For Liver Disease could Scorpion Venom Inspire New Treatments

Researchers summarized the therapeutic potential, mechanisms, structural classes, applications, limitations, and future development of scorpion venom peptides for inflammatory and hepatic disorders.

Study

Research on scorpion venom has evolved from traditional medicinal use to its application in structure-based drug discovery. In the mid-to-late 20th century, protein separation technologies, such as high-performance liquid chromatography (HPLC), provided tools to separate toxic macromolecular forms from bioactive peptide fractions.

Later, advances in genome and transcriptome sequencing helped identify peptide precursor sequences despite the limited availability of venom. In addition, nuclear magnetic resonance (NMR) spectroscopy and X-ray crystallography techniques elucidated the conserved structures, while molecular docking and molecular dynamics simulations supported peptide design.

Peptides derived from scorpion venom can generally be grouped into two categories: disulfide-bridged peptides (DBPs) and non-disulfide-bridged peptides (NDBPs). DBPs contain conserved internal disulfide bonds that provide thermal, chemical, and proteolytic stability. They can modify voltage-gated sodium, potassium, calcium, and chloride channels. Their targets include voltage-gated potassium channel 1.3 (Kv1.3), expressed on chronically activated effector memory T cells. NDBPs are generally shorter, linear, and often amphipathic. They can interact with cell membranes or toll-like receptor 4 (TLR4), influencing inflammatory signaling.

Several peptides demonstrate targeted immunomodulatory activity in experimental models. BmKK2, a thermostable DBP from Buthus martensii Karsch, blocks Kv1.3 on macrophages and T cells and downregulates the TLR4/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, reducing inflammasome activation and the release of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β). BmKTX and analogs show nanomolar affinity for Kv1.3. ToAP3 and ToAP4 reduce inflammatory cytokine production and alter antigen presentation and costimulatory molecules.

Venom peptides have been investigated for their roles in neurological inflammation and pain. BotAF has shown potent analgesic activity in rodents. Scorpion venom heat-resistant peptide (SVHRP) crosses the blood-brain barrier and reduces microglial hyperactivation in models of neuroinflammation. Ts14 has been associated with angiogenesis, reduced extracellular matrix deposition, and reduced myeloperoxidase (MPO) and N-acetyl-β-D-glucosaminidase (NAG) activities in tissue repair.

In animal studies, whole crude scorpion venom can cause sublethal hepatotoxicity, including transient hepatocyte swelling, granular degeneration, and elevated serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) following systemic envenomation.

Chronic nonviral hepatic disorders include metabolic dysfunction-associated steatohepatitis (MASH), alcohol-associated liver disease (ALD), drug-induced liver injury (DILI), and progressive cirrhosis. These disorders involve interactions among Kupffer cells, infiltrating leukocytes, and hepatic stellate cells (HSCs).

In mice, a processed Buthus martensii Karsch venom gland aqueous extract containing BmKK2 significantly ameliorated diet-induced non-alcoholic steatohepatitis (NASH), reducing hepatic steatosis, inflammation, and fibrosis by attenuating Kv1.3-mediated macrophage activation and suppressing the NF-κB/TNF-α signaling axis.

The review describes a proposed link among macrophage signaling, transforming growth factor-beta 1 (TGF-β1), HSC activation, and extracellular matrix accumulation; direct hepatic validation remains necessary.

Findings

Smp76, a 76-amino-acid DBP from Scorpio maurus palmatus, targets extracellular viral particles and prevents host-cell entry; it also increases interferon-beta (IFN-β) expression through interferon regulatory factor 3 (IRF3) phosphorylation. It acts against hepatitis C virus (HCV), dengue virus (DENV), and Zika virus (ZIKV). Ctry2459 derivatives neutralize HCV particles and reduce intracellular viral protein accumulation.

For hepatitis B virus (HBV), BmKDfsin4 inhibits viral replication in vitro in a dose-dependent manner, reducing HBV DNA and the viral antigens HBeAg and HBsAg with low cytotoxicity. Mucroporin-M1 reduces expression of hepatocyte nuclear factor 4 alpha (HNF4α), a host factor required for HBV replication. Eval418-FH5 shows improved amphipathic alpha-helicity and metabolic stability, with antiviral activity against herpes simplex virus type 1 (HSV-1).

Peptides can be difficult to isolate and purify, may undergo enzymatic degradation, have short plasma half-lives and poor oral bioavailability, and can produce immune responses or off-target effects. Large-scale production can be technically difficult and expensive, while regulatory, ethical, and target-identification issues add complexity.

Many venom peptides lack experimentally resolved three-dimensional structures, limiting computational analysis. The review highlights artificial intelligence and machine learning, high-throughput molecular display, and bioinformatics as tools that may accelerate peptide discovery and engineering.

Nanoformulations, including liposomes and polymeric and lipid nanoparticles, may protect peptides from degradation, extend systemic half-lives, and support tissue-specific delivery. A phase I trial of chlorotoxin (CLTX)-directed chimeric antigen receptor (CAR) T-cell therapy in recurrent glioblastoma demonstrated feasibility and safety, providing clinical evidence that a scorpion-venom peptide can serve as a targeting component in an advanced therapeutic platform.

Conclusion

Scorpion venom peptides represent a diverse source of bioactive molecules with anti-inflammatory, analgesic, immunomodulatory, antiviral, and potentially hepatic applications. The review summarizes experimental activity against inflammatory pathways, pain-associated processes, viral infections, and diet-induced liver disease in animal or cellular models.

A processed Buthus martensii Karsch venom gland extract containing BmKK2 provides direct preclinical evidence for attenuation of diet-induced NASH in mice, whereas Smp76, Ctry2459, BmKDfsin4, and Mucroporin-M1 demonstrate antiviral mechanisms relevant to hepatitis. However, structural uncertainty, enzymatic instability, pharmacokinetic limitations, immunogenicity, manufacturing challenges, and limited direct hepatic efficacy data remain barriers.

Artificial intelligence, nanodelivery, and rigorous hepatic models may support eventual progression toward clinical evaluation of the most promising candidates. Further research is needed to clarify the mechanisms of action, pharmacokinetics, toxicity, and clinical feasibility.

Source:

https://www.news-medical.net/news/20260908/Could-scorpion-venom-inspire-new-treatments-for-liver-disease.aspx