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Conference Paper

Virtual Screening the Interaction of Various Compound from Indonesian Plants with the HGXPRT Enzyme to Find a Novel Antimalarial Drug

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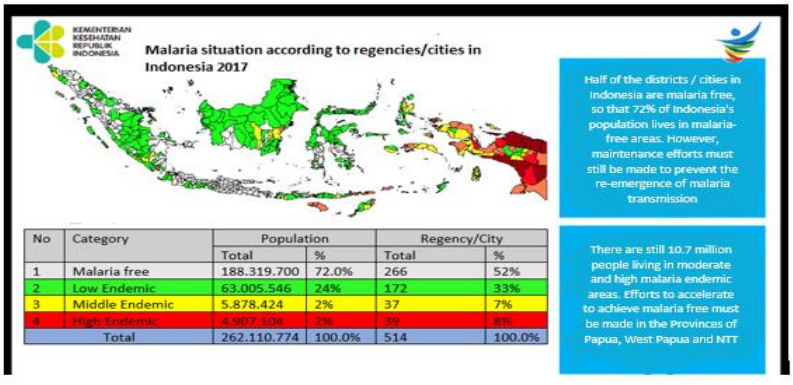
ABSTRACT

Medicinal plants have been a notable source for antimalarial agents. This study was aimed to investigate the antimalarial potency of Indonesian medicinal plants used traditionally in malarial fever therapy. A total of 238 compounds derived from 43 plants traditionally used to alleviate malarial fever were collected and loaded into molecular docking protocol. The compounds were screened against Hypoxanthine-Guanine-XanthinePhosphoribosyltransferase (HGXPRT, 3OZF) using the AutoDock Vina software 1.1.2. The compound is important for the purine synthesis of the parasite. The experiment resulted in AM125 (20-isoveratramine) from *Cyanthillium patulum* to possess the highest affinity with free energy (ΔG)-11 kcal/mol, which is better than HGXPRT native ligands (-6.4kcal/mol). This suggested *Cyanthillium patulum* was a potential source for antimalarial agents in which its constituents, 20-isoveratramine might responsible for the claims.

Keywords: HGXPRT inhibitor, molecular docking, antimalarial, Cyanthillium patulum

Introduction

One of the serious global health is Malaria. Malaria is an infectious disease caused by single-cell parasites, namely *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale* which is transmitted through the bite of Anopheles mosquitoes (Gardiner et al., 2009). Until now there are around 102 malaria-endemic countries and there are 300-500 new cases of malaria in the world. The WHO recorded there were 219 million cases of malaria in 2018 (World Health Organization, 2018). In Indonesia there were 180.205 malaria cases, the number decreased from 2017 which was 261,761 malaria cases (Kemenkes, 2019). Besides, in the same year, 2017 there were 10.7 million people who were still living in malaria-endemic areas, namely Papua, West Papua, and NTT as shown in Figure 1. Most malaria infections in eastern Indonesia were dominated by *P.falciparum* and *P. vivax* (Indonesia PK, 2018).



No	Category	Population		Regency/City	
		Total	%	Total	%
1	Malaria free	188.319.700	72.0%	266	52%
2	Low Endemic	63.005.546	24%	172	33%
3	Middle Endemic	5.878.424	2%	37	7%
4	High Endemic	4.907.104	2%	39	8%
	Total	262.110.774	100.0%	514	100.0%

Figure 1. Cases of malaria in district / city in Indonesia (Indonesia PK, 2018)

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To reach 2030 targeted Indonesia is free from malaria, the government is trying to eliminate malaria cases every year. However, there are challenges in carrying out these efforts, namely resistance to several anti-malarial drugs (Ditjen Pencegahan dan Pengendalian Penyakit, 2017). The cause of resistance is due to the mutation of genes from the Plasmodium parasite. The drugs used to treat malaria cases are a combination of artemisinin-based (ACT) and treatment with this drug is quite effective (Elyazar et al., 2011). However, the spread of drug administration is still uneven, so the need for the discovery of anti-malarial drugs that can be used as an alternative in the treatment of malaria.

Indonesia is a country with very biodiversity, has many herbal plants. It was recorded that more than 7,000 medical plants have been used for generation treatments including anti-malaria plants (Nugraha & Keller, 2011). Docking can be used to try to predict the bound conformation of know binders to obtain leads for further drug development (Fias et al., 2008). This study was aimed to investigate the antimalarial potency of Indonesian medicinal plants used traditionally in malarial fever therapy. This study focused on the bioprospecting of 238 compounds from Indonesian medicinal plants commonly used as a reduction in malaria fever by the community with the enzyme Hypoxanthine-Guanine-Xanthine Phosphoribosyltransferase (HGXPRT, 3OZF). The enzymes that play a role in purine synthesis converts Hypoxanthine that is carried into the cytoplasm from plasma into inosinemonophosphate (IMP). Where IMP is then used for the next stages of nucleic acid synthesis (Downie et al., 2008).

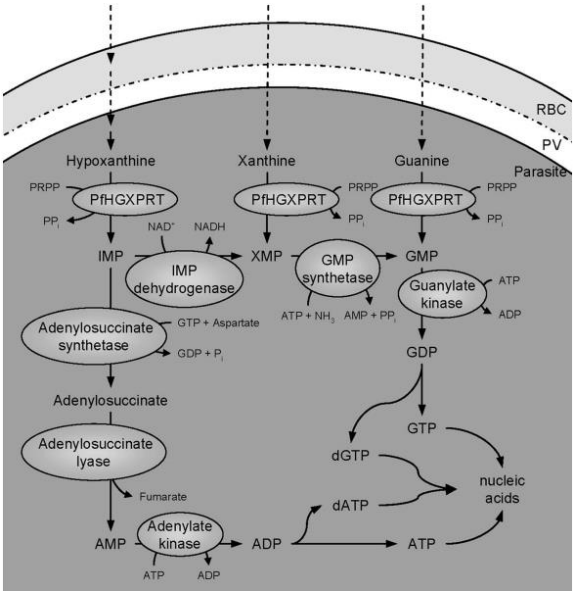


Figure 2. 3D Syntesis Nucleic acid from*P. Falciparum* (Downie et al., 2008)

Purines are very important in the survival of an organism including the Plasmodium parasite. If the HGXPRT enzyme is inhibited, the IMP will not be formed and the process of nucleic acid synthesis in the parasite will fail and the parasite will die (Mbewe et al., 2007).

Material and Methods

Preparation of Indonesian antimalarial plants

Information on antimalarial plants was obtained from several related journals, the Indonesian Medicinal Plants Book, and Herb Index. A total of 238 compounds from 43 plants commonly used as fever-reducing fever in malaria cases were obtained for further analysis.

Enzyme preparation

Enzyme preparation was started by downloading the target protein file at www.rscb.org with the ".pdb" format. The protein used is Hypoxanthine-Guanine-Xanthine Phosphoribosyltransferase (HGXPRT, 3OZF). Moreover, ligand removal was performed using Pymol software. Autodock tools were used later to prepare enzymes by adding polar hydrogen.

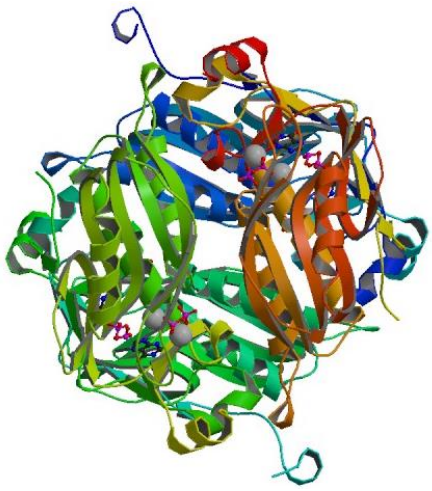


Figure 3. 3D Structure of Hypoxanthine-Guanine-Xanthine-Phosphoribosyltransferase (RSCB, 2019).

Ligand preparation

Ligand preparation begins by drawing a structure in ChemDraw or you can download it in Pubchem with the ".pdb" format. Furthermore, it is converted into 3D and optimized by minimizing energy than stored with the format ".pdbqt". The next stage was to prepare the ligands using Autodock tools and save them in the ".pdbqt" format.

Griding

Ligand preparation begins by drawing a structure in ChemDraw or you can download it in Pubchem with the ".pdb" format.

Docking molecular

This process was carried out using AutoDock Vina software 1.1.2. Enzyme and ligand files with the extension ".pdbqt"were saved in one folder as many as 238 folders according to the number of compounds. Then added conf.txt, a text with the extension ".txt" containing the file name, and the griding region of the position attached to the ligand.

Visualization

After the docking process, the results were obtained and for visualization using Pymol then the interactions are seen and the information needed is needed for further analysis.

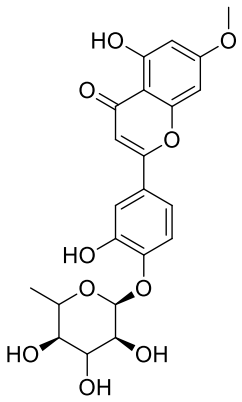
Results and Discussion

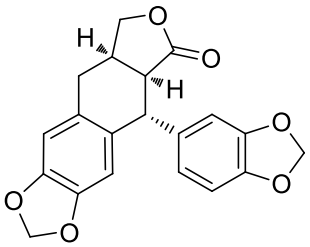
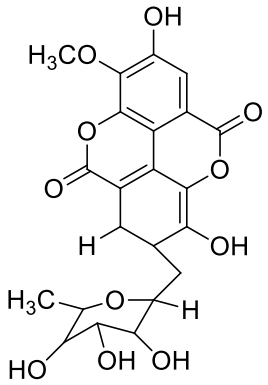
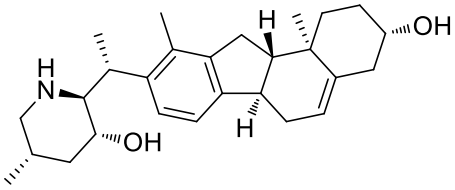
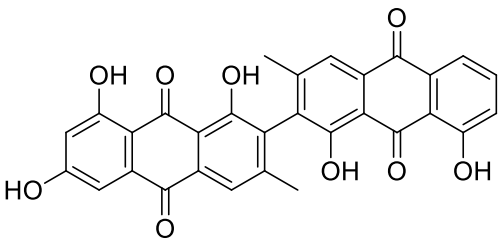
Molecular docking can be one of the stages in a study that can provide an overview of the bonding and conformation ligand-enzymes (Pudjiastuti et al., 2014). The results of redocking the native ligand with the same binding site showed an RMSD value of 0.933Å.RMSD *(Root Mean Square Deviation)*is a parameter used to determine the similarity of the two structures. A good RMSD value is <2Å (Sargsyan et al., 2017). Besides RMSD, free energy (ΔG) is also a parameter used in this study. Free energy is used as a sign of affinity, which is more negative, indicating a

higher affinity. Affinity shows the strength of ligand binds with the receptor. The higher affinity indicates ligand binding with the stronger receptor (Pratama & Aziz, 2019). Because all free energy values are negative, it shows that interactions between all test ligands and receptors on enzymes occur spontaneously (Vikram Sin & Mishra, 2019).

Of the 238 compounds, there are 5 compounds with the best interaction with the HGXPRT enzyme shown in Table 1 namely AM39, AM59, AM65, AM125, AM200. Each compound was isolated from Indonesian medicinal plants respectively *Blumea balsamifera*, *Bursera simatuba*, *Caesalpinia crista*, *Cyanthillium patulum*, and *Senna siamea* (Saewan et al., 2011; Peraza-Sanchez & Pena-Rodriguez, 1992; Kumar et al., 2014; Tezuka et al., 1998; Kumar et al., 2013). That plant is used to treat malaria by people in various regions (Septiana et al., 2017; Badan Penelitian dan Pengembangan Kesehatan, 2006). Previous research related to the treatment of malaria with plant extracts has been done, but the mechanism does not exist. This interaction occurs because the residual amino acid bond with the hydrogen bond is shown in Figures 4 – 9. The native ligand can bind to -6.4 kcal/mol of energy needed and the five compounds of the bind requires less energy than the native ligand. There are -10.5, -10.9, -10.4, -11.0, and -10.6 kcal/mol and the compound which has the highest potential is AM125, which is a 20-isoveratramine compound from the *Cyanthillium patulum* plant with free energy -11.0 kcal/mol. Each of the five compounds interacted with different amino acids of HGXPRT enzyme (Table 2). AM39 is hydrogen-bonded with two amino acids, SER91 and ASN47. AM59 binds only to amino acids, namely ARG80 whereas AM65 has a bond with amino acids reside, LYS51, LYS88, THR84, and ARG210. AM200 compounds interacted with only one amino acid, TYR201. Four amino acids of the HGXPRT enzyme produced intermolecular bonding with AM65. Although AM65 interacted with 4 amino acids than AM125 (3 amnio acid interaction), aliphatic residue on AM65 prevents the molecules to use less energy during the interaction. The high value of affinity not only dependent on the number of amino acids which interact with the compounds, but also on the molecular properties of the ligand. These properties included also molecular weight and polarity. With these results, AM125 compound (20-isoveratramine) can be used as an IMP formation inhibitor which deters Plasmodium life cycle through nucleic acids synthesis inhibition. AM125 compound (20-isoveratramine) is one of *Cyanthillium patulum* constituents in which the medicinal plant has been used by Indigenous people of Indonesia to treat malarial fever. This investigation supports *Cyanthillium patulum* as the source anti-malarial agen

Tabel 1. Results of the 5 best docking compounds

Code Name	Plant Source	Structure and Compound	Affinity
AM39	*Blumea balsamifera*	 (Luteolin-7-methyl-ether)	- 10.5
To be continued			

AM59	*Bursera simatuba*	 (Picropolygamain)	- 10.9
AM65	*Caesalpinia crista*	 (3-O-Methylellagic acid-3'O-α-rhamnopyranoside)	- 10.4
AM125	*Cyanthillium patulum*	 (20-isoveratramine)	- 11.0
AM200	*Senna siamea*	 (Cassiamin A)	- 10.6

Tabel 1. Amino acid residues

Ligand	HGXPRT Ligand	AM39	AM59	AM65	AM125	AM200
Amino acid residues	ASP204 VAL198	SER91 ASN47	ARG80	LYS51 LYS88 THR84 ARG210	GLY81 THR84 ALA85	TYR201

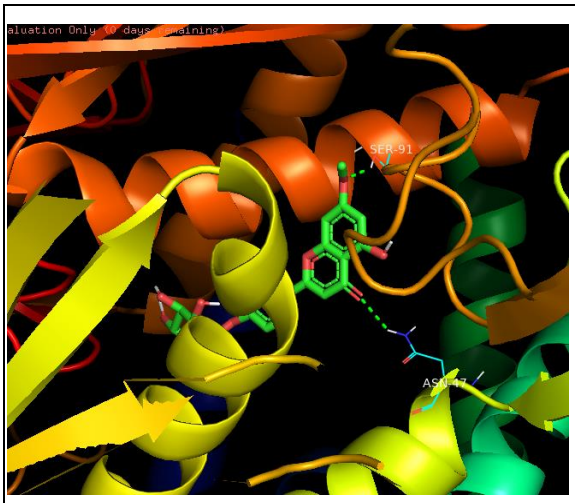


Figure 4. Interaction visualization AM39 against HGXPRT showing hydrogen bonding with SER91 and ASN47

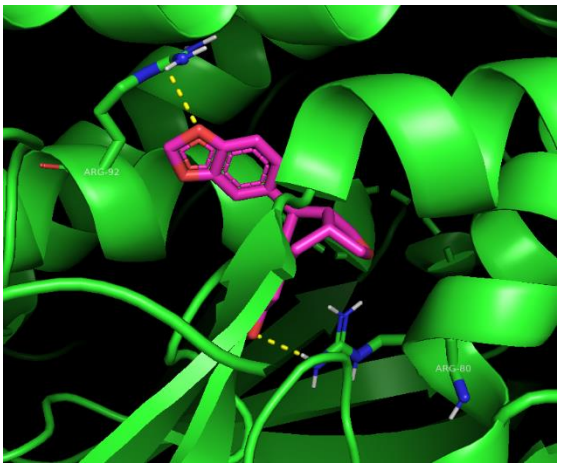


Figure 5. Interaction visualization AM59 against HGXPRT showing hydrogen bonding with ARG92 andARG80

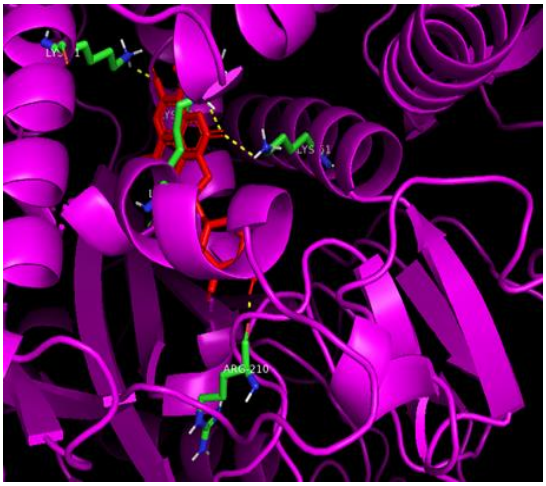


Figure 6. Interaction visualization AM65 against HGXPRT showing hydrogen bonding with LYS51, LYS88, THR84 and ARG210

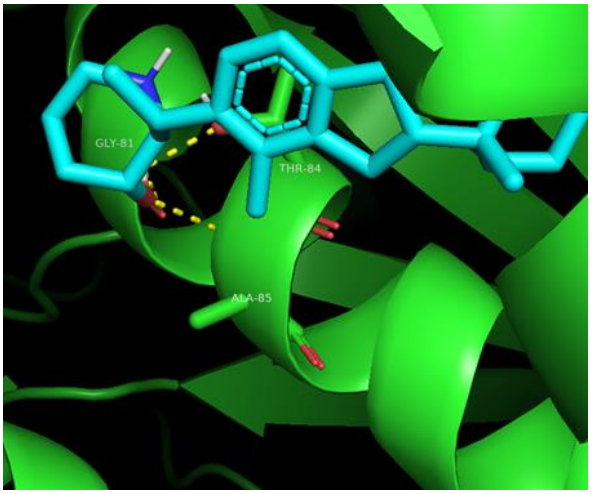


Figure 7. Interaction visualization AM125 against HGXPRT showing hydrogen bonding with GLY81, THR84, and ALA85

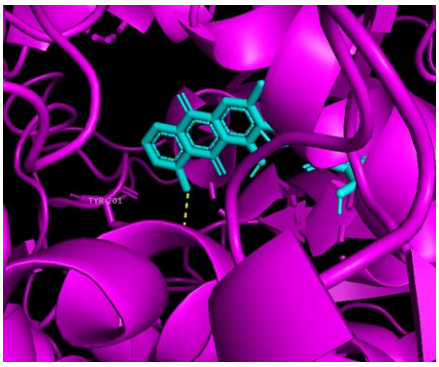


Figure 8. Interaction visualization AM200 against HGXPRT showing hydrogen bonding with TYR201

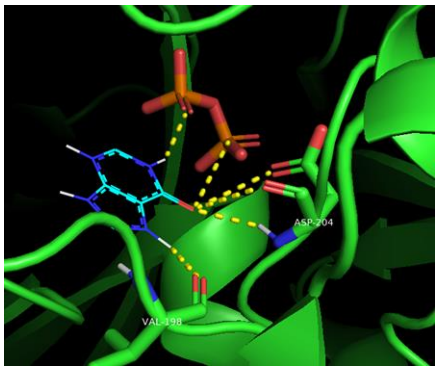


Figure 9. Interaction visualization Native Ligand hydrogen bonding with ASP204 and VAL198

Conclusion

In conclusion, a computational-based experiment successfully discovers 20-isoveratramine to have the best fit as an antimalarial candidate. The study revealed the potency of the Indonesian medicinal plant, *Cyanthillium patulum*, as a source for anti-malarial agents

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