are non-venomous.

This phylum encompasses well-known groups, such as snails, clams, squids, and octopuses, as well as less familiar ones, including chitons and tusk shells. Their diversity is expressed through significant variation in size (from microscopic to giant squid), form,

and complexity, ranging from sessile filter feeders to highly intelligent, mobile predators. Marine mollusc species release a variety of toxins, including peptides and alkaloids, that play roles in defence and prey capture. These toxins, such as conotoxins and tetrodotoxin, have diverse structures and target specific physiological processes, making them valuable for research and potentially for drug development. However, some toxins, like those causing paralytic shellfish poisoning (PSP), can also pose risks to human health when ingested through contaminated shellfish [3].

There are two categories of toxins: the first, synthesized by molluscs; and the second, produced by other organisms and stored inside molluscs, mainly marine species. Based on synthesis, secretion and bioaccumulation, these marine toxins are classified into two groups (Figure 1). Most of these biotoxins are not produced by the molluscs themselves but are accumulated from toxic algae that they consume during their filter-feeding process (Figure 1). Consumption of contaminated shellfish can lead to severe illness or death from these toxins. Molluscs, such as cone snails, store toxic substances generated by the algae. These toxins can be poisonous to humans and are categorized by the type of shellfish poisoning they cause, including paralytic (PSP), amnesic (ASP), diarrhetic (DSP), and neurotoxic (NSP) shellfish poisoning. While some toxins are produced directly by the mollusc for defence or predation, others, such as marine biotoxins, are acquired through the food chain and can pose a significant public health risk [5].

There are diverse categories of mollusc toxins which are produced by living creatures within these species. Saxitoxin (STX) is a neurotoxin produced by certain dinoflagellates that accumulate in shellfish. Domoic acid (DA), a toxin produced by diatoms like *Pseudo-nitzschia pungens*, okadaic acid (OA) and dinophysitoxins (DTXs), produced by the *Dinophysis* genus of algae. The *Karenia* genus of algae produces brevetoxins. Conotoxin is produced by cone snails and is used to paralyse prey. Some molluscs, such as certain cone snails and blue-ringed octopuses, have venomous bites or stings that pose a direct hazard to humans [6].

Shell-bearing molluscs are used as functional foods with notable health benefits. These mollusc species are commercially

exploited and shipped as part of the international trade in shellfish, while other species are harvested, sold, and consumed locally. Many species of molluscs are eaten worldwide, either cooked or raw. These products offer excellent nutritional value and are rich in functional ingredients, including essential omega-3 fatty acids, vitamins, minerals, and proteins. Edible molluscs are harvested from saltwater, freshwater, and land. These are clams, scallops, oysters, octopus, squid and chitons [7]. These are collected for dietary purposes and contribute to a rich chemical diversity, containing beneficial compounds such as proteins, polysaccharides, lipids, polyphenolic pigments, enzymes, and vitamins, which highlights their potential in food and medical applications.

Besides their nutritional uses, marine molluscs secrete various toxins that show promise in drug discovery, particularly in developing anti-microbial, anti-inflammatory, antioxidant, and anti-cancer agents, highlighting their potential pharmaceutical applications. These toxins are also used in traditional medicines globally for various therapeutic uses. These novel bioactive molecules are used to combat emerging diseases and drug-resistant infections and can potentially replace toxic existing medications. This review article explains the various types of toxins synthesised or secreted by molluscs. This also explains the mechanism of action and therapeutic effects of important marine toxins.

Data collection and analysis

For writing this comprehensive research review on marine mollusc toxins, their toxicity, and their therapeutic, pharmacological and biomedical uses. Since a wide variety of toxins are produced, some of which are not always harmful but also have diverse medicinal benefits. Various electronic databases were searched, using keywords, for collection of relevant information, specific terms such as major mollusc toxin, pharmaceutical/medicinal use, bio-accumulated toxins of mollusc and pathogenesis, medical subject heading and keytext words, such as "conotoxin", "saxitoxin", and other mentions toxin names, their toxicity level and also their use in MEDLINE till 2025. For various database searches, the emphasis was on collecting scientific information on "marine toxins" and their global impact on human health, mainly related to invasion, their toxicity levels, immune responses, pathogenesis, symptoms, control measures, and precautions.

Most especially for retrieving all articles about emerging mollusk toxins, electronic bibliographic databases, including PubMed, Scopus, EMBASE, Web of Science, Cochrane Library, SwissProt, and Google Scholar, were thoroughly searched for papers published up to 2025 to compile comprehensive and current information. Backwards citation tracking of a few chosen research articles yielded more pertinent data. Peer-reviewed publications, surveillance reports, outbreak investigations, epidemiological bulletins, and policy documents were among the numerous sources examined.

Types of toxins

Conotoxins

Marine cone snails are the primary source of conotoxins, which are disulfide-rich peptides. These are a wide variety of substances

that resemble venom and are transmitters, receptors, and transporters in the nervous system (Figures 2 and 3). They are highly effective at paralysing prey. Because conotoxins interact with ion channels, they possess significant neurobiological implications. These are pharmacologically significant, useful molecular tools and promising therapeutic candidates for various illnesses, including epilepsy, Parkinson's disease, and Alzheimer's disease [8]. *Conus marmoreus* venom contains thousands of conopeptides. Cone snails inject bioactive venom peptides into their prey using a tubular proboscis. TTX-resistant sodium channels are blocked by conotoxins from *Conus striatus* and *Conus kinoshitai*. These bind to ion channels and voltage-gated receptor channels (Table 1) (Figure 4).

Table 1: Important mollusc toxins.

Sr. No.	Name of spp.	Toxins	Type	Biological effects	References
1	Snail <i>Conus pennaceus</i>	Conotoxins	Neurotoxic peptides: toxins block depolarising	Their potent effects, particularly affecting ion channels and by blocking receptors and causing muscle paralysis	[8]
2	Bivalves (either <i>Crassostrea gigas</i> or <i>Ruditapes philippinarum</i>)	Saxitoxins (STX)	Paralytic Shellfish Poisoning (PSP) Toxins	Lead to nausea, numbness, breathing difficulties, paralysis, and potentially death.	[10]
3	<i>Tetodontidae</i> family such as pufferfish pufferfish	Tetrodotoxin (TTX)	Neurotoxin (venom peptide)	peri-oral paresthesia, headache, difficulty in respiration, nausea and vomiting, blurring of vision, and vertigo	[12]
4	Dinoflagellate genus <i>Dinophysis</i> and <i>Prorocentrum</i> spp.	Okadaic acid (OA)	Diarrhetic Shellfish Poisoning (DSP) Toxins	Resulting in gastrointestinal issues.	[38]
5	Blue mussels (<i>Mytilus edulis</i>)	Domoic acid (DA)	Amnesic Shellfish Poisoning (ASP) Toxins	Causing gastrointestinal and/or neurological symptoms	[11]
6	Greenshells mussels (<i>Perna canaliculus</i>) and oysters (<i>Crassostrea virginica</i>)	Brevetoxins (PbTx)	Neurotoxic Shellfish Poisoning (NSP) Toxins	Causing various neurological symptoms. fatalities	[15]
7	Mussel (<i>Mytilus galloprovincialis</i>)	Yessotoxin (YTX)	Polyether compounds	Cardiotoxin	[20]
8	Bioaccumulate in oysters, mussels and clams	Gymnodimine (GYM)	Cyclic imine (CI) and Lipophilic marine toxin	Affects the neuromuscular system and antagonistic to the Acetylcholine receptor (AChR)	[27]
9	Algal blooms (HABs)	Neosaxitoxin (NEO)	Paralytic shellfish poisoning (PSP)	Block voltage gated sodium channels	[73]
10	Marine dinoflagellates (<i>Gymnodinium</i>) and freshwater cyanobacteria	Gonyautoxin (GTX)	Paralytic shellfish toxins (PSTs)	Neurotoxins	[19]

11	bivalve mollusks, such as fish,	Dinophysistoxin (DTXs)	Lipophilic toxin	Diarrhetic Shellfish Poisoning (DSP)	[34]
12	Marine Dinoflagellates (Dinophysis)	Pectenotoxins (PTXs)	Lipophilic polyether toxin	Diarrhetic Shellfish Poisoning (DSP)	[43]
13	Irish blue mussels (<i>Mytilus edulis</i>)	Azaspiracids (AZAs)	Phycotoxin inhibits ERG (voltage-gated potassium channels)	Nausea, vomiting, diarrhoea, stomach cramps	[74]
14	<i>Mytilus galloprovincialis</i>	Spirolides (SPX)	Cyclic imines (bio-toxin)	Affects the nervous and muscular system as well as AChR	[75]
15	Blue mussels (<i>Mytilus edulis</i>) and Spanish mussels (<i>Mytilus galloprovincialis</i>)	Fatty acid ester of OA (DTX3)	Lipophilic compound hydrolysed in the human gut	Diarrhetic shellfish poisoning toxin	[58]
16	<i>Conus geographus</i>	Conantokin -G (CGX-1007)	Peptide family	Inhibits NMDARs	[68]
17	<i>Conus geographus</i>	Contulakin - G (CGX- 1160)	Peptide toxin	Inhibit the binding of neuropeptides to its receptors.	[68]
18	<i>Conus catus</i>	CVID (AM336)	Omega conotoxin (peptide family)	Effect spinal nerve ligation	[69]
19	<i>Conus marmoreus</i>	MrIA (Xen 2174)	Synthetic peptide, a modified version of conotoxin	Inhibits norepinephrine transporter (NET)	[70]
20	<i>Conus magus</i>	MVIIA (Prialt)	Peptide toxin	Inhibitor of N-type calcium channel	[71]
21	<i>Conus victoriae</i>	Vc1.1 (ACV-1)	Neurotoxin peptide	Inhibit binding of epibatidine to neuronal AChRs	[72]

Toxins classification

Self produced toxins

1. Conotoxins
2. Domoic acid (DA)
3. Brevetoxins (PbTx)
4. Yessotoxin (YTX)
5. Dinophysistoxin (DTXs)
6. Azaspiracids (AZAs)
7. Spirolides (SPX)

Bioaccumulated toxins

1. Saxitoxins (STX)
2. Tetrodotoxin (TTX)
3. Okadaic acid (OA)
4. Gymnodimine (GYM)
5. Neosaxitoxin (NEO)
6. Gonyautoxin (GTX)
7. Pectenotoxins (PTXs)

Figure 1: Shows the classification of marine toxins from different mollusc species.

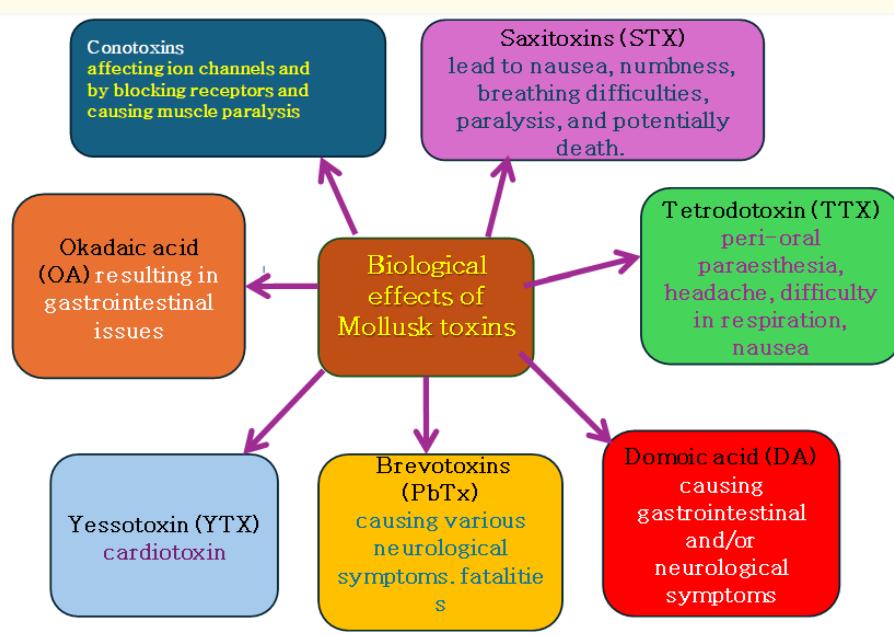


Figure 2: Shows various biological effects of marine toxins.

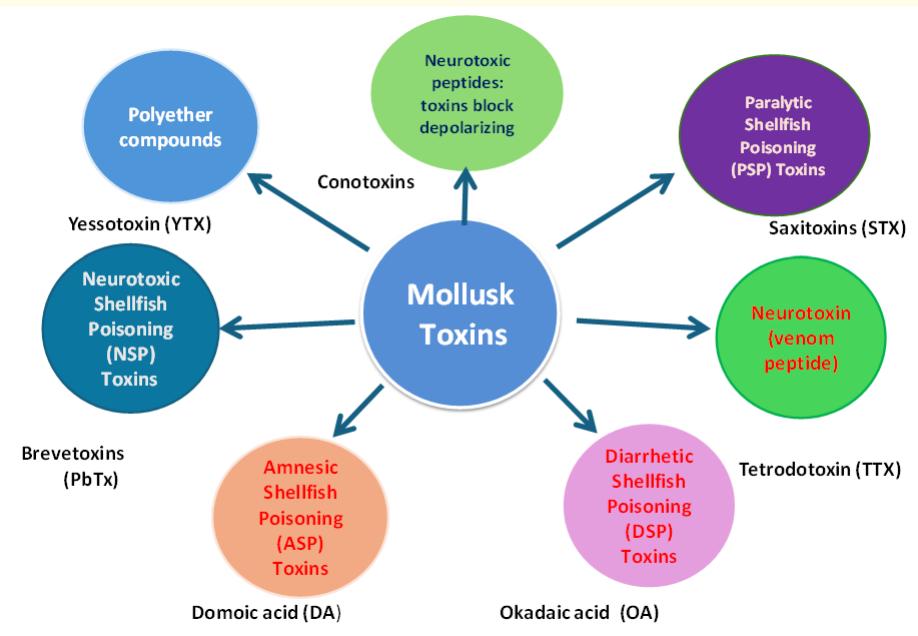


Figure 3: Shows various marine toxins from molluscs.

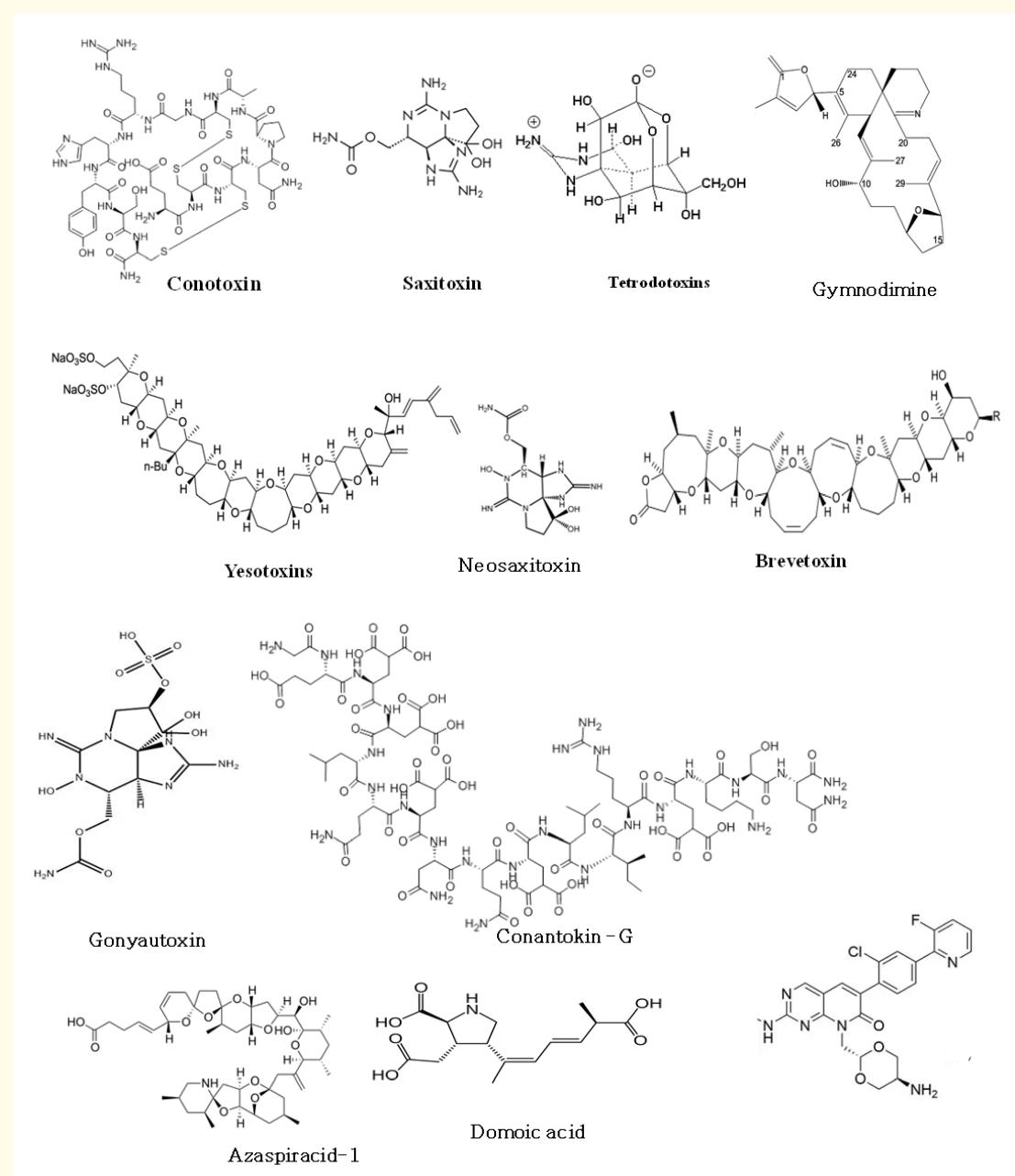


Figure 4: Shows the chemical structures of various mollusc toxins isolated from different species.

Conus consors poison (CcTx) and conotoxin EVIA, specifically target Na^+ channels in axons and nerve terminals without influencing skeletal muscle filaments. Comparable action is detailed in two novel TTX-resistant sodium channel blockers, mu-conotoxins SIIIA and KIIIA. The omega-conotoxins are known to be exceedingly powerful and particular blockers of voltage-sensitive calcium channels. These are moreover included within the discharge of acetylcholine from motor nerve endings [9] (Figure 2 and 3). CcTx is a conotoxin that targets neuronal voltage-gated sodium channels [9]. CcTx, by particularly actuating neuronal voltage-gated sodium channels at the resting film potential, created Na^+ passage into nerve terminals and axons. Conotoxins poison act specifically on axons and motor nerve terminals through a Na^+ -dependent mechanism. Other conotoxins target voltage-gated calcium channels, which control neurotransmitter release at neural connections, or potassium channels, which help repolarise nerve membranes after an electrical impulse has been generated. These small, stable structures could be used to develop computational tools for exploring diverse therapeutic uses (Table 1) [8].

Saxitoxins

Saxitoxin is a potent neurotoxin that blocks sodium channels, which disturbs nerve and muscle function (Figure 4). It mainly comes from contaminated shellfish like mussels, clams, and oysters, causing paralytic shellfish poisoning (PSP) in humans. Symptoms include tingling and numbness, which can lead to respiratory paralysis and death. There is no specific antidote for poisoning, so treatment focuses on supportive care. Saxitoxin is also used in scientific diagnostic tools for food safety and in the development of new anaesthetics [10]. One molecule of saxitoxin binds to a sodium channel, blocking sodium ion flow. The toxin affects potassium channels and also influences calcium channels. Saxitoxin's production begins with the enzyme SxtA, a unique polyketide synthase (Table 1).

Saxitoxin, similar in function, causes paralytic shellfish poisoning (PSP), with symptoms like numbness, muscular weakness, and respiratory failure. It targets voltage-gated sodium channels in nerve and muscle cells, leading to respiratory paralysis and potential death (Figure 2).

Tetrodotoxins

Tetrodotoxin, found in the blue-ringed octopus, paralyses its prey, while in pufferfish, it acts as a pheromone. Tetrodotoxin (TTX) is a neurotoxin derived from marine animals that blocks voltage-dependent sodium channels. It has therapeutic uses in managing cancer-related pain, neuropathic pain, and withdrawal symptoms from heroin and cocaine (Figure 4).

TTX binds to sodium channels in the body, blocking nerve conduction and causing muscle paralysis. Symptoms of TTX poisoning appear 10–45 minutes after ingestion and include perioral numbness, motor paralysis, and respiratory failure, potentially leading to death from respiratory and cardiac collapse. There is no antidote for TTX poisoning, and although TTX does not exhibit genotoxic activity, various TTX analogues have been found in marine animals [11]. There are multiple binding sites on sodium channels that neurotoxins can target to interfere with their function. These sites include Site I, targeted by small-molecule toxins like TTX; Site II, which binds lipid-soluble alkaloids; and Sites III and IV, which interact with peptide toxins. Other sites, such as V and VI, also have specific toxins that bind, and ongoing research is investigating their mechanisms [12] (Figure 2).

Different animals, like frogs and newts, have been found to produce or contain various TTX structures. Tetrodotoxin (TTX) is a potent neurotoxin produced by bacteria such as *Pseudomonas* and *Vibrio*. TTX is also utilised by other animals, such as the blue-ringed octopus, which uses it to paralyse prey. These exist in various isomer forms and related compounds, such as epimers and oxidised versions. Some members of the TTX family include amino acids, reflecting their complexity. The recent discovery of new TTX analogues from newts has spurred hypotheses about how TTX is synthesised in these animals [13]. TTX poses risks to food security and can be deadly, but it also has medical uses (Table 1). TTX may help prevent brain damage after strokes or cardiac arrests. This is used as an anaesthetic and a tumour suppressor drug (Figure 2).

Okadaic acid (OA)

Okadaic acid is a polyether derivative of 38-carbon fatty acid and is implicated as the causative agent of diarrhetic shellfish poi-

soning [13]. Okadaic acid (OA) and dinophysistoxins (DTXs) are lipophilic toxins found in filter-feeding shellfish, leading to gastrointestinal syndrome, diarrhetic shellfish poisoning (DSP) in humans. These toxins are potent protein phosphatase inhibitors that affect cell signalling pathways and cause symptoms such as gastrointestinal distress, nausea, vomiting, abdominal pain, headache, chills, and fever. DSP has no antidote, and chronic exposure to OA may increase the risk of gastrointestinal cancer (Table 1). The oral LD₅₀ of DSP toxins reveals that DTX1 is more toxic than OA [11]. It is a potent tumour promoter that is not an activator of protein kinase C, but is a potent inhibitor of protein phosphatases 1 and 2A (PP1 and PP2A). PP1 and PP2A are the dominant protein phosphatases acting on a wide range of phosphoproteins. Okadaic acid mimics insulin's effect on glucose transport in adipocytes; a serine/threonine phosphorylation event stimulates this process [14] (Figure 2 and 3).

Domoic acid (DA)

Domoic acid (DA) is a potent neurotoxin and excitatory amino acid found in the vertebrate central nervous system and other organs that express glutamate receptors. DA's low bioavailability and rapid elimination in the kidneys cause damage to the brain, causing neurotoxicity through NMDA receptor activation. This toxin is an excitatory amino acid with a high affinity for the propanoic acid receptors (AMPA) and kainite subclasses of glutamate receptors that are present in the central nervous system (CNS) and myocardium [11].

Brevetoxin

Brevetoxins (BTXs) are a family of lipophilic heat-stable cyclic polyether compounds produced by the dinoflagellate *Karenia brevis*. Brevetoxins pass the blood-brain barrier and can cause a transient self-resolving inhalation syndrome characterized by respiratory problems and eye irritation. The discovery of the natural BTX antagonist, brevenal, produced by *K. brevis*, may have therapeutic value in the treatment of NSP. Brevetoxins are respiratory irritants that elicit an inflammatory response, but the persistence of respiratory disturbances after inhalation may involve neuroimmune interactions. These also include nausea, vomiting, abdominal pain, and diarrhoea. NSP is not fatal but rapidly absorbed and widely

distributed to all organs, with the highest concentration found in the liver [15] (Table 1). These also cause nausea and vomiting, paresthesias of the mouth, lips, and tongue, as well as distal paresthesias, ataxia, slurred speech, and dizziness [15]. Brevetoxins induce the Na⁺ channel to open and abolish rapid inactivation, leading to repetitive action potentials and membrane depolarization. Ciguatoxin and Goniopora toxins share similar physiologic effects, whereas pyrethroids exhibit delayed inactivation. Brevetoxins are used as a stroke therapy due to potential neuroinflammation [15] (Figure 2).

These toxins induce bronchoconstriction in sheep and negatively affect airway function; they may also represent potential therapeutic targets for mucociliary dysfunction [16]. PbTx are genotoxic substances. PbTx could induce chromosomal aberrations and inhibit cellular proliferation in CHO-K1-BH4 cells, and PbTx are potent inducers of CHO-K1-BH4 chromosome damage [17]. PbTx-6 acts via a classic AhR-mediated mechanism to evoke gene expression changes [18]. Brevetoxins are produced by the unarmored marine dinoflagellate *Gymnodinium breve* (*Prychodiscus brevis*), specifically toxins. *G. breve* is a unicellular alga which is the causative organism of red tide resulting from blooms of this toxic dinoflagellate [19]. PbTx-6 acts via a classic AhR-mediated mechanism to evoke gene expression changes [18].

Yessotoxin (YTX)

Yessotoxin (YTX) is a marine polyether toxin. YTXs have been associated with diarrhetic shellfish poisoning (DSP). YTXs do not cause either diarrhoea or inhibition of protein phosphatases. YTX, the precise mechanism of action is currently unknown. Abundance of YTXs in both bivalves and dinoflagellates [20]. Produced by phytoplanktonic dinoflagellates, which accumulate in filter-feeding organisms, of lipophilic toxins [21]. Consumption of seafood contaminated by algal toxins, mainly due to paralytic shellfish poisoning (PSP), neurotoxic shellfish poisoning (NSP), amnesic shellfish poisoning (ASP), diarrheic shellfish poisoning (DSP), ciguatera fish poisoning (CFP) and azaspiracid shellfish poisoning (ASP) [21]. Yessotoxin reduced Alzheimer's markers while activating protein kinase C pathways. Yessotoxin showed potential benefits against Alzheimer's disease markers in a specific cellular model [23]. YTXs

impact the heart and liver, causing cytotoxic effects and damage. YTXs modulate calcium levels in human lymphocytes and may cause neuronal damage in the brain [24] (Table 1). Toxins reduce β -amyloid plaques and tau hyperphosphorylation, thereby preventing Alzheimer's disease progression [25] (Figure 2).

Yessotoxin (YTX) is a marine toxin produced by *Protoceratium*. It has a unique ladder-shaped structure composed of ether rings and a long side chain bearing sulfate groups. YTX can cause cell death in various cell types and enhances the activity of phosphodiesterases, which help regulate signaling in cells. Its effects vary based on the cell line and treatment time, including changes in calcium and cAMP levels, and damaging genetic material, which could be significant for tumor progression. YTX also impacts immune function by reducing phagocytic activity and altering T-cell receptor expression. Additionally, YTX may have potential uses in treating Alzheimer's disease and metabolic disorders related to lipids and glucose [26].

Gymnodimines and spirolides

Gymnodimine (GYM), an algal toxin identified as a cyclic imine toxin with an imino nitrogen attached to the loop-coil. The imine functional group is the toxic moiety of the toxin. GYM has a low oral toxicity, but its acute lethal toxicity is of intraperitoneal injection [27]. Gymnodimines and spirolides are cyclic imine phycotoxins and known antagonists of nicotinic acetylcholine receptors (nAChRs) intracellular calcium levels ($[Ca]$) of GYM A or SPX 1 induced an increase in $[Ca]$, mediated by acetylcholine receptors (AChRs) and inhibited further activation of AChRs by acetylcholine (ACh) [28]. Gymnodimine D (GYM D), 16-desmethyl gymnodimine D (16-desmethyl GYM D), and twotetrodotoxin analogues [29]. The growth and gymnodimine A (GYM-A) production of *K. selliformis*. The GYM-A production levels of *K. selliformis* increased. The growth of *K. selliformis* was significantly inhibited by the deficiency in N or P [30] (Table 1). The absence of the triketal ring system in GYM A may provide the basis for a selective activation of mAChRs [28]. Gymnodimines block muscle nicotinic receptors without directly affecting elicited twitches [31]. PnTX G levels are highest; seasonality confirmed for GYM [32] (Figure 2).

Neosaxitoxin (NEO)

Neosaxitoxin (NEO) and gonyautoxin V (GTX5) are the predominant toxins in cellular content, with saxitoxin (STX), GTX6, and de-carbamoylsaxitoxin (dcSTX) making up the rest. Toxin content is stable at salinities of 24% or higher but triples at 20%. It decreases by half and chlorophyll content triples with reduced light intensity. Changes in temperature and light intensity affect toxin content. At 22°C, NEO is 65% while at 34°C, GTX5 increases to 55%. When light intensity drops [33].

Neosaxitoxin (NeoSTX) and related paralytic shellfish toxins have been successfully utilised as local anaesthetics and muscle relaxants for the treatment of various ailments. The primary action of toxins blocking voltage-gated sodium channels is achieved with compounds such as TTX, lidocaine, or their derivatives. Toxins such as saxitoxin and gonyautoxin inhibit mammalian Na (+) channels at varying concentrations. These toxins were tested for toxicity in neuroblastoma cells. Na channels are crucial for high-affinity block by tetrodotoxin (TTX) and saxitoxin (STX) in different isoforms. In mammalian heart Na channels, cysteine substitution reduces TTX/STX affinity and increases sensitivity to Zn²⁺ and Cd²⁺. Paralytic shellfish toxins (PSTs) are natural toxins found in marine bivalves that accumulate in various tissues. Components in the kidney were dominated by high- (NEO) and saxitoxin (STX), suggesting that the kidney is a primary organ for the transformation of PSTs [34] (Figure 3) (Table 1).

The Na channel is an essential determinant of high-affinity block by tetrodotoxin (TTX) and saxitoxin (STX) in Na channel isoforms. In mammalian heart Na channels, this residue is substituted with cysteine, resulting in low affinity for TTX/STX and enhanced sensitivity to block by Zn²⁺ and Cd²⁺. Paralytic shellfish toxins (PSTs) are a group of natural toxic substances often found in marine bivalves. Accumulation, anatomical distribution, biotransformation and depuration of PSTs in different tissues of bivalves, PSTs in six different tissues, namely gill, mantle, gonad, adductor muscle, kidney, and digestive gland, Components in the kidney were dominated by high-potency neosaxitoxin (NEO) and saxitoxin (STX), sug-

gesting that the kidney is a primary organ for the transformation of PSTs (Liu Y, *et al.* 2020) [34]. NeoSTX effect on lipopolysaccharide (LPS)-activated macrophages. NeoSTX (1 μ M) significantly inhibited the release of NO, TNF- α , and expression of iNOS, IL-1 β , and TNF- α in LPS-activated macrophages [35] (Figure 2).

Neosaxitoxin (NeoSTX) blocks Na⁺ channels in neurons. NeoSTX in the ovary blocks sympathetic nerves and PCO induced by oestradiol valerate (EV). It decreases NA levels, increases the number of corpora lutea, and reduces testosterone levels [36].

Gonyautoxin (GTX)

Gonyautoxins (GTX) are a few similar toxic molecules produced naturally by algae. They are part of the group of saxitoxins, a large group of neurotoxins along with a molecule that is also referred to as saxitoxin (STX), neosaxitoxin (NSTX) and decarbamoylsaxitoxin (dcSTX). Currently, eight molecules are assigned to the group of gonyautoxins, known as gonyautoxin 1 (GTX-1) to gonyautoxin 8 (GTX-8) (Table 1). Ingestion of gonyautoxins through the consumption of molluscs contaminated by toxic algae can cause a human illness called paralytic shellfish poisoning (PSP). Gonyautoxins are naturally produced by several marine dinoflagellate species (*Alexandrium* sp., *Gonyaulax* sp., *Protogonyaulax* sp.) (Figure 2).

Dinophysistoxin

Dinophysistoxin-1 (DTX-1) has the most potent toxicity in DSTs (Li Z, *et al.* 2020). In filter-feeding bivalves, okadaic acid (OA) and its analogues, dinophysistoxin 1 (DTX1) and dinophysistoxin 2 (DTX2), accumulate due to their lipophilicity and heat stability. DTX1 exhibits greater oral toxicity than OA and DTX2, as it can damage Caco-2 monolayers, whereas OA and DTX2 do not significantly harm them [37]. Okadaic acid (OA), dinophysistoxin-1 (DTX-1), and dinophysistoxin-2 (DTX-2) increase adult mortality from 24 hours post-exposure. DTX-2 notably increases reactive oxygen species (ROS) production, while each toxin affects antioxidant enzyme activity differently [38] (Table 1). These toxins inhibit specific protein phosphatases, which affects the intestines. DTX-1 is more toxic than OA and DTX-2, impacting particular signalling pathways and DNA repair regulation [39]. Regarding DTX-1, among the 12 selected genes, only three (rfc1, rfc4, and rpa1), which encode proteins involved in DNA repair and replication, showed significant

changes in expression [39]. Dinophysistoxin-1 (DTX1) and pectenotoxin-2 (PTX2) exclusively accumulated in the digestive gland, with only low levels being detected in the gills, mantles, gonads, and adductor muscles [40] (Figure 2).

Pectenotoxins (PTXs)

Pectenotoxin (PTX)-group toxins are polyether-lactone toxins produced only by *Dinophysis* species. They are found in bivalve molluscs, such as oysters and mussels, and are heat-stable, but can be destroyed in strong basic conditions. Pectenotoxins (PTXs) are produced by *Dinophysis* spp., along with okadaic acid, dinophysistoxin 1, and dinophysistoxin 2. The okadaic acid group toxins cause diarrhetic shellfish poisoning (DSP) and are therefore regulated as pectenotoxins within the DSP regulations. As pectenotoxins and okadaic acid have different mechanisms of action, meaning that their toxicities are not additive, pectenotoxins have very low oral toxicity [41]. Pectenotoxins (PTXs) are a group of toxins associated with diarrhetic shellfish poisoning (DSP) and isolated from DSP toxin-producing dinoflagellate algae [42] (Table 1). The PTXs are polyether lactones, some of which are hepatotoxic to mice by intraperitoneal injection. Filter-feeding bivalves retain toxic planktonic microalgae and other suspended matter, acting as vectors of the toxins. Bivalves contaminated with DTXs pose a threat to public health [43] (Figure 2 and 3).

Anticancer activity

Marine molluscs also possess anticancer bioactive compounds which are highly effective against chemotherapy-resistant cancer cells. Notable mollusc-derived compounds include Dolastatin 10 and Dolastatin 15 from *Dolabella auricularia*, Kahalalide F from *Elysia rufescens*, and others, such as Keenamide A and Spisulosine ES-285, which demonstrate various mechanisms of action, including apoptosis induction and metastasis inhibition. Other significant compounds identified include Zalypsins, Aplyronine A, Jorumycin, and Bursatellanin [44-47]. The paralytic shellfish toxin, saxitoxin, enters the cytoplasm and induces apoptosis of oyster immune cells through a caspase-dependent pathway (Table 1) (Figure 2 and 3).

Conus magus, a carnivorous cone snail, and three dolastatin derivatives sourced initially from the tissue of the sea hare *Dolabella*

auricularia: Brentuximab vedotin and Polatuzumab vedotin for the treatment of hematologic cancers (e.g., Hodgkin's lymphoma) and Enfortumab vedotin for urothelial cancer.

Anti-proliferative activity

Mytilus edulis Shellfish are waste components, but these have shown strong potential as anti-proliferative agents. These were found to be active against cancerous cell lines, including A549, BT549, HCT15, and PC3 [48]. More specifically, glycosaminoglycan-like polysaccharides derived from the marine mollusc *Mytilus edulis* showed antiproliferative activity [49] (Table 1). Both dolastatins and kahalalides, compounds which are effective against cancer, are derived from marine molluscs. These showed high antiproliferative potency against cancer cells *in vitro*. These act via nonapoptotic signalling pathways [50] (Figure 2 and 3).

Sea cucumber: *Pearsonothuria graeffei* (Pg), lollyfish: *Holothuria atra* (Ha), and sea hare: *Aplysia dactylomela* (Ad), secrete bioactive components. These were found to induce G₀/G₁ cell cycle arrest for HepG2 cells. These induce apoptosis in the HepG2 cell line at the pre-G1 phase, supplemented by their anticancer activity via proapoptotic protein Bax, caspase-3, and cleavage of PARP, and antiapoptotic protein Bcl-2 downturn [51].

Mytilus edulis Shellfish waste components are used as by-products. These contain high-value products with strong potential as anti-proliferative agents and promising active ingredients in functional foods. Glycosaminoglycan-like polysaccharides derived from Marine Molluscs, *Mytilus edulis*, showed antiproliferative activity [52]. Shellfish waste components contain significant levels of high-quality protein. These were found to be active against cancerous cell lines A549, BT549, HCT15, and PC3 [48]. Dolastatins and kahalalides, compounds which are effective against cancer, are derived from marine molluscs. These showed high antiproliferative potency against cancer cells *in vitro*, with preferential inhibition of cancer cell proliferation over normal cells, a mechanism of action via non-apoptotic signalling pathways, circumvention of the multidrug resistance phenotype, and high activity *in vivo*, among other properties [43]. In blue mussel (*Mytilus edulis*) by-products, shellfish waste components (protein) possess anti-proliferative agents against PC3 cell lines, HCT15 and 81% for BT549 cell lines [48].

The polysaccharide from the common cockle (*Cerastoderma edule*) exhibits anti-proliferative activity against chronic myelogenous leukaemia and relapsed acute lymphoblastic leukaemia cell lines. This sulfated polysaccharide exhibits antiproliferative activity against chronic myelogenous leukaemia and relapsed acute lymphoblastic leukaemia cell lines. This activity is due to the presence of glycosaminoglycans, a new heparan sulfate/heparin-like polysaccharide with potent anticancer effects [49] (Figure 2 and 3).

Sea cucumber: *Pearsonothuria graeffei* (Pg), lollyfish: *Holothuria atra* (Ha), and sea hare: *Aplysia dactylomela* (Ad), secrete Bioactive constituents found to induce G₀/G₁ cell cycle arrest for HepG2 cells side by side with their inhibition of CDK2 on all three cell lines while all extracts were also showed to induce apoptosis in HepG2 cell line at pre-G₁ phase supplemented by their anticancer activity via proapoptotic protein Bax, caspase-3, and cleavage PARP increase, and antiapoptotic protein Bcl-2 downturn [51].

Anti-angiogenic activity

The methanolic extract of *Euchelus asper* has shown significant anti-angiogenic activity, particularly by reducing the number of branching points in blood vessels in chick chorioallantoic membrane (CAM) models. This extract also exhibits moderate cytotoxicity against non-small cell lung carcinoma (A549) cell lines, affecting cell proliferation and the expression of matrix metalloproteinases (MMPs) involved in angiogenesis [53].

A similar experiment in the chick chorio-allantoic membrane assay was conducted on four methanolic extracts of marine molluscan species, *viz*—*Meretrix meretrix*, *Meretrix casta*, *Telescopium telescopium* and *Bursa crumena* methanolic extracts. Only the methanolic extract of *Telescopium telescopium* exhibited the most noticeable inhibition (42.58%) of the corneal neovascularisation in rats [54].

Anti-inflammatory activity

Conotoxins are a family of highly toxic neurotoxins composed of cysteine-rich peptides produced by marine cone snails. These neurotoxic peptides (α -conotoxins) from molluscs of the *Conus* genus showed anti-inflammatory activities associated with cholinergic transmission and have shown analgesic effects in the case of chemotherapy-induced neuropathic pain [55]. Most α -conotoxins bind to $\alpha 3\beta 2$, $\alpha 1\gamma\delta$, and $\alpha 7$ subtypes of human nAChRs [56].

Inflammation is a biological response associated with oxidative stress and often leads to pain requiring medical treatment. Certain marine molluscs, such as *Bursatella leachi* and *Aplysia dactylomela*, contain unique compounds, including Ziconotide and 6-bromoisoat, that exhibit significant analgesic effects. Ziconotide is derived from *Conus geographus* and *Conus magus*, while 6-bromoisoat comes from *Dicathais orbita*. Additional compounds, such as Scalarial, Punaglandin, and Dactyloiterpenol acetate, also exhibit both anti-inflammatory and analgesic properties. Other notable compounds include Malyngamide S from *Bursatella leachii*, disesteroid from *Babylonia spirata*, and derivatives from *Crassostrea madrasensis* and *Perna viridis*, all of which demonstrate similar effects. Furthermore, tetrodotoxins from bivalve molluscs and other substances, such as 1-methyl-isoguanosine and a polybrominated diphenyl ether from *Aplysia dactylomela*, also exhibit analgesic properties [57] (Figure 2 and 3).

Anti-oxidant activity

Nutraceutical and Medicinal Importance of *Marine molluscs* [58]. Notable compounds with antioxidant properties include 3,5-dihydroxy-4-methoxybenzyl alcohol (40), isolated from *Crassostrea gigas*, as well as Chlorophyllonic acid A methyl ester (41) and Chlorophyllone A (42), derived from *Ruditapes philippinarum* (Figure 2 and 3).

Anti-allergic activity

Marine Organisms that live inside marine molluscs possess potent anti-allergic compounds [59].

Proteolytic activity

Rapanavenosa, V., (1846). *Mytilus galloprovincialis*, Lamarck, 1819 and *Donax trunculus*, Linnaeus, 1758. venoms and tissues contain proteases and exhibit significant proteolytic activity. These proteolytic enzymes play crucial roles in biological processes, including prey envenomation, tissue degradation, and venom bio-synthesis and maturation [60] (Figure 4) (Table 1).

Antidiabetic activity

Marine cephalopods possess bioactive compounds that exhibit strong anti-diabetic and anti-inflammatory activities. The ethyl acetate-methanol extracts of *C. indicus* exhibited significantly greater

($p < 0.05$) cyclooxygenase inhibition activities ($IC90 \sim 1$ mg/mL, respectively) compared to other cephalopod species. The solvent extracts derived from the members of the order Octopoda demonstrated fairly good α -amylase inhibitory activity ($IC90 \leq 2.5$ mg/mL). Dipeptidyl peptidase-4 inhibitory activity of the ethyl acetate-methanol extract of *C. indicus* was found to be significantly greater ($IC50$ 2.51 mg/mL) than other species of cephalopods ($IC50$ 3.4-5.4 mg/mL; $p < 0.05$). Similar activity is reported in *Abelmoschus esculentus* [61] (Table 1) (Figure 2 and 3).

Antimicrobial activity

Molluscs are invertebrates that live in various habitats and protect themselves from predators, parasites, and microbial infections. Research has been conducted on numerous extracts from various molluscs, including sea snails and cephalopods, which have shown activity similar to that of novel antibiotics. These antimicrobial agents are very high in demand in the pharmaceutical sector due to the toxicity of existing drugs and the development of resistance. These are also used in traditional medicine for treating human diseases. These compounds act through various mechanisms, including disrupting microbial cell membranes, inhibiting vital enzymes, and generating oxidative stress in bacterial cells. These could be used as substitutes for antibiotics against which drug-resistant bacterial strains of *S. aureus* [62] are resistant. These compounds have also shown vigorous antimicrobial activity against Gram-positive *Streptococcus epidermidis* and Gram-negative *Escherichia coli* (Table 1) (Figure 2 and 3).

Molluscs also synthesise antimicrobial peptides (AMPs) that exhibit antimicrobial activity against a broad range of pathogens. *N. versicolor*-derived peptides represent new AMP sequences and have the potential to be optimized and developed into antibiotic alternatives against bacterial and fungal infections [63]. Additionally, specific antimicrobial peptides derived from marine molluscs demonstrate essential roles in immune defense, showcasing their potential as novel pharmaceutical agents. Pom-1 from *P. poeyana* showed high activity against the Gram-negative bacteria *Pseudomonas aeruginosa* and moderate activity against *Klebsiella pneumoniae* and *Listeria monocytogenes* (González Gar) [64]. Similar antimicrobial activity is reported in methanol, ethanol and acetone tissue extracts of two molluscs, *Pinctada radiata* (*P. radiata*) and

Brachidonta variabilis (*B. variabilis*). These were also found to be active against five nosocomial bacteria, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*. Anti-microbial peptides (AMPs) from bivalves are defensins and myticins, demonstrating a broad immune defence capability. These compounds inhibit essential bacterial enzymes, such as DNA gyrase and RNA polymerase, which are crucial for microbial growth and transcription. These compounds, including glycoproteins, peptides, and indole alkaloids, can also induce oxidative stress in bacteria by producing reactive oxygen species (ROS).

Anti-parasitic activity

The shell powder of *Donax faba*, a type of mollusc, was found active against human and fish pathogens and parasites [65] (Figure 2).

Anthelmintic

Marine molluscs, particularly those like *Holothuria polii*, have shown significant anti-helminthic activity. These molluscs contain bioactive compounds that have been found to induce rapid paralysis and death of worms, outperforming traditional anthelmintics like albendazole. *Allolobophora caliginosa*, revealing their effectiveness in treating helminthic infections [66].

Treatments for cardiovascular diseases (CVDs)

Mollusc toxin peptides are also used to treat cardiovascular diseases (CVDs). For example, conotoxins from marine snails inhibit voltage-gated calcium channels, indicating their potential as anti-hypertensive agents. Molluscan Compounds Provide Drug Leads for the Treatment and Prevention of Respiratory Disease (Figure 4).

Wound healing

Amino Acids from *Mytilus galloprovincialis* (L.) and *Rapana venosa* Molluscs Accelerate Skin Wound Healing via Enhancement of Dermal and Epidermal. Molluscs could be a valuable source of natural compounds for wound healing and other health applications. Anti-inflammatory compounds in molluscan medicines provide

leads for novel anti-inflammatory drugs in the future [67]. Shell powder from the marine mollusc *Cypraea moneta* showed significant antipyretic effects and effective wound healing properties.

Conclusion

Mollusc toxins selectively activate various ion channels and cause neurotransmitter release and neuronal excitability. Ciclonotide, a synthetic conotoxin, blocks calcium channels in the spinal cord, thereby inhibiting neurotransmitter release. These drugs are currently in preclinical or clinical trials for conditions such as epilepsy, Parkinson's disease, and cancer. Various toxin templates from molluscs can be used to develop new medicines that may be highly potent and have clear actions on neurological targets. These toxins can be transformed into drugs which could be used to treat chronic pain, epilepsy, and Parkinson's disease. Many species of molluscs are used in traditional medicines and have been utilized to treat illnesses such as cancer and inflammation. Researchers are exploring these molluscs for their bioactive compounds, which show potential as antimicrobial, anti-inflammatory, antioxidant, and anti-cancer agents. These could be used as natural medicinal drugs. Molluscs could become a natural source of modern drugs, especially for cancer treatment. Further research on their medicinal and nutraceutical potential could improve people's health and advance medical science. Additionally, further investigation is required to understand their modes of action, the mechanism of receptor binding and potential adverse effects.

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Conflict of Interest

The authors declare no conflict of interest regarding the publication of this paper.

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