Scorpion Venom

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Scorpion venom may cause severe medical complications and untimely death if injected into the human body. A wide range of bioactive molecules can be found in scorpion venoms. Advances in separation, characterization, and biotechnological approaches have enabled not only the development of more effective treatments against scorpion envenomings, but have also led to the discovery of several scorpion venom peptides with interesting therapeutic properties. Thus, scorpion venom may not only be a medical threat to human health, but could prove to be a valuable source of bioactive molecules that may serve as leads for the development of new therapies against current and emerging diseases.

scorpion venom | potassium channel toxins | calcins | scorpionism | fungicide | parasiticide | bradykinin potentiating peptide | analgesics | antivenom

1. Introduction

According to national public health data, about 1.5 million scorpion envenomings, resulting in 2000–3000 deaths, are annually recorded [1][2]. While large regions in the Northern Hemisphere, such as the United States, Canada, Europe, and Russia, as well as Australia in the Southern Hemisphere are not associated with severe scorpionism [3], more than two billion people living in northern Saharan Africa, African Sahel, South Africa, Near and Middle East, southern India, eastern Andes, Mexico, and South America are at risk of being stung by scorpions [1]. Climate change together with urban expansion and poor city sanitation management in many of these areas have increased the likelihood of encountering scorpions. For instance, since 2012, in Brazil alone, malign incidences with scorpions have nearly doubled from 64,000 to 124,000 annual envenoming cases [4].

To date, over 2000 scorpion species have been described. The vast majority of the scorpion species that are dangerous to humans belong to the Buthidae family [5], but some species in the families of Scorpionidae and Hemiscorpiidae have also been classified as harmful [6][7]. Local pain is often the first symptom of scorpion envenoming, which may set in only minutes after a sting has occurred. Depending on the scorpion species, the symptoms can progress to severe complications over the course of a few hours. Inducing a massive release of neurotransmitters, scorpion venom neurotoxins usually cause sweating, nausea, vomiting, hypersalivation, restlessness, and, in more severe cases, arrhythmia, unconsciousness, and heart failure, which may lead to death [8]. However, in spite of the hazardous and life-threatening effects of scorpion envenoming, therapeutic properties of scorpion body parts and venoms have been utilized by humans for thousands of years [8]. Nowadays, the

potential therapeutic value of different scorpion venom compounds is being increasingly investigated, as these compounds may represent promising leads for the development of new pharmaceuticals.

2. Benefits of Scorpion Venom: Ongoing Research on Scorpion Toxins with Potential Therapeutic Applications

Scorpion venom is a rich source of bioactive compounds, and as such, their toxins are of interest to the pharmaceutical and biotech industries. However, despite the fact that substantial research efforts are ongoing, and the prospects for scorpion-derived therapeutic peptides are very promising, chlorotoxin is the only toxin from scorpion venom that has been taken into clinical trials [9]. Moreover, no scorpion toxin-based drug is currently available in the market [10]. The potential applications of scorpion venom compounds are presented in Figure 1.

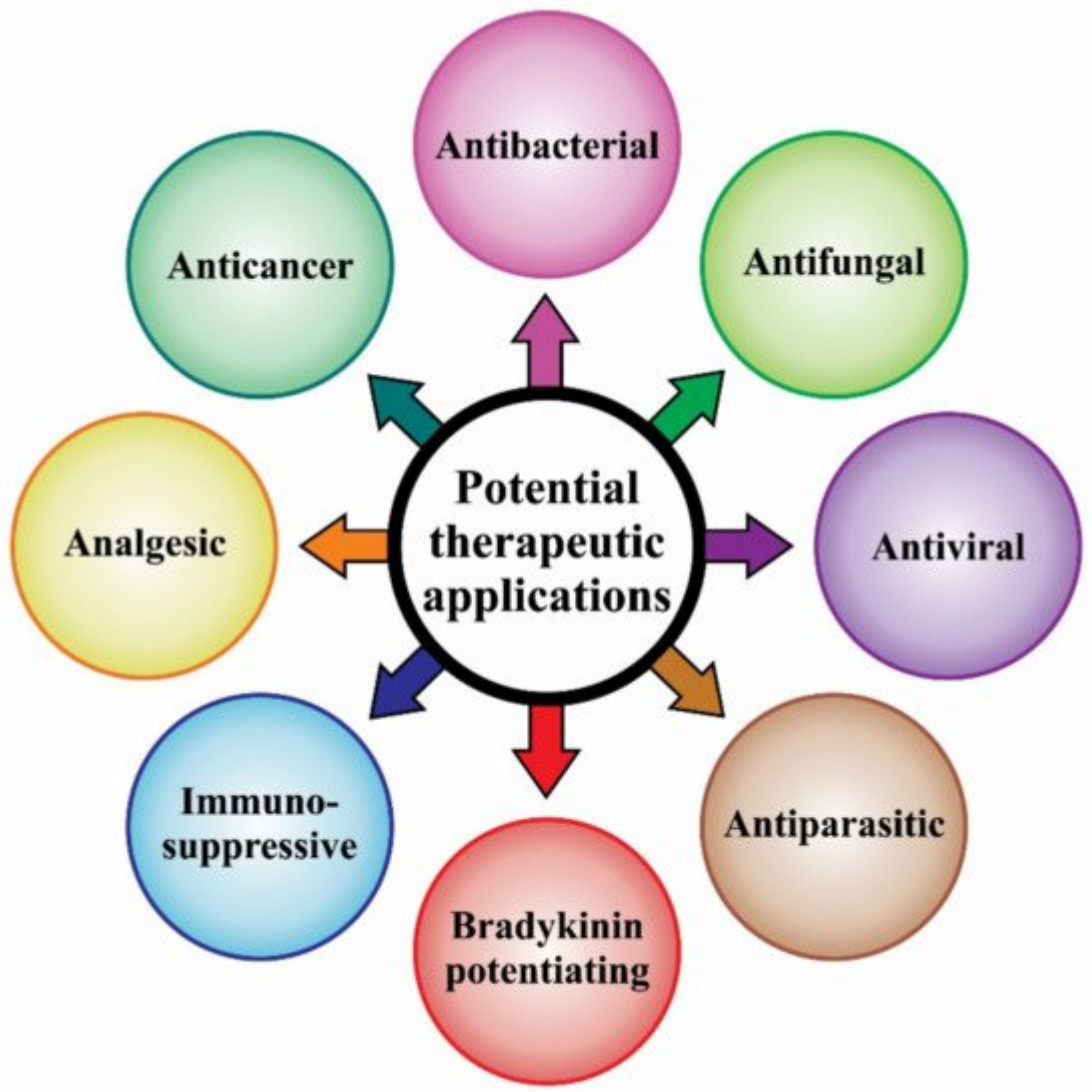

Figure 1. The potential therapeutic applications of scorpion venom compounds discussed in this article.

2.1. Antibacterial Effects

In the past century, antimicrobial drugs revolutionized the control of diseases caused by microorganisms, such as bacteria, fungi, viruses, and parasites. However, due to the global problem of antimicrobial resistance (AMR) development, new antimicrobial agents are crucially needed for the 21st century. These agents must be discovered at a rate that is sufficiently fast to combat the evolving rate of multidrug resistance (MDR) in microorganisms [11]. Natural product research holds promise for providing new molecules as a basis for novel antimicrobial drug development. In 1991, it was reported that the folding pattern of charybdotoxin, a KTx isolated from *L. quinquestriatus hebraeus* venom, was strikingly similar to that of the insect antibacterial component, defensin [12]. This discovery set the stage for studies on scorpion-derived antimicrobial peptides (AMPs), which have led to a large number of discoveries that may be of relevance for therapeutic applications. For instance, native scorpion AMPs, UyCT3, and UyCT5 from *U. yaschenkoi* and an enhanced UyCT peptide (designated as D3) were demonstrated to be potential bioinsecticides and promising candidates for the engineering of aphid-resistant crops. When pea aphids (*Acyrthosiphon pisum*), which are known as severe agricultural pests, were fed with UyCT3 and UyCT5, the number of aphid bacterial symbionts reduced which led to a reduction in pest survival and a delay in pest reproduction [13]. Meucin-49 from *M. eupeus* also showed insecticidal activity in addition to having broad-spectrum activity against Gram-positive and Gram-negative bacteria [14]. The red and blue benzoquinones from *D. melici* are multifunctional components that, besides showing antibacterial activity, also exert cytotoxic effects on neoplastic cell lines. In mouse models of MDR tuberculosis infection, blue benzoquinone showed comparable activity to commercially available antibiotics, while it did not cause adverse side effects in healthy mice [15]. Similarly, the low molecular mass chitosan obtained from *M. gibbosus* had a strong inhibitory effect against the bacterium *L. monocytogenes* and the yeast *C. albicans*. In addition, its antibacterial activity against *B. subtilis* and *S. enteritidis* was higher than the antibiotic, gentamicin [16]. However, despite the desirable potent action against microbes, natural scorpion AMPs generally have cytotoxic effects on eukaryotic cells, which is an obstacle that must be overcome. To this end, protein engineering techniques have been used to improve the potency and spectra of antimicrobial activity of the natural scorpion AMPs [17][18][19]. Employing these techniques, it has been demonstrated that scorpion AMPs can be effectively used as scaffolds to design more specific and less harmful antibiotics [20][21]. In addition, combining low concentrations of fast-killing scorpion AMPs with classical antibiotics is another approach that can be pursued in order to circumvent their cytotoxic effects against eukaryotic cells [22]. All in all, using natural scorpion AMPs as scaffolds for the rational design of novel antimicrobial agents and mixed formulations of antibiotics opens a new window of research to be pursued in the future.

2.2. Antifungal Effects

The most important opportunistic fungal pathogens that are responsible for high mortality, especially in hospitalized and immunocompromised and/or critically ill patients, belong to *Candida*, *Aspergillus*, *Cryptococcus*, and *Pneumocystis* genera [23]. Among them, *Candida* is the most common cause of fungal infections worldwide, and invasive candidiasis occurs in more than 100,000 patients every year [24]. Antifungal drug resistance among *Candida* species is increasingly reported, and the emergence of MDR *C. glabrata*, which can acquire resistance following exposure to antifungal agents, presents significant challenges in many medical centers [25]. Moreover, only three drug classes are licensed for monotherapy against *Candida* infections including azoles,

polyenes, and echinocandins [25]. Therefore, new antifungal drug candidates from additional drug classes are sought after.

Stigmurin, selected and synthesized based on transcriptomic analysis of the *T. stigmurus* venom gland, exhibits both antibacterial and antifungal activity. It is effective against the Gram-positive bacterial species, *S. aureus*, including methicillin-resistant strains. Stigmurin has also been demonstrated to be effective against the fungi *C. albicans*, *C. krusei*, and *C. glabrata*, with low toxicity against healthy human erythrocytes [26]. These data suggest that stigmurin could be considered for the treatment of candidiasis. More recently, two analog peptides, StigA6 and StigA16, were designed from the original peptide that demonstrated improved antimicrobial and antifungal activity. These peptides could inhibit the growth of both Gram-positive and Gram-negative bacteria, as well as *C. albicans*, *C. krusei*, and *C. glabrata*, at lower minimal inhibitory doses compared to stigmurin [27]. StigA6 and StigA16 also showed high antiparasitic activity against *Trypanosoma cruzi*. This study demonstrated that rational design using scorpion toxins as scaffolds may be useful for obtaining leads with improved therapeutic features against a wide range of pathogens, including fungi.

2.3. Antiviral Effects

Few antiviral vaccines and drugs are commercially available against the more than 200 viruses known to infect humans [28], which is a situation that has been highlighted by the current SARS-CoV-2 pandemic and puts an emphasis on the importance of the discovery and development of new antiviral agents. To this end, venomous animals are considered by many researchers as promising sources for such discoveries [28][29]. While some scorpion toxins show specific antiviral effects against just one type of virus, other toxins are active against several different viruses. Mucroporin-M1, a derivative of mucroporin from the *Lychas mucronatus* venom, presents antiviral activities against three RNA viruses: measles (MeV), severe acute respiratory syndrome-related coronavirus (SARS-CoV), and influenza (H5N1). Given the dual inhibitory activities against viruses and bacteria, mucroporin-M1 may be considered as a lead compound for treating viral and bacterial co-infections. Mucroporin-M1 also serves as an example demonstrating the potential of peptides from scorpion venoms to be used as scaffolds for designing multifunctional antiviral agents.

Another example is the recombinant peptide, rEv37, from the scorpion *Euscorpiops validus*, which was demonstrated to possess inhibitory effects against dengue virus type 2 (DENV-2), hepatitis C virus (HCV), Zika virus (ZIKV), and herpes simplex virus type 1 infections at non-cytotoxic concentrations. The inhibitory effects of rEv37 against DENV-2, HCV, and ZIKV infections were determined in the hepatoma cell line Huh7 via real-time fluorescent quantitative PCR for mRNA in the infected cells. rEv37 was able to reduce the level of DENV-2, HCV, and ZIKV infection at the mRNA level at a concentration of 10 μM by 91%, 97%, and 87%, respectively. Since the cellular entry processes of these four viruses are similar, it has been suggested that a specific molecular mechanism, in which the rEv37 peptide alkalizes acidic organelles to prevent low pH-dependent fusion of the viral membrane to the endosomal membrane, blocks the release of the viral genome from the endosome to the cytoplasm and thus restricts viral late entry [30]. The propensity to cause adverse reactions, lack of or low efficacy,

and the high price of the very few vaccines and therapeutics that are available against the aforementioned viruses [31][32] emphasize that rEv37 may be a relevant lead that possibly could be developed into an antiviral drug.

Smp76, a scorpine-like peptide from the venom of *S. maurus palmatus*, is another recent example of a scorpion-derived agent that is effective against different viruses. The recombinantly expressed peptide (rSmp76) can inhibit RNA replication and protein synthesis of DENV-2 and ZIKV in primary mouse macrophages, the human lung adenocarcinoma cell line (A549), the Huh7 cell line, and the human monocytic cell line (THP-1) in a dose-dependent manner. Although the detailed molecular mechanisms of the rSmp76-induced inhibitory effects need to be elucidated, it seems that the mechanism of inhibition did not include direct inactivation of the viral particles. It has been suggested that rSmp76 suppresses an established viral infection by upregulating interferon-β expression through the phosphorylation of the interferon regulatory factor 3, which enhances type-I IFN responses and thus inhibits viral infection [33]. Since the achievement of viral clearance is very difficult, antiviral agents, such as rSmp76, that can suppress established viral infections are considered to be more efficient than traditional antiviral therapeutics, which exert their antiviral effects through the direct inactivation of viral particles or the inhibition of viral cell entry [33]. Enhancing the protective effects of host innate immunity, such as interferon (IFN) activation, by antiviral agents, such as rSmp76, may potentially circumvent the development of drug resistance and the effects of genetic variability in the viral genome [34]. These examples, selected from dozens of ongoing studies, demonstrate the potential of scorpion-derived peptides to be developed as antiviral therapeutics.

2.4. Antiparasitic Effects

Parasitic diseases are considered a health problem, particularly in developing countries, where people are frequently infected by parasites belonging to the genera *Plasmodium*, *Trypanosoma*, and *Leishmania* among others [35][36]. Since antiparasitic therapeutic agents available for clinical use are often toxic [37], there is an urgent need for the discovery and development of novel therapeutics [38].

Scorpion toxins have been demonstrated to possess inhibitory effects against a number of parasites. Scorpine, purified from *Pandinus imperator* venom, was the first isolated scorpion toxin that demonstrated antiprotozoan effects against *Plasmodium berghei* [39]. Later on, recombinantly expressed scorpine produced 98% mortality in the sexual stage of *P. berghei* and 100% reduction in *P. falciparum* parasitemia [40]. Similarly, meucin-24 and meucin-25, two linear non disulfide bridged peptides (NDBPs) synthesized from a cDNA library of the *M. eupeus* venom gland, demonstrated antimalarial activity. Both peptides inhibited the development of *P. berghei* and killed intra-erythrocytic *P. falciparum* parasites at micromolar concentrations without harming mammalian cells [41], making them potential candidates for antimalarial therapies.

Scorpion-derived agents can be effective against other parasites as well. *Taenia solium* (pork tapeworm) is a parasite responsible for taeniasis (intestinal infection) and cysticercosis (tissue infection) in humans [42]. In 2010, *T. solium* cysticercosis was added to the list of major Neglected Tropical Diseases (NTDs) of the World Health Organization (WHO) [43]. *T. crassiceps* is another species of the Taeniidae family of tapeworms that, due to extensive antigen similarity with *T. solium*, functions as an experimental model to test and screen promising antigens before testing them in pigs [44]. It has been demonstrated *in vitro* that Hge36, a naturally occurring

truncated form of a scorpine-like peptide from the *Hoffmannihadrurus gertschi* venom, can reduce the viability of *T. crassiceps* larval cysts at submicromolar concentrations while having a minimal effect on human lymphocytes [45].

Human African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas disease) are induced upon infection with the protozoan parasites, *T. brucei* and *T. cruzi*, respectively. Being considered endemic in Latin America, Chagas disease is a potentially life-threatening illness that affects 6–7 million lives according to the WHO [46]. In an *in vitro* assay, it was recently demonstrated that stigmurin and its analogs, StigA6, StigA16, StigA25, and StigA31, show high antiparasitic activity against epimastigote forms of *T. cruzi* that is a form naturally found in the gut of infected insect vectors [27][19]. StigA6 and StigA16 have also been shown to have activity against trypomastigote forms of *T. cruzi*, which are mainly found in the blood of patients in the acute phase of Chagas disease. In addition, these peptides demonstrate higher antiparasitic activity at a lower concentration compared to benznidazole, which together with nifurtimox are currently available as Chagas disease medicines [29].

It has been demonstrated that *Leishmania* parasites are sensitive to peptides with antimicrobial and ion channel inhibitory activity. Since scorpion venoms are rich sources of such peptides, Borges et al. could demonstrate that *T. discrepans* crude venom and its main fractions (TdI, II, and III) were able to inhibit the growth of promastigote forms (the motile, long-elongated flagellated infective form of the *Leishmania* parasite that develops in the midgut of the sandfly) of *L. mexicana*, *L. braziliensis*, and *L. chagasi* that eventually led to parasite death *in vitro* [47]. The leishmanicidal activity of compounds from the venoms of other scorpion species/families has not been reported, and it should be investigated whether the leshmanicidal effects are restricted to the genus *Tityus*.

2.5. Bradykinin-Potentiating Effects

Bradykinin is a potent endothelium-dependent vasodilator peptide with hypotensive properties that belongs to the kinin group of proteins. The angiotensin-converting enzyme (ACE) inactivates bradykinin by degrading it [48][49]. The inhibition of ACE via bradykinin-potentiating peptides (BPPs), such as captopril, which is derived from a peptide found in the venom of the lancehead viper (*Bothrops jararaca*), has been established as a clinically approved strategy for preventing hypertension [50].

It has been demonstrated that the C-terminal fragment of BmKbpp, an AMP from *M. martensii* venom with antibacterial and antifungal activities, shows significant sequence similarity with the peptide K12, which is a known ACE inhibitor from *B. occitanus* venom. In an *in vitro* assay, both BmKbpp whole peptide and its C-terminal fragment (BmKbpp-C) demonstrated bradykinin-potentiating activity at a concentration of 50 nM. However, BmKbpp whole peptide and BmKbpp-C were less potent than peptide K12, with BmKbpp-C being more active than the whole peptide [51]. The sequence similarity between a fragment of a toxin and BPPs is also observed for *T. serrulatus* venom peptides. The N-terminal of Ts3, an α-toxin acting on voltage-gated sodium channels, demonstrated a striking sequence similarity with Ts10 (former Peptide T) which is a known BPP [52]. Ts10 was originally reported as an ACE inhibitor, since it could inhibit the ACE-catalyzed hydrolysis of bradykinin [53]. Later, using male Wistar rats and their aortic rings, *in vitro* and *in vivo* assays demonstrated that the N-terminal of Ts3 ($Ts3_{1\text{-}14[C12S]}$) and Ts10 were not able to directly inhibit ACE activity; instead, they induced a strong vasodilatory

effect that could be reversed in the presence of the nitric oxide (NO) synthase inhibitor, N(ω)-nitro-L-arginine methyl ester (L-NAME). This suggests that Ts10 and $Ts3_{1-14[C12S]}$ play their role by activating molecular targets in the vascular endothelium, which leads to NO production and eventually vasodilation [52]. In addition, it has been reported that *T. serrulatus* hypotensins (TsHpt-I, II, III, and IV) and TistH from *T. stigmurus* also potentiate bradykinin through the improvement of the endothelial function and NO release in rats [54][55]. These cases show that scorpion peptides can potentiate bradykinin through mechanisms other than ACE inhibition.

Besides vasodilation and hypotension, scorpion-derived BPPs play important roles in other physiological processes. It is estimated that a considerable number of cancer patients receive radiation therapy during their course of illness [56]. However, radiation therapy might lead to side effects, including radiation-induced heart disease (RIHD) in patients having lymphoma, breast, lung, and esophageal cancer [57][58]. It has been demonstrated that BPPs obtained from *L. quinquestriatus* improved cardiomyopathy induced by γ-radiation in rats, probably by acting as a scavenger of free radicals to protect the heart from negative effects derived from radiation exposure [59].

2.6. Immunosuppressive Effects

Several scorpion toxins can modulate the immune system [60]. Indeed, the contribution of released inflammatory mediators (e.g., cytokines, eicosanoids, and reactive oxygen species) and activation of the complement system is well explored in the envenoming pathophysiology following scorpion stings [61][60][62]. For instance, an increase in the regulatory cytokines, interleukin (IL)-10 and IL-4, has been observed in experimental envenomings by *A. australis hector* and *C. noxius*, as well as in real human envenomings by *T. serrulatus* [63][64][65][66]. Although most of the studied scorpion toxins exhibit pro-inflammatory effects and activate the immune system [67][68][63][69][70], a few of them demonstrate potential therapeutic applications by controlling the immune responses and acting as immunosuppressive agents.

The most studied class of immunosuppressive scorpion toxins is the blockers of voltage-gated potassium channel type 1.3 ($K_v1.3$). Although many cells express $K_v1.3$, most of the studies have focused on effector memory T cells (T_{EM}) due to the high expression profiles of $K_v1.3$. The T_{EM} cells are a subpopulation of T cells regarded as an attractive pharmacological target because of their role in the development of autoimmune diseases [71]. A recent review covering the structure and function of these channels, as well as the therapeutic implications of blocking $K_v1.3$ using toxins derived from scorpion venom, has summarized the studies of more than 60 scorpion toxins from the *Androctonus*, *Buthus*, *Mesobuthus*, *Lychas*, *Parabuthus*, *Leiurus*, *Centruroides*, and *Tityus* genera [72].

Beside $K_v1.3$ channels, other ion channels, such as $K_v3.1$ and $K_v2.1$, have also been demonstrated to be important for T-cell activation and function [73][74]. Pucca et al. described Ts6 and Ts15, from *T. serrulatus*, which block $K_v2.1$ and inhibit the proliferation and function of different T-cell subpopulations in vitro. The study also showed that Ts15 was capable of inhibiting delayed-type hypersensitivity (DTH) response *in vivo*, indicating the potential of the peptide to be developed into a treatment for autoimmune diseases [74]. Another study performed by Xiao et al. described the immunosuppressive and anti-inflammatory properties of St20, a disulfide-bridged α-KTx found in the venom of *Scorpiops tibetanus*. *In vitro* functional studies showed that this peptide was able to inhibit the expression

of the cell surface marker CD69, as well as the secretion of IL-2, tumor necrosis factor (TNF)-α, and IFN-γ in activated human T cells. *In vivo* experiments using a rat autoimmune disease model showed that DTH was ameliorated in the presence of St20 [75]. Thus, new immunosuppressive therapeutic drugs may be derived from scorpion venom toxins, which can be optimized in regard to structure and function, possibly facilitating the future use of such agents in clinical settings.

2.7. Analgesic Effects

Generally, scorpion stings are reported as very painful events. Most known scorpion toxins are known to modulate voltage-gated ion channels (mainly sodium and potassium channels) [67]. Voltage-gated sodium (Na_v) channels play a key role in nociception (pain) [76]. The Na_v channels comprise a family of nine homologous α-subunits ($Na_v1.1$–$Na_v1.9$), which together with β-units (β1–β4) generate the ion-conducting pore [77]. However, only four Na_v channel subtypes are involved in pain: $Na_v1.1$, $Na_v1.6$, $Na_v1.7$, and $Na_v1.9$ [78][79][80][81]. Throughout the last decades, scorpion toxins capable of inducing pain mediated by these channels have been widely explored [67][82][83][84][85]. Most recently, two peptides, Hj1a and Hj2a, have been isolated from the *Hottentotta jayakari* venom that are potent agonists of $Na_v1.1$. Demonstrating dual α/β activity by modifying both the activation and inactivation properties of the channel, Hj1a and Hj2a may be used as alternative tools for developing selective $Na_v1.1$ modulators for the treatment of epileptic diseases, such as Dravet syndrome [86]. In addition, scorpion toxins that induce pain, mediated by different ion channels, such as voltage-gated potassium channel 4.2 ($K_V4.2$) [87] and TRPV1 [88][89], have also been encountered.

Moreover, scorpion toxins capable of controlling pain (i.e., analgesics) have been reported in the literature. Many of these analgesic toxins are not toxic to mammals, as they belong to a group of insect-specific neurotoxic α or β-toxins that interact with Na_v, K_v, and/or Ca_v pathways [20][90][91][92][93][94]. During the last two decades, over 20 scorpion venom-derived peptides and proteins have been reported to exert anti-nociceptive effects in vitro and in vivo. Due to the absence of toxicity in mammals and comparable effects to the standard of care medications, such as carbamazepine, most of the scorpion-derived proteins are intriguing agents that could be used for the future development of analgesics. The scorpion *M. martensii* (previously known as *B. martensii Karsch*) has been thoroughly studied as the source of more than 15 analgesic peptides [95][96]. Analgesic properties have also been reported in *A. mauretanicus mauretanicus* (AmmVIII, α-anatoxin), *L. quinquestriatus quinquestriatus* (LqqIT2, β-toxin), *H. laoticus* (Hetlaxin, α-toxin), *B. occitanus tunetanus* (BotAF, β-toxin), and *T. serrulatus* (TsNTxP). However, there is still more unexplored venom territory for future discovery in the field of analgesic venom components.

In 2019, Rigo et al. reported the presence of anti-nociceptive effects of a non-toxic protein from *T. serrulatus*, TsNTxP [97]. This protein is described to be structurally similar to Na_v-modulating neurotoxins, such as Ts7. However, TsNTxP is non-toxic to animals. Effects of TsNTxP were studied in 184 adult male and female Swiss mice in regard to acute and neuropathic pain. The results demonstrated that TsNTxP has potent anti-nociceptive properties in both models, which is potentially due to a substantial reduction of glutamate release. These results, combined with the lack of acute adverse effects, suggest that TsNTxP may possibly be utilized in future pain treatment.

2.8. Anticancer Effects

The discovery of specific and selective anticancer drugs that can directly act on tumors, display a synergistic effect with existing chemotherapeutics, or function as cargoes for drugs with low bioavailability is significantly on the rise [98]. Chlorotoxin (CTx) from *L. quinquestriatus* venom is a molecule that interacts with chloride channels. CTx was the first scorpion-derived agent that demonstrated inhibitory effects on glioma cell migration and invasion. It also exhibited the advantage of being able to penetrate deep into tumor tissue [99][100]. Since the discovery of CTx, the list of scorpion crude venoms and isolated toxins with anticancer activity has been growing rapidly, hence a comprehensive review of all reported compounds exceeds the scope of this review, but can be found elsewhere [98][99][100][101]. Here, we present a few cherry-picked recent studies with the most significant findings.

T. serrulatus crude venom was tested in 2019 for possible anticancer effects against the SiHa and HeLa cervical cancer cell lines, and the venom was shown to induce apoptosis in HeLa cells [102]. Wang et al. had previously obtained similar results with the crude venoms of *H. liangi* and *M. martensii*. The two venoms were tested for potential anticancer effects toward HeLa cells, and both venoms showed dose-dependent anti-proliferative and apoptosis-inducing effects through upregulation of the CDK-inhibitor, p21. However, neither of the venoms showed significant effects on non-cancer HUVEC-21 cells, suggesting specificity toward cancer cells [103]. Additionally, the venoms of *A. crassicauda* and *L. quinquestriatus* have been examined using breast (MDA-MB-231) and colorectal (HCT-8) cancer cell lines [104]. This examination revealed that the venoms exhibited significant time and dose-dependent cytotoxicity, and that they caused an increase in the number of apoptotic cells and reactive oxygen species for both cancer cell lines when the cell lines were subjected to the venoms. The observed arrests in the cell cycle could be an indication of tumor suppressor p21 upregulation and could, hence, suggest selectivity toward cancer cells. Anticancer properties have been recently associated with the crude venom of *Rhopalurus junceus* and a mix of five peptides from the same venom [105][106]. Despite generating promising results, further investigations on the aforementioned scorpion crude venoms are needed to characterize the effective anticancer constituents among other venom components.

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