ELSEVIER

Paracelsus' legacy in the faunal realm: Drugs deriving from animal toxins

Thomas Fischer, Rainer Riedl *

Center of Organic and Medicinal Chemistry, Institute of Chemistry and Biotechnology, Zurich University of Applied Sciences ZHAW, Einsiedlerstrasse 31, 8820 Wädenswil, Switzerland

Given the vast number of venomous and poisonous animals, it is surprising that only relatively few animal-derived toxins have been explored and made their way into marketed drugs or are being investigated in ongoing clinical trials. In this review, we highlight marketed drugs deriving from animal toxins as well as ongoing clinical trials and preclinical investigations in the field. We emphasize that more attention should be paid to the rich supply of candidates that nature provides as valuable starting points for addressing serious unmet medical needs.

Keywords: Animal toxins; Drug discovery; Natural products; Venom; Medicinal chemistry; Peptides

Introduction

Over the course of millions of years of evolution, animals have adapted weapons to defend themselves against predators or to capture their prey. One effective strategy is the production of toxic substances in tissues or organs such as venom glands, which are introduced into the prey with a specialized apparatus or by ingestion.[1] Toxins from poisonous and venomous animals such as annelids, cnidarians, echinoderms, mollusks, arthropods, and vertebrates, have significant effects on prey organisms because of long periods of evolutionary arms race in the predator–prey relationship. Components of these poisons, such as inorganic salts and small organic molecules, as well as peptides and enzymes, display a range of pharmacological activities because their biological targets, such as ion-channels and cardiovascular targets, have important roles in human disease.[2–4] Therefore, toxin-derived compounds are of interest in pharmaceutical research and several venoms, or components thereof, have already been used for the design of novel therapeutic agents.[5–9]

Animal toxin-derived compounds are on the market for a variety of diseases, in ongoing clinical trials, or in preclinical investigations (Fig. 1). With ~ 100 million annual prescriptions in the USA alone, between 2008 and 2018, the angiotensin-converting enzyme (ACE)-inhibiting hypertensive drug lisinopril (derived from the poison of the Brazilian viper, *Bothrops jararaca*) is among the top-selling drugs worldwide. With a compound annual growth rate for ACE inhibitors projected at 0.8% for the period of 2018–2026, it remains high selling for the foreseeable future.[10,11] This success story of a venom-derived drug raises the expectation for other animal-derived drugs to be developed. Here, we outline past successes as well as ongoing research in the search for animal toxin-based drugs to encourage scientists to make use of nature's treasure box for future drug discovery projects. Table 1.

Snakes

Snakes produce significantly higher amounts of venom than other animals, making it easier to handle. Therefore, snake venom-derived drugs pioneered the field of animal toxin-based drugs in modern medicine.

Captopril was the first marketed drug derived from snake venom. It was developed at Bristol-Myers Squibb during the 1980s as an ACE inhibitor for the treatment of hypertension.[12,13] Consecutive development led to enalapril, ramipril, and lisinopril (Fig. 2), which also target ACE. Lisinopril (Prinivil®, Zestril®), the most successful member of this set of drugs, was developed at

* *Corresponding author.Riedl, R. (rainer.riedl@zhaw.ch)*

https://doi.org/10.1016/j.drudis.2021.10.003

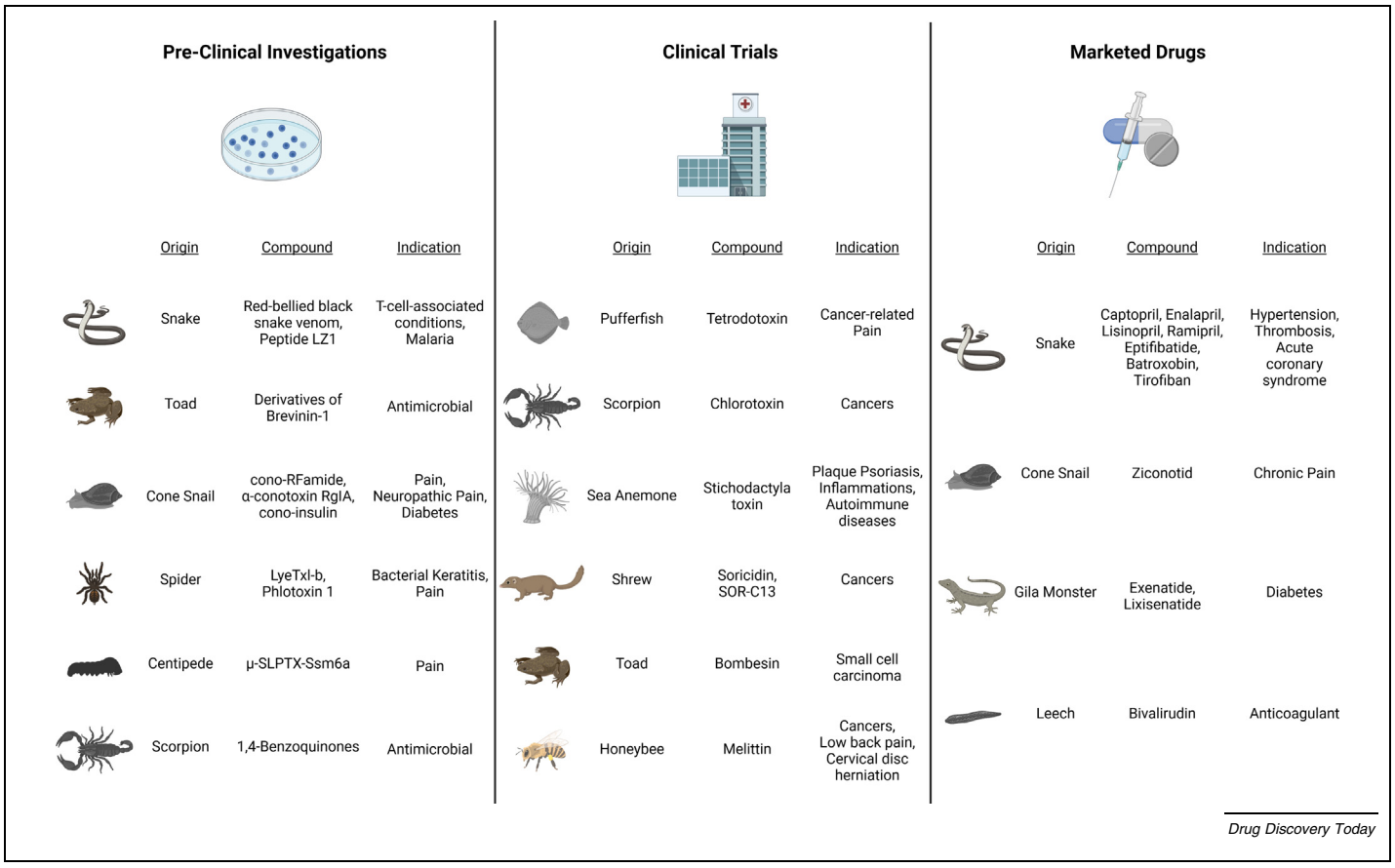

FIGURE 1
Examples of animal toxin-derived compounds of pharmaceutical relevance. Figure created with BioRender (BioRender.com).

Merck; however, because they were already selling enalapril, it was licensed to Astra Zeneca, who marketed the drug with tremendous success. Not only did it turn out to be a blockbuster with annual sales of more than US$1 billion, but it also remains one of the top three most-prescribed drugs worldwide.[10] Three more marketed drugs [tirofiban (Aggrastat®), batroxobin (Defibrase®), and eptifibatide (Integrilin®)] can be traced back to snake venom, and are approved antiplatelet drugs for the inhibition of thrombosis.[14] Except for batroxobin, which is a serine protease that contains 231 amino acid residues, snake venom-derived marketed drugs are generally small synthetic molecules. In addition to these marketed drugs, preclinical research is evaluating the use of snake venom and derivatives thereof for the treatment of other diseases. For example, the venom of the red-bellied black snake *Pseudechis porphyriacus* shows immunosuppressive potential, and a peptide, deriving from a snake cathelicidin, displays antimalarial activity both *in vitro* and *in vivo*.[15,16]

Cone snails

Numerous marine organisms produce toxins either for protection or to hunt.[17] Ziconotide (Prialt®, Fig. 2) is a synthetically accessible 25-amino acid cyclic peptide, originating from *Conus magus*.[18] The peptide is stabilized by three intramolecular sulfide bridges and used unmodified in pain therapy. Ziconotide was developed by Neurex (now Perrigo) and was approved by the US Food and Drug Administration (FDA) in 2004 and the European Medicines Agency (EMA) in 2005 as an analgesic and is marketed by TerSera® therapeutics under its brand name Prialt®.[19,20] In its function as an *N*-type voltage-gated calcium channel blocker, ziconotide inhibits the release of nociceptive neurochemicals, resulting in pain relief. Compared with morphine, ziconotide is three orders of magnitude more potent for the treatment of chronic pain, whereas it lacks tolerance development and the threat of respiratory depression.[21] Owing to the low efficacy of ziconotide when administered orally or intravenously, it must be administered intrathecally into the spinal fluid. In addition to ziconotide, preclinical research is ongoing with a peptide found in the venom of *Conus textile* that targets the proton-gated ion channel ASIC3 and enhances acid-induced muscle pain in mice after injection.[22] Furthermore, the α-conotoxin RgIA from *Conus regius* was found to be a subtype specific inhibitor of the α9 and α10 nicotinic acetylcholine receptors.[23,24] The 13-residue peptide, as well as derivatives thereof, are being investigated for their analgesic potency.[25,26] Furthermore, a specialized cono-insulin, identified in the venom of *Conus geographus*, is under investigation for the treatment of diabetes.[27,28]

Gila monster

Within the lizards, the venomous Gila monster has a bite that is both painful and potentially fatal to humans. One of the components of its venom is exendin-4, which shares 53% sequence

TABLE 1

Examples of animal venoms and derivatives thereof in different development stages.

Drug name	Stage	Origin organism	Indication	Molecular mechanism	Refs
Captopril (Capoten®)	Marketed	*Bothrops jararaca*	Hypertension	ACE inhibitor	
Enalapril (Vasotec®)	Marketed	*B. jararaca*	Hypertension	ACE inhibitor	
Lisinopril (Prinivil®, Zestril®)	Marketed	*B. jararaca*	Hypertension	ACE inhibitor	
Ramipril	Marketed	*B. jararaca*	Hypertension	ACE inhibitor	
Eptifibatide (Integrilin®)	Marketed	*Sistrurus miliarus barbouri*	Thrombosis	Glycoprotein IIb/IIIa inhibitor	
Tirofiban (Aggrastat®)	Marketed	*Echis ocellatus*	Acute coronary syndrome	Glycoprotein IIb/IIIa inhibitor	
Batroxobin, reptilase (Defibrase®)	Marketed	*Bothrops moojeni*	Thrombosis	Serine protease	
Ziconotide (Prialt®)	Marketed	*Conus magnus*	Chronic pain	N-type voltage-gated calcium channel blocker	
Exenatide (Byetta®, Bydureon®)	Marketed	*Heloderma suspectum*	Diabetes	Glucagon-like peptide-1 receptor agonist	
Lixisenatide (Lyxumia®, Adlyxin®)	Marketed	*H. suspectum*	Diabetes	Glucagon-like peptide-1 receptor agonist	
Bivalirudin (Angiox®)	Marketed	*Hirudo medicinalis*	Anticoagulant	Direct thrombin inhibitor	
Tetrodotoxin (Halneuron®)	Clinical trials	*Pseudoalteromonas*; *Pseudomonas vibrio*	Cancer-related pain	Voltage-gated sodium channel inhibitor	
Chlorotoxin (tozuleristide)	Clinical trials	*Leiurus quinquestriatus*	Cancers; NCT04214392; NCT03579602	Chloride channels	
Stichodactyla toxin (dalazatide)	Clinical trials	*Stichodactyla helianthus*	Plaque psoriasis; NCT02446340; NCT02435342; inflammation; autoimmune disease	Voltage-gated potassium channel inhibitor	
Soricidin and SOR-C13	Clinical trials	*Blarina brevicauda*	Cancers; NCT01578564	Sodium channel blocker, TRPV6 calcium channel blocker	
Bombesin	Clinical trials	*Bombina bombina*	Marker of small cell carcinoma; NCT02440308; NCT02488070	G-protein-coupled receptor activator	
Melittin	Clinical trials	*Apis mellifera*	Cancers; low back pain; NCT03879447; cervical disc herniation; NCT03959098	No data available	
LyeTxI-b	Preclinical	*Lycosa erythrognatha*	Bacterial keratitis; antibiotic	No data available	89,90
N-terminal derivatives of a novel brevinin-1 peptide	Preclinical	*Odorrana schmackeri*	Antimicrobial	No data available	110
Venom of red-bellied black snake	Preclinical	*Pseudechis porphyriacus*	T cell-associated conditions	Inhibition of interleukin-2 secretion and tumor necrosis factor	15
Peptide LZ1 derived from snake cathelicidin	Preclinical	*Bungarus fasciatus*	Malaria	No data available	16
Phlotoxin 1 and synthetic variants	Preclinical	*Phlogiellus genus*	Pain	Voltage-gated sodium channel blocker	111
Antiviral peptide	Preclinical	*Alopecosa nagpag*	Viruses	NS2B–NS3 protease inhibitor	112
Mastoparan-L	Preclinical	*Vespula lewisii*	Antimicrobial; immunomodulator	Permeabilizing bacterial outer membrane	113
1,4-Benzoquinones	Preclinical	*Diplocentrus melici*	Antimicrobial	No data available	53
Cono-RFamide	Preclinical	*Conus textile*	Pain	Acid-sensing ion channel 3	22
α-Conotoxin RgIA	Preclinical	*Conus regius*	Neuropathic pain	α9α10 nicotinic acetylcholine receptor blocker	23,24
Cono-insulin	Preclinical	*Conus geographus*	Diabetes	Glucose transporter type 4	27
Double-knot spider-venom peptide	Preclinical	*Hadronyche infensa*	Stroke	Acid-sensing ion channel 1a inhibitor	88
μ-SLPTX-Ssm6a	Preclinical	*Scolopendra subspinipes mutilans*	Pain	Voltage-gated sodium channel 1.7 inhibitor	103
Honeybee venom and melittin	Preclinical	*A. mellifera*	Triple-negative breast cancer	No data available	77

identity with glucagon-like peptide-1 and, therefore, could find use in the regulation of insulin and glucagon metabolism in humans.[29] The synthetically approachable version of exendin-4 is the 39-amino acid peptide exenatide (Byetta®, Bydureon®), which was developed by Amylin Pharmaceuticals and is now commercialized by Astra Zeneca. Exenatide is used for the treatment of type 2 diabetes mellitus (T2DM) and was approved by the FDA in 2005 and by the EMA in 2006.[30,31] It is prescribed more than 1.3 million times per year in the USA alone.[32] Its common application is via subcutaneous injection in the abdomen, twice daily for Byetta® and once weekly for Bydureon®. Chemical modification of exendin-4, by omitting a proline and adding six lysine residues, resulted in the 44-amino acid peptide lixisenatide (Adlyxin®, Lyxumia®, Fig. 2), which was developed at Zealand

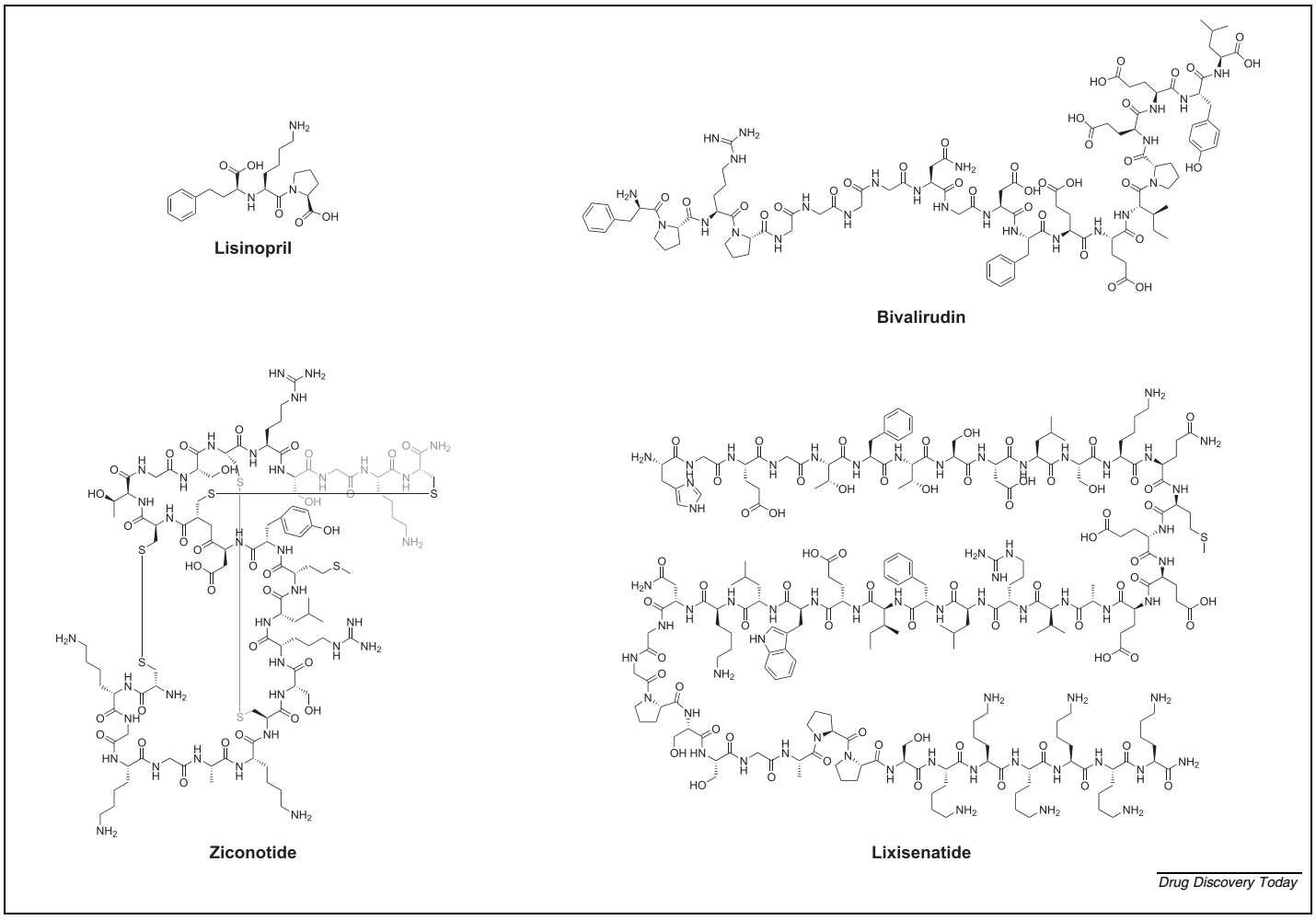

FIGURE 2
Chemical structures of four marketed drugs derived from animal venom: lisinopril from snake venom; ziconotide from cone snail venom; lixisenatide from Gila monster venom; and bivalirudin from leech venom.

Pharma and is now manufactured by Sanofi. Lixisenatide was approved by the EMA in 2013 and by the FDA in 2016 for the treatment of T2DM.[33,34]

In addition to the diseases for which they are approved, both exenatide and lixisenatide have shown promising results for the treatment of other conditions. Exenatide demonstrated long-lasting improvements in motor and cognitive function in a rat model for the treatment of Parkinson's disease (PD),[35] whereas lixisenatide showed neuroprotective effects in a mouse model of Alzheimer's disease (AD).[36]

Leeches

Species of the Hirudinea have been used for medical applications for hundreds of years for the treatment of several diseases, including rheumatic pain and fever.[37] The observation that they secret peptides and proteins that prevent blood from clotting led to the development of anticoagulants to inhibit thrombosis. Although secreted hirudin is not used in its native form, the synthetic derivatives desirudin and bivalirudin (Fig. 2) are used as direct thrombin inhibitors.[38,39] Iprivask® and Revasc® were marketed drugs with the active ingredient desirudin, but both were withdrawn from the market for commercial reasons. Bivalirudin was developed by The Medicines Company, which is now incorporated into Novartis. Under the brand names Angiox® and Angiomax®, the 20-amino acid containing peptide bivalirudin was marketed around the world. Angiomax® was approved by the FDA in 2000 as a direct thrombin inhibitor indicated for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty, among others.[40] Angiox® was used to prevent blood clots in adult patients undergoing percutaneous coronary intervention, including patients with myocardial infarction. Angiox® has since been withdrawn at the request of the marketing authorization holder and is no longer in use in the European Union (EU).[41]

Clinical trials are either planned or underway to investigate the safety and efficacy of the delayed continuous use of bivalirudin injection 4 h after percutaneous coronary intervention in patients with coronary heart disease (NCT04120961), and the pharmacokinetics (PK) of bivalirudin for pediatric anticoagulation in patients undergoing cardiac catheterization, cardiac surgical procedures using cardiopulmonary bypass, or extracorporeal membrane oxygenation (NCT03532399).

Pufferfish

Tetrodotoxin is a highly toxic poison from the ovaries of pufferfish. Even though it is hypothesized that the toxin originates from other organisms and is ingested by pufferfish, it is named after the Tetraodontidae.[42,43] Tetrodotoxin is one of the most toxic nonpeptidic poisons. It is a low-molecular-weight voltage-gated sodium channel ($Na_V1.7$) inhibitor that blocks sodium channels on neurons. At low doses, tetrodotoxin can prevent pain by inhibiting the initiation and conduction of nerve impulses in the peripheral nervous system, making it a valuable alternative to opioids in the treatment of cancer-related pain.[44] WEX Pharmaceuticals is investigating the effect of tetrodotoxin in their product Halneuron®, with several clinical studies already completed and more Phase III trials in preparation.[45] Compared with widely used opioid derivatives, tetrodotoxin shows no evidence of addiction or side effects including dizziness, nausea, and respiratory depression, among others, seen with opioid derivatives. An efficacy and safety study of intramuscular tetrodotoxin in patients with severe cancer-related pain revealed that 17 out of 31 treatments resulted in clinically meaningful reductions in pain intensity, with the relief of pain persisting for up to 2 weeks or longer with generally mild nausea and other toxicities, such as paresthesia and headache.[46] For the minimization of systemic or local toxicity, conjugation to a biocompatible and biodegradable polymer [poly(triol dicarboxylic acid)–co-poly (ethylene glycol), TDP] is reported for the prolonged duration of pain relief from a single injection.[47]

Scorpions

The venomous yellow scorpion injects toxin into the prey with its tail sting. As a highly potent component of the venom, chlorotoxin paralyzes the envenomated organism by blocking chloride channels.[48] The 36-amino acid peptide gained clinical significance because it was found to preferentially bind to glioma cells, leading to the development of methods for the diagnosis and treatment of different cancers.[49,50] The synthetically derived chlorotoxin, TM-601, has undergone clinical trials in patients with recurrent malignant glioma and solid tumors.[51,52] Novel trials are currently recruiting patients with recurrent or progressive glioblastoma (NCT04214392) and pediatric patients with central nervous system tumors undergoing surgery (NCT03579602).

In addition to the peptidic component of scorpion venom, 1,4-benzoquinone compounds were found in the venom of a scorpion indigenous to Mexico.[53] Chromatographic purification resulted in two venom-derived colored 1,4-benzoquinone derivatives [the blue 5-methoxy-2,3-bis(methylthio)cyclohexa-2,5-diene-1,4-dione and the red 3,5-dimethoxy-2-(methylthio)cyclo hexa-2,5-diene-1,4-dione] in very low concentrations, which could be resynthesized for further testing. The red compound demonstrated activity against *Staphylococcus aureus* with a minimum inhibitory concentration (MIC) of 4 μg/ml, whereas the blue benzoquinone showed activity against *Mycobacterium tuberculosis* with a MIC of 4 μg/ml and almost equal effectiveness against a multidrug-resistant strain. Both benzoquinone derivatives demonstrated bactericidal effects with comparable activity as the commercially available antibiotics currently used against these pathogens. These promising results suggest the potential of these compounds for the development of novel antimicrobial agents, especially because the blue benzoquinone was also effective in an *in vivo* mouse model of multidrug-resistant TB.[53]

Sea anemones

Sea anemones are predatory marine animals that occur from the surface to the abyssal zone. Two potassium channel toxins were found in sea anemones: the 37-residue peptide BgK is a neurotoxin secreted by *Bundosoma granulifera* and is mostly used for research on potassium channels.[54,55] The 35-residue peptide *Stichodactyla* toxin (ShK) was isolated from the whole-body extract of *Stichodactyla helianthus* and displayed structural similarities to BgK but differs from other potassium channel inhibitors.[56,57] With an IC_{50} of 11 pM against $K_V1.3$ and 16 pM against $K_V1.1$, it proved highly potent and displayed appealing selectivity over other potassium channels.[58] Engineering of ShK yielded the selective $K_V1.3$ channel blocker ShK-186, which is now known as Dalazatide.[59,60] Dalazatide was brought to clinical trials by $K_V1.3$ Therapeutics (formerly Kineta One LLC) for the investigation of dose safety in healthy volunteers (NCT02446340) and a 4-week Phase I study of the safety, tolerability, and PK in patients with active plaque psoriasis (NCT02435342), in which the drug was well tolerated and improved psoriatic skin lesions in nine out of ten patients, with only mild adverse effects, such as hypoesthesia and paresthesia.[61] With $K_V1.3$ being involved in various diseases, Dalazatide, and variations thereof, bear promise for the treatment of inflammatory bowel disease, autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, or neuroinflammations, such as AD.[62–64]

Shrews

The northern short-tailed shrew is a venomous mammal that occurs in the northeastern region of North America. Its saliva contains two peptidic toxins that are secreted from its submaxillary and sublingual glands. Blarina toxin is a 282-amino acid serine protease that is toxic enough to kill small animals through paralysis of the respiratory center and it is used to paralyze prey.[65] The other toxin, contained in the saliva, is soricidin, a 54-amino acid oligopeptide that inhibits sodium channels and blocks nerve impulses in prey organisms. Furthermore, it has been found to inhibit the transient receptor potential vanilloid type 6 (TRPV6) calcium channel.[66] Given that TRPV6 represents a target for a variety of cancers, soricidin and derivatives thereof bear promise as anticancer drugs.[67,68] Soricimed Biopharma has developed SOR-C13, a synthetic 13-amino acid peptide that derives from the C-terminal region of soricidin, for the treatment of ovarian and pancreatic cancer.[66] A Phase I clinical trial (NCT01578564) with patients with different solid tumor cancers revealed no serious drug-related adverse events. SOR-C13 proved safe and suggested antitumor activity with best response of a 27% reduction in a pancreatic tumor.[69] SOR-C13 was awarded orphan drug status by the FDA for the treatment of ovarian cancer and pancreatic cancer. A further Phase I clinical trial (NCT03784677) is recruiting patients with advanced refractory solid tumors to study the side effects as well as optimal dose of SOR-C13 for the treatment of patients who do not respond to other treatment.

Bufo toads

The genus of bufo toads comprises more than 100 species, many of which produce a secretion that consists of various compounds with toxic and hallucinogenic properties.

In traditional Chinese medicine, secretions from bufo toad have been used to treat cancers for over 1000 years. A dried and dissolved aqueous dosage form, named cinobufacini (HuaChanSu), is currently in a Phase II clinical trial for use in combination with thoracic radiotherapy in patients with esophageal squamous cell carcinoma (NCT02647125). A Phase II/III clinical trial (NCT02871869) is recruiting patients with diffuse large B cell lymphoma to explore whether cinobufacini has synergistic effects in the treatment of the disease. Furthermore, cinubufacini has shown to be an effective inducer of apoptosis and inhibits epithelial–mesenchymal transition in human hepatocellular carcinoma cells.[70,71]

Bombesin is a 14-amino acid peptide that was first isolated from the skin of the European fire-bellied toad and also has homologs in mammals. It is a tumor marker for small cell carcinoma and was investigated in Phase II clinical trials (NCT02440308 and NCT02488070) as an imaging agent (68 Ga-DOTA-bombesin) for positron emission tomography and magnetic resonance imaging in patients with prostate cancer.[72] Furthermore, bombesin was shown to induce gastroprotection through the release of endogenous gastrin, which activates sensory neurons in the gastric mucosa.[73]

Bats

The saliva of vampire bats contains the 411-amino acid enzyme desmoteplase, which was shown to have thrombolytic properties. Therefore, it was investigated for the treatment of patients with acute ischemic stroke in a Phase III clinical trial (NCT00790920) in which it was administered 3–9 h after symptom onset. Treatment of the patients with desmoteplase did not cause safety concerns, but also did not improve the functional outcome when given to patients beyond 3 h of symptom onset.[74]

Honeybees

Honeybees produce a venom known as apitoxin, which is embedded in the sting apparatus and comprises mainly melittin, a basic 26-amino acid peptide, and biologically active enzymes, such as phospholipase A2.[75] Bee venom has already been investigated in a Phase II clinical trial (NCT01341431) for the treatment of PD, in which it was generally well tolerated in patients, without allergic reactions, but demonstrated no evidence of disease-modifying effects compared with placebo.[76] Two clinical trials are recruiting patients for the investigation of bee venom for the treatment of low back pain (NCT03879447) and for cervical disc herniation (NCT03959098).

Recent preclinical investigations of honeybee venom and melittin demonstrated potent induction of cell death, particularly in aggressive triple-negative and HER2-enriched breast cancer subtypes.[77] Furthermore, melittin showed antitumor effects in non-small cell lung cancer via inhibition of miR-183[78] in human glioblastoma cells, in which it also suppressed matrix metalloproteinase-2 expression.[79] In ovarian cancer cells, it induced death receptors and inhibited the JAK2/STAT3 pathway,[80] and in pancreatic ductal adenocarcinoma, it inhibited cell growth and metastasis.[81] In the human cervical cancer HeLa cell line, it induced apoptosis[82] and has shown positive effects in several other cancers, including prostate, lung, liver and bladder cancers.[83]

For neuroprotection in PD, bee venom phospholipase A2 was investigated in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse models, in which it suppressed dopaminergic neuronal cell death, suggesting the potential of phospholipase A2 purified from bee venom for the treatment of PD.[84]

Spiders

Spiders produce significantly smaller amounts of venom compared, for example, to snakes; thus, the significance of these toxins for pharmaceutical research has been relatively low. As a result of improved analytical tools and screening approaches, these toxins are now finding their way into drug discovery efforts. Several spider-derived toxins and derivatives thereof are currently under preclinical investigations for diverse medical applications.[85]

The antimicrobial peptide gomesin, isolated from *Acanthoscurria gomesiana*, dose dependently reduces the viability and proliferation of melanoma cells and induces cell cycle arrest. Inhibition of human melanoma growth in two independent *in vivo* melanoma xenograft tumor models suggests the therapeutic utility of this peptide.[86]

The venom of the Australian funnel-web spider *Hadronyche infensa* comprises four peptides with marked similarity to psalmotoxin 1, originally isolated from the venom of *Psalmopoeus cambridgei*, which is the prototypical inhibitor of the acid-sensing ion channel 1a (ASIC1a).[87] Among the peptides found in the venom of *H. infensa*, Hi1a is the most potent inhibitor of ASIC1a, and demonstrated potent neuroprotection after stroke in rodent models.[88]

LyeTxl-b is a potent antibiotic that derived from the antimicrobial peptide LyeTxl found in the venom of *Lycosa erythrognatha*.[89] It has proven antibacterial efficacy against Gram-positive and Gram-negative bacteria *in vitro* and *in vivo* and has delivered promising results against resistant bacterial keratitis in rabbits. LyeTxl-b also reduced biofilm viability with a minimum inhibitory concentration (MIC) of 3.6 μmol/l in planktonic bacteria.[90]

The voltage-gated sodium channel $Na_V1.7$ is a therapeutic target for the treatment of pain. The peptide μ-theraphotoxin-Pn3a, isolated from venom of the tarantula *Pamphobeteus nigricolor*, potently inhibits $Na_V1.7$ with a pIC_{50} of 9.06, displaying selectivity over all other Na_V subtypes.[91] In combination with subtherapeutic doses of opioids, Pn3a produced profound analgesia in a mouse model, whereas Pn3a alone had no analgesic activity.[91] With respect to the important sodium channels, there are numerous additional spider-derived peptides under investigation as inhibitors or modulators.[92–95] Protoxin-II from *Thrixopelma pruriens* is an antagonist of human $Na_V1.7$,[96] HpTx1 from *Heteropoda venatoria* restores nociception by activation of $Na_V1.9$ in $Na_V1.7$ knockout mice,[97] CI6a and CI6b, originating from *Cyriopagopus longipes*, inhibit tetrodotoxin-sensitive but not TTX-

resistant sodium channels,[98] and μ-TRTX-Ca2a from *Cyriopagopus albostriatus* inhibits $Na_V1.7$, leading to an analgesic effect.[99]

Centipedes

Centipedes are a diverse class of arthropods that are found worldwide. Most representatives are venomous and inject their venom through bites or pincer-like appendages. The peptides comprising centipede venom predominantly act on sodium, potassium, and calcium ion channels.[100] The recently identified venom named Ssm Spooky Toxin (SsTx) is a 76-amino acid peptide that, after cleavage of a signal peptide, results in a 53-amino acid peptide. As an inhibitor of potassium channels, such as KCNQ (IC_{50} of 2.5 μM against KCNQ4), the toxin enables *Scolopendra subspinipes mutilans* to subdue prey many times its own weight.[101] SsTx and the three orthologous proteins SsdTx1–3 also inhibit the human Kir6.2 potassium channel with K_D values < 300 nM.[102] The 46-residue peptide μ-SLPTX-Ssm6a was identified as a potent $Na_V1.7$ sodium channel blocker that is under investigation as a treatment for chronic pain. In rodent pain models, Ssm6a proved to be more analgesic than morphine, while not displaying limiting adverse effects.[103] With respect to calcium voltage channels, the 83-amino acid peptide ω-SLPTX-Ssm1a was found to act as an activator, whereas the shorter 54-amino acid ω-SLPTX-Ssm2a inhibits Ca_V channels expressed in dorsal root ganglion neurons.[104] Peptides isolated from *S. s. mutilans*, such as scolopendrasin II, scolopendrasin V, and scolopendrasin VII, have shown antimicrobial activities, rendering them useful candidates for the development of novel antibiotic agents.[105–107] Scolopendrasin VII has further displayed anticancer activity, whereby it decreased the viability of Jurkat leukemia cells in MTS assays.[108]

Concluding remarks

Given their enormous potency and target specificity, animal venoms and poisons are a rich source of potent molecules to be used as starting points for the development of novel therapeutics. Several drugs that are already marketed and derive from animal toxins, or are the toxin itself for clinical application, prove the feasibility of this approach. With examples such as lisinopril, which is a small molecule that derives from a much larger-sized venom, most pharmaceutically promising animal toxins are peptides. Advances in the modification and formulation of peptides for oral delivery could have a beneficial impact on toxin-based peptide drugs.[109] So far, only a very small fraction of toxins from venomous animals has been investigated in pharmaceutical research, with promising results. Given that nature's treasure box bears significant potential to address serious unmet medical needs, future work should also focus on as yet unexplored organisms, including jellyfish, cuttlefish, stonefish, rays, salamanders, wasps, and ants, for further drug development projects.

Declaration of interest

The authors have no conflicts of interest to declare.

Acknowledgment

The authors acknowledge financial support from ZHAW funding AS-2021-1.

References

1 K.C.F. Bordon, C.T. Cologna, E.C. Fornari-Baldo, E.L. Pinheiro-Júnior, F.A. Cerni, F.G. Amorim, et al., From animal poisons and venoms to medicines: achievements, challenges and perspectives in drug discovery, Front Pharmacol 11 (2020) 1132.
2 G.F. King, Venoms as a platform for human drugs: translating toxins into therapeutics, Expert Opinion on Biological Therapy 11 (11) (2011) 1469–1484.
3 A.H. de Oliveira, V. Monge-Fuentes, A. Biolchi Mayer, G.A. Alves Campos, K. Soares Lopes, L.C. Camargo, et al., Animal venoms: therapeutic tools for tackling Parkinson's disease, Drug Discovery Today 24 (11) (2019) 2202–2211.
4 Q. Liao, Y. Feng, B. Yang, S.-M.-Y. Lee, Cnidarian peptide neurotoxins: a new source of various ion channel modulators or blockers against central nervous systems disease, Drug Discovery Today 24 (1) (2019) 189–197.
5 J. Giribaldi, J.J. Smith, C.I. Schroeder, Recent developments in animal venom peptide nanotherapeutics with improved selectivity for cancer cells, Biotechnol Adv 50 (2021) 107769.
6 A. Harvey, From demons to darlings: drugs from venoms, Drug Discovery Today 3 (12) (1998) 531–532.
7 M. Holford, M. Daly, G.F. King, R.S. Norton, Venoms to the rescue, Science 361 (6405) (2018) 842–844.
8 M. Muttenthaler, G.F. King, D.J. Adams, P.F. Alewood, Trends in peptide drug discovery, Nat Rev Drug Discov 20 (4) (2021) 309–325.
9 M.W. Pennington, A. Czerwinski, R.S. Norton, Peptide therapeutics from venom: current status and potential, Bioorganic & Medicinal Chemistry 26 (10) (2018) 2738–2758.
10 Lisinopril – Drug Usage Statistics 2013–2019, ClinCalc DrugStats Database. https://clincalc.com/DrugStats/Drugs/Lisinopril [Accessed October 11, 2021].
11 Insights CM. Global Angiotensin Converting Enzymes (ACE) Inhibitors Market to Surpass US$ 12.4 Billion by 2026. www.prnewswire.com/news-releases/global-angiotensin-converting-enzymes-ace-inhibitors-market-to-surpass-us-12-4-billion-by-2026—300874252.html [Accessed October 11, 2021].
12 M.A. Ondetti, B. Rubin, D.W. Cushman, Design of specific inhibitors of angiotensin-converting enzyme: new class of orally active antihypertensive agents, Science 196 (4288) (1977) 441–444.
13 D.W. Cushman, M.A. Ondetti, History of the design of captopril and related inhibitors of angiotensin converting enzyme, Hypertension 17 (4) (1991) 589–592.
14 T. Mohamed Abd El-Aziz, A.G. Soares, J.D. Stockand, Snake venoms in drug discovery: valuable therapeutic tools for life saving, Toxins 11 (10) (2019) 564.
15 R.Y.M. Ryan, V.P. Lutzky, V. Herzig, T.B. Smallwood, J. Potriquet, Y. Wong, et al., Venom of the red-bellied black snake *Pseudechis porphyriacus* shows immunosuppressive potential, Toxins 12 (11) (2020) 674.
16 Y. Fang, X. He, P. Zhang, C. Shen, J. Mwangi, C. Xu, et al., *In vitro* and *in vivo* antimalarial activity of LZ1, a peptide derived from snake cathelicidin, Toxins 11 (7) (2019) 379.
17 G.S. Shen, R.T. Layer, R.T. McCabe, Conopeptides: from deadly venoms to novel therapeutics, Drug Discovery Today 5 (3) (2000) 98–106.
18 J.A. Williams, M. Day, J.E. Heavner, Ziconotide: an update and review, Expert Opinion on Pharmacotherapy 9 (9) (2008) 1575–1583.
19 Drug Approval Package: Prialt (Ziconotide Intrathecal Infusion) NDA #021060. www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21–060_Prialt.cfm [Accessed October 11, 2021].
20 Anonymous. Prialt. European Medicines Agency. Published September 17, 2018. www.ema.europa.eu/en/medicines/human/EPAR/prialt [Accessed October 11, 2021].
21 J.G. McGivern, Ziconotide: a review of its pharmacology and use in the treatment of pain, Neuropsychiatr Dis Treat 3 (1) (2007) 69–85.
22 C. Reimers, C.H. Lee, H. Kalbacher, Y. Tian, C.H. Hung, A. Schmidt, et al., Identification of a cono-RFamide from the venom of *Conus textile* that targets ASIC3 and enhances muscle pain, Proc Natl Acad Sci USA 114 (17) (2017) E3507–E3515.

23 M. Ellison, C. Haberlandt, M.E. Gomez-Casati, M. Watkins, A.B. Elgoyhen, J.M. McIntosh, et al., α-RgIA: a novel conotoxin that specifically and potently blocks the α9α10 nAChR, Biochemistry 45 (5) (2006) 1511–1517.

24 M. Ellison, Z.P. Feng, A.J. Park, X. Zhang, B.M. Olivera, J.M. McIntosh, et al., α-RgIA, a novel conotoxin that blocks the α9α10 nAChR: structure and identification of key receptor-binding residues, Journal of Molecular Biology 377 (4) (2008) 1216–1227.

25 N. Zheng, S.B. Christensen, A. Blakely, C. Dowell, L. Purushottam, J.M. McIntosh, et al., Development of conformationally constrained α-RgIA analogues as stable peptide antagonists of human α9α10 nicotinic acetylcholine receptors, J Med Chem 63 (15) (2020) 8380–8387.

26 A.C. Kennedy, A. Belgi, B.W. Husselbee, D. Spanswick, R.S. Norton, A.J. Robinson, α-Conotoxin peptidomimetics: probing the minimal binding motif for effective analgesia, Toxins 12 (8) (2020) 505.

27 H. Safavi-Hemami, J. Gajewiak, S. Karanth, S.D. Robinson, B. Ueberheide, A.D. Douglass, et al., Specialized insulin is used for chemical warfare by fish-hunting cone snails, Proc Natl Acad Sci USA 112 (6) (2015) 1743–1748.

28 Specialized insulin in the venom of cone snails: a new drug for diabetes? | Results In Brief | CORDIS | European Commission. https://cordis.europa.eu/article/id/202204-specialized-insulin-in-the-venom-of-cone-snails-a-new-drug-for-diabetes [Accessed October 11, 2021].

29 M.K.K. Yap, N. Misuan, Exendin-4 from *Heloderma suspectum* venom: from discovery to its latest application as type II diabetes combatant, Basic & Clinical Pharmacology & Toxicology 124 (5) (2019) 513–527.

30 Drug Approval Package: Byetta (Exenatide) NDA #021773. www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021773_byettatoc.cfm [Accessed October 11, 2021].

31 Anonymous. Byetta. European Medicines Agency. www.ema.europa.eu/en/medicines/human/EPAR/byetta [Accessed October 11, 2021].

32 Exenatide – Drug Usage Statistics, ClinCalc DrugStats Database. https://clincalc.com/DrugStats/Drugs/Exenatide [Accessed October 11, 2021].

33 Anonymous. Lyxumia. European Medicines Agency. www.ema.europa.eu/en/medicines/human/EPAR/lyxumia Accessed October 11, 2021.

34 Adlyxin (lixisenatide) Injection. www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208471Orig1s000TOC.cfm [Accessed October 11, 2021].

35 D.S. Kim, H.-I. Choi, Y. Wang, Y. Luo, B.J. Hoffer, N.H. Greig, A new treatment strategy for Parkinson's disease through the gut–brain axis, Cell Transplant 26 (9) (2017) 1560–1571.

36 P.L. McClean, C. Hölscher, Lixisenatide, a drug developed to treat type 2 diabetes, shows neuroprotective effects in a mouse model of Alzheimer's disease, Neuropharmacology 86 (2014) 241–258.

37 I.S. Whitaker, J. Rao, D. Izadi, P.E. Butler, Historical Article: *Hirudo m*edicinalis: ancient origins of, and trends in the use of medicinal leeches throughout history, British Journal of Oral and Maxillofacial Surgery 42 (2) (2004) 133–137.

38 T.J. Graetz, B.R. Tellor, J.R. Smith, M.S. Avidan, Desirudin: a review of the pharmacology and clinical application for the prevention of deep vein thrombosis, Expert Rev Cardiovasc Ther 9 (9) (2011) 1101–1109.

39 T.D. Gladwell, Bivalirudin: a direct thrombin inhibitor, Clin Ther 24 (1) (2002) 38–58.

40 Drug Approval Package: Angiomax (Bivalirudin) NDA # 20–873. www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20873_Angiomax.cfm [Accessed October 11, 2021].

41 Anonymous. AngPublished September 17, 2018. Accessed August 30, 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/angiox [Accessed October 11, 2021].

42 R. Chau, J.A. Kalaitzis, B.A. Neilan, On the origins and biosynthesis of tetrodotoxin, Aquatic Toxicology 104 (1) (2011) 61–72.

43 J. Lago, L.P. Rodríguez, L. Blanco, J.M. Vieites, A.G. Cabado, Tetrodotoxin, an extremely potent marine neurotoxin: distribution, toxicity, origin and therapeutical uses, Mar Drugs 13 (10) (2015) 6384–6406.

44 R. González-Cano, M.C. Ruiz-Cantero, M. Santos-Caballero, C. Gómez-Navas, M.à. Tejada, F.R. Nieto, Tetrodotoxin, a potential drug for neuropathic and cancer pain relief?, Toxins 13 (7) (2021) 483

45 Clinical Experience. WEX Pharmaceuticals Inc - Halneuron for Pain Management. https://wexpharma.com/clinical-trials/clinical-experience/ [Accessed October 11, 2021].

46 N.A. Hagen, K.M. Fisher, B. Lapointe, P. du Souich, S. Chary, D. Moulin, et al., An open-label, multi-dose efficacy and safety study of intramuscular tetrodotoxin in patients with severe cancer-related pain, Journal of Pain and Symptom Management 34 (2) (2007) 171–182.

47 C. Zhao, A. Liu, C.M. Santamaria, A. Shomorony, T. Ji, T. Wei, et al., Polymer–tetrodotoxin conjugates to induce prolonged duration local anesthesia with minimal toxicity, Nature Communications 10 (1) (2019) 2566.

48 J.A. DeBin, G.R. Strichartz, Chloride channel inhibition by the venom of the scorpion *Leiurus quinquestriatus*, Toxicon 29 (11) (1991) 1403–1408.

49 J. Deshane, C.C. Garner, H. Sontheimer, Chlorotoxin inhibits glioma cell invasion via matrix metalloproteinase-2, Journal of Biological Chemistry 278 (6) (2003) 4135–4144.

50 P.G. Ojeda, C.K. Wang, D.J. Craik, Chlorotoxin: structure, activity, and potential uses in cancer therapy, Peptide Science 106 (1) (2016) 25–36.

51 A.N. Mamelak, D.B. Jacoby, Targeted delivery of antitumoral therapy to glioma and other malignancies with synthetic chlorotoxin (TM-601), Expert Opin Drug Deliv 4 (2) (2007) 175–186.

52 A.N. Mamelak, S. Rosenfeld, R. Bucholz, A. Raubitschek, L.B. Nabors, J.B. Fiveash, et al., Phase I single-dose study of intracavitary-administered iodine-131-TM-601 in adults with recurrent high-grade glioma, JCO 24 (22) (2006) 3644–3650.

53 E.N. Carcamo-Noriega, S. Sathyamoorthi, S. Banerjee, E. Gnanamani, M. Mendoza-Trujillo, D. Mata-Espinosa, et al., 1,4-Benzoquinone antimicrobial agents against *Staphylococcus aureus* and *Mycobacterium tuberculosis* derived from scorpion venom, Proc Natl Acad Sci USA 116 (26) (2019) 12642–12647.

54 A. Aneiros, I. García, J.R. Martínez, A.L. Harvey, A.J. Anderson, D.L. Marshall, et al., A potassium channel toxin from the secretion of the sea anemone *Bunodosoma granulifera*. isolation, amino acid sequence and biological activity, Biochimica et Biophysica Acta (BBA) - General Subjects 1157 (1) (1993) 86–92.

55 S. Braud, P. Belin, J. Dassa, L. Pardo, G. Mourier, A. Caruana, et al., BgK, a disulfide-containing sea anemone toxin blocking K+ channels, can be produced in *Escherichia coli* cytoplasm as a functional tagged protein, Protein Expression and Purification 38 (1) (2004) 69–78.

56 O. Castañeda, V. Sotolongo, A.M. Amor, R. Stöcklin, A.J. Anderson, A.L. Harvey, et al., Characterization of a potassium channel toxin from the Caribbean sea anemone *Stichodactyla helianthus*, Toxicon 33 (5) (1995) 603–613.

57 J.E. Tudor, P.K. Pallaghy, M.W. Pennington, R.S. Norton, Solution structure of ShK toxin, a novel potassium channel inhibitor from a sea anemone, Nat Struct Mol Biol 3 (4) (1996) 317–320.

58 K. Kalman, M.W. Pennington, M.D. Lanigan, A. Nguyen, H. Rauer, V. Mahnir, et al., ShK-Dap22, a potent Kv1.3-specific immunosuppressive polypeptide, J Biol Chem 273 (49) (1998) 32697–32707.

59 M.W. Pennington, C. Beeton, C.A. Galea, B.J. Smith, V. Chi, K.P. Monaghan, et al., Engineering a stable and selective peptide blocker of the Kv1.3 channel in T lymphocytes, Mol Pharmacol 75 (4) (2009) 762–773.

60 M.W. Pennington, S.C. Chang, S. Chauhan, R. Huq, R.B. Tajhya, S. Chhabra, et al., Development of highly selective Kv1.3-blocking peptides based on the sea anemone peptide ShK, Mar Drugs 13 (1) (2015) 529–542.

61 E.J. Tarcha, C.M. Olsen, P. Probst, D. Peckham, E.J. Muñoz-Elías, J.G. Kruger, et al., Safety and pharmacodynamics of dalazatide, a Kv1.3 channel inhibitor, in the treatment of plaque psoriasis: a randomized phase 1b trial, PLoS ONE 12 (7) (2017) e0180762.

62 G. Tajti, D.C.C. Wai, G. Panyi, R.S. Norton, The voltage-gated potassium channel KV1.3 as a therapeutic target for venom-derived peptides, Biochemical Pharmacology 181 (2020) 114146.

63 Q. Liao, G. Gong, S.W.I. Siu, C.T.T. Wong, H. Yu, Y.C. Tse, et al., A novel ShK-like toxic peptide from the transcriptome of the cnidarian *Palythoa caribaeorum* displays neuroprotection and cardioprotection in zebrafish, Toxins 10 (6) (2018) 238.

64 E.J. Tarcha, V. Chi, E.J. Muñoz-Elías, D. Bailey, L.M. Londono, S.K. Upadhyay, et al., Durable pharmacological responses from the peptide ShK-186, a specific Kv1.3 channel inhibitor that suppresses T cell mediators of autoimmune disease, J Pharmacol Exp Ther 342 (3) (2012) 642–653.

65 M. Kita, Y. Nakamura, Y. Okumura, S.D. Ohdachi, Y. Oba, M. Yoshikuni, et al., *Blarina* toxin, a mammalian lethal venom from the short-tailed shrew *Blarina brevicauda*: isolation and characterization, Proc Natl Acad Sci USA 101 (20) (2004) 7542–7547.

66 C.V. Bowen, D. DeBay, H.S. Ewart, P. Gallant, S. Gormley, T.T. Ilenchuk, et al., *In vivo* detection of human TRPV6-rich tumors with anti-cancer peptides derived from soricidin, PLoS ONE 8 (3) (2013) e58866.

67 J.M. Stewart, TRPV6 as a target for cancer therapy, J Cancer 11 (2) (2020) 374–387.

68 H. Xue, Y. Wang, T.J. MacCormack, T. Lutes, C. Rice, M. Davey, et al., Inhibition of transient receptor potential vanilloid 6 channel, elevated in human ovarian cancers, reduces tumour growth in a xenograft model, J Cancer 9 (17) (2018) 3196–3207.

69 S. Fu, H. Hirte, S. Welch, T.T. Ilenchuk, T. Lutes, C. Rice, et al., First-in-human phase I study of SOR-C13, a TRPV6 calcium channel inhibitor, in patients with advanced solid tumors, Invest New Drugs 35 (3) (2017) 324–333.

70 F. Qi, A. Li, L. Zhao, H. Xu, Y. Inagaki, D. Wang, et al., Cinobufacini, an aqueous extract from *Bufo bufo gargarizans* Cantor, induces apoptosis through a mitochondria-mediated pathway in human hepatocellular carcinoma cells, J Ethnopharmacol 128 (3) (2010) 654–661.

71 F. Qi, J. Wang, L. Zhao, P. Cai, W. Tang, Z. Wang, Cinobufacini inhibits epithelial-mesenchymal transition of human hepatocellular carcinoma cells through c-Met/ERK signaling pathway, Biosci Trends 12 (3) (2018) 291–297.

72 R. Minamimoto, S. Hancock, B. Schneider, F.T. Chin, M. Jamali, A. Loening, et al., Pilot comparison of ^{68}Ga-RM2 PET and ^{68}Ga-PSMA-11 PET in patients with biochemically recurrent prostate cancer, J Nucl Med 57 (4) (2016) 557–562.

73 S.D. West, D.W. Mercer, Bombesin-induced gastroprotection, Ann Surg 241 (2) (2005) 227–231.

74 G.W. Albers, R. von Kummer, T. Truelsen, J.K. Jensen, G.M. Ravn, B.A. Grønning, et al., Safety and efficacy of desmoteplase given 3–9 h after ischaemic stroke in patients with occlusion or high-grade stenosis in major cerebral arteries (DIAS-3): a double-blind, randomised, placebo-controlled phase 3 trial, Lancet Neurol 14 (6) (2015) 575–584.

75 J. Chen, S.-M. Guan, W. Sun, H. Fu, Melittin, the major pain-producing substance of bee venom, Neurosci Bull 32 (3) (2016) 265–272.

76 A. Hartmann, J. Müllner, N. Meier, H. Hesekamp, P. van Meerbeeck, M.O. Habert, et al., Bee venom for the treatment of Parkinson disease – a randomized controlled clinical trial, PLoS ONE 11 (7) (2016) e0158235.

77 C. Duffy, A. Sorolla, E. Wang, E. Golden, E. Woodward, K. Davern, et al., Honeybee venom and melittin suppress growth factor receptor activation in HER2-enriched and triple-negative breast cancer, NPJ Precision Oncology 4 (1) (2020) 1–16.

78 D. Gao, J. Zhang, L. Bai, F. Li, Y. Dong, Q. Li, Melittin induces NSCLC apoptosis via inhibition of miR-183, Onco Targets Ther 11 (2018) 4511–4523.

79 M. Sisakht, B. Mashkani, A. Bazi, H. Ostadia, M. Farnaz Zarea, Z. Avvala, et al., Bee venom induces apoptosis and suppresses matrix metaloprotease-2 expression in human glioblastoma cells, Rev Bras Farmacogn 27 (3) (2017) 324–328.

80 M. Jo, M.H. Park, P.S. Kollipara, B.J. An, H.S. Song, S.B. Han, et al., Anti-cancer effect of bee venom toxin and melittin in ovarian cancer cells through induction of death receptors and inhibition of JAK2/STAT3 pathway, Toxicology and Applied Pharmacology 258 (1) (2012) 72–81.

81 X. Wang, H. Li, X. Lu, C. Wen, Z. Huo, M. Shi, et al., Melittin-induced long non-coding RNA NONHSAT105177 inhibits proliferation and migration of pancreatic ductal adenocarcinoma, Cell Death & Disease 9 (10) (2018) 1–11.

82 H. Zarrinnahad, A. Mahmoodzadeh, M.P. Hamidi, M. Mahdavi, A. Moradi, K.P. Bagheri, et al., Apoptotic effect of melittin purified from Iranian honey bee venom on human cervical cancer HeLa cell line, Int J Pept Res Ther 24 (4) (2018) 563–570.

83 I. Rady, I.A. Siddiqui, M. Rady, H. Mukhtar, Melittin, a major peptide component of bee venom, and its conjugates in cancer therapy, Cancer Letters 402 (2017) 16–31.

84 K.H. Kim, S.Y. Lee, J. Shin, J.-T. Hwang, H.N. Jeon, H. Bae, Dose-dependent neuroprotective effect of standardized bee venom phospholipase A2 against MPTP-induced Parkinson's disease in mice, Front Aging Neurosci 11 (2019) 80.

85 N.J. Saez, V. Herzig, Versatile spider venom peptides and their medical and agricultural applications, Toxicon 158 (2019) 109–126.

86 M.P. Ikonomopoulou, M.A. Fernandez-Rojo, S.S. Pineda, P. Cabezas-Sainz, B. Winnen, R.A.V. Morales, et al., Gomesin inhibits melanoma growth by manipulating key signaling cascades that control cell death and proliferation, Scientific Reports 8 (1) (2018) 11519.

87 P. Escoubas, J.R. De Weille, A. Lecoq, S. Diochot, R. Waldmann, G. Champigny, et al., Isolation of a tarantula toxin specific for a class of proton-gated Na+ channels, J Biol Chem 275 (33) (2000) 25116–25121.

88 I.R. Chassagnon, C.A. McCarthy, Y.K. Chin, S.S. Pineda, A. Keramidas, M. Mobli, et al., Potent neuroprotection after stroke afforded by a double-knot spider-venom peptide that inhibits acid-sensing ion channel 1a, Proc Natl Acad Sci USA 114 (14) (2017) 3750–3755.

89 P.V.M. Reis, D. Boff, R.M. Verly, M.N. Melo-Braga, M.E. Cortés, D.M. Santos, et al., LyeTxI-b, a synthetic peptide derived from *Lycosa erythrognatha* spider venom, shows potent antibiotic activity *in vitro* and *in vivo*, Front Microbiol 9 (2018) 667.

90 C.N.D. Silva, F.R.D. Silva, L.F.N. Dourado, P.V.M.D. Reis, R.O. Silva, B.L.D. Costa, et al., A new topical eye drop containing LyeTxI-b, a synthetic peptide designed from a *Lycosa erithrognata* venom toxin, was effective to treat resistant bacterial keratitis, Toxins 11 (4) (2019) 203.

91 J.R. Deuis, Z. Dekan, J.S. Wingerd, J.J. Smith, N.R. Munasinghe, R.F. Bhola, et al., Pharmacological characterisation of the highly Na V 1.7 selective spider venom peptide Pn3a, Scientific Reports 7 (1) (2017) 40883.

92 Eagles DA, Chow CY, King GF. Fifteen years of NaV1.7 channels as an analgesic target: why has excellent *in vitro* pharmacology not translated into *in vivo* analgesic efficacy? *British Journal of Pharmacology*. Published online November 18, 2020. http://dx.doi.org/10.1111/bph.15327

93 R.A. Neff, A.D. Wickenden, Selective targeting of Nav1.7 with engineered spider venom-based peptides, Channels 15 (1) (2021) 179–193.

94 F.C. Cardoso, R.J. Lewis, Structure–function and therapeutic potential of spider venom-derived cysteine knot peptides targeting sodium channels, Frontiers in Pharmacology 10 (2019) 366.

95 K. Yin, J.R. Deuis, Z. Dekan, A.H. Jin, P.F. Alewood, G.F. King, et al., Addition of K22 converts spider venom peptide Pme2a from an activator to an inhibitor of NaV1.7, Biomedicines 8 (2) (2020) 37.

96 H. Xu, T. Li, A. Rohou, C.P. Arthur, F. Tzakoniati, E. Wong, et al., Structural basis of Nav1.7 inhibition by a gating-modifier spider toxin, Cell 176 (4) (2019) 702–715.

97 X. Zhou, T. Ma, L. Yang, S. Peng, L. Li, Z. Wang, et al., Spider venom-derived peptide induces hyperalgesia in Nav1.7 knockout mice by activating Nav1.9 channels, Nat Commun 11 (1) (2020) 2293.

98 Q. Zhang, Y. Si, L. Yang, L. Wang, S. Peng, Y. Chen, et al., Two novel peptide toxins from the spider *Cyriopagopus longipes* inhibit tetrodotoxin-sensitive sodium channels, Toxins 12 (9) (2020) 529.

99 Y. Zhang, D. Peng, B. Huang, Q. Yang, Q. Zhang, M. Chen, et al., Discovery of a novel Nav1.7 inhibitor from *Cyriopagopus alboiostriatus* venom with potent analgesic efficacy, Frontiers in Pharmacology 9 (2018) 1158.

100 Y. Chu, P. Qiu, R. Yu, Centipede venom peptides acting on ion channels, Toxins 12 (4) (2020) 230.

101 L. Luo, B. Li, S. Wang, F. Wu, X. Wang, P. Liang, et al., Centipedes subdue giant prey by blocking KCNQ channels, Proc Natl Acad Sci USA 115 (7) (2018) 1646–1651.

102 Y. Ramu, Z. Lu, A family of orthologous proteins from centipede venoms inhibit the hKir6.2 channel, Scientific Reports 9 (1) (2019) 14088.

103 S. Yang, Y. Xiao, D. Kang, J. Liu, Y. Li, E.A. Undheim, et al., Discovery of a selective NaV1.7 inhibitor from centipede venom with analgesic efficacy exceeding morphine in rodent pain models, Proc Natl Acad Sci USA 110 (43) (2013) 17534–17539.

104 S. Yang, Z. Liu, Y. Xiao, Y. Li, M. Rong, S. Liang, et al., Chemical punch packed in venoms makes centipedes excellent predators, Mol Cell Proteomics 11 (9) (2012) 640–650.

105 Y.N. Kwon, J.H. Lee, I.W. Kim, S.H. Kim, E.Y. Yun, S.H. Nam, et al., Antimicrobial activity of the synthetic peptide scolopendrasin ii from the centipede *Scolopendra subspinipes mutilans*, J Microbiol Biotechnol 23 (10) (2013) 1381–1385.

106 J.H. Lee, I.-W. Kim, M.-A. Kim, M.-Y. Ahn, E.-Y. Yun, J.S. Hwang, Antimicrobial activity of the scolopendrasin V peptide identified from the centipede *Scolopendra subspinipes mutilans*, J Microbiol Biotechnol 27 (1) (2017) 43–48.

107 Y.J. Park, H.Y. Lee, Y.S. Jung, J.S. Park, J.S. Hwang, Y.-S. Bae, Antimicrobial peptide scolopendrasin VII, derived from the centipede *Scolopendra subspinipes* mutilans, stimulates macrophage chemotaxis via formyl peptide receptor 1, BMB Rep 48 (8) (2015) 479–484.

108 J.H. Lee, I.W. Kim, S.H. Kim, M.A. Kim, E.Y. Yun, S.H. Nam, et al., Anticancer activity of the antimicrobial peptide scolopendrasin vii derived from the centipede, Scolopendra subspinipes mutilans. J Microbiol Biotechnol. 25 (8) (2015) 1275–1280.

109 Zizzari AT, Pliatsika D, Gall FM, Fischer T, Riedl R. New perspectives in oral peptide delivery. *Drug Discovery Today*. Published online January 23, 2021.

110 X. Zhou, Y. Liu, Y. Gao, Y. Wang, Q. Xia, R. Zhong, et al., Enhanced antimicrobial activity of N-terminal derivatives of a novel brevinine-1 peptide from the skin secretion of *Odorrana schmackeri*, Toxins 12 (8) (2020) 484.

111 T.C. Gonçalves, P. Lesport, S. Kuylle, E. Stura, J. Ciolek, G. Mourier, et al., Evaluation of the spider (*Phlogiellus* genus) phlotoxin 1 and synthetic variants as antinociceptive drug candidates, Toxins 11 (9) (2019) 484.

112 M. Ji, T. Zhu, M. Xing, N. Luan, J. Mwangi, X. Yan, et al., An antiviral peptide from *Alopecosa nagpag* spider targets NS2B–NS3 protease of flaviviruses, Toxins 11 (10) (2019) 584.

113 O.N. Silva, M.D.T. Torres, J. Cao, E.S.F. Alves, L.V. Rodrigues, J.M. Resende, et al., Repurposing a peptide toxin from wasp venom into antiinfectives with dual antimicrobial and immunomodulatory properties, Proc Natl Acad Sci USA 117 (43) (2020) 26936–26945.