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A SYSTEMATIC LITERATURE REVIEW: PVK12 AND PFK13 GENE MUTATIONS AS MARKERS OF RESISTANCE TO ARTEMISIN

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ABSTRACT
P. falciparum and P. vivax are among the most dangerous types of plasmodium , as they cause morbidity and mortality. Long-term use of Anti-Malaria Drugs (OAM) causes resistance. The purpose of this study was to determine the mutation of the pvk12 and pfk13 genes as a marker of resistance to artemisinin . This study used a systematic review method that was compiled based on the Preferred Reporting Items for Systematic Reviews and Meta Analyzes (PRISMA). The article search used five databases, namely PubMed, Google Scholar, BMC, Portal Garuda and the National Library (Perpusnas) of Indonesia. The keywords and boolean operators used in the literature search were "artemisinin", "resistance", "mutation", "gen", "plasmodium falciparum", "kelch 12", "kelch 13", "PvK12" PfK13" The inclusion criteria for this study were articles published at least in 2018 (the last 5 years). The exclusion criteria were paid articles, textbooks , articles systematic literature review , articles that use languages other than English and Indonesian. The results of a systematic review use 688 articles and finished of 10 articles showed that 8 articles found that there were no mutations in the pvk12 and pfk13 genes as markers of resistance to artemisinin and 2 articles found that there were mutations in the pvk12 and pfk13 genes as markers of resistance to artemisinin.

Keywords: PvK12; PfK13; resistance

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INTRODUCTION

Malaria is one of the infectious diseases that is a problem for public health in the world, most susceptible to affecting ages such as children and the elderly which usually occurs in the rainy season (Cowman et al., 2016) . Malaria is an infectious disease caused by the Plasmodium parasite that lives and reproduces in human red blood cells. This disease is naturally transmitted through the bite of a female anopheles mosquito. Plasmodium species in humans are Plasmodium falciparum, P. Vivax, P. Ovale and P. Malariae . Malaria is easily transmitted through the bite of the Anopheles mosquito . females containing Plasmodium , attack all individuals regardless of gender and age. Sufferers will complain of symptoms of fever , chills, headaches and nausea. (Sillehu & Utami, 2018) .Malaria remains a global problem with 1.5-2.7 million deaths per year. Based on data from the World Health Organization (WHO) in 2021, around 247 million cases were reported from 84 malaria-endemic countries and the estimated deaths caused by malaria were 619,000 cases. Most deaths from malaria were reported in the African region, with almost 76% of total deaths recorded in children under 5 years of age (WHO, 2023)

Malaria cases in Indonesia reached 94,610 cases in 2021 compared to 226,364 cases the previous year. Judging from the trend, in Indonesia in 2018 malaria cases decreased. However , in 2019 it increased to 250,628 cases. Then, from 2020 to 2021 it decreased again. In Indonesia, the highest malaria cases are in the eastern region, namely Papua Province, which in 2021 reached 86,022 cases (90.9%) of the total cases in Indonesia. (Ministry of Health of

the Republic of Indonesia, 2022a)Various efforts have been made to reduce morbidity and mortality due to malaria, including establishing malaria elimination policies globally, nationally and locally. Malaria as a global problem including Indonesia has received attention to be eliminated. In 2007, a global agreement was made at the 60th World Health Award (WHA) meeting in Geneva that every country needs to provide support in order to eliminate malaria by 2030. Following up on the World Health Assembly (WHA) agreement, the Indonesian Government has set a policy by issuing the Decree of the Minister of Health no: 293/Menkes/SK/IV/2009 concerning the elimination of malaria in Indonesia. The objective of the Decree of the Minister of Health 293 of 2009 is to realize a society that lives healthily and is free from malaria transmission gradually by 2030; with the targets being the Seribu Islands (DKI Jakarta Province), Bali Island and Batam Island in 2010; Java Island, NAD Province and Riau Islands Province in 2015; Sumatra Island (except NAD Province and Riau Islands Province), NTB Province, Kalimantan Island and Sulawesi Island in 2020; and Papua Province, West Papua Province, NTT Province, Maluku Province and North Maluku Province in 2030. (Ministry of Health of the Republic of Indonesia, 2022a)

Artemisinin is a sesquiterpene lactone (C15H22O5), a secondary metabolite compound isolated from Qinghao, also known as Artemisia year. The special feature of artemisinin that distinguishes it from other antimalarial drugs is the presence of a peroxide bridge in its chemical structure. This peroxide bridge has been found to play an important role in antimalarial activity based on several proposed mechanisms of artemisinin efficacy (Ma et al., 2020. Artemisinin resistance and its derivatives in P. vivax are known to be related to multiple single nucleotide polymorphisms (SNPs) on chromosome 12 of P. vivax, namely kelch12 (K12) (Rahmasari et al., 2022) . Mutations in the propeller domain of the Plasmodium vivax Kelch12 (PvK12) gene are closely related to artemisinin resistance. The presence of mutations in this gene will change the response of P. vivax to oxidative stress caused by artemisinin by involving the proteasome-ubiquintin pathway . Mutations in this gene are located in the third-blade propeller domain. The K12 protein consists of 3 Plasmodium- specific domains , namely the Tho2 super family domain, BTB-POZ, and a 6-blade propeller domain , where the majority of mutations related to artemisinin resistance are located in the propeller domain of the protein (Tripura et al., 2017) .

Artemisinin resistance in Plasmodium falciparum is associated with mutations in several genes that alter the function of the proteins they produce. One of the genetic markers reported as a dominant factor in artemisinin resistance is mutations in the kelch13 (k13) gene. In Plasmodium falciparum , the k13 (Pfk13) gene encodes the K13 protein, a 726-amino acid protein consisting of an Apicomplex-specific early N-terminal region and three highly conserved annotated domains (Coppée et al., 2019) . The k13 gene is reported to be essential for the asexual intraerythrocytic stage of Plasmodium falciparum . However, the defined function and suggested role of the K13 protein require further elucidation. The K13 protein propeller domain displays multiple protein-protein interaction sites and facilitates distinct cellular functions, such as ubiquitin-regulated protein degradation and oxidative stress response (Straimer et al., 2015; Xie et al., 2020) .

Malaria control has been carried out for a long time through various efforts, for example malaria vector control, patient treatment and environmental improvement. The phenomenon of resistance to chloroquine and the combination of sulfadoxine pyrimethamine that occurs in malaria-endemic countries, has caused WHO to recommend the use of ACT (Artemisinin Combination Therapy) as an OAM (Anti-Malaria Drug) for Plasmodium falciparum sufferers since 20015. The Indonesian government issued a policy on the use of artemisinin-based ACT in 20046 . Currently there are 3 ACT regimens used in the malaria program, namely

artesunate-amodoquine, artemether-lumefantrine and dihydroartemisinin-piperaquine specifically for the Papua region.

Nationally, there are 318 districts/cities or 61.9 % that have been declared malaria-free in 2020. This number has increased compared to 2019 which was 300 districts/cities. The condition in 2020 was that Papua was the highest province with a malaria morbidity rate of 63.12 per 1,000 population, far above other provinces. Manado City is located in North Sulawesi Province with a malaria incidence percentage of 0.07 % . In 2021, North Sulawesi Province experienced an increase in malaria cases to 0.17% (Ministry of Health of the Republic of Indonesia, 2022b) . The aim of this research is to determine PVK12 and PFK13 gene mutations as markers of resistance to artemisin

METHOD

This study uses a systematic review method that is compiled based on the Preferred Reporting Items for Systematic Reviews and Meta Analyzes (PRISMA). Article searches use five databases, namely PubMed, Google Scholar, BMC, Science Direct , Portal Garuda and the National Library (Perpusnas) of Indonesia. Keywords and boolean operators used in the literature search are "artemisinin", "resistance", "mutation", "gen", "plasmodium falciparum", "kelch 12", "kelch 13", "PvK12" PfK13" The inclusion criteria for this study are articles published at least in 2018 (the last 5 years). The exclusion criteria are paid articles, textbooks, systematic literature review articles, articles using languages other than English and Indonesian. Articles that have been selected to the inclusion and exclusion criteria will be assessed for quality using The Joanna Briggs Institute (JBI) Critical Appraisal according to the study design in the article. Article quality research will be conducted by both researchers. Articles that have passed the quality test will be analyzed using descriptive analysis techniques, namely interpreting and explaining in more depth the research results and their relationships with each other through narratives. The results of 688 articles, 10 articles were used.

RESULT

Table 1.
Article Analysis

No	Author/Year/ Title	Objective	Methods	Result
1.	(Nesan et al., 2023) Identification of Kelch 13 Gene Mutations as Resistance Markers in Plasmodium falciparum with ACT Treatment After 3 Days in Manokwari, West Papua	The aim of this study was to identify resistance marker mutations of the Kelch 13 gene in Plasmodium falciparum with ACT treatment after 3 days.	- The type of research used is exploratory. - The place of blood sampling and examination (RDT & microscopy) at Amban Health Center Manokwari West Papua. Furthermore, DNA isolation, PCR amplification and agarose gel electrophoresis at the Molecular Biology Laboratory of Muhammadiyah University of Semarang, while for DNA sequencing of the *Kelch 13 gene target* at PT. *Science* Genetika Indonesia. - The population in this study were all patients who came to the Amban Health Center Laboratory, Manokwari Health Office, West Papua with malaria examination. The sample size in this study was from 51 patient samples, 11 patient samples were obtained that met the inclusion criteria, namely ACT treatment for 3 days which still showed *Plasmodium falciparum parasites* and the samples were collected on dry *blood spots* using wathman paper .	There is a mutation in the Kelch 13 gene, 3 mutation variants, namely substitution (transition & transversion), silent mutation (codon C3T 1 cysteine-cysteine), and missense mutation (codon T4A 2 tryptophan)

No	Author/Year/ Title	Objective	Methods	Result
2.	(Lê et al., 2022) Molecular Profiles of Multiple Antimalarial Drug Resistance Markers in Plasmodium falciparum and Plasmodium vivax in the Mandalay Region, Myanmar	Molecular epidemiologic al analysis was conducted for antimalarial drug resistance genes in Plasmodium. falciparum and P. vivax from Mandalay region, Myanmar.	Blood samples were collected from patients infected with Plasmodium falciparum and P. vivax in four townships, Mandalay, Tha Beik Kyin, Naung Cho, and Pyin Oo Lwin, around the Mandalay region, Myanmar. Plasmodium species were identified by examination. Microscopic examination of thin and thick blood smears stained with Giemsa. Before antimalarial drug treatment, finger prick blood samples were collected from patients, dripped onto 3 mm Whatman filter paper (GE Healthcare, Pittsburg, PA, USA), dried in air, and stored individually in sealed plastic bags at room temperature until Furthermore.	High or moderate level mutations detected in genes such as pfmdr-1, pfcrt, and pvmdr-1 associated with chloroquine resistance. While low or no mutation frequencies were found in pfk13, pfubp-1, pfcytb, and pvk12 parasites. The overall molecular profile of antimalarial drug resistance genes in malaria parasites in the Mandalay region suggests that the parasite population in the region has a high mutation rate substantial factors that cause antimalarial drug resistance.
3.	(Zhao et al., 2020) Molecular surveillance for drug resistance markers in Plasmodium vivax isolates from symptomatic and asymptomatic infections at the China-Myanmar border	This study aims to investigate potential gene variations. related to drug resistance in P. vivax populations in the China-Myanmar border region. In addition, this study also wanted to know whether there were differences between the parasite populations associated with asymptomatic and asymptomatic infections. Infection.	A total of 66 P. vivax isolates were obtained from acute malaria patients who came to the clinic in the Laiza area, Negara. Kachin State, Myanmar in 2015. In addition, 102 P. vivax isolates associated with asymptomatic infections were identified by screening volunteers without signs or symptoms from surrounding villages. Slide-positive samples were verified by nested PCR detecting the 18S rRNA gene. Multiclonal infections were further excluded by genotyping the msp-3ÿ and msp-3ÿ genes. Parasite DNA from 60 symptomatic cases and 81 asymptomatic infections was used to amplify and sequence genes potentially associated with drug resistance, including pvmdr1, pvcrt-o, pvdhfr, pvdhps, and pvk12	No mutations were found in the pvk12 gene.
4.	(Manirakiza et al., 2022) Molecular identification and anti-malarial drug resistance profile of Plasmodium	This study identified different Plasmodium species in malaria-positive patients, and their profiles antimalarial	- This study was a cross-sectional study where samples were analyzed to identify Plasmodium species and anti-malarial resistance markers of P. falciparum from patients with clinical symptoms of malaria at Kisoro District Hospital.	There were 134 samples showing PCR amplification, confirming the species as Plasmodium. Plasmodium falciparum (N=122), Plasmodium malariae (N=6), Plasmodium ovale (N=4), and Plasmodium vivax (N=2) were the various Plasmodium species and their proportions. Kelch13 C580Y mutation was not

No	Author/Year/ Title	Objective	Methods	Result
	falciparum from patients attending Kisoro Hospital, southwestern Uganda	drug resistance for Plasmodium falciparum using DBS samples collected from hospitalized patients at Kisoro Hospital in Kisoro district, South Western Uganda.	- Venous blood samples from patients who tested positive for malaria between March and August 2020 and DBS were prepared on Whatmann® 903™ filter paper (Ref: 10530143 Rev.AA) by placing a drop of finger prick blood sample onto each filter paper cycle. Samples were air-dried for up to 24 hours away from wind and direct sunlight. After air-drying, the filter paper was placed into ziplock bags with two desiccant sachets in each pack and stored at room temperature (25°C to 28°C). The samples were then analyzed at the Genomics and Translational Laboratory, Department of Microbiology, Mbarara University of Science and Technology.	detected.
5.	(Oboh et al., 2018) Status of Artemisinin Resistance in Malaria Parasite Plasmodium falciparum from Molecular Analyzes of the Kelch13 Gene in Southwestern Nigeria	To understand the molecular epidemiology of the Pf13 gene causing resistance to ART in two states southwest nigeria	Malaria symptomatic patients presenting to one of four selected hospitals (Gbagada, Ikorodu, Akodo, and Ikate) in Lagos and two general hospitals (Central and Stella) in Edo were screened using rapid diagnostic test (RDT) and field microscopy. Blood from each patient was used to make two to three spots on Whatman no. 3 filter paper and transported to ICMR-National Institute for Tribal Health Research, Jabalpur, India, after obtaining ethical approval and a permit for transport of obtained materials (IRB/16/347) from the Nigerian Institute of Medical Research, Yaba, Lagos State, Nigeria. In the laboratory, genomic DNA was isolated separately from a total of 436 symptomatic malaria blood samples (using the QIAamp DNA Blood Mini Kit; Qiagen, Hilden, Germany) and subjected to diagnostic PCR for four malaria parasites. PCR-positive samples for P. falciparum were further	None of the validated Pf13 gene mutations and AA candidates conferring resistance to ART were detected in P. falciparum samples from two southwestern Nigerian states. Furthermore, sequencing and DNA sequence analysis did not indicate evolutionary selection pressure on the Pf13 gene or association of mutations in the Pf13 gene with mutations in the other three genes conferring resistance to CQ and SP.

No	Author/Year/ Title	Objective	Methods	Result
			processed for amplification of a DNA fragment (831 nucleotide base pairs) containing validated and candidate Pf13 gene mutations using published primers. Successful PCR products showing a single band in the gel were then subjected to PCR purification (using FastAP alkaline phosphatese and exonuclease I) and further processed for DNA sequencing by Sanger method (ICMR-NIRTH in-house facility, Jabalpur) at 2X coverage (sequencing in both forward and reverse directions).	
6.	(Chidimatembue et al., 2021) Molecular surveillance for polymorphisms associated with artemisinin-based combination therapy resistance in Plasmodium falciparum isolates collected in Mozambique, 2018	The aim of this study was to analyze the prevalence of markers molecular factors associated with P. falciparum resistance to antimalarial drugs on the pfk13, pfmdr1, and pfcrt genes in samples collected during TES 2018 at four sentinel sites in Mozambique.	This study was a sub-study of the TES that evaluated the efficacy and safety of AL and ASAQ in the treatment of uncomplicated P. falciparum malaria in children aged 6–59 months in Mozambique. Potential participants were screened for malaria parasites using microscopy at each study site. Patients were eligible for enrollment if they had uncomplicated P. falciparum monoinfection with an asexual blood density between 2000 and 200,000/μL, were aged 6–59 months, and had fever on presentation (axillary temperature ÿ37.5 °C) or a history of fever in the previous 24 hours. Dried blood spots on 3 mm Whatman paper were prepared using 50 μL of blood collected on the day of enrollment (day 0/pre-treatment) and on any other day the patient had a recurrent malaria infection during follow-up (post-treatment).	no molecular resistance markers pfk13 or pfcrt were observed, the results of this study corroborate the related TES findings showing AL and ASAQ to be effective
7.	(Si et al., 2023) What exactly does the PfK13 C580Y mutation in Plasmodium falciparum influence?	We analyzed the effects of PfK13 mutations on the transcriptome and proteome of P. falciparum at different times.	count , hemozoin count, and growth of P. Falciparum 3D7C580Y and P. falciparum 3D7WT compared. The impact of iron supplementation on the number of merozoites from P.falciparum 3D7C580Y also checked.	These results reveal that PfK13 mutations reduce hemoglobin consumption, leading to artemisinin resistance, most likely by reducing arasite's need for heme and iron. This study helps explain the mechanism of artemisinin resistance due to PfK13 mutations.

No	Author/Year/ Title	Objective	Methods	Result
8.	(da Silva et al., 2023) Anti-malarial resistance in Mozambique: Absence of Plasmodium falciparum Kelch 13 (K13) propeller domain polymorphisms associated with resistance to artemisinins	The aim of the study was to determine artemisinin resistance in 3 provinces (Niassa, Manica and Maputo) in Mozambique	The cross-sectional study recruited 450 participants with malaria infection detected by Rapid Diagnostic Test, from three different study sites (Niassa, Manica and Maputo) between April and August 2021. Matched blood samples were collected on filter paper (Whatman® FTA® cards), parasite DNA was extracted and the pfk13 gene was sequenced using method . SIFT (Sorting Intolerant From Tolerant) software was used, predicting whether amino acid substitutions affect protein function.	No pfkelch13-mediated artemisinin resistance gene mutations were detected in this study.
9.	(Ikegbunam et al., 2021) Absence of Plasmodium falciparum artemisinin resistance gene mutations eleven years after the adoption of artemisinin-based combination therapy in Nigeria	The aim of the research was to identify mutations in artemisinin resistance genes.	This cross-sectional study was conducted in the South-West and South-East geopolitical zones of Nigeria. A total of 150, 217, and 475 participants were enrolled for the study in the South-West (2004_Group A), South-West (2015_Group B), and South-East (2015_Group C), respectively. Blood samples were collected from study participants for DNA extraction and nested PCR for identification of P. falciparum. Samples positive for P. falciparum were genotyped for the pfk13 gene using Sanger sequencing method. Nucleotide polymorphisms were analyzed using Bioedit software.	None of the mutations observed in this study were previously validated to be associated with ART resistance.
10.	(Sitompul & Asnaily, 2019) Identification of Plasmodium Falciparum Pfatp6 Gene Mutations as Artemisinin Resistance Markers in Jambi Province	The purpose of the research is to found mutations in the PfATP6 gene of *P. falciparum* in 74 patients malaria in Jambi Province	This study is a molecular test in the form of a descriptive laboratory study to identify the *genotype mutations L263E, S769N* and *E431K of the PfATP6 gene. P.falciparum.* The study was conducted in malaria endemic areas in Jambi, namely in Sarolangun, Merangin, Muaro Jambi, Tebo, Batang Hari and Kota Jambi. The study was conducted from July to December 2016. Blood samples of patients were examined at the local Hospital / Health Center Laboratory and at the Biomolecular Laboratory of the FK Unsri for *Polymerase Chain*	*P. falciparum* isolates from Jambi Province in the PfATP6 gene associated with artemisinin resistance markers did not show mutations.

No	Author/Year/ Title	Objective	Methods	Result
			Reaction (PCR) examination. The population was all malaria suspects (clinical malaria) who came for treatment at the polyclinic and/or who were treated in the inpatient department of the Health Center / Hospital of Sarolangun, Merangin, Muaro Jambi, Tebo, Batang Hari and Jambi City. The samples were all malaria suspects that meet the inclusion criteria of the study. Sampling technique The sample size is not limited to the specified time limit . Sampling is done by *passive case detection* (PCD), which is waiting for suspected malaria patients to come to the laboratory for examination of peripheral blood smears and/or blood samples brought by nurses from the inpatient room of the Regional Public Hospital/Health Center, and *active case detection* (ACD), which is actively looking for malaria patients in endemic areas.	

DISCUSSION

The use of artemisinin as OAM in various parts of the world in the long term raises concerns about resistance phenomena such as chloroquine. Several studies have been conducted to determine the position of mutations in the PfATP6 gene as a marker of resistance by inhibiting the work of sarcoplasmic endoplasmic reticulum calcium ATPase / SERCA . Plasmodium falciparum resistance to artemisinin was first reported in 2009 in Cambodia and has now spread to several other countries such as Vietnam, Thailand, India, Africa, etc. One of the causes of artemisinin resistance in Plasmodium falciparum that has been known is the presence of mutations in the propeller protein of the K13 gene of Plasmodium falciparum . Mutations were found in several alleles including C580Y, R539T, Y493H, I543T F446L, N458Y, P574L, R561H, A578S, where each malaria endemic area with artemisinin resistance has a different mutation position pattern (Manirakiza et al., 2022)Mutations in this gene will cause an increase in the cell response to oxidative stress so that cells are not degraded even after artemisinin administration. In addition to modifying the cell stress response, K13 mutations can also increase PI3K levels and activity so that they indirectly affect the basal levels of PI3P which are essential for the parasite to continue development from the ring stage to the schizont. Phenotypic changes in artemisinin resistance that appear include lengthening of the ring stage and temporary shortening of trophozoite development. Resistance to artemisinin can be overcome by, among others, extending the duration of treatment (from a 3-day regimen to 4 days) and combining artemisinin with proteasome inhibitor drugs (Anindita et al., 2017)

Resistance of P. vivax to artemisinin is caused by mutation of PvK12 gene in a way that artemisinin enters the body in an inactive form that will be activated by Fe+2 (result of hemoglobin degradation) to produce highly reactive free radicals and will react with parasite protein causing protein alkylation. Alkylation can cause cell death and parasite death. However, in P. vivax with K12 mutation there is an increase in stress response due to the involvement of the proteasome-ubiquintin pathway, so that cells survive (Popovici & Ménard, 2015) .Protein K12 In parasites that are sensitive to artemisinin, it will bind to a transcription factor and regulate degradation, while in parasites that are resistant to artemisinin, K12 cannot bind to the transcription factor, causing upregulation of genes related to the antioxidant response. In this condition, the parasite is able to cope with oxidative stress from artemisinin better. The results of the study (Zhao et al., 2020) showed that no mutations were found in the pvk12 gene. The study (Lê et al., 2022) also showed that low frequency mutations or none at all were found in the pvk12 parasite.

The results of the study (Wiyani et al., 2021) the results of the amplification of 35 positive samples of P. vivax malaria in SAD in Batang Hari district only showed 2 samples showing positive results or bands at 792 bp, which indicated the presence of a mutant allele of the Pvk12 gene as a marker of artemisinin resistance. The remaining 33 samples were negative or did not show bands. In sample no. 8, the sequencing results showed a mutation at point 1253, this mutation did not occur at the marker point of P. vivax resistance to artemisinin. Other mutations have occurred in the Jambi P. vivax sample , but not at the marker point. This mutation cannot be concluded as a marker of malaria drug resistance in Jambi patients, because it was not taken from the isolate of patients who experienced resistance but from the results of surveillance. This shows that there has been no resistance of P. vivax to artemisinin in SAD, so that artemisinin drugs can still be used in SAD in Batang Hari Regency, Jambi.

CONCLUSION

The results of a systematic review of 10 articles showed that 8 articles found that there were no mutations in the pvk12 and pfk13 genes as markers of resistance to artemisinin and 2 articles found that there were mutations in the pvk12 and pfk13 genes as markers of resistance to artemisinin

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