Área: MED

Computational modeling of Angiotensin Converting Enzyme I inhibition by Ts3 and Ts10 toxins, present in the venom of the scorpion T*ityus serrulatus.*

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Highlights

This study explores an alternative treatment for *Tityus serrulatus* poisoning, using molecular modeling to understand the inhibition of ACE 1 by the Ts3 and Ts10 toxins, present in the scorpion's venom.

Abstract

Accidents involving venomous animals are on WHO official list of neglected tropical diseases, wich persist in poor and marginalized areas, affecting more than a sixth of the world's population. In Brazil, the scorpion *Tityus serrulatus* accounts for the majority of these accidents. Although most cases receive treatment within three hours, a significant percentage (around 10%) of cases are delayed, which can result in complications such as acute pulmonary edema, the leading cause of death after *Tityus serrulatus* poisoning. Conventional anti-scorpion serum is produced from the plasma of horses hyperimmunized with *Tityus serrulatus* venom, but it requires specific storage and transport conditions, which makes it expensive, leading to uneven distribution of the drug and limiting access for small and riverside communities.Thus, there is a pressing need for alternative treatments to conventional antiscorpion serum, which can reduce production and distribution costs, expanding access to treatment. The angiotensin-converting enzyme (ACE 1) is associated with clinical manifestations of arrhythmia, respiratory and cardiac failure, shock and hypertension caused by *Tityus serrulatus* venom. Targeting this enzyme requires studying inhibitors to interrupt its effects. Understanding inhibitors of this enzyme can, of course, also be applied to combating hypertension. The well-known drug "Captopril" comes from the venom of the *Bothrops Jararaca* snake. There are also components in *Tityus Serrulatus* venom that may have antihypertensive properties. While there are conflicting findings from other researchers regarding the function of the Ts3 and Ts10 toxins from scorpion venom, this study aimed to clarify how these toxins interact with ACE 1 at a molecular level, in case it occurs. Ts10, a peptide consisting of 13 amino acids, with 12 being repeats, was compared to the first 13 amino acids of the N-terminal portion of Ts3, which comprises 64 amino acids. Initially, Ts3 was modeled using Alphafold, followed by protein-peptide docking using Hpepdock. Since there's no crystal structure of the Ts3 and Ts10 complex with ACE 1, a control complex between ACE 1 and a natural peptide inhibitor from the venom of the snake *Gloydius blomhoffii* (PDB code: 4APJ) was chosen. The method was validated through crossdocking (RMSD: 0.414, energy score: -109.772) and redocking (RMSD: 0.434, energy score: -117.036). It involved 35 runs with a limited number of amino acids known to be crucial for ACE inhibition, thereby restricting the size of the interaction box. Subsequently, docking between ACE 1 and the first four amino acids of the toxins' N-terminal portion resulted in an energy score of -112.077. As future steps, molecular dynamics will be employed to incorporate the remaining amino acids into the toxins and assess the stability of the complex.

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