ML-OPTIMIZED NEEM-TULSI REPELLENTS FOR KARNATAKA DENGUE CONTROL: DOCKING, QSAR AND FIELD TRIALS

Project Reference No.: *49S_MSC_0117*

College : Garden City University, Bengaluru
Branch : Department of Life Sciences
Guide(s) : Dr. Chemmugil. P
Dr. Shanmuga Priya V.G
Student(s) : Mr. Mubarak.S
Ms. Janet Jessica.A

Keywords:
Neem–Tulsi Phytochemicals; OBP1 Molecular Docking; QSAR and Machine Learning; Mosquito Repellent Development; Dengue Vector Control

Introduction:

In silico screening and profiling of phytocompounds from selected plant species with insect repellent activity against dengue mosquito (Aedes aegypti) odorant-binding proteins. Dengue fever, a rapidly spreading vector-borne disease in tropical and subtropical countries, has seen regular outbreaks in Karnataka owing to conducive climatic conditions for Aedes aegypti. Conventional chemical repellents, while effective, raise toxicity, environmental persistence and resistance concerns. This has prompted a dire need for safer, plant-based alternatives. Neem (Azadirachta indica) and Tulsi (Ocimum sanctum) are well-known medicinal plants with established insect-repellent and antimicrobial properties. Their phytochemical diversity includes terpenoids, flavonoids and alkaloids, many of which exhibit bioactivity against insect olfactory systems. Recent advances in computational biology, particularly molecular docking and machine learning (ML)-based QSAR (Quantitative Structure–Activity Relationship) modeling, allow rapid screening and optimization of bioactive compounds. Mosquito odorant-binding proteins (OBPs), particularly OBP1 and OBP47, play a critical role in host-seeking behavior, making them an ideal molecular target for repellent design. In this study, approximately 50 phytocompounds derived from neem and tulsi were identified and screened against OBP1 and OBP47 using molecular docking approaches. Several compounds demonstrated strong binding affinity, indicating their potential as effective mosquito repellents. These findings are further integrated with ML-based QSAR modeling and field validation to develop optimized, safe, and sustainable repellents for dengue control in Karnataka.

Objectives:

1. **Dengue Burden on the Rise in Karnataka:** With more than 15,000 dengue cases, rural Mandya and Mysore are confronted with severe outbreaks of the disease vectored by Aedes aegypti, which is resistant to synthetic repellents and results in an estimated ₹10,000/ha annual loss to farmers because of illness and reduced productivity.

2. Potential of Neem–Tulsi Larvicides: Neem and tulsi, on one hand, from laboratory studies, are showing ~90% larvicidal activity, but precise molecular targeting of mosquito odorant-binding proteins AgamOBP1 is required to have high field stability with traditional mixtures.
3. AI-based Phytochemical Screening: More than 200 phytochemicals of neem and tulsi, which are abundantly found in Karnataka, will be screened through AutoDock Vina to identify the top 5 molecules that have a very strong binding (< –7 kcal/mol) to AgamOBP1 for targeted mosquito repellency. List the objectives 3 of project
4. QSAR-Driven Repellency & Safety Validation: scikit-learn QSAR models, trained on ECOTOX/EAWAG datasets, will predict each compound's repellency (>80% efficacy), biodegradability, and ADMET safety (nontoxic, LD50 > 500 mg/kg) to ensure suitability for rural use.
5. Prototype Development & Field Trials: A low-cost neem–tulsi prototype (₹5,000) will be extracted and tested in Mandya/Mysore dengue hotspots using WHO-standard traps, targeting ≥50% reduction in Aedes mosquitoes within 7 days compared to control sites.

Methodology:

1. The three-dimensional structure of the OBP1 protein was retrieved from the Protein Data Bank and prepared by removing water molecules, adding hydrogen atoms, and performing energy minimization using the AMBER99 force field in MOE. The active site residues (Tyr54, Ile125, Leu76, His77, Leu80, Ala88, Met89, Met91, Gly92, Trp114, Arg94, Phe59, Ala62) were defined as the docking pocket. Neem-derived phytochemical structures were obtained from the PubChem database and literature, followed by hydrogen addition and energy minimization using the MMFF94X force field. The prepared ligands were saved in suitable formats and compiled into a database for docking studies. Molecular docking was performed using MOE, and complexes were ranked based on S-scores, with top candidates analyzed for interactions with key active-site residues.
2. he protein–ligand complex was solvated in a cubic box using the SPC/E water model and neutralized by adding counter ions (Na^+/Cl^-). Energy minimization was carried out to remove steric clashes, followed by equilibration under NVT and NPT ensembles at 300 K and 1 atm pressure. Production MD simulation was conducted for an appropriate time scale (e.g., 50–100 ns) to study the stability of the OBP1–ligand interactions. Trajectory analysis including RMSD, RMSF, hydrogen bonding, and SASA was performed using GROMACS analysis tools to evaluate binding stability.

Result and Conclusion:

Docking and simulation studies of selected phytochemicals of neam and tulsi leaves against OBP1 protein showed existence of various stable complex conformations, implying that the ligand-protein interaction was good. All the screened compounds showed the best binding affinity in the active site of OBP1. Subsequent detailed interaction analysis showed that the compound made interaction with important residues of the binding pocket, such as Tyr54,

Ile125, Leu76, His77, Leu80, Ala88, Met89, Met91, Gly92, Trp114, Arg94, Phe59 and Ala62. Many of these residues are found to be important for the stabilization of ligand through hydrophobic interactions and van der Waals forces. All the selected compounds showed interaction with important residues present in the OBP1 binding pocket, pointing towards their potential to interfere with the odorant recognition mechanism of the mosquito. Additionally, residues such as Trp114, Arg94 and Leu76, which showed significant contribution in ligand binding, can be considered as conserved and functionally important in the olfactory process mediated by OBP1. All the screened compounds are natural compounds and expected to have less toxicity and side effects when compared to chemical synthetic repellents. Thus, it is expected that neem phytochemicals can be good candidates for mosquito repellent development. Wet-lab experiments and field trials are required to confirm their effectiveness against the mosquito vectors.

References:

1. [1] I. Sarkar and S. K. Sarkar, “Lethal efficacy and mode of action of Indian medicinal plant extracts against dengue mosquito vectors,” *Green Health*, vol. 2, no. 1, 2026.
2. [2] M. A. S. da Costa *et al.*, “Exploring the potentiality of natural products from essential oils as inhibitors of odorant-binding proteins,” *ACS Omega*, vol. 4, pp. 22475–22486, 2019.
3. [3] S. Kritsi *et al.*, “2D fingerprinting and molecular docking studies identified potent mosquito repellents targeting OBP1,” *Acta Tropica*, 2023.
4. [4] B. J. Okoli *et al.*, “Vitex negundo essential oil: odorant binding protein efficiency using molecular docking approach,” *Insects*, vol. 12, no. 12, p. 1061, 2021.
5. [5] S. Pandey *et al.*, “Potential mosquito repellent compounds of Ocimum species against OBPs,” *3 Biotech*, vol. 6, 2016.
6. [6] M. A. A. Khan *et al.*, “Identification of bioactive compounds from Azadirachta indica using docking and machine learning,” *Heliyon*, vol. 11, no. 4, 2025.
7. [7] K. Devillers, “QSAR and artificial neural network modeling in mosquito repellent research,” *SAR and QSAR in Environmental Research*, 2018.
8. [8] E. F. Pettersen *et al.*, “UCSF Chimera—A visualization system for exploratory research,” *J. Comput. Chem.*, vol. 25, no. 13, pp. 1605–1612, 2004.
9. [9] M. J. Abraham *et al.*, “GROMACS: High performance molecular simulations,” *SoftwareX*, vol. 1–2, pp. 19–25, 2015.

Future Scope:

The future scope of this project includes:

1. AI-driven optimization: Integration of advanced machine learning and deep learning models to design more potent OBP1-targeting repellent molecules.
2. Nano-formulation development: Use of nano-encapsulation techniques to improve stability, controlled release, and long-lasting repellent activity.
3. Multi-target validation: Expansion of studies to other mosquito olfactory proteins (e.g., OBP family members) and different vector species like *Aedes*, *Anopheles*, and *Culex*.
4. Large-scale field trials: Implementation of community-level trials across multiple dengue-prone regions in Karnataka for real-world validation.
5. Commercialization and policy integration: Development of market-ready herbal repellent products with regulatory approval and integration into public health vector control programs.