

In silico Screening of *Plectranthus ampoinicus* and *Hyptis suaveolens* Phytochemicals: Novel Repellents Targeting Odorant Binding Proteins of *Aedes aegypti* and *Aedes albopictus*

Thomas Jebastin

Bishop Heber College (Affiliated to Bharathidasan University)

Jeyaraj John Wilson

Ayya Nadar Janaki Ammal College (Autonomous)

Natarajan Sisubalan

Chiang Mai University

Dharmarajan Raja Sudhakar

Bishop Heber College (Affiliated to Bharathidasan University)

Bhagavathi Sundaram Sivamaruthi

Chiang Mai University

Mohamed Husain Syed Abuthakir

Bharathiar University

Subramanian Sevarkodiyone

Ayya Nadar Janaki Ammal College (Autonomous)

Chaiyavat Chaiyasut (✉ chaiyavat@gmail.com)

Chiang Mai University

Research Article

Keywords: *Aedes aegypti*, *Aedes albopictus*, *Hyptis suaveolens*, *Plectranthus ampoinicus*, Molecular docking

Posted Date: November 14th, 2023

DOI: <https://doi.org/10.21203/rs.3.rs-3578471/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Mosquitoes pose a significant threat to public health, transmitting various dangerous diseases to both humans and animals. Conventional insecticide spraying, while common, has limitations in effectively controlling vector-borne diseases. Many chemical pesticides harm humans and animals, some persist in the environment and causing toxic effects. Recently, there has been renewed interest in plant-based products due to concerns about insecticide resistance, cross-resistance, potential toxicity associated with synthetic options, and rising costs. In this study, we conducted molecular docking analyses using specific plant-derived compounds from *Hyptis suaveolens* and *Plectranthus ampoenicus*. We focused on their interaction with odorant binding proteins (OBPs) from dengue and chikungunya vectors (*Aedes aegypti* and *Aedes albopictus*). The selected phytochemical compounds exhibited strong binding with the OBP of both *Ae. aegypti* and *Ae. albopictus*. Tetrahydrofuran-2-carboxylic acid, Carvacryl acetate, and Brallobarbitol showed high binding affinity and significant interaction with *Ae. aegypti*. Tetrahydrofuran-2-carboxylic acid and 3-Methyl-4-isopropylphenol also demonstrated substantial binding affinity and effective interaction with *Ae. albopictus* OBP. These findings suggest that these compounds can potentially disrupt the mosquito's attraction to humans, thus reducing human-vector contact. They may offer a promising alternative for developing natural and efficient mosquito repellents, surpassing currently used synthetic options like N, N-diethyl-meta-toluamide and other conventional repellents.

Introduction

Mosquitoes are one of the main carriers of dangerous viruses that spread severe and fatal diseases worldwide (Edwin et al. 2016; Priya et al. 2023). Mosquitoes spread the greatest number of fatal diseases, including malaria, dengue, chikungunya, elephantiasis, and other arthropods (Priya et al. 2023). Within the Culicidae family, Genus *Aedes* is known to pose a significant global public health threat. *Aedes aegypti* is particularly noteworthy among its species due to its wide-ranging distribution across temperate and tropical climates. This mosquito, along with *Aedes albopictus*, is a primary carrier of various human arboviruses. Specifically, both *Ae. aegypti* and *Ae. albopictus* are responsible for transmitting dengue virus (DENV) (Thammasittirong and Thammasittirong, 2023), chikungunya virus (CHIKV), and yellow fever virus (YFV) on a global scale (Kamgang et al. 2019). In South and Southeast Asia, chikungunya virus (CHIKV) is predominantly spread in urban areas through a cycle involving *Ae. aegypti* and *Ae. albopictus* mosquitoes, with humans serving as the vertebrate host (Sivan et al., 2015). In India, outbreaks of chikungunya, caused by a newly identified virus variant, are primarily attributed to *Ae. aegypti* mosquito species (Pialoux et al., 2007).

Ae. albopictus is an adaptable and invasive species that coexists with or displaces *Ae. aegypti* in various regions (Rao et al., 2011). Factors such as widespread deforestation, climate change, and increased global trade have compelled this mosquito to adapt to breeding in human-made containers in homes and semi-domestic settings (Delatte et al., 2008). Controlling these vectors is a global challenge, and efforts to control mosquitoes may target their immature or adult stages. Diseases transmitted by mosquitoes not only lead to high levels of illness and death but also result in significant economic consequences,

including reduced productivity in commercial and labor sectors, particularly in tropical and subtropical countries. Notably, no part of the world is completely immune to these diseases (Fradin and Day, 2002). While the most common method for vector control involves residual insecticide spraying, the effectiveness of insecticides in managing diseases transmitted by vectors is limited (Coulibaly et al., 2023).

The application of larvicides and adulticides for controlling mosquitoes has not received much attention, primarily due to technical and environmental concerns. Environmentally friendly repellents, which serve as deterrents and contribute to ecological management, are primarily implemented in epidemic outbreaks. Repeated application of chemical insecticides poses risks to both human health and the environment. Even N, N-diethyl-meta-toluamide (DEET), widely recognized as the most effective mosquito repellent globally, has been found ineffective against certain hazardous mosquito species, necessitating frequent reapplication (Schmidt, 2005). The low potential for irritation may pose a significant danger to personal protection, and in some instances, the use of these products indoors has been associated with respiratory irritation (Fischer and Bialek, 2002). Various preparations derived from natural sources serve as repellents for specific insects. Employing scientifically validated non-chemical approaches and minimizing pharmaceutical use are considered safer options for both the environment and human health. Numerous plant-based products have been identified for their ability to deter insects from feeding (Isman, 2006).

It has been discovered that pharmaceuticals with plant origins are effective against several illnesses, including cancer, Alzheimer's disease, dementia, cardiovascular disease, and diabetes respectively (D'Onofrio et al., 2017; Ranjan et al., 2019; Howes et al., 2011; Gaikwad et al., 2014; Pop et al., 2018 and Al-Khayri et al., 2023). Nearly 80,000 higher plants have been found to have therapeutic qualities worldwide. One of the top 12 biodiverse regions in the world is situated in India, where approximately 45,000 of these can be found (Al-Khayri et al., 2023). Different traditional tribes have used pharmaceutical medications with a plant origin and have been mentioned in ancient medical systems like Ayurveda and Unani (Dai et al., 2019; Al-Khayri et al., 2023), which ultimately helps to overcome numerous modern-day diseases.

Due to medicinal plants' variety of health benefits and therapeutic potential, pharmaceutical and nutrition sciences have recently noticed an increase in scientific literature keen on their use (Shahid et al., 2023). Studies utilizing Molecular Docking and Virtual Screening at the molecular level have become a crucial aspect of contemporary drug discovery efforts that rely on structural information. Therefore, comprehending the interactions between proteins, ligands, and specific drugs can yield valuable insights into their binding mechanisms and relative effectiveness (Nagarajan et al., 2023).

In modern drug design, Molecular Docking methods are commonly employed to gain insights into how proteins interact with ligands. The three-dimensional arrangement of the protein-ligand complex serves as a valuable resource for understanding how proteins interact with each other to carry out biological functions. Consequently, achieving a detailed atomic-level understanding of the structure of protein-

ligand complexes (known as molecular recognitions) is a significant challenge in biological sciences (Dou et al., 2023).

Molecular recognition, which encompasses interactions between drugs and proteins, plays vital roles in various biological processes like signal transmission, cellular regulation, and the assembly of large molecules. Thus, elucidating how the constituent molecules in molecular recognition bind and the strength of their affinity is crucial for comprehending interaction mechanisms and designing effective therapeutic interventions. Given the challenges and costs associated with experimental methods for determining complex structures, computational approaches like molecular docking are sought to predict potential binding modes and affinities (Kolb et al., 2009). The present study aimed to investigate how odorant binding proteins in mosquitoes, specifically *Ae. aegypti* and *Ae. albopictus* interacts with key ligands from plants like *Plectranthus ampoinicus* (Lour.) Spreng and *Hyptis suaveolens* (L.) Poit.

Materials and methods

Selection of plant material

Two aromatic plants, namely *P. ampoinicus* Lour. Spreng and *H. suaveolens* (L.) Poit was chosen for phytochemical analysis. *H. suaveolens* L. is a commonly occurring plant that often grows as a weed in various regions of Tamil Nadu, India. Leaves of both *P. ampoinicus* and *H. suaveolens* were gathered from the campus of Ayya Nadar Janaki Ammal College, Sivakasi, situated at latitude 9.4726° N and longitude 77.7514° E, in the Virudhunagar district of Tamil Nadu, India.

Ligand Structure Retrieval

After the GC – MS analysis, the ligand structure of *P. ampoinicus* and *H. suaveolens* was retrieved from the PubChem database. Compounds lacking a 3D structure in PubChem were transformed into a 3D structure using Open Babel.

Protein Structure retrieval

The Protein structure of odorant binding protein (OBP) from *Ae. aegypti* and *Ae. albopictus* retrieved from Protein Data Bank (PDB) and AlphFold database.

Structure validation

The protein structures obtained from the AlphaFold database underwent validation for their structural integrity using PDBSum. The uploaded structures were assessed for their "stereochemical quality," which involved generating various postscript plots to analyze the overall and residue-specific geometry of the modeled protein structure. Following the submission of the protein structure, a Ramachandran plot was generated. This plot provides insights into regions that conform to permissible structural arrangements and those that deviate from the norm. Utilizing these data, the structures were further validated through PROCHECK.

Preparation of protein structures for docking

The process assumes that the initial protein structure in a PDB-format file contains a co-crystallized ligand and lacks explicit hydrogen atoms. The three-dimensional protein structures were imported into Maestro. Water molecules were removed or adjusted in conjunction with the protein, metal ions, and cofactors. Charges, bond orders, and formal changes of cofactors were rectified. The prepared structures were thoroughly inspected. The protein structure was refined to ensure accurate formal charges and protonation states, with any necessary final adjustments made. The positioning of water molecules and other functional groups, such as hydroxyls and amides, was verified.

Grid generation

Grid files contain information about the physical characteristics of a specific receptor region, the active site. These properties are explored during the process of docking a ligand. In this exercise, the complex was stored in two separate files: one containing the receptor information and details about the ligand.

Ligand preparation and Docking

Retrieved molecules were prepared for docking using the LigPrep module from the Schrodinger suit. The docked complex was visualized using XP (Xtra Precision) Visualizer. The glide score of each ligand and interactions against the target protein are analyzed.

Results and discussion

Screening of phytochemicals

The GC-MS analysis identified several compounds from the GC fractions of the organic solvent extracts of *H. suaveolens* and *P. ampoinicus* leaves. Specifically, the GC-MS results showed eleven significant peaks in *H. suaveolens*, indicating the presence of eleven distinct phytochemical constituents. Additionally, a separate GC-MS analysis demonstrated the existence of three compounds in the ethanol extract of *P. ampoinicus*. The GC-MS data are in supplementary files 1 and 2.

In silico analysis of phytochemical compounds

The structure of secondary metabolites of *H. suaveolens* and *P. ampoinicus* were retrieved from PubChem, and their structure and properties are shown in Table 1.

Molecular docking

Examining the enzymatic capabilities of phyto-constituents through in vitro analysis is ideal. However, this was not feasible due to the exceedingly low concentration of these compounds in the plant extract and the unavailability of certain compounds in the market (Shahid et al., 2023). Consequently, a virtual assessment of these substances can be carried out using molecular docking studies. This approach helps predict the bioactive substances responsible for enzymatic activities. In contemporary drug

development, computational techniques like molecular docking play a crucial role. They enable the anticipation and identification of low binding energies and high affinities and provide improved insights into protein-ligand interactions (Shahid et al., 2023).

Plant extracts are recognized for their effectiveness as natural biocides, driving the demand for new drugs. A method called docking is employed to predict potential drugs, which allows for a detailed exploration of the interactions between a ligand and the target protein. Schrodinger, for instance, conducts grid-based ligand docking with energetics to search for favorable interactions between small ligand molecules and larger receptor molecules, typically proteins (Bhowmik et al., 2023). The current study aims to assess the potential of repellent compounds from the plants *H. suaveolens* and *P. ampoinicus* in blocking the odorant binding proteins of dengue and chikungunya vectors (*Ae. aegypti* and *Ae. albopictus*). Additionally, the study aims to understand their significant role in influencing the host-seeking and feeding behaviors of mosquitoes using in silico approaches.

In rational drug design, the initial step involves obtaining the structure of the target protein and the ligand molecule. Databases like PDB and PubChem provide access to a vast repository of compounds and proteins, numbering in the millions (Kim et al., 2019, 2021; Trudeau et al., 2023). A set of analytical techniques is applied with computer-assisted tools to identify compounds that exhibit the most favorable interactions with the protein target and thus merit consideration for drug synthesis.

Because there were no available three-dimensional structures for the Odorant Binding Protein (OBP) of *Ae. albopictus*, the structure was obtained from the AlphaFold database. The three-dimensional structures of the Odorant Binding Proteins from *Ae. aegypti* (PDB ID: 3K1E) and *Ae. albopictus* are depicted in Fig. 1.

The three-dimensional SDF structures of the processed ligands from the plants *H. suaveolens* and *P. ampoinicus* were obtained from the PubChem database (see Table 1) and prepared for docking with the mosquito odorant binding proteins. The calculations were carried out using Glide, a Schrodinger tool that conducts grid-based ligand docking with energetic considerations, seeking favorable interactions between small ligand molecules and a typical receptor molecule, usually a protein (Saini et al., 2023). Molecular docking was executed with the protein kept rigid, allowing the ligand to find its most suitable conformation.

Molecular docking analysis of *Ae. aegypti* OBP with compounds of *H. suaveolens* and *P. ampoinicus*

The simplest way to assess the accuracy of a docking procedure is to determine how closely it predicts the lowest energy pose, which represents the binding conformation. Three main parameters are considered in evaluating the results: G-score, hydrogen bond energy, and residual interaction. These parameters are used to discuss the binding affinity of the ligand towards the odorant binding receptor. A more negative G-score indicates a strong binding affinity between the ligand and the odorant binding receptor. A higher number of hydrogen bonds in the structure suggests that the ligand has a favorable

binding mode with the receptor. The residual interaction provides information about the specific amino acid of the protein to which the ligand binds (Wang et al., 2023).

The results of molecular docking, as indicated by the G-score, hydrogen bonding, and interaction with residues, demonstrate the binding affinity of the ligands to the odorant binding protein. Specifically, chosen phytochemical compounds were used in the docking studies, and all these compounds successfully formed bonds with the *Ae. aegypti* odorant binding protein. The glide score, distance of hydrogen bonds, and the specific residues involved are presented in Table 2.

Table 2
Molecular docking of *Aedes aegypti* odorant binding protein (OBP) with different compounds from *Hyptis suaveolens* and *Plectranthus ampoinicus*

S. No.	Plant source	Compound Name	Dock Score (kcal/mol)	Interacting Residues	Bond Length (Å)
1.	<i>H. suaveolens</i>	N-dibenzofuran-3-yloxolane-2-carboxamide	-10.4	Ala88, His111, Trp114(3)	1.85, 5.25, 3.61, 4.16, 4.13
2.	<i>H. suaveolens</i>	Carvacryl acetate	-8.9	His111, Phe123	5.36, 1.94
3.	<i>H. suaveolens</i>	Brallobarbitol	-8.4	Phe123	1.98
4.	<i>H. suaveolens</i>	2-Ethylacridine	-8.1	His111(2), Phe123(2)	4.93, 5.35, 2.32, 4.35
5.	<i>H. suaveolens</i>	Benzoic acid, 4-methyl-, hydrazide	-5.9	His111, Phe123	4.82, 2.08
6.	<i>H. suaveolens</i>	Aziridine, 1-(2-buten-1-yl), (E)-	-5.1	Phe123(2)	1.85, 4.35
7.	<i>P. ampoinicus</i>	3-Methyl-4-isopropylphenol	-7.5	His111, Phe123	5.48, 1.82
8.	<i>P. ampoinicus</i>	Thymol	-7.1	Phe123	2.00

Compound Tetrahydrofuran-2-carboxylic acid exhibited a good docking score – 10.4 (Kcal/mol) and formed a 5 H – bond with target OBP, and the amino acid residue was observed to be ALA 88, HIS 111 and TRP 114. The distance was recorded to be as 1.85Å, 5.25Å, 3.61Å, 4.16Å and 4.13Å respectively. The compound Carvacryl acetate, when docked with *Ae. aegypti* odorant binding protein recorded a docking score of –8.94 (Kcal/mol) and formed a 2 H – bond with target OBP, and the amino acid residue was observed to be HIS 111 and PHE123. The distance was recorded to be as 5.36 Å and 1.94 Å. The

diagrammatic representation of the ligands Tetrahydrofuran-2-carboxylic acid, dibenzofuran-3-ylamide, Carvacryl acetate and Brallobarbitol docked against *Ae. aegypti* OBP is represented in Figs. 2–4.

These results suggest that N-dibenzofuran-3-yloxolane-2-carboxamide, Carvacryl acetate and Brallobarbitol exhibited a notable strong binding affinity and interaction with the *Ae. aegypti* Odorant Binding Protein (OBP). This suggests their potential to inhibit the mosquitoes' tendency to seek out humans, ultimately reducing contact between humans and the vector.

Molecular docking analysis of *Ae. albopictus* OBP with the compounds of *H. suaveolens* and *P. ampoinicus*

Compound Tetrahydrofuran-2-carboxylic acid and 3-Methyl-4-isopropylphenol exhibited good dock score (-7.88 (Kcal/mol and -6.9 (Kcal/mol)), and the number of H bonds were 5 and 1. The interactive residues of OBP with Tetrahydrofuran-2-carboxylic acid, dibenzofuran-3-ylamide are TRP148 and TYR390. The interactive residues of OBP with 3-Methyl-4-isopropylphenol is SER 144. The interaction of the ligand N-dibenzofuran-3-yloxolane-2-carboxamide and 3-Methyl-4-isopropylphenol docked against *Ae. albopictus* OBP is depicted in Figs. 5 and 6.

The results of molecular docking studies are displayed in Table 3. Similarly, OBP structures have been employed in homology modeling and molecular docking screening investigations to identify active semiochemicals in various insect pests. These pests include the oriental fruit fly (*Bactrocera dorsalis*) (Kamala Jayanthi et al., 2014), the Chilean scarab beetle (*Hylamorpha elegans*) (González-González et al., 2016), codling moth (*Cydia pomonella*) (Liu et al., 2016a), the leaf beetle (*Ambrostoma quadriimpressum*) (Wang et al., 2017), the polyphagous mirid bug (*Adelphocoris lineolatus*) (Sun et al., 2017), and the jujube bud weevil (*Pachyrhinus yasumatsui*) (Hong et al., 2022). Likewise, The larvicidal potential of the essential oil derived from *H. suaveolens* was examined, determining that the essential oil exhibits significant efficacy as a larvicide against *Ae. aegypti* (Moola et al. 2023).

Table 3

Molecular docking of *Aedes albopictus* odorant binding protein (OBP) with different compounds from *Hyptis suaveolens* and *Plectranthus ampoinicus*

S. No.	Plant Source	Compound Name	Dock Score (kcal/mol)	Interacting Residues	Bond Length (Å)
1.	<i>H. suaveolens</i>	N-dibenzofuran-3-yloxolane-2-carboxamide	-7.8	Trp148(3), Tyr390(2)	3.92, 4.15, 3.89, 2.15, 5.08
2.	<i>H. suaveolens</i>	2-Ethylacridine	-6.5	Trp148(5), Tyr390(2)	4.27, 4.32, 3.58, 4.34, 4.35, 5.25, 4.68
3.	<i>H. suaveolens</i>	6-Chloro-3-ethyl-2-methyl-4-phenylquinoline	-5.6	Trp148, Lys180, Tyr390	3.58, 6.47, 5.37
4.	<i>H. suaveolens</i>	Carvacryl acetate	-5.3	Trp148(2), Tyr390	3.43, 4.23, 5.34
5.	<i>H. suaveolens</i>	4-methylbenzohydrazide	-5.2	Ser144, Trp148, Tyr390	2.06, 4.26, 4.74
6.	<i>H. suaveolens</i>	Brallobarbitol	-4.9	Lys180	1.85
7.	<i>H. suaveolens</i>	1-[(E)-but-2-enyl] aziridine	-3.5	Trp148(2), Tyr390	4.68, 4.70, 4.47
8.	<i>H. suaveolens</i>	N-Methyl-1-adamantaneacetamide	-3.1	Leu177	1.77
9.	<i>H. suaveolens</i>	Cyclopentadecanone Oxime	-3.0	Pro178	2.31
10.	<i>P. ampoinicus</i>	3-Methyl-4-isopropylphenol	-6.9	Ser144	1.66
11.	<i>P. ampoinicus</i>	Thymol	-6.8	Ser144, Tyr390	1.83, 5.08

The compounds from *H. suaveolens* and *P. ampoinicus* demonstrated promising potential as natural mosquito repellents and offered a harmless alternative to conventional chemical pesticides. Molecular docking analyses reveal their strong interaction with OBP in *Ae. aegypti* and *Ae. albopictus*, crucial vectors of dengue and chikungunya. Tetrahydrofuran-2-carboxylic acid and Carvacryl acetate exhibit particularly high binding affinity with *Ae. aegypti*, while Tetrahydrofuran-2-carboxylic acid and 3-Methyl-4-isopropylphenol show significant interaction with *Ae. albopictus* OBP, highlighting their potential to disrupt mosquito attraction to humans.

Conclusions

These findings lead to the conclusion that Tetrahydrofuran-2-carboxylic acid, Carvacryl acetate, and 3-Methyl-4-isopropylphenol being natural compounds, exhibit repellent properties against the dengue vectors *Ae. aegypti* and *Ae. albopictus*. These compounds are promising candidates for developing an effective natural mosquito repellent. Compared to the presently utilized synthetic alternatives like DEET and other established mosquito repellents, these natural compounds may offer a safer and more environmentally friendly solution for preventing mosquito-borne diseases. This suggests a potential shift in the approach to mosquito vector control. Further extensive clinical studies may be required for the large-scale production and commercialization of repellent formulations.

Declarations

Author contributions: T.J., J.J.W. conceived and designed the study. The acquisition of data was performed by N.S., D.R.S. and B.S.S., and data analysis by T.J., M.H.S.A. and J.J.W. C.C. and S.S. had extensive editorial and technical inputs to the manuscript and participated in the discussion. All authors contributed to the interpretation of results and writing the manuscript.

Acknowledgement: T.J. and D.R.S. greatly acknowledge the support of Bishop Heber College (Autonomous), Tiruchirappalli, Tamil Nadu, India. J.J.W. and S.S. thank Ayya Nadar Janaki Ammal College (Autonomous), Sivakasi, Tamil Nadu, India, for providing the necessary facilities. The Chiang Mai University, Chiang Mai, Thailand, partially supported the study. N.S., B.S.S., and C.C. are greatly acknowledged to Chiang Mai University, Thailand, for their support. N.S. is thankful to Chiang Mai University for the support of the Postdoctoral Fellowship.

Funding: No external funding was received to assist with the preparation of this manuscript.

Data availability: All relevant data have been presented within the manuscript text, tables, and figures.

Conflict of Interest: There is no conflict of interest to declare.

Financial interests: The authors declare they have no financial interests.

Informed consent: All the authors of this manuscript accepted that the article is submitted for publication in Pest Management Science. This article has not been published or accepted for publication in another journal and is not under consideration at another journal.

References

1. Al-Khayri JM, Dubey S, Thirumoorthy G, Nagella P, Rezk AA, Shehata WF (2023) In Silico Identification of 1-DTP Inhibitors of *Corynebacterium diphtheriae* Using Phytochemicals from *Andrographis paniculata*. *Molecules* 28(2):909.
2. Bhowmik R, Manaihiya A, Vyas B, Nath R, Qureshi KA, Parkkila S, Aspatwar A (2023) Navigating bioactivity space in anti-tubercular drug discovery through the deployment of advanced machine

- learning models and cheminformatics tools: a molecular modeling based retrospective study. *Front Pharmacol* 2023:14.
3. Coulibaly ZI, Gowelo S, Traore I, Mbewe RB, Ngulube W, Olanga EA, DePina AJ, Sanou A, Coleman S, Tangena JA (2023) Strengthening adult mosquito surveillance in Africa for disease control: Learning from the present. *Curr Opin Insect Sci* 3:101110.
 4. D'Onofrio G, Sancarolo D, Ruan Q, Yu Z, Panza F, Daniele A, Greco A, Seripa D (2017) Phytochemicals in the Treatment of Alzheimer's Disease: A Systematic Review. *Curr Drug Targets* 18: 1487–1498.
 5. Dai Y, Chen SR, Chai L, Zhao J, Wang Y, Wang Y (2019) Overview of Pharmacological Activities of and Its Major Compound Andrographolide. *Crit Rev Food Sci Nutr* 59: S17–S29.
 6. Delatte H, Paupy C, Dehecq JS, Thiria J, Failloux AB, Fontenille D (2008) *Aedes albopictus*, vector of chikungunya and dengue viruses in Reunion Island: Biology and control. *Parasite* 15: 3–13.
 7. Dou B, Zhu Z, Merkurjev E, Ke L, Chen L, Jiang J, Zhu Y, Liu J, Zhang B, Wei GW (2023) Machine learning methods for small data challenges in molecular science. *Chem Rev* 123(13):8736–80.
 8. Edwin ES, Vasantha-Srinivasan P, Senthil-Nathan S, Thanigaivel A, Ponsankar A, Pradeepa V, Selin-Rani S, Kalaivani K, Hunter WB, Abdel-Megeed A, Duraipandiyar V, Al-Dhabi NA (2016) Anti-dengue efficacy of bioactive andrographolide from *Andrographis paniculata* (Lamiales: Acanthaceae) against the primary dengue vector *Aedes aegypti* (Diptera: Culicidae). *Acta Trop* 163:167–78. doi: 10.1016/j.actatropica.2016.07.009.
 9. Fischer PR, Bialek R (2002) Prevention of malaria in children. *Clin Infect Dis* 34 (4):493–8.
 10. Fradin MS, Day JF (2002) Comparative efficacy of insect repellents against mosquito bites, *N Engl J Med* 347: 13–18.
 11. Gaikwad SB, Krishna Mohan G, Rani MS (2014) Phytochemicals for Diabetes Management. *Pharm Crop* 5: 11–28.
 12. González-González A, Palma-Millanao R, Yáñez O, Rojas M, Mutis A, Venthur H, Quiroz A, Ramírez CC (2016) Virtual Screening of Plant Volatile Compounds Reveals a High Affinity of *Hylamorphia elegans* (Coleoptera: Scarabaeidae) Odorant-Binding Proteins for Sesquiterpenes From Its Native Host. *J Insect Sci* 16(1):30. <https://doi.org/10.1093/jisesa/iew008>.
 13. Hong B, Chang Q, Zhai Y, Ren B, Zhang F (2022) Functional characterization of odorant binding protein PyasOBP2 from the jujube bud weevil, *Pachyrhinus yasumatsui* (Coleoptera: Curculionidae). *Front Physiol* 13: 900752.
 14. Howes MJR, Perry E (2011) The Role of Phytochemicals in the Treatment and Prevention of Dementia. *Drugs Aging* 28: 439–468.
 15. Isman MB (2006) Botanical insecticides, deterrents and repellents in modern agriculture and an increasing regulated world. *Annu Rev Entomol* 51: 45–66.
 16. Kamala Jayanthi PD, Kempuraj V, Aurade RM, Kumar Roy T, Shivashankara KS, Verghese A (2014) Computational reverse chemical ecology: virtual screening and predicting behaviorally active semiochemicals for *Bactrocera dorsalis*. *BMC Genom* 15: 209.

17. Kamgang B, Vazeille M, Yougang AP, Tedjou AN, Wilson-Bahun TA, Mousson L, Wondji CS, Failloux AB (2019) Potential of *Aedes albopictus* and *Aedes aegypti* (Diptera: Culicidae) to transmit yellow fever virus in urban areas in Central Africa. *Emerg Microbes Infect* 8(1):1636–1641.
18. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, Li Q, Shoemaker BA, Thiessen PA, Yu B, Zaslavsky L, Zhang J, Bolton EE (2019) PubChem 2019 update: improved access to chemical data. *Nucleic Acids Res* 47: D1102–9.
19. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, Li Q, Shoemaker BA, Thiessen PA, Yu B, Zaslavsky L, Zhang J, Bolton EE (2021) PubChem in 2021: new data content and improved web interfaces. *Nucleic Acids Res* 49: D1388–95.
20. Kolb P, Ferreira RS, Irwin JJ, Shoichet BK (2009) Docking and chemoinformatic screens for new ligands and targets. *Curr Opin Biotechnol* 20(4):429–36.
21. Liu J, Tian Z, Zhang Y, (2016a) Structure-based discovery of potentially active semiochemicals for *Cydia pomonella* (L.). *Sci Rep* 6: 34600.
22. Moola AK, Ayyadurai T, Balasubramani S, Vignesh R, Mohan PK, Sathish S, Diana RK (2023) Chemical composition and larvicidal activity against *Aedes aegypti* larvae from *Hyptis suaveolens* (L.) Poit essential oil. *Journal of Natural Pesticide Research*. 3:100018.
23. Gackowski M, Madriwala B, Koba M (2023) In silico design, docking simulation, and ANN-QSAR model for predicting the anticoagulant activity of thiourea isosteviol compounds as FXa inhibitors. *Chemical Papers* 3:1–8.
24. Pialoux G, Gaüzère BA, Jauréguiberry S, Strobel M (2007) Chikungunya, an epidemic arbovirosis. *Lancet Infect Dis* 7(5):319–27.
25. Pop RM, Popolo A, Trifa AP, Stanciu LA (2018) Phytochemicals in Cardiovascular and Respiratory Diseases: Evidence in Oxidative Stress and Inflammation. *Oxid Med Cell Longev*. 2018, 1603872.
26. Priya SS, Vasantha-Srinivasan P, Altemimi AB, Keerthana R, Radhakrishnan N, Senthil-Nathan S, Kalaivani K, Chandrasekar N, Karthi S, Ganesan R, Alkanan ZT (2023) Bioactive Molecules Derived from Plants in Managing Dengue Vector *Aedes aegypti* (Linn.). *Molecules* 28(5):2386.
27. Ranjan A, Ramachandran S, Gupta N, Kaushik I, Wright S, Srivastava S, Das H, Srivastava S, Prasad S, Srivastava SK (2019) Role of Phytochemicals in Cancer Prevention. *Int J Mol Sci* 20: 4981.
28. Rao BB, Harikumar PS, Jayakrishnan T, George B (2011) Characteristics of *Aedes* (Stegomyia) *albopictus* Skuse (Diptera: Culicidae) breeding sites. *Southeast Asian J Trop Med Public Health* 42(5):1077–82.
29. Saini A, Kumar A, Jangid K, Kumar V, Jaitak V (2023) Identification of terpenoids as dihydropteroate synthase and dihydrofolate reductase inhibitors through structure-based virtual screening and molecular dynamic simulations. *J Biomol Struct Dyn* 12:1–19.
30. Schmidt CW (2005) Outsmarting Olfaction: The next generation of mosquito repellents. *Environ Health Perspect* 113: 68.
31. Setlur SA, Karunakaran C, Pandey S, Sarkar M, Niranjana V (2023) Molecular interaction studies of thymol via molecular dynamic simulations and free energy calculations using multi-target approach

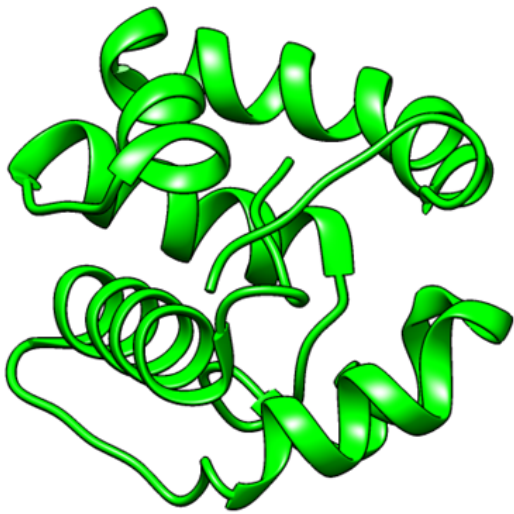
against *Aedes aegypti* proteome to decipher its role as mosquito repellent. *Molecular Simulation* 49(4):325–40.

32. Shahid A, Rao H, Aati HY, Sherif AE, Khan DA, Basit A, Umair M, Mueed A, Esatbeyoglu Korma TSA (2023) Phytochemical Profiling of the Ethanolic Extract of *Zaleya pentandra* L. Jaffery and Its Biological Activities by In-Vitro Assays and In-Silico Molecular Docking. *Applied Sciences* 13(1):584.
33. Sivan A, Shriram AN, Sunish IP, Vidhya PT (2015) Host-feeding pattern of *Aedes aegypti* and *Aedes albopictus* (Diptera: Culicidae) in heterogeneous landscapes of South Andaman, Andaman and Nicobar Islands, India. *Parasitol Res* 114:3539–46.
34. Sun L, Wang Q, Yang S, Wang Q, Zhang Z, Khashaveh A, Zhang YJ, Guo YY (2017) Functional analysis of female-biased odorant binding protein 6 for volatile and nonvolatile host compounds in *Adelphocoris lineolatus* (Goeze). *Insect Mol Biol* 26: 601–615.
35. Thammasittirong A, Thammasittirong SN (2023) Aromatic Residues on the Side Surface of Cry4Ba-Domain II of *Bacillus thuringiensis* subsp. *israelensis* Function in Binding to Their Counterpart Residues on the *Aedes aegypti* Alkaline Phosphatase Receptor. *Toxins* 15(2):114.
36. Trudeau SJ, Hwang H, Mathur D, Begum K, Petrey D, Murray D, Honig B (2023) PrePCI: A structure- and chemical similarity-informed database of predicted protein compound interactions. *Protein Sci* 32(4):e4594.
37. Wang J, Ren B, Bak KH, Soladoye OP, Gagaoua M, Ruiz-Carrascal J, Huang Y, Zhao Z, Zhao Y, Fu Y, Wu W (2023) Preservative effects of composite biopreservatives on goat meat during chilled storage: Insights into meat quality, high-throughput sequencing and molecular docking. *LWT* 26:115033.
38. Wang Y, Jin Y, Chen Q, Wen M, Zhao H, Duan H, Ren B (2017) Selectivity and ligand-based molecular modeling of an odorant-binding protein from the leaf beetle *Ambrostoma quadriimpressum* (Coleoptera: chrysomelidae) in relation to habitat-related volatiles. *Sci Rep* 7: 15374.

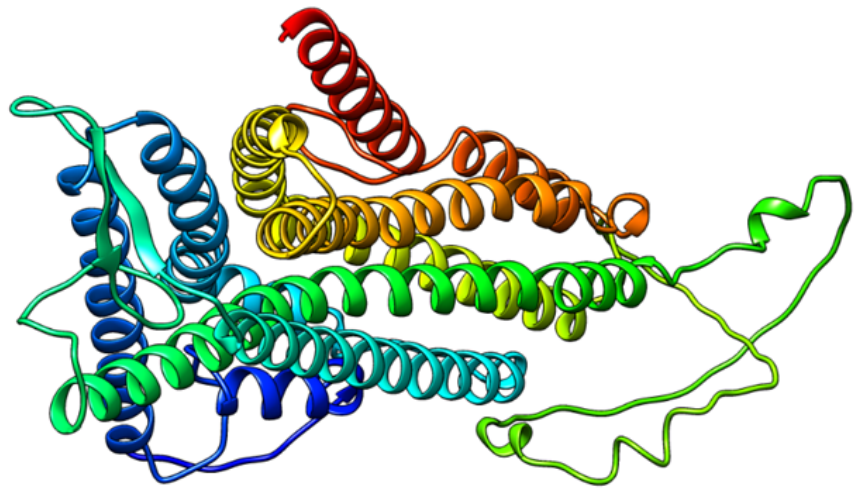
Tables

Table 1 is available in the Supplementary Files section.

Figures



(A) *Aedes aegypti*



(A) *Aedes albopictus*

Figure 1

3D structures of odorant binding proteins from (A) *Aedes aegypti* and (B) *Aedes albopictus*.

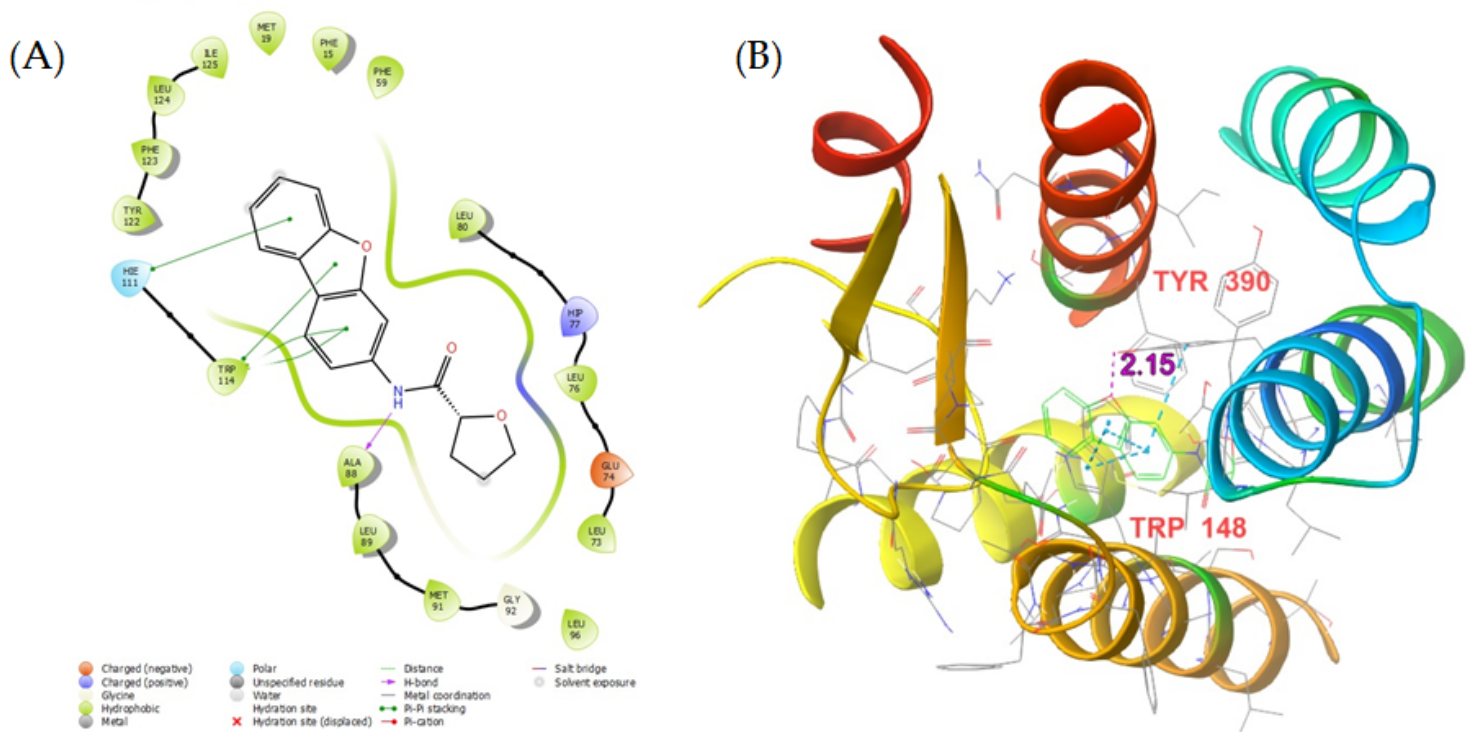


Figure 2

2D (A) and 3D (B) interactions of *Aedes aegypti*OBP (PDB ID: 3K1E) with N-dibenzofuran-3-yloxolane-2-carboxamide.

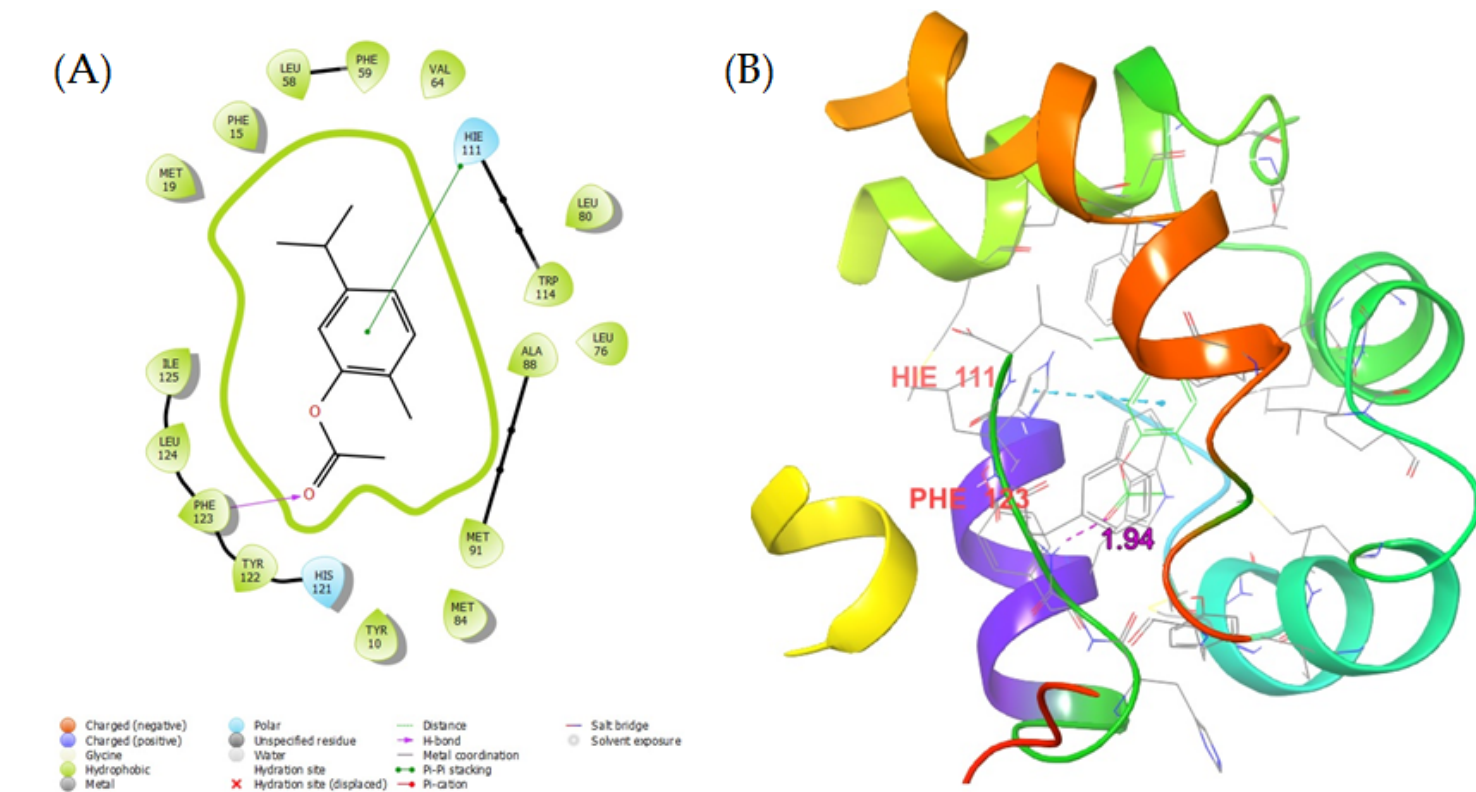


Figure 3

2D (A) and 3D (B) interactions of *Aedes aegypti*OBP (PDB ID: 3K1E) with carvacryl acetate.

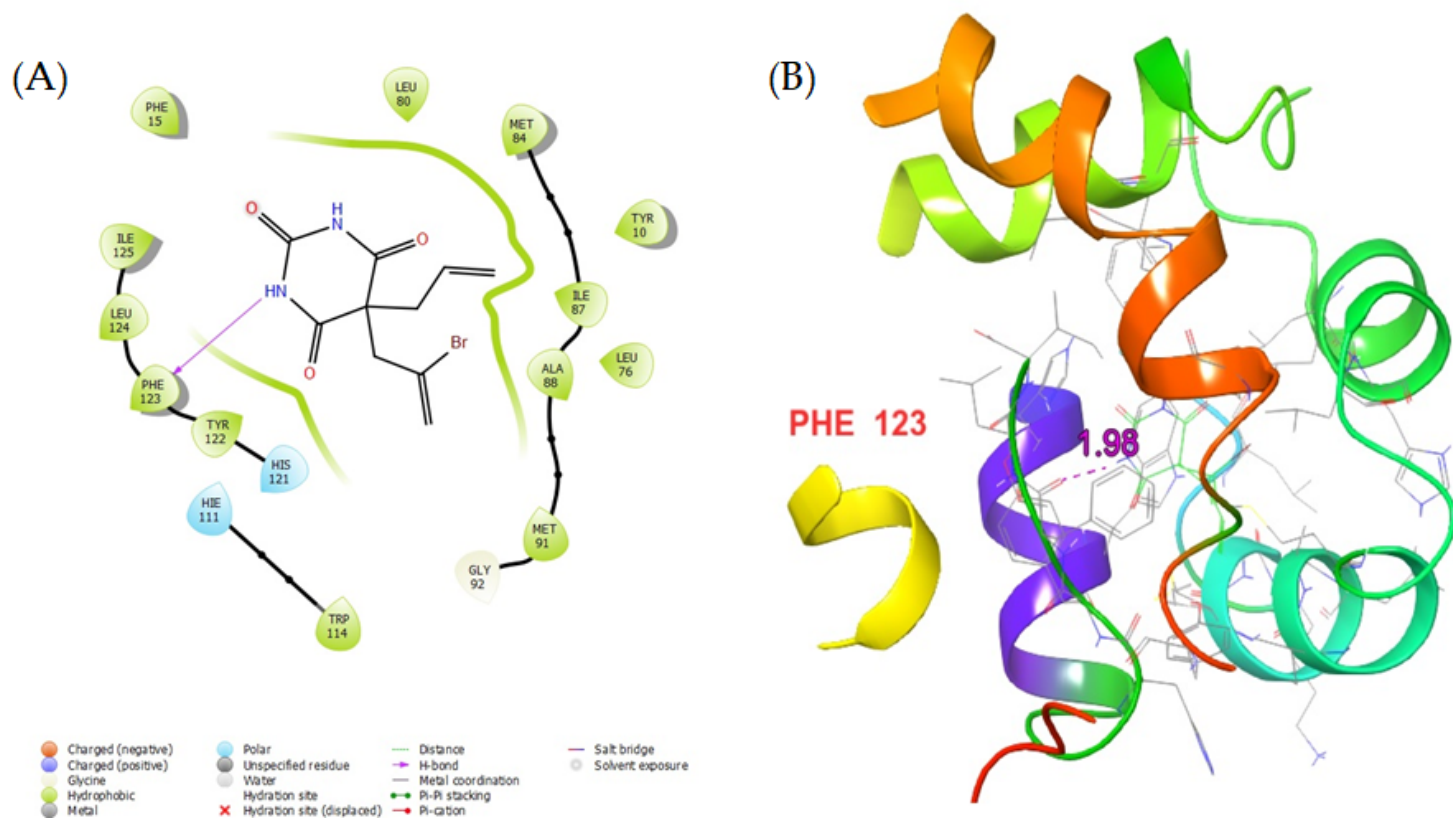


Figure 4

2D (A) and 3D (B) interactions of *Aedes aegypti* OBP (PDB ID: 3K1E) with brallobarbital.

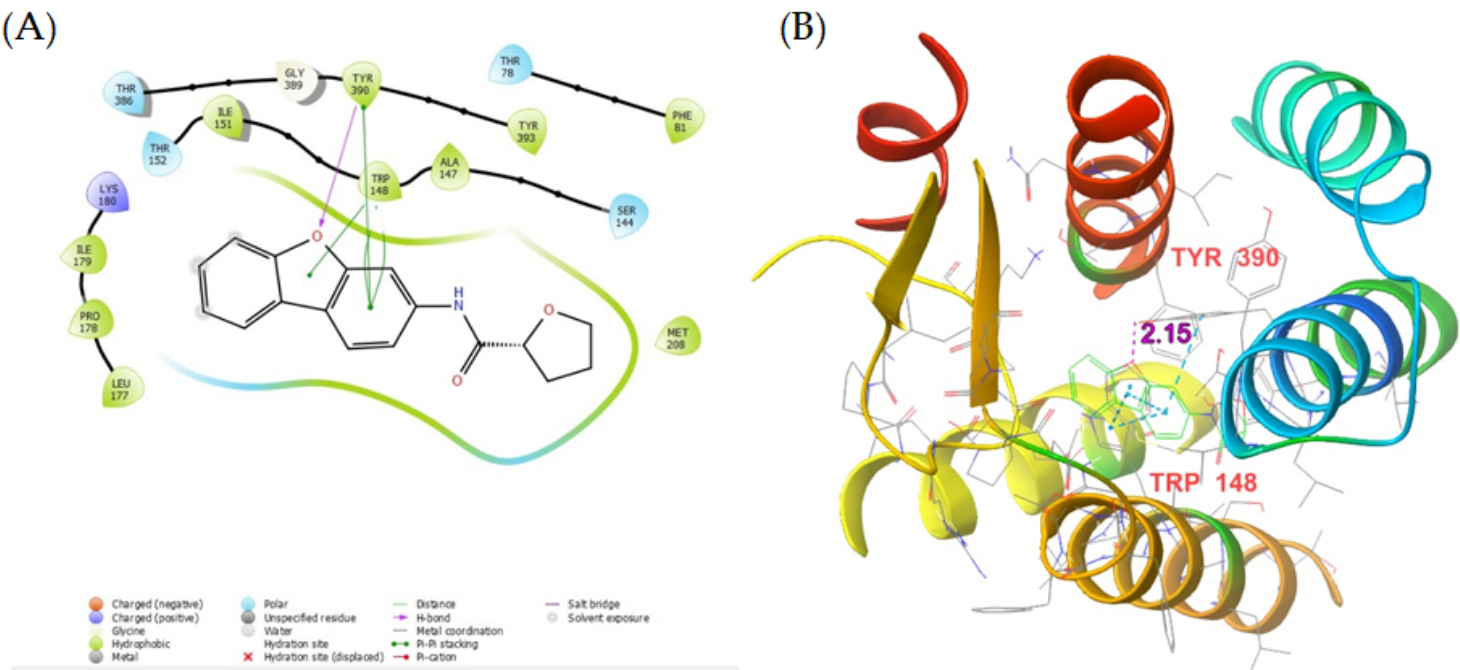


Figure 5

2D (A) and 3D (B) interactions of *Aedes albopictus* OBP with N-dibenzofuran-3-yloxolane-2-carboxamide.

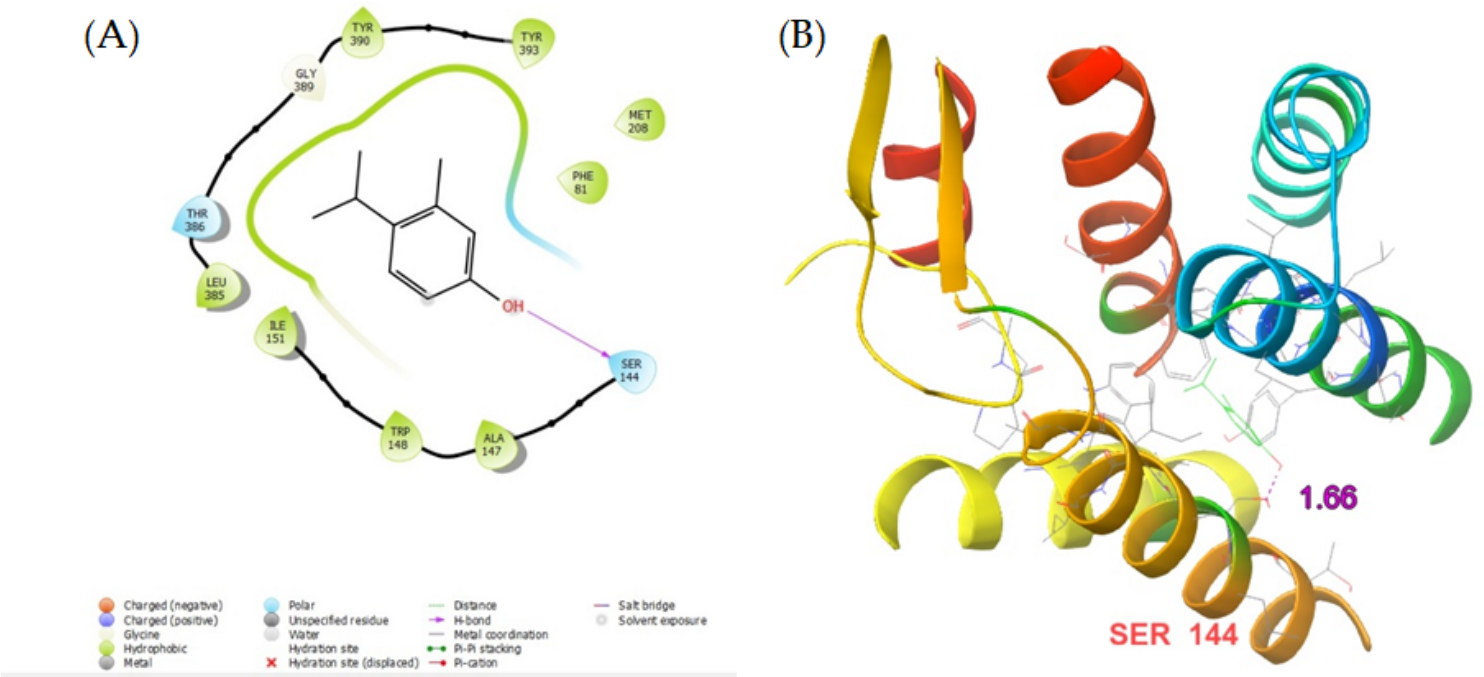


Figure 6

2D (A) and 3D (B) interactions of *Aedes albopictus* OBP with 3-Methyl-4-isopropylphenol.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.docx](#)
- [Supplementaryfile1.xps](#)
- [Supplementaryfile2.xps](#)