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Brief Report

Promising Venom-derived Peptides as Innovative Health Solutions for Treating the Metabolic Disorders: A Policy Brief

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Abstract

Background: Metabolic disorders, particularly hyperlipidemia, are recognized as rising global health issues and pose significant public health challenges, especially in low- and middle-income countries (LMICs). Despite the widespread use of chemical drugs such as statins and fibrates, issues like side effects, drug resistance, and poor adherence limit their long-term effectiveness.

Objectives: This policy brief explores the untapped potential of venom-derived peptides, specifically LVP1, a lipolysis-activating peptide isolated from scorpion venom, as innovative, natural therapeutic candidates for treating metabolic diseases.

Methods: Recent transcriptomic studies of Iranian scorpion species demonstrated that although LVP1s derived from Iranian scorpion venom vary in sequence and origin, these peptides share conserved structural motifs, suggesting functional consistency and potential bioactivity in lipid metabolism modulation without the neurotoxic effects.

Results: These findings highlight the dual important opportunity: Conserving biodiversity and investing in venom-based drug discovery as a promising avenue in biopharmaceutical innovation.

Conclusions: The policy brief outlines specific policy recommendations with the aim of supporting venom peptide research, promoting biotechnology partnerships, and integrating biodiversity considerations into national health strategies. With strategic investment and international cooperation in this field, countries like Iran, which are rich in venomous animals, can play a leading role in the advancement and development of next-generation treatments for non-communicable diseases such as hyperlipidemia.

Keywords: Scorpion Venom Peptide, Hyperlipidemia, Metabolic Diseases, Bioactive Peptides

1. Background

The global rise in metabolic disorders such as hyperlipidemia, including both forms, hypercholesterolemia and hypertriglyceridemia, has become an enormous burden on healthcare systems worldwide (1), particularly in low- and middle-income countries (LMICs). This can lead to an increased risk of cardiovascular disease, obesity, diabetes, other chronic illnesses, and stroke (1-5). According to the World Health Organization, elevated cholesterol levels are responsible for one-third of ischemic heart disease incidence worldwide. Thus, hyperlipidemia is recognized as a global public health problem (6). Although chemical drugs such as statins and fibrates are widely used for controlling metabolic disorders, their effectiveness is often challenged by side effects, poor patient adherence, and growing concerns about drug resistance. These limitations highlight the need for researchers and policymakers to find new approaches and alternative treatments to control hyperlipidemia. Nature, particularly venomous animals like scorpions, seems to be a promising resource for natural compounds for alternative treatments of a wide range of diseases, including cancers (7-11), infections (12, 13), cardiovascular (14), autoimmune (15), and metabolic diseases (16),

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potentially with fewer side effects (17-20). Although no FDA-approved drug has yet been developed from scorpion venom components, unlike several medications derived from snake venom, research in this area is actively ongoing across Asia, Europe, and the Americas, and some of these studies have already progressed into different phases of clinical trials (10, 21).

LVP1 (lipolysis activating peptide 1), discovered from the venom gland of scorpion species (22-25), is structurally classified as an α-toxin-like peptide targeting voltage-gated Na^+ channels. However, unlike classical neurotoxins that induce toxicity by disrupting neuronal ion flux, LVP1 has demonstrated non-toxic behavior (22, 23). Recent experimental assays suggest that this peptide may stimulate lipolysis in adipocytes in a dose-dependent manner, potentially through cAMP-mediated pathways. Experimental evidence demonstrated that the LVP1 protein increases the permeability of adipocyte membranes to Ca^{2+} ions, leading to elevated levels of intracellular Ca^{2+}. This initial elevation in calcium concentration activates the classical cAMP/protein kinase A (PKA) signaling pathway, which is a well-known cascade for the activation of lipolytic enzymes such as hormone-sensitive lipase (HSL). Following the activation of PKA, HSL and possibly other related enzymes become phosphorylated, and finally, triglycerides hydrolyze into glycerol and free fatty acids. This activity could ultimately reduce fat accumulation in the body and contribute to the improvement of the lipid profile over the long term (22, 24). This functional divergence from classical neurotoxins positions LVP1 as a novel promising candidate for modulating lipid metabolism and controlling hyperlipidemia without the adverse neurological effects typically associated with venom components (22-27). This mechanism presents several advantages. It directly targets lipolysis without interfering with cholesterol synthesis or other metabolic pathways. Moreover, its rapid function, immediately upon entry into the body, leads to fast lipolysis after administration. Furthermore, in vitro assays demonstrated that LVP1 can directly activate lipolysis in adipocytes in the absence of external hormones such as epinephrine (22). This nervous system-independent mechanism can be considered a promising therapeutic candidate for the treatment of metabolic disorders such as hyperlipidemia and hypercholesterolemia. Additionally, LVP1, due to its distinct mode of action, can be combined with existing lipid-lowering agents (such as statins) without drug interactions.

2. Scientific Basis

In two complementary transcriptomic studies (26, 27), the venom gland profiles of five Iranian scorpion species, intrinsic to Khuzestan province, including *Hottentotta zagrosensis*, *Mesobuthus eupeus* (recently changed to *M. crucittii*), *Androctonus crassicauda*, *H. saulcyi*, and *Hemiscorpius lepturus*, were assessed using next-generation sequencing (NGS) and bioinformatic analysis. These investigations focused on identifying isoforms of the LVP1 protein family, which were expressed across all species (26, 27). A total of 15 alpha and beta subunits of the LVP1 protein related to different isoforms were identified and structurally characterized from four species, except for *H. lepturus*. The predicted three-dimensional conformations, disulfide connectivity, electrostatic surfaces, and hydrophobic domains were closely similar to those of known bioactive LVP1 proteins previously reported in other scorpion species. The conserved structural motifs observed in the structure of LVP1 derived from different scorpion species, coupled with the demonstration of the degradative effect of this peptide in vitro of their similar peptides in other studies (22-27), suggest that LVP1 holds therapeutic promise and could potentially be optimized.

Although the computational and bioinformatics analysis and structural modeling suggest possible biological functions, it is important to consider that these findings are at a preclinical stage. Well-designed experimental assays are needed to verify how these peptides might work in a biological setting. Indeed, LVP1s are an example of naturally derived pharmaceutical peptides that are considered a bridge between traditional biological resources and modern therapeutic development, suggesting new approaches for treating and controlling the growing challenge of metabolic diseases worldwide. In addition to its therapeutic implications, the identification and characterization of LVP1 highlight the important role of scorpion biodiversity as a source of valuable pharmacological compounds. Venomous animal species represent a largely untapped resource of novel biomolecules. Therefore, the preservation of these

ecosystems is not only critical for ecological balance but also for biomedical innovation in the future.

Considering the richness of Iran in scorpion species, with more than 92 species recorded in the country (28), Iran offers a unique opportunity for conducting research projects in this field. The need to preserve biological ecosystems is essential to maintain scorpion diversity in this country. Taken together, these results highlight the Iranian scorpion venom repertoire as a promising reservoir of bioactive molecules that need to be preserved and investigated to determine the therapeutic relevance and functional roles of their compounds.

3. Implications for Global Health, Research, and Policy

The findings from both studies demonstrate how biological components produced in scorpion venom, especially the LVP1 subunits, could play a valuable role in developing new types of medications. These natural macromolecules show promise for treating metabolic disorders, cardiovascular conditions, and other inflammation-related diseases. Venomous animal species represent a largely untapped reservoir of biologically active molecules, some of which have pharmacological potential. This underscores the importance of preserving ecosystems that support these species for maintaining biodiversity and ecological stability, as well as for securing future biomedical innovations. Neglecting the policies necessary to preserve these environments may result in losing access to valuable compounds with therapeutic potential.

From a health policy perspective, the identification and evaluation of the performance of such natural compounds with significant medicinal potential require strategic investment in research. Policy support for applied research initiatives that facilitate the movement of venom-derived therapies from laboratory discovery to clinical application should be considered. This requires the establishment of basic frameworks that streamline research pathways while ensuring safety and efficacy.

For research in health systems, there is a clear need to investigate the clinical utility, safety profiles, and cost-effectiveness of venom-based therapies. Such research will be critical for making evidence-based decisions about integrating these treatments into mainstream conventional healthcare, ultimately improving patient access to innovative and potentially life-saving drugs.

4. Policy Recommendations

4.1. Supporting Venom Peptide Research

National and international organizations should prioritize molecular and pharmacological studies on venom-derived compounds. Specific funding should be allocated to develop research in this field, if possible.

4.2. Develop Venom Biobanks and Genomic Resources

Establish regional repositories of venom gland transcriptomes and proteomes, especially from medically significant scorpions in biodiversity-rich regions.

4.3. Promoting and Encouraging Applied Biotechnology Research

Encourage partnerships between academia and industry to advance the development of venom-based drugs aimed at treating and controlling metabolic and non-communicable diseases.

4.4. Integrating Biodiversity with Health Policies

Recognize venomous animals not only as valuable assets in global health innovations but also for their importance in conservation strategies to protect their natural ecosystems.

4.5. Facilitating International Collaboration

Encourage collaborations with countries that have made significant progress in venom-based drug development. For example, researchers in the United States have developed Tumor Paint, a fluorescent imaging agent derived from the venom of the scorpion, *Leiurus quinquestriatus*. This compound selectively binds to cancer cells, enabling surgeons to illuminate malignant tissue during operations, thereby improving surgical precision and patient outcomes. Additionally, Cuba and Brazil have successfully invested in toxin-based pharmaceutical research through their national biotechnology programs, leading to the development of venom-derived therapies such as CIGB-258 and anti-cancer peptides. These initiatives were made possible by targeted government support and institutional

cooperation between toxinologists and medical researchers.

Iran, with its rich biodiversity and scorpion fauna, is well-positioned to adopt similar strategies by integrating venom-based biopharmaceutical development into national health innovation policies. To replicate the successes achieved in Cuba and Brazil, Iran could facilitate the development of venom-based drugs by creating legal frameworks that recognize venom as a national biological asset. Establishing fast-track regulatory pathways for the expansion of venom-derived therapies under the supervision of the Iranian Food and Drug Administration could aid in this direction. Additionally, introducing tax exemptions, financial assistance, and intellectual property protection to stimulate investment in venom research and peptide drug development would be very beneficial.

5. Expected Outcomes

A. Enhanced innovation in treatment options for hyperlipidemia and metabolic disorders.

B. Strengthened scientific leadership in toxin-based pharmacology.

C. Improved public health through novel, safe, and cost-effective therapeutics derived from native biodiversity.

6. Conclusions

The identification of LVP1 in the venom gland of some Iranian scorpion species represents a significant step towards discovering natural bioactive compounds aimed at treating metabolic diseases. Policymakers and researchers must consider the potential of venom-based therapeutics and the importance of biodiversity conservation as part of a comprehensive strategy to address the burden of non-communicable diseases.

Footnotes

Authors' Contribution: M. B. is the only author of the article and the study was solely carried out by the author.

Conflict of Interests Statement: The author declares no conflict of interest.

Data Availability: All related data is available at two articles before published: doi.org/10.3389/fphar.2024.1464648 and doi.org/10.1038/s41598-023-49556-6 .

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