

A Review: An In-Silico Docking Study of Herbal Mosquito Repellent Activity

Kranti Biradar ¹, Prajakta Kothawade ², Shashikant Dhole ³, Sushma Ghuge ¹, Raksa Amle ¹

¹ PES Modern College of Pharmacy, (for ladies) Moshi, Pune; krantibiradar30@gmail.com (K.B.); sushmavghuge10@gmail.com (S.D.); amaleraksha@gmail.com (R.A.);

² Department of Chemistry, PES Modern College Of Pharmacy (for ladies), Moshi, Pune; prajaktakothawade12@gmail.com;

³ Principal, Department of Pharmaceutics, PES Modern College Of Pharmacy (for ladies) Moshi, Pune; shashikantdhole27@gmail.com;

* Correspondence: prajaktakothawade12@gmail.com;

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Abstract: From ancient periods, different herbal plants have been used for diseases that are spread to people by mosquitoes. Different herbal phytoconstituents play an imperative role in the mosquito repellent. A literature survey concludes that about 800 herbal plants possess mosquito-repellent activity. Drugs are used to spread mosquito-borne diseases, so further advances in developing new drugs with fewer side effects are needed. However, very little work has been done on the *in silico* activity of herbal mosquito repellents. So, the present review focuses on *in silico* studies of phytoconstituents, such as Acetylcholinesterase in *Artemisia pallens*, pectolarigenin in *Lantana camara*, and linalool, alpha-pinene, and myrcene in *Vitex negundo*. Sitosterol in *Hyptis suaveolens* L, thujone in *Elaeagnus indica*, (E) β -caryophyllene in *Artemisia vulgaris*, alpha-Murolene, alpha-phellandrene in *Schinus molle* L, Desulphosinigrin in *Coffea arabica* L., Vitamin D, Beta amyryn, Alpha amyryn, and Stigmasterol in *Kalanchoe pinnata*, gamma-Sitosterol, DL-alpha-Tocopherol, and Lycopersin in *Osmium tenuiflorum* which showed good binding activity with different receptors like OBP,3N7H, AeSCP-2, NS3/NS2B, etc. compare to other constituents present in herbal plants. From these studies, we can conclude that in the future, the listed phytoconstituents compound may be used as a mosquito repellent to prevent mosquito-borne disease.

Keywords: mosquito repellent; docking studies; phytoconstituents; molecular dynamics.

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1. Introduction

Mosquitoes are the most annoying blood-sucking insects that torment mortal beings. Their blood-sucking mouthfuls can transmit more than two potentially deadly conditions. Conditions spread by mosquitoes include Dengue, Malaria, Yellow Fever, Chikungunya Virus, Zika Virus, and West Nil Virus. According to the WHO, 4.5 million cases and over 4,000 dengue-related deaths have been reported from 80 countries as of 2023 the beginning of November. Chemical germicides such as malathion, methoprene, DDT, carbamates, diflubenzuron, fenthion, and pyriproxyfen generally control mosquitoes. Frequent, constant, and arbitrary use of these chemicals has affected human health, contaminated the environment, developed resistance to pests, and led to the emergence of refractory vector behavior [1-4]. The

science of Ayurveda uses herbal remedies. Numerous of these herbal remedies have been widely used in ancient India to treat mosquito-borne conditions, including infectious diseases. Even the World Health Organization (WHO) supports using plant-based medicine to treat several conditions. In the design and layout of novel drugs, molecular docking is commonly used in modern drug design to understand protein-ligand interactions [5,6]. Computer tools similar to molecular docking methods provide insight into the interactions between phytochemicals and receptors, predicting the target protein's binding orientation to the ligand within the targeted list. These techniques more easily discover effective bioactive compounds with larvicidal and mosquitocidal properties [7]. The three-dimensional structure of the protein-ligand complex could serve as a valuable resource for understanding how proteins interact with one another and perform biological functions [8]. Due to problems encountered in detecting natural products and the economic cost of the experimental method, computational methods similar to molecular docking are desired for predicting protein-ligand binding and their affinities [9]. In the present review, we have listed various herbal phytoconstituents, their molecular docking interactions with various receptors, molecular dynamics studies, etc. Responsible for the mosquito larvicidal, pupicidal, adulticidal, and repellent activity [10].

2. *In silico* Docking Studies of Herbal Phytoconstituents

2.1. *Artemisia pallens* -(*Davana*).

Artemisia pallens Wall. is a small, annual herbaceous plant widely distributed in the humid habitats of India. Compared with aqueous extract, various phytoconstituents, including a complex mixture of phenols, tannins, flavonoids, glycosides, alkaloids, terpenes, and steroids, exhibit larvicidal activity. The essential oil from *Artemisia pallens* was found to possess antibacterial, antifungal, analgesic, anti-inflammatory, and antidiabetic activities, making it significant in the medical industry [11,12].

The current study aimed to examine the larvicidal efficacy of the leaf extracts (aqueous, methanol, and chloroform) of *Artemisia pallens* against *Culex quinquefasciatus* larvae in the fourth instar stage, to analyze the chemical composition of the two promising extracts by GC-MS, and to prove the insecticidal potential of three compounds (among the best extracts) against Acetylcholinesterase enzyme by in-silico docking method.

The *Culex quinquefasciatus* acetylcholinesterase sequence (Q867X2) was retrieved from the Uniprot database, and, as the acetylcholinesterase structure was unavailable, it was modeled using the Swiss Model server with the template 5X61 – A Chain.

Molecular docking: The SMILES data for valproic acid, α -terpineol, and pseudo-solasodine diacetate were retrieved from PubChem using ChemSketch software. Its 3D structure was generated, optimized, and saved as a .mol file, then converted to the open BABEL molecular converter program and saved in PDB format. The ligands (valproic acid, α -terpineol, and pseudo-solasodine diacetate) were docked against acetylcholinesterase using AutoDock, and the results were visualized in Accelrys Discovery Studio Visualizer.

The larvicidal activities of the two potent extracts (methanol and chloroform) of *Artemisia pallens* might be due to the presence of an appreciable amount of phytoconstituents as a complicated mixture of phenols, tannins, flavonoids, glycosides, alkaloids, terpenes, and steroids when compared to the aqueous extract.

The acetylcholinesterase structure was not available in the PDB database. Hence, it was modeled using the Swiss Model server with template 5X61 – A Chain. The modeled structure

was highly plausible, with 93.94% sequence identity. Moreover, they showed that 87.7% of residues were in the most favored regions of the Ramachandran plot and none in the disallowed region—3D molecular interaction of acetylcholinesterase with pseudo-solasodine diacetate. The compound Pseudo-solasodine diacetate (Figure 1) could act as an insect repellent by inhibiting AChE and disrupting neurotransmission. It has the potential to be included under insecticides.

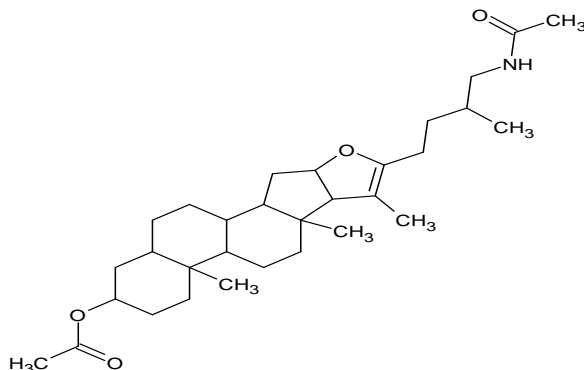


Figure 1. Pseudo-solasodine diacetate acts as an insect repellent by blocking AChE.

Based on the literature review, this is the first report on the effect of binding to acetylcholinesterase with a high binding energy (-9.86 kcal/mol) than the normal substrate acetylcholine (-6.4 kcal/mol) [13].

2.2. *Lantana camara*-(Red Sage).

The genus *Lantana camara* L. is an important medicinal, ornamental, and essential oil-producing plant in the family Verbenaceae, described by Linnaeus in 1753. *L. camara* possesses therapeutic potential due to its various bioactive components, including steroids, triterpenoids, oligosaccharides, iridoid glycosides, naphthoquinones, phenylpropanoid glycosides, alkaloids, flavonoids, tannins, and saponins [14,15].

These essential oils obtained from *L. camara* from different localities have been reported, and their important biological activities, including anti-inflammatory, antioxidant, and antibacterial properties, have been documented [16]. The ethanolic leaf extract of *L. camara* L. was analyzed by gas chromatography-mass spectrometry (GC-MS), which identified 30 phytochemicals with a range of medicinal uses. [17].

GC-MS has been used for the identification of compounds, including alkaloids, alcohols, nitro compounds, long-chain hydrocarbons, steroids, esters, amino acids, and organic acids, and for the detection of functional groups in a small fraction of a crude plant extract [18,19].

Molecular docking- *L. camara* L. leaves were collected in Nagercoil, Kanniya Kumari district, Tamil Nadu, India. Using GC-MS technology, the phytoconstituent of the *L. camara* L. extract was detected. The phytochemicals of *L. camara* L. identified by GC-MS were selected for docking investigations using the Lipinski rule of five criteria. The chemical structures of the phytochemicals were obtained from the PubChem-NCBI database (<http://www.pubchem.ncbi.nlm.nih.gov/>) and converted to three-dimensional structures for the study using an online SMILES translator. The 3D structure of *Aedes aegypti* L. larvae's sterol carrier protein-2 (1PZ4) was obtained from the Protein Data Bank (<http://www.rcsb.org/>) and examined using the Discovery Studio program in order to conduct protein modeling experiments. Molecular-Docking analysis. Lastly, docking studies for *L. camara* L.

phytocompounds (ligands) and the target protein 1PZ4. used Auto Dock Vina (version 4) to complete. Using Lipinski's rule of five, 10 potentially active phytocompounds were selected from the GC-MS data of *L. camara* and molecularly docked with sterol carrier protein-2 (1PZ4). 1PZ4 and pectolarigenin complex (-8.7 Kcal/mol).

The phytocompound pectolarigenin (Figure 2) showed the highest affinity (-8.7 Kcal/mol) for protein 1PZ4, followed by gamolenic acid (-7.8 Kcal/mol), decahydro-2,2-dimethyl (-7.9 Kcal/mol), and naphthalene. In the present study, phytocompounds of *L. camara L.* are docked with sterol carrier protein-2 (1PZ4) to anticipate larvicidal activity. The studies signify the fact that out of 10 phytoligands, 3 phytoligands showed the best interaction with the protein 1PZ4. Pectolarigenin has shown the highest binding affinity of -8.7 Kcal/mol. In the study, 30 phytocompounds were identified from the ethanolic leaf extract of *L. camara L.* The ten compounds were selected and subjected to molecular docking studies. The results of this work have demonstrated unequivocally that the plant chemical of *L. camara L.* has the ability to bind with the amino acid residues in the active site of the Sterol carrier protein-2 (AeSCP-2) of *Ae. aegypti* larvae, thereby inhibiting its function [20].

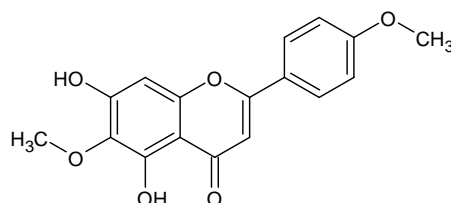


Figure 2. Pectolarigenin shows the best affinity with protein (1PZ4) and shows larvicidal activity.

2.3. *Vitex negundo*-(*Nisinda*).

Vitex negundo belongs to the family *Verbenaceae* and grows as a small tree with thin grey bark. All parts of the plant, especially its leaves, contain several secondary metabolites, such as alkaloids, phenols, flavonoids, glycosidic iridoids, tannins, and terpenes. *Vitex negundo* is a woody, aromatic deciduous shrub growing to a small tree. *Vitex negundo* is also known as the five-leafed chaste tree or monk's pepper. Besides its antimicrobial properties, it is also reported for its larvicidal, insecticidal, repellent, and pesticidal activity. This plant also contains a number of polyphenolic compounds, terpenoids, glycosidic iridoids, and alkaloids [21,22].

Molecular docking- the odorant binding proteins (OBPs) were selected as a target based on their application as bio-recognition elements and biosensors for small ligands. The three-dimensional (3D) structures of four *A. gambiae* OBPs: OBP 1 (PDB ID 3N7H), OBP 7 (PDB ID 3R1O), OBP 4 (PDB ID 3Q8I), and OBP (PDB ID 2ERB) were retrieved from the Protein Data Bank.

The crystal structures of the OBPs were processed by removing existing ligands and water molecules, and missing hydrogen atoms were added according to the amino acid protonation state at pH 7.0 using AutoDock 4.2. In this study, six ligands (α -pinene (PubChem CID 6654), linalool (PubChem CID 6549), cis-sabinene hydrate (PubChem CID 101629835), citronellal (PubChem CID 7794), verbenone (PubChem CID 29025), and bornyl acetate (PubChem CID 6448) identified through the GC-MS analysis in all essential oils irrespective of the collection location were retrieved from the PubChem database (www.pubchem.ncbi.nlm.nih.gov (accessed on 12 February 2021) in the Structure Data Format (SDF) [23-25].

Molecular docking was carried out using PyRx-Python Prescription 0.8 software. (Hangzhou, Zhejiang, China). The input file was in the form of the PDB code of the receptor

or PDB file format, and the molecules were in PDB file format. The output file was a docking report. The docked image was viewed by “BIOVIA Discovery Studio Visualizer” software (Waltham, MA, USA) to review the interactions between ligands and proteins and the length of the interaction along with amino acids.

The ligands were imported into PyRx 0.8 via the Open Babel plug-in for each docking phase, with the Universal Force Field (UFF) as the energy minimization method and conjugate gradient descent as the optimization algorithm. The coordinates of the active sites of the four *A. gambiae* odorant-binding proteins were determined using the grid boxes used in the docking studies. All the selected ligands demonstrated a multiplicity of binding properties and varying degrees of interaction within the proteins' active pockets, except for OBP4, which only has affinity for α -pinene, linalool, verbenone, and β -pinene.

As a result, myrcene has been identified as an inhibitor of the main olfactory proteins involved in host recognition signals (OBP1 and OBP), which aid in collecting and transporting hydrophobic odorants into and through the fluid.

Pure α -pinene (Figure 4), linalool (Figure 3), and myrcene (Figure 5) could be employed as a safe active ingredient in the development of a new mosquito repellent, according to ADME/tox and docking studies. According to ADME/tox and docking results, α -pinene, linalool, and myrcene could be used as safe active components in the development of an environmentally friendly new mosquito repellent. Docking showed that these ligands bind to OBPs and may play an important role in blocking the olfactory receptor (ORs) coreceptor and inhibiting specific ORs, causing disorientation and confusion in *A. gambiae* [26].

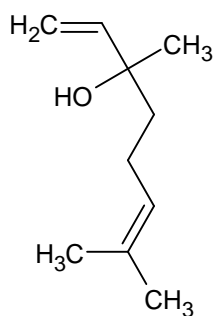


Figure 3. The structure of linalool.

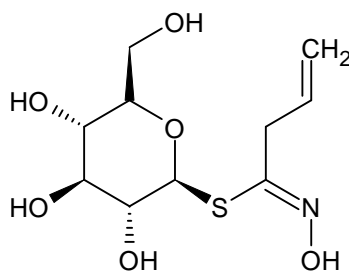


Figure 4. The structure of 5 α -pinene.

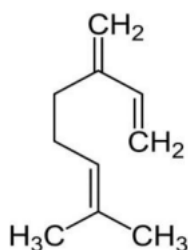


Figure 5. The structure of myrcene.

2.4. *Hyptis suaveolens* L-(vilayti tulsi).

Hyptis suaveolens is a wild plant generally known as the “Sirna Thulasi” or “Adavi Thulasi” and belongs to the family of *Lamiaceae*. Essential oils of *H. suaveolens* are known to exhibit antioxidant activity and antimicrobial activity. The extracts of *H. suaveolens* are the source of natural insecticides for mosquito control. The phytochemicals were analyzed by GC-MS (SHIMADZU QP 2010 [27,28])

Molecular docking is the process by which two molecules fit together in 3D space. It is a key tool in structural biology and computer-aided drug design. Using Tsar's easy-to-use chemical spreadsheet interface, the limits were observed, and 2D structures were converted to 3D structures with physicochemical properties to analyze and promote activity. For the molecular docking analysis, the Schrodinger-aided drug design software was used [29].

The 3D structure of the receptor was downloaded from the PDB and modified. This included removing water molecules from the cavity, stabilizing charges, filling in missing residues, generating side chains, etc., according to the available parameters. After modification of the receptor, it is biologically active and stable [30]. The ligand is docked onto the receptor, and the interactions are checked. The scoring function generates scores depending on which ligand with the best fit was selected. Docked compounds screened against the 3N7H Odorant Binding Protein 1 of *Anopheles gambiae*, with its Glide docking scores of DEET and gamma sitosterol of *H. suaveolens* with Agam OBP 1 were recorded and discussed.

Among all methanolic compounds of *H. suaveolens* tested in the present study, gamma sitosterol (Figure 6) exhibits insect maximum repellent activity when compared with known DEET against 3N7H Crystal structure of odorant Binding Protein 1 from *Anopheles gambiae*. The interactivity of the compounds with the amino acid residues of the 3N7H protein at the active site was confirmed using Schrödinger Computer-Aided Drug Design Software. Sitosterol is 0.2, which is greater than DEET. Methanolic extracts of *Hyptis suaveolens* L. were characterized by the GC-MS method, and 13 compounds were docked using Schrodinger Maestro software. Among the 13 compounds, gamma sitosterol was found to be an effective mosquito repellent. The identified compound, gamma sitosterol, is a natural compound with repellent activity. We therefore suggest that this compound may be used as a mosquito repellent to prevent mosquito-borne diseases [31].

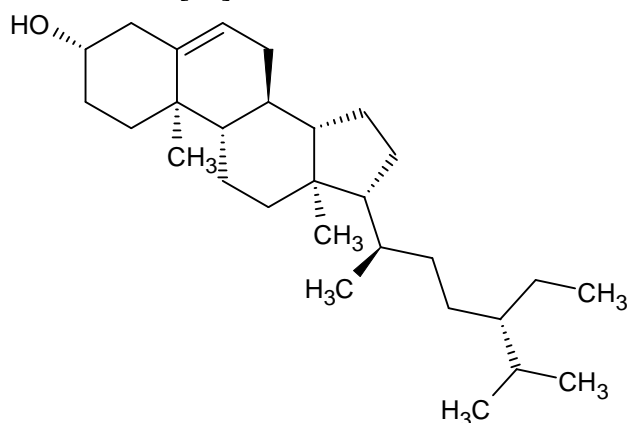


Figure 6. Γ -sitosterol shows repellent activity, binding with the OBP1 protein.

2.5. *Elaeagnus indica*-(silverberry).

Indica elaeagnus. Typically found on trees, Servett. (*Elaeagnaceae*) is a large, woody, climbing shrub with branches heavily covered in silvery scales. Numerous secondary

metabolites with a range of biological characteristics, including flavonoids, alkaloids, glycosides, and tannins, are known to be present in plants. Leaf extracts from this plant's crude solvent have been shown to exhibit a variety of biological properties, including antibacterial, anticancer, and mosquito larvicidal effects. [32].

The larvicidal principle was isolated from crude acetone leaf extract of *E. indica* using a bioassay-guided method that involved 1D (¹H and ¹³C) chromatography techniques and 2D NMR (HMBC and HSQC) spectra recorded (DMSO-d₆) using a Bruker AV-500 MHz NMR spectrometer with tetramethylsilane as an internal standard. Molecular Docking: Using Schrödinger's GLIDE (Grid-based Ligand Docking with Energetics) (GLIDE, 2009) software v5.5 running on a Red Hat Enterprise Linux 5 (RHEL5) workstation, a molecular modeling study of isolated thujone with *Aedes aegypti* Sterol Carrier Protein-2 (AeSCP-2) was conducted. Every stage of ligand and protein preparation, as well as Induced Fit Docking (IFD) was carried out using the Maestro v9.0 Graphical User Interface (GUI) workspace (Maestro, 2009). Crystal coordinates of the ligands, palmitic acid and thujone, were employed in this molecular docking investigation. The LigPrep (Schrödinger Suite, 2009a, b) module of Schrödinger Suite v2.3 was used to prepare the ligands (2009a, b). An inhibitor-complexed AeSCP-2 X-ray crystal structure (PDB ID: 1PZ4) was obtained from the Protein Data Bank (PDB) database (<http://www.rcsb.org/pdb>). By eliminating all water molecules and assigning suitable valences, atomic charges, bond orders, bond angles, and topology, the structure of AeSCP-2 was optimized.

Numerous insect/pest larvae have been shown to be toxic to thujone (Figure 7). A monoterpene ketone is thujone. A number of monoterpene ketones significantly hampered the growth and development of larvae. According to this study, thujone, isolated from the bioactive acetone extract of *E. indica*, exhibits strong larvicidal activity against *A. stephensi* and *A. aegypti*. This compound could be utilized in the future to control mosquito larvae. Thujone interacts well with the AeSCP-2 active site, according to a computational study. *In silico* molecular docking results indicate that thujone shows good interactions with *Aedes aegypti* Sterol Carrier Protein-2, with a significant docking score (−8.2693) and Glide energy (−42.44 kcal/mol) [33].

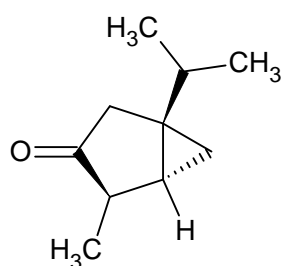


Figure 7. Thujone exhibits larvicidal activity. The surface diagram shows the binding at the active site of AeSCP-2.

2.6. *Artemisia vulgaris*-(Mugwort).

A. vulgaris is a kind of aromatic, medicinal plant that is a member of the Asteraceae family. [34].

The essential oil of the *A. vulgaris* plant, which is used to treat dengue fever vectors, contains a number of volatile compounds that are known to have both insecticidal and allelopathic effects. In a histological test of newly ecdysis *A. aegypti* larvae, the mortality rate was highest for third- and fourth-stage larvae. The essential oil of *A. vulgaris* contains the following important insecticidal terpenoid compounds: camphor (26.99%), α -humulene

(0.72%), β -caryophyllene (0.81%), and β -caryophyllene oxide (15.87%), respectively. GC-MS was used to identify the chemical constituents of the essential oil using PerkinElmer Clarus 500, Turbo mass version 5.2.0 [35]. The results of molecular docking with small-molecule inhibitors were used in molecular dynamics (MD) simulations. Docking small-molecule inhibitors from databases, virtual screening, and pharmacophore searches were all performed using the homology model. The outcomes of MD simulations offer valuable insights into developing medications to treat DV infections and provide a clear understanding of ligand-receptor interactions at the molecular level. The homology model for the DENV NS2B/NS3 protease was first generated by Brinkworth and co-workers. [36, 37].

To find the most effective molecule, the key active components (E)- β -caryophyllene, (Z)- β -caryophyllene, α -humulene, and β -caryophyllene oxide were docked into the NS3 protease's active site. The nature of the interaction between the ligand and NS3 protease may provide insight into protein-ligand interactions [38].

It is discovered that (E)- β -caryophyllene (Figure 8) interacts with a variety of noncovalent forces, including hydrophobic and ionic interactions. LEU76, MET49, TRP83, LEU85, ILE139, VAL146, VAL147, LEU149, TYP150, and ILE165 are the amino acid residues of NS3 protease with which (E)- β -caryophyllene primarily interacts hydrophobically; ASP75 and GLU88 have charged (negative) interactions with NS3 protease [39, 40]

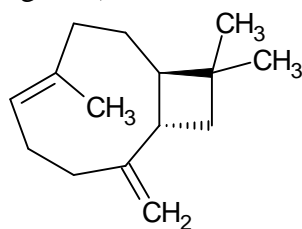


Figure 8. (E)- β -caryophyllene.

2.7. *Schinus molle* L. - (Pepper Tree).

Schinus molle is a medicinal plant used in traditional Peruvian medicine for rheumatic pain and as an anti-inflammatory. Their biological activities have been reported as insecticidal, antibacterial, antifungal, antiviral, antimalarial, anti-depressive, anticancer, antimutagenic, anti-inflammatory, antioxidant, hepatoprotective, analgesic, and antipyretic [40,41].

This study determines the total volatile component of the essential oil from *S. molle* leaves by gas chromatography-mass spectrometry (GC-MS) to evaluate the antioxidant activity using the ABTS, DPPH, and FRAP methods and to determine the insecticidal activity using a virtual screening of the EO from *S. molle* leaves on the mosquito juvenile hormone-binding protein from *Aedes aegypti*. Chemical composition of the volatile oil of *Schinus molle* leaves: tricyclene, terpinolene, alpha-pinene, camphene, sabinene, beta-pinene, beta-myrcene, alpha-murolene, etc. [42]

Molecular docking- the molecules isolated from phytochemicals of essential oil were docked against the mosquito juvenile hormone-binding protein (PDB id: 5V13). To validate the docking, the crystal structures were docked with the native ligand, pyriproxyfen, and with JH3 bound to X-ray structures of the mosquito juvenile hormone-binding protein. The binding cavity residues comprised mainly TYR33, LEU37, TRP50, AL51, TRP53, TYR64, SER69, TYR129, TYR133, ILE140, PHE269, TRP278, and ALA281. Protein and ligand preparations were performed using AutoDock Tools. This evaluation was carried out on the dock complexes

for α -phellandrene (the most abundant in GC-MS analysis) and α -murolene (the most active in molecular docking analysis) with the mosquito juvenile hormone-binding protein (mJHBP) using the Desmond 2020.1 from Schrödinger, LLC.

They both show mosquito-repellent activity and bind to the juvenile hormone protein.

Molecular dynamics (MD) simulations were carried out to assess the stability and convergence of mJHBP + α -phellandrene and mJHBP + α -Murolene complexes. RMSD plots are within the acceptable range, signifying the stability of mJHBP in the ligand-bound state before and after simulation, and it can also be suggested that ligand α -phellandrene (Figure 9) and α -Murolene (Figure 10) bound to mJHBP are quite stable in the complex due to the higher affinity of the ligand. Therefore, from the RMSF plots, it can be suggested that the structures of mJHBP were stable during simulation in α -phellandrene- and α -Murolene bound conformations. The essential oil of *S. molle* leaves contained 34 volatile constituents, as determined by gas chromatography-mass spectrometry (GC-MS). Therefore, from the RMSF plots, it can be suggested that the structures of mJHBP were stable during simulation in α -phellandrene- and α -Murolene bound conformations. The *in silico* evaluation was carried out using one mosquito juvenile hormone-binding protein, mJHBP (PDB: 5V13), with an insecticidal approach [43].

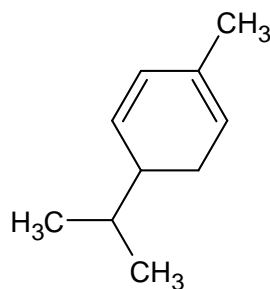


Figure 9. The structure of α -phellandrene.

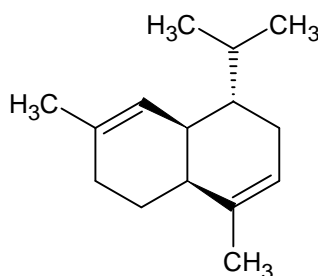


Figure 10. The structure of α -Murolene.

2.8. *Coffea arabica* L.- (Arabian Coffee).

The skin of Arabica coffee has many active compounds, including flavonoids, polyphenols, tannins, caffeine, and chlorogenic acid. The active compounds have potential anti-inflammatory and antibacterial effects [44]. Pulp *Coffea arabica* L. methanol extract contains 30 active compounds, with desulphosinigrin, caffeine, n-hexadecanoic acid, hexadecanoic acid methyl ester, and 3-O-methyl-d-glucose having the highest percentage compound [45]. This study aims to determine the potential active component in the methanol extract of the skin fruit of Arabica coffee and its effectiveness as a mosquito repellent.

Molecular docking- the molecular docking study uses tools and materials, including Computers (Lenovo Ideapad), Microsoft Windows 10 Home 64-bit, AutoDock Vina 1.1.2, Open Babel, and BIOVIA Discovery Studio. The 3D structure of the OBP1 protein (PDB ID 6LU7) and the 3D structure of the GC-MS compound results were downloaded from the

PubChem Compound page (<https://pubchem.ncbi.nlm.nih.gov/>). The 3D structure of the receptor Odorant Binding Protein 1 (OBP1) has been downloaded from PDB ID 3N7H. Ligand preparation can be obtained from the PubChem database page in format .sdf. Molecular docking was performed using AutoDock Vina.

In the *in silico* studies, molecular docking was used to analyze the active compound in coffee fruit skin extract, which has the potential to be a mosquito repellent against *Anopheles sp.* Repellent is an alternative insecticide that can protect the skin from mosquito bites [46].

The odorant-binding protein 1 (OBP1) is an alternative structure-based mosquito repellent design that is more effective because it targets the olfactory ligand [47]. The results of the GC-MS chromatogram showed that desulphosinigrin has the highest percentage of the compound in this extract. In this study, desulphosinigrin shows greater inhibition of OBP1 than the other active compounds. Hydrogen bonding and hydrophobic interactions can simultaneously increase the stability of the ligand at the binding site and enhance binding affinity and drug efficacy.

Desulphosinigrin forms hydrophobic interactions and hydrogen bonds with the OBP1 target protein used in the *in silico* study. Pulp *Coffea arabica L.* methanol extract compounds have potential as repellents. It can be concluded that the active compound desulphosinigrin (Figure 11) has the potential to be a repellent. This study concludes that the active compounds in the methanol extract of Arabica coffee skin have the potential to serve as a repellent [48].

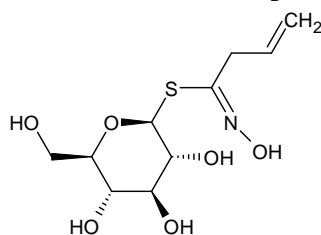


Figure 11. Desulphosinigrin binds with OBP1 protein and shows effective mosquito-repellent properties.

2.9. *Kalanchoe Pinnata*- (air, life plant).

Kalanchoe pinnata belongs to the Kingdom Plantae (Plants) and the family Crassulaceae (Stonecrop family). *Kalanchoe* is a medicinal plant largely used in folk medicine for the treatment of kidney stones, gastric ulcers, pulmonary infections, and rheumatoid arthritis [49]. The plant contains alkaloids, flavonoids, phenolic compounds, tannins, macronutrients (magnesium, calcium, potassium, phosphorus, and sodium), micronutrients (iron, zinc), and vitamins (ascorbic acid, riboflavin, thiamine, and niacin).

The computational prediction of potential drugs by molecular docking, and the important bioactive phytochemicals of the plant *Kalanchoe pinnata*, such as Vitamin D, Beta-amyrin, Alpha-amyrin, and Stigmasterol, were selected from two different solvents (acetone and benzene) extracts of plant leaves by GC-MS analysis.

Molecular docking studies were performed using Schrödinger 9.5. Docking was performed using the XP docking protocol. In the present study, molecular docking analysis was performed using secondary metabolites selected from *Kalanchoe pinnata* against the glutathione S-transferase protein of *Wuchereria bancrofti*. The present study has been based on a platform to understand the molecular docking interaction mechanism of pi-class glutathione-S-transferase (detoxification enzyme) of *W. bancrofti* (nematode parasite) with the selected significant ligands from the plant *K. pinnata*.

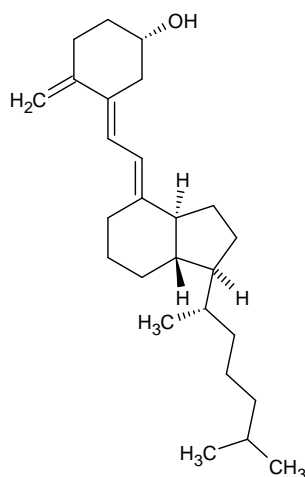


Figure 12. The structure of vitamin D.

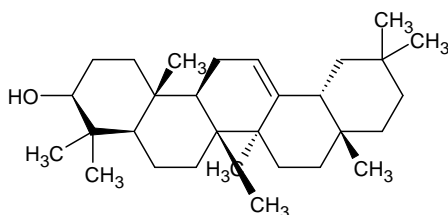


Figure 13. The structure of β -amyrin.

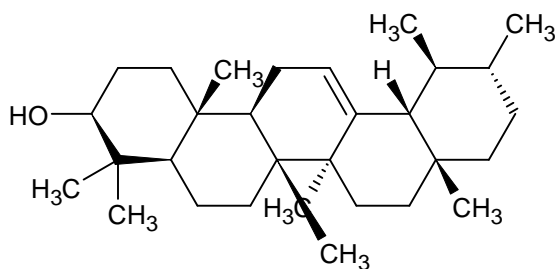


Figure 14. The structure of α amyrin.

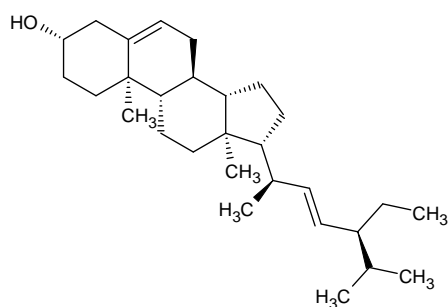


Figure 15. The structure of stigmasterol.

Vitamin D, beta amyrin, alpha amyrin, and stigmasterol bonded with glutathione-S-transferase protein and showed good scores for repellent activity.

Among the four best ligands from the fifty-six phytochemicals were docked against the enzyme of the nematode worm. The bonding interaction between the receptor and ligand can be visualized to control lymphatic filariasis using the phytochemical from *K. pinnata*. The present docking result confirmed that the target protein (ID: PDB 5D73) has the best binding affinities of four compounds (Vitamin D, beta-amyrin, alpha-amyrin, and stigmasterol) among the 56 phytochemicals through the GC-MS analysis.

The ADME properties of four compounds are within the 100% acceptable range for human use, thereby indicating their potential as drug-like molecules. A molecular docking

study reveals that the plant *Kalanchoe pinnata* residues play an important role in binding to the active site of the pi-class GST in filarial parasites. The result suggested that among the four bioactive compounds, viz., vitamin D (Figure 12), beta-amyrin (Figure 13), alpha-amyrin (Figure 14), and stigmasterol (Figure 15), bound to the Pi-class glutathione-S-transferase protein (PDB ID: 5D73), producing a good glide score [50].

2.10. *Osmium tenuiflorum*-(Tulsi).

The genus *Ocimum* comprises more than 150 species and is considered the largest genus of the *Lamiaceae* family. Large numbers of *Ocimum* species have been documented as traditional insect-repellent plants and are effective against mosquitoes [51]. It has a broad range of medicinal properties with effective therapeutic uses like analgesic activity and mosquito-repellent properties. The key objective of the present review is to identify efficient mosquito-repellent compounds from *Ocimum* species [52].

Molecular docking is the process by which two molecules fit together in 3D space. GC-MS analysis was performed using SHIMADZU QP2010, and a gas chromatograph interfaced with a mass spectrometer (GC-MS)—the volatile oil compounds of *O. Tenuiflorum* var. CIM-AYU were docked against 3Q8I (Odorant binding protein) of *Anopheles gambiae*.

DL-alpha-tocopherol, gamma-sitosterol, and Lycopersin show high binding affinity against OBP 3Q8I and have the best mosquito-repellent activity. When the docking scores were close to each other, the (RMSD) was used to select the best conformation. All compounds obtained from the GC-MS analysis of *O. tenuiflorum* are docked with the 3Q8I. *O. tenuiflorum* var. CIM-AYU gained researchers' attention because its essential oils possess mosquito-repellent properties. The volatile oils extracted from *O. americanum* were evaluated as contemporary repellents against both day- and night-biting mosquitoes.

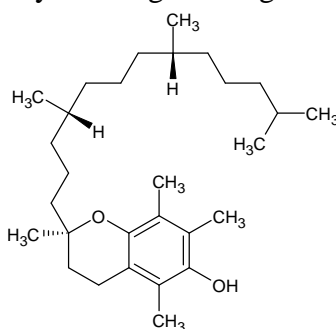


Figure 16. The structure of α -tocopherol.

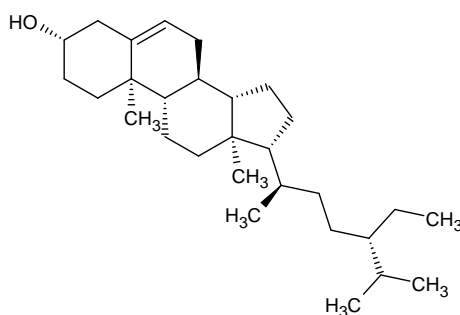


Figure 17. The structure of γ -sitosterol.

The compounds extracted from *O. tenuiflorum* var. CIM-AYU species obtained from GC-MS analysis were docked into the active site of 3Q8I. Studies are needed to validate and develop an efficient mosquito repellent with minimal impact on human health and the

environment. Molecular docking results reveal that the three compounds, viz., dl-alpha-tocopherol (Figure 16), gamma-sitosterol (Figure 17), and Lycopersin (Figure 18), exhibit high binding affinity for the Odorant binding receptor protein 3Q8I of *Anopheles gambiae* [53].

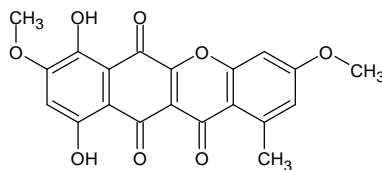


Figure 18. The structure of Lycopersin.

3. Conclusions

Herbal medicines have no side effects and can be used as mosquito repellents.

Dengue, malaria, etc., are diseases throughout the world, so effective medicines without side effects are needed in the future. More *in silico* work is needed to develop formulations for plant-derived products. Modern scientific methods such as docking, homology modeling, molecular dynamics, and 3D QSAR have become increasingly popular recently. From various *In silico* studies on plants, it is suggested that herbal compounds exhibit significant binding affinity for different target proteins and can thus be used to develop new drugs. The present review focuses on recent plant studies using docking methods to assess mosquito-repellent activity. Most of the studies were performed on Auto Dock software. (Table 1). Targets for docking studies, such as OBP and OBP1, are used very frequently. The current review may be useful for the design of novel lead molecules for mosquito-repellent activity. So, we imply that this compound may be used in the future as a mosquito repellent to prevent mosquito-borne disease.

Table 1. Chemical constituents of some herbal mosquito repellents.

| Sr. No | plant | Chemical constituent | Receptor | Software used |
|--------|---|---|-------------------------------------|-----------------|
| 1 | <i>Artemisia pallens</i> -(Davana) | Pseudo-solasodine | Acetylcholinesterase | Autodock |
| 2 | <i>Lantana Camara</i> -(Red Sage) | Pectolinarigenin | AeSCP-2 | Autodock vina |
| 3 | <i>Vitex Negundo</i> -(Nisinda) | Linalool, Alpha-Pinene, myrcene | OBPs, OBP1, BOP4, OBP7 | Pyrex-python |
| 4 | <i>Hyptis Suaveolens L</i> -(Vilayti Tulsi) | sitosterol | 3N7H | CADD |
| 5 | <i>Elaeagnus indica</i> -(Silverberry) | Thujone | AeSCP-2 | GLIDE |
| 6 | <i>Artemisia Vulgaris</i> -(Mugwort) | (E)Beta-caryophyllen. | NS3/NS2B | GLIDE |
| 7 | <i>Schinus Molle L.</i> -(Pepper Tree) | Alpha-mummrolene, Alpha-phellandrene. | Pyriproxifen/JH3 | Autodock |
| 8 | <i>Coffea Arabica L.</i> -(Arabian Coffee) | Desulphosigrin. | OBP1 | Autodock vina |
| 9 | <i>Kalanchoe Pinnata</i> -(Air,Life plant) | vitamin D, beta-amyrin, alpha-amyrin, stigmasterol. | pi-class Glutathione-S-transferase. | Schrodinger 9.5 |
| 10 | <i>Osmium Tenuiflorum</i> -(Tulsi) | Gamma-sitosterol, dl-.alpha.-Tocophero, Lycopersin | 3Q8I | ShimadzuQP |

Author Contributions

All authors confirm their agreement with the contribution statement before submission.

Institutional Review Board Statement

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Informed Consent Statement

Not applicable.

Data Availability Statement

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Conflicts of Interest

The authors have no conflict of interest.

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