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Molecular docking analysis of selected natural products from *Halymenia* sp. and *Laurencia* sp. seaweeds against plasmepsins as antimalarials

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Abstract. Malaria is one of the most important public health problems worldwide, with nearly half of the global population exposed to the risk of contamination. The disease is found in 91 countries, mostly in the tropics and subtropics of the planet. There are several previous research that identifies Plasmepsins as a potential target to develop novel antimalarial drugs from the malaria parasite Plasmodium that play a role in the breakdown of globin into amino acids. Given the above, it is important to find novel and effective drugs that can decrease this disease, especially from natural products such as medicine. Seaweed is a potential source of bioactive compounds to be used as antimalarials, such as species from the genera Laurencia and Halymenia. This recent study has studied the molecular docking approach to identify the potential of *Halymenia* sp. and *Laurencia* sp. against Plasmepsin by using PyRx 0.8 software. It showed that the compounds in *Halymenia* sp. and *Laurencia* sp. were able to react and inhibit the action of plasmepsin, seen from the binding affinity value, which was quite small at -4.3, this value is higher than the two bioactive compounds in seaweed, namely Stigmasterol and p-hydroxybenzaldehyde which have binding affinity values of -8.5 and 6.5, respectively. Judging from this, the compounds contained in *Laurencia* sp and *Halymenia* sp have potential as candidates for antimalarial drugs.

1. Introduction

Malaria is one of the most serious public health issues in the world. Malaria happens in over 90 countries in the world, such as Africa, Central, and South America, Asia, and Oceania, which are the primary locations where malaria occurs, along with certain subtropical areas [1]. Based on World Health Organization (WHO) report, there was a steady reduction from 2000-2019 in Malaria deaths, from 896.000 in 2000 to 559.000 in 2019. Death caused by malaria increased to 12% in 2020 compared with 2019. Due to service disruptions during the COVID-19 pandemic, it was estimated an additional 69.000 deaths [2].

Malaria is primarily caused by unicellular protozoan parasites from the genus Plasmodium. There are five species of Plasmodium that may naturally infect people and cause malaria in many parts of the world: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi* [3]. It is mostly caused by parasites that can infect humans through the bites of female Anopheles mosquitoes that are infected [4].

Different targets and methods of action are used in antimalarial medications. Numerous drugs include heme in the parasite food vacuole, including chloroquine, amodiaquine, mefloquine, and quinine [5]. It is generally known that the principal mechanism of action of 4-aminoquinolines against malaria is the suppression of β-hematin polymerization [6]. The new target of this class of drugs is to inhibit the plasmepsin enzymes. Shalini *et al*. stated that one of the compounds is hydroxyethyl amine, which has been demonstrated to target plasmepsins, a family of *P. falciparum* aspartic proteases involved in several cellular processes, including hemoglobin degradation [7]. Plasmodium needs amino acid metabolism and hemozoin for parasite growth during the invasion [8,9]. Therefore, the parasite will die if the formation of amino acid metabolism and hemozoin is blocked.

Chloroquine is an effective and affordable 4-aminoquinoline antimalarial [10]. After an oral dosage, chloroquine is nearly completely absorbed after 2-4 hours. Following the consumption, the concentration of 4AQs in the body's tissues changes [11]. The concentration of chloroquine for a single dosage in pigmented rats' tissues is as follows: uvea > liver > lung > kidney > vitreous > heart > skin > hair > brain > blood > serum [12]. However, due to the current phenomenon of chloroquine resistance, it must be immediately replaced with new antimalarial drugs.

Seaweed is a potential source of bioactive compounds [13] to be used as antimalarials, such as species from the genera Laurencia and Halymenia. Based on Deepak *et al*. research in 2019, it was found that one of the compounds identified in *Halymenia palmata* that has potential as an antimalarial is Phytol [14]. Antiplasmodial activity of Phytol was also tested in vitro against chloroquine-sensitive *P. falciparum* NF54 by measuring parasite-specific lactate dehydrogenase (pfLDH) by Saxena *et al*., which showed moderate activity (IC50 211.5 ± 0.93 M). These findings confirm the suitability of phytol derivatives as a novel chemical entity for further investigation of malaria management [15].

Based on Topcu *et al*. research in 2003, halogenated sesquiterpenes, diterpenes, and acetylenes are known to be abundant in the red algae of the genus *Laurencia* (Rhodomelaceae). One of the sesquiterpenes is Stigmasterol [16]. Zhai *et al*. showed that stigmasterol has potential as antimalarial through characterization using NMR and Mass Spectrometry methods [17]. In addition to stigmasterol, according to Martinez *et al*., p-hydroxybenzaldehyde, which is an important component of *Laurencia caraibica,* and *Laurencia papillosa* is also an antimalarial compound [18]. Based on the description above, an in-silico test using the Reverse docking technique was carried out to clarify the antimalarial potential of *Halymenia* sp. and *Laurencia* sp.

2. Methods

2.1. Preparation

PyMoL version 2.3.4 was used for the receptor preparation. The crystal structure of plasmepsin enzymes (PDB ID: 2ANL), which was generated from the Protein Data bank, was used for this investigation. The structure was cleaned from water and any heteroataom molecules, and then hydrogen atoms were added.

2.2. Ligand preparation

The 3D structure of the positive control of Chloroquine and the potential natural compounds from *Halymenia* sp. and *Laurencia* sp. seaweeds (Phytol, Stigmasterol, and p-hydroxybenzaldehyde were generated by PubChem. These structures are then prepared by Pymol by adding Hydrogen atoms. The ligands of chloroquine, phytol, stigmasterol, and p-hydroxybenzaldehyde were studied using the conjugate gradient algorithm in Open Babel of PyRx.

2.3. *Molecular docking*

To find a potential candidate for treating Malaria, this study employed molecular docking on the binding site of the pocket Plasmepesin enzyme. Docking studies of *Halymenia* sp. and *Laurencia* sp. compounds ligands were performed using PyRx version 0.8 with AutoDock Vina, against the selected Plasmepsin enzyme. In the region around the protein's active site, the receptor's grid was placed with center X: 56.67 Å, Y: 11.71 Å, Z :23.43 Å.

3. Results and discussion

The 3D structures of Plasmepsin are constructed from 327 residues (2ANL PDB ID) with 8 α-helices, 25 β-sheets, and 29 Loops (Figure 1). The actives site of the enzyme is located on the cleft with residues: Asp34, Thr35, Gly36, Ser37, Ile75, Thr76, Tyr77, Gly78, Ser79, Ile123, Leu131, Ile133, Leu191, Ile213, Asp214, Gly216, Thr217, Ser218, Thr219, Thr221, Val292, Ile294, and Ile300.

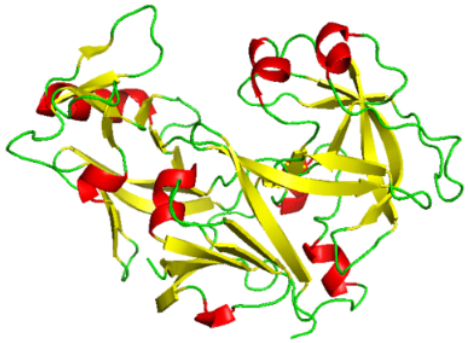


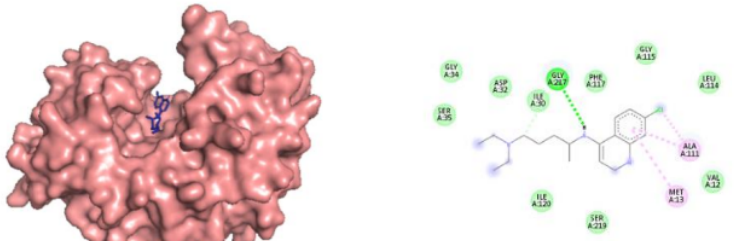
Figure 1. The 3D-Structure of Plasmepsin Enzyme (PDB ID:2ANL)

Table 1. The binding affinity of the ligands against Plasmepsin enzyme.

Ligand	Binding Affinity (kcal/mol)
Chloroquine (control)	-5.3
Phytol	-4.3
Stigmasterol	-8.5
p-hydroxybenzaldehyde	-6.5

The docking study between all ligands and Palsmepsin enzyme showed that the ligands were bound to the binding precisely at the cleft with several interaction. To compare the strong interaction between ligand, this study employed Chloroquine as the positive control, which has five molecular interactions with Met13, Ile30, Ala111, and Gly217. Meanwhile, the natural compounds of *Halymenia* sp. and *Laurencia* sp. : Phytol, Stigmasterol, and p-hydroxybenzaldehyde showed more interaction with residues in the active site than Chloroquine. The molecular interactions between stigmasterol and enzyme were divided into 10 interactions with Met12, Ile30, Trp39, Phe109, Ala111, Phe117, and Ile120. The interaction of phytol and the enzyme has seven interactions with amino acids in the binding site, they are Val12, Met13, Ile30, Pro110, Ala111, Phe117, and Ile12 while the interaction between p-

hydroxybenzaldehyde and the enzyme has 5 molecular interactions with Met13, Ile120, Gly217, and Ser219.



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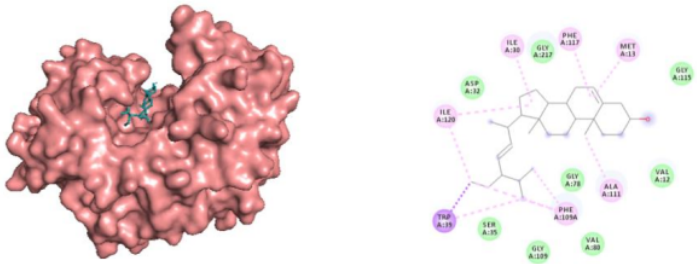

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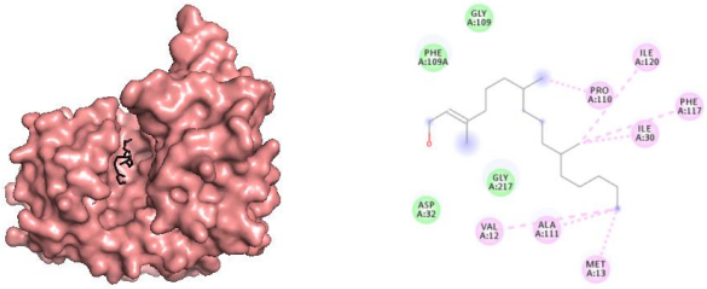

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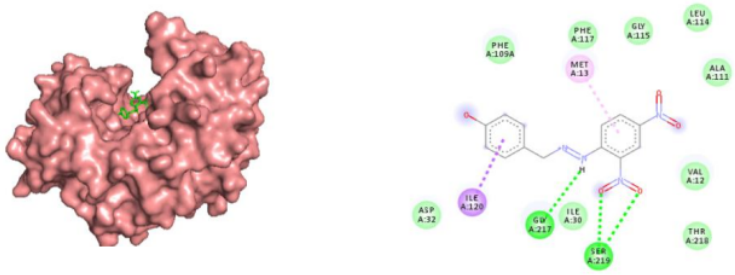

(d)

Figure 2. The molecular interactions between ligands and Plasmepsin enzyme. (a) Chloroquine (purple), (b) stigmasterol (blue), (c) phytol (black), and (d) p-hydroxybenzaldehyde (green).

Based on the results of molecular docking using PyRx 0.8 application (Table 1), the compounds in *Laurencia* sp. and *Halymenia* sp. were able to react and inhibit the action of plasmepsin, seen from the value of binding affinity, which was quite small. Based on Saputri *et al*., Binding affinity is a measure of a drug's ability to bind to a receptor. The smaller the binding affinity value, the higher the affinity between the receptor and the ligand and vice versa if the greater the binding affinity value, the lower the affinity between the receptors [19]. The binding affinity control value, which is a synthetic drug that is often used as an anti-malarial is -5.3, this value is higher than the two bioactive compounds in seaweed, namely Stigmasterol and p-hydroxybenzaldehyde, which have binding affinity values of -8.5 and -6.5. Judging from this, the compounds contained in *Halymenia* sp. and *Laurencia* sp. have potential as candidates for antimalarial drugs.

4. Conclusion

This study has found that the potential natural compounds from *Halymenia* sp. and *Laurencia* sp. could be potential compounds as anti-malaria compared to the positive control, Chloroquine. Further studies are needed to optimize the potential of these compounds, such as in vitro and in vivo studies.

Acknowledgments

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