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Decoding the molecular symphony of CSTX of *Cupiennius Salei* spider using an approach of bioinformatics

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Abstract
Spider venoms are complex mixtures of bioactive molecules with important ecological roles and growing biomedical interest. This study focuses on CSTX (Cupiennin Spider Toxin) peptides from *Cupiennius salei* and explores their structural and evolutionary characteristics using bioinformatics approaches. This study places CSTX peptides within a broader venom biology framework by interpreting their structural and physicochemical features in the context of the multicomponent nature of spider venom. CSTX peptides are discussed alongside enzymatic components such as hyaluronidases and proteases that facilitate tissue penetration and venom dissemination, as well as polyamines and small bioactive molecules that modulate neuronal signaling and enhance venom efficacy. In addition, the membrane-active and amphipathic characteristics of CSTX are considered in relation to antimicrobial peptides present in spider venoms, highlighting shared mechanisms of membrane disruption and cytolytic activity. Sequence retrieval, physicochemical profiling, secondary and three-dimensional structure prediction, and phylogenetic analysis were carried out to understand the diversity and organization of CSTX peptides. Together, this integrative perspective emphasizes spider venom as a coordinated biochemical system and situates CSTX within a wider evolutionary and functional context rather than as an isolated toxin. Overall, the findings highlight the structural conservation and functional diversity of CSTX peptides and emphasize spider venom as a promising natural resource for future research.

Keywords: Spider venom, cstx peptides, *cupiennius salei*, bioinformatics analysis, venom biology, secondary structure prediction, evolutionary analysis, neurotoxic peptides

Introduction

Spider venoms represent one of nature's most sophisticated biochemical arsenals, evolved over millions of years to facilitate prey capture, immobilization, defense, and microbial suppression [1, 2]. Unlike simple toxic secretions, spider venoms consist of synergistic mixtures of neurotoxic peptides, cytolytic molecules, antimicrobial peptides, enzymes, polyamines, and small signaling compounds that act collectively on multiple physiological targets [3, 4].

Among venomous spiders, the wandering spider *Cupiennius salei* has emerged as a model organism due to its production of Cupiennin Spider Toxins (CSTX), which exhibit potent neurotoxic, antimicrobial, and cytolytic properties [1, 5]. CSTX peptides are amphipathic, cysteine-rich molecules capable of disrupting ionic gradients and depolarizing neuronal membranes [2, 6]. Early biochemical and physiological studies established CSTX-1 as a powerful blocker of voltage-gated calcium channels, leading to rapid paralysis in prey organisms [1, 3].

Advances in computational biology have enabled molecular-level dissection of venom peptides through sequence databases, physicochemical profiling, structure prediction, and evolutionary analysis [7–9]. These approaches have accelerated venom-based research, positioning spider toxins as promising templates for ion-channel modulators, non-opioid analgesics, and antimicrobial agents [8–10].The present study integrates CSTX-focused bioinformatics analysis with broader venom biology to decode the molecular logic underlying spider venom efficiency.

Materials and Methods

Experimentally resolved membrane-associated proteins and ion channels relevant to spider venom activity were referenced from the Protein Data Bank (PDB; https://www.rcsb.org) to provide structural context for interpreting CSTX functional behavior. CSTX peptide sequences were retrieved from the UniProt database (https://www.uniprot.org) and the National Center for Biotechnology Information (NCBI; https://www.ncbi.nlm.nih.gov) using curated identifiers such as P81694, P58604, and B3EWT0 [7]. Structural features of CSTX peptides were analyzed using sequence-based predictions. Secondary structure prediction of CSTX peptides was performed using the PSIPRED server (http://bioinf.cs.ucl.ac.uk/psipred) to identify α-helical, coil, and disordered regions based on amino acid sequence composition. Evolutionary relationships among CSTX peptides were examined through multiple sequence alignment and phylogenetic tree construction using the Clustal Omega tool (https://www.ebi.ac.uk/Tools/msa/clustalo) [14].

Results

Target Proteins Of CSTX

In below Figure1 A–D presents representative membrane-associated proteins used to provide biological context for CSTX functional interpretation. These include the human voltage-gated sodium channel Nav1.4 (PDB ID: 6AGF), the potassium channel Kv1.3 (PDB ID: 3LUT), a bacterial membrane pore protein (PDB ID: 2N5Z), and the Na^+/K^+-ATPase pump (PDB ID: 3WGU). These proteins represent physiologically relevant membrane systems commonly affected by venom-derived peptides and serve as comparative structural references rather than direct interaction models. Their inclusion highlights the membrane-centric environment in which CSTX peptides exert biological activity.

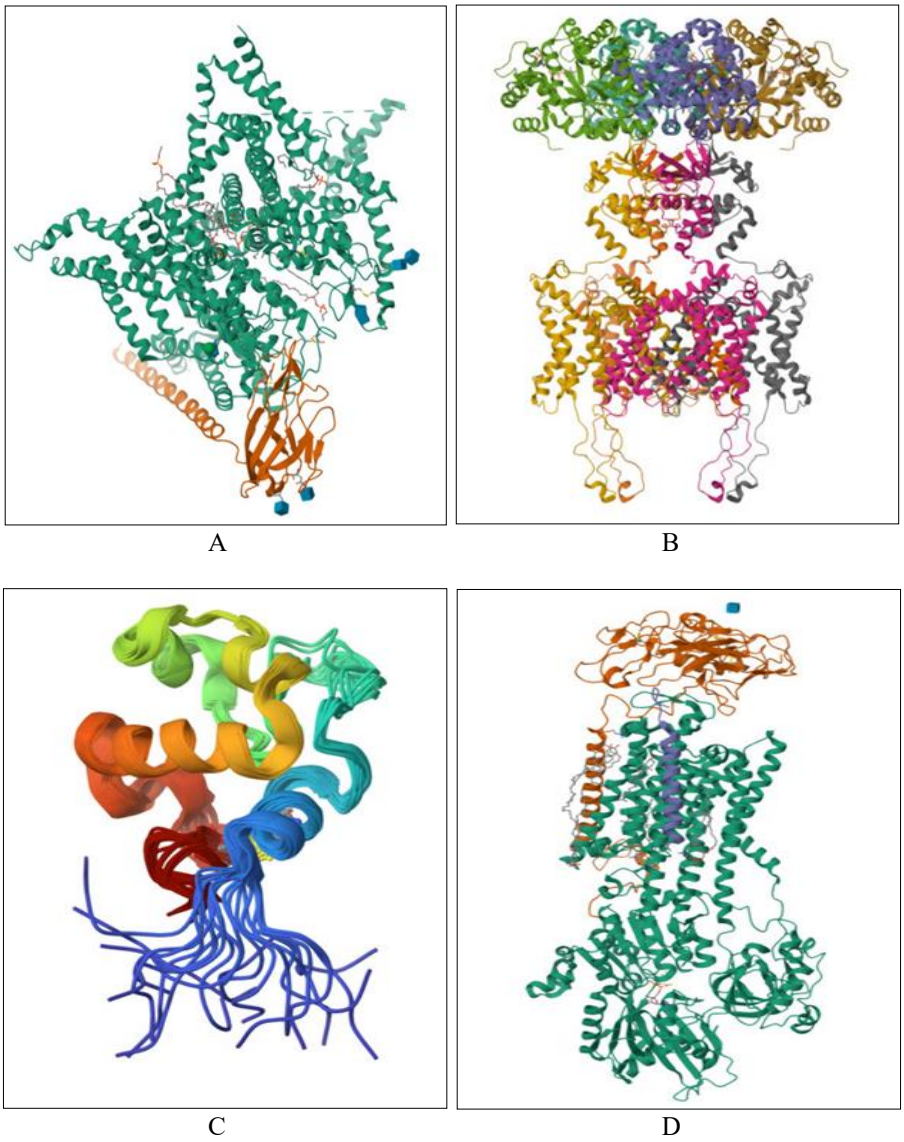

Fig 1: A-D shows 3D target protein structures of CSTX. A-Human voltage-gated sodium channel Nav1.4 (PDB ID: 6AGF),B-Potassium channel Kv1.3 (PDB ID: 3LUT).C- Bacterial membrane pore protein (PDB ID: 2N5Z).D- The Na^+/K^+-ATPase pump (PDB ID: 3WGU)

The sequence panel on the right displays the primary amino acid sequences of multiple CSTX variants retrieved from UniProt. Despite variability in sequence length, the CSTX family exhibits conserved cysteine residues and positively charged amino acids, suggesting preservation of structural stability and membrane affinity across variants. Signal peptide regions are evident in several sequences, indicating secretion and venom-specific targeting. Sequence conservation patterns observed across CSTX isoforms support the presence of a shared functional scaffold, while variations in length and composition likely contribute to functional diversification within the venom system.

Sequence Characterization

A total of fourteen CSTX peptide sequences shown in Table 1 were retrieved from the UniProt and NCBI databases using curated identifiers. The retrieved peptides ranged in length from 14 to 122 amino acids, reflecting substantial size variability within the CSTX family. Despite differences in length, the sequences exhibited conserved cysteine residues and charge distributions, suggesting preservation of core structural and functional features across CSTX variants.

Sequences

>sp|P81694|TXC1_CUPSA Toxin CSTX-1 OS=Cupiennius salei OX=6928 PE=1 SV=2
MKVLIISAVLFITIFSNISAEIEDDFLEDESFEAEDIIPFF
ENEQARSCIPKHEECTNDK
HNCCRKGLFKLKCQCSTFDDESGQPTERCACGRPMG
HQAIETGLNIFRGLFKGKKKNKKT
KG
>sp|B3EWT0|TXC10_CUPSA Toxin CSTX-10 OS=Cupiennius salei OX=6928 PE=1 SV=2
MKVLVIFAVLSLVIFSNCSAETDEDFFGEESFEADDIIP
FIAKEQVRKDKENCIGKHHEC
TDDRDNCCKGKLFRYQCQCFKVIDGKKETKRCACVT
PLHYKMAEMAVSVFKKMFKN
>sp|B3EWS5|TXC8_CUPSA Toxin CSTX-8 OS=Cupiennius salei OX=6928 PE=1 SV=2
MKVLVICAVLFLAIFSNSSAETEDDFLEDESFQADDVI
PFLASEQVRSDCTLRNHDCTDD
RHSCCRSKMFKDVCKCFYPSQRSETDRAKKELCTCQ
QPKHLKYIEKGLQKAKDYATG
>sp|P58604|TXC9A_CUPSA Toxin CSTX-9 OS=Cupiennius salei OX=6928 PE=1 SV=2
MKVLVICAVLFLAIFSNSSAETEDDFLEDESFEADDVI
PFLAREQVRKDDKNCIPKHHEC

TNDKKNCCKKGLTKMKCKCFTVADAKGATSERCAC DSSLLQKFGFTGLHIIKGLF
>sp|B3EWT1|TXC11_CUPSA Toxin CSTX-11 OS=Cupiennius salei OX=6928 PE=1 SV=1
KDKENCIGKHHECTDDRDSCCKGKLFRYQCQCFKVI DGKKETKRCACVTPLHYKMAEMAV SVFKKMFKN
>sp|B3EWS6|TXC12_CUPSA Toxin CSTX-12 OS=Cupiennius salei OX=6928 PE=1 SV=2
MKVLVICAVLFLTIFSNSSAETEDDFLEDESFEADDVI PFLAREQVRSDCTLRNHDCTDD RHSCCRSKMFKDVCKCFYPSQRSDTARAKKELCTCQ QDKHLKFIEKGLQKAKVLVAG
>sp|P83919|TXC13_CUPSA Neurotoxic enhancer CSTX-13 OS=Cupiennius salei OX=6928 PE=1 SV=3
MKVLVIFAVLSLVIFSNCSAETDEDFFGEESFEADDIIP FIAKEQVRSDCTLRNHDCTDD RHSCCRSKMFKDVCTCFYPSQRSETARAKKELCTCQ QPKHLKYIEKGLQKAKDYATG
>sp|B3EWS7|TXC14_CUPSA Toxin CSTX-14 (Fragment) OS=Cupiennius salei OX=6928 PE=1 SV=1
SDCTLRNHDCTDDRHSCCRSKMFKDVCKCFYPSQAK KELCTCQQDKHL
>sp|B3EWS8|TXC15_CUPSA Toxin CSTX-15 (Fragment) OS=Cupiennius salei OX=6928 PE=1 SV=1
SDCTLRNHDCTDDRHSCCRSKMFKDVCTCFYPSQAK KELCTCQQPKHL
>sp|B3EWS9|TXC16_CUPSA Toxin CSTX-16 (Fragment) OS=Cupiennius salei OX=6928 PE=1 SV=1
NFLEMLKENCKLLWKRQKQKFRIPMPESLCQILKKK KQ
>sp|B3EWT2|TX20A_CUPSA Toxin CSTX-17 OS=Cupiennius salei OX=6928 PE=1 SV=1
GCIPKHKRCTWSGPKCCNNISCHCNISGTLCKCRPGL FGW
>sp|B3EWT3|TX27A_CUPSA Toxin CSTX-18 OS=Cupiennius salei OX=6928 PE=1 SV=1
GLWIKGNYCLRGRCLPGGRKCCNGRPCECFAKICSC KPKLIGKLSALKKHT
>sp|B3EWT4|TX27B_CUPSA Toxin CSTX-19 OS=Cupiennius salei OX=6928 PE=1 SV=1
NYCVAKRCRPGGRQCCSGKPCACVGKVCKCPRDNS

Table 1: Structural and Functional Characteristics of CSTX -Cupiennin Spider Toxin Peptides

Sr.No	CSTX Name	Uniprot Id	Amino Acids	Size (Da)	Ld_{50} On Drosophila	Bioactivity Description
1.	CSTX-20	—	86	9,918	—	Largest; ion-channel modulation
2.	CSTX-1	P81694	122	8,352	0.35 pmol/mg	L-type calcium channel blocker, knottin
3.	CSTX-10	B3EWT0	69	8,110	—	Calcium channel blocker, cytolytic
4.	CSTX-11	B3EWT1	69	8,083	—	Similar to CSTX-10
5.	CSTX-9	P58604	68	7,529	10.6 pmol/mg	Sodium channel blocker
6.	CSTX-8	—	63	7,378	—	Modulates neuromuscular function
7.	CSTX-12	B3EWS6	63	7,312	—	Likely cytolytic
8.	CSTX-13	P83919	63	7,359	16.3 nmol/g	Ion channel altering, cytolytic
9.	CSTX-14	—	48	5,657	—	Reduces excitability
10.	CSTX-15	B3EWS8	48	5,612	—	Supports pain signaling
11.	CSTX-18	—	51	5,611	—	Disrupts nerve transmission
12.	CSTX-16	—	38	4,748	—	Possible antimicrobial
13.	CSTX-19	B3EWT4	35	3,748	—	Venom diffusion support
14.	CSTX-17	—	14	4,410	—	Weak toxicity, minimal structure

Key: CSTX-Cupiennin Spider Toxin,LD_{50} -LETHAL DOSE

Structural Analysis

Most CSTX peptides adopt amphipathic α-helical conformations stabilized by cysteine-rich motifs and multiple disulfide bridges. These structural features confer conformational stability, resistance to proteolytic degradation, and strong interactions with biological membranes. The abundance of positively charged residues, such as lysine and arginine, enhances membrane association and cytolytic activity, explaining the antimicrobial and membranolytic behavior observed in several CSTX variants [6, 19]. The absence of a resolved CSTX structure necessitates the use of structurally characterized target proteins to investigate CSTX interactions using computational and comparative approaches.

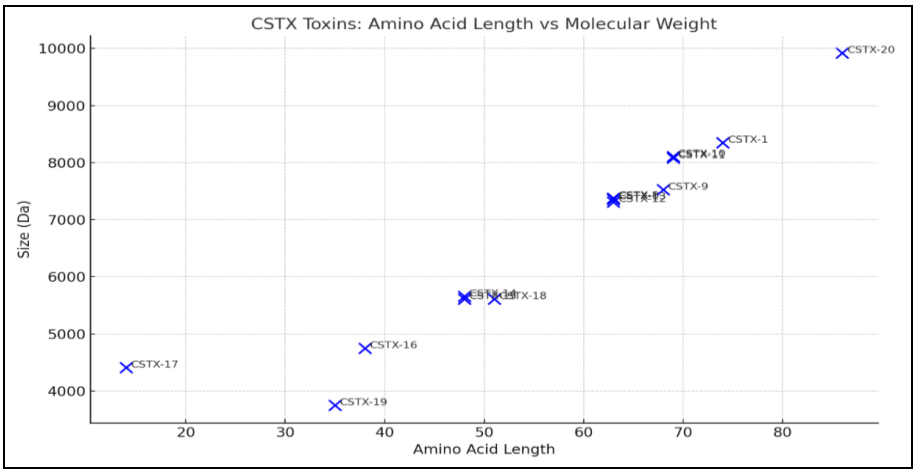

Fig 2: Scatter Plot of CSTX protein and molecular weight Interpretation

The scatter plotshown in figure 2 illustrates the relationship between amino acid length and molecular weight of CSTX peptides derived from *Cupiennius salei*. Each data point represents an individual CSTX toxin, plotted according to its sequence length (X-axis) and corresponding molecular weight in Daltons (Y-axis). A clear positive correlation is observed, indicating that molecular weight increases proportionally with amino acid length, reflecting consistency in primary sequence composition across the CSTX family.CSTX-20 appears as the largest peptide, exhibiting both the highest amino acid count and molecular weight, suggesting greater structural complexity and potentially broader functional roles. CSTX-1, although smaller than CSTX-20, occupies the upper range of the plot, consistent with its well-documented high biological potency.

Most CSTX peptides cluster within the 60–75 amino acid range and 7–8.5 kDa molecular weight, indicating a conserved size window that may be optimal for venom efficacy. In contrast, shorter peptides such as CSTX-17, CSTX-19, and CSTX-16 occupy the lower region of the plot, reflecting reduced structural complexity and likely auxiliary or supportive roles within the venom. Overall, the plot highlights both structural conservation and diversity within the CSTX peptide family, demonstrating that while size and molecular weight are correlated, functional specialization does not strictly depend on peptide length.

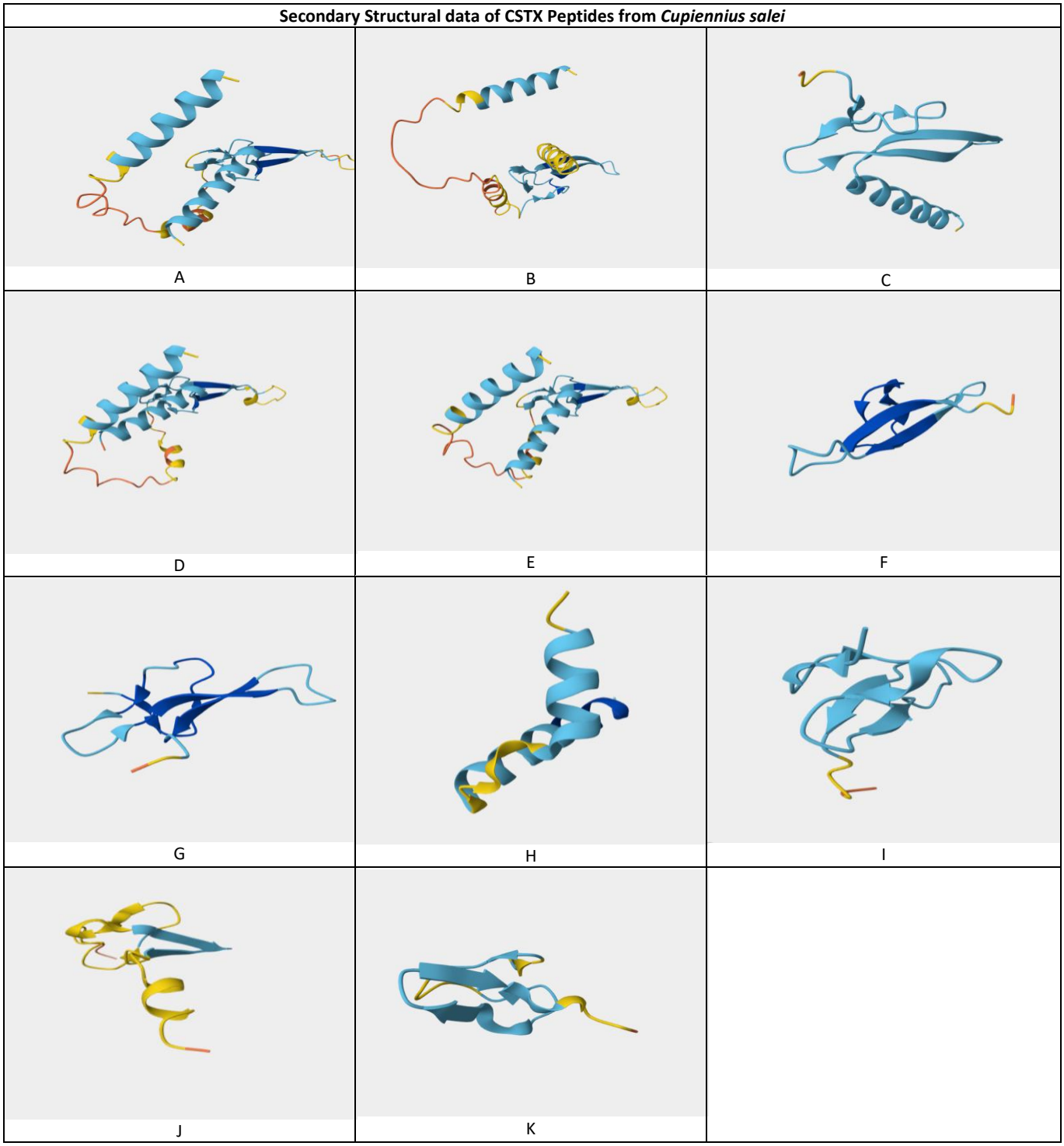

Fig 3: Comparative Secondary Structure Analysis of different CSTX Peptides A-CSTX-8,B- CSTX-9, C-CSTX-11,D-CSTX-12,E- CSTX-13,F- CSTX-14,G- CSTX-15, H-CSTX-16, I-CSTX-18, J-CSTX-17,K-CSTX-19

Figure 3 shows Comparative Secondary Structure Analysis of different CSTX Peptides Cysteine residues were conserved in both number and relative positioning across multiple CSTX sequences, supporting the formation of stabilizing disulfide bridges as a common structural feature. While CSTX-1 contains a well-defined signal peptide and hydrophobic N-terminal helix, shorter CSTX peptides displayed truncated N-terminal regions but retained cysteine-rich cores and helical motifs. Variability was more pronounced in the C-terminal regions, where differences in length and charge distribution were observed; however, enrichment of positively charged residues remained a shared characteristic, reinforcing the membrane-active nature of CSTX peptides. Overall, the comparative analysis indicates that CSTX-1 represents the canonical structural blueprint of the CSTX family, with other variants maintaining core α-helical and cysteine-rich features while exhibiting sequence-level diversification that may contribute to functional specialization within spider venom. secondary structure

The plot presents a combined analysis of CSTX peptides from *Cupiennius salei*, integrating sequence-derived size variation with predicted secondary structural features. The scatter plot on the left illustrates the relationship between amino acid length and molecular weight of CSTX peptides, showing a strong positive correlation, which confirms consistency in primary sequence composition across the CSTX family. CSTX-20 appears as the largest peptide, exhibiting the highest amino acid count and molecular weight, suggesting increased structural complexity. CSTX-1, although smaller than CSTX-20, occupies the upper range of the plot, consistent with its well-documented high biological potency. The majority of CSTX peptides cluster within the 60–75 amino acid range and 7–8.5 kDa molecular weight, indicating a conserved size window that may be optimal for venom function. Smaller peptides such as CSTX-17, CSTX-19, and CSTX-16 fall in the lower region of the plot, reflecting reduced structural complexity and likely auxiliary or supportive roles within the venom.

The panel on the right displays predicted secondary structures of representative CSTX peptides (A–K), revealing a predominance of α-helical conformations interspersed with coil regions and minimal β-sheet content. Despite variation in peptide length, a conserved structural framework is evident across CSTX variants, characterized by amphipathic helices and compact folds. Several peptides exhibit well-defined helical bundles, while others show shorter helices with flexible terminal regions, indicating structural diversification built upon a common scaffold. This combination of size-dependent variation and conserved secondary structural motifs highlights the evolutionary optimization of CSTX peptides, where structural stability and functional diversity are balanced to enhance venom efficacy.

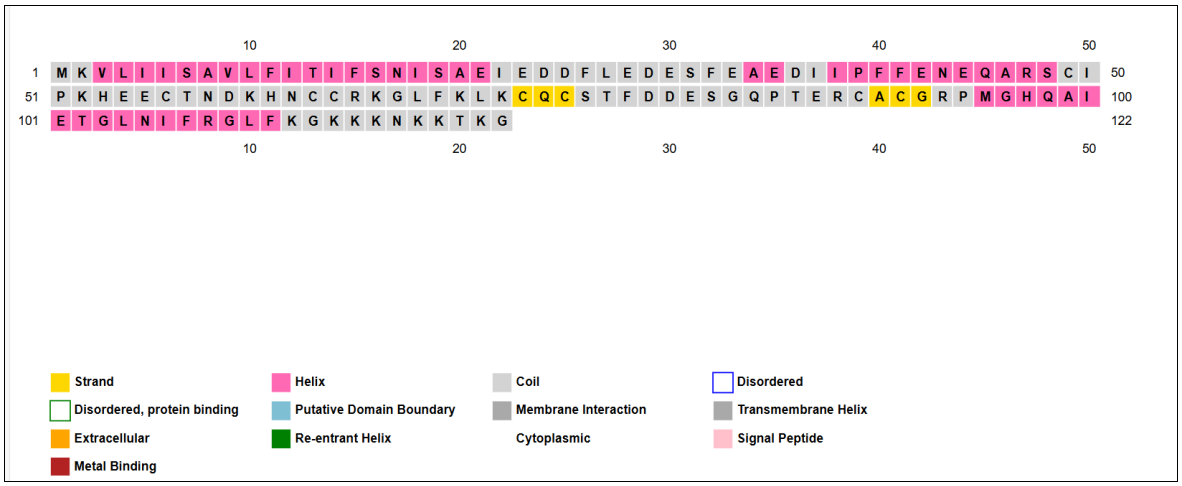

Fig 4: PSIPRED result for CSTX-1 (uniprot id: p81694)

Interpretation of PSIPRED Secondary Structure Prediction for CSTX

The PSIPRED secondary structure predictionin figure 4 indicates that CSTX is predominantly composed of α-helical segments, interspersed with short coil regions, and lacks extensive β-strand elements. The N-terminal region of CSTX shows a pronounced helical stretch enriched in hydrophobic residues, suggesting an amphipathic α-helix that is characteristic of membrane-active venom peptides. This region also overlaps with a predicted signal peptide and membrane-interacting segment, indicating its role in secretion and initial membrane association.

Multiple cysteine residues are distributed throughout the sequence, particularly in the central and C-terminal regions, which supports the formation of disulfide bridges that stabilize the peptide's tertiary structure. The presence of these cysteine-rich motifs is a hallmark of spider venom toxins and contributes to structural rigidity and resistance to proteolytic degradation. Additionally, the C-terminal region displays enrichment of positively charged residues (lysine and arginine), consistent with electrostatic attraction to negatively charged biological membranes.Notably, the prediction shows minimal disordered regions and no extended transmembrane helices, indicating that CSTX does not span membranes but instead associates peripherally with lipid bilayers, facilitating cytolytic and antimicrobial activity. Overall, the PSIPRED profile reveals CSTX as a structurally organized, amphipathic, α-helical peptide optimized for membrane interaction and venom efficacy.

Comparative PSIPRED-based secondary structure analysis across CSTX family peptides revealed a highly conserved structural framework, with CSTX-1 (UniProt ID: P81694) serving as a representative model. Similar to CSTX-1, other CSTX peptides exhibited a predominance of amphipathic α-helical regions, particularly within the N-terminal and central segments, indicating a conserved helical architecture

across the toxin family. Although sequence length varied substantially among CSTX variants, the distribution of predicted helices and coil regions remained broadly consistent, suggesting functional conservation despite primary sequence divergence.

Phylogenetic Analysis

Phylogenetic analysis shown in figure 5 revealed functional diversification within the CSTX family. TXC16_CUPSA showed the highest divergence score, indicating potential specialization, while CSTX-1, CSTX-9, CSTX-10, and CSTX-11 clustered tightly, reflecting conserved neurotoxic roles (14).

The phylogenetic tree illustrates the evolutionary and functional relationships among spider venom peptides of the CSTX (TXC) family from *Cupiennius salei*. The tree highlights divergence and conservation a mong CSTX isoforms, with numerical values representing relative functional or sequence-based scores derived from comparative analysis. TXC16_CUPSA (B3EWS9) exhibits the highest score (0.43284), indicating pronounced evolutionary divergence and potential functional specialization within the CSTX family. Its distant branching suggests unique structural or biochemical features that may distinguish it from other CSTX peptides.

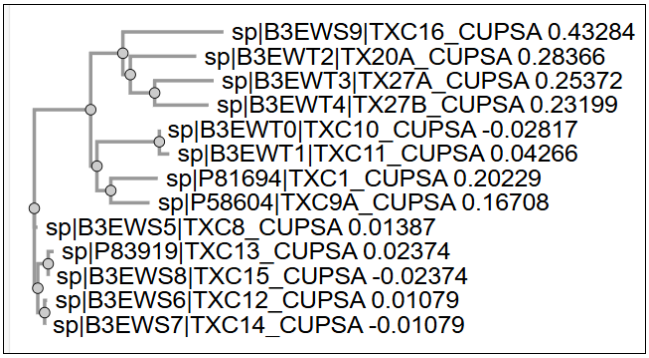

Fig 5: Phylogenetic tree of CSTX (TXC) family peptides from *Cupiennius salei* based on sequence similarity and functional annotation

Peptides such as TX20A, TX27A, and TX27B also display relatively high scores (0.23–0.28) and cluster together, suggesting closer evolutionary relationships and potentially shared functional roles. In contrast, CSTX-1 (P81694), CSTX-9A (P58604), CSTX-10, and CSTX-11 form a moderately scoring, tightly grouped cluster, reflecting conserved structural and functional characteristics typical of core CSTX peptides involved in venom activity. Toward the base of the tree, CSTX-8, CSTX-13, CSTX-12, CSTX-14, and CSTX-15 exhibit lower to slightly negative values, suggesting reduced divergence, auxiliary roles, or diminished functional contribution within the venom system. Notably, CSTX-14 (−0.01079) and CSTX-15 (−0.02374) represent the least divergent profiles, potentially corresponding to less potent or evolutionarily conserved isoforms.

Overall, this phylogenetic analysis provides insight into the evolutionary diversification of CSTX peptides and highlights both conserved and specialized members of the toxin family, contributing to a deeper understanding of spider venom evolution and functional complexity.

Discussion

Spider venoms are highly optimized biochemical systems in which multiple bioactive components act together to achieve rapid prey immobilization and effective defense [1–4]. Consistent with earlier experimental studies on *Cupiennius salei*, the present bioinformatics analysis confirms that CSTX peptides constitute a major functional component of this venom system, characterized by conserved cysteine-rich motifs and amphipathic sequence features that contribute to stability and biological activity [1, 2, 5, 6]. Early purification and biochemical characterization of CSTX-1 demonstrated its potent neurotoxic properties, and the conserved sequence patterns identified in the present study support these findings by indicating preservation of structural determinants essential for venom efficacy [1, 6].

Comparative analysis with previously reported spider venom peptides indicates that CSTX peptides share common structural principles with other arachnid neurotoxins, including compact architectures, conserved cysteine spacing, and enrichment of positively charged residues that facilitate membrane association [3, 5, 6]. Such features are widely recognized as hallmarks of venom peptides involved in membrane destabilization and neurotoxicity [6, 19, 22]. The evolutionary conservation observed among CSTX variants in this study aligns with broader venom evolution models, which propose strong selective pressure to maintain functional efficiency while allowing diversification in peptide length and sequence composition [4, 14, 15].

Importantly, this study places CSTX peptides within a broader venom biology framework rather than treating them as isolated molecular entities. Previous studies have shown that venom enzymes such as hyaluronidases and proteases enhance toxin diffusion, while polyamines and small bioactive molecules modulate neuronal signaling and amplify venom potency [2, 20, 21]. The physicochemical and sequence-based structural features identified in CSTX peptides are consistent with such synergistic venom strategies, reinforcing the concept of venom as a coordinated, multi-target biochemical system [15, 20]. Comparative venom data from Indian spider species further support the idea that similar venom architectures and functional principles are conserved across diverse spider taxa [18, 23].

Overall, this bioinformatics-driven analysis complements existing experimental knowledge by providing an integrated view of CSTX peptide structure, conservation, and evolutionary significance. By focusing on sequence-based and comparative approaches, the study offers a cost-effective framework for understanding venom peptide function and supports the continued exploration of spider venoms as valuable sources of bioactive molecules with potential biomedical applications [10, 19, 25].

Conclusion

This comprehensive bioinformatics analysis provides several important benefits by systematically characterizing CSTX peptides from *Cupiennius salei* at the sequence, structural, and evolutionary levels. First, the study establishes a clear structural framework for CSTX peptides by identifying conserved cysteine motifs, amphipathic α-helical regions, and charge distribution patterns that underlie their stability and membrane-active nature. This enhances understanding of how venom peptides achieve high

biological potency despite sequence variability. Second, comparative analysis across CSTX variants highlights both structural conservation and functional diversification, allowing the identification of key peptides such as CSTX-1, CSTX-9, and CSTX-13 as biologically significant venom components. Third, the evolutionary profiling situates CSTX peptides within a broader venom biology context, demonstrating that these toxins follow conserved strategies observed across spider species, including medically important Indian spiders. Collectively, these insights provide a cost-effective, non-experimental framework for prioritizing venom peptides for future experimental validation. By offering mechanistic understanding without reliance on invasive assays, this analysis positions spider venom as a valuable bioresource and supports its potential application in the development of next-generation neurotherapeutic and antimicrobial agents, particularly in addressing neurological disorders and antimicrobial resistance.

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