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Bee Venom as a Source of Anti-Angiogenic Agents: A Computational Study

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INTRODUCTION & AIM

Angiogenesis, the formation of new blood vessels, is a key process in tumor growth, invasion, and metastasis. Because of its central role in cancer progression, targeting angiogenesis remains a major focus in modern oncology. Natural sources, such as animal venoms, have gained attention for their rich diversity of bioactive peptides with therapeutic potential. Bee venom, in particular, contains peptides known for their anti-inflammatory, antimicrobial, and cytotoxic properties—some of which may also modulate angiogenic signaling. In this *in silico* study, we explored the anti-angiogenic potential of bee venom-derived peptides through computational modeling. We assessed their ability to bind and modulate key molecular targets involved in angiogenesis using molecular docking, molecular dynamics simulations, and functional enrichment analysis. Our aim is to highlight bee venom peptides as promising natural candidates for future anti-angiogenic cancer therapies.

METHOD

Proteins and Peptides: 3D structures of key angiogenesis-related receptors were retrieved from public databases. Several peptides from bee venom, including melittin, tertiapin, and others, were selected based on their therapeutic potential. All structures were prepared for computational analysis.

Molecular Docking: Docking simulations were performed to predict the interactions between bee venom peptides and angiogenic receptors. The most promising complexes were selected based on binding affinity and analyzed for interaction quality.

Molecular Dynamics: MD simulations were used to assess the stability of peptide–receptor complexes in a simulated physiological environment, providing insight into their potential biological activity.

Pathway Analysis: Functional enrichment analysis was conducted to identify biological pathways associated with the targeted receptors, with a focus on angiogenesis-related processes potentially influenced by the peptides.

RESULTS & DISCUSSION

- **Docking analysis**

Docking analysis revealed variable binding affinities between bee venom peptides and angiogenesis-related receptors. Melittin and tertiapin showed the strongest interactions, particularly with PDGFR-α, VEGFR-1, and Integrin αvβ3, suggesting high anti-angiogenic potential. In contrast, peptides like procamine and MCD displayed weaker affinities, indicating limited receptor targeting (Fig. 1).

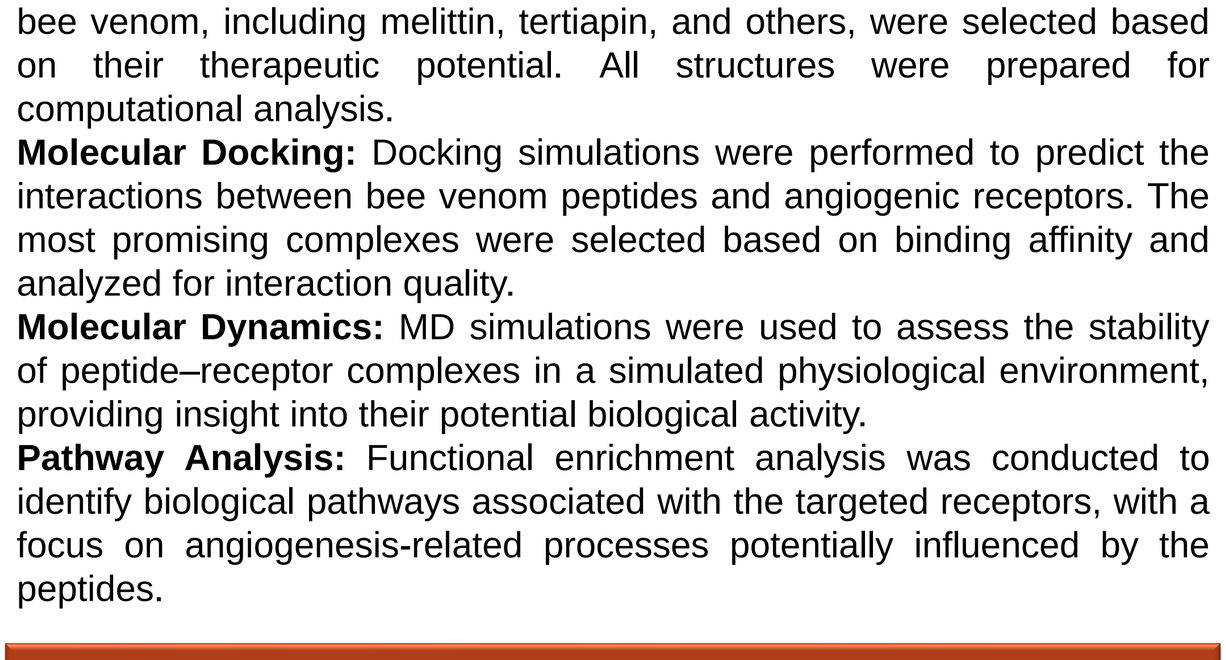

Fig. 1 Comparative docking analysis of six peptides derived from bee venom against receptors involved in tumor angiogenesis.

- **Protein-Peptide interaction**

Figure 2 shows key interactions between bee venom peptides and angiogenic receptors. Melittin binds to PDGFR-α, occupying a hydrophilic pocket and potentially blocking ligand activation. Tertiapin interacts with integrin αvβ3 at a broad surface region, suggesting possible allosteric effects. These interactions support the potential of both peptides to disrupt tumor-driven angiogenesis.

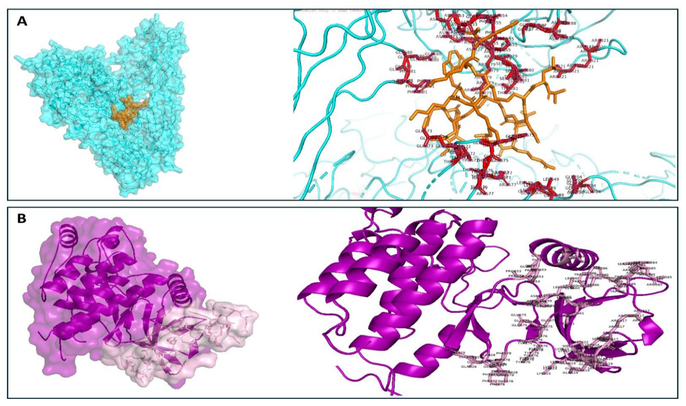

Fig. 2 Protein–protein interactions between (A) Melittin/PDGFR-α and (B) Tertiapin/integrin αvβ3.

- **Molecular dynamics of high-affinity peptide complexes**

RMSD analysis shows stable conformational shifts upon binding, indicating specific interactions between PDGFR-α–Melittin and Integrin (αvβ3)–Tertiapin. The complexes maintain consistent RMSD values, reflecting structural adaptation. RMSF results reveal reduced flexibility at key regions, confirming defined binding interfaces and supporting the presence of specific, rather than non-specific, ligand–receptor interactions.These findings highlight the structural basis for selective binding and potential functional relevance of each complex.

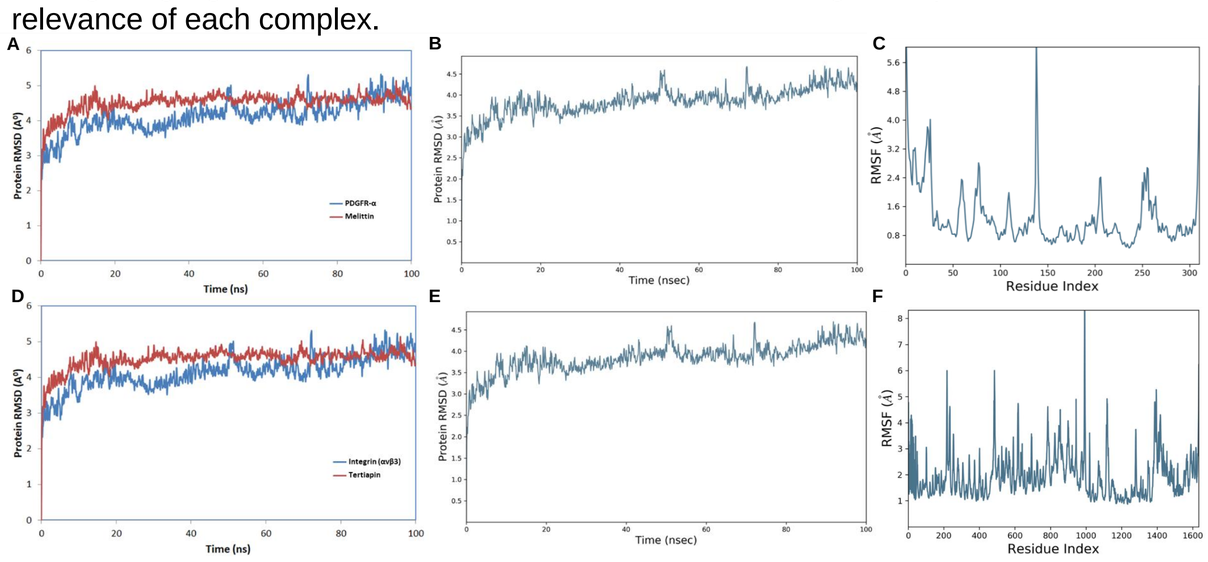

Fig. 3 RMSD and RMSF analyses of PDGFR-α with Melittin (A–C) and Integrin (αvβ3) with Tertiapin (D–F), showing structural shifts and flexibility in unbound and bound states.

- **Pathway enrichment analysis**

Combined inhibition of PDGFR-α (melittin) and integrin αvβ3 (tertiapin) impacts key angiogenic pathways (Fig. 4). Enrichment of PDGFR-related and L1CAM signaling indicates disruption of endothelial activation and guidance. Additional effects on RUNX2 and PLCγ1 pathways suggest reduced cell migration and neovascularization.

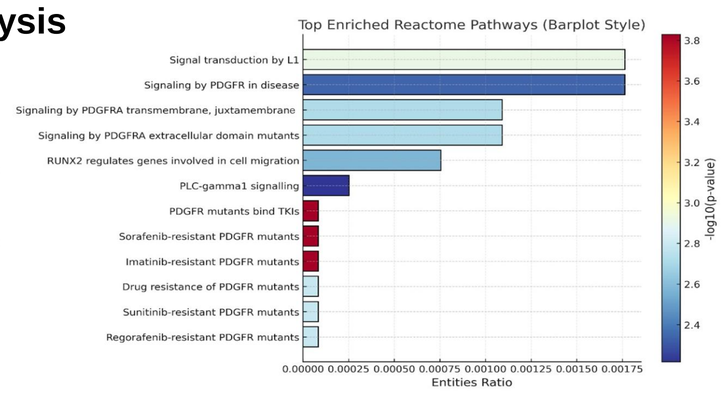

Fig. 4 Reactome enrichment of pathways affected by melittin (PDGFR-α) and tertiapin (integrin αvβ3).

CONCLUSION

This *in silico* study highlights the anti-angiogenic potential of bee venom peptides, particularly melittin and tertiapin, which showed stable and specific interactions with angiogenesis-related targets. These findings suggest that bee venom is a promising natural source of bioactive compounds for cancer therapy.

FUTURE WORK / REFERENCES

- Validate peptide–receptor interactions using *in vitro* angiogenesis assays (e.g., tube formation, migration).
- Assess cytotoxicity and selectivity of bee venom peptides in cancer vs. normal endothelial cells.
- Conduct *in vivo* studies to evaluate anti-angiogenic and anti-tumor effects in animal models.
- Explore peptide modifications or delivery systems (e.g., nanoparticles) to enhance stability and bioavailability.