Reviews in Pharmacy and Pharmaceutical Sciences

PRIME OPEN ACCESS

Volume 2, Issue 1

Research Type

Date of Submission: 18 Aug, 2025
Date of Acceptance: 28 Aug, 2025
Date of Publication: 10 Sep, 2025

In Silico Antiviral Potential of Essential Oil Compounds Against Chikungunya Virus: A Molecular Docking Evaluation

Alessandro Careglio*

Draft study project by Alessandro careglio Doctor of Herbal Sciences, Italy

***Corresponding Author:** Alessandro Careglio, Draft study project by Alessandro careglio Doctor of Herbal Sciences, Italy.

Citation: Careglio, A. (2025). In Silico Antiviral Potential of Essential Oil Compounds Against Chikungunya Virus: A Molecular Docking Evaluation. *Rev Pharm Pharm Sci, 2*(1), 01-06.

Abstract

Chikungunya virus (CHIKV) represents a growing global health threat. In the absence of specific therapies, prevention strategies, such as the use of repellents, are crucial for disease control. This study explores the dual-action potential of compounds derived from essential oils: as mosquito repellents and as direct antiviral inhibitors. For an empirical evaluation, a mixture of essential oils from rosemary, lavender, and marjoram was prepared using an innovative urea-based distillation method, which showed preliminary repellent efficacy against Aedes albopictus. To investigate the antiviral action, molecular docking simulations were performed using the CB-Dock2 server. Key essential oil compounds were tested against two key CHIKV targets: The Capsid Protein (PDB ID: 5h23) and the NS2-NS3 Protease (PDB ID: 3TRK). The results revealed that various terpenes, particularly Gamma terpinene (-5.7 kcal/mol) and Para-cymene (-5.8 kcal/mol), show a favorable binding affinity with the capsid protein, suggesting a potential inhibition of viral assembly. Surprisingly, Ibuprofen, an anti-inflammatory drug, showed an exceptional binding affinity (-7.4 kcal/mol) with the capsid protein, outperforming the reference ligand. While the results are computational in nature, they suggest that essential oil compounds and Ibuprofen may offer a mode of action beyond their known roles. Future in vitro and in vivo studies are necessary to validate these findings and fully unlock the potential of these molecules as adjuvants in therapies against Chikungunya virus.

Keywords: Chikungunya Virus, Essential Oils, Molecular Docking, Capsid Protein, NSAIDs, Ibuprofen, Biorepellents

Introduction

Chikungunya virus (CHIKV), an alphavirus of the family Togaviridae, represents a growing threat to global health. Primarily transmitted by the Aedes aegypti and Aedes albopictus mosquitoes, the virus causes chikungunya fever, an acute febrile illness characterized by severe polyarthralgia and myalgia. While the infection is often self-limiting, the joint and muscle symptoms can persist for years, with a significant impact on patients' quality of life and economic productivity. Due to climate change and the increasing globalization of trade and travel, the habitat of Aedes mosquitoes is expanding, increasing the likelihood of epidemics in new regions, as demonstrated by its recent spread in Southern Europe, including Italy [1].

Because of their role as vectors of pathogens and parasites, mosquitoes are considered one of the primary threats to global health, responsible for a higher number of deaths than those caused by wars, terrorism, and armed violence combined [2]. Chikungunya virus is among the most widespread mosquito-borne infections, along with malaria, dengue, and Zika. In the absence of specific vaccines or antiviral treatments, preventive strategies are the most effective line of defense to reduce human-mosquito contact. These strategies include the use of insecticide-treated bed nets and personal repellents, which work by creating a chemical or spatial barrier to prevent mosquitoes from biting.

However, the use of conventional chemical insecticides has led to the development of biological resistance in mosquitoes and raises environmental concerns. Consequently, research is focusing on the development of sustainable and cost-effective alternatives, such as plant-based repellents. Compounds like limonene, citronellol, eucalyptol (1,8-cineole), and geraniol, found in essential oils, show proven repellent activity and, thanks to their complex chemical structures, make it difficult for mosquitoes to develop resistance [2].

The need to develop new antiviral therapies is therefore urgent. A promising approach consists of identifying and evaluating the activity of natural compounds that, in addition to their known function, can act directly against the virus. In particular, several essential oils are widely recognized for their repellent and insecticidal properties against vector mosquitoes. One of the key mechanisms in the Chikungunya virus replication cycle is the interaction between the capsid protein (CP) and the cytoplasmic tail of the E2 protein (cdE2), an essential interaction for virion assembly and budding. Recent studies have revealed that the CHIKV capsid protein possesses a conserved hydrophobic pocket that serves as a binding site for small molecules and can be targeted to block the interaction with the E2 protein, effectively inhibiting viral assembly [3]. Since this pocket is hydrophobic, it is highly probable that it can accommodate lipophilic and aromatic compounds, such as the terpenes that make up the majority of essential oils. An example of this potential synergy is thymol, a compound found in plants like oregano (Origanum majorana), which has shown larvicidal and adulticidal activity against mosquitoes (Anopheles gambiae) and a potential antimalarial effect [4]. This evidence suggests the possibility that other components of essential oils, known as mosquito repellents, may also possess a direct antiviral action.

The present study aims to investigate, through a computational molecular docking approach, the potential of some key compounds found in essential oils to act as inhibitors of crucial viral proteins for the Chikungunya virus replication cycle. The objective is to explore a dual action: the repellent capacity against the mosquito and a potential direct antiviral effect on the virus itself. We concentrated our analysis on two fundamental protein targets:

- The capsid protein (PDB ID: 5h23), chosen because a recent study has confirmed the existence of a hydrophobic pocket that can be targeted by small molecules for binding.
- The NS2-NS3 protease (PDB ID: 3TRK), which plays an essential role in viral replication, making it a validated drug target.

Our compounds of interest include molecules like menthol, pinene, and bornyl acetate, which are present in essential oils with repellent activity. The docking results were compared not only with molecules experimentally confirmed as capsid ligands (S)-(+)-mandelic acid and ethyl 3-aminobenzoate) [3], but also with potent protease inhibitors from other viruses (Telaprevir and Indinavir). Due to the significant size difference between natural molecules and the reference drugs, we also calculated the ligand efficiency to provide a more equitable comparison, normalizing the binding energy based on the number of atoms. The computational approach does not establish a cure but rather suggests a promising research direction, paving the way for future experimental investigations.

Materials and Methods

Biorepellent Essential Oil Preparation

The repellent essential oil blend was obtained through an innovative steam distillation process with a urea solution, previously described and developed by the author [4]. This method was chosen for its ability to improve the extraction efficiency and yield of volatile compounds compared to distillation with water alone. The procedure is based on the thermal decomposition of urea in an aqueous environment, which generates ammonia (NH_3) and carbon dioxide (CO_2) vapor, as described by the reaction: $NH_2CONH_2 \rightarrow 2NH_3 + CO_2$. The resulting alkaline vapor promotes the breakdown of the membranes of the glandular secretory hairs of the plants, where the essential oils are stored, facilitating their release.

For the preparation, 3 kg of fresh rosemary (Salvia rosmarinus), 2 kg of fresh lavender (Lavandula subsp.), and 1 kg of fresh marjoram (Origanum majorana) were used. The fresh plants were placed in a 30-liter distiller along with 3.5 liters of tap water and 100 grams of granular urea. During distillation, 15 grams of menthol were added to be co-distilled with the essential oils. At the end of the process, the essential oil was separated from the distillate, yielding a final amount of 44.7 grams.

Preliminary Repellent Efficacy Test

For an empirical evaluation of the repellent efficacy of the essential oil blend, a preliminary self-application test (pilot study) was conducted on the operator and one verification subject. The test was performed in an outdoor area with a notable presence of tiger mosquitoes (Aedes albopictus). The oil was applied by rubbing it directly onto the skin of one leg, while the other leg was left untreated as a control.

The choice of cutaneous application is based on the principle that lipophilic compounds, such as the terpenes in essential oils, can be absorbed by passive diffusion through the skin's stratum corneum. This absorption pathway is relevant not only for long-term repellent efficacy (as the compounds volatilize slowly) but also for the hypothesis of a potential systemic antiviral action in the event of significant absorption. This study did not measure skin absorption, but data from other transdermal pharmacokinetic studies suggest that some terpenic compounds are capable of reaching the systemic circulation, thus offering a potential route of action against viruses that infect peripheral tissues, as is the case with Chikungunya.

Molecular Docking Simulations

To evaluate the antiviral potential of the selected compounds, molecular docking simulations were performed using the CB-Dock2 web server [7]. This platform is an improved version that combines traditional blind docking with a

homologous template-based approach for greater accuracy in predicting the binding site. The process is based on the positioning and orientation of a small molecule (ligand) within the binding site of a protein (receptor) to predict binding affinity and molecular interactions.

Preparation of Ligands and Receptors

The ligands, i.e., the compounds present in the essential oils, were selected based on their known repellent activity. The 3D SDF files for each compound listed in Table 1 were downloaded from the PubChem database [6]. Tested Essential Oil Compounds:

- **Marjoram (Origanum majorana):** Carvacrol, Gamma terpinene, Para-cymene, Thymol.
- **Rosemary (Salvia rosmarinus):** Alpha-pinene, Beta-Myrcene, Borneol, Camphor, Eucalyptol.
- **Lavender (Lavandula subsp.):** Linalyl acetate, Linalool, Bornyl-acetate.
- **Menthol:** Reference compounds, used for comparison, were also downloaded from PubChem. The files for the ligands and receptors were uploaded to the CB-Dock2 platform, which automatically handles the preparation of the structures for docking. Ibuprofen was chosen for testing, despite not having a known antiviral activity, due to its structural similarity to ethyl 3-aminobenzoate (EAB) proposed as a ligand for the hydrophobic pocket of the capsid protein by Sharma et al. [3].

The Chikungunya virus protein receptors were obtained from the Protein Data Bank (PDB) database [5]. Two protein targets were used:

- **The capsid protein (PDB ID: 5h23):** This structure was selected for its conserved hydrophobic pocket, a target of interest for the development of viral assembly inhibitors.
- **The NS2-NS3 protease (PDB ID: 3TRK):** This protein was chosen for its critical role in viral replication, making it a validated pharmacological target.

Docking Setup

The CB-Dock2 server uses a dual approach:

- **Template-Based Docking:** If the submitted receptor protein has homology with protein-ligand complex structures in the BioLip2 database, the software uses this information as a "template" to predict and guide docking to the correct binding site. This approach was managed by the integrated FitDock method.
- **Independent Blind Docking:** In the absence of a homologous template, the software performs "blind" docking using the AutoDock Vina (version 1.2.0) software to locate binding pockets and position the ligands. The docking grid was automatically calculated by the server based on the detection of protein cavities.

Results Analysis

The results were analyzed based on two main parameters provided by the software:

- **Binding Affinity:** The predicted binding score, expressed in kcal/mol. A lower score (more negative value) indicates a more stable binding and thus a higher affinity between the ligand and the receptor.
- **Ligand Efficiency:** A parameter that normalizes the binding score by the number of heavy (non-hydrogen) atoms in the ligand. This allows for a more equitable comparison of the efficiency of molecules of different sizes. Ligand efficiency is calculated as:

$$LE = \frac{\Delta G}{NHA}$$

Where:

- ΔG is the binding free energy (the Vina score obtained in kcal/mol).
- NHA is the number of heavy (non-hydrogen) atoms in the molecule.

The results of all simulations were tabulated and compared with the values of the reference ligands, providing a basis for discussing the antiviral potential of the essential oil compounds.

Molecular Docking Simulation Results

The molecular docking simulations allowed for the prediction of the binding affinity of essential oil compounds and reference ligands with the Chikungunya virus (CHIKV) protein targets. The results, which include the binding affinity score (in kcal/mol) and ligand efficiency, are summarized in Table 1.

Compound	Protein Target	Binding Affinity Score (kcal/mol)	Number of Heavy Atoms	Ligand Efficiency (LE)
Essential Oil Compounds				
Carvacrol	Capsid Protein	-5,9	11	-0,536
Gamma terpinene	Capsid Protein	-5,7	10	-0,57
Linalool	Capsid Protein	-4,8	11	-0,436
Para-cymene	Capsid Protein	-5,8	10	-0,58
Thymol	Capsid Protein	-5,6	11	-0,509

Alpha-pinene	Capsid Protein	-4,7	10	-0,47
Beta-Myrcene	Capsid Protein	-5,2	10	-0,52
Borneol	Capsid Protein	-4,6	11	-0,418
Bornyl-acetate	Capsid Protein	-5,8	14	-0,414
Camphor	Capsid Protein	-4,7	11	-0,427
Eucalyptol	Capsid Protein	-4,6	11	-0,418
Linalyl acetate	Capsid Protein	-5,9	14	-0,421
Bornyl-acetate	NS2-NS3 Protease	-5,3	14	-0,379
Alpha-pinene	NS2-NS3 Protease	-4,7	10	-0,47
Reference Ligands				
(S)-(+)-Mandelic Acid	Capsid Protein	-6,1	11	-0,554
Ethyl 3-aminobenzoate	Capsid Protein	-5,9	12	-0,492
Telaprevir	NS2-NS3 Protease	-9,7	49	-0,198
Indinavir	NS2-NS3 Protease	-9,6	45	-0,213
Other				
Ibuprofen	NS2-NS3 Protease	-6,5	15	-0,433
Ibuprofen	Capsid Protein	-7,4	15	-0,493
Menthol	Capsid Protein	-5,9	11	-0,536
Menthol	NS2-NS3 Protease	-5,9	11	-0,536

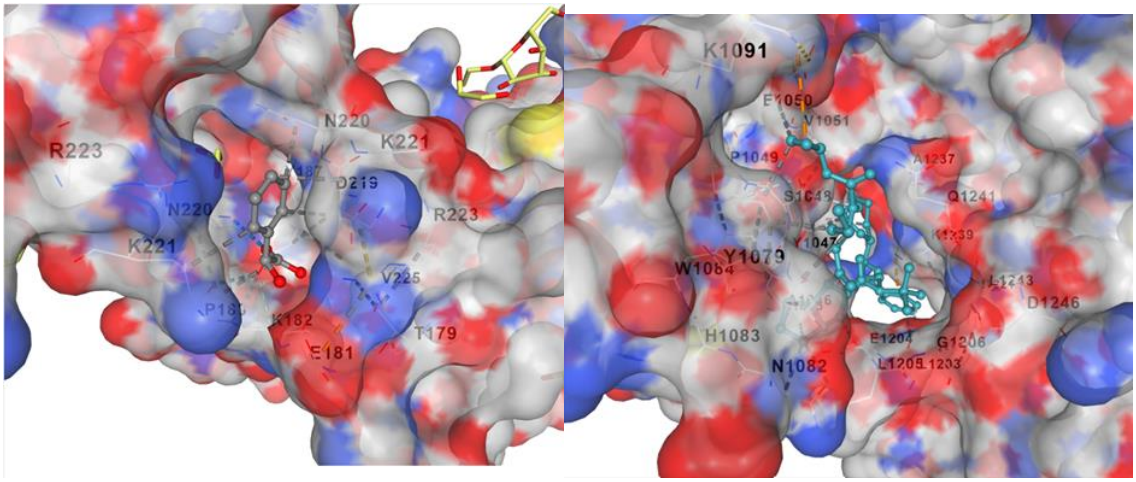
The details of the molecular interactions (such as hydrogen bonds and hydrophobic interactions) between the compounds with the highest binding affinity scores and the amino acids of the binding site were visualized and analyzed. In particular, an excellent integration of the compounds into the capsid protein's hydrophobic pocket was observed, confirming the hypothesis that the lipophilic nature of terpenes is crucial for binding in this region.

The results show that most of the analyzed terpenes exhibited negative affinity scores, suggesting an energetically favorable interaction with the binding sites of the viral proteins. For the capsid protein, compounds such as Carvacrol, Gamma terpinene, Para-cymene, Thymol, Beta-Myrcene, Bornyl-acetate, Linalyl acetate, and Menthol showed affinity scores (between -5.2 and -5.9 kcal/mol) comparable to the reference ligand Ethyl 3-aminobenzoate (-5.9 kcal/mol) and only slightly lower than (S)-(+)-Mandelic Acid (-6.1 kcal/mol). It is interesting to note how Ibuprofen showed the highest score (-7.4 kcal/mol) among all the tested ligands for this target.

The analysis of ligand efficiency (LE), a parameter that normalizes the binding score by the number of heavy atoms, provided a different perspective. As the graph shows, essential oil compounds, being smaller molecules, generally showed a higher binding efficiency compared to larger reference ligands such as Telaprevir and Indinavir. Specifically, Para-cymene (-0.58), Gamma terpinene (-0.57), and Menthol (-0.54) showed LE values very similar to, and in some cases higher than, those of the reference ligands. (S)-(+)-Mandelic Acid showed the highest ligand efficiency (-0.554) among the reference ligands. Ibuprofen also showed an excellent LE (-0.493), while Telaprevir and Indinavir, despite having very low affinity scores, showed a decidedly lower ligand efficiency due to their large molecular sizes.

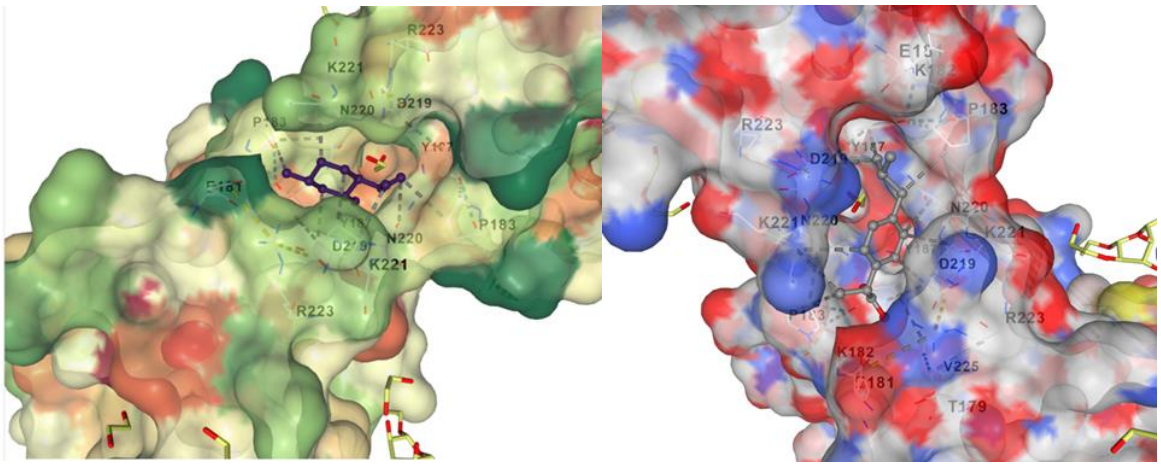
The docking results for the NS2-NS3 protease showed that most of the essential oil compounds have a lower binding affinity compared to the reference ligands, which are specific protease inhibitors. However, Ibuprofen (-6.5 kcal/mol) and Menthol (-5.9 kcal/mol) still showed significant binding. In this case as well, the analysis of ligand efficiency confirms the greater efficiency of smaller compounds like Alpha-pinene (-0.47) and Ibuprofen (-0.433) compared to Telaprevir and Indinavir.

In summary, the computational results suggest that several compounds present in essential oils, particularly Gamma terpinene, Para-cymene, Carvacrol, and Menthol, can effectively bind to the hydrophobic pocket of the CHIKV capsid protein. This binding could potentially interfere with the protein's function, offering a theoretical basis for exploring a direct antiviral action of these substances, in addition to their known repellent activity.



(S)-(+)-mandelic acid (MDA) on capsid protein

Telaprevir on NS2-NS3 proteases



Menthol on capsid protein

Ibuprofen on capsid protein

Figure 1: Representation of MDA, Telaprevir, Menthol, and Ibuprofen in the Binding Pockets of the Two Proteins, Capsid and NS2-NS3, Obtained from the Cao Lab Molecule Viewer [7]

Discussion

The rising incidence of Chikungunya virus, coupled with the lack of specific therapies and vaccines, makes the exploration of new strategies for disease control urgent. This study has addressed the challenge from a dual perspective: prevention through essential oil-based repellents and the search for potential compounds with direct antiviral action, both with a particular focus on accessible methods and practical solutions.

Ibuprofen and Its Potential Antiviral Role

In a clinical context, non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are widely recommended for managing the symptoms of Chikungunya fever, particularly to alleviate the fever and severe joint and muscle pain associated with the acute phase of the disease. Their role is considered symptomatic, aimed at reducing inflammation and pain, without acting directly on the virus.

The results of our molecular docking study suggest a potential and unexpected dual role for ibuprofen. Computational data indicate that, in addition to its known anti-inflammatory action, ibuprofen may also possess significant direct antiviral activity. Our data show a binding affinity score of -7.4 kcal/mol with the CHIKV capsid protein (PDB ID: 5h23) and -6.5 kcal/mol with the NS2-NS3 protease (PDB ID: 3TRK).

The binding affinity score for the capsid protein is particularly noteworthy. With a value of -7.4 kcal/mol, the predicted binding of ibuprofen is more energetically favorable than that of all the essential oil compounds tested and is even better than that of the reference ligand, (S)-(+)-Mandelic Acid (-6.1 kcal/mol), which is known to bind to the capsid's hydrophobic pocket. This result is consistent with the hypothesis that molecules with a lipophilic nature, such as

terpenes and ibuprofen, can be accommodated in this pocket. The high binding score of ibuprofens to the capsid protein, combined with its widespread clinical use, raises a fascinating hypothesis: the clinical efficacy of ibuprofen in managing Chikungunya symptoms might not depend solely on its anti-inflammatory action but could be potentiated by direct interference with the viral replication cycle. If this hypothesis were to be confirmed by in vitro and in vivo studies, ibuprofen could represent an interesting candidate for the repurposing of an existing drug as a potential antiviral adjuvant.

Conclusions and Future Perspectives

This study has explored an innovative and integrated approach to managing the Chikungunya virus, combining the search for practical methods for preparing biorepellents with a computational analysis of the antiviral potential of specific phyto-compounds.

We have demonstrated that several compounds present in essential oils, particularly Gamma terpinene, Para-cymene, Carvacrol, and Menthol, show energetically favorable binding affinity scores towards the Chikungunya virus capsid protein. These results suggest that essential oil compounds may not only act as mosquito repellents but could also have a potential dual role, offering direct therapeutic activity.

In particular, it emerged that Ibuprofen, despite being a drug known for its symptomatic anti-inflammatory action, shows an exceptional binding affinity with the capsid protein, superior to that of some reference ligands. This finding opens an interesting perspective on the repurposing of existing drugs.

The results of this study, although promising, are computational in nature. The logical and necessary step to validate these discoveries is to conduct in vitro studies. Future investigations should focus on testing the antiviral efficacy of these compounds in the laboratory, verifying whether the computationally predicted inhibitory activity translates into an actual therapeutic effect against the Chikungunya virus. Only through the combination of computational and experimental approaches will it be possible to fully unlock the potential of these natural compounds and contribute to the development of more effective and sustainable strategies to combat vector-borne diseases.

References

1. Bartholomeeusen K, Daniel M, LaBeaud DA, Gasque P, Peeling RW, Stephenson KE, Ng LFP, Ariën KK. Chikungunya fever. Nat Rev Dis Primers. 2023 Apr 6;9(1):17.
2. Hazarika, H., Krishnatreyya, H. Technological Advancements in Mosquito Repellents: Challenges and Opportunities in Plant-Based Repellents. Acta Parasit. 70, 117 (2025).
3. Sharma R, Kesari P, Kumar P, Tomar S. Structure-function insights into chikungunya virus capsid protein: Small molecules targeting capsid hydrophobic pocket. Virology. 2018 Feb;515:223-234.
4. Careglio, A. (2025). Low-Cost Phytochemical Methods: From the Characterization of Artemisia Annua to the Development of Biorepellent Formulations. Rev Pharm Pharm Sci, 2(1), 01-10.
5. RCSB Protein Data Bank.
6. PubChem.
7. Cao Lab. CB-Dock2.