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REVIEW PAPER

Scorpion Venom Peptides as Therapeutic Agents in Cardiovascular Diseases: A Systematic Review

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Abstract

Background Scorpions have evolved a highly efficient venom that serves both to capture prey and for self-defense. As a result, peptides isolated from the venom of various scorpion species show great potential for the development of new medicines.

Purpose This systematic review provides an overview of the therapeutic potential of peptides isolated from scorpion venom that act on the cardiovascular system.

Methods We systematically searched PubMed, Scopus, Web of Science, EMBASE, and the Virtual Health Library for relevant studies published until December 2023, using the terms "peptides," "scorpion," "bradykinin potentiating factor," "effects on cardiovascular diseases," and "antihypertensive effects."

Results The literature search yielded 240 references. After applying the inclusion criteria, 17 studies were selected for analysis. Our review yielded five key findings: First, the identification of canonical bradykinin-potentiating peptides, which act as inhibitors of the angiotensin-converting enzyme, and non-canonical bradykinin-potentiating peptides, which act as B2 receptor agonists, enhancing the physiological effects of bradykinin. Second, a peptide regulating cardiomyocyte proteins was discovered. Third, an inotropic peptide was identified. Fourth, a potent hERG blocker peptide was found. Finally, a peptide with significant sodium current blocking capabilities in ventricular myocytes was identified.

Conclusion The high specificity and potency of these scorpion venom-derived molecules underscore their potential as novel therapeutic agents in the cardiovascular field. This research highlights the importance of exploring natural bioactive compounds for the development of innovative treatments for cardiovascular diseases.

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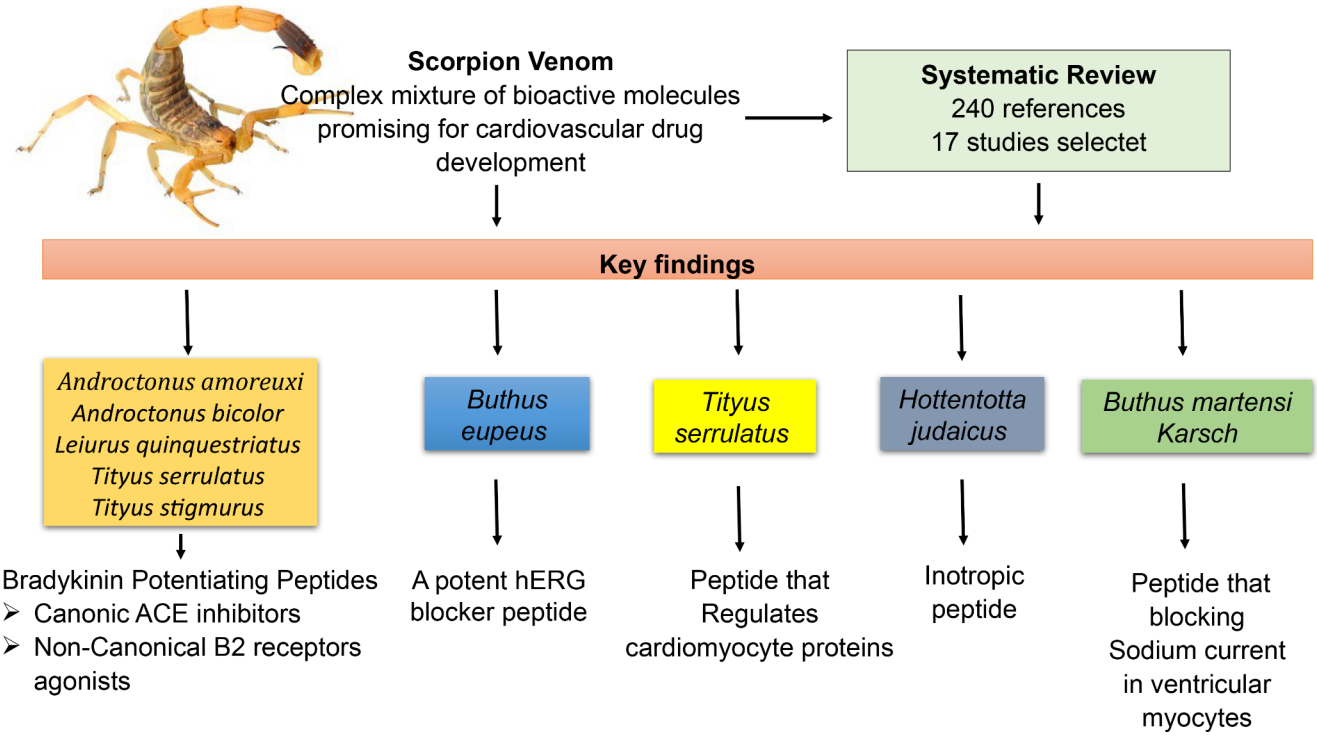
Graphical Abstract



Keywords Venom peptides · Scorpion venom · Cardiovascular diseases · Systematic review

Introduction

Animal venoms contain a complex mixture of bioactive molecules, many of which have evolved to immobilize or kill prey. However, some of these venom components also exhibit properties that make them promising candidates for drug development and therapeutic applications. Peptides isolated from the venom of various scorpion species hold promise for the development of new medicines. Scorpions, which have existed for approximately 400 million years, have largely preserved their morphology throughout their evolutionary history. During this time, they have developed an efficient venom that serves their needs for capturing prey and self-defense (Froy et al. 1999; Zhijian et al. 2006).

There are 1,500 known species of scorpions, and their venoms contain approximately 100,000 peptides with biological activity (Possani et al. 2000). Most toxic peptides in scorpion venom are structured with 3–4 disulfide bridges and possess various bioactive functions, including toxicity to animals and acting as ion channel ligands (Zhijian et al. 2006). The membrane-bound ion channels targeted by the disulfide-bridged peptide (DBP) family of scorpion peptides include Na+, K+, Ca2+, and Cl − channels (Possani et al. 1999). Scorpion venom peptides that lack disulfide bonds represent an important class of peptides due to their high diversity in both primary structures and bioactivities (Zhijian et al. 2006; Almaaytah and Albalas 2014). These non-disulfide-bridged peptides (NDBPs) of scorpion toxins range in size from 13 to 50 amino acids and exhibit low degrees of similarity (Luo et al. 2005; Zeng et al. 2005). Unlike scorpion DBPs that target membrane-bound ion channels, with their functions predicted through sequence analysis of their mature peptides, NDBPs do not appear to exhibit conserved relationships between sequence and function (Almaaytah and Albalas 2014).

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, accounting for approximately 17.9 million deaths each year, representing 31% of all global deaths (Organization 2021). This staggering statistic underscores the urgent need for continued advancements in medical treatments to combat these pervasive health threats. Although biologically active toxins with therapeutic potential have been identified in scorpion venoms, drug development involves preclinical and clinical studies that can be lengthy (Bordon et al. 2020). Developing new medications is crucial in addressing the global CVD crisis. Despite significant progress in cardiovascular medicine, many patients do not respond adequately to existing treatments, and some drugs have adverse side effects that limit

their use. Innovative therapies and personalized medicine approaches, are essential to improve patient outcomes and reduce the global disease burden (Benjamin et al. 2019). The continuous development of new cardiovascular drugs is not only vital for enhancing the quality of life for millions of patients but also for reducing healthcare costs associated with long-term management of chronic conditions. As the global population ages, the demand for effective cardiovascular treatments will inevitably increase, making pharmaceutical innovation a cornerstone of public health strategy (Bloom et al. 2012).

The high incidence and mortality rates associated with cardiovascular diseases highlight the necessity for ongoing research and development of new medications. This systematic review provides an overview of therapeutic potential of peptides isolated from scorpion venom that act on the cardiovascular system, based on the existing literature.

Materials and Methods

The present systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al. 2009) and the PRISMA 2020 checklist (Page et al. 2021).

Search Strategy and Selection Criteria

We systematically searched PubMed, Scopus, Web of Science, EMBASE, and the Virtual Health Library for relevant studies published until December 2023, using the terms "peptides," "scorpion," and "bradykinin potentiating factor" or "effects on cardiovascular diseases" or "antihypertensive effects." A manual review of the reference lists in each identified study was also conducted. When applicable, attempts were made to contact investigators for clarification or additional unpublished data. No language restrictions were imposed.

Two authors (FFS and MS) independently conducted the search. In case of disagreement, three investigators were consulted (IMM). Any discrepancies among the reviewers were resolved through consensus.

Inclusion/Exclusion Criteria

In this review, we included studies that met the following criteria: full research articles reporting in vitro or in vivo experimental studies evaluating the effects of scorpion peptides on bradykinin potentiating factor, cardiovascular diseases, and antihypertensive effects. Studies were excluded if they were duplicates, editorials, letters to the editor, theses, dissertations, reports, or articles outside the scope of this review.

Data Extraction

Three investigators independently conducted data extraction. The extracted data included study characteristics (authors and publication year), scorpion species, studied peptides, study models, and outcomes.

Results

Search Results

Figure 1 depicts the flowchart of the identified studies. The literature search yielded 240 references. After excluding those that did not meet the inclusion criteria, 22 references remained. These 22 potentially relevant articles underwent full-text evaluation. Five articles were excluded for the following reasons: no effects on the cardiovascular system (3) and unavailability of the article (2). Consequently, 17 studies were included in the systematic review. The characteristics of these 17 studies are presented in Table 1.

Peptides with action on the cardiovascular system were isolated from twelve species (refer to Table 1). Bradykinin Potentiating Factor (BPF), also known as Bradykinin-potentiating peptide (BPP) or Bradykinin-Potentiating Activity (BPA), was isolated from four species (*Androctonus amoreuxi*, *Androctonus bicolor*, *Leiurus quinquestriatus*, *Tityus serrulatus*). Additionally, it was traceable in the venom of three other species: *Hottentotta saulcyi*, *Odontobuthus doriae*, *and Mesobuthus eupeus.*

BPF extracted from *Androctonus amoreuxi* venom inhibits the protein expression of angiotensin II and increases AMP-activated protein kinase (AMPK) overexpression, which decreases the inflammatory and fibrotic response to doxorubicin-induced hepatotoxicity. This peptide, along with low doses of γ-irradiation (LDR), attenuates oxidative stress, improves liver function, and alleviates histopathological symptoms of doxorubicin-induced hepatic injury (Hasan et al. 2022). The use of BPF from *Androctonus amoreuxi* as a natural product is comparable to the chemical compound losartan (LOS), as both BPF and LOS treatments induce a significant reduction in sodium and uric acid levels. Treatment of irradiated animals with BPF or LOS significantly improves radiation-induced changes (Ashry et al. 2012). Additionally, a BPF from *Androctonus bicolor* venom significantly mitigates the biochemical and histopathological consequences of radiation through the control of the renin-angiotensin system (RAS) and suppression of

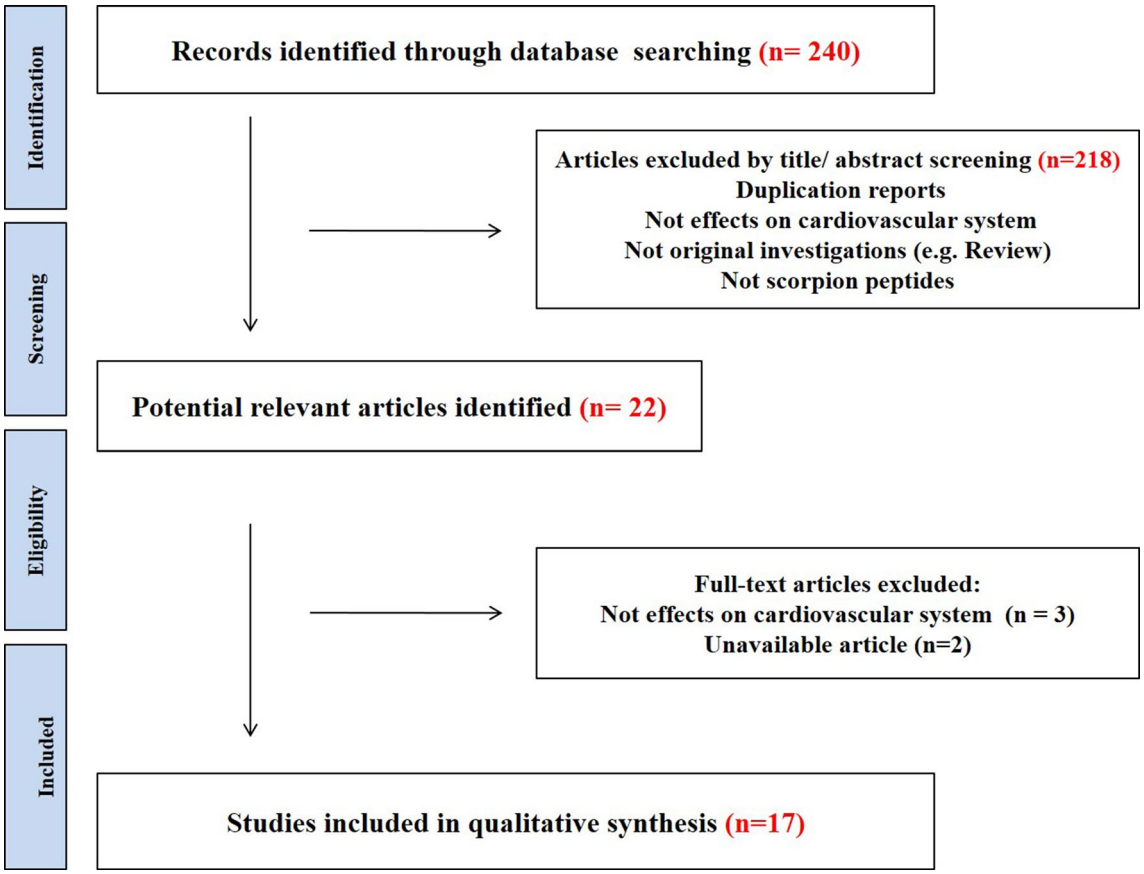


Fig. 1 Flowchart for literature search and study selection. Source: Authors, 2024

Angiotensin Converting Enzyme (ACE) in the lung (Hasan et al. 2021).

The BPA of a gamma-irradiated detoxified fraction of *Leiurus quinquestriatus* scorpion venom elicited a superior cardioprotective effect compared to that of the native fraction against Doxorubicin-induced acute cardiotoxicity in rats (Ahmed et al. 2021). Additionally, one BPF from *Leiurus quinquestriatus* venom, by remodeling the Renin-Angiotensin-Aldosterone System (RAAS) pathway, significantly ameliorated radiation-induced cardiomyopathy. This was evidenced by a notable improvement in disturbed biochemical parameters and histological damage observed through histological and immunohistochemical examinations. Moreover, it acted as a potent scavenger of free radicals, protecting the heart against the deleterious effects of ionizing radiation (Hasan et al. 2020). Nontoxic fractions of isolated venom components from three species of medically important scorpions in Iran, *H. saulcyi*, *O. doriae*, and *M. eupeus*, revealed traces of BPF (Goudarzi et al. 2019).

Hypotensins TsHpt-I (AEIDFSGIPEDIIKQIKETNAKPPA), TsHpt-II (AEIDFSGIPEDIIKEIKETNAKPPA), TsHpt-III (AEIDFSGIPEDIIKQIKETNAKPP), and TsHpt-IV (AEIDFSGIPEDIIKEIKETNAKPP) were isolated from fraction III of *Tityus serrulatus* Venom (TsV) (Verano-Braga et al. 2008). TsHpt-I and the analogue TsHpt-$I_{[KETNAKPPA]}$ decreased mean arterial pressure and induced vasorelaxation in rats in vivo and ex vivo experiments, respectively. At least two pharmacological events occurred in the presence of such peptides: a fast and transient hypotension that seemed to be related to NO release and Bradykinin -independent, and a delayed Bradykinin (BK) potentiation effect (Verano-Braga et al. 2008). TsHpt-I acts as an agonist of the bradykinin B2 receptor, causing fast and transient hypotension without inhibiting angiotensin-converting enzyme but activating the release of nitric oxide (NO). This effect is also mediated by the synthetic TsHpt-I[KPP] analogue but not by TsHpt-I[acKPP], demonstrating that the positive charge located toward the Lys side chain is crucial for this effect (Verano-Braga et al. 2010). Another study demonstrated that TsHpt-I and II increase ACE activity at different levels, while TsHpt-I is a non-competitive inhibitor of neprilysin (NEP), suggesting other hypotensive mechanisms for this peptide, whereas TsHpt-II showed weak inhibition of NEP. Both peptides consist of 25 amino acid residues and feature two consecutive prolines in their C-terminal region. They differ by a single amino acid at position 15: TsHpt-I has a glutamine, while TsHpt-II has a glutamic acid (Duzzi et al. 2021). Other peptides from

Table 1 Characteristics of included studies

First author (year)	Specie	Peptide	Models	Findings
Hasan et al. (2022)	*Androctonus amoreuxi*	Bradykinin Potentiating Factor (BPF)	γ-irradiation (LDR) on doxorubicin (DOX) induced hepatotoxicity in rats	BPF reduce the protein expression of Ang II and increased the proteins of AMPK as an anti-inflammatory and anti-fibrotic marker
Hasan et al. (2021)	*Androctonus bicolor*	BPF	γ-irradiation in rats	BPF leads to ACE inhibition decreased Ang II, increased Ang (1–7) production
Gómez-Mendoza et al. (2020)	*Tityus serrulatus*	Ts14 cryptide KPP (Lys-Pro-Pro)	Cardiac myocytes isolated from C57BL/6 mice	KPP led to AKT phosphorylation, dephosphorylation of PLN leading to reduced contractility of treated cardiomyocytes
Ahmed et al. (2021)	*Leiurus quinquestriatus*	Native fraction and irradiated fraction of Bradykinin-potentiating peptide (BPP)	Doxorubicin -Induced Acute Cardiotoxicity in rats	Irradiated fraction with BPP elicited a greater ameliorative and cardioprotective efect than that of the native fraction in rats with Dox-induced acute cardiotoxic
Setayesh-Mehr et al. (2021)	*Hemiscorpius lepturus*	HL-7 and HL-10 peptides	Hypertension induced by DOCA-salt in mice	Both peptides reduced in a dose-dependent manner systolic blood pressure (SBP) and diastolic blood pressure (DBP). Also, both peptides diminished the mean arterial blood pressure (MAP) in a dose-dependent manner
De Waard et al. (2020)	*Buthus eupeus*	BeKm-1	Cardiomyocytes derived from human-induced pluripotent stem cells	The peptide showed better IC50 values than the reference compounds E4031 and dofetilide. Also, the peptide is favorably selective for hERG channels
Duzzi et al. (2021)	*Tityus serrulatus*	TsHpt- I; TsHpt-II	Murine macrophage	Both peptides increased the catalytic activity of ACE, and TsHpt-I was more effective than TsHpt-II in activating the enzyme. The peptides inhibit enzyme NEP. TsHpt-I inhibit NEP's catalytic activity, in contrast with TsHpt-II. TsHpt-I behaved as a non-competitive inhibitor of NEP
Hasan et al. (2020)	*Leiurus quinquestriatus*	BPF	Cardiomyopathy in irradiated rats	BPF significantly minimized the serum levels of ANP, troponin I and CK, improved the serum levels of LDH, iNOS and endothelin I. Also, reduced MAP significantly. AngII and aldosterone levels recovered significantly in the group of rats exposed to irradiation and treated with BPF and, prevented a histopathological and immunohistochemical alterations in the heart
Goudarzi et al. (2019)	*Hottentotta saulcyi*, *Odontobuthus doriae*, *Mesobuthus eupeus*	BPF	Isolated tissues of guinea-pig ileum and rat uterus	BPF were traceable in the venom of all three scorpion species: the peptides, including Z1 and Z2 regions in the venom fractions of the Hottentotta saulcyi, Z2 in Odontobuthus doriae, as well as Z2 and Z3 in Mesobuthus eupeus
Rocha-Resende et al. (2017)	*Tityus serrulatus*	TS10, Peptide hidden in the N-terminal of Ts3 (Ts31-14[C12S])	Male Wistar rats: Bradykinin potentiating activity, mean arterial pressure and heart rate, vascular reactivity and ACE activity experiments	The peptides potentiate the hypotensive effect of BK. None of these peptides was able to induce a long-lasting BK-potentiating effect. Ts10 and mainly Ts31-14[C12S] induced a strong vasodilation depending of functional endothelium and NO production. Vasodilation was via mAChRs M2 (Ts31) and M3 (Ts31, Ts10)
Kirchhof et al. (2015)	*Hottentotta judaicus*	BjIP - An inotropic peptide	Freshly dissected heart tissue. Isolated hearts of wild type mice. Ventricular murine cardiomyocytes and brain slices of rats	BjIP increased intracellular calcium and prolonged inactivation of the cardiac sodium current. BjIP did not alter the function of Nav1.5, but selectively activated the brain-type sodium channels Nav1.6 or Nav1.3
Machado et al. (2015)	*T. stigmurus*	T. stigmurus Hypotensin (TistH), which are a bradykinin-potentiating peptide (BPP)	Wistar rats. Cardiovascular measurements, Bradykinin-potentiation test, Mesenteric artery rings assay and ACE inhibition	In normotensive rats TistH potentiate the hypotensive action of BK and induced a vasorelaxant effect by endothelium dependent release of NO, and ACE independent inhibition

Table 1 (continued)

First author (year)	Specie	Peptide	Models	Findings
Ashry et al. (2012)	*Androctonus amoreuxi*	BPF	Male albino rats are categorized in six groups which were used losartan (LOS), BPF and irradiated animals using Gamma Cell– 40 (137 Cesium) biological irradiator Isolated rat ileum	Serum aldosterone, sodium, urea and creatinine levels showed a significant increase while a significant drop was recorded for haematological values, calcium and uric acid levels in irradiated animals. BPF or LOS treatment induced a significant drop of sodium and uric acid, and had normalization of aldosterone and calcium levels
Verano-Braga et al. (2010)	*Tityus serrulatus*	TsHpt-I– a bradykinin-potentiating peptide (BPP)	Wistar male rats: Bradykinin- potentiating assay; Aortic ring assay; The ACE inhibition assay; Isolated left ventricle cardiomyocytes	C-terminal Pro-Pro doublet is crucial for the ability of TsHpt-I to potentiate the BK effect. The capacity of this peptide to activate B2 receptor, releasing NO, was also affected by the absence of Lys' side-chain positive charge
Wang et al. (2009)	*Buthus martensi Karsch*	Recombinant BmKIM (poly-peptide)	Rabbits isolated ventricular myocytes. Whole-cell patch-clamp technique. Standard transmembrane action potentials in rabbit hearts in vivo	BmKIM inhibited I(Na) in a voltage-dependent manner, prolonged the recovery of inactivation of I(Na) and shortened 50% and 90% of action potential duration and reduced action potential amplitude. The Q-T duration was shortened and heart rate significantly increased post BmKIM injection. BmKIM significantly reduced incidence of aconitine induced ventricular arrhythmias (77.8%)
Verano-Braga et al. (2008)	*Tityus serrulatus*	Hypotensins (TsHpt) - TsHpt-I and TsHpt-I[17–25]	Male Wistar rats: BK-potentiating assays Enzymatic digestion using carboxipeptidase Y (CPY). Aortic rings assay. ACE inhibition	The peptides induced endothelium-dependent vasorelaxation dependent on NO release. Both TsHpt could not inhibit ACE activity. TsHpt-I was able to potentiate the hypotensive effects of BK in normotensive rats. TsHpt native and synthetic showed relevant hypotensive effect, independent on BK. The peptides induced endothelium-dependent vasorelaxation dependent on NO release. Both TsHpt could not inhibit ACE activity
Peng et al. (2002)	*Buthus martensii* Karsch	BmKIM	Sprague–Dawley (SD) rats and adult rabbit ventricular myocyte. Dorsal root ganglia (DRG) neurons from the lumbar region of albino rats, and neurons isolated	recombinant BmKIM inhibited the sodium current in rat dorsal root ganglion neurons and ventricular myocytes and protected against aconitine induced cardiac arrhythmia

Abbreviations: Ang II, angiotensin II; AMPK, AMP-activated protein kinase; ACE, Angiotensin Converting Enzyme; AKT, PKB (protein kinase B); PLN, phospholamban; DOCA, desoxycorticosterone acetate; hERG, Kv11.1 channel; NEP, neprilysin; ANP, Atrial Natriuretic Peptide; CK, creatine kinase; LDH, lactate dehydrogenase; iNOS, inducible nitric oxide synthase; BK, bradykinin; NO, nitric oxide; mAChRs, muscarinic acetylcholine receptors; TTX, tetrodotoxin; NPY, neuropeptides Y; I(Na), sodium current

Source: authors, 2024

TsV include Ts10 (KKDGYPVEYDRAY) and $Ts3_{1-14[C12S]}$ (KKDGYPVEYDNSAY), a peptide hidden in the N-terminal of Ts3. Both peptides potentiate the hypotensive effect of BK. Ts10 and $Ts3_{1-14[C12S]}$, at high concentrations and in combination with NOS inhibitor or muscarinic acetylcholine receptors blockers, led to vasoconstriction. Ts10 is a potential agonist of the muscarinic acetylcholine receptor (mAChR) M2 and not an Angiotensin Converting Enzyme inhibitor (ACEi). The Nav α-neurotoxin Ts3 potentially has a vasoactive cryptide embedded in its N-terminal that acts via mAChRs M2/M3 activation (Rocha-Resende et al. 2017).

Another peptide, the tripeptide KPP (Lys-Pro-Pro), is a peptide encrypted in the C-terminus of Ts14–a 25-mer peptide from the venom of *Tityus serrulatus* scorpion. KPP up-regulates proteins associated with apoptosis at nucleic and cytoplasmic levels. It also regulates proteins related to cellular stress, such as mitochondrial energetic shift, protein turnover, and muscle contraction. Additionally, KPP induces the dephosphorylation of cardiac phospholamban (PLN), inhibiting the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2a) and subsequently reducing the rate of Ca^{2+} uptake to the sarcolemma, thereby reducing myocardial contractility. KPP also increases NO production via AKT activation (Gómez-Mendoza et al. 2020). *T. stigmurus* Hypotensin (TistH) is a peptide capable of potentiating the hypotensive action of BK and inducing a vasorelaxant effect dependent on the release of NO (Machado et al. 2015).

BeKm-1, a peptide isolated from *Buthus eupeus* venom, delays cardiomyocyte repolarization, induces early afterdepolarizations, and reduces spontaneous action potentials, calcium transients, and contraction frequencies in human-induced pluripotent stem cells (hiPS-CMs). BeKm-1 selectively interacts with the extracellular face of the Kv11.1 channel (hERG), which mediates the IKr current, a major component of cardiac repolarization. BeKm-1 is a 36-amino acid peptide with a molecular weight of 4091.7 Da, containing three disulfide bridges. Based on its homology with other toxins, BeKm-1 belongs to the γ-KTx subfamily of scorpion toxins. Its most notable feature is its high selectivity and affinity for hERG channels, which it blocks in the closed state through a pore obstruction mechanism (Waard et al. 2020).

Kirchhof et al. (2015) conducted pilot experiments demonstrating that an inotropic peptide (BjIP), isolated from the *Hottentotta judaicus* venom, fraction 21 (MKRILVLIAFSLVLIGADA), increased calcium levels in ventricular cardiomyocytes and prolonged the inactivation of the cardiac sodium current. Low concentrations of tetrodotoxin (200nM) abolished the effect of BjIP on calcium transients and sodium current. BjIP did not alter the function of Nav1.5 but selectively activated brain-type sodium channels Nav1.6 or Nav1.3 in cellular electrophysiological recordings obtained from rodent thalamic slices. Nav1.3 (SCN3A) mRNA was detected in human and mouse heart tissue (Kirchhof et al. 2015).

A poly-peptide derived from the Asian Scorpion *Buthus martensi Karsch*, recombinant BmKIM, exhibits a toxic effect on mice only for intravenous injection but not for subcutaneous and intracerebroventricular injection. It is possible that the toxic effect of rBmKIM on mammals is related to cardiotoxicity, as the effect on dorsal root ganglia neurons was not sufficient to kill mice. Therefore, ventricular myocytes may be the direct target of rBmKIM by intravenous injection (Peng et al. 2002). Wang et al. (2009) demonstrated that BmKIM significantly blocks sodium current (I(Na) by affecting the inactivated state of I(Na) in rabbit ventricular myocytes. Additionally, BmKIM attenuates the influx of I(Na), thereby shortening action potential duration amplitude and reducing the incidence of aconitine-induced arrhythmias (Wang et al. 2009).

Discussion

We believe that the solution to many human diseases lies in nature. While the venoms produced by venomous animals are primarily used for defense and prey capture, these venoms also contain peptides and proteins with potential therapeutic applications. Thus, although some components in these venoms can be lethal, others have the potential to cure various diseases. Cardiovascular diseases remain the leading cause of death worldwide, claiming more lives each year than any other illness. Therefore, it is crucial to implement preventive measures and develop new therapeutic drugs to effectively control these diseases. The primary objective of this systematic review was to describe the therapeutic potential of peptides isolated from scorpion venom concerning the cardiovascular system, as outlined in the literature.

The first key finding of the present study is the identification of canonical Bradykinin-potentiating peptides, which act as inhibitors of the angiotensin-converting enzyme, as well as non-canonical Bradykinin-potentiating peptides. The latter act as B2 receptor agonists, augmenting the physiological effects of bradykinin. One notable example of canonical Bradykinin-potentiating peptides is Captopril, an angiotensin-converting enzyme inhibitor used to treat hypertension and heart failure. Captopril's development was inspired by a peptide found in the venom of the Brazilian pit viper (*Bothrops jararaca*). The peptide inhibits the ACE enzyme, which plays a crucial role in regulating blood pressure by converting angiotensin I to the potent vasoconstrictor angiotensin II. By inhibiting this enzyme, Captopril effectively lowers blood pressure and reduces the workload on the heart (Cushman et al. 1982).

The BPA from *Leiurus quinquestriatus* venom shows promise in mitigating doxorubicin (Dox)-induced acute cardiotoxicity. Dox is a chemotherapeutic agent utilized in tumor treatment, yet it triggers dose-dependent acute and chronic cardiotoxic side effects (Sawyer et al. 2010; Kalyanaraman 2020). Gamma-irradiated fractions with BPA have been found to alleviate the severity of cardiac injury caused by Dox (Ahmed et al. 2021). Other peptides, HL-7 and HL-10, derived from *Hemiscorpius lepturus* venom inhibit ACE by binding to its active sites (Setayesh-Mehr and Asoodeh 2017). In a DOCA (Deoxycorticosterone Acetate) salt-induced mice model, it was observed that HL-7 and HL-10 peptides led to a significant decrease in blood pressure among hypertensive mice compared to the control group, in a dose-dependent manner (Setayesh-Mehr et al. 2021). Hence, these peptides hold significant promise as potential antihypertensive agents. Ashry et al. (2012) compared the effects of a BPF isolated from the venom of the Egyptian scorpion *Androctonus amoreuxi* with those of LOS in modulating radiation-induced damage. They found that treatment with either BPF or LOS significantly improved radiation-induced changes in the animals. This discovery is crucial as it highlights potential new avenues for developing treatments to mitigate the harmful effects of radiation exposure. A BPF found in the venom of the scorpion *Androctonus bicolor* significantly reduces lung injury markers associated with angiotensin II when enhanced by

7 Gy gamma irradiation. This effect is achieved through ACE inhibition and the preservation of Ang (1–7) (Hasan et al. 2021).

Non-canonical Bradykinin-potentiating peptides are found in the venoms of *Tityus serrulatus* (TsHpt-I, Ts10, Ts31-14[C12S]) and *T. stigmurus* (TistH). Kininogens are glycoproteins circulating in the blood, primarily synthesized by the liver. When cleaved by proteolytic enzymes called kallikreins, kininogens produce kinins, such as BK and kallidin (KD), in plasma or tissues. Both BK and KD are highly unstable peptides and can be rapidly degraded by enzymes like ACE. Kinins exert their effects by activating two receptor subtypes, B1 and B2. The B2 receptor exhibits high affinity for bradykinin. Bradykinin, in turn, reduces blood pressure and peripheral resistance by relaxing vascular smooth muscle. Additionally, it can stimulate the release of intermediate vasodilatory mediators from the endothelium (Wirth et al. 1991). TistH has a three-dimensional structure solved by homology modeling. It was able to potentiate the action of BK and induce relaxation in mesenteric artery rings, independent of ACE inhibition, and without displaying cytotoxicity (Machado et al. 2015). Therefore, TsHpt-I, Ts10, Ts31-14[C12S], and TistH emerge as intriguing candidates for use in the treatment of vascular diseases.

A second key finding is the discovery of a peptide that regulates cardiomyocyte proteins. Ischemic heart disease is a global epidemic, affecting millions of people worldwide. According to the World Health Organization (WHO), it is the leading cause of death worldwide, responsible for one in every four deaths. The incidence of this condition varies according to factors such as age, sex, ethnicity, lifestyle, and underlying health conditions. From this perspective, the tripeptide KPP (Lys-Pro-Pro) regulates cardiomyocyte proteins. Gómez-Mendoza et al. (2020) studied the cell signaling triggered by the Ts14 cryptide KPP, incubating cardiac myocytes isolated from C57BL/6 mice with KPP (10–7 mol.L-1) for 0 min, 5 min, or 30 min and explored the proteome and phosphoproteome. They found that KPP induced dephosphorylation of cardiac phospholamban at S16 and T17, suggesting that KPP reduces cardiac contractility. In addition, KPP induced phosphorylation of proteins interacting with PLN, such as myosin-binding protein C, cardiac-type. Besides, KPP reduces cardiomyocyte fractional shortening after 5 min of KPP treatment. Taken together, these effects imply that KPP has a negative inotropic effect. Their findings propose a potential beneficial effect of this cryptide on ischemic cardiac injuries (Goméz-Mendoza et al. 2020). Conversely, the third key finding is that pilot experiments conducted by Kirchhof et al. (2015) indicate that the selective activation of TTX-sensitive neuronal sodium channels can safely enhance cardiac contractility. Therefore, the BjIP peptide not only increases cardiac contractility but also does so without inducing ventricular arrhythmias or extending cardiac repolarization. These findings, which are highly promising, suggest that BjIP could serve as a lead compound for the development of a novel class of positive inotropic agents; thus, paving the way for new therapeutic avenues in cardiac care.

Dysfunction in hERG channels is associated with cardiac arrhythmias that can lead to sudden cardiac death (Waard et al. 2020). Class III antiarrhythmic drugs are characterized as K^+ channel blockers, prolonging the duration of the action potential (Maior et al. 2011). These medications are used to treat severe heart rhythm disturbances, symptomatic ventricular tachycardia, symptomatic supraventricular tachycardia, and rhythm changes associated with Wolff-Parkinson-White syndrome. The fourth key finding is that BeKm-1, considered by Waard et al. (2020), is one of the most potent hERG blockers. This peptide is highly selective for hERG channels, with no other known targets (Waard et al. 2020). Unlike small molecule drugs that need to cross the plasma membrane to block hERG from the cytosolic side, BeKm-1 blocks the channel from its outer mouth in a closed state. This property makes BeKm-1 a valuable tool for investigating the proarrhythmic characteristics of hERG blockers. Additionally, as a peptide that can be easily modified, it serves as an ideal molecular platform for designing new hERG modulators with additional functionalities (Waard et al. 2020).

Finally, BmKIM is a promising peptide that mitigates the toxicity of aconitine. Pharmacological studies have shown that aconitine is effective in treating cancer, pain, inflammation, and immune-related diseases (Tai et al. 2015). However, aconitine is a highly poisonous alkaloid. It can cause hepatotoxicity, cardiotoxicity, and neurotoxicity in both animal models and humans (Gao et al. 2022). The cardiotoxicity of aconitine may be linked to alterations in ion channels, energy metabolism, and oxidative damage (Fu et al. 2007; Sun et al. 2014). Comparative analyses have found that low doses of aconitine can produce cardioprotective effects by inhibiting K + channels and decreasing heart rate, while high doses induce cardiotoxicity by activating Na + channels, inhibiting L-type calcium channels, or regulating gene expression (Gao et al. 2022). BmKIM has the potential to reduce aconitine toxicity through a method of compatibility, as this peptide attenuates the influx of I(Na), shortens action potential duration, and reduces action potential amplitude.

Recently, several medications derived from venoms have been developed to treat cardiovascular diseases. Tirofiban, is a non-peptide antiplatelet agent derived from a compound found in the venom of the saw-scaled viper (*Echis carinatus*). Tirofiban acts as a glycoprotein IIb/IIIa inhibitor, preventing platelets from aggregating and forming blood clots, which is crucial in the management of acute coronary

syndromes. This inhibition of platelet aggregation reduces the risk of myocardial infarction and other thrombotic cardiovascular events (Gan et al. 1988; Lazarovici et al. 2019). Eptifibatide is another glycoprotein IIb/IIIa inhibitor, derived from a peptide in the venom of the southeastern pygmy rattlesnake (*Sistrurus miliarius barbouri*). Like Tirofiban, Eptifibatide prevents platelet aggregation, thereby reducing the risk of clot formation in coronary arteries. It is commonly used during percutaneous coronary interventions to prevent complications such as restenosis and thrombosis (Scarborough et al. 1993; Oliveira et al. 2022). Additionally, research into the venom of the cone snail (*Conus magus*) led to the development of Ziconotide, a non-opioid analgesic. Although not primarily a cardiovascular drug, Ziconotide has shown potential in managing severe chronic pain, which can be a comorbidity in patients with cardiovascular disease. Ziconotide works by blocking N-type calcium channels on neurons, thus inhibiting the transmission of pain signals (Miljanich 2004). These examples underscore the potential of animal venoms as sources of novel pharmaceuticals.

According to Tamimi and Ellis (2009), potential drug candidates derived from venoms must undergo a comprehensive array of in vitro and in vivo tests. These tests are essential to thoroughly understand their pharmacological and biochemical properties and to assess their carcinogenicity and effects on the reproductive system, ensuring their safety before progressing to clinical trials (Tamimi and Ellis 2009).

Conclusion

Scorpion venoms are rich sources of bioactive molecules with significant potential in the treatment of cardiovascular diseases. The studies included in this review highlight that toxins isolated from various scorpion species exhibit high selectivity for their specific targets. This selectivity is promising for the development of effective cardiovascular drugs. Moreover, the unique properties of these toxins could lead to innovative treatments for conditions such as hypertension, arrhythmias, and heart failure. The high specificity and potency of scorpion venom-derived molecules underscore their potential as novel therapeutic agents in the cardiovascular field.

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