PHARMACIA

Pharmacia 71: 1–14
DOI 10.3897/pharmacia.71.e116095

Review Article

Malaria in Indonesia: current treatment approaches, future strategies, and potential herbal interventions

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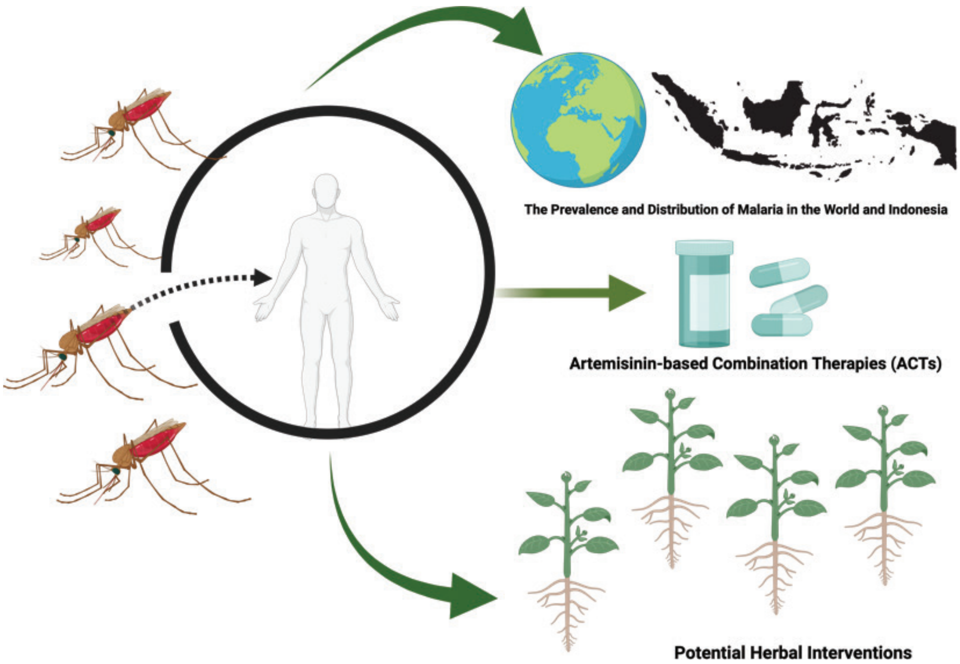
Received 22 November 2023 ♦ **Accepted** 12 December 2023 ♦ **Published** 15 February 2024

Citation: Tobing TCL, Wahrianto, Saputri E, Wafa NI, Zulfianti PD, Sihaloho LI, Husna AR, Salsabila D, Hotasi Silalahi FH, Sitohang AI, Sabrina A, Hasyati Harianja AD, Barus SA, Sabina S, Rahma AA, Velaro AJ, Khairunnnisa K, Salim E, Nurkolis F, Abdi Syahputra R (2024) Malaria in Indonesia: current treatment approaches, future strategies, and potential herbal interventions. Pharmacia 71: 1–14. https://doi.org/10.3897/pharmacia.71.e116095

Abstract

Malaria remains a significant public health challenge in Indonesia, with varying prevalence across regions, particularly in eastern provinces like Papua and West Papua. This parasitic disease, transmitted by *Plasmodium*-infected *Anopheles* mosquitoes, continues to burden affected populations. Contemporary treatment approaches predominantly rely on Artemisinin-based Combination Therapy (ACT). However, the emergence of drug resistance, coupled with environmental and demographic factors, presents ongoing challenges. This paper explores current malaria treatment strategies in Indonesia, emphasizing the importance of vigilance in the face of drug resistance and the need for innovative approaches. Additionally, it discusses the potential of herbal interventions, drawing from the rich traditional knowledge of medicinal plants in Indonesia. Secondary metabolites found in herbs, including flavonoids, terpenoids, and alkaloids, show promise as antimalarial agents. As Indonesia and the global community strive to combat malaria, research, surveillance, and healthcare infrastructure development must remain at the forefront of strategies. Despite the complex nature of malaria control, continued dedication and collaboration offer hope for reducing the disease's impact and progressing towards its eventual elimination.

Graphical abstract:



Keywords

Malaria, Indonesia, Herbal Interventions, and Artemisinin-based Combination Therapy (ACT)

Introduction

Malaria in Indonesia: a persistent health challenge

The protozoan parasites belonging to the *Plasmodium* genus, which are responsible for causing malaria, reside and undergo reproduction within the erythrocytes of human hosts (Supranefly et al. 2021). According to UNICEF (2022), the four most commonly observed parasites include *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*. The transmission of the disease occurs through natural means, specifically when a female *Anopheles* mosquito engages in biting behavior. The initial symptoms commonly encountered by individuals afflicted with malaria are influenza-like symptoms, such as fever, chills, and headaches. This condition can impact individuals across all age groups. According to Supranefly et al. (2021), the symptoms of malaria often manifest within a period ranging from 10 days to 4 weeks and commonly include fever, headache, vomiting, and shivering. Throughout history, malaria has been recognized as a significant infectious illness with a profound impact on the human population. With its high rates of morbidity and mortality, the infectious disease in question has garnered significant attention from the scientific community and is a prominent issue for global health organizations (Garrido-Cardenas et al. 2019). According to the World Health Organization's World Malaria Report of 2022, there has been a consistent decrease in global malaria fatality rates, with figures dropping from 887,000 in 2000 to 573,000 in 2015 and further reducing to 568,000 in 2019. In the year 2020, the number of deaths attributed to malaria was around 625,000, indicating a 10% increase compared to the previous year, 2019. The projected mortality figure for the year 2021 underwent a marginal decrease, resulting in a revised estimate of 619,000 fatalities. Between the years 2019 and 2021, the COVID-19 pandemic resulted in a total of 63,000 fatalities due to disruptions in critical malaria services. The World Health Organization (WHO) South-East Asia Region exhibited a secondary position, accounting for 10% of reported cases and 3% of fatalities. Conversely, the WHO Africa Region demonstrated a substantial avoidance of both cases (82%) and deaths (95%), constituting the majority in each category. The factors contributing to the increase in malaria transmission encompass the swift dissemination of quinoline-resistant malaria parasites, alterations in the environment that may facilitate the emergence of novel mosquito breeding habitats, societal instability prompting individuals to relocate to regions with elevated malaria transmission rates, and voluntary migration of non-immune populations susceptible to malaria (Dale et al. 2005). According to the World Health Organization (WHO 2020), there is a prevalent issue of malaria in 87 countries around the globe, with Indonesia being one of them. Indonesia is a prominent nation in Southeast Asia where instances of malaria are observed. In 2019, the World Health Organization (WHO) reported an estimated 658,380 cases of malaria and 1170 deaths attributed to malaria. The presence of multispecies infections and the challenges associated with identifying the specific locations of persistent transmission provide significant obstacles to the eradication of malaria in Indonesia, as well as in numerous other Southeast Asian nations. In the year 2017, it was ascertained that a majority of the districts in Indonesia had achieved the status of being free from malaria. Indonesia's remarkable achievement can be attributed to its dispersed population, which exceeds 260 million individuals and spans over 5,000 islands. Additionally, the country's significant internal migration, socioeconomic disparities, and decentralized governance contribute to its outstanding status. Moreover, it is worth noting that Indonesia has a rather balanced distribution of *Plasmodium falciparum* and *Plasmodium vivax* infections. Furthermore, the country harbors approximately 25 distinct species of *Anopheles* mosquitoes, which have developed resistance to malaria. With the exception of Bhutan and Indonesia, all nations have successfully attained the Global Technical Strategy (GTS) 2020 objective of reducing case incidence by over 40%. However, there exists a deficiency in the health system as evidenced by the persistence of high malaria transmission in the provinces of West Papua and Papua within the Papua region (Fadilah et al. 2022; UNICEF 2022). In the country of Indonesia, there exists a total of 80 distinct species of *Anopheles* mosquitoes that serve as vectors for the transmission of malaria. Among these species, 24 have been identified as posing a significantly elevated risk in terms of their ability to spread the illness. The distribution of these vectors, namely An. sundaicus, An. subpictus, An. barbirostris, An. maculatus, An. aconitus, and An. balabacensis, in Indonesia varies depending on the breeding location. Malaria manifests itself in various forms within the Indonesian context. The environment, encompassing physical, economical, and behavioral factors, has a significant role in enhancing the probability of malaria transmission in Indonesia (Dale et al. 2005). The growth, development, and reproduction of vectors are influenced by various physical factors, including temperature, precipitation, humidity, wind patterns, dispersed and inaccessible mosquito nesting places, and unsanitary environmental conditions. Socioeconomic factors such as nocturnal or early morning excursions, limited educational attainment, and lower middle-income status have the potential to influence the transmission of malaria. The characteristics mentioned above have been commonly associated with increased occurrences of malaria. Specifically, substandard housing circumstances and engagement in agricultural work have been identified as factors that elevate the likelihood of catching the disease (Dale et al. 2005; Lewinsca et al. 2021).

The importance of Malaria research in Indonesia

Malaria continues to pose a significant public health challenge in Indonesia, with a substantial number of individuals affected and a considerable number of deaths occurring annually. Indonesia has a substantial historical background in conducting research and development pertaining to malaria, as well as implementing strategies for the eradication of vector-borne diseases. Nevertheless, because to the intricate nature of transmission epidemiology inside this archipelago, there exists limited knowledge regarding the diverse array of mosquito species belonging to that particular type. The significance of Indonesia's malaria research cannot be overstated in the pursuit of the ambitious goal of malaria eradication by 2030. The nation of Indonesia has a diverse and intricate epidemiology of malaria, encompassing a variety of transmission patterns, parasite species, and vectors across its numerous islands. Hence, it is imperative to do research on malaria in order to gain insights into the dynamics of the disease, advance the development and assessment of novel tools and approaches, and provide a foundation for evidence-based policies and interventions (UNICEF 2022). In the context of Indonesia, malaria research encompasses various areas, including: The field of epidemiology in relation to malaria encompasses the objectives of monitoring and assessing the trends and patterns of malaria cases and fatalities, identifying the factors that contribute to the transmission of the disease, and mapping the distribution and prevalence of malaria parasites and vectors. This approach facilitates the strategic distribution of resources, the prioritization of areas with high risk, and the customization of actions based on specific local circumstances.As an illustration, the study titled "Assessment of Malaria Risk Factors in Aceh Besar, Indonesia: Utilizing Active and Passive Surveillance Data in a LowEndemic Malaria Elimination Context with *Plasmodium knowlesi*, *Plasmodium vivax*, and *Plasmodium falciparum*" was conducted by Herdiana et al. in 2016. 2) The objective of malaria research in Indonesia is to enhance the precision, sensitivity, specificity, and cost-effectiveness of malaria diagnostic techniques, with a particular focus on distant and resource-constrained environments. This practice aids in guaranteeing prompt and suitable medical intervention, mitigating the occurrence of problems and fatalities, and diminishing the proliferation of medication resistance. For example, a research about evaluated the performance of a novel rapid diagnostic test (RDT) that can detect low-density *Plasmodium falciparum* and *Plasmodium vivax* infections in Mimika Regency, Papua, Indonesia (Fransisca et al. 2015). 3) Treatment: The focus of malaria research in Indonesia is to enhance the effectiveness, safety, tolerability, and adherence of malaria treatment protocols, with particular emphasis on drug-resistant strains and groups at high risk. This intervention facilitates the recovery of patients, mitigates the risk of relapses and recrudescence, and diminishes the likelihood of transmission.

An illustrative study was conducted by Kenangalem et al. (2019) to assess and compare the effectiveness and safety of two artemisinin-based combination treatments (ACTs) in the treatment of uncomplicated malaria. Another area of research in malaria is focused on vector control, disease surveillance, prevention, and program management. Malaria is a significant public health challenge in developing nations such as Indonesia. According to the Indonesian Basic Health Research, there was a 6.0% increase in malaria cases in 2013 compared to 2012, with a higher prevalence observed in eastern regions of Indonesia. According to available data, a significant proportion of Indonesia's administrative divisions, specifically 54% of its 497 districts and cities, are characterized by a high prevalence of malaria. According to Hasyim et al. (2019), it has been observed that malaria is endemic in five out of the thirty-three provinces in Indonesia, namely Sulawesi Tengah, Nusa Tenggara Timur, Maluku, Papua, and Papua Barat. The probability of contracting malaria can be heightened by many risk factors, with a notable emphasis on the availability and utilization of basic healthcare services. The dissemination of knowledge regarding malaria and the provision of aid to afflicted patients are imperative responsibilities for healthcare practitioners. Various medical facilities such as government hospitals, private hospitals, primary health services (puskesmas), clinics, midwife practices, posyandu, village health posts, and village maternity clinics can be utilized to prevent the transmission of malaria to individuals within the community. The successful eradication of malaria necessitates the implementation of basic healthcare services within the community and its associated network. This healthcare holds particular significance for individuals who are vulnerable to this illness, including pregnant women, infants, and young children (Hasyim et al. 2019).

There are several other febrile conditions, such as dengue fever, typhoid fever, the common cold, respiratory infections, dyspepsia, and pneumonia, that exhibit symptoms similar to those of malaria. This paper discusses the methodologies employed for the detection of malaria in individuals, encompassing parasitology, microscopy, and rapid diagnostic tests. Nevertheless, there are certain areas where parasitology testing is not yet available, hence posing challenges in the detection of malaria and elevating the likelihood of erroneous diagnosis and inappropriate presumptive therapy. As a consequence of these issues, individuals may inadvertently consume inappropriate antimalarial drugs due to a limited comprehension of crucial malaria symptoms and non-symptom-based criteria utilized in the clinical diagnosis of malaria. The aforementioned matter is also considered a noteworthy concern that motivates scholars to investigate prominent symptoms of malaria. The objective is to utilize these symptoms as a foundation to assist healthcare practitioners in the clinical identification of malaria and to enhance public awareness. This, in turn, enables individuals to adopt measures to protect their well-being and maintain a malaria-free environment (Bria et al. 2020).

The epidemiology of Malaria in Indonesia

The prevalence and distribution of Malaria

Malaria, an infectious disease of significant global concern, presents a substantial obstacle to public health worldwide. Based on the extant records, it has been noted that this specific sickness demonstrates endemic attributes in a collective of 87 countries, including Indonesia as one of the afflicted nations. Indonesia is classified as one of the poor countries within the Association of Southeast Asian Nations (ASEAN) that demonstrates a significantly elevated prevalence of malaria. Preceding the year 2007, an estimated 80% of the nation's rural regions and urban hubs have received official declarations of being malaria-free. According to Budiarti et al. (2020), there was a decrease in the incidence of malaria from 2.9% in 2007 to 1.9% in 2013. According to the statistics presented by the Ministry of Health of the Republic of Indonesia, it has been noticed that the region of Papua, which is known for its high prevalence and widespread occurrence of malaria, accounts for around 97% of the overall reported cases of malaria in Indonesia (Lusiyana and Ahdika 2022). According to Fadilah et al. (2022), Indonesia has become a significant area of concern for malaria within the South-East Asia region of the World Health Organization. This is evident from the estimated statistics of 784,854 cases and 1443 fatalities expected for the year 2020. Since the commencement of a malaria eradication campaign in Indonesia in 2009, there has been a sustained reduction in the prevalence of the disease in the western regions of the nation. As of the year 2020, a total of more than 300 districts and municipalities have successfully attained the designation of being free from malaria. Nevertheless, there has been a recent development stemming from the widespread occurrence of zoonotic malaria in Sumatra and Kalimantan, which correspond to the Indonesian region of Borneo (Lempang et al. 2022). The provinces of West Papua and Papua, situated in the Papua Region, are presently contending with a notable escalation in the transmission rate of the virus. Based on the findings of Fadilah et al. (2022), it was seen that in the year 2020, the two provinces under consideration were associated with approximately 90% of the reported cases on a national level. The Indonesian province of Papua has officially documented a total of 2,046,833 cases of malaria during the years 2011 and 2020. Among the overall number of reported cases, a significant majority of 1,820,566 instances (accounting for 89% of the total) were found in Papua, and the remaining 266,267 cases (representing 11% of the total) were recorded in West Papua. *Plasmodium falciparum* and *Plasmodium vivax* have been identified as responsible for approximately 90–95% of the aforementioned diseases. Fadilah et al. (2022) attributed the remaining instances to *P. malariae* and *P. ovale*. The geopolitical boundary between the Indonesian state of Sabah and the northernmost province of North Kalimantan is situated on Sebatik Island. Sebatik Island is recognized as one of the regions in Nunukan District that is endemic to malaria. Based on the findings of the Health Agency of Nunukan District (2010), there was an observed rise in the Annual Malaria Incidence (AMI) from 10.58 cases per 1000 individuals in 2008 to 12.53 cases per 1000 individuals in 2009. According to a study conducted by Sugiarto et al. (2017), it was found that in the year 2013, a total of 61 individuals out of the population of 7525 residents in Sungai Nyamuk Village tested positive for *P. falciparum*. The incidence rate of *P. falciparum* in this population was reported to be 8.11 per 1000 persons. The annual incidence of malaria parasites in North Sumatera was recorded as 0.07 in the year 2020. As of the year 2020, a total of 21 out of the 33 regencies/cities have been officially recognized as malaria-free. According to Fahmi et al. (2022), the prevalence of zero counts for *P. falciparum* and *P. vivax* was 1477 out of 1584 (93.3%) and 1387 out of 1584 (87.6%), respectively. The Asahan Regency, situated in the North Sumatra Province, exhibits a notable incidence of malaria. Nevertheless, it is anticipated that via the implementation of various strategies, the region would achieve the eradication of malaria by the year 2020, so transforming it into an area free from the burden of malaria. In a study conducted by Sembiring et al. (2020), it was noted that there was a documented rise in the incidence of malaria in Asahan District between the years 2010 and 2014, culminating in a prevalence rate of 3.38% or a total of 2,389 reported cases. Between the years 2015 and 2017, there was a notable decline in the incidence of malaria, as evidenced by a morbidity rate of 0.65% or a total of 469 reported cases. The aforementioned statistics indicate that Asahan Regency exhibits the greatest rates of morbidity compared to other districts and cities within North Sumatra Province.

Regions and populations at elevated risk

Malaria is a prominent global health concern, particularly in regions with tropical climates, despite sustained international efforts to address the disease (Bria et al. 2020). Based on data provided by the Ministry of Health of the Republic of Indonesia, it is evident that Papua demonstrates a substantial prevalence and widespread distribution of malaria, as shown by an Annual Parasite Index (API) value exceeding 5 per 1000 individuals (Lusiyana and Ahdika 2022). The provinces of East Nusa

Tenggara, Central Sulawesi, Maluku, Papua, and West Papua have the highest prevalence rates of malaria. Furthermore, the provinces of Papua and West Papua, which are the largest provinces located on the island of Papua in Indonesia, exhibit an estimated annual parasite incidence (API) rate of approximately 67%. The province of Papua exhibits notable variations in air quality, as seen by the Air Pollution Index (API) indicators. The regions of Keerom, Jayapura, Timika, Sarmi, and Boven Digoel Regency stand out as the five areas with the highest API readings. According to Budiarti et al. (2020), the three districts in West Papua that demonstrate the highest API indicators are Manokwari, South Manokwari, and Wondama Bay Regency. The likelihood of recurring episodes of malaria is dependent on various variables. The aforementioned characteristics include age, gender, ethnicity, employment status, and a prior known risk factor for malaria, specifically, a familial susceptibility to the disease (Lusiyana and Andhika 2022). The increased prevalence of malaria in Papua and West Papua can be ascribed to a variety of factors. Factors contributing to the persistence of disease-causing parasites include the emergence of treatment-resistant strains, insufficient governmental initiatives, particularly in underdeveloped countries, and a dearth of healthcare infrastructure in remote areas (Budiarti et al. 2020). The province of North Sumatera is situated in the northern section of the island of Sumatra, Indonesia. Fahmi et al. (2022) assert that Medan functions as the nation's capital and principal metropolitan hub. In terms of geographical location, it is situated at coordinates 0.589°S, 101.0°E. In the year 2016, the province of North Sumatra exhibited the greatest prevalence of malaria cases compared to other regions including the island of Sumatra. Hakim et al. (2018) reported that North Sumatra Province is positioned as the fifth province with the highest malaria prevalence among the provinces of Papua, NTT, Papua West Papua, Maluku, and North Sumatra in Indonesia. The geographical region in the eastern part of Northern Sumatera has been recognized as the focal location where both endemic and imported cases of malaria are concentrated. The eastern section of the island in North Sumatera stands out due to its coastline terrain and significant population density, distinguishing it from other regions within the province. The location of the site is characterized by the presence of wetland areas, river systems, and the Hindia ocean in its vicinity. The primary occupations in this geographical area consist of fishing and agricultural pursuits. There exists a subset of persons that demonstrate an increased vulnerability to contracting malaria, as indicated by Fahmi et al. (2022). The data can be seen in the Fig. 1.

Present approaches in the treatment of Malaria

Primary antimalarial medications

Artemisinin-based Combination Therapy (ACT) is widely employed as the primary and secondary treatment strategy for malaria in numerous regions affected by the disease. The ACT regimen is composed of a synergistic blend of artemisinin or its derivatives, along with other pharmacological agents known as partner medicines, as explicated by Arya et al. in their scholarly publication of 2021. The standard first-line treatment for malaria, known as ACT (Artemisinin-based Combination Therapy), combines a powerful artemisinin derivative with a companion medicine that has a longer duration of action. Prominent instances encompass artemether–lumefantrine (CoArtem) and amodiaquine–artesunate (Coarsucam) as indicated

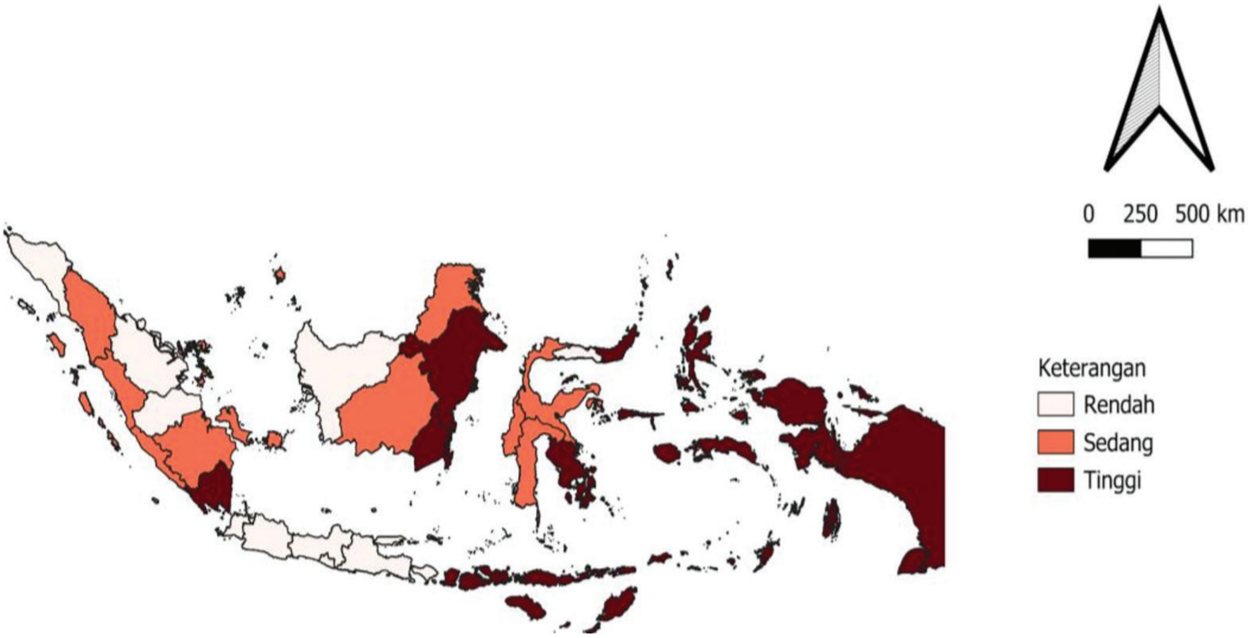


Figure 1. High risk region and populations of malaria in Indonesia. (The data from the Ministry of Health, Republic of Indonesia, 2019).

by Ecker et al. (2012). Within the historical framework of Africa, it has been a prevailing practice to recommend a singular predominant therapeutic intervention or pharmaceutical agent for the management of uncomplicated malaria. In response to the escalating levels of drug resistance, the predominant strategy has been to substitute the existing medication with a newly developed alternative that remains unaffected by resistance. This scenario is demonstrated by the case observed in Kenya. The replacement of chloroquine with sulfadoxine-pyrimethamine as the predominant therapeutic strategy took place in the year 1998. During the time frame from 2004 to 2006, artemether-lumefantrine, an artemisinin-based combination therapy (ACT), replaced sulfadoxine-pyrimethamine as the preferred treatment option. The approach outlined above, known as the “wait-and-switch” strategy, presents significant obstacles for monitoring networks and public health systems in economically disadvantaged nations. Based on the study conducted by Boni et al. (2008), it has been shown that this specific methodology yields suboptimal outcomes in terms of both morbidity and mortality. A potentially more sustainable approach would involve the proactive utilization of presently accessible antimalarial drugs to decrease both mortality and morbidity, while concurrently delaying the emergence of resistance and the incidence of treatment failures. The global treatment of malaria cases is now guided by the World Health Organization (WHO), which recommends six various Artemisininbased Combination Therapies (ACTs). The antimalarial drug combinations that have been identified are as follows: a) the combination of artesunate and amodiaquine, b) artemether paired with lumefantrine, c) artesunate combined with sulfadoxinepyrimethamine, d) artesunate in conjunction with mefloquine, e) artesunate together with pyronaridine, and f) dihydroartemisinin jointly administered with piperaquine. The utilization of multiple artemisinin-based combination therapies (ACTs) is a fundamental aspect of the therapeutic approaches implemented by different nations facing the challenge of malaria prevalence (Arya et al. 2021). Indonesia has notably adopted a primary therapeutic strategy, utilizing artemisinin-based combination therapies (ACTs) that consist of artesunate and amodiaquine (Mutabingwa 2005).

Secondary and alternative therapeutic approaches

The need of conducting follow-up assessments to determine the prevalence of susceptible strains among malaria patients is underscored by the utilization of secondline treatment for drug-resistant malaria in artemisinin-based combination therapy (ACT). The present analysis observed that all identified SNPs related to the transcription factor (TF) were shown to be linked with the artemether derivative’s companion medicine. Furthermore, a meta-analysis performed by Arya et al. (2021) unveiled that the utilization of artesunate and sulfadoxine-pyrimethamine exhibited a greater propensity for the creation of drug resistance when contrasted with lumefantrine. In contrast, it was shown that the utilization of dihydroartemisinin and piperaquine resulted in a comparatively reduced risk as compared to lumefantrine. There was no statistically significant variation detected among the different combinations of lumefantrine with artesunate and mefloquine, artesunate and amodiaquine, and artesunate and sulfadoxine-pyrimethamine. Hence, in countries where the adoption of artemisinin-based combination therapy (ACT) is lacking, a plausible approach to address the emergence of resistance to ACT may involve the utilization of dihydroartemisinin and piperaquine, as it demonstrates the lowest probability of resistance development to artemisinin-based treatments. An alternative strategy to maintain the efficacy of artemisinin-based combination therapy (ACT) would entail the intermittent utilization of alternative antimalarial medications, such as chloroquine, in areas where the efficiency of ACT has been seen to be reduced. Laufer et al. (2006) documented the reemergence of plasmodial susceptibility to chloroquine in Malawi subsequent to the discontinuation of this antimalarial medication. This finding suggests that the reintroduction of chloroquine, in conjunction with other drugs as part of artemisinin-based combination therapy (ACT), may present a promising strategy for primary treatment in these regions. Furthermore, it is important to acknowledge that the implementation of Artemisininbased Combination Therapies (ACTs), which incorporate numerous partner medications, commonly known as "triple ACTs," has generated considerable debate. The study conducted by Arya et al. (2021) has recently examined and urged for the implementation of this alternate technique.According to a study conducted by Rahmalia et al. (2023) in Papua, a significant proportion of the study participants demonstrated a prevailing belief in the effectiveness of biomedical interventions for the management of malaria. In contrast, the utilization of traditional or herbal remedies was perceived as supplementary in nature, primarily aimed at alleviating symptoms rather than being considered a curative strategy. A wide range of nettles was administered externally to the skin, resulting in sensations of itching or heat, with the main objective of alleviating joint pain and overall physiological discomfort. It is worth mentioning that a few of persons deliberately grew these nettles in their private gardens. One particular type of nettle, known as Laportea decumana, was frequently found in local markets, where it was typically sold by vendors from highland Papuan villages. Moreover, it has been noted that bloodletting was a prevalent tradition among highland communities, utilized with the purpose of alleviating localized discomfort, such as by extracting blood from the forehead to treat migraines. The antimalaria drug action can be seen in the Table 1.

Obstacles in the accessibility and adherence of treatment

Based on the findings of the 2013 Riskesdas survey, it has been found that individuals living in urban regions, where Artemisinin-based Combination Therapy (ACT) is easily available, have somewhat higher rates of treatment compared to individuals live in rural areas, as described by Kinansi et al. in 2021. Moreover, a research conducted by Rahmalia et al. (2023) in the Papua region reveals that the mining corporation has contributed to the improvement of malaria treatment accessibility. The aforementioned improvement is demonstrated by the facilitation of complimentary healthcare services to the Kamoro and Amungme communities, as well as five other indigenous groups residing in highland areas, namely the Damal, Dani, Mee, Moni, and Nduga populations. These groups are recognized as being directly affected by mining operations. Mutabingwa (2005) highlighted notable obstacles in the acceptability and implementation of Artemisinin Combination Therapies (ACTs) in the context of malaria control. The challenges included increased expenses, higher rates of malaria transmission, a significant number of asymptomatic infections among individuals with partial immunity, improper use of pharmaceutical drugs, inadequate diagnostic infrastructure and capabilities, a lack of knowledgeable policy-makers, and weaknesses in public health systems. This study employed a comprehensive mixed-methods approach to examine the extent to which patients adhere to the radical curative treatment for Malaria. The results provide valuable insights into the important findings within the subject area. There are two key findings in Rahmalia et al.'s recent study in 2023. Firstly, ethnicity plays a significant role in determining adherence to treatment, thereby impacting its effectiveness. Secondly, individuals' perceptions and experiences with healthcare providers from diverse backgrounds have a significant influence on treatment outcomes.

The qualitative component of Rahmalia et al.'s (2023) study sheds light on how structural factors related to ethnicity can help explain the differences in treatment adherence that are reported among various ethnic groups. The Papuan population experiences significant social and economic marginalization, resulting in limited educational

Table 1. Summary of Some Antimalarial Drugs, Mechanism of Action, Site of Action, and Mechanism of Resistance (Shibeshi et al. (2023)).

Antimalaria drugs	Mechanism of action	Site of action	Mechanism of resistance
Antifolates (pyrimethamine and cycloguanil)	Inhibitor of dihydrofolate reductase (DHFR)	Cytosol	Mutations of dihydrofolate reductase
Antifolate (sulfadoxine)	Inhibit Dihydropteroate synthetase	Cytosol	Dihydroteroate synthetase (DHPS)
Naphthoquinones (Atovaquone)	Inhibits mitochondrial electron transport	Inside the apicoplast	A single point mutation in the cytochrome b subunit (CYTb) of the bc I complex
Antibiotics (Clidamycin and Doxycycline)	Inhibit protein and lipids	Er, Vesicular structures	A point mutation in the apicoplast encoded 235 rRNA (CLD)
Artemisinin (ART)	Alkylation of proteins and lipids	ER, vesicular structures	Mutation in K13

and vocational opportunities compared to non-Papuan individuals. In order to address this concern, there is potential in implementing a strategy that involves community health workers who reside within the same village or neighborhood as the individuals requiring treatment. These community health workers can provide oversight and support, tailoring their visitation schedules and explanations of medication to align with the socio-ethnic background of the patients. This approach shows promise as a means of mitigating the issue at hand. Within the complex sociocultural context being examined, there exists a phenomenon wherein individuals often engage in self-diagnosis of malaria by assessing their own symptoms. In general, individuals tend to see a healthcare professional more than 24 hours after the initial appearance of symptoms. This is mostly done to validate their self-diagnosis and acquire suitable medical intervention. It is important to highlight that, similar to many other countries, Indonesia lacks a sufficient number of studies that investigate the epidemiology of febrile diseases. The implementation of point-ofcare diagnostic technologies for different etiologies of fever has the potential to improve the effectiveness of malaria control initiatives. The choice of a healthcare provider is influenced by various factors, such as familiarity, the financial costs connected with treatment and transportation, waiting times, and the perceived quality of healthcare services. Prior to seeking medical advice, patients often assess the intensity of their symptoms by self-administering therapies using leftover prescriptions from past illnesses or easily accessible over-the-counter remedies. Moreover, the application of herbal topical and oral remedies functions as supplementary approaches in mitigating symptoms, rather than acting as replacements for biological treatment modalities. Rahmalia et al. (2023) reported on the impact of supervision strategy on adherence. In the supervised arm of the investigation, qualitative investigations unveiled that both participants in the trial and the staff responsible for field supervision shared the perception that the supervised treatment schedule of alternating days was suboptimal. The participants' reliance on face-to-face interactions with field supervision workers for the purpose of obtaining their tablets was identified as the cause of this phenomenon. If persons are not present at their residence during supervision visits, they would be unable to administer the necessary amount for that specific day.

Prospective approaches for Malaria management

The emergence of drug therapies and vaccines

Alongside the utilization of pesticides and malarial treatments, some adverse societal and economic factors play a role in the dissemination of malaria. The emergence of drug resistance poses a significant challenge to the eradication of malaria. It is widely recognized that the existing tools at our disposal are inadequate to attain complete eradication. Presently, the field of malaria biology relies on the use of "single-omics" methodologies in conjunction with state-of-the-art technology. Each stratum of omics data generated establishes unique associations with this pathogenic condition (Zhou et al. 2021). The advancements in "single-omics" techniques have resulted in a wide range of novel targets, including molecular markers, that can be utilized for the diagnosis of malaria. However, at present, our comprehension of the biological aspects of malaria remains insufficient. The comprehensive elucidation of all relevant molecular pathways is limited by the inherent constraints of "single-omics" methodologies, shown by the genetic variants of malaria identified through genomewide association studies (GWAS). Given the aforementioned evidence, it is imperative to employ "multi-omics" methodologies to augment our understanding of the intricate dynamics of molecular and cellular information in both *Plasmodium* and infected human hosts. In recent times, the field of malaria research has witnessed the effective utilization of "multi-omics" methodologies. The majority of participants endeavored to establish connections between many data levels simultaneously. Several prior studies have employed advanced computational methods to reveal previously unnoticed or undiscovered hidden structures related to "multi-omics" from highly informative information. Several studies using mosquitoes also employed "multiomics" approaches. According to Zhou et al. (2021), the utilization of "multi-omics" data has the potential to facilitate the development of novel drugs and vaccines, leading to the exploration of personalized approaches in the clinical management of malaria. This approach has promise in addressing the current challenge of drug resistance. To facilitate the advancement of novel antimalarial therapeutics, it is imperative to tackle challenges associated with drug resistance, liver stage infections, sexual plasmodial blood in individuals, transmission-blocking interventions, and relapse prevention. In 2018, the Food and Drug Administration (FDA) granted authorization for tafenoquine (TQ) as one of the newly approved drugs. In the context of avoiding relapses caused by *P. vivax*, the efficacy of the intervention in inhibiting heme polymerase during the blood stage surpasses that of its predecessors. The medications for malaria venture (MMV) has identified novel treatment options that show promise in terms of both product development and clinical evaluation. Natural products have been described as a valuable resource with significant potential for the advancement of medicine. Ethnopharmacology is regarded as a highly promising approach in the development of anti-malarial medications, since it serves as a valuable avenue for accessing indigenous information pertaining to herbal remedies. The antimalarial efficacy of phytochemicals derived from traditional medicine, including flavonoids, terpenoids, phenolics, coumarins, steroids, quinones, xanthones, and alkaloids, has been proven (Zhou et al. 2021). The RTS,S vaccine has emerged as the initial malaria vaccine to successfully undergo clinical trials. The presence of the circumsporozoite protein (CSP) can be observed in a recombinant fusion protein

(RTS) that has been employed in this particular vaccine (Zhou et al. 2021). Presently, there are ongoing efforts to create several types of vaccines, including RTS,S vaccines like R21, as well as other anti-infective vaccines such as attenuated or irradiated whole sporozoite vaccines (PSPZ). Over the course of several decades, extensive efforts have been dedicated to the advancement of anti-infective vaccines. Notably, monoclonal antibodies have emerged as a promising class of therapeutic agents, exhibiting substantial anti-infective properties. The identification of new targets and chemistries for malaria vaccines is an ongoing requirement. However, thus far, the health advantages derived from allocating resources to clinical trials and the development of vaccines have not been deemed sufficient to warrant the associated expenses (Penny et al. 2020).

Novel approaches to vector control measures

Numerous strategies have been employed in the administration of diseases transmitted by mosquitoes. However, the implementation of vector control remains a crucial component in several disease control endeavors. Throughout the course of history, the prevailing methodology for successfully eliminating malaria in diverse geographical areas worldwide has predominantly centered on the implementation of vector control measures. According to Ogunah et al. (2020), copper aceto arsenite and pyrethrum were utilized as larvicides in Brazil for the aim of pest control. The overview of Overview of vector-control tools for malaria control can be seen in Table 2.

Enhancing the resilience of healthcare infrastructure

The available literature indicates that the degree to which hospitals may effectively contribute to the improvement of primary healthcare (PHC) is highly contingent upon the particular circumstances. Nevertheless, these contributions can be broadly classified as a continuum that spans a range of activities. The activities encompass a spectrum of interventions, including the direct delivery of healthcare services and outreach initiatives that target the problem of restricted availability of high-quality primary care. Additionally, efforts are made to improve the provision and demand for frontline primary care services, such as gatekeeping and practical support. Furthermore, it is worth noting that hospitals have the potential to contribute to the advancement of integrated care, a concept that seeks to enhance the seamless and well-coordinated delivery of healthcare services to individuals (Freijser et al. 2023). Hospitals possess the capacity to function as "systems-focused hospitals" through acknowledging the interrelatedness and the necessity of engaging in collaboration with other components of the healthcare system to achieve these goals. The framework outlined in the preceding section has been constructed using an iterative approach, using pertinent scholarly sources and complemented by data gathered from a case study of a specific nation. The degree to which hospitals contribute to the improvement of primary healthcare (PHC) in different capacities is dependent on multiple factors. The elements in question cover the accessibility to primary care services at the forefront, the quality of these services, the degree of integration within the wider healthcare system, and the overall orientation of the health system, which may prioritize prevention, community-based care, or population health.

Potential herbal interventions

Traditional herbal remedies in indonesian culture

The development of innovative antimalarial medications that demonstrate strong efficiency against plasmodium parasites is currently a pressing requirement. Compounds originating from botanical sources have been exploited for therapeutic purposes since ancient times and are now included as ingredients in modern pharmaceutical formulations. A significant advantage linked to the application of chemical compounds derived from medicinal plants in the development of innovative pharmaceuticals is their considerable propensity to bind to biological receptors present in the human body. Indonesia, as a nation, harbors a diverse array of plant species that exhibit promising properties as antimalarial agents. The plant materials utilized in this study consist of the leaves of puspa (*Schima wallichii* Kort), senai (*Wedelia bifora*), and kembang bunga (*Tithonia diversifolia* (Hemley) A Gray), as well as the bark of cempedak (*Artocarpus champeden* Spreng), papaya leaves (*Carica papaya*), and the leaves of sambiloto (*Andrographis paniculata* Nees) (Alkandahri et al. 2018; Teng et al. 2019). The short summary of medicinal plant againts malaria can be seen in Table 3.

Scientific evaluation of herbal anti-malaria agent

Puspa leaves (*Schima wallichii kort*)

Barliana et al. have conducted a study to investigate the antimalarial properties of puspa leaves. The majority of activities primarily take place inside a fraction of ethyl acetate. The component present in the ethyl acetate fraction has been characterized using various spectroscopic techniques, including infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR), and liquid chromatography-mass spectrometry (LC-MS). The analysis has revealed the presence of a flavonoid complex known as 5,7,4'-trihydroxy-3-β-ramnoside flavon. The active molecule known as kaempferol-3O-rhamnoside exhibits the potential to effectively hinder the growth of parasites.

Specifically, it demonstrates a reduction in parasitic growth of 54.3% after 24 hours of incubation, 83.9% after 48 hours of incubation, and an impressive 96% after 72 hours of incubation, when compared to a controlled trial.

Table 2. Overview of vector-control tools for malaria control (Takken and knols (2023)).

Method	Mechanism
House improvement	Prevention of house entry
Indoor residual spraying (IRS)	Repellent and/or killing of adult mosquitoes
Long-lasting insecticide-treatednets (LLITNs)	Repellent and/or protection against biting; killing of adult mosquitoes
Entomopathogenic fungi	Slow killing
Entomopathogenic viruses	killing
Removal trapping and/or confusion techniques	Reduction of mosquito abundance
Spatial repellents	Prevention against biting
Genetically engineered mosquitoes	Prevention of parasite development in mosquito; reduction of longevity
Sterile insect technique	Reduction or eradication of mosquito population
Environmental modification (e.g. larval habitat modification)	Prevention of oviposition and/or larva development (e.g. stream clearing)
Bacillus thuringiensis israelensis or Bacillus sphaericus	Killing of larvae
Insect-growth regulators	Killing of larvae
Predators (fish)	Killing of larvae

Table 3. Short summary of medicinal plants againts malaria.

Name of plant	Active compound	Mechanism of Action
Puspa leaves (*Schima wallichii* Korth.)	Kaempherol-3-Orhamnosida	Antimalaria
Sernai leaves (*Wedelia biflora*)	Kaur-16-en-18-oic acid.	Antimalaria
Kembang bulan leaves (*Tithonia diversifolia* (Hemley) A. Gray)	Tagitinin C.	Antimalaria
Bark of cempedak (*Artocarpus champeden* Spreng.)	Heteroflavanon C.	Antimalaria
Sambiloto leaves (*Andrographis paniculata* Nees.)	Andrographolide	Antimalaria
Papaya leaves (*Carica papaya*)	Carpaine	Antimalaria

A prior investigation conducted by Muhtadi et al. demonstrated the antimalarial effects of puspa leaves derived from the ethyl acetate fraction, buthanol fraction, and ethanol extract. The effective doses (ED50) for these fractions were found to be 72.81, 122.87, and 358.13 mg/kg body weight, respectively. Kaempferol-3-O-rhamnoside, being classified as a polyphenol, exhibits the capacity to impede the process of lipid peroxidation as well as suppress the activity of cyclooxygenase enzymes, specifically COX-1 and COX-2. Therefore, it is possible to propose that the observed antiplasmodial activity of kaempferol-3-Orhamnoside may be attributed to its antioxidant capabilities (Alkandahri et al. 2018).

Senai leaves (*Wedelia biflora*)

A study conducted by Isa has demonstrated that the methanol extract derived from sernai leaves have the capability to suppress the tropozoite stage of *Plasmodium falciparum*. The observed impact is hypothesized to be attributed to the presence of a triterpenoid molecule in sernai leaves. In an experimental analysis employing Gas Chromatography-Mass Spectrometry (GC-MS), a total of 45 distinct compounds were detected. Among these compounds, the one exhibiting the highest concentration, amounting to 27.92%, was recognized in the database as kaur-16-en-18-oic acid. The bioactivity test findings for the antiplasmodium effect in vivo indicate that the extract derived from sernai leaves exhibits activity, as evidenced by an ED50 value of 39.952 mg/kg BW. The antiplasmodium activities of the methanol extract of sernai leaf were demonstrated in previous in vitro studies conducted by Isa et al. and Rinidar et al. These studies found that the IC50 value of the extract was 5.253 µg/ml after 32 hours of incubation (Alkandahri et al. 2018).

Kembang Bunga leaves (*Tithonia diversifolia* (Hemley) A Gray)

The presence of tagitinin C, a sesquiterpene lactone, has been detected in the extract of kembang bulan leaves. This chemical has demonstrated significant antiplasmodium activity, namely against the FCA strain of *P. falciparum*, with an IC50 value of 0.75 µg/mL. In a laboratory-based investigation, Afiyah conducted a study to examine the antiplasmodium properties of the ether fraction of the methanol extract derived from kembang bulan leaves. The study specifically focused on its ability to block heme polymerization in the *P. falciparum* FCR-3 strain. Basilico et al. demonstrated that the inhibitory effects on heme polymerization can be attributed to one or two mechanisms. Firstly, the interaction between terpenoid, phenol, and sterol compounds with the heme electrolysis system plays a significant role. Secondly, chemicals containing hydroxyl groups have the ability to attach to heme iron ions, contributing to the inhibitory qualities (Alkandahri et al. 2018).

Bark of Cempedak (*Artocarpus champeden* Spreng)

The research conducted by Widyawaruyanti et al. reveals that the dichloromethane extract of cempedak bark shell resulted in the isolation of nine compounds, two of which were identified as novel compounds. Additionally, this work aims to investigate the in vitro antimalarial activity of nine compounds derived from the fractionation and separation of dichloromethane extracts produced from cempedak bark. According to this stipulation, the flavonoid component derived from the isolated dichloromethane extract of cempedak bark has antimalarial properties. The chemical heteroflavanone C exhibits the most potent antimalarial activity, as evidenced by its IC50 value of 0.001 μM. According to the available report, it has been observed that the IC50 value of conventional chloroquine antimalarial medications is 0.006 μM. The antimalarial characteristic of the heteroflavanone C compound is hypothesized to be enhanced by the incorporation of an isoprene chain at the C-8 position. The inclusion of an isoprenyl moiety in heteroflavanone C results in an increased hydrophobicity and lipophilicity, enabling it to effectively traverse the parasite cell membrane and exert its antimalarial properties. Hence, it may be inferred that heteroflavanon C exhibits a greater antimalarial efficacy compared to chloroquine. This observation implies that heteroflavanon C holds greater promise as a prospective alternative to chloroquine, which has lost its effectiveness as an antimalarial medicine (Alkandahri et al. 2018).

Sambiloto leaves (*Andrographis paniculata* Nees)

According to a study conducted by Mishra, it was found that the combination of andrographolide with curcumin and artesunate exhibited a synergistic effect. In the in vivo experiment, it was observed that andrographolide-curcumine had an 81% greater antimalarial efficacy compared to the control group. Furthermore, this compound demonstrated the ability to extend the lifespan of the subjects by 2–3 times. According to the study conducted by Gudhate et al. a lactone component has been identified in the sambiloto leaf of andrographolide. Andrographolide is classified as a member of the trihidroksilactone group, characterized by its chemical formula C20H30O5. According to Risdawati, the antimalarial feature of andrographolide is attributed to its mode of action, which involves the disruption of the parasite's antioxidant defense system. This is supported by the observed drop in glutathione (GSH) content and the activity of the enzyme thioredoxin reductase (TrxR) (Alkandahri et al. 2018).

Papaya leaves (*Carica papaya*)

Historically, Carica papaya has been widely utilized in the therapeutic management of several medical conditions. Various components of the plant provide distinct therapeutic properties, with the leaves commonly employed in the treatment of ailments such as malaria, dengue, and jaundice, owing to their antiviral and immunomodulatory attributes. Furthermore, many chemical constituents have been identified in distinct anatomical regions of this botanical specimen, encompassing flavonoids, alkaloids, phenolic compounds, β-carotene, lycopene, anthraquinone glycosides, and other substances. In their study, Teng et al. (2019) conducted scientific research to investigate the possible utilization of this particular plant as an antimalarial agent. The researchers tested the efficacy of the plant against two strains of *Plasmodium falciparum*, namely 3D7 parasites and Dd2 strains. The findings demonstrated a moderate level of antimalarial activity. The substance accountable for this particular activity is known as carpaine, which falls under the category of alkaloids. Multiple studies have additionally demonstrated the plant's efficacy in exhibiting anti-inflammatory, anticancer, and antihypertensive characteristics, while also being utilized for the treatment of hypoglycemia, fertility issues, and wound healing. the antimalarial activity of carpaine is possibly due to a direct inhibitory action on parasite rather than non-selective toxicity to host and target cells (Teng et al. 2019; Budiarti et al. 2020).

Integrating traditional and modern approaches

Throughout history, natural compounds have held a significant and enduring role in pharmaceutical research and development, particularly in the exploration of antimalarial drugs. Notable examples of antimalarial drugs derived from natural sources include quinine, obtained from the Cinchona plant, and artemisinin, extracted from the Artemisia plant. A study by Newman and colleagues (2016) revealed that over 60% of newly discovered antiparasitic compounds between 1981 and 2014 had their roots in natural compounds. This underscores the substantial contribution of these natural compounds to drug development. Over time, antimalarial drugs like quinine, chloroquine, amodiaquine, sulfadoxine-pyrimethamine, mefloquine, piperaquine, and halofantrine have encountered a common fate—*Plasmodium* parasites developing clinical resistance in specific geographic regions, leading to the spread of resistance globally (Roman et al. 2019). Presently, artemisinin derivatives, such as artesunate, artemether, and dihydroartemisinin (DHA), are the primary therapeutic drugs for malaria treatment. Both monotherapy and artemisinin combination therapies (ACT) are employed, combining artemisinin-based drugs with longer-acting antimalarials like amodiaquine, piperaquine, mefloquine, or sulfadoxine-pyrimethamine (Shah and Valecha 2016). Concerns have arisen about multidrug resistance and increased resistance to ACT, particularly in the Cambodia-Thailand border region (Dondorp et al. 2009). It is widely accepted in the scientific community that quinine, chloroquine, mefloquine, and amodiaquine, as well as 4substituted quinolines, share a similar mechanism of action against *Plasmodium* parasites. These drugs enter the parasite's acidic digestive vacuole and disrupt the conversion of heme into non-toxic hemozoin, leading to the accumulation of toxic heme and the parasite's demise (Egan 2008). *Plasmodium* parasites can develop resistance to conventional antimalarials through mutations in drug targets or changes in drug transporters (Bras and Durand 2003; Petersen et al. 2011). In the past two decades, extensive efforts have been made to develop more effective chloroquine derivatives. Modifications to the side chain, including the incorporation of various heterocyclic structures, have been successful while retaining the desired biological activity. The quinoline core, serving as the pharmacophore, has remained consistent. These modified structures, often referred to as "hybrid structures," aim to introduce a dual mode of action that could potentially overcome resistance mechanisms (CQresistant). While many hybrid structures have demonstrated strong antiplasmodium effects against chloroquine-resistant *Plasmodium falciparum*, there may be limited experimental evidence to attribute the enhanced activity to a dual mechanism. Nonetheless, these innovative chloroquine analogs with functionalized side chains show promise for developing novel antimalarial drugs (Walle et al. 2020). The author's primary goal in this context was to synthesize quinoline derivatives with a piperidine moiety in their side chains, inspired by the structural features of quinine and mefloquine. Piperidine, as a heterocyclic structure in antimalarial quinoline analogs, has been relatively understudied compared to other heterocycles like triazine, triazole, and pyrimidine. The inclusion of a piperidine moiety is believed to enhance the drug's uptake and retention within the acidic digestive vacuole, following a mechanism similar to quinine and mefloquine. The author chose bridging and monocyclic functionalized piperidine scaffolds for conjugation with various quinoline cores. This article outlines the synthetic procedures used to create four distinct sets of novel quinoline derivatives with added piperidine side chains. These compounds were then evaluated for their antiplasmodium activity against both a chloroquinesensitive strain (NF54) and a chloroquine-resistant strain (K1) of *Plasmodium falciparum*, as well as their cytotoxicity in a mammalian Chinese hamster ovary (CHO) cell line (Walle et al. 2020).

Challenges and opportunities

Malaria remains a significant public health challenge, particularly in developing countries, with a high mortality rate worldwide (Ramadani et al. 2017). Four species of *Plasmodium*, namely *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*, can cause malaria in humans. *P. falciparum* is responsible for the majority of malaria-related morbidity and mortality. The emergence of resistance to artemisinin, the primary class of antimalarial drugs, poses a serious threat to global malaria control efforts. Therefore, there is an urgent need to identify and develop new lead compounds for potential therapeutic interventions. Traditional medicine, particularly ethnopharmacology, holds promise in identifying plant-based molecules that can serve as templates or lead compounds in the development of antimalarial drugs. Nature offers a rich source of potential antimalarial substances due to the diverse chemical compounds found in plants (Noronha et al. 2020). Artemisinin, a key antimalarial drug, is typically extracted from the Artemisia plant. Various parts of the plant, including leaves, stems, buds, flowers, and seeds, can be used to extract artemisinin. Different solvents such as petroleum ether, ethyl acetate, hexane, and chloroform are employed in the extraction process at elevated temperatures. Another method involves yeast fermentation to produce artemisinic acid, which is then chemically converted into artemisinin, known as the semisynthetic approach (Azmi et al. 2023). The primary challenge in managing malaria effectively is the development of resistance to antimalarial treatments. Chloroquine resistance emerged in the late 1950s, followed by resistance to mefloquine and sulfadoxine-pyrimethamine. Artemisinin-based combination therapies (ACTs) have been used to combat the disease, but the emergence of artemisinin-resistant *Plasmodium falciparum* strains threatens these efforts. Despite the use of ACTs, there has been a rise in the prevalence of parasites resistant to these drugs. Artemisinin resistance is characterized by reduced treatment effectiveness, prolonged parasite clearance times, and gametocytemia (Azmi et al. 2023). Artemisinin is a fast-acting antimalarial drug effective against various stages of parasite growth. Resistance to artemisinin-based combination therapies (ACTs) has been associated with mutations in the kelch13 (k13) gene. *P. falciparum* parasites with this mutation exhibit reduced haemoglobin endocytosis, leading to decreased haemoglobin digestion and reduced activation of artemisinins, ultimately affecting their efficacy (Azmi et al. 2023). Future research and development efforts should focus on several key areas, including understanding the molecular basis of artemisinin resistance, identifying mutations and molecular markers associated with resistance, elucidating the molecular mechanisms of resistance, exploring novel antimalarial drug discovery, advancing vaccine development, and improving molecular diagnostic tools. Continuous surveillance of treatment failures and declining parasite susceptibility to ACTs is vital for assessing treatment parameters and effectiveness. Molecular markers associated with artemisinin resistance play a crucial role in detecting and monitoring the spread of resistant parasites. Comprehensive research on the molecular mechanisms of artemisinin resistance is essential for vaccine development and the discovery of effective antimalarial therapeutics (Azmi et al. 2023). Resistance to artemisinin and other antimalarial drugs highlights the need for screening processes and the development of novel lead compounds to combat malaria (Noronha et al. 2020). Ethnomedicine, or traditional medicine, has the potential to play a significant role in this effort. Ethnomedicine encompasses a comprehensive system of knowledge, skills, and practices rooted in cultural traditions and passed down through generations. It includes traditional herbal remedies that have been used for healthcare and disease prevention long before the advent of modern medicine (Taek et al. 2019). Approximately 80% of the global population relies on plant-based traditional healthcare products as their primary means of accessing healthcare services. Traditional medicine is often preferred for its perceived natural composition, safety, and effectiveness in mitigating the adverse effects associated with synthetic pharmaceuticals. It also offers personalized healthcare tailored to individual needs and enhances public access to health information. Herbal medicines are commonly used to treat various diseases, including potentially fatal ones like malaria (Noronha et al. 2020). In Indonesia, as in many other regions, traditional medicinal plants have been used historically to treat malaria. Some of these plants, such as Tithonia diversifolia, Cyclea barbata, Tinospora crispa, Arcangelisia flava, and Pycnarrhena cauliflora, have been selected based on ethnobotanical data as potential sources of antimalarial compounds (Ramadani et al. 2017). These plants have been studied for their pharmacological and antiplasmodial properties. It is important to note that while herbal treatments offer potential benefits, they are not universally safe and may have adverse effects. Plants contain a wide range of chemicals, some of which can be toxic. Proper dosing, preparation, and quality control are crucial to ensuring the safety and effectiveness of herbal treatments. Regulatory frameworks for herbal medicines vary between countries, and the World Health Organization (WHO) has issued guidelines to help assess the safety and quality of herbal medicines (Calixto 2000). In conclusion, malaria remains a significant global health challenge, exacerbated by the emergence of drug resistance. Traditional medicine, particularly the use of medicinal plants, offers potential opportunities for the discovery of new antimalarial compounds. However, safety and quality concerns must be addressed, and research efforts should focus on understanding drug resistance mechanisms, developing novel therapies, advancing vaccine development, and improving diagnostic tools to combat this deadly disease.

Summary

In conclusion, malaria remains a significant public health concern in Indonesia and many other parts of the world. This parasitic disease, transmitted by female *Anopheles* mosquitoes of the *Plasmodium* genus, poses a substantial burden on affected populations. While there is regional variation in malaria prevalence within Indonesia, some areas, particularly in eastern provinces like Papua and West Papua, experience a higher incidence of malaria cases. Researchers have explored the potential of secondary metabolites found in herbal ingredients, such as flavonoids, terpenoids, and alkaloids, as antimalarial agents. This approach taps into the rich traditional knowledge of medicinal plants and offers a promising avenue for the development of new treatments. Artemisinin-based Combination Therapy (ACT) has emerged as the primary treatment for malaria in many endemic regions, including Indonesia. However, the ongoing challenges of climate change, population mobility, and the persistent threats posed by mosquitoes and drug resistance continue to complicate malaria control efforts. These challenges underscore the need for ongoing vigilance and innovative approaches in the fight against malaria. As Indonesia and the global community work to combat this deadly disease, it is crucial to continue investing in research, surveillance, and healthcare infrastructure to reduce malaria's impact and ultimately work toward its elimination. Malaria control remains a complex and dynamic endeavor, but with continued dedication and collaboration, progress can be made in reducing its toll on human health.

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