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# Computational Prediction of Antimalarial Potential of *Eurycoma longifolia* Phytochemicals Targeting *Plasmodium falciparum*

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**Abstract**

Falciparum malaria, caused by *Plasmodium falciparum*, remains a major global hea threat, complicated by the emergence of drug-resistant strains that undermine t efficacy of current artemisinin-based therapies. *Eurycoma longifolia* Jack (Pasak Bumi) medicinal plant native to Southeast Asia, has long been used in traditional medicine t treating malaria and infectious diseases. Given the growing resistance of *Plasmodiu falciparum* to existing antimalarial drugs, exploring novel therapeutic agents has becor increasingly important. Since bioactive constituents of *Eurycoma longifolia* have be reported to interact with cell membranes, this study aims to predict their potent antimalarial activity using a computational approach targeting *P. falciparu dihydroorotate dehydrogenase* (PfDHODH), a crucial enzyme in the parasite's pyrimidi biosynthesis pathway. Ten phytochemicals were selected and their 3D structures we prepared using PyRx and Open Babel. Molecular docking simulations were conduct using AutoDock Vina, with artemisinin as a control. Docking validation achieved an RM of 0.823 Å, confirming protocol reliability. Among the tested ligands, syringic a showed the highest binding affinity -6.7 kcal/mol, followed by scopoletin -6.6, a fraxidin -6.4, with key interactions involving residues His185, Val532, and Phe18 Toxicological predictions indicated variability, with 1,1'-biphenyl-3,3'-dicarboxylic a exhibiting the highest acute toxicity. Despite no compound surpassing the native ligan binding energy -7.9 kcal/mol, several exhibited promising interactions and favoral safety profiles. This study highlights *E. longifolia* as a promising source of phytochemic for antimalarial drug discovery. Further experimental studies and molecular dynam simulations are recommended to validate these findings and optimize compou efficacy.

**Keywords**: *Eurycoma longifolia*, antimalarial, molecular docking, *Plasmodium falciparu*

## Introduction

Falciparum malaria, caused by *Plasmodium falciparum*, is the most lethal form of malaria and remains a major global public health concern, particularly in tropical and subtropical regions (Weiss et al., 2025). This parasite is transmitted through the bite of an infected female *Anopheles* mosquito and has a complex life cycle involving both a liver stage and red blood cell invasion (Li et al., 2024). Compared to the other four *Plasmodium* species that infect humans *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi* *P. falciparum* exhibits the highest rates of morbidity and mortality (Fikadu & Ashenafi, 2023). According to WHO (2023), approximately 244 million cases of falciparum malaria were reported globally in 2022, resulting in 697,000 deaths, with 76% of these occurring in children under five years of age in Africa (Venkatesan, 2024). Severe infections can lead to life-threatening complications such as severe anemia, kidney failure, pulmonary edema, and cerebral malaria if not treated promptly (Bur et al., 2024).

Efforts to control falciparum malaria face significant challenges due to the emergence of drug resistance (Thellier et al., 2024). Genetic mutations in *P. falciparum*, such as K13 (C580Y), *PfCRT*, and *PfMDR1*, have been associated with reduced efficacy of artemisinin-based therapies (Ramírez et al., 2025). While ACTs remain the first-line treatment, triple artemisinin-based combination therapies (triple ACTs) are being introduced to combat resistance. Additionally, the development of malaria vaccines such as RTS,S/AS01 (Mosquirix) and R21/Matrix-M offers new hope, with R21 showing up to 77% efficacy in late-

stage clinical trials (Ramírez et al., 2025). On the other hand, although most antimalarial treatments are generally well tolerated, some serious adverse effects have been reported, including seizures, encephalopathy, cardiac arrhythmias, autoimmune hemolysis, and post-artesunate delayed hemolysis (PADH) (Abanyie et al., 2023; de Freitas et al., 2024; Habtamu et al., 2024). As such, post-treatment monitoring, particularly hematological assessments, is essential to prevent potentially fatal complications, especially in high-risk patients (Louvois et al., 2022). Therefore, exploring alternative treatments using natural plant-based compounds has become increasingly urgent as a complementary strategy to overcome drug resistance and reduce reliance on conventional antimalarial therapies.

*Eurycoma longifolia* Jack (Pasak bumi), an indigenous plant of Indonesia and other Southeast Asian regions, has long been utilized in traditional medicine as an antipyretic, energy tonic, and treatment for various infectious diseases, including malaria (Farag et al., 2023). Ethnobotanically, the roots of this plant are typically boiled and consumed as a herbal decoction to alleviate fever and fatigue commonly associated with Plasmodium parasitic infections (Farag et al., 2023; Rehman et al., 2016)). The pharmacological activity of *E. longifolia* is primarily attributed to its secondary metabolites, including bioactive compounds from the quassinoid group like eurycomanone, eurycomalactone, β-carboline and canthin-6-one alkaloids, as well as various phenolic and flavonoid compounds (Farag et al., 2023). Specific compounds identified with antiparasitic activity include 9,10-dimethoxycanthin-6-one, 9-methoxycanthin-6-one, heptamethoxyflavone, fraxidin, and scopoletin. In addition, phenolic components such as vanillic aldehyde, vanillic acid, syringic acid, and 1,1'-biphenyl-3,3'-dicarboxylic acid have also been detected in root extracts and are believed to contribute to the plant's antioxidant and immunomodulatory effects (Mutschlechner et al., 2018; Serag et al., 2023). Based on systematic review findings, the majority of experimental studies have demonstrated significant antimicrobial and antiparasitic activities of these compounds (Latip et al., 2022). Consequently, *E. longifolia* stands out as a promising source of phytopharmaceuticals that supports the development of evidence based natural therapies, particularly for tropical infectious diseases (Latip et al., 2022).

With the increasing resistance of *Plasmodium falciparum* to conventional antimalarial drugs such as chloroquine and artemisinin, the search for novel antimalarial agents has become crucial (Ippolito et al., n.d.). *Eurycoma longifolia* has shown significant potential as an antimalarial candidate, mainly through its major active constituent, eurycomanone, which has been demonstrated to possess selective antiparasitic activity (Turck et al., 2021). Previous studies have shown that eurycomanone can inhibit the intraerythrocytic growth of Plasmodium, most likely by disrupting the parasite's protein biosynthesis pathway or compromising the integrity of its cell membrane (Latip et al., 2022). However, despite its promising biological activity, the specific molecular mechanisms of these compounds against malaria target proteins remain inadequately understood. Therefore, computational approaches such as molecular docking are essential to identify interactions between active compounds and key Plasmodium target proteins (Ferreira et al., 2015). These methods not only accelerate the screening process but also provide in-depth insights into the affinity and selectivity of molecular interactions, which are crucial for rational drug design. Given the pharmacological potential and diversity of bioactive constituents in *E. longifolia*, computational research serves as a strategic preliminary step that can be followed by experimental validation. This study aims to evaluate the potential of active compounds in *Eurycoma longifolia* Jack as candidate antimalarial agents through a computational approach.

## Methods

### *Preparation of Receptor and Test Ligands*

The target receptor employed in this study is *Plasmodium falciparum* dihydroorotate dehydrogenase (PfDHODH), retrieved from the Protein Data Bank (PDB ID: 6GJG; https://www.rcsb.org/). This protein was selected based on its relevance as a potential antimalarial target, as previously reported by Owoloye et al (2020). The receptor was prepared using BIOVIA Discovery Studio, which involved the removal of non-protein entities such as co-crystallized ligands, water molecules, and cofactors to isolate a clean protein chain suitable for docking studies. Test ligands included active phytochemicals derived from *Eurycoma longifolia*, selected based on their reported bioactivities. The 2D chemical structures of these compounds were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and converted to 3D formats using Open Babel, embedded within PyRx software. The selected compounds were: Vanillic acid (CID: 8468) Syringic acid (CID: 10742) Vanillic aldehyde (CID: 1183) Scopoletin (CID: 5280460) 1,1'-Biphenyl-3,3'-dicarboxylic acid (CID: 170991677) Fraxidin (CID: 3083616) Heptamethoxyflavone (CID: 44229628) 9-Methoxycanthin-6-one (CID: 9881423) 9,10-Dimethoxycanthin-6-one (CID: 10446368) Artemisinin (CID: 68827) used as a control (Mutschlechner et al., 2018; Serag et al., 2023). All ligand structures underwent energy minimization to achieve the most stable conformation prior to molecular docking.

### *Molecular Docking Simulation*

Molecular docking simulations were performed using AutoDock Vina through the PyRx platform. Before proceeding with the docking of test ligands, a redocking protocol was implemented to validate the reliability of the docking approach. This involved re-docking the native ligand into its original binding site in the crystal structure of 6GJG. The root mean square deviation (RMSD) between the original and redocked poses was computed, with a threshold of <2.0 Å indicating acceptable prediction accuracy (Chandel et al., 2022). The validated grid box dimensions (X, Y, Z) and coordinates derived from the native ligand binding site were used for all subsequent docking runs. Binding affinities for each ligand-protein interaction were recorded, and more negative binding energy values were interpreted as stronger predicted interactions (Chandel et al., 2022).

### *Visualization and Interaction Analysis*

Docking results were analyzed and visualized using PyMOL and BIOVIA Discovery Studio Visualizer. Superimposition of the native and redocked ligands enabled RMSD calculation and visual validation of docking precision. Furthermore, ligand-

receptor interactions were evaluated to identify key amino acid residues involved in binding. Both hydrogen bonding and hydrophobic interactions were mapped to better understand the molecular basis of ligand affinity (Farid et al., 2025).

*Toxicological Predictions*

To evaluate the drug-likeness and safety profiles of the test ligands, in silico predictions of pharmacokinetics and toxicity were performed using the ProTox-II web server (https://tox.charite.de/protox3/). The Canonical SMILES of each compound obtained from PubChem served as input data for prediction(Banerjee et al., 2024).

**Results**

*Plasmodium falciparum* dihydroorotate dehydrogenase (PfDHODH) was selected as a drug target because it plays a critical role in the parasite's de novo pyrimidine biosynthesis pathway, which is essential for its survival. Unlike human cells that can salvage nucleotides from external sources, *P. falciparum* relies entirely on this pathway to produce the DNA and RNA it needs to grow and replicate. Therefore, inhibition of PfDHODH disrupts a vital metabolic process, making it an attractive target for antimalarial drug development. The therapeutic relevance of this enzyme has also been validated by the advancement of PfDHODH inhibitors like DSM265 into clinical trials, highlighting its potential in addressing the ongoing challenge of drug resistance in malaria treatment (Kokkonda et al., 2018).

In this study, molecular docking simulations were conducted using a target protein formatted in the macro.pdbqt file. To ensure accurate ligand binding predictions within the natural binding site, the grid box center coordinates were defined based on the position of the native ligand bound in the crystal structure of the target protein. The grid center was set at x = 12.4989, y = -11.6029, z = -2.0349, precisely corresponding to the active site that was utilized for all docking simulations. The dimensions of the search space were adjusted to fully encompass the active pocket, with grid sizes of 9.8875 Å (x), 17.8127 Å (y), and 20.0491 Å (z). The exhaustiveness parameter was set to 10, providing a balance between computational accuracy and efficiency. Following the docking simulations, spatial validation between the docked ligand (post-dock) and the native ligand was carried out using the alignment feature in PyMOL. The superimposition results showed that four atoms from both ligands were precisely aligned, yielding an RMSD value of 0.823 Å, which indicates a good spatial match and confirms the reliability of the docking protocol.

As presented in Table 1, the docking results showed that the native ligand exhibited the highest binding affinity at -7.9 kcal/mol, serving as the reference for evaluating the test compounds. Among the tested molecules, Syringic acid ranked highest with a binding affinity of -6.7 kcal/mol, followed by Scopoletin -6.6, Fraxidin -6.4, and Vanillic acid -6.1. Conversely, compounds such as Artemisinin and Heptamethoxyflavone demonstrated significantly weaker interactions with the target protein, with affinities of -1.6 and -0.2 kcal/mol, respectively. These results suggest that although none of the tested compounds exceeded the affinity of the native ligand, certain phenolic and coumarin derivatives exhibited promising interactions within the active site and warrant further investigation as potential alternative inhibitors.

Interaction analysis between ligands and amino acid residues at the target protein's active site revealed a relatively consistent binding pattern across several compounds. Notably, His185, Val532, Phe188, Leu531, and Arg265 were recurrently involved in ligand interactions. His185 emerged as the most frequently interacting residue, engaging in both hydrogen and non-hydrogen bonds, and was detected in nearly all ligands, including the native ligand, Artemisinin, Scopoletin, and Syringic acid. Additionally, Val532 and Phe188 often formed contacts with ligands, highlighting their role in stabilizing the protein–ligand complex. Non-hydrogen interactions with hydrophobic residues such as Leu531, Phe227, and Ile263 further contributed to ligand binding through van der Waals forces and π–π interactions, particularly in aromatic compounds like 9-Methoxycanthin-6-one and Fraxidin. Polar residues including Arg265 and Tyr528 also facilitated the formation of significant polar interactions, enhancing the complexity and stability of ligand orientation within the binding pocket.

Toxicological profiling of the 10 compounds revealed variability across 13 toxicity parameters, as summarized in Table 2. Scopoletin and Fraxidin showed the highest toxicological activity, each exhibiting activity in eight toxicity endpoints, including nephrotoxicity, respiratory toxicity, immunotoxicity, and clinical toxicity. In contrast, 1,1'-Biphenyl-3,3'-dicarboxylic acid displayed the lowest toxicity, with only three active parameters. Based on LD50 values a common indicator of acute toxicity Heptamethoxyflavone demonstrated the highest LD50 (5000 mg/kg), indicating the lowest acute toxicity, while 1,1'-Biphenyl-3,3'-dicarboxylic acid had the lowest LD50 (500 mg/kg), suggesting the highest potential for acute toxicity.

**Discussion**

The use of the native ligand's coordinates as the center of the docking grid provides a significant advantage in ensuring the accuracy of molecular docking simulations, as this position represents the actual biological site of ligand-target interaction. This approach ensures that the docking process occurs within a physiologically relevant context. The obtained RMSD value of 0.823 Å from ligand superimposition indicates that the docking simulation accurately reconstructed the ligand's binding position within the active pocket. In docking validation, an RMSD below 2.0 Å is generally considered acceptable and reflects the method's success in predicting a ligand orientation that closely resembles its native conformation (Chandel et al., 2022). Accordingly, the grid parameters derived from the native ligand proved effective for generating valid binding predictions. This protocol also provides a robust basis for further studies, such as ligand affinity estimation, molecular dynamics simulations, and structure-based compound optimization in drug design.

Based on the docking simulations, several test compounds demonstrated notable binding affinities to the active site defined by the native ligand. Syringic acid showed the strongest binding among tested molecules with an affinity of -6.7 kcal/mol, followed by Scopoletin -6.6, Fraxidin -6.4, and Vanillic acid -6.1. Although these values did not surpass that of the native ligand -7.9 kcal/mol, they indicate strong and specific interactions with

the target. These results suggest that the compounds are capable of occupying the active site and may potentially interfere with the biological function of the target protein, which is crucial for the survival of the malaria parasite.

The consistent involvement of key residues such as His185, Val532, and Phe188 across multiple ligands highlights their significance as part of the active pocket, likely playing an essential role in the parasite's biological processes. Hydrogen bonds involving polar residues like His185 and Arg265 enhance ligand affinity and specificity, while the involvement of aromatic and hydrophobic residues such as Phe188, Leu531, and Phe227 suggests the contribution of non-covalent interactions that stabilize the protein ligand complex (Naveenkumar et al., 2025). These stable interactions within the binding site are crucial for the rational design of effective inhibitors. Compounds such as Syringic acid and Scopoletin exhibited extensive and diverse binding interactions with these key residues, strengthening the hypothesis that they could inhibit enzymatic or structural functions of the malaria parasite's target protein (Gao et al., 2024).

The presence of aromatic and hydroxyl functional groups in these compounds contributes to π–π stacking and hydrogen bonding, offering a competitive advantage over lower-affinity compounds such as Heptamethoxyflavone or Artemisinin used as controls (Owoloye et al., 2020). Multiple contacts within the active pocket suggest that the ligands can effectively occupy the catalytic cavity, potentially obstructing the access of the natural substrate. In the context of malaria control, tight binding to a vital Plasmodium protein could disrupt its life cycle. Hence, these findings support the potential of phenolic derivatives such as Syringic acid and Vanillic acid as promising antimalarial candidates (Mamede et al., 2020). In addition to their binding affinity, these compounds are pharmacologically known for their antioxidant, antimicrobial, and anti-inflammatory properties, which may enhance their antiparasitic activity. This is particularly relevant in malaria pathophysiology, where Plasmodium exploits enzymatic and redox pathways to survive within host cells. Therefore, compounds like Syringic acid and Scopoletin have the potential to inhibit critical parasite proteins either directly through active site binding or indirectly via modulation of the host's cellular environment (Gao et al., 2024).

The docking results from this study align with previous experimental evidence supporting the antimalarial activity of *Eurycoma longifolia*. For example, Omagha et al (2022) demonstrated that oral administration of plant mixtures containing *Eurycoma longifolia* at a dose of 800 mg/kg in mice infected with Plasmodium berghei resulted in parasitemia suppression of 96.95% and 99.13% ($P < 0.05$), indicating strong dose-dependent efficacy. Similarly, Ridzuan et al (2007) reported that combining standard *E. longifolia* extract (TA164) with artemisinin significantly suppressed parasitemia by 80% at a 60 mg/kg dose over four days ($P < 0.05$), suggesting a promising synergistic effect. Supporting pharmacokinetic data from (Low et al., 2011) indicated that the major quassinoid, 13α(21)-epoxyeurycomanone, exhibited oral bioavailability 9.5 times greater than other compounds, contributing to its high antimalarial efficacy.

In vitro studies have also corroborated this potential. Sholikhah et al (2018) reported $IC_{50}$ values ranging from 2.21 to 64.73 µg/mL for *E. longifolia* isolates against Plasmodium falciparum, with a selective index of up to 316.51 ($P < 0.05$), reflecting potent antiplasmodial activity and favorable safety. Additionally, Wernsdorfer et al (2009) observed superior in vitro activity of *E. longifolia* root extracts compared to individual quassinoids, suggesting synergistic effects among constituents. However, (Sitanggang et al., 2018) noted that although the extract affects antioxidant enzymes such as SOD and CAT, its antimalarial mechanism likely involves more than just antioxidant activity. Overall, the docking results demonstrating stable interactions and high-affinity binding of *E. longifolia* derived compounds with Plasmodium target proteins provide strong molecular validation of the pharmacological and pharmacokinetic evidence (Wijayanti & Sholikhah, 2020).

Toxicity analysis revealed that the number of active toxicity parameters does not always correlate directly with acute toxicity levels. For instance, Fraxidin and Scopoletin showed broader toxicological activity but retained high $LD_{50}$ values (3800 mg/kg), suggesting that higher doses are needed to elicit acute toxic effects. In contrast, 1,1'-Biphenyl-3,3'-dicarboxylic acid exhibited greater acute toxicity despite fewer active toxicological endpoints, indicating potential danger upon short-term exposure (Negru et al., 2025). From a safety and drug development perspective, compounds that are inactive in critical toxicity parameters such as carcinogenicity, mutagenicity, and hepatotoxicity warrant further exploration. Heptamethoxyflavone and Artemisinin are promising candidates in this regard, as both showed minimal toxicity and relatively high $LD_{50}$ values. Additionally, activity related to the blood-brain barrier (BBB), as seen with 9,10-Dimethoxycanthin-6-one and Scopoletin, may offer therapeutic advantages in treating central nervous system infections, although systemic safety must be further evaluated (Negru et al., 2025).

To date, no studies have explicitly applied molecular docking to evaluate the bioactive compounds of *Eurycoma longifolia* against specific Plasmodium target proteins. Therefore, this study serves as a valuable complement to existing in vivo and in vitro evidence demonstrating the plant's significant antiplasmodial activity. The consistency between predicted molecular interactions like binding affinities and key interacting residues and prior pharmacological data reinforces the hypothesis that *E. longifolia* compounds act through specific mechanisms targeting parasite biology. These findings represent a strategic step toward developing nature-derived antimalarial agents, particularly in response to the growing challenge of drug resistance. The clinical implication is the potential identification of lead compounds suitable for optimization via structure based drug design (SBDD) in further stages of drug development.

Nonetheless, this study has several limitations that warrant consideration. The approach employed is strictly in silico, which, while effective for early screening, cannot replace experimental data in assessing compound efficacy or safety. The number of analyzed ligands is limited, which may not fully represent the chemical diversity of E. longifolia. Furthermore, the stability of protein ligand complexes under biologically relevant conditions has not yet been explored via molecular dynamics (MD) simulations. Therefore, further studies are needed expanding compound libraries, conducting in vitro and in vivo evaluations in Plasmodium culture and animal models, and validating target isoforms in human cells to assess selectivity and side-effect

potential. Future research should adopt a multi-tiered approach, integrating docking, MD simulations, pharmacodynamic assays, and toxicological evaluations as part of a comprehensive workflow for the development of plant-derived antimalarial candidates.

**Conclusion**

This study systematically validated the docking protocol by aligning the docked ligand with the native ligand, resulting in a low RMSD value of 0.823 Å, confirming the accuracy of the docking simulation. The docking results revealed that Syringic acid had the best binding affinity -6.7 kcal/mol among the tested compounds, followed by Scopoletin -6.6 and Fraxidin -6.4, although none surpassed the native ligand -7.9. Visualization of ligand-protein interactions showed consistent binding at key residues such as His185, Val532, and Phe188, indicating strong and specific interactions within the active site. However, this study has limitations, including its reliance on in silico methods and a limited number of compounds. Future research should include molecular dynamics simulations, in vitro and in vivo validation, and a broader range of ligands. These steps are essential to fully explore and optimize the antimalarial potential of *Eurycoma longifolia* derivatives.

**Conflict of Interest**

No potential competing interest.

**Acknowledgement**

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**Author contribution**

**Tabel 1.** Docking simulation results

| Ligand | Binding Affinity | Hydrogen Interaction | Non-Hydrogen Interaction |
|---|---|---|---|
| Native ligand | -7.9 | Tyr 528, Gly 181, His 185, | Phe 188, Ile 272, Ile 263, Leu 531, Phe 227, Leu 176, Arg 265, Cys 185, Val 532 |
| Artemisinin (control) | -1.6 | His 185, Arg 265, | His 185, Cys 175, Leu 176, Cys 184, Leu 172, Phe 188, Val 532, Leu 531, Phe 227, Ile 263 |
| 9,10-Dimethoxycanthin-6-one | -5.8 | Arg 265, | His 185, Leu 531, Met 536, Phe 227, Phe 188, Leu 172, Leu 176, Cys 184, Unk 1, Val 532 |
| 9-Methoxycanthin-6-one | -5.9 | His 185, | Val 532, Phe 188, Met 536, Unk 1 |
| Heptamethoxyflavone | -0.2 | Arg 265, Gly 181, His 185. Val 532, Tyr 528 | Tyr 528, His 185. Val 532 Ile 263, Unk 1, Leu 176, Cys 175, Cys 184, Leu 172, Phe 188, Phe 227, Ile 272 |
| Fraxidin | -6.4 | His 185, | Val 532, Phe 188, Leu 240, Ile 237, Phe 227 Leu 531, Met 536 |
| 1,1'-biphenyl-3,3'-dicarboxylicacid | -4.2 | Tyr 528, | Val 532, Ile 263, Ile 272 |
| Scopoletin | -6.6 | Arg 265 | Phe 188, Val 532, Cys 184, Ile 263 |
| Vanillic aldehyde | -6 | His 185, Arg 265 | Cys 184, Val 532, Phe 227, Phe 188 |
| Syringic acid | -6.7 | Arg 256, | His 185, Tyr 528, Val 532, Cys 184, Leu 176, Leu 172, Cys 175, Leu 531 |
| Vanillic acid | -6.1 | Leu 531, Gly 181 | His 185, Cys 184, Val 532, Arg 265 |

**Tabel 2.** Toxicity prediction results

| Ligand | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanillic acid | - | - | + | - | - | - | - | - | + | - | - | + | - | 2000 |
| Syringic acid | - | - | + | - | - | - | - | - | + | - | - | + | - | 1700 |
| Vanillic aldehyde | - | - | + | - | - | - | - | - | + | - | - | - | - | 1000 |
| Scopoletin | - | - | + | + | - | + | + | - | - | - | + | + | + | 3800 |
| 1,1'-biphenyl-3,3'-dicarboxylicacid | - | - | + | - | - | - | - | - | + | - | - | + | - | 500 |
| Fraxidin | - | - | + | + | + | - | + | - | - | - | + | + | + | 3800 |
| Heptamethoxyflavone | - | - | + | + | - | - | - | - | + | - | + | - | + | 5000 |
| 9-Methoxycanthin-6-one | - | + | - | - | - | - | + | + | - | + | + | + | - | 1000 |
| 9,10-Dimethoxycanthin-6-one | - | + | - | + | - | - | + | + | - | + | + | + | - | 1000 |
| Artemisinin | - | - | - | - | + | - | + | - | - | + | - | - | - | 4228 |

*Legend: 1: Hepatotoxicity, 2: Neurotoxicity, 3: Nephrotoxicity, 4: Respiratory toxicity, 5: Cardiotoxicity Toxicity, 6: Carcinogenicity, 7: Immunotoxicity, 8: Mutagenicity 9: Cytotoxicity, 10: BBB-barrier, 11: Ecotoxicity, 12: Clinical toxicity 13: Nutritional toxicity, 14: LD50 (mg/kg). -: inactive, +: active

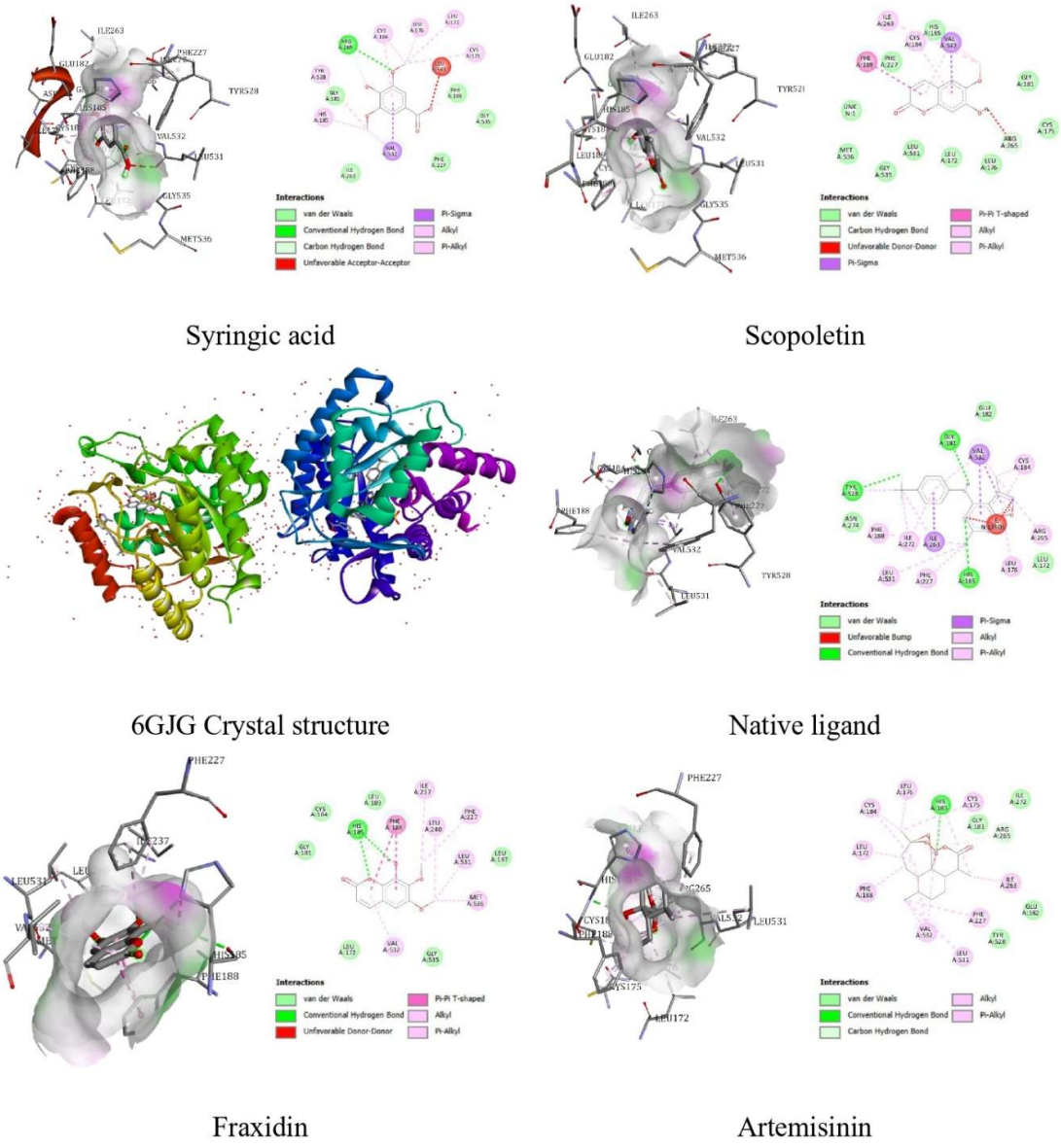


**Figure 1.** Best pocket interaction after docking simulation

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