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Review Article

Exploration of *Streptomyces hygroscopicus* Secondary Metabolite Compound as a Development of Antimalarial Drug Candidate

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ABSTRACT

Background: Malaria has become a major global health disease among humans. Globally, an estimated 228 million cases of malaria occurred and resulted in 405,000 deaths in 2018. The treatment of *Plasmodium falciparum* malaria relies on derivatives of artemisinin (ART) as a core component of ART-based combination therapy (ACTs). However, some malaria-endemic areas have started showing cases of artemisinin resistance. Thus, research related to antimalarial drugs from plant and microbial sources is needed. **Methods:** The keywords *Streptomyces hygroscopicus*, Antimalarial/antiplasmodium, and secondary metabolite were used to search the important literature materials on PubMed, Google scholar and Science direct. **Results:** From the literature review results, it was found that 61 compounds were isolated from *Streptomyces hygroscopicus*. Of the isolates, seven compounds have been tested for antimalarial activity. Two compounds were tested *in silico*, five compounds tested *in vitro* on *Plasmodium* culture, and three compounds tested *in vivo*. Eponemycin and geldanamycin are the two compounds that have been tested *in vitro* and *in vivo* as antimalarials that can inhibit *Plasmodium* spp. growth and inhibit cerebral malaria in the experimental animals. **Conclusion:** *In silico, in vitro* and *in vivo* studies of *S. hygroscopicus* exhibited potential antimalarial activity.

Key words: *Streptomyces hygroscopicus*, Secondary metabolites, antimalarial, *in silico, in vitro, in vivo*.

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INTRODUCTION

Climate change and migration are some of the factors that have contributed to the increase in infectious diseases, one of which is malaria. In 2018, it was estimated that 228 million cases of malaria and 405,000 malaria deaths occurred globally, while in 2017 there were 231 million cases of malaria with 416,000 deaths. In 2018, child mortality accounted for 67% (272,000) of all malaria deaths worldwide.[1]

Malaria-endemic countries have changed the therapeutic policies from monotherapy to artemisinin-based combination therapy (ACTs).[2] However, in 2008, the first case of artemisinin resistance appeared in West Cambodia, and since then there has been an increase in the incidence rate of artemisinin (ART) combination resistance in Southeast Asia (Duru *et al*., 2016). Based on the data, the development of new antimalarial agents is necessary and plant sources and microorganisms (one of which is *Streptomyces hygroscopicus*)[3] are promising sources. *Streptomyces* is a gram-positive, filamentous bacteria in the Phylum Actinobacteria, Order *Streptomycetales*, Family *Streptomycetaceae*.[4] *Streptomyces* is widespread in nature[5] and can be found in soil habitats, water sediments,[4] sea,[6] mangroves,[7] and plants.[8] The most interesting characteristic of *Streptomyces* is its ability to produce bioactive secondary metabolites, such as antifungal, antiviral, antitumoral, antihypertensive, and immunosuppressant compounds, as well as antibiotics.[9] *Streptomyces* is thought to produce up to 100,000 different antimicrobial compounds, but only a small number has been identified so far. There are numerous types of *Streptomyces* strains known, such as *Streptomyces celicolor, S. avermitilis, S. griseus, S. bringchenggensis, S. scabiei, S cattleya, S platensis, S. roseosporus,*[9] *S. mutomycini* and *S. hygroscopicus.*[10]

A number of studies showed that several *Streptomyces* species have antimalarial activity. The crude extract of *Streptomyces* sp. BCC26924 showed antimalarial, anti-*C. albicans*, and anti-tuberculosis activities.[11] Further, research showed that diketopiperazine gancidin W (GW) is one of the metabolites responsible for the *in vivo* antimalarial activity of the crude extract ethyl acetate from *Streptomyces* SUK10. The results presented show that *Streptomyces* SUK10, which lives endophytically on the *Shorea ovalis* tree, is a source of potential antimalarial agents with relatively low toxicity.[12]

In this study, the content and mechanisms of secondary metabolites in *Streptomyces hygroscopicus* as an antimalarial are discussed using a literature-review method.

METHODS

The keywords (*Streptomyces hygroscopicus*, antimalarial, antiplasmodial and secondary metabolites) were used to search literature materials in PubMed, Google Scholar and Science Direct. The selected materials were analyzed qualitatively and compiled according to: identification of secondary metabolites, identification of *in silico, in vitro* and *in vivo* antimalarial activity, and antimalarial mechanism of *S. hygroscopicus*. Bibliographies that were not available in database were searched manually.

RESULTS AND DISCUSSION

Secondary metabolites in *S. hyroscopicus*

Based on Table 1, 61 compounds are identified from *Streptomyces hygroscopicus*, most of which are macrolide, naphthoquinone, benzoquinone, aminoglycoside, polyketide, epoxyketone, and isoquinoline alkaloid.

Of the 61 compounds identified in Table 1, only seven compounds (Table 2) have been tested for antimalarial activity. There are two compounds tested *in silico*, five compounds tested *in vitro* on *Plasmodium* culture, and three compounds tested *in vivo*. The eponemycin and geldanamycin compounds have been tested both *in vitro* and *in vivo*; and from the two test methods, it was found that there was an inhibitory

activity on *Plasmodium* growth.

In silico Study on Antimalarial Activity of Secondary Metabolites

There are two mechanisms of antimalarial activity of secondary metabolites *Streptomyces hygroscopicus* that have been studied *in silico*.

Table 1: Classification of *Streptomyces hygroscopicus* metabolites.

No.	Secondary Metabolites	Compounds
1	Guanidine with Polyhydroxyl Macrolides[13]	Copiamycin A
		Azalomycin F, F3a, F4a, F5a
		Niphimycin (scopafungin)
		Shurimycin A, B
		Dihydroniphimycin
		Polaramycin A, B
		Guanidyfungina A, B
2	Maytansionoid (derivative compound of maytansin-ansamycin macrolide class)[14]	Ansamitocin
3	Macrodiolides (Macrolides)[15]	Elaiophylin (Azalomycin B)
4	Macrolides (linear polyketides with d-lactone terminus)[16]	Pterocidin
5	Macrolides[17,18]	Rapamycin (Sirolimus)
		Ascomycin
		Milbemycin beta 9, 10, 11, 12
		Milbemycin D, E, F, G, H, J, K
		Milbemycin α 20, 21
6	Naphthaquinone macrolides[19]	Hygrocins A, B
7	Macrocyclic lactones[20]	Guanidolide
		Neocopiamycin B
8	Naphthaquinone-derived polyol macrolactone[21]	Astolides A, B
9	Benzoquinone ansamycin[22]	Geldanamycin
10	Benzoquinoid ansamycin[23]	Herbimycin A
11	α,β′-epoxyketon[24]	Dihydroeponemycin
		Eponemycin
12	Clavam (Penicillin)[25]	Clavamycin A, B, C, D, E, F
		Clavamycin
13	Aminoglycosides (Aminocyclitol)[26]	Hygromycin B
14	Aminoglycosides[27]	Validamycin A, B
15	Hydroxamic acid derivatives[28]	Trichostatin A (TSA)
16	Polyether carboxylate antibiotics[29]	1-metilesternigericin
		Nigericin
17	Phosphinothricin analogues[30]	Bialaphos
18	Monosaccharides[31]	Deoxypentulosa
19	C-nucleoside antibiotics[31]	Minimycin (MIN)
21	Nucleosides[32]	Carbocyclic coformycin
22	Spiro Nucleosides[33]	Hydantocidin
23	Polyolefin polyketides[34]	Clethramycin
24	Isoquinoline derivatives (alkaloid group)[2]	6,7-dinitro-2- [1, 2, 4] triazole-4-yl-benzo [de] isoquinoline-1,3-dione

The first mechanism in the compound 6,7-dinitro-2- [1, 2, 4] triazole-4-yl-benzo [de] isoquinoline-1,3-dione is the ligand that binds to adenylosuccinate synthetase, thus reacting to form hypoxanthine. In *P. falciparum*, hypoxanthine is used for formatting purine bases as the main components of nucleic acid, cofactor, and nucleic acid synthesis in the intraerythrocytic cycle.[2,35] and resistance to artemisinin has been reported in the Southeast Asian region. In the previous study, the active compound of *Streptomyces hygroscopicus* subsp. *hygroscopicus* (*S. hygroscopicus*).

The second mechanism for dihydroeponemycin compounds is the ligand that inhibits UPS (Ubiquitin Proteasome System) in *P. falciparum*. UPS in *P. falciparum* is involved in a variety of cellular functions and host-pathogen interactions. The ubiquitin system is vital for the development of the malaria parasite life cycle. Ubiquitin can covalently attach to the target protein through the combined action of three classes of enzymes that are the activating enzyme ubiquitin (E1), the conjugate enzyme ubiquitin (E2), and ubiquitin-protein ligase (E3).[36,37]

In vitro Study on Antimalarial Activity of Secondary Metabolites

New molecular targets of antimalarial may be developed through enzymes pathway that involved in post-translational modifications (PTMs) of histones. Histones affect many chromatin-based events such as transcription, DNA replication and repair.[38] Post translational modifications are reversible, dynamic, and catalysed by a large number of enzymes. One of the covalent modifications of histones, lysines acetylation is best understood. Histone acetylation occurs at multiple lysines and is regulated by hystine acetyl-transferase (HATs) and histone deacetylases (HDACs). Histon acetyltransferase divided into five families, one of them are MYST.[39]

In the *in vitro* molecular mechanism, hyperacetylation of histone lysines can occur in two ways. The first pathway is through increased *Plasmodium falciparum* MYST (*Pf*MYST) protein expression.[40] *Pf*MYST is a lysine acetyltransferase, an enzyme that catalyzes the acetylation of lysine.[39]

The second pathway is through inhibition of HDAC activity that can be proven by the increasing alpha-tubulin II expression.[41] The inhibition of HDAC activity causes no enzymes to release acetyl groups on lysine histones.[42]

Histone hyperacetylation causes changes in the composition of lysine in histones and changes in DNA transcription of *Plasmodium falciparum*. This dynamic nature of histone acetylation is important for maintaining genomic stability. Disturbances in histone acetylation can also affect the solidification of chromatin up to the opening of the chromatin structure.[43]

In vivo Study on Antimalarial Activity of Secondary Metabolites

The infection from the protozoan parasite *P. falciparum* can rapidly develop into a deadly neurological syndrome, known as cerebral malaria (CM). Cerebral malaria occurs through the activation of mTOR, which is a central regulatory protein for the immune response that drives the invasion of antigen-stimulated $CD4^+$ and $CD8^+$ T cells into inflamed tissues (Sinclair LV *et al.*, 2008). Rapamycin can inhibit mTOR activation, so there is no T cell increase in inflamed brain tissue. Simultaneously, active T cells remain in the spleen, allowing an increased clearance of infected red blood cells.[44-46]

Secondary metabolites of *Streptomyces hygroscopicus* is also known to have inhibitory activity against *Plasmodium berghei* UPS *in vivo*. There was an increase of ubiquitinated protein accumulation after the crude extracts were treated into the infected mice. The accumulations were shown by the present of ubiquitin specific-tagged band smear of western

Table 2: Test of Streptomyces *hygroscopicus* metabolite compounds.

No	Secondary Metabolites	Author(s)	Research Type	Results
1	Dihydroeponemycin (α′,β-epoxyketone)	Mardhiyyah *et al*., 2019	*In silico*	Protein: Plasmodium UPS (E2 dan E3) Results: *Binding affinity* protein E3 -4,8 kcal/mol, and *binding affinity* protein E2 -4.9 kcal/mol.
2	6,7-dinitro-2- [1, 2, 4] triazole-4-yl-benzo [de] isoquinoline-1,3-dione (alkaloid isoquinoline)	Nugraha, *et al*., 2020	*In silico*	Results: The compound has the best binding affinity (−9.4kcal/mol) with adenylosuccinate synthetase protein target.
3	Eponemycin (α′,β′- epoxiketone)	Fitri *et al*., 2019	*In vitro*	Culture: *P. falciparum* 3D7 Results: The doses of 2.6 mg/ml and 13 mg/ml have the highest effect with 69.8% and 67.3% inhibition rate, respectively.
4	Geldanamycin (Benzoquinone ansamycin)	Kumar R. *et al*., 2003	*In vitro*	Culture: *P. falciparum* strain 3D7 (chloroquine resistant) Results: Has antimalarial activity with IC_{50} 20 nM.
5	Nigericin (Polieter carboxylate)	Gumilla C. *et al*., 1997	*In vitro*	Culture: *P. falciparum* Results: IC_{50} at the schizont stage was 1.6 ng/ml. IC_{50} at the ring and trophozoite stages were 7 and 9 ng / ml, respectively.
6	Trichostatin A (TSA) (Hydroxamic acid derivatives)	Andrews *et al*., 2012	*In vitro*	Culture: *P. falciparum* 3D7 Results: The dose of 50 nM TSA was able to change the transcript of the alpha tubulin II genome by 17% in the tropozoite phase.
		Chua *et al*., 2012 (the jurnal is locked by Nanyang Tech. University)	*In vitro*	Culture: *P. falciparum* Results: TSA changed the P. falciparum epigenome by methylation of H3K4 and H4K20 proteins.
		Miao *et al*., 2013	*In vitro*	Culture: *P. falciparum* 3D7 Results: TSA administration at a concentration of 3 or 4 x IC_{50} (IC_{50}: 16-64 nM) caused acetylation of PfMYST protein (relative acetylation level: +210) in the ring form of P. falciparum 3D7.
		Gupta *et al*., 2016	*In vitro*	Culture: *P. falciparum* 3D7 Results: TSA at a concentration of 50 μM could induce hyperacetylation of P. falciparum 3D7 H3 and H4 proteins.
		Ngwa *et al*., 2017	*In vitro*	Culture: *P. falciparum* NF54 Results: TSA could inhibit the formation of gametocyte stage IV and V by 43% with IC_{50}: 29 nM. At IC_{90} (0.26 μM) TSA was able to inhibit 67% less than the control (chloroquine 6 nM).
		Coetzee *et al*., 2020	*In vitro*	Culture: *P. falciparum* 3D7 dan NF54 Results: Inhibits the asexual phase of P. falciparum 3D7: IC_{50}: 0.078 ± 0.008 μM, early gametocyte phase of P. falciparum NF54: IC_{50}: 0.09 ± 0.01 μM, final gametocyte phase of P. falciparum NF54: IC_{50}: 0.07 ± 0.02 μM.
	Rapamycin (sirolimus) (Macrolides)	Veletzky *et al*., 2014	*In vitro*	Culture: *P. falciparum* Dd2 (chloroquine resistant), 7G8 (chloroquine resistant), and 3D7 (sensitive to all frequently used antimalarials). Results: IC_{50} in *P. falciparum* 3D7: 8.1 μmol/L, IC_{50} in *P. falciparum* 7G8: 6.7 μmol/L, IC_{50} in *P. falciparum* Dd7: IC90: 12.3 μmol/L.
7		Monaghan *et al*., 2017	*In vitro*	Culture: *P. falciparum* 3D7 Results: Rapamycin inhibited the tropozoite phase by> 90%.
		Martínez-Flórez *et al*., 2020	*In vitro*	Culture: P. falciparum 3D7 is sensitive to chloroquine Results: The results of rapamycin administration after 48 hr in the intraerythrocyte form of P. falciparum 3D7 yielded IC_{50}: 2.50 μM.

Continued...

Table 2: Cont'd.

No	Secondary Metabolites	Author(s)	Research Type	Results
	Eponemycin (α′, β′- epoxiketone)	Rivo *et al*., 2013	*In vivo*	Experimental animals: Balb/C mice infected by *P. berghei* Results: Has antimalarial activity ED50 9,418 µg/kgBW.
8		Fitri *et al*., 2017	*In vivo*	Experimental animals: Balb/C mice infected by: *P. berghei* Results: The dose of 2600 µg/kgBW from the secondary metabolite extract could suppress the degree of parasites on almost all of the experiment days.
9	Geldanamycin (Benzoquinone ansamycin)	Mout R. *et al*., 2012	*In vivo*	Experimental animals: Swiss mice infected lethal *P. yoelii* (17XL) strain Results: Two geldanamycin derivatives (17-AAG and 17-PEG-Alkyn-GA) at a dose of 300 nmol could reduce the degree of parasitemia by <4%.
10	Rapamycin (sirolimus) (Macrolides)	Gordon *et al.,* 2015	*In vivo*	Experimental animals: female mice C57BL / 6 and C57BL / 6- [KO] RAG-1 (7-10 weeks old) Results: Rapamycin at a dose of 1 mg/kg could function as an mTOR inhibitor
		Mejia *et al*., 2015	*In vivo*	Experimental animals: C57BL / 6J wild and mutant type female mice (ob / ob, db / db) (8–10 weeks old) Results: Rapamycin at a concentration of 5 mg/kg could reduce the accumulation of CD4 + and CD8 + T cells in the brain.
		Mejia *et al*., 2017	*In vivo*	Experimental animals: wild-type female mice C57BL / 6J (8-10 weeks old) Results: Rapamycin at a dose of 25 mg / kg could increase the survival rate of mice by >75%.

blot analysis. After treatment, there was no relapse of parasitaemia during 28 days of follow up.[47]

In vivo test results of secondary metabolites in other *Streptomyces hygroscopicus* showed a decrease in the percentage rate of parasitemia. This is consistent with the results of *in vitro* tests that showed that *Streptomyces hygroscopicus* can inhibit the growth of *Plasmodium* parasites in the schizont, ring, trophozoite, and gametocyte phases.

CONCLUSION

The results of *in silico, in vitro*, and *in vivo* tests showed that there is an inhibition to *Plasmodium* growth in the sexual and asexual phases through molecular mechanisms of inhibition of purine base formation, blocking the protein turn over system of *Plasmodium* via the UPS route, and changing the *Plasmodium* epigenome through histone lysine hyperacetylation. Furthermore, compounds such as geldanamycin, rapamycin, and eponemycin can prevent cerebral malaria. Based on the results of these studies, *Streptomyces hygroscopicus* is a potential microorganism to be developed as a novel all stage antimalarial therapy. Further research is needed to screen and determine the most active compound as antimalaria, to purify, and to study the pharmacokinetic and toxicity profile of the active compounds from *Streptomyces hygroscopicus*.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ACT: Artemisinin-based combination therapy; **TSA:** Trichosatatin A; **MIN:** Minimycin; **UPS:** Ubiquitin protease system; **PTMs:** Post-translational modifications; **HATs:** Hystine acetyl-transferase; **HDACs:** Histone deacetylases; **MYST:** MOZ, Ybf2/Sas3, Sas2, and TIP60; **CM:** Cerebral malaria.

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