UNIVERSITI PUTRA MALAYSIA

A SYSTEMATIC REVIEW ON MEDICINAL PLANTS WITH ANTI – MALARIAL PROPERTIES IN SOUTHEAST ASIA

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FPSK2 2021 9

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A PROJECT PAPER SUBMITTED AS PARTIAL REQUIREMENT FOR THE DEGREE OF BACHELOR OF SCIENCE (BIOMEDICAL SCIENCES)

DEPARTMENT OF BIOMEDICAL SCIENCES
FACULTY OF MEDICINE AND HEALTH SCIENCES
UNIVERSITI PUTRA MALAYSIA

2021

ABSTRACT

A Systematic Review on Medicinal Plants with Anti – Malarial Properties in Southeast Asia

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Introduction: The elevated rise in resistance and adverse effects towards anti-malarial drugs in the Southeast Asia (SEA) region addresses the need for new therapeutic approaches. There are various studies conducted on medicinal plants found in SEA as a source for new anti-malarial agents. However, there isn't a comprehensive summary on the findings of these studies. **Objective:** This systematic review aims to evaluate the existing evidence and to identify the medicinal plant(s) in the SEA region with high potential of anti-malarial activity. It also aims to compare the IC50 doses & percentage of parasitemia inhibition of medicinal plants with anti-malarial properties in Southeast Asia using statistical tools. **Methodology:** The systematic search was conducted using a customised search strategy in databases such as PubMed, Science Direct, Scopus, Google Scholar and Wiley Online Library. Data were collected from a total of 36 articles meeting the inclusion criteria. Microsoft Excel was used to summarize the data using descriptive statistics. **Results:** A total of 115 extracts of 39 plant species from 19 families were categorised as very good, good, moderate, weak and inactive for in vitro and in vivo studies, respectively. Most of the reports are from Thailand followed by Malaysia and Indonesia. Plant species from family Annonaceae contributed the most among these 36 studies. Leaves were reported as the most used part of plants in antimalarial investigation and methanol was the most used solvent for the extraction process. Among the 115 extracts, 77.78% of the tested extracts in in vivo studies showed higher than moderate antimalarial activity followed by 72.85% in in vitro studies and 50% of extracts in mixed design studies. For the risk of bias assessment, most studies presented with low to medium risk of bias. **Discussion:** Annonaceae family contributed to the most activities as it is widely used to treat malaria. Most good and very good activities came from Asteraceae and Menispermaceae families. Leaves were most used part because they possess ethno pharmacological relevance and antimalarial activity due to the high content of bioactive compounds present. Moreover,

alcohol based solvents yielded extraction with the highest bio compound content and biological activity. **Conclusion:** In comparison to the huge number of naturally occurring plants in Southeast Asia, only a small number of medicinal plant species have been evaluated. Thus, a system for systematically investigating and exploring unexplored plant genera must be devised.

Keywords: Medicinal plants, anti-malaria, anti-plasmodial, Southeast Asia region, systematic review

ABSTRAK

Kajian Sistematik terhadap Tumbuhan Perubatan dengan Sifat Antimalarial di Asia Tenggara

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Pengenalan: Peningkatan rintangan dan kesan buruk terhadap ubat-ubatan anti-malaria di perantauan Asia Tenggara (AT) menunjukkan perlunya pendekatan terapi baru. Terdapat pelbagai kajian yang dilakukan terhadap tumbuhan perubatan yang terdapat di AT sebagai sumber agen anti-malaria baru. Walau bagaimanapun, data ini mempunyai pelbagai tahap perbezaan dan tiada ringkasan komprehensif mengenai penemuan kajian ini. **Objektif:** Kajian sistematik ini bertujuan untuk menilai bukti yang wujud dan mengenal pasti tumbuhan perubatan di perantauan AT yang berpotensi tinggi untuk aktiviti anti-malaria. Kajian juga bertujuan untuk membandingkan dos IC50 dan peratusan penghambatan parasitemia oleh tumbuhan perubatan di AT menggunakan kaedah statistic. **Metodologi:** Pencarian sistematik dilakukan melalui pangkalan data seperti PubMed, Science Direct, Scopus, Google Scholar dan Wiley Online Library. Data dikumpulkan dari 36 artikel yang memenuhi kriteria inklusif. Microsoft Excel digunakan untuk meringkaskan data menggunakan statistik deskriptif. **Hasil kajian:** Sebanyak 115 ekstrak daripada 39 spesies tumbuhan (19 keluarga) dikenal pasti dan dikategorikan sebagai sangat baik, baik, sederhana, lemah dan tidak aktif untuk kajian in vitro dan kajian in vivo. Majoriti kajian berasal dari Thailand, diikuti oleh Malaysia dan Indonesia. Spesies tumbuhan dari keluarga Annonaceae menyumbang sebahagian besar aktiviti antimalarial di antara 36 kajian ini. Daun dilaporkan sebagai bahagian tumbuhan yang paling banyak digunakan dalam penyelidikan antimalaria dan metanol adalah pelarut yang paling banyak digunakan untuk proses pengekstrakan. Antara 115 ekstrak, 77.78% ekstrak yang diuji dalam kajian in vivo menunjukkan aktiviti antimalarial yang lebih tinggi daripada kategori sederhana diikuti oleh 72.85% dalam kajian in vitro dan 50% ekstrak dalam kajian reka bentuk campuran. Untuk penilaian risiko bias, kebanyakan kajian menunjukkan risiko bias rendah hingga sederhana. **Perbincangan:** Keluarga Annonaceae menyumbang

aktiviti paling banyak kerana digunakan secara meluas untuk merawat malaria. Aktiviti yang paling baik dan sangat baik berasal dari keluarga Asteraceae dan Menispermaceae. Daun adalah bahagian yang paling banyak digunakan kerana mempunyai relevansi etnofarmakologi dan aktiviti antimalarial kerana kandungan sebatian bioaktif yang tinggi. Selain itu, pelarut berasaskan alkohol menghasilkan pengekstrakan dengan kandungan sebatian bio dan aktiviti biologi tertinggi**. Kesimpulan:** Jika dibandingkan dengan bilangan tumbuhan semula jadi di AT, hanya sebilangan kecil spesies tumbuhan perubatan yang telah dinilai. Oleh itu, satu sistem untuk menyiasat dan meneroka genera tumbuhan yang belum diterokai secara sistematik perlu diperkenalkan.

Kata kunci: Tumbuhan perubatan, anti-malaria, anti-plasmodial, rantau Asia Tenggara, kajian sistematik

ACKNOWLEDGEMENT

First and foremost, my sincere gratitude goes to my supervisor, Associate Prof Dr. Abdah Md Akim. Throughout my Final Year Research Project (FYP) journey, she continuously supported me and guided me to complete my thesis. Her kind encouragement motivated me through all the challenges I faced during this journey. Her words of wisdom and teachings will always be close to my heart and will be carried on with me in my future endeavours.

I am also thankful to my coordinator Dr Hasni for the support and guidance. She never hesitated to guide me and my fellow classmates and always answered our questions no matter how silly it was. Not only did she aid us with the technicalities and protocols of submissions but also provided us with moral support and encouragement to complete our FYP.

My appreciation also extends to my project team members, Nur Shafira, Abdull Assaqireen and Linesh Kumar for always sharing their insights on the project. We motivated each other on writing this systematic review and helped

each other both emotionally and academically. Without their inspiration and support, I would not be able to complete my thesis.

Furthermore, I would like to extend my appreciation to my parents, brother, boyfriend and best friends for never giving up on me. They will forever be my pillars of strength who gave me continuous love and support. They believed in me during times where I lost hope and confidence in myself. For that reason, I was able to push myself not only in my thesis but towards my growth in general.

Lastly, my gratitude extends to God for guiding me throughout this journey. In Him, I found my path and the will to be who I am today. Because of Him, I am blessed with wonderful, loving people around me and for that I will forever be grateful. This dissertation stands as a testament to everyone's support.

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LIST OF ABBREVIATIONS

%	Percentage
µ	Micro
µg	Microgram
µM	Micro molar
ACT	Artemisinin based combination therapy
CDC	Centre for Disease Control and Prevention
CQ	Chloroquine
CRIS	Checklist for Reporting In-vitro Studies
DHA	Dihydroartemisinin
IC_{50}	Half maximal inhibitory concentration
JabRef	Java, Alver, Batada, Reference
kg	kilogram
MOA	Mechanism of action
mg	microgram
PbANKA	Plasmodium berghei ANKA
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RoB	Risk of Bias
SEA	Southeast Asia
SYRCLE	Systematic Review Centre for Laboratory Animal Experimentation
US	United States
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Malaria is a disease that has been in existence for decades. Yet, it remains one of the world's leading health crises. According to the World Health Organization, an estimation of 229 million malaria cases and 409 000 malarial deaths occurred globally in the year 2019 (World Health Organization, 2020). The total number of countries that are endemic to malaria is 87 as reported by WHO in the latest World Malaria Report 2020. Among the endemic countries, the Southeast Asia (SEA) region holds the second highest malaria burden accounting for 10% of malarial cases and 3% deaths due to malaria. Groups that are most susceptible to malaria include infants, young

children and pregnant women (CDC - Malaria - Malaria Worldwide - Impact of Malaria, 2021).

Currently, a total of US$ 3.0 billion has been invested into research and development of antimalarial agents with 9% allocated to the SEA region (World Health Organization, 2020). Studies are being conducted in various fields with traditional medicine and natural products as one of the most encouraging fields. Natural products have the potential to become an antimalarial agent or source of novel drug structure for the treatment of malaria (Lemma et al., 2017). Moreover, looking into natural products and medicinal plants is a less expensive approach towards antimalarial discovery in comparison to chemical synthesis (Nisar et al., 2018).

1.2 Problem statement

Over the years, there has been an elevation of malarial cases and deaths due to malaria. Many interventions and approaches have been conducted by WHO as well as the respective governments of the infected countries. Yet, cases still remain at an alarming rate. Even though SEA has the highest

number of people susceptible to the disease, unfortunately, it is highly neglected (Bharati & Ganguly, 2013).

Furthermore, current treatment options for malaria have developed resistance in many parts of malaria endemic countries including those in SEA making the situation worse (Hamilton et al., 2019). Furthermore, studies have also shown that current treatment causes adverse side effects among malarial patients (Braga et al., 2015) (Lee et al., 2017) (Nevin & Croft, 2016). These situations urges the need for new antimalarial agents. Fortunately, there are various studies conducted at the moment on medicinal plants in SEA as a source for new antimalarial agents (R. Basir et al., 2012) (Thiengsusuk et al., 2013). However, these studies and data vary in many aspects such as study designs, outcomes, doses and plants used (Ekasari et al., 2019) (Khasanah et al., 2021) (Widyawaruyanti et al., 2020). The available information is not standardized and difficult to analyse separately.

1.3 Justification of the study

A systematic review is conducted to summarize findings of relevant individual studies and provide a comprehensive overview for an easier access towards information (Ganeshkumar & Gopalakrishnan, 2013). It allows access

towards available evidence providing concise answers eliminating the need for further research, saving resources (Elsevier, 2019).

SEA, as previously mentioned, has the second highest malaria burden in the world. The search for a more effective antimalarial agent is further accelerated due to the rise in multidrug resistant strains of *Plasmodium* and adverse effects of current treatments (Alebie et al., 2017). The studies conducted vary in many aspects such as design, doses, extracts used and more (Ekasari et al., 2019) (Khasanah et al., 2021) (Widyawaruyanti et al., 2020).

Even though many studies have been conducted, there is no systematic review on medicinal plants exhibiting antimalarial properties in SEA. Thus, in this context, a systematic review on medicinal plants with antimalarial properties in SEA is needed to summarize the individual studies and report on the most effective plant extracts in treating malaria. It will provide a comprehensive summary of all studies conducted in a standardized manner for easier access for future research.

1.4 Study objectives

1.4.1 General objectives

To synthesize the existing evidence of medicinal plants with anti-malarial properties in Southeast Asia.

1.4.2 Specific objectives

i. To identify the types of medicinal plants extracts exhibiting anti-malarial properties in Southeast Asia.

ii. To compare the IC_{50} doses and percentage of parasitemia inhibition of medicinal plants with anti- malarial properties in Southeast Asia using established categorization and statistical tools.

iii. To conduct risk of bias assessment on the included studies in the systematic review.

1.5 Hypotheses

i. The systematic review will identify the medicinal plants with antimalarial properties in Southeast Asia to be used as an alternative therapeutic approach in treating malaria.

ii. Statistical analysis in comparing the IC_{50} dose and percentage of parasitemia inhibition of medicinal plants in Southeast Asia against malaria will identify the plants that are more effective in treating malaria.

CHAPTER 2

LITERATURE REVIEW

2.1 Malaria

Malaria is a communicable disease of great age. According to Celli (1993), (cited in Cox, 2010), the disease was first described in a Chinese document dated back to about 2700 BC, followed by Mesopotamia from 2000 BC, 1570 BC in Egyptian papyri and Hindu texts dating back to the sixth century BC which was later confirmed as malaria. Back in those days, diseases were believed to be caused by spoiled air in which malaria got its name, from Italian word mal'aria for bad air. In 1880, the discovery of the malarial parasite was made by Charles Louis Alphonse Laveran followed by the involvement of mosquitoes as vectors studied by Ronald Ross in 1897 (Cox, 2010). These

discoveries enhanced our understanding towards the disease and thus began the search for a cure for this fatal disease.

2.1.1 Pathophysiology of malaria

Malaria is a vector borne disease that takes place predominantly in tropical countries and found in 87 countries in the world (WHO, 2020). It is caused by the *Plasmodium* species transmitted through the infected female *Anopheles* mosquitoes, malaria vectors (CDC - Malaria - About Malaria, 2021). There are over 120 *Plasmodium* species in existence, but only five are known to be infectious to humans; *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale* and *Plasmodium knowlesi*, which is a zoonotic disease. (Ashley et al., 2018; Herchline, 2021). *P. falciparum* and *P. vivax* are the most responsible for malaria infections (WHO, 2021). The infective species can be distinguished based on the morphology of a blood smear. Infected individuals can present a range of symptoms, from mild fevers to serious complications such as cerebral malaria, anemia due to malaria or death (Buck & Finnigan, 2021). Recurrent episodes of the disease are associated with morbidity.

2.1.1.1 Biology

A summary of the life cycle of malaria of the human stage is presented in Figure 2.1. According to the Centers for Disease Control and Prevention (CDC, 2021), malarial infection occurs in a cyclical manner between humans and the female A*nopheles* mosquitoes. Firstly, the parasites are transmitted into the human system during a blood feed. The female *Anopheles* mosquitoes transmit the motile sporozoites into the dermis (White et al., 2014). Then, the multiplication of the parasites occurs primarily in the liver cells followed by the red blood cells in humans.

When the parasites are in the liver, they continue to grow, forming pre-erythrocytic schizonts that are dormant. These schizonts release merozoites into the bloodstream and destroy the red blood cells along the process. The merozoites develop into an early ring form called trophozoite. The trophozoite consists of the early stage and late stage. Late stage trophozoite undergoes several mitotic divisions which establishes the schizont form. Schizont turns into several merozoites which are released when the schizont ruptures. The cycle resumes as the

merozoites invade other red blood cells (Ashley et al., 2018; Basu & Sahi, 2017; CDC - Malaria - About Malaria - Biology, 2021).

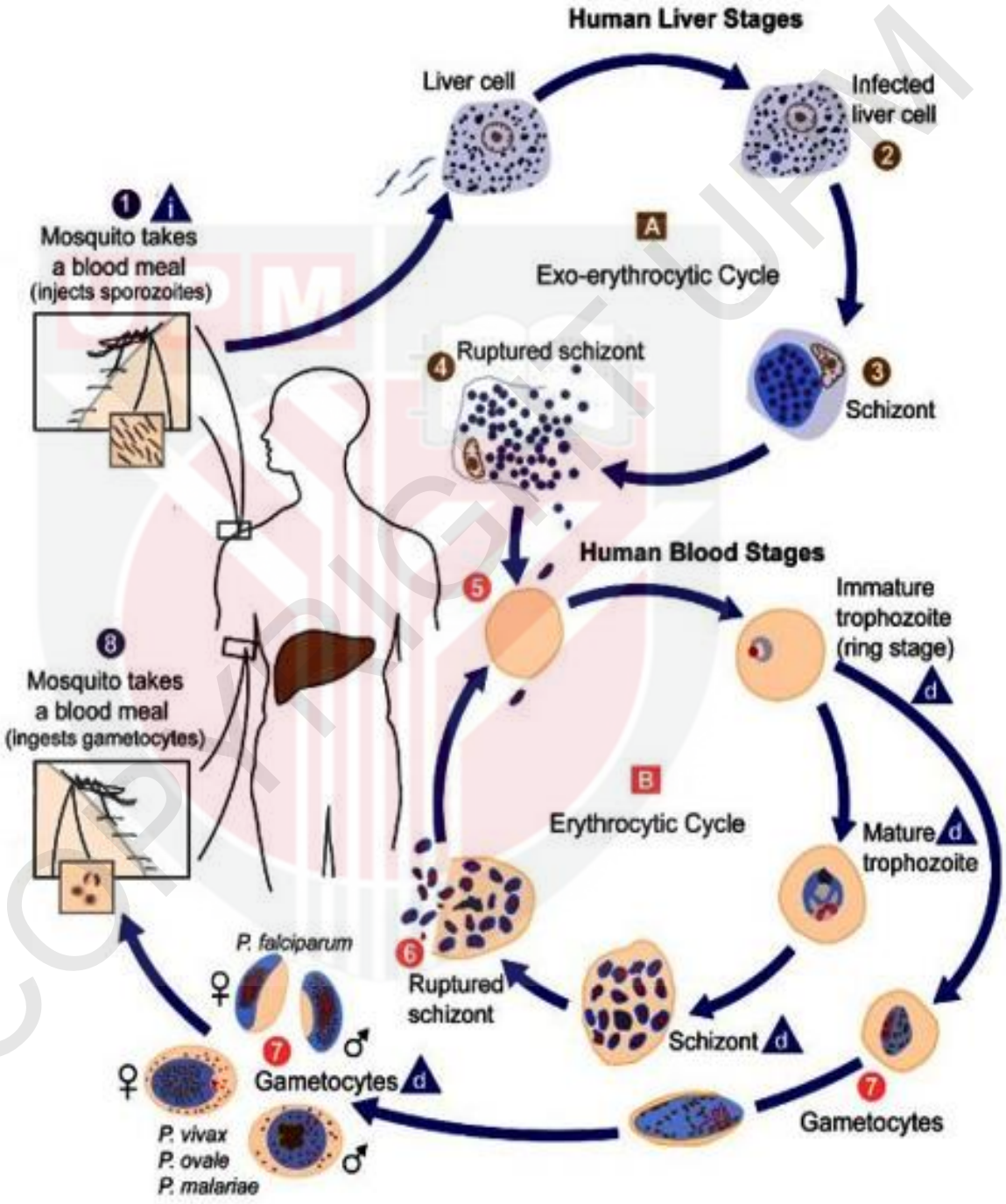


Figure 2.1: Life cycle of the malaria parasite in the human stage. (Adapted from source: CDC – Malaria - About Malaria - Biology. (2021).

2.1.1.2 Clinical presentation

The clinical presentation of malaria can be categorised into two; uncomplicated and complicated/severe malaria (Ashley et al., 2018). Each presentation requires a different diagnostic and therapeutic approach. The presentation of uncomplicated malaria is non-specific and consists of several symptoms. These include nausea and vomiting, fever, sweats, headaches, body aches, general malaise and chills (CDC, 2021). Most symptoms by patients with uncomplicated malaria are typical and very few abnormal symptoms are present (White et al., 2014).

However, for severe malaria, if it is left untreated, it is fatal (Sharma & Dutta, 2011). The complications vary and include organ failures as well as abnormal findings in the patients' blood or metabolism. The manifestations of severe malaria are influenced by age. For instance, in children, severe anemia and hypoglycemia are more common while in adults, acute kidney injury and jaundice are more common (White et al., 2014). Other manifestations of severe malaria are cerebral

malaria, haemoglobinuria, low blood pressure, acute respiratory distress syndrome, metabolic acidosis, blood coagulation abnormalities and hyperparasitemia (Basu & Sahi, 2017; CDC, 2021).

2.1.2 Prevalence of malaria

According to the World Malaria Report 2020 (WHO, 2020), in 2019, there were about 229 million malaria cases throughout 87 countries (see Figure 2.2). This number was lower in comparison to 238 million cases in 2018. There was a decline of 27% from the year 2000 to 2015. However, from the year 2015 to 2019, the decline was less than 2%. This reduction shows that the decline in cases of malaria has reached an almost plateau phase. This could be contributed by several factors that will be discussed further in upcoming subtopics. Among all the regions, most cases, 94%, was contributed by the African region with an estimation of 215 million in 2019 (see Figure 2.3).

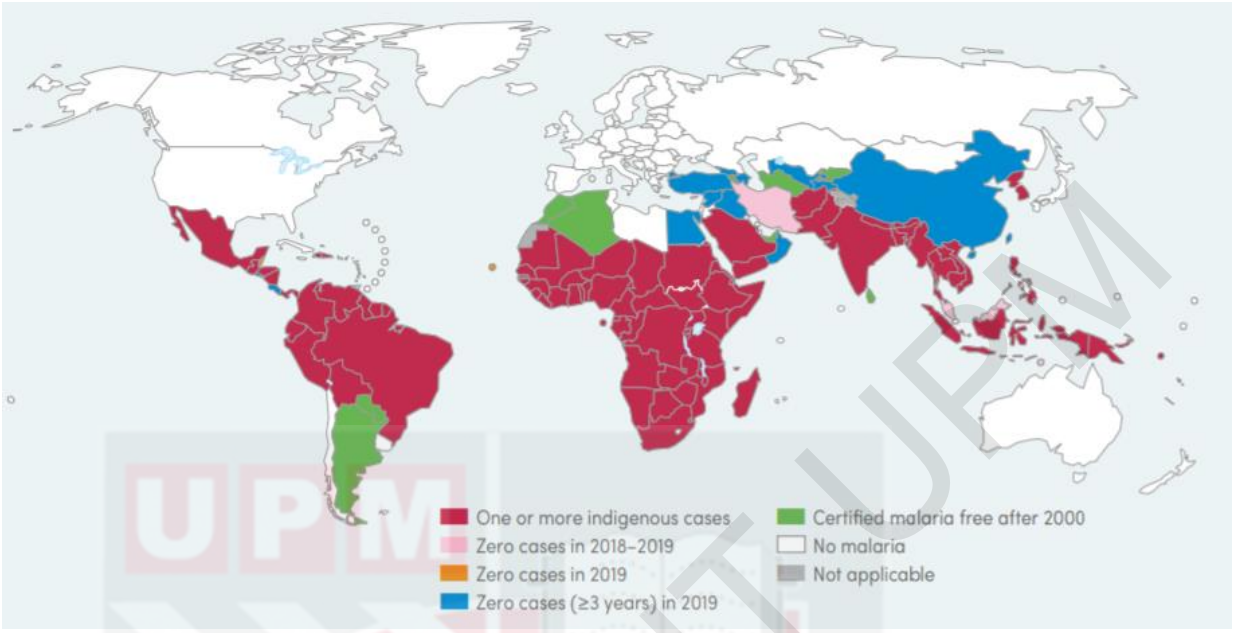


Figure 2.2: Global burden of malaria cases. (Source: World Malaria Report 2020, (WHO, 2020).

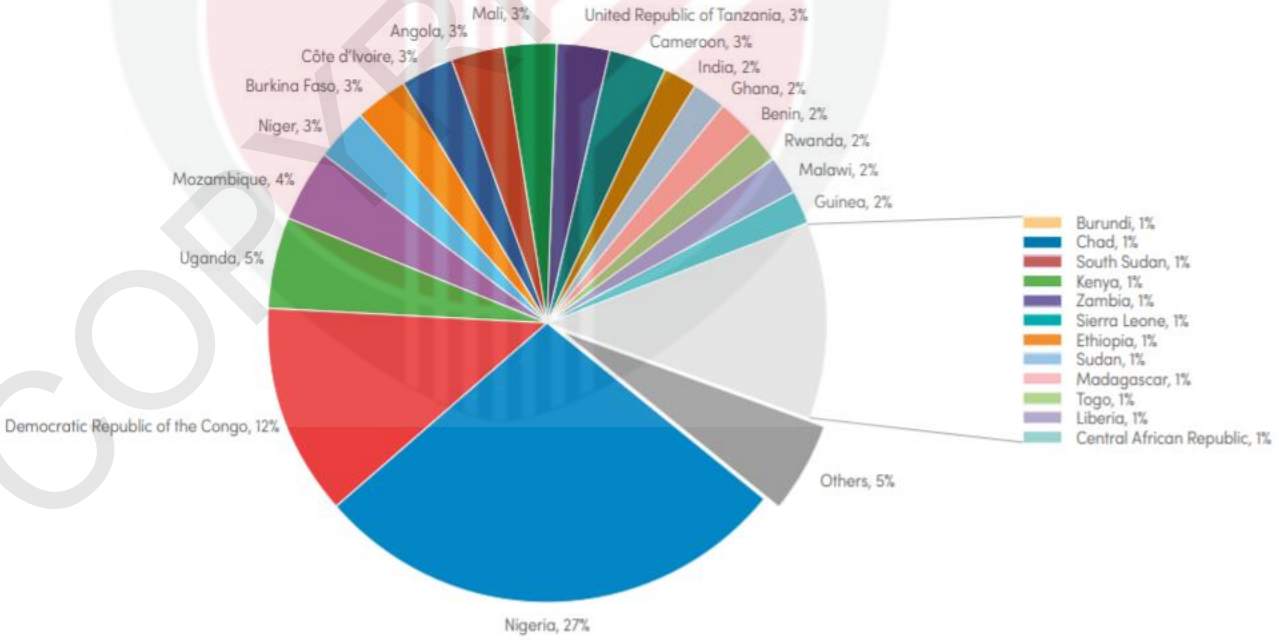


Figure 2.3. Malaria cases breakdown based on countries. Most cases were contributed by countries in the Africa region. (Source: World Malaria Report 2020, (WHO, 2020).

In the year 2019, an estimated total number of 409 000 deaths occurred globally due to malaria. The rate of mortality has reduced from 12 in 2015, to 10 per 1000 000 population at risk in 2019. The recent years, as stated by WHO, saw a decline in the reduction of the rate of mortality. In the region contributing most of the malaria cases, Africa, 386 000 deaths (40 per 100 000 population at risk) occurred (see Figure 2.4). Furthermore, 35% (12 million) pregnant women were exposed to malaria infection in the year 2019, in this region.

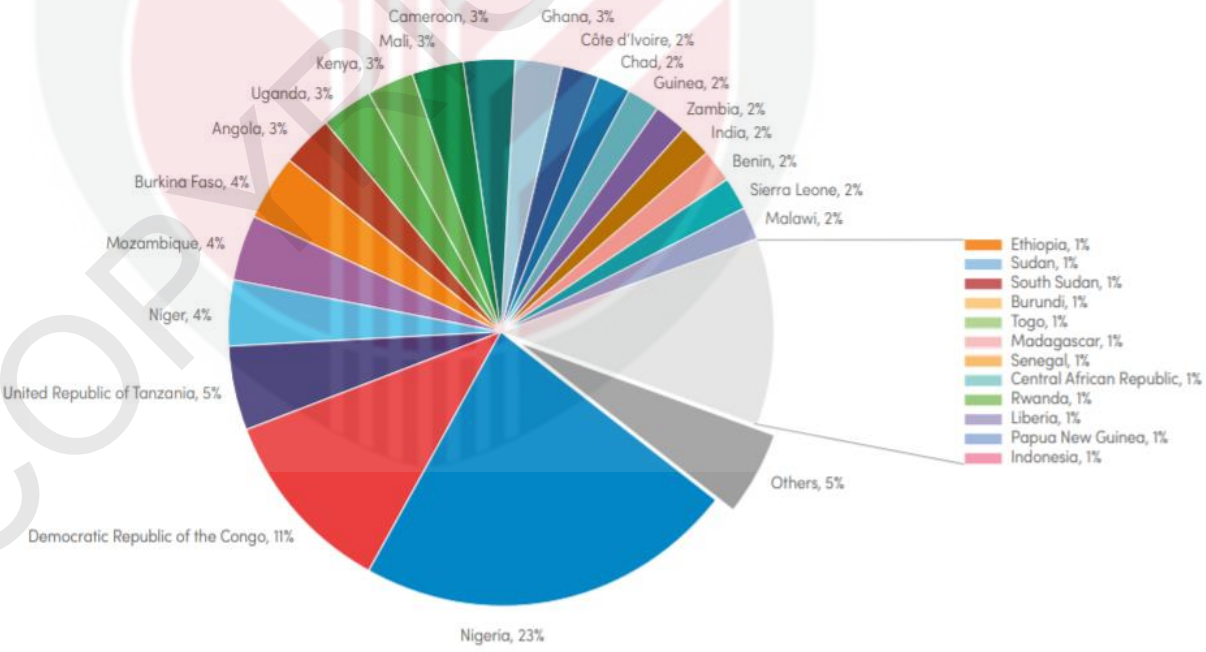


Figure 2.4. Malaria deaths breakdown based on countries. Most deaths were contributed by countries in the Africa region. (Source: World Malaria Report 2020, (WHO, 2020)

2.1.3 Malaria in Southeast Asia

Up to this point, despite efforts and visibility, malaria still remains a major concern in the SEA region (Gething et al., 2012) (Roy & Khatun, 2015). The burden of the disease was due to the underestimation of these cases. This could be contributed by the tropical weather of SEA countries providing an efficient environment for the mosquito vectors, instability in the socioeconomic sector and lack of resources to carry out effective control programmes (CDC, 2021). Based on the World Malaria Report 2020, (WHO, 2020), SEA holds the second highest malaria burden in the world with over 6.3 million cases in the year 2019. This number comprises 3% of the total malaria cases globally. 9000 malaria deaths occurred in SEA in the year 2019. Although the number of cases and deaths have reduced over the years (see Figure 2.5 & 2.6), the battle against malaria in SEA is not won yet.

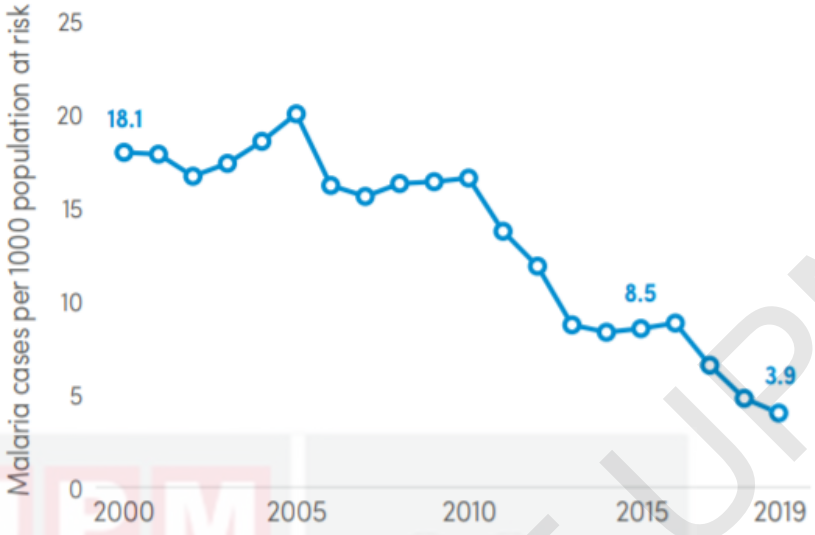


Figure 2.5. Malaria cases per 1000 population at risk in SEA over the years. (Source: World Malaria Report 2020, (WHO, 2020).

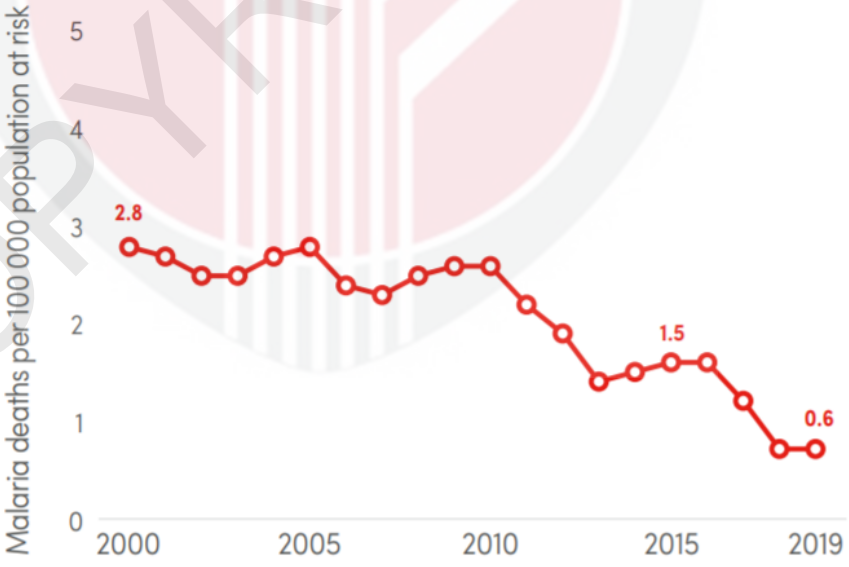


Figure 2.6. Malaria deaths per 1000 population at risk in SEA over the years. (Source: World Malaria Report 2020, (WHO, 2020).

From the year 2006-2011, the prevalence rate of malaria increased in Myanmar from 43.573 to 96.261, while it decreased from 4.503 to 3.581 in Thailand and from 15.428 to 10.555 in Indonesia. This statistic showed that Myanmar had one of the highest malaria prevalence rates at that given time. (Roy & Khatun, 2015). A study conducted in the border of Thailand-Myanmar, Cambodia and Vietnam showed that a great number of individuals were asymptomatic carriers of *Plasmodium* parasite (Imwong et al., 2015). In Malaysia, there were 16, 500 cases reported from the year 2013-2017 in which most of the cases were contributed by Sabah (43.3%) and Sarawak (34.4%) (Hussin et al., 2020). In Thailand, malaria is the 7th most common cause of death (Kondrashin AV, 2019) and a study conducted by Bhumiratana et al., (2013) reported that rubber tappers have the highest malaria incidence rate in Thailand accounting for 46.29% of the cases.

Plasmodium vivax and *Plasmodium falciparum* contributed to most of the malaria cases in SEA where Myanmar and Indonesia presented the highest disease burden (Gething et al., 2011; Gething et al., 2012). In Indonesia, *Plasmodium falciparum* and *Plasmodium vivax* infections occurred at 54.4% and 32.5% respectively when 68,361 patients were analysed from 2004 to 2013 (Dini et al., 2020). Whereas, a study

conducted in Malaysia reported that *Plasmodium knowlesi* caused 58% of malaria cases in the indigenous communities (Singh et al., 2004). Furthermore, *Plasmodium knowlesi* infections were found in all SEA countries except Timor Leste, where Malaysia contributed the highest number of 18,687 cases from 2010-2018 (Jeyaprakasam et al., 2020).

2.2 Treatment for malaria

Treatment for malaria is influenced by many factors. These include the severity of the disease, the parasite species causing the disease and the geographical location in which this disease occurred (CDC, 2021). The aim of the treatment is to cure the patients completely, preventing the disease from progressing to a severe state or the occurrence of a relapse (Basu & Sahi, 2017). The history of malaria treatment dates back to the 2nd century BC, where the plant Qinghai (*Artemisia annua)* was used in China (Hsu, 2006). Following that, the Spanish people used cinchona medication obtained from the Cinchona tree bark in the 16th century. This practice then led to the isolation and discovery of quinine by French chemists, Pierre Joseph Pelletie, and Joseph Bienaimé Caventou in 1820 (Achan et al., 2011; Meshnick & Dobson, 2011; Talapko et al., 2019). In 1970, Dr Youyou Tu won the Nobel Prize for isolating artemisinin

from the plant *Artemisia annua,* a drug that is actively used in treatment of malaria (Meshnick & Dobson, 2011; Talapko et al., 2019).

2.2.1 Current treatment and practices

Over the last decade, the initiatives to eradicate malaria have increased globally. This has led to a major progress into the discovery of antimalarial drugs (Roberts & Enserink, 2007). The four classes of drugs that were developed in the 20th century still remain the treatment approach for malaria. These classes include quinolone derivatives, sulfadoxine-pyrimethamine, artemisinin and atovaquone (Raphemot et al., 2016). According to the 21st list of WHO Model List of Essential Medicines (2019), there are 14 and 6 medications, both as individual compounds or combinations, for antimalarial curative treatment and chemoprevention respectively. Treatment approaches taken for patients include schizonticidal medications, supportive care, and hospitalization (Buck & Finnigan, 2021).

Malaria treatment approach is taken based on the severity of the disease; uncomplicated and complicated malaria using an algorithm (see Figure 2.7). According to WHO (2015), if the parasite responsible for uncomplicated malaria is either *Plasmodium vivax, ovale, malariae* or *knowlesi,* the approach taken is to give a chloroquine based treatment or an artemisinin-based combination therapy (ACT) to patients in areas with chloroquine-susceptible infections. Chloroquine belongs to the quinolone family and is considered one of the most triumph drugs in terms of cost and efficacy (Sudre et al., 1992). The drug acts by inhibiting heme from polymerizing into hemozoin in the parasite's which contributes to the parasitemia (Sullivan et al., 1996). In areas with chloroquine-resistant infections, the ACT approach is taken. In contrast, for pregnant women, the treatment given is quinine. Quinine acts by interfering with the haemoglobin digestion ability of the parasite (Achan et al., 2011). However, if the parasite species is not confirmed, it is treated as *Plasmodium falciparum* malaria (WHO, 2015).

Uncomplicated *Plasmodium falciparum* malaria requires an ACT treatment approach as the monotherapies such as chloroquine and sulfadoxine-pyrimethamine are failing (Hanboonkunupakarn & White, 2020). ACT treatment consists of artemisinin that acts rapidly and an

antimalarial that is long acting (Basu & Sahi, 2017). The treatment is provided for three days. The ACT combinations are artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, dihydroartemisinin + piperaquine and artesunate + sulfadoxine-pyrimethamine (WHO, 2015).

On the other hand, complicated malaria is considered a medical emergency and treatment must be initiated without delay for parasitological confirmation (Basu & Sahi, 2017). Based on WHO guidelines (2015), all adults, children and even infants as well as pregnant women are treated with intravenous or intramuscular artesunate for 24 hours if they have complicated malaria. In two randomized controlled trials, artesunate was observed to reduce mortality in both Southeast Asia adults and children by 34.7% and African children by 22.5% (Dondorp et al., 2005; Dondorp et al., 2010).

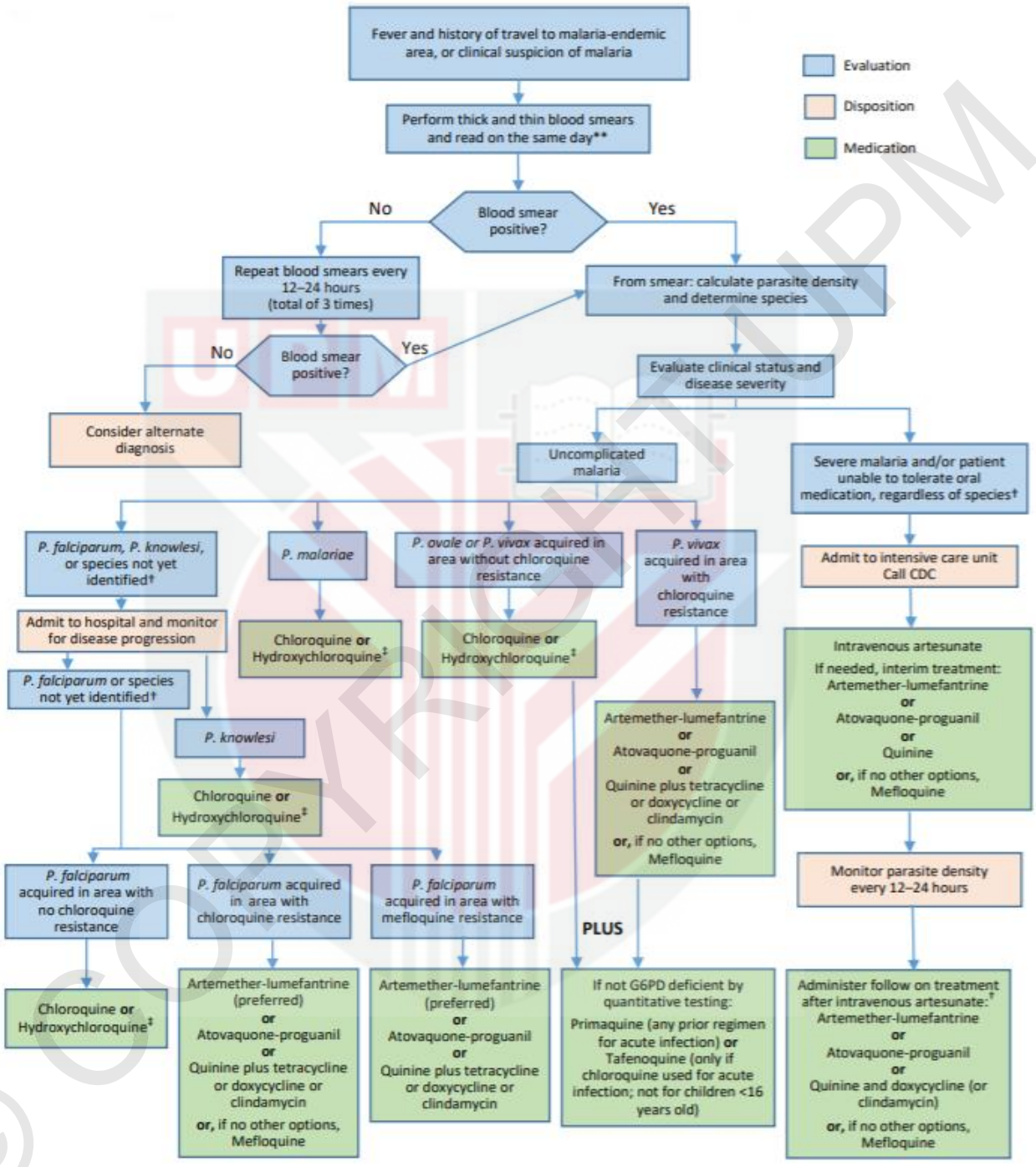


Figure 2.7. Algorithm for the treatment of malaria. (Source: CDC 2021).

2.2.2 Adverse effects of current treatment

Adverse drug reaction is defined as an unpleasant or harmful reaction that is resulted from usage or a medicinal product. Any substance that elicits a therapeutic effect also has the potential to cause adverse effects. There is no such medication that is 100% safe as the possibility of causing effects can be as low as 1% (Edwards & Aronson, 2000). The same can be said for antimalarial drugs. Regardless of the efficacy it plays in treating malaria, it can also cause unwanted reactions (Taylor & White, 2004).

Chloroquine is one of the widely used drugs in malaria treatment. However, several studies have shown that chloroquine or its metabolite, hydroxychloroquine is capable of causing ocular damage that includes deposition of cornea, ciliary body dysfunction, optic disc pallor and loss of macular pigment (Mavrikakis et al., 2003; Michaelides, 2011; Stokkermans et al., 2021; Yam & Kwok, 2011; Yusuf et al., 2017). A research conducted by Braga et al., (2015) demonstrated that upon treatment with chloroquine, patients experienced an increase in symptoms such as nausea, diarrhoea, abdominal pain and hypochondria pain by 48%, 26%, 38% and 32% respectively. Other

adverse effects of chloroquine observed in this study include visual acuity, insomnia, pruritus and paraesthesia. Furthermore, usage of chloroquine has also been associated with idiosyncratic neuropsychiatric effects in chemoprophylaxis usage (Maxwell et al., 2015).

Another popular drug used for malaria treatment is mefloquine which has been used since the mid-1980s. In a study conducted in Thailand, patients treated with mefloquine exhibited gastrointestinal symptoms such as anorexia, nausea, vomiting and abdominal pain as well as neuropsychiatric symptoms such as headaches, dizziness and sleep disturbances. The study also reported that three patients died during the process (Lee et al., 2017). Moreover, a 36 year old man from Italy presented mefloquine-associated rhabdomyolysis upon prophylaxis treatment (Comelli et al., 2016). Another drug, sulfadoxine-pyrimethamine was reported to have cardiovascular effects with changes in the electrocardiograph and reduction in heart rate (Ngouesse et al., 2001).

ACT has been the go to therapeutic approach for malaria in many countries. The combination of a rapid acting drug and a long acting drug makes ACT the preferred choice for malaria treatment. However, a study conducted in Nigeria showed that 32.9% of respondents undertaking ACT experienced at least one adverse reaction from the treatment. These reactions included pruritus, vomiting, nausea, abdominal discomfort and general body weakness (Adisa et al., 2008). These findings were very similar to a study conducted in India, where 50.2% of patients taking ACT had adverse reactions that included nausea, vomiting and dizziness. The highest number of reactions were seen in treatment of artesunate + mefloquine and artesunate + sulfadoxine-pyrimethamine (Belhekar et al., 2012). Similarly, in Uganda, 22.5% of patients complained of adverse reactions with over 245 reactions reported as some patients experienced more than one reaction. These reactions comprised of disorders from gastrointestinal system (30.6%), musculoskeletal and connective tissue (26.9%), nervous system (26.5%), skin and subcutaneous tissue (5.7%), and respiratory, thoracic and mediastinal (4.1%) (Ndagije et al., 2018).

2.2.3 Resistance towards current treatment

Antimalarial drug resistance is defined as the ability of the strain of the parasite to survive and/or proliferate even after antimalarial drug has been administered and absorbed in doses equal or higher than the normal recommendation (WHO, 2015). Drug resistance towards antimalarials is considered a global threat and has a higher impact on poorer countries as changing the routine treatment approach is expensive (Na-Bangchang & Congpuong, 2007). Resistance toward antimalarials developed as a result of inappropriate use of these drugs. In turn, this puts a strong selective pressure on the parasites to undergo mutations or gene amplifications which results in resistance towards current therapeutic approaches (WHO, 2015). An example is the PfKelch13 mutation that contributed to the resistance towards artemisinin found in parasite isolates from Cambodia (Ariey et al., 2013; WHO, 2020).

Resistance towards drugs like chloroquine and sulfadoxine-pyrimethamine started occurring during the 1990's (Ashley et al., 2014). Chloroquine was the preferred drug for treating *Plasmodium vivax* and *Plasmodium falciparum* infections as the treatment was inexpensive and

cheap. The frequent use of this, however, led to the development of resistance (Dayananda et al., 2018). Endemic places in Southeast Asia (SEA) were seen to have resistance of chloroquine in *Plasmodium vivax* with most cases seen in North-eastern coast of Indonesian Papua (Sumawinata et al., 2003). The multidrug resistant strain of *Plasmodium falciparum* developed quickly spreading throughout SEA in the 1980s-1990s. The most severe strains were seen in the border of Cambodia-Thailand (Song et al., 2011). On the other hand, resistance towards sulfadoxine-pyrimethamine was first reported on Thai-Cambodian during the 1960s (Malikkul, 1988). Thus, to minimise the spread of resistance and increase the effectiveness of malaria treatment, WHO recommended the usage of ACT (Song et al., 2011; Zhang et al., 2020). ACT offered the best first line treatment for all species of *Plasmodium* infecting humans (White et al., 2014).

However, years of ACT usage in SEA has resulted in the development of artemisinin resistance in this region. The use of this drug as a monotherapy could have played a role in this resistance development (Ashley et al., 2018). Artemisinin resistant *Plasmodium falciparum* parasites emergence was first seen in the Greater Mekong sub region and was later spread to India and Africa (Imwong et al.,

2020). The rise towards artemisinin resistance portrayed a threat toward ACT as it selects for the resistance toward the partner drug (Ashley et al., 2015) (Dondorp et al., 2012). In Myanmar, ACT comprising of artesunate – mefloquine treatment failed and dihydroartemisinin–piperaquine saw a failure across Cambodia, northeast Thailand, and southern Vietnam (Amaratunga et al., 2016) (Phyo et al, 2016) (Thanh et al, 2017).

Ashley et al., (2015) reported that the rise in the artemisinin resistance was caused by the mutations in the Kelch 13 region of *Plasmodium falciparum*. Among 50 *Pf*-K13 mutations studied, nine have been associated with artemisinin resistance (Chhibber-Goel & Sharma, 2019). An increase in resistant strains toward current treatment is a threat to the global initiative of malaria eradication leading towards the urgency of new antimalarial discovery (WHO, 2020).

2.3 Medicinal plants

Since the beginning of time, natural products extracted from plants and animal sources have been used in traditional medicine (Lemma et al., 2017; Newman et al., 2000). Historical records that date back 5000 years ago showed evidence on the usage of plants for medicinal purposes (Süntar, 2019). Thus, medicinal plants (as a whole or parts of the plant) have been conventionally used as a source of therapeutic agents in drug discoveries due to their diverse chemical structures (Amit Koparde et al., 2019). Nowadays, an estimated 80% of drugs ranging from antimicrobial to anticancer originated from plant sources (Pan et al., 2013). Yet, out of 75, 000 species of plants in the world, only 10 % have been utilised in traditional medicine and only 1 to 5 % of plants have been studied (Amit Koparde et al., 2019). This shows the potential of medicinal plant exploration for new drug discovery.

2.3.1 Medicinal plants and Southeast Asia

Since ancient times, there was a strong association between medicinal plants and SEA countries (Lee & Houghton, 2005). History of medicinal plants in Indonesia were found on the walls of ancient

temples on Java while the earliest reports of the usage of traditional Indonesian plants were found in the 16th century. In Malaysia, the history of medicinal plants is strongly associated with its cultural diversity, having the influence from cultures of China, India and Java. The Thai traditional medicine system was adapted from the Ayurvedic system with a strong influence from Thai culture (Padua et al., 1999). This long history of medicinal plants usage is vital in the pharmaceutical industry (Mitra et al., 2007) (Sanusi et al., 2017).

Today, medicinal plant usage still remains popular in SEA among both populations living in the city as well as rural areas (Shein, 2001). Lack of access towards modern medicine, low socioeconomic and unavailability of health care services are contributing factors towards the widespread of traditional medicine usage in SEA (de Boer & Cotingting, 2014). Thus, studies on medicinal plants in this region are vital to develop safe traditional medicine practices.

SEA is the home for over 2200 medicinal plants with only 59% of it being explored leaving the remaining diverse plants unexplored (Anuar & Ismail, 2020). This diversity serves as a potential for the exploration of novel biologically active compounds (Mitra et al., 2007).

Several studies have proved that plants found in SEA have angiotensin converting enzyme inhibiting properties, usage in women's healthcare, anti-cytotoxic, anti-tuberculosis as well as anti-diabetic properties (Anuar & Ismail, 2020; de Boer & Cotingting, 2014; Lee & Houghton, 2005; Sanusi et al., 2017; Wan Ahmad Wan-Nadilah et al., 2019). These findings prove the importance and potential of medicinal plants in SEA to be explored as new therapeutic agents.

2.3.2 Medicinal plants with antimalarial activity

There has always been a strong association between medicinal plants and antimalarial drugs since the beginning of time. In fact, the modern antimalarial drugs are derived from medicinal plants, their analogues were designed using the pharmacophores from these plants (Silva et al., 2011). According to Bourdy et al., (2008), some of the actively used antimalarial drugs have a connection with medicinal plants (see Table 2.1).

Table 2.1: Antimalarial drugs formulated from medicinal plants (Bourdy et al., 2008).

Medicinal plant	Natural compound	Derivatives
***Cinchona* spp. (Rubiaceae)**	Quinine	Quinidine, cinchonine and stereoisomeric cinchonidine
***Artemisia annua* L. (Asteraceae)**	Artemisinin	Arteether, artemether, artesunate, artelinate, dihydroartemisinin
***Tabebuia* spp. (Bignoniaceae)**	Lapachol	Atovaquone

Looking back into history, in 1820, quinine was the first isolated active compound from the barks of cinchona tree utilized for the treatment of malaria. Since then many natural and synthetic products were developed such as mepacrine, chloroquine, mefloquine and halofantrine (Tse et al., 2019). As the resistance towards these agents rose, the search for another natural based product started leading to the discovery of *Artemisia annua* from Chinese herbal medicine (David Phillipson & Wright, 1991; Newman et al., 2000). Medicinal plants from the genus *Artemisia*, *Cinchona*, *Cryptolepis*, and *Tabebuia* genera are not the only ones used in antimalarial drug discovery. Other herbs such as *Syzygium cordatum* Hochst. ex Krauss, *Scrophularia umbrosa* Dumort, *Astrodaucus persicus* (Boiss.) Drude and *Eremostachys molucelloides* Bunge were also studied for their antimalarial potency

(Mohammadi et al., 2020). This proves that medicinal plants are often used to synthesize antimalarial agents.

A study conducted in Ethiopia highlighted 200 different species of medicinal plants from 71 different plant families that were used in traditional malaria treatment (Alebie et al., 2017). Furthermore, Ntie-Kang et al., (2014) reported on chalcones, flavanones, isoflavonoids and retinoids derived from African medicinal plants showed promising antimalarial properties. Tajuddeen & Van Heerden (2019) reported on 447 compound studied from 2010 to 2017 that had an IC_{59} value of ≤ 3.0 μM against *Plasmodium falciparum.* 39% of these compounds were novel and has potential to be developed into antimalarial drugs. Another study conducted reported that 1277 species from herbal plants were used in treating malaria (Willcox & Bodeker, 2004). Similarly, 187 compounds from African medicinal plants showed significant antimalarial activity in studies conducted between 2013 and 2019 (Bekono et al., 2020).

According to Burkill (1966), as cited (David Phillipson & Wright, 1991), SEA consists of 210 medicinal plants that were listed as potential treatments for malaria. Medicinal plants of Malaysian origin such as *Piper sarmentosum*, *Andrographis paniculata* and *Tinospora crispa* demonstrated antimalarial activities in in vivo and in vitro studies (Najib Nik A Rahman et al., 1999). In Indonesia, plants such as *Alstonia scholaris* and C*arica papaya* exhibited antimalarial activities in in vitro assays (Budiarti et al., 2020). All of these studies and findings can conclude that medicinal plants in SEA countries has the potential to be developed into new antimalarial agents.

CHAPTER 3

METHODOLOGY

3.1 Study process

This systematic review was conducted in accordance with the (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) PRISMA guidelines. These guidelines were developed to allow researchers to produce an accurate reporting of systematic review. This in turn will aid evidence based decision making. The guidelines of the protocol (Page et al., 2021) have been supplemented (see Appendix A). The study process commenced with the development of a research question to identify the objectives needed to achieve. This acted as a guide to aid the researcher in

achieving the goals throughout the study. This section presents the eligibility criteria, information sources and the search strategy respectively.

3.1.1 Eligibility criteria

The eligibility criteria was formed based on the SPIDER guidelines (Cooke et al., 2012) to ease the construction of the search protocol.

3.1.1.1 Sample

All medicinal plants or traditionally used plants from SEA were included in this study. The plants must be of SEA origin and widely distributed in this region.

3.1.1.2 Phenomenon of Interest

The study looked into the antimalarial/ antiplasmodial properties exhibited by the medicinal plants found in SEA.

3.1.1.3 Design

All experimental studies involving animal models (in vivo) and in vitro studies were included in this systematic review.

3.1.1.4 Evaluation

The evaluation of the phenomenon of interest was done based on the percentage of inhibition of parasitemia for in vivo studies. For in vitro studies, the evaluation was done based on the IC_{50} value of the extracts.

3.1.1.5 Research type

All qualitative, quantitative and mixed-methods research was searched for and included in this study.

3.1.2 Information sources

Only online bibliographic databases for published journal articles were used in this systematic review. A total of five databases were used for the search; PubMed, Scopus, Science Direct, Google Scholar and Wiley Online Library. These databases are well established, hold a large number of peer-reviewed journals and are kept up to date. More than two databases were chosen to make sure the search is comprehensive and to reach an accurate conclusion (Zhao, 2014).

3.1.3 Search strategy

The search protocol was constructed based on the above SPIDER guidelines. A combination of keywords (medicinal plants, Southeast Asia and anti-malarial) was adopted to formulate the search protocol. Other techniques such as the usage of Boolean operators, truncation and filters were applied and customised for each database. The search limits for the review were (i) journal articles in English language, (ii) availability of full text articles and (iii) articles published within a 20 year range. Non English articles, thesis, reviews and conference articles

were excluded from this systematic review. The search protocol used for each database is as follow:

3.1.3.1 PubMed

(Traditional OR medicinal* plant* OR herb* OR extract*) AND (Southeast Asia OR south-east Asia OR Myanmar OR Thailand OR Malaysia OR Indonesia OR Laos OR Vietnam OR Timor-Leste OR Brunei OR Singapore OR Philippines OR Cambodia) AND (anti-malaria * OR anti-malarial* OR anti malaria OR antimalarial OR anti plasmodium OR antiplasmodial)

3.1.3.2 Scopus

(Traditional OR medicinal* plant* OR herb* OR extract*) AND (Southeast Asia OR south-east Asia OR Myanmar OR Thailand OR Malaysia OR Indonesia OR Laos OR Vietnam OR Timor-Leste OR Brunei OR Singapore OR Philippines OR Cambodia) AND (anti-malaria * OR anti-malarial* OR anti malaria OR antimalarial OR anti plasmodium OR antiplasmodial)

3.1.3.3 Science Direct

(Traditional OR medicinal plant OR herb OR extract) AND Southeast Asia AND (anti malaria OR antimalarial OR anti plasmodium OR antiplasmodial)

3.1.3.4 Google Scholar

(Traditional OR medicinal plant OR herb) AND (southeast Asia OR south-east Asia OR Myanmar OR Thailand OR Malaysia OR Indonesia OR Laos OR Vietnam OR Timor-Leste OR Brunei OR Singapore OR Philippines OR Cambodia) AND (antimalaria OR anti plasmodium)

3.1.3.5 Wiley Online Library

(Traditional OR medicinal* plant* OR herb* OR extract*) AND (southeast Asia OR south-east Asia OR Myanmar OR Thailand OR Malaysia OR Indonesia OR Laos OR Vietnam OR Timor-Leste OR Brunei OR Singapore OR Philippines OR Cambodia) AND (anti-malaria * OR anti-malarial* OR anti malaria OR antimalarial OR anti plasmodium OR antiplasmodial)

3.2 Study selection

All studies that fulfilled the eligibility criteria and search limits were included in the systematic review. The following steps were conducted by two independent reviewers.

3.2.1 Screening

All articles screened were collected into reference manager Mendeley and Java, Alver, Batada, Reference (JabRef). The selection process was conducted in 3 phases. The flowchart of the process is presented in the figure below (Figure 3.1).

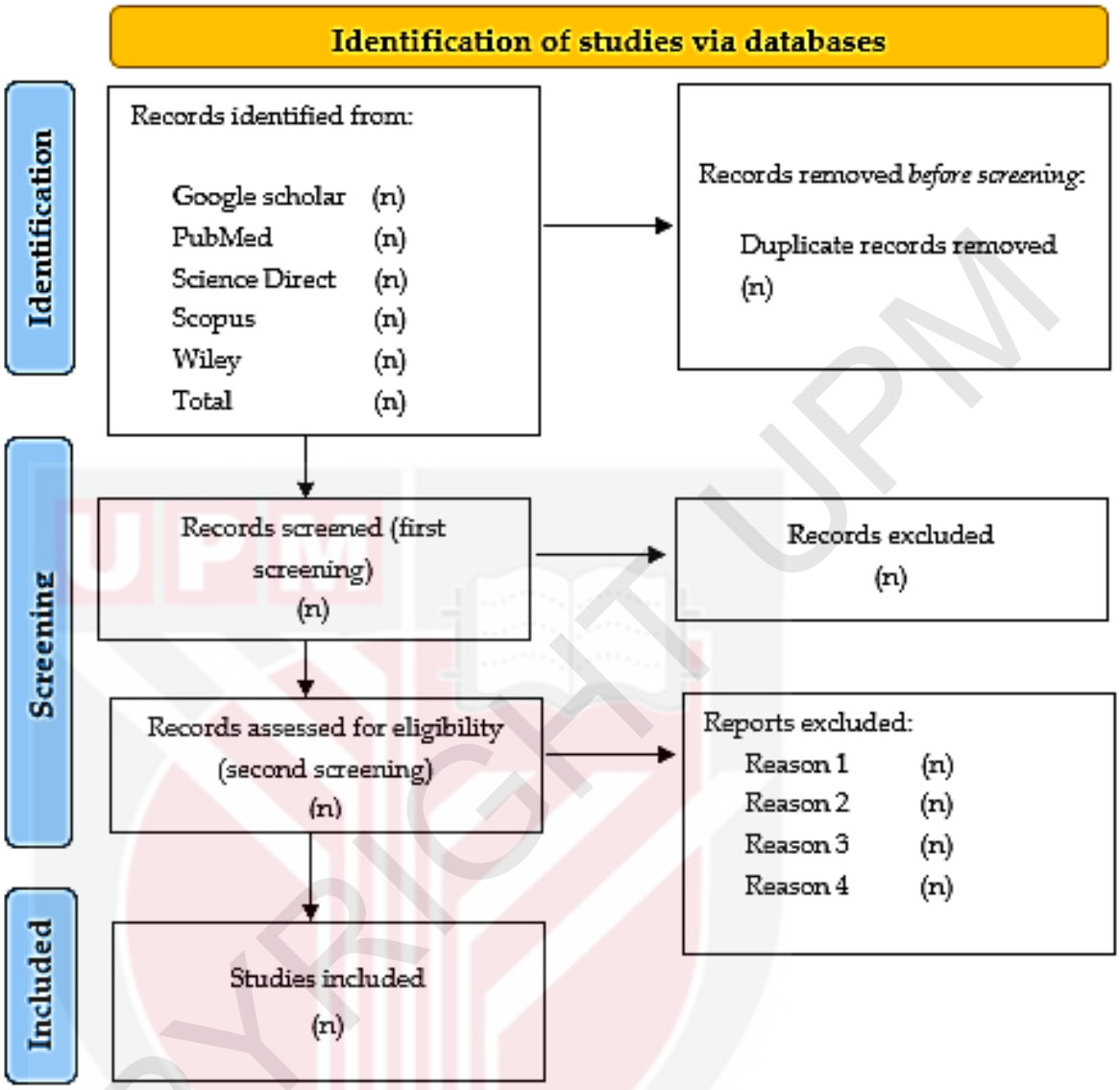


Figure 3.1: PRISMA flow diagram of study selection. The three phases are identification, screening and inclusion.

3.2.1.1 Identification of articles

Through the search in five databases using their respective search protocols, the articles were identified. The articles were collected into the reference managers to remove any duplicates.

3.2.1.2 First screening

The first screening was done based on the title and abstract of the articles. After excluding the duplicates, the remaining articles were screened. Papers with titles and abstracts unrelated to the systematic review were excluded.

3.2.1.3 Second screening

For the second screening, all remaining articles were accessed by reading the full text version of the articles. Articles that did not fulfil the eligibility criteria were excluded with reasons. This final step allowed the researcher to proceed with data extraction and analysis of the remaining papers.

3.2.2 Optimization

Optimization for the previous protocol was done to ensure a more updated and comprehensive results can be obtained. The initial search limit of the protocol was within a 20 year range. However, this yielded backdated results in which most findings were dismissed during the later years. Thus, upon discussion, it was agreed to amend the search limit of 20 years to 6 years. This allowed the researcher to obtain newer studies and produce a more focused systematic review.

3.3 Data extraction

All relevant data from the included studies were extracted using Microsoft Excel spreadsheet. The information extracted included (i) author's name, (ii) title, (iii) year of study, (iv) place of plant collection, (v) name of plant, (vi) part of plant used, (vii) extract used, (viii) active compound, (ix)study design, (x) antimalarial assay, (xi) IC_{50} doses, (xii) percentage of parasitemia inhibition, (xiii) comparison, (xiv) mechanism of action and (xv) outcome. The template has been supplemented (see Appendix B). The extraction process was conducted independently by two reviewers. It was then followed by the risk of bias (quality) in individual studies assessment.

3.3.1 Risk of bias in individual studies

The risk of bias (RoB) in individual studies assessment or quality assessment is an important step to ensure there is transparency in the synthesized data and results of the systematic review. Different studies require different RoB tools. Thus, this section discusses the RoB tools used for the in vitro and in vivo studies respectively.

3.3.1.1 In vitro RoB tool

For the assessment of in vitro studies, the Checklist for Reporting In-vitro Studies (CRIS) (Krithikadatta et al., 2014) was used. There is no established tool to evaluate the quality of in vitro studies. Thus, based on previous systematic reviews of in vitro studies, the CRIS tool was implied with some modifications. This tool assessed the 6 domains of reporting bias, performance bias, detection bias, selection bias, attrition bias and other biases. The domains were given low, unclear or high RoB assessments (Ebrahimzadeh Attari et al., 2017).

3.3.1.2 In vivo RoB tool

For the assessment of in vivo studies, the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) tool was used. It is an enhanced version of the Cochrane Rob tool. This tool comprises 10 items to assess the quality of method of animal intervention studies (Ma et al., 2020). The 10 entries are linked to 6 types of bias which are performance bias, reporting bias, selection bias, attrition bias and other biases. The checklist (Hooijmans et al., 2014) has been supplemented (see Appendix C).

3.4 Data synthesis

The data were analysed according to the objectives and research question of the study. Two types of numerical data were obtained depending on the type of study; percentage of parasitemia inhibition for in vivo studies and IC_{50} values for in vitro studies. The findings were summarized in a narrative and statistical synthesis and are shown in the next chapter.

The data of in vivo studies were analysed according to the classification by Deharo et al (2001). The extracts that exhibited a percentage of parasitemia inhibition of more than 50% at 750 mg/kg/day, equal or >50% at the dose of 500 mg/kg/day, ≥50% at the dose of 250 mg/kg/day and equal to 50% at the dose of 100 mg/kg/day were classified as weak, moderate, good and very good antimalarial activity respectively (see Table 3.1).

Table 3.1: Classification of antimalarial activity for in vivo studies

Dose of extract (mg/kg)	Percentage of parasitemia inhibition	Category of activity
750	>50%	Weak
500	>50%	Moderate
250	≥50%	Good
100	50%	Very good

The modified classification by Rasoanaivo et al (2004) was adapted to classify the IC_{50} values of the in vitro studies. The IC_{50} values of < 0.1, 0.1–1, 1–10, 10–25 and >25 μg/ml were categorised as having very good, good, moderate, weak and inactive antimalarial activity respectively (see Table 3.2). Results in μM will be converted to μg/ml using an online convertor.

Table 3.2: Adapted classification of antimalarial activity for in vitro studies

IC_{50} (μg/ml)	Category of activity
< 0.1	Very good
0.1–1	Good
1-10	Moderate
10-25	Weak
>25	Inactive

3.4.1 Statistical analysis

Statistical procedures were carried out using Microsoft Excel. The analysed data is presented in the form of tables and charts using descriptive statistical methods. All results are presented in the next chapter.

CHAPTER 4

RESULTS

4.1 Search results

The keywords used as search items for each database are specified in the previous chapter (see section 3.1.3). A total of 2723 papers were retrieved from five databases. This consisted of 1113 papers from Google scholar, 502 papers from PubMed, 850 papers from ScienceDirect, 5 papers from Scopus and 253 papers from Wiley Online Library. The total number of papers was reduced to 2610 upon removal of 113 duplicates through Mendeley as well as manually.

The first screening was conducted based on the title and abstracts of the paper to eliminate those unrelated to the objectives of this study. A total of 2305 papers were excluded leaving 305 papers for the second screening. During the second screening, the papers were evaluated based on the previously mentioned eligibility criteria (see section 3.1.1). Here, a total of 183 papers that did not meet the eligibility criteria were removed resulting in 122 papers included for the analysis. The reasons for exclusion of the 183 papers will be discussed in the next section. Upon reviewing the 122 papers, optimization of the methodology was conducted (see section 3.2.2). Finally, a total number of 36 papers were chosen for the data analysis and synthesis. A summary of the search results is illustrated in Figure 4.1 based on the PRISMA flow diagram.

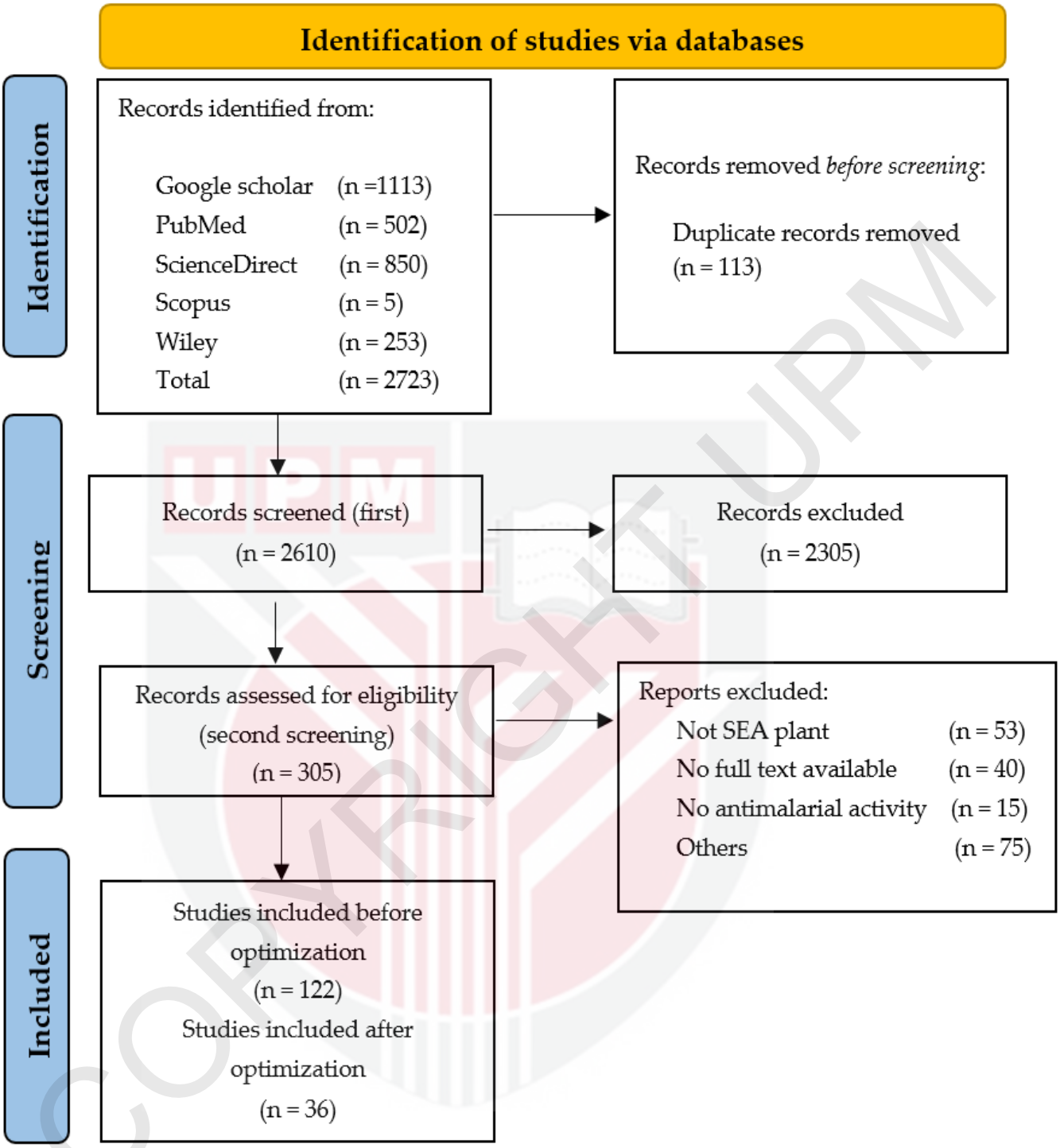


Figure 4.1: PRISMA flowchart of search results.

4.2 Study selection

A total of 36 papers from the year 2016 to 2021 were chosen for the analysis. The studies selected for the data analysis are listed in Table 4.1. Among the reasons for selection of the papers were the plants investigated in the studies were originated or predominantly found in Southeast Asia, the plants' antimalarial activity were investigated, an in vivo or in vitro model was used to study the plant and the results obtained in each study were significant.

For the excluded papers, a total of 53 papers were excluded as the plants investigated weren't of SEA origin. Other than that, 40 papers were excluded due to the inability to access the full article of these studies. The researchers of these papers were contacted for access, but no reply was obtained. 15 papers were excluded as it lacked antimalarial activity evaluation and 75 papers were excluded because of other reasons such as study design that was not suitable for this systematic review, poor methodology and results of the study were not significant. The full list of excluded studies is supplemented (see Appendix D).

4.3 Data extraction

The 36 studies were subjected to data extraction for the analysis. The data items extracted are mentioned in the previous chapter (see section 3.3). The complete data extraction based on the data items is listed according to type of study designs in Table 4.1, Table 4.2, and Table 4.3.

Table 4.1: Data extracted from in vitro studies selected for the data analysis.

PLANT COLLECTION	PLANT NAME	EXTRACT & PLANT PART	ACTIVE COMPOUND	BIOASSAY	IC50 DOSES	COMPARISON	MOA	OUTCOME	REFERENCE
Malaysia	Uvaria grandiflora, Chilocarpus costatus, Leuconotis eugenifolius, Tabernaemontana peduncularis, Amomum subulatum, Curcuma aeruginosa	chloroform extract of leaves, stems, leaves, stems, fruits, rhizomes	pinoresinol (costatus), zeylenol and ferrudiol (grandiflora), leuconolam (4) and epi-gallocatechin (eugenifolius), furanodienone (aeruginosa)	P. falciparum 3D7, K1 strains	furanodienone (17, K1), 3.7 (grandiflora), 1.3 (costatus), 3.0 (eugenifolius), 1.1 (pedunculris), 4.8 (subulatum), 4(aeruginosa)	chloroquine and dihydroartemisinin	not mentioned	plant extracts exhibited antimalarial activity	Azman et al., 2018
	Phoebe tavoyana	hexane followed by chloroform extract of leaves	roemerine (3), laurolitsine (4), boldine (5), and sebiferine (6)	P. falciparum 3D7 clone	0.89 (3), 1.49 (4), 1.65 (5), and 2.76 (6) mg/ml	chloroquine	not mentioned	growth inhibition	Omar et al., 2018
	Alseodaphne corneri Kosterm and Dehaasia longipedicellata	DCM extract of Leaves (ac), barks (dl)	isocorydine (1) and norisocorydine (2), boldine (3)	chloroquine-resistant FcB1 strain of P. falciparum	19.8 (2), 51.30 (1), 2.6 (3)	chloroquine	antioxidant properties of active compounds	plant extracts exhibited antimalarial activity	Zahari et al., 2016a
	alseodaphne corneri Kosterm	DCM extract of Bark	gyrolidine (1), O-meth-yllimacusine (2), 2-	chloroquine resistant P. falciparum strain K1	0.666 (gyrolidine), 1.193 (methyllimaa),	chloroquine diphosphate	inhibition of hemozoin formation	plant extracts exhibited antimalarial activity	Zhari et al., 2016b

			norobaberine (3), -norstephasubine (4),-stephasubine (5), and laurotetanine(6)		0.743 (noro), 0.189 (laura), 0.116 (norstep), 1.315 (step)				
	Quercus infectoria	acetone, methanol, ethanol and aqueous extracts of galls	phytochemicals (non-specific)	Chloroquine-sensitive P. falciparum (3D7 strain)	acetone (5.85), methanol (10.31), ethanol (20), aqueous (30.95)	artemisinin	antioxidant properties of active compounds	plant extracts exhibited antimalarial activity	Zin et al., 2020
	Goniothalamus lanceolatus Miq.	hexane, DCM and methanol extracts of stem bark and roots	comp c - Parvistone D	chloroquine-sensitive (3D7) and chloroquine-resistant (K1) strains of P. falciparum	DC, leaves (12.6), hexane leaves (25.1), hexane stem (25.1), hexane root (11.4), methanol stem (11.4), methanol root extract (2.7 µg/ml), comp C (7.5), comp D (19.5)	chloroquine diphosphate and artemisinin	not mentioned	plant extracts exhibited antimalarial activity	Kaharudin et al., 2020
Thailand	Uvaria cherrevensis	methanol extract of fruit	cherrevenones (1) and 3), uvarindole C (5), and uvarindole A (11)	Plasmodium falciparum (TM4/8.2, a wild type sensitive strain and	1 - 21 (K1) , 3 - 43.5 (K1), 5-28.3 (K1) & 11 -, 29.3 (K1), µM	cyclogianil and pyrimethamine	not mentioned	compound 1,3,5 and 11 showed antimalarial activity	Auranwiwat et al., 2018

				K1CB1, a multidrug resistant strain)					
	Uvaria cherrevensis	acetone extract of stem and root	cherrevenapthalenes A (1), cherrevenapthalenes B (2) & 2-hydroxy-3-methoxy-6-(4′-hydroxyphenyl)naphthalene (5)	(TM4/8.2, a wild type sensitive strain and K1CB1, multidrug resistant strain)	1 - 21.1 (T), 24.2 (k1), 2 - 18.8 (T), 23,4 (K1), 5 - 22.3 (T), 23.4 (K1)	cyclogianil and pyrimethamine	not mentioned	compounds 1,2 and 5 showed antimalarial activity	Auranwiwat et al., 2017
	Brucea javanica	aceetone extract of stems	brujavanol C (1) and brujavanol D (2), brujavanol A (3), bruceine E (4), 5a,14b,15b-trihydroxyklaineanone (5), bruceine D (6), bruceine H (7), and bruceine F (8)	Plasmodium fal- ciparum (K1, multidrug-resistant strain)	1.41 (com 6), 1.06 (comp 7). 4.37 (comp 4), 3.85 (comp 8), 5.39 (comp 5), 25.35 (comp 1), 30.49 (comp 2)	dihydroartemisinine	structure of a,b-unsaturated ketone group at C-2 in the A-ring and an oxymethylene bridge linking C-8 and C-13	compounds 1,2,6 and 7 showed antimalarial activity	Chumkaew et al., 2016
	Kaempferia parviflora, punica granatum, and Annona muricata L	ethanol extracts of rhizome (kp), fruit peel and bark (pg) leaves (am)	not mentioned	P. falciparum 3D7	28.7 (kp), 7.8 (pg fruit peel), 4.9 (pg bark) and 46.1 (am)	chloroquine	Pg-FET inhibit proinflammatory mechanisms	plant extracts exhibited antimalarial activity	Leesombun et al., 2019

	tiliacora triandra	methanol extract of stem	tiliacorinine and yanangcorinine	chloroquine-sensitive strain (Pf3D7) and a chloroquine-resistant strain (PfW2) of Plasmodium falciparum	1.33 (3D7), 3.42 (pfW2), tiliacorinine (2.14), yanang (1.55) for pfw2	chloroquine diphosphate	not mentioned	plant extracts exhibited antimalarial activity	Nutmakul et al., 2016
	Tiliacora triandra	DCM extracts of stem and roots	tiliacorinine and yanangcorinine	Plasmodium falciparum chloroquine-resistant strain (PfW2)	tilia (0.94), yanang (0.51), tt stem (4.57), tt roots (4.73), BLW stems (4.1), BLW root (5.58)	chloroquine diphosphate	apoptosis of parasites in ring stage	growth inhibition	Nutmakul et al., 2020
	Miliusa velutina	hexane, ethyl acetate and methanol extract of fruits and flowers	Miliusanone A (2), Miliusanone B (3), methyl-2-(1′β- geranyl-5′β-hydroxy-2′-oxocyclohex-3′-enyl)acetate (6), 2-(1′β-geranyl- 5′β-hydroxy-2′-oxocyclohex-3′-enyl)acetic acid (7)	Plasmodium falciparum (K1, multidrug resistant strain)	3.8 92) 5.2 (3) 3.3 (6) and 3.9 (7) μg/mL	mefloquine and dihydroartemisinin	not mentioned	compounds 2,3,6 and 7 demonstrated antimalarial activity	Promgool et al., 2019

	Mitrephora tomentosa	methanol extract of leaves and twigs	mitrephentosin C (3), mitrephentosin E (5), mitrephentosin F (6)	Plasmodium falciparum TM4/8.2 (a wild type sensitive strain) and K1CB1 (a multidrug-resistant strain)	3 - 14.9 (TM4) 13.3 (K1), 5 - 24.6 (TM4), 6 - 20.4 (TM4), 18.7 (K1)	cyclogianil and pyrimethamine	not mentioned	compounds3,5 and 6 showed antimalarial activity	Wongsombon et al., 2021
	Garcinia mckeaniana	acetone extract of flowers and twigs	1,3,6-trihydroxy-7-methoxyxanthone (15) & [1,10-biphenyl]-2-(3-methyl-2-butenyl)-3-methoxy-4,40,5,6-tetraol (16)	Plasmodium falciparum strains, TM4/8.2 and K1CB1 (wildtype and multidrug resistant strains)	23.6 (15) and 39.4 (16) against TM4/8.2 and 27.1 (15) and 43.1 (16) μM against K1CB1	none	not mentioned	compounds 15 and 16 showed antimalarial activity	Auranwiwat et al., 2019
Indonesia	Alectryon serratus	ethanol extract of leaves	gallic acid, methyl gallate, Kempferol-3-O-rhamnoside)	chloroquine sensitive P. falciparum 3D7 strain (chloroquine sensitive)	0.013, 0.0025, and 1.495 μg/mL (gallic acid, methyl gallate, kaempferol),	not mentioned	antioxidant properties of active compounds	reduced parasitemia and growth inhibition	Khasanah et al., 2021
	Dipterocarpus littoralis	methanol extract of stem bark	α-VINIFERIN	P. falciparum 3D7 clone	ethyl acetate fraction (3.42), comp 1 (2.76)	chloroquine	not mentioned	plant extracts exhibited antimalarial activity	Lulan et al., 2020

	Tithonia diversifolia	methanol extract of leaves	F6 - terpenes	Plasmodium falciparum FCR3 strain (chloroquine -resistant)	F6 (13.63±1.43), F7 (23.27 ±2.07)	not mentioned	cytocidal effects at early rings to late trophozoit es	reduced parasitemia and growth inhibition in a dose and time dependent manner	Syarif et al., 2018
	Garcinia celebica	Leaves	catechin	Chloroquine-resistant P. falciparum strain DD2	198 μM (dose dependent)	chloroquine	inductionn of oxidative stress	reduced parasitemia and growth inhibition is a dose and time dependent manner	Abdullah et al., 2017
	Tabernaemo ntana macrocarpa Jack	methanol extract of barks	dimeric alkaloid, 16-demeth-oxycarbonylvo acamine	P. falciparum strain 3D7	28.8 μM	artemisinin	not mentioned	fraction 9 and compound 4 showed antimalarial activity	Amelia et al., 2019
Vietnam	Stephania dielsiana	methanol extract of leaves	thailandine	chloroquine-sensitive 3D7 and chloroquine-resistant W2 strain	MB2L-CH (4.5 μg/mL), MB2L-B (5.8 μg/mL)	chloroquine, mefloquine and dihydroartemisinin	endocytosi s inhibition of parasites	growth inhibition	Knockleby et al., 2020
	Stephania venosa	DCM extract of tubers	stephanine, crebanine, O-methylbulboca pnine	chloroquine-susceptible 3D7 and chloroquine-resistant strain W2	dichlorometth ane extract - 0.31 ± 0.12 μg/mL, 0.33 ± 0.15 μg/mL (3D7, W2). Stephanine	chloroquine, monodesethylamod iaquine, lumefan-trine, mefloquine and dihydroartemisinin	not mentioned	plant extracts exhibited antimalarial activity	Le at al., 2017

					(0.69 ± 0.15 μM (0.21 ± 0.06 μg/mL) against 3D7 and 1.32 ± 0.38 μM (0.41 ± 0.12 μg/mL) against W2). crebanine, exerted IC50 of 1.56 ± 0.22 μM (0.21 ± 0.07 μg/mL) against 3D7 and 2.16 ± 0.38 μM (0.73 ± 0.13 μg/mL) against W2. O-methylbulbocapnine 5 showed IC50 of 2.81 ± 0.46 μM (0.95 ± 0.16 μg/mL) against 3D7 and 5.71 ± 0.62 μM (1.93 ± 0.21 μg/mL) against W2.				

Table 4.2: Data extracted from in vivo studies selected for the data analysis.

PLANT COLLECTION	PLANT NAME	EXTRACT & PLANT PART	ACTIVE COMPOUND	BIOASSAY	INHIBITION %	COMPARISON	MOA	OUTCOME	REFERENCE
Malaysia	Curcuma longa	not mentioned	curcumin	CQ-sensitive P. berghei NK65 strain	67.60%	chloroquine	inhibition of GSK3b causing NF-jB activation inhibited	reduced parasitemia in a dose dependent manner	Ali et al., 2017
	Tinospora crispa	methanol extract of stem	13(S)-HPODE (fraction 5)	P. berghei ANKA strain (chloroquine sensitive)	42.85% ± 0.58% (crude extract) and 41.01% ± 0.46% (fraction F4), 54.32 (fraction F5)	chloroquine	schizonticidal activity	reduced parasitemia in a dose dependent manner	Lee at al., 2020
Thailand	Betula alnoides	Aqueous extract of stems	suggested (triterpenoids)	chloroquine-sensitive P. berghei ANKA	58.39 % (400 mg/kg), 71.26 % (600 mg/kg), dose dependent	artesunate	not mentioned	reduced parasitemia in a dose dependent manner	Chaniad et al., 2019
	Moringa oleifera	Aqueous extract of leaves	phytochemicals (non-specific)	Chloroquine sensitive strain of Plasmodium berghei ANKA (PbANKA)	40 (100 mg/kg), 80 (1000 mg/kg), 85 (2000 mg/kg), curative test - 25 (100), 65 (1000), 70 (2000)	chloroquine diphosphate	antioxidant, free radical scavenging, immunomodulatory, intercalation in DNA, inhibition of protein synthesis, interference with the invasion of	plant extracts exhibited antimalarial activity	Dondee et al., 2016

							new erythrocytes by parasites		
	Moringa oleifera	aqeuous extract of leaves	not mentioned	Plasmodium berghei strain ANKA (PbANKA)	98%	none	antioxidant properties of active compounds	reduced parasitemia in a dose dependent manner	Nakinchat et al., 2017
	Tinospora baenzigeri	aqueous extract of stems	not mentioned	chloroquine-sensitive Plasmodium berghei ANKA strain (PbANKA)	22.02% (100 mg/kg) 50.81% (250 mg/kg), and 74.95% (500 mg/kg)	chloroquine	free radical scavenging, immunomodulatory, interference of protein synthesis, and inhibition of parasite invasion of new RBCs.	reduced parasitemia in a dose dependent manner	Ounjaijean et al., 2019
	Zingiber officinale	not mentioned	zingerone	Chlor- oquine-sensitive Plasmodium berghei strain ANKA (PbANKA)	45.75% (100 mg/kg), combo 1:1, zing:DHA - 95.01%	dihydroartemisinine	free radical scavenging, immunomodulatory, interference of protein synthesis, and inhibition of parasite invasion of new RBCs.	reduced parasitemia in a dose dependent manner	Ounjaijean et al., 2020
	Gynostemma pentaphyll	aqueous extract of leaves	phytochemicals (non-specific)	Drug sensitive-Plasmodium	55 (2000 mg/kg gp), combination (6	artesunate	not mentioned	reduced parasitemia in a dose	Somsak et al., 2016

	um and Moringa oleifera			berghei strain ANKA (PbANKA)	artesunate and 500 gp - 78, 1000 gp - 91, 2000 gp - 96), 50 (2000 mo), combination (6 artesunate and 500 mo - 73, 1000 mo - 82, 2000 mo - 91)			dependent manner	
	Gynostemma pentaphyllum	aqueous extract of leaves	phytochemicals (non-specific)	Plasmodium berghei ANKA (PbANKA)	57.6 (100 mg/kg), 78.4 (500 mg/kg), 89.6 (1000 mg/kg)	not mentioned	antioxidant properties of active compounds	plant extracts exhibited antimalarial activity	Somsak et al., 2017
	Annona muricata	aqueous extract of leaves	phytochemicals (non-specific)	Plasmodium berghei ANKA (PbANKA)	75.25 (500 mg/kg), 85.61 (1000 mg/kg)	chloroquine	inhibition of heme polymerization	reduced parasitemia	Somsak et al., 2016
Indonesia	Artocarpus champeden	methanol extract of stem bark	not mentioned	P. berghei ANKA	57.36% (±9.18)(20mg/kg), 64.48% (±5.38)(50 mg/kg), and 72.24% (±4.30)(100 mg/kg)	not mentioned	not mentioned	reduced parasitemia in a dose dependent manner	Widyawaruyanti et al., 2020
	Delonix regia and Carica papaya	ethanol extract of bark (DR), Leaves (CP)	phytochemicals (non-specific)	P.berghei	97%	sulfadoxine	not mentioned	reduction in parasite density and growth inhibition	Fatmawaty et al., 2017

Table 4.3: Data extracted from mixed design studies selected for the data analysis.

PLANT COLLECTION	PLANT NAME	PLANT PART	ACTIVE COMPOUND	BIOASSAY	IC50 DOSES	INHIBITION %	COMPARISON	MOA	OUTCOME	REFERENCE
Indonesia	Helianthus annuus	ethanol extract of roots and flowers, stems and seed	not mentioned	in vitro (Plasmodium falciparum strain 3D7 (chloroquine-sensitive), in vivo P. berghei	2.3 (roots), 4.3 (leaves), 4.8 (flowers)	63.6 (roots), 59.3 (leaves)	doxycycline	inhibition of heme detoxification	plant extracts exhibited antimalarial activity	Ekasari et al., 2019
Thailand	Pogostemon Cablin (Blanco) Benth	ethanol extract of aerial	phytochemicals (non-specific)	in vitro - chloroquine-resistant P. falciparum K1 strain. In vivo - Plasmodium ber- ghei strain ANKA	24.49 (in vitro)	38.41 (200 mg/kg), 45.12 (400 mg/kg) and 89.00% (600 mg/kg)	artesunate	not mentioned	plant extracts exhibited antimalarial activity	Phuwajaroanpong et al., 2020

4.4 Study characteristics

In this section, the included studies' characteristics are further discussed and illustrated in the form of graphs and charts. These include the types of studies if it is an in vivo or in vitro based study, year of publication, countries in which the plants were collected, the types of assay used to and the comparison to a standard drug.

4.4.1 Types of studies

Based on the included studies, the types of studies can be divided into three categories, in vitro, in vivo and mixed design. Mixed design studies are studies with both in vitro and in vivo experimentation. Among the included studies, 61% (22 papers) were in vitro studies, 33% (12 papers) were in vivo studies and 6% (2 papers) were mixed studies (see Figure 4.2). More in vitro studies were conducted in comparison to others. This could be due to the fact that in vitro screening are important primary steps in search for new antimalarial agents (Lima et al., 2015).

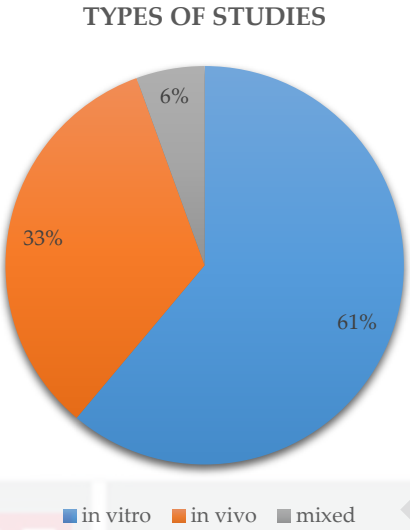
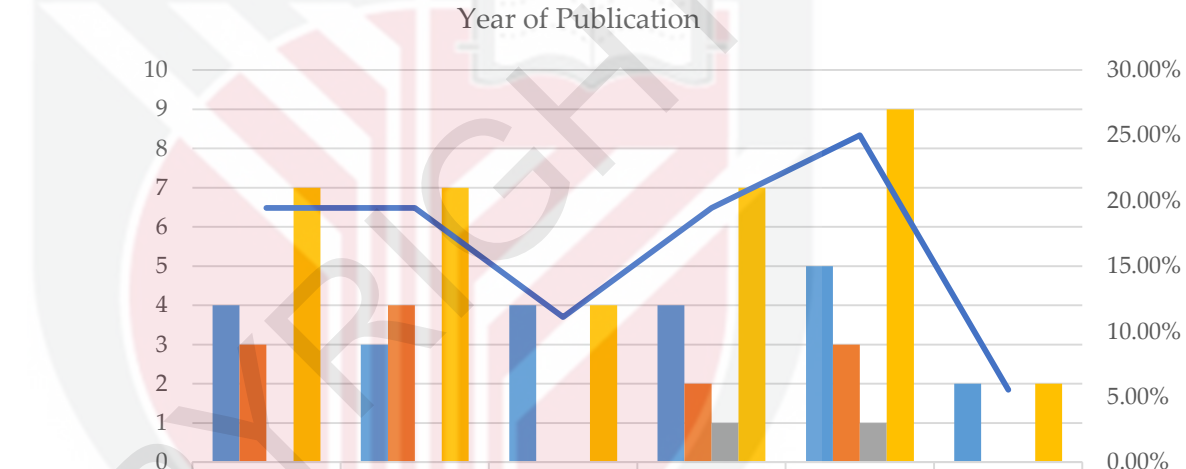


Figure 4.2: Types of studies based on the 36 included studies. 22 papers were in vitro studies, 12 were in vivo studies and 2 were mixed studies.

4.4.2 Year of publication

The year of publication for the included studies ranges from 2016 to 2021. The highest number of papers were published in the year 2020 with a total of 9 papers contributing to 25% of the data. Following this are the years 2016, 2017, 2019, 2018 and 2021 with 7, 7, 7, 4 and 2 papers respectively. The least number of papers were published in 2021. However, this low number could be contributed by the fact that the literature search was done in early February and ended in early March, thus not including all the months in 2021. A trend of increment in studies on medicinal plants in Southeast Asia (SEA) with antimalarial

activity can be seen from the year 2018 to 2020. If all months of 2021 were included, there is a possibility of seeing the same trend. This increment could be due to the urgency to look for new antimalarial drugs due to the widespread resistance towards current drugs in SEA (WHO, 2020). A summary of the data of year of publication is presented in Figure 4.3.



	2016	2017	2018	2019	2020	2021
In vitro	4	3	4	4	5	2
In vivo	3	4	0	2	3	0
Mixed	0	0	0	1	1	0
Total	7	7	4	7	9	2
Percentage	19.45%	19.45%	11.10%	19.45%	25.00%	5.55%

Figure 4.3: Year of publication of included studies.

4.4.3 Countries of plant collection

Based on the data of the included studies, there were four countries involved for the plant collection; Thailand, Malaysia, Indonesia and Vietnam. The country with the highest number of studies was Thailand with 18 studies, followed by Malaysia and Indonesia with 8 studies each and 2 studies from Vietnam (see Figure 4.4).

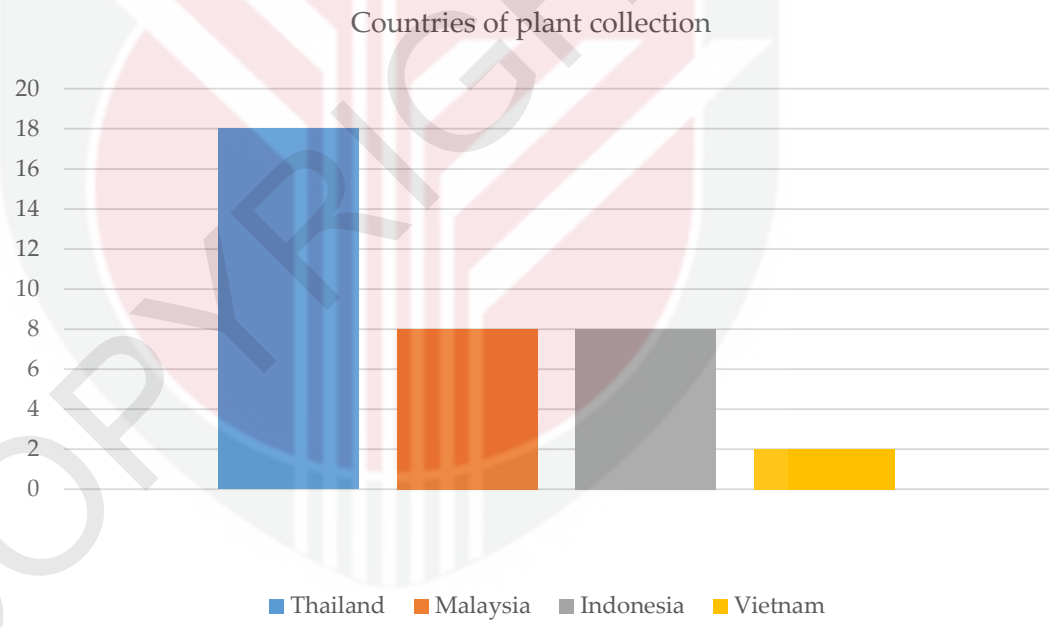


Figure 4.4: Countries of plant collection of included studies.

4.4.4 Types of bioassay

In the included studies, various bioassays were used to investigate the antimalarial properties of the plants under investigation. Based on the collected data, 69% of the studies were conducted using one type of bioassay while the other 31% used more than one type of bioassay in their investigation (see Figure 4.5). The analysis showed that most studies (13 papers) used Chloroquine sensitive *P.berghei* ANKA (CSPB ANKA) strain for their investigation while the least used bioassays were Chloroquine resistant *P.falciparum* FCR3 (CRPF FCR3) strain, Chloroquine resistant *P.falciparum* DD2 (CDPF DD2) strain as well as Chloroquine resistant *P.falciparum* FcB1(CRPF FcB1) strain with only one paper each. Other bioassays include Chloroquine sensitives *P.falciparum* 3D7 (CSPF 3D7) strain, multidrug resistant *P.falciparum* K1 (MRPF K1) strain and Chloroquine resistant *P.falciparum* W2 (CRPF W2) strain. Figure 4.6 shows a summary on the types of bioassay used in the included studies.

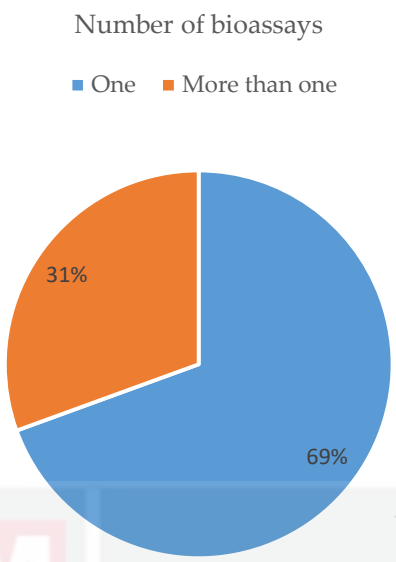


Figure 4.5: Number of bioassays used in the included studies to investigate the antimalarial properties of plant extracts.

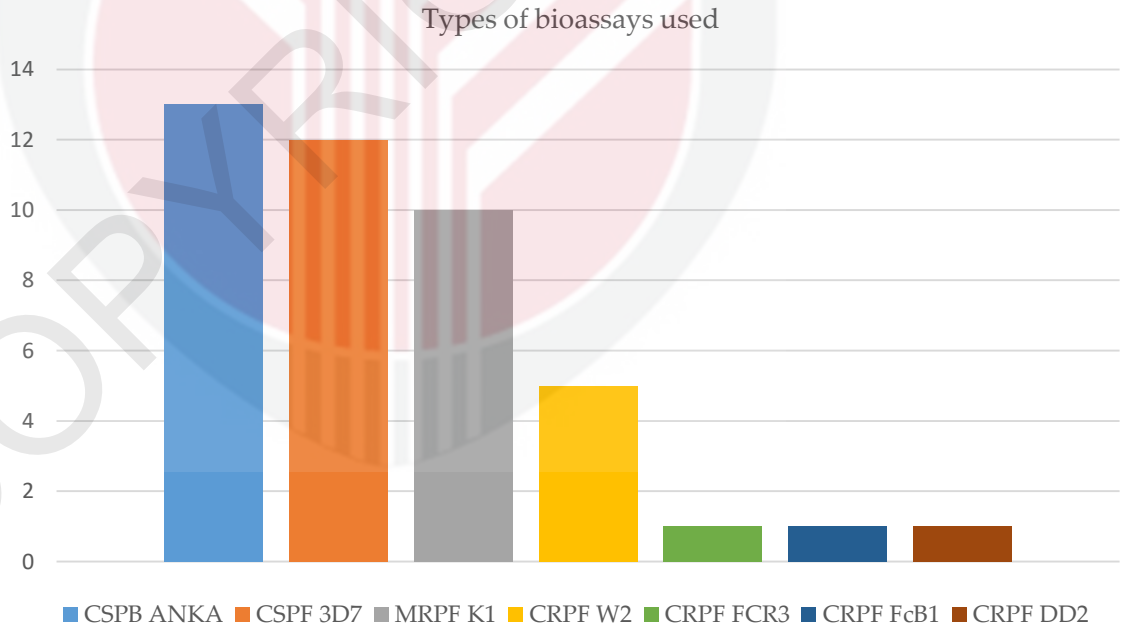


Figure 4.6: Types of bioassays used in the included studies to investigate the antimalarial properties of plant extracts.

4.4.5 Comparison

It is vital to have a standard drug as comparison when conducting an investigation against potential new therapeutic agents. In the included studies, 78% of the studies used only one comparison while 22% of the studies used more than one type of comparison (see Figure 4.7). The most used standard drug comparison is chloroquine in which 17 studies used it while the least drug used were sulfadoxine and doxycycline with one paper each that used it. Surprisingly, 6 papers had no comparison or did not mention the comparison of standard drugs used in the studies. A lack of standard drug usage could render the antimalarial potential of the studied plant questionable. A summary of the standard drugs used as comparison is illustrated in Figure 4.8.

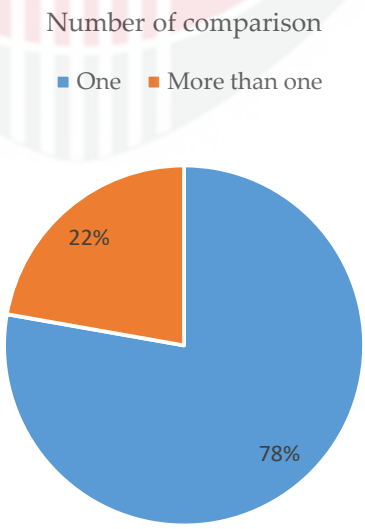


Figure 4.7: Number of standard drugs used in the included studies as comparison.

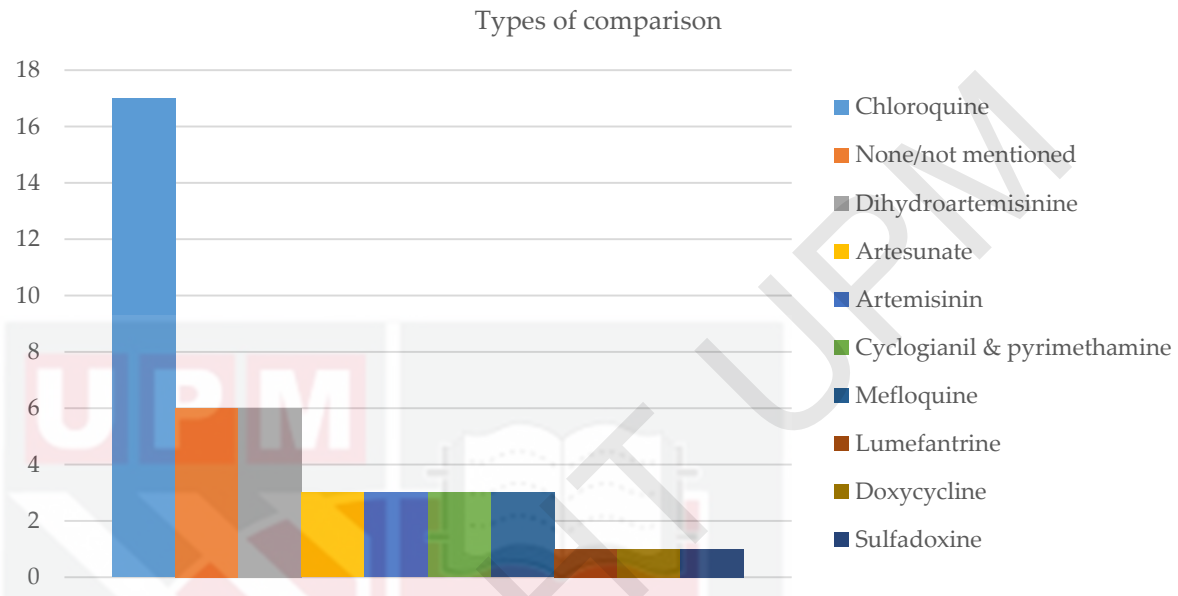


Figure 4.8: Types of standard drugs used as comparison in the included studies.

4.5 Medicinal plants with antimalarial properties

Overall, the 36 studies identified a total of 39 plant species throughout Southeast Asia that were studied for their antimalarial properties. Some studies were conducted on the same plant species, such as *Annona muricata* (Leesombun et al., 2019; Somsak et al., 2016b), *Gynostemma pentaphyllum* (Somsak et al., 2016a; Somsak et al., 2017), *Moringa oleifera* (Dondee et al., 2016; Nakinchat & Somsak, 2017; Somsak et al., 2016a) and *Uvaria cherrevensis* (Auranwiwat et al., 2017; Auranwiwat et al., 2018).

4.5.1 In vitro studies

Table 4.4 shows the plants studied using an in vitro based design in the included studies. The plants can be categorised based on 12 families (see Figure 4.9). These families are Annonaceae (6 plants) Apocynaceae (4 plants), Asteraceae (1 plant), Clusiaceae (2 plants), Dipterocarpaceae (1 plant), Fagaceae (1 plant), Lauraeae (3 plants), Menispermaceae (3 plants), Punicaceae (1 plant), Sapindaceae (1 plant), Simaroubaceae (1 plant) and Zingiberaceae (4 plants). The most number of plants were from the Annonaceae family. This could be because species of this family are predominantly found in SEA and have been widely used in traditional medicine as well (Chatrou et al., 2012). Plants from this family include *Uvaria cherrevensis, Uvaria grandiflora, Goniothalamus lanceolatus Miq, Annona muricata, Miliusa velutina* and *Mitrephora tomentosa*. Some plants belong to the same genus such as *Uvaria cherrevensis* and *Uvaria grandiflora, Curcuma aeruginosa* and *Curcuma longa, Garcinia celebica* and *Garcinia mckeaniana* as well as *Stephania dielsiana* and *Stephania venosa.*

Table 4.4: List of plants studied in the included in vitro studies.

PLANT COLLECTION	PLANT NAME	AUTHOR
Malaysia	Tabernaemontana macrocarpa Jack	Amelia et al. (2019)
	Uvaria cherrevensis	Auranwiwat et al. (2018)
	Uvaria grandiflora	Azman et al (2018)
	Leuconotis eugenifolius	
	Chilocarpus costatus	
	Tabernaemontana peduncularis	
	Amomum subulatum	
	Curcuma aeruginosa	
	Goniothalamus lanceolatus Miq	Kaharudin et al. (2020)
	Phoebe tavoyana	Omar et al. (2018)
	Alseodaphne corneri Kosterm	Zahari et al (2016)a
	Dehaasia longipedicellata	Zahari et al. (2016)b
	Quercus infectoria	Zin et al. (2020)
Thailand	Garcinia mckeaniana	Auranwiwat et al (2017)
	Brucea javanica	Chumkaew et al (2016)
	Kaempferia parviflora	Leesombun et al. (2019)
	Punica granatum	
	Annona muricata	
	Tiliacora triandra	Nutmakul et al. (2016)
	Tiliacora triandra	Nutmakul et al. (2020)
	Miliusa velutina	Promgool et al. (2019)
	Mitrephora tomentosa	Wongsomboon et al. (2021)
Indonesia	Garcinia celebica	Abdulah et al. (2017)
	Uvaria cherrevensis	Auranwiwat et al (2019)
	Alectryon serratus	Khasanah et al. (2021)
	Dipterocarpus littoralis	Lulan et al. (2020)
	Tithonia diversifolia	Syarif et al. (2018)
Vietnam	Stephania dielsiana	Knockleby et al. (2020)
	Stephania venosa	Le Mai et al. (2017)

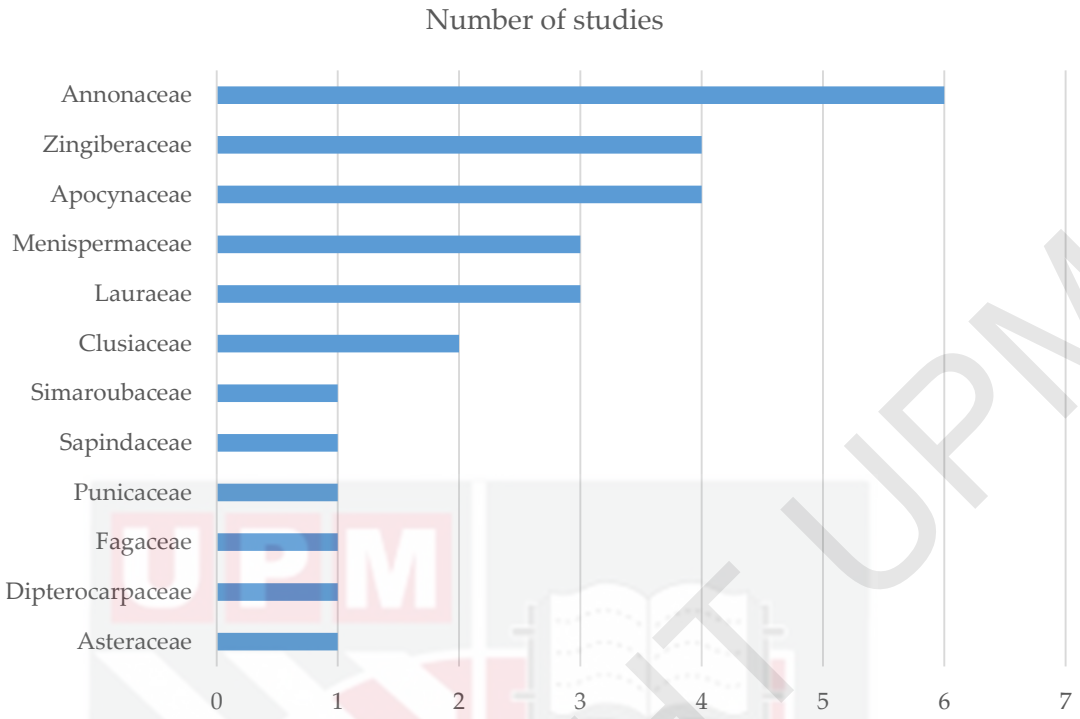


Figure 4.9: Number of plants in in vitro studies based on their families.

4.5.2 In vivo studies

Table 4.5 shows the plants studied using an in vivo based design in the included studies. Unlike the in vitro studies, here, the plants belong to fewer families of 9 families. There are 2 plants each in the families Menispermaceae and 1 plant each in the families Annnonaceae, Betulaceae, Cucurbitaceae, Caricaceae, Fabaceae, Moraceae and Moringaceae (see Figure 4.10). Some studies are conducted on the same species such as *Moringa oleifera* and *Gynostemma pentaphyllum.* Among

these plants, 2 plants belong to the same genus; *Tinospora crispa* and *Tinospora baenzigeri*.

Table 4.5: List of plants studied in the included in vivo studies.

PLANT COLLECTION	PLANT NAME	AUTHOR
Malaysia	Curcuma longa	Ali et al. (2017)
	Tinospora crispa	Lee et al. (2020)
Thailand	Betula alnoides	Chaniad et al. (2019)
	Moringa oleifera	Dondee et al. (2016)
		Nakinchat & Somsak (2017)
	Zingiber officinale	Ounjaijean & Somsak (2020)
	Tinospora baenzigeri	Ounjaijean (2019)
	Moringa oleifera	Somsak et al. (2016a)
	Gynostemma pentaphyllum	
	Annona muricata	Somsak et al. (2016b)
	Gynostemma pentaphyllum	Somsak et al. (2017)
Indonesia	Artocarpus champeden	Widyawaruyanti et al. (2020)
	Delonix regia	Fatmawaty et al. (2017)
	Carica papaya	

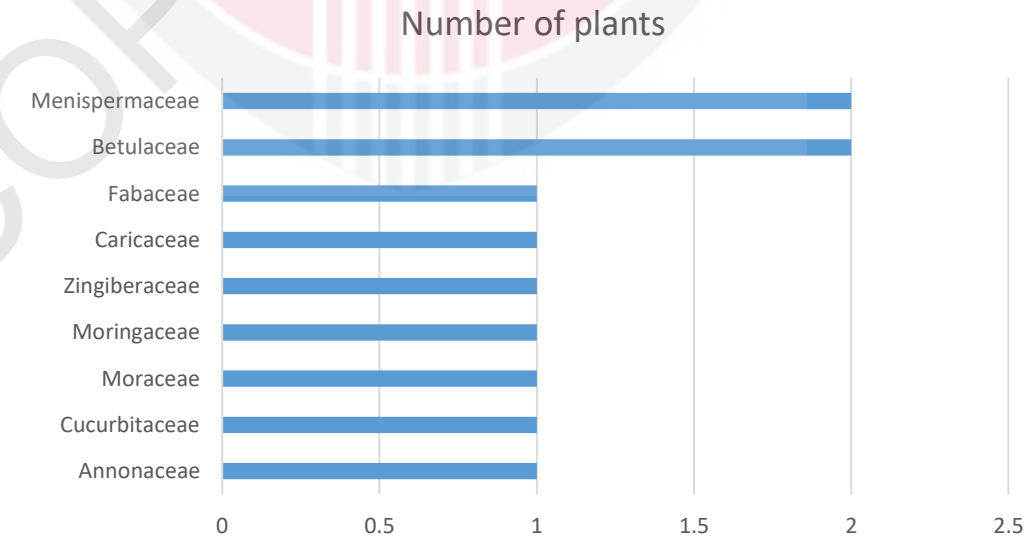


Figure 4.10: Number of plants in in vivo studies based on their families

4.5.3 Mixed studies

Table 4.6 shows the plants studied using mixed studies design in the included studies. In the mixed studies, only 2 families of plants were studied which are Asteraceae (Helianthus annuss) and Lamiaceae (Pogostemon Cablin (Blanco) Benth).

Table 4.6: List of plants studied in the included mixed studies.

PLANT COLLECTION	PLANT NAME	AUTHOR
Indonesia	Helianthus annuus	**Ekasari et al. (2019)**
Thailand	Pogostemon Cablin (Blanco) Benth	**Phuwajaroanpong et al. (2020)**

4.6 Part of plants used

One of the objectives of this systematic review was to collect information on the types of plant parts used in the investigation of antimalarial properties of plants in SEA. Among the included studies, 64% (23 papers) of the papers only used one plant part in their investigation while the other 31% (11 papers) of papers used more than one plant part (see Figure 4.11).

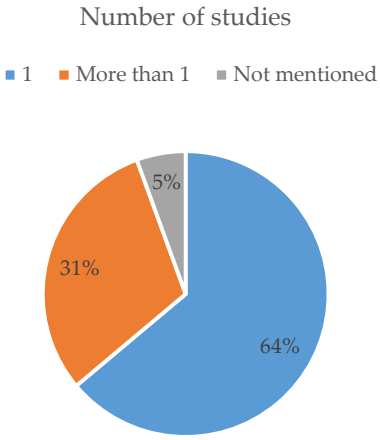
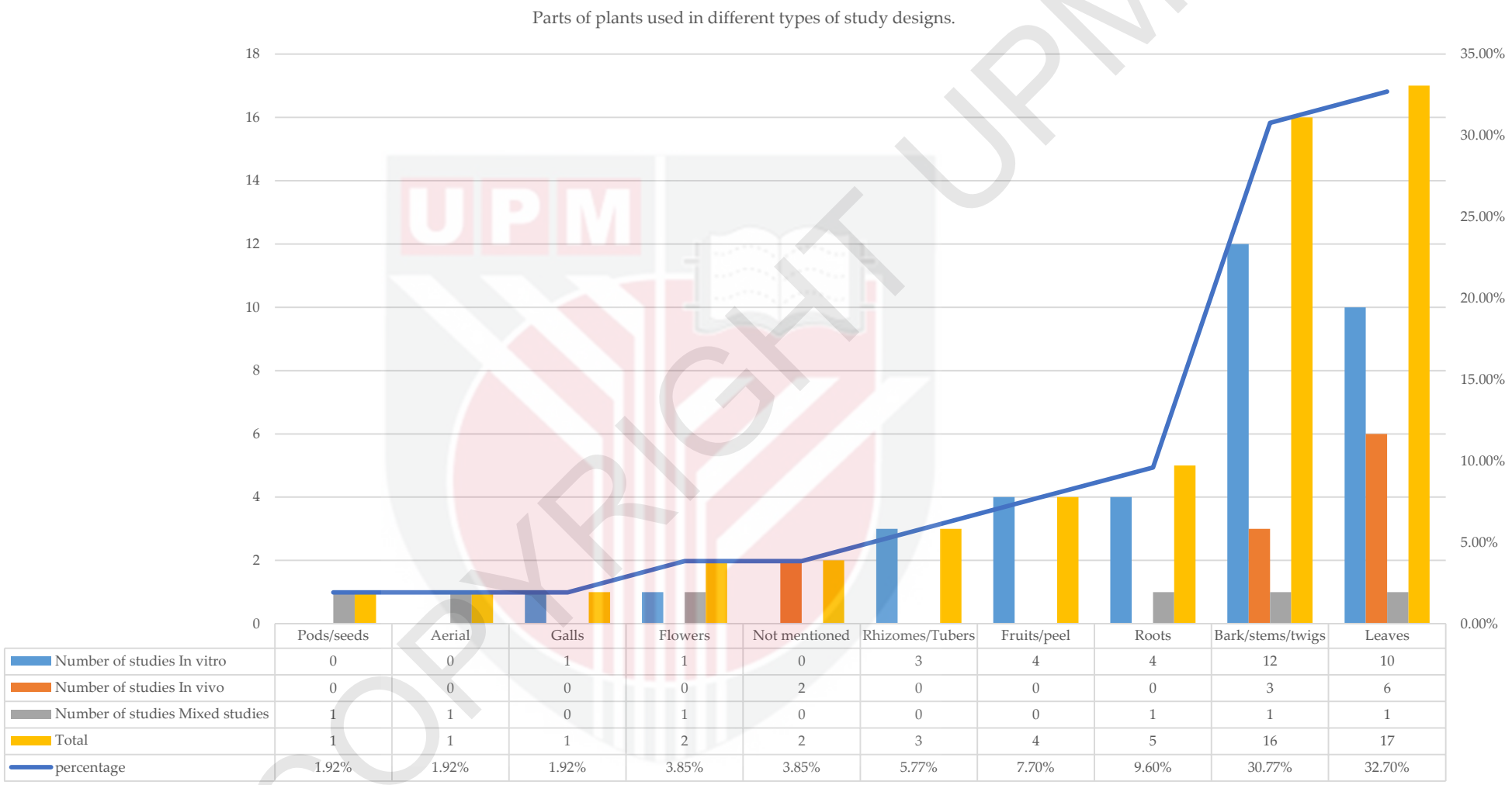


Figure 4.11: Number of plant parts used in the included studies to study the antimalarial properties of the plants.

The types of plant parts used in the different types of study designs for the included studies is summarised in Figure 4.12. The most used part of the plant is the leaves with 10 studies from in vitro, 6 studies from in vivo and 1 mixed design study. This contributes to 32.7% among all the other parts used in these studies. The second most used part were the stems. Bark, twigs and stem were considered from the same category and contributed 30.77% of the overall total. 12 in vitro studies, 3 in vivo studies and 1 mixed design study conducted the investigations using this part of the plant.

The least used parts of the plant were the pods/seeds, aerial and galls of the plant which contributed 1.92% each of the total sum. These parts are rarely investigated and not all plants have these parts resulting in the low

percentage of studies using these parts. Surprisingly, 2 in vivo studies didn't mention the part of the plant used in their studies. This is because the study was conducted using the active compound which was readily isolated from the plant (Ali et al., 2017; Ounjaijean & Somsak, 2020). Interestingly, fruits and its peel as well as rhizomes/tubers and galls were only used in in vitro studies. On the other hand, the aerial part of the plant were only used in the mixed study.



	Pods/seeds	Aerial	Galls	Flowers	Not mentioned	Rhizomes/Tubers	Fruits/peel	Roots	Bark/stems/twigs	Leaves
Number of studies In vitro	0	0	1	1	0	3	4	4	12	10
Number of studies In vivo	0	0	0	0	2	0	0	0	3	6
Number of studies Mixed studies	1	1	0	1	0	0	0	1	1	1
Total	1	1	1	2	2	3	4	5	16	17
percentage	1.92%	1.92%	1.92%	3.85%	3.85%	5.77%	7.70%	9.60%	30.77%	32.70%

Figure 4.12: Number and types of plant parts used in the included studies to study the antimalarial properties of the plants.

4.7 Extracts used

One of the objectives of this systematic review was to collect and analyse the data in the types of extracts used in investigating antimalarial properties of the plants. Based on the data, 83% of the studies (30 papers) used only one type of extract to carry out their investigation while 11% of the studies (4 papers) used more than one type of extract to study the plants (see Figure 4.13). Interestingly, 6% of the papers didn't mention any extract used. This is because these studies were conducted using active compounds extracted from the plants instead of the crude plant extracts (Ali et al., 2017; Ounjaijean & Somsak, 2020).

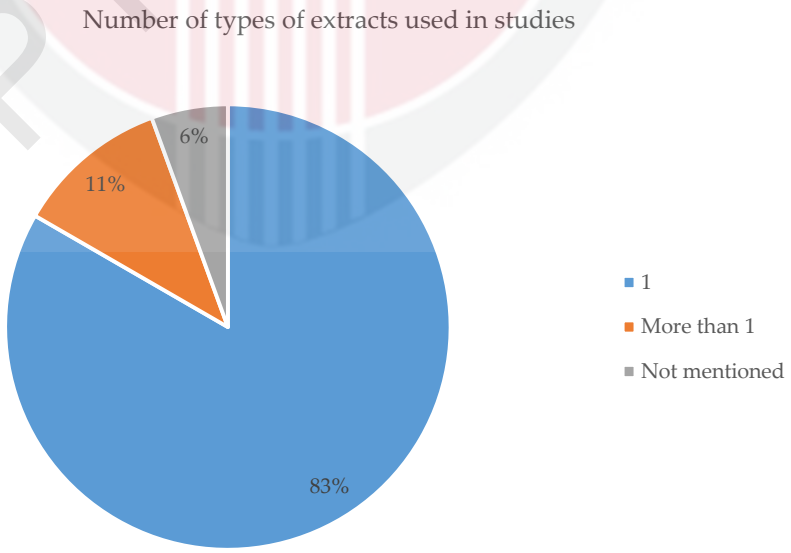
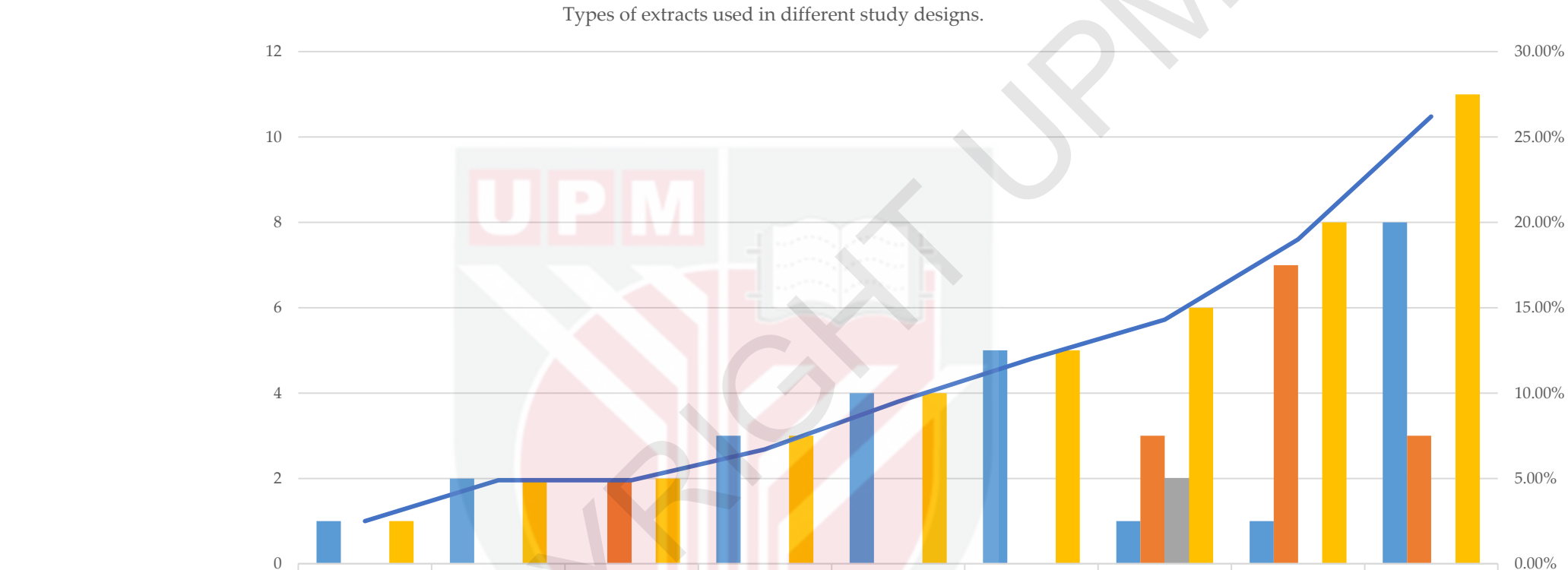


Figure 4.13: Number of types of extracts used in the included studies to study the antimalarial properties of the plants.

The different types of extracts based on the different types of study designs are summarized in Figure 4.14. In short, the most used extract is methanol which comprises 26.2% of the total number. This is further broken down into 8 in vitro studies and 3 in vivo studies resulting in the total number of 11 studies conducted using methanol as the extract. The second most used extract is aqueous extract which is done using distilled water. The 19% is broken down into 1 in vitro study and 7 in vivo studies. Interestingly, when comparing the methanol and aqueous extracts, the in vitro studies used methanol extract more while in vivo studies used aqueous extract more. From the data, it can also be seen that alcohol based extracts comprised 40.5% of the types of extracts used; methanol and ethanol.

Among the extracts, chloroform was the least used with only 1 in vitro study using it. Surprisingly, 2 in vivo studies did not mention the type of extract used for the investigation. Furthermore, the mixed design studies only reported on using ethanol as their extract.



	Chloroform	Ethyl acetate	Not mentioned	Hexane	Acetone	Dichloromethane	Ethanol	Aqueous	Methanol
Number of studies In vitro	1	2	0	3	4	5	1	1	8
Number of studies In vivo	0	0	2	0	0	0	3	7	3
Number of studies Mixed studies	0	0	0	0	0	0	2	0	0
Total	1	2	2	3	4	5	6	8	11
Percentage	2.50%	4.90%	4.90%	6.70%	9.50%	12.00%	14.30%	19.00%	26.20%

Figure 4.14: Number and types of extracts used in the included studies to study the antimalarial properties of the plants.

4.8 Category of activity

The included studies were analysed based on the strengths of the investigated plants in respective studies. The plants were then categorised into very good, good, moderate, weak and inactive for in vitro studies and very good, good and moderate for in vivo studies (see section 3.4). The mixed design studies were synthesized using both definitions accordingly. The data were further synthesized according to the parts of plant and extract used according to the three study designs of the included studies.

4.8.1 In vitro studies

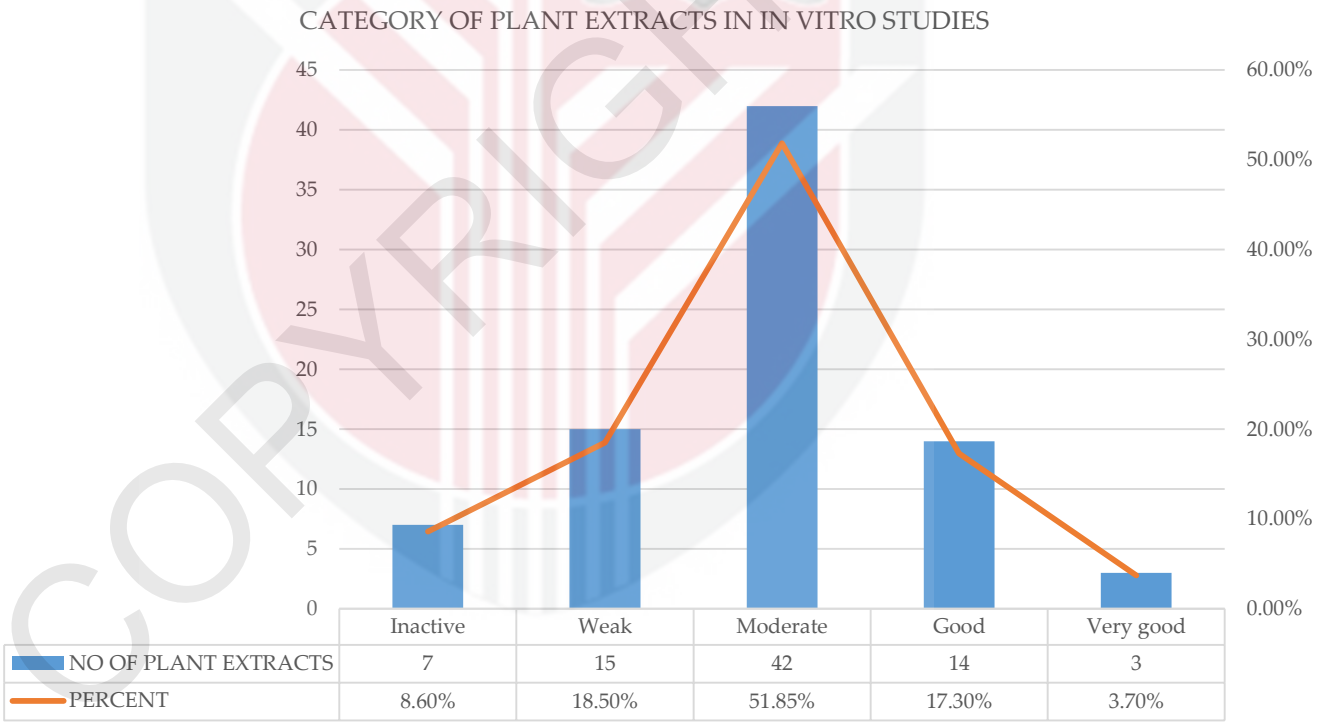
Table 4.7 shows the complete list of the categories of activity exhibited by the plants in in vitro studies. Based on the analysis (see Figure 4.15), 51.85% (42 extracts) of the investigated plants based on different parts and extracts showed moderate antimalarial activity. These finding showed that more than half of the studies plant extracts have the potential to be developed into antimalarials. 14 extracts which make up 17.3% of the plant extracts showed good antimalarial activity while 3 extracts which make up 3.70% showed very good antimalarial

activity. These plants should be investigated further as they have very high potential of being developed into new antimalarial agents. However, 7 of the investigated plant extracts were inactive and 15 showed weak antimalarial activity.

For the analysis of plant parts and extracts used, only moderate, good and very good plant extracts were looked into. This would allow a more focused discussion on plant extracts that could serve as potential new antimalarials. The summary of this analysis is shown in Figure 4.16. In short, excluding the active compounds investigated, there are 42 crude plant extracts that showed moderate antimalarial activity, 10 showed good antimalarial activity and 3 showed very good antimalarial activity. Among these categories, dichloromethane (DCM) extract showed the highest number of activity while ethyl acetate extract showed the least number of activity.

Furthermore, based on the data, it can be observed that leaves showed the most activity while seeds/pods showed the lowest. It can also be observed that among the plant extracts that showed moderate antimalarial activity, acetone stem extract of the plants had the most activity. This was followed by methanol leaves extracts that exhibited

highest moderate antimalarial activity. On the other hand, DCM stem extract showed the highest number of good antimalarial activity followed by acetone stem extract. Lastly, under the very good category, the highest number of activity was shown by ethanol leaves extract. Overall, it can be said that acetone and DCM stem extracts showed the most potential as potential antimalarials.



	Inactive	Weak	Moderate	Good	Very good
NO OF PLANT EXTRACTS	7	15	42	14	3
PERCENT	8.60%	18.50%	51.85%	17.30%	3.70%

Figure 4.15: Category of plant extracts in in vitro studies.

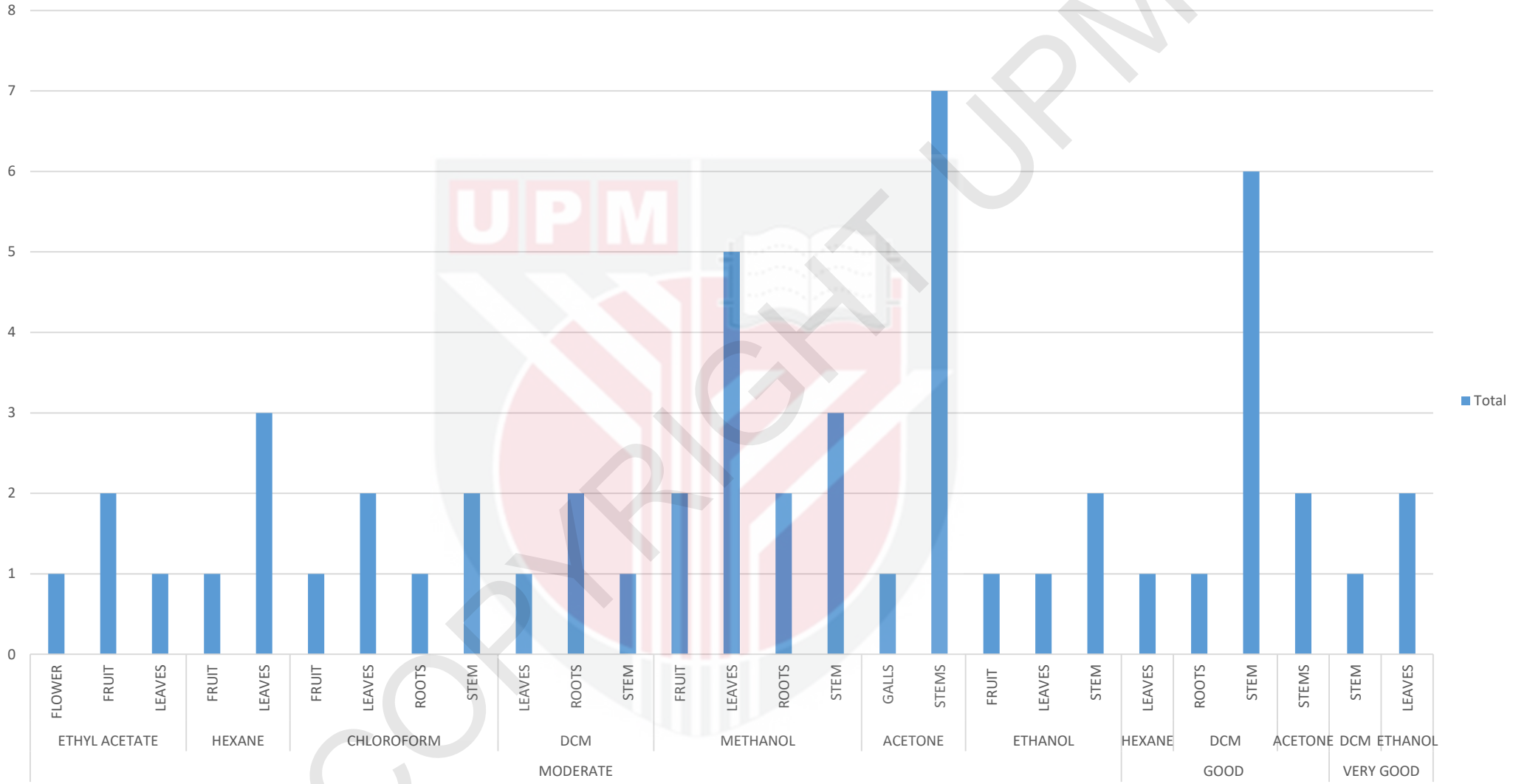


Figure 4.16: Category of antimalarial activity based on the types of plant extract and plant part used in in vitro studies.

Table 4.7 List of medicinal plants from in vitro studies and their respective IC_{50} values and category of antimalarial activity.

PLANT COLLECTION	PLANT NAME	PLANT EXTRACT	PLANT PART	IC50 (μg/ml)	CATEGORY	AUTHOR
Malaysia	Phoebe tavoyana	Hexane	Leaves (C3)	0.89	Good	Omar et al. (2018)
			Leaves (C4)	1.49	Moderate	
			Leaves (C5)	1.65	Moderate	
			Leaves (C6)	2.76	Moderate	
	Uvaria grandiflora	Chloroform	Leaves	3.7	Moderate	Azman et al (2018)
	Leuconotis eugenifolius		Leaves	3	Moderate	
	Chilocarpus costatus		Stems	1.3	Moderate	
	Tabernaemontana peduncularis		Stems	1.1	Moderate	
	Amomum subulatum		Fruits	4.8	Moderate	
	Curcuma aeruginosa		Rhizomes	4	Moderate	
	Alseodaphne corneri Kosterm	Dichloromethane	Bark (C1)	0.4151	Good	Zahari et al (2016)a
			Bark (C2)	0.7436	Good	
			Bark (C3)	0.4527	Good	
			Bark (C4)	0.1089	Good	
			Bark (C5)	0.06857	Very good	
			Bark (C6)	0.4315	Good	
			Leaves (C1)	17.513	Weak	Zahari et al. (2016)b
			Leaves (C2)	6.4825	Moderate	
	Dehaasia longipedicellata		Bark	0.8511	Good	
	Goniothalamus lanceolatus Miq		Leaves	12.6	Weak	Kaharudin et al. (2020)
			Root (CC)	7.5	Moderate	
			Stem bark (CD)	19.5	Weak	
		Hexane	Leaves	25.1	Inactive	
			Stem bark	25.1	Inactive	
			Roots	11.4	Weak	
			Stem bark	11.4	Weak	
			Roots	2.7	Moderate	
	Quercus infectoria	Acetone	Galls	5.85	Moderate	Zin et al. (2020)
		Methanol	Galls	10.31	Weak	
		Ethanol	Galls	20	Weak	
		Aqueous	Galls	30.95	Inactive	
Thailand	Brucea javanica	Acetone	Stems (C1)	10.475	Weak	

			Stems (C2)	12.11	Weak	Chumkaew et al (2016)
			Stems (C4)	1.802	Moderate	
			Stems (C5)	2.22	Moderate	
			Stems (C6)	0.5786	Good	
			Stems (C7)	0.553	Good	
			Stems (C8)	1.642	Moderate	
	Uvaria cherrevensis		Stem and root (C1)	4.02	Moderate	Auranwiwat et al (2017)
			Stem and root (C2)	6.95	Moderate	
			Stem and root (C5)	7.357	Moderate	
	Garcinia mckeaniana		Twigs (C15)	7.431	Moderate	Auranwiwat et al (2019)
			Twigs (C16)	13.63	Weak	
	Kaempferia parviflora	Ethanol	Rhizomes	28.7	Inactive	Leesombun et al. (2019)
	Punica granatum		Fruit peel	7.8	Moderate	
			Bark	4.9	Moderate	
	Annona muricata		Leaves	46.1	Inactive	
	Tiliacora triandra	Dichloromethane	Stem	4.57	Moderate	Nutmakul et al. (2020)
			Roots	4.73	Moderate	
			Tiliacorinine	0.94	Good	
			Yanangcorinine	0.51	Good	
		Methanol	Stem	3.42 ± 0.42	Moderate	Nutmakul et al. (2016)
			Tiliacorinine	2.14 ± 0.49	Moderate	
			Yanangcorinine	1.55 ± 0.26	Moderate	
			Roots	5.73 ± 1.15	Moderate	
	Uvaria cherrevensis		Fruits (C1)	9.935	Moderate	Auranwiwat et al. (2018)
			Fruits (C3)	21.97	Weak	
			Fruits (C5)	9.717	Moderate	
			Fruits (C11)	12.76	Weak	
	Mitrephora tomentosa		Leaves (C3)	9.704	Moderate	Wongsomboon et al. (2021)
			Leaves (C5)	17	Weak	
			Leaves (C6)	13.32	Weak	
	Miliusa velutina	Ethyl acetate	Flower (C7)	3.9	Moderate	Promgool et al. (2019)
			Fruit (C2)	3.8	Moderate	
			Fruit (C3)	5.2	Moderate	
		Hexane	Fruit (C6)	3.3	Moderate	

Indonesia	Garcinia celebica	Ethanol - ethyl acetate fraction	Leaves	57.471	Inactive	Abdulah et al. (2017)
	Alectryon serratus	Ethanol	Leaves (gallic acid)	0.013	Very good	Khasanah et al. (2021)
			Leaves (methyl gallate)	0.0025	Very good	
			Leaves (kaemferol)	1.495	Moderate	
	Tithonia diversifolia	Methanol	Leaves (F6)	13.63±1.43	Moderate	Syarif et al. (2018)
			Leaves (F7)	23.27 ±2.07	Moderate	
	Tabernaemontana macrocarpa Jack		Bark (C4)	18.62	Weak	Amelia et al. (2019)
	Dipterocarpus littoralis		Stem bark	98.88	Inactive	Lulan et al. (2020)
			Stem bark (ethyl acetate fraction)	3.42	Moderate	
			Stem bark (C1)	2.76	Moderate	
Vietnam	Stephania venosa	Dichloromethane	Tubers	0.31 ± 0.12	Good	Le Mai et al. (2017)
			Stephanine	0.21 ± 0.06	Good	
			Crebanine	0.21 ± 0.07	Good	
	Stephania dielsiana	Methanol	Leaves (MB2L-CH)	4.5	Moderate	Knockleby et al. (2020)
			Leaves (MB2L-B)	5.8	Moderate	

4.8.2 In vivo studies

Table 4.7 shows the complete list of the categories of activity exhibited by the plants in in vivo studies. The data analysis is shown in Figure 4.17. Based on the data, 38.89% of the plant extracts showed good antimalarial activity which comprises 7 plant extracts. 4 plant extracts were categorised as very good and weak, each contributing 22.22% each to the total sum. 16.67% (3 plant extracts) was observed to have moderate antimalarial activity. These findings show that more than 50% of the plant extract tested have good and very good antimalarial activity. Here, it can be seen that 16 plant extracts possess the potential to be expanded as new antimalarials.

For the analysis of types of extracts and plant parts used, only those with moderate, good and very good antimalarial activity were analysed. The data of this analysis is presented in Figure 4.18. Only three extracts were seen throughout the analysis which were aqueous, methanol and ethanol. Among these, plants extracted using distilled water (aqueous) were observed to have the highest number of antimalarial activity. For the plant part, the highest number of

antimalarial activity was shown by stem extracts. Interestingly, all extracts only had 1 activity per plant part and category.

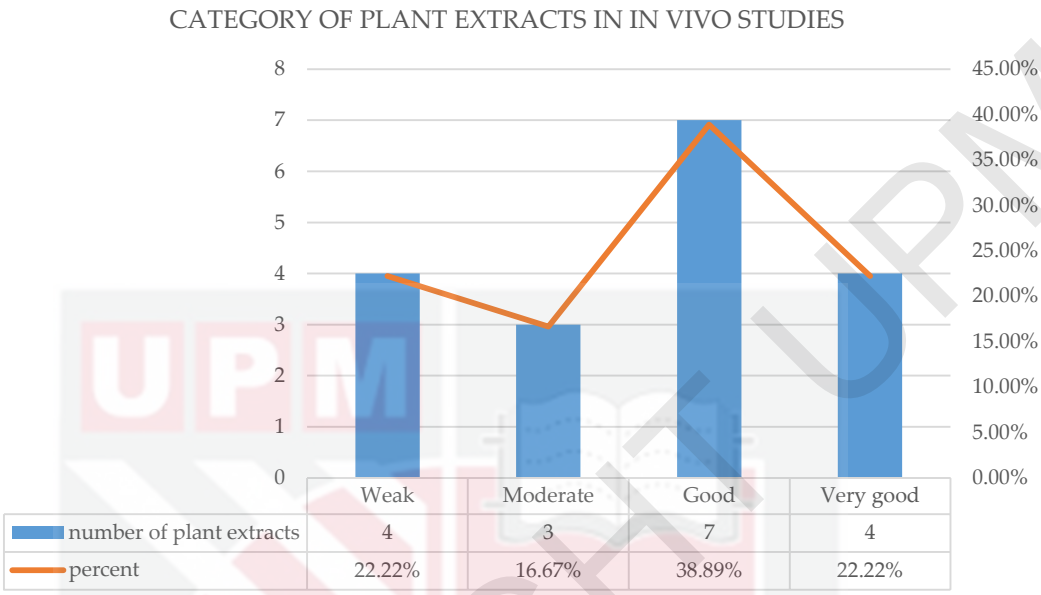


Figure 4.17: Category of plant extracts in in vivo studies.

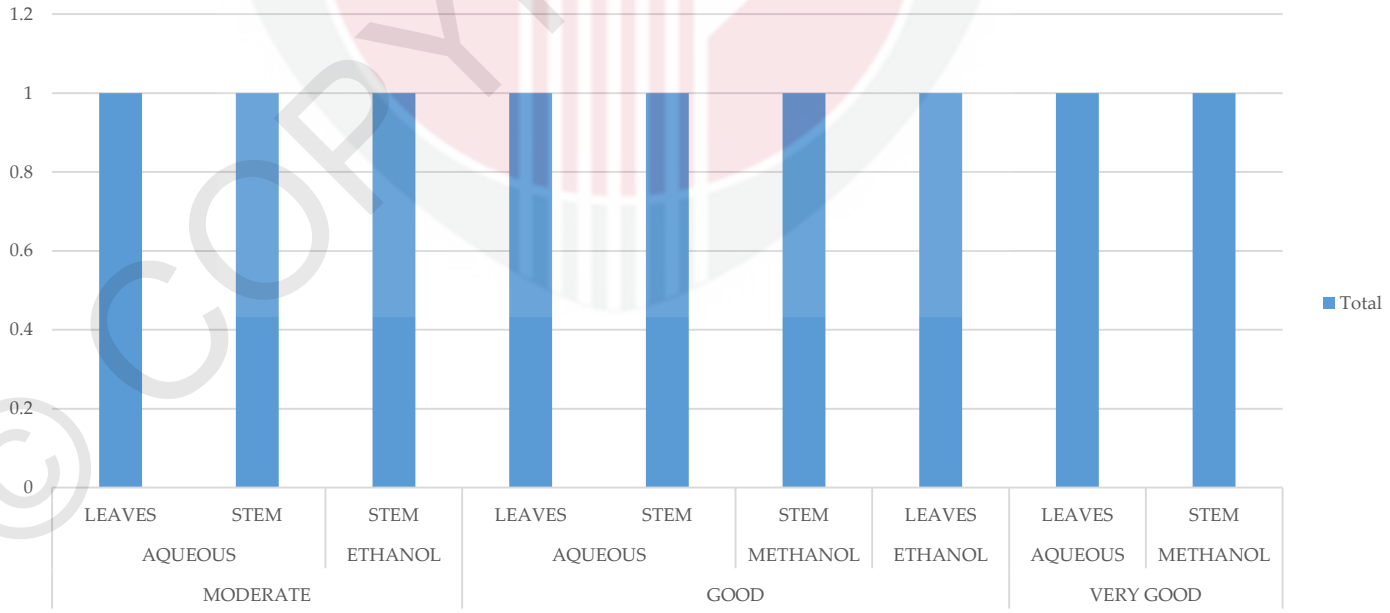


Figure 4.18: Category of antimalarial activity based on the types of plant extract and plant part used in in vivo studies.

Table 4.8 List of medicinal plants from in vivo studies and their respective inhibition values and category of antimalarial activity.

PLANT COLLECTION	PLANT NAME	PLANT PART	PLANT EXTRACT	% INHIBITION	DOSE (mg/kg)	CATEGORY	AUTHOR
Malaysia	Tinospora crispa	Stems	Methanol	42.85% ± 0.58%	100	Good	Lee et al. (2020)
		Fraction 4		41.01% ± 0.46%	100	Good	
		Fraction 5		54.32% ± 0.24%	100	Very good	
	Curcuma longa	Curcumin	Active compound	67.60%	30	Very good	Ali et al. (2017)
Thailand	Moringa oleifera	Leaves	Aqueous	40%	100	Good	Dondee et al. (2016)
				80%	1000	Weak	
	Gynostemma pentaphyllum			35%	500	Weak	Somsak et al. (2016a)
				45%	500	Weak	
	Annona muricata			75.25%	500	Moderate	Somsak et al. (2016b)
	Gynostemma pentaphyllum			57.60%	100	Very good	Somsak et al. (2017)
	Moringa oleifera			98%	1000	Weak	Nakinchat & Somsak (2017)
	Tinospora baenzigeri	Stems		50.81%	250	Good	Ounjaijean et al. (2019)
	Betula alnoides			58.39%	400	Moderate	Chaniad et al. (2019)
	Zingiber officinale	Zingerone	Active compound	45.75%	100	Good	Ounjaijean & Somsak (2020)
Indonesia	Artocarpus champeden	Stems	Methanol	72.24% ±4.30%	100	Very good	Widyawaruyanti et al. (2020)
	Delonix regia	**Bark**	Ethanol	**66.25%**	**487.5**	**Moderate**	Fatmawaty et al. (2017)
	Carica papaya	Leaves	Ethanol	83.75%	240	Good	
		Combination	Ethanol	97%	240	Good	

4.8.3 Mixed studies

Table 4.8 shows the lists of plant extract used in the mixed design studies and their respective antimalarial activity categories. The 2 mixed studies were evaluated using both the in vitro and in vivo definitions. Only ethanol was used as the extract in these studies. For the plant parts, roots, leaves, flowers, stems, seeds and aerial parts were used. In in vitro evaluation, the ethanol roots, leaves and flower extracts showed moderate antimalarial activity. Interestingly, these extracts showed different categories of activity in in vivo study. The leaves, flowers and stems showed good antimalarial activity in in vivo followed by the roots and seeds which exhibited very good antimalarial activity. However, these findings were contrast when compared to the in vitro findings. The seeds and stems showed weak antimalarial activity in vitro but showed potential in the in vivo studies. The aerial parts of the plant showed weak antimalarial activity both in vitro and in vivo evaluation at all concentrations. Figure 4.19 shows the summary of the analysis.

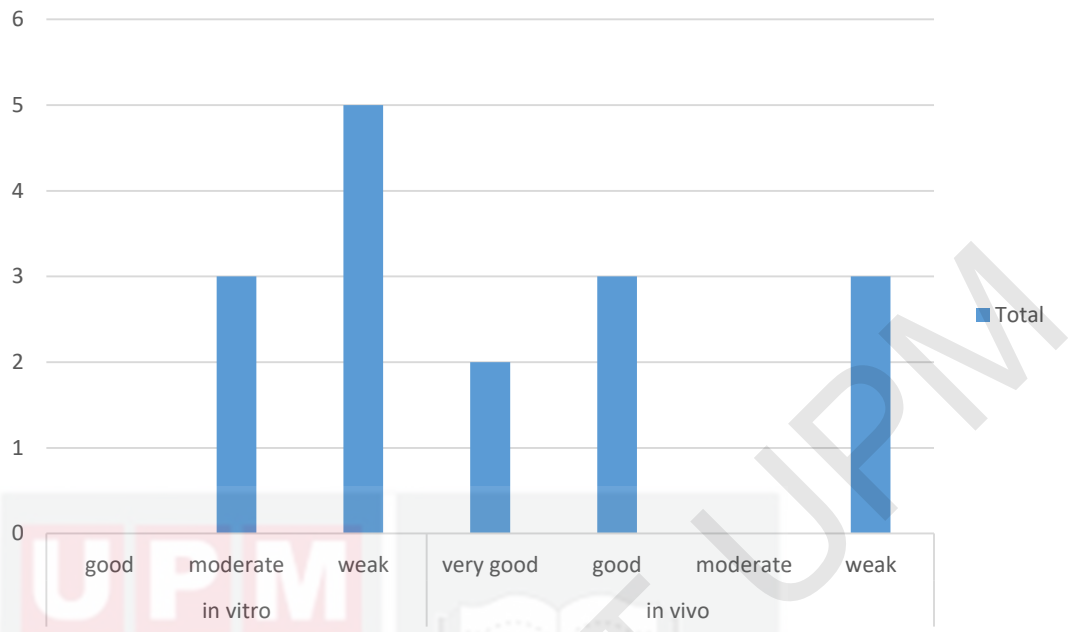


Figure 4.19: Category of plant extracts in mixed design studies.

Table 4.9 List of medicinal plants from mixed studies and their respective IC_{50} and inhibition values and category of antimalarial activity.

PLANT COLLECTION	PLANT NAME	PLANT EXTRACT	PLANT PART	IC50	% INHIBITION	DOSE (mg/kg)	CATEGORY		AUTHOR
							IN VITRO	IN VIVO	
Indonesia	Helianthus annuus	Ethanol	Roots	2.3 ± 1.4	63.6 ± 8.0	100	Moderate	Very good	Ekasari et al. (2019)
			Leaves	4.3 ± 2.2	40.3 ± 8.2	100	Moderate	Good	
			Flowers	4.8 ± 0.0	41.5 ± 4.4	100	Moderate	Good	
			Stems	10.2 ± 5.0	35.9 ± 4.6	100	Weak	Good	
			Seeds	19.3 ± 5.5	59.3 ± 13.2	100	Weak	Very good	
Thailand	Pogostemon Cablin (Blanco) Benth		Aerial	24.49 ± 0.01	38.41 ± 0.00	200	Weak	Weak	Phuwajaroanpong et al. (2020)
					45.12 ± 0.27	400		Weak	
					89.00 ± 0.32	600		Weak	

4.9 Mechanism of action

Most of the studies didn't study the mechanism of action behind the antimalarial activity of the plant extracts. This is due to the fact that most of the studies were a preliminary screening of the plant extracts and focused on evaluating if the extracts exhibited antimalarial activity. Further investigations must be carried on the potential plant extracts to understand the mechanism of action towards the malaria parasites.

However, 6 studies explained that the exhibited antimalarial activity could be contributed by the antioxidant properties of the active compounds present in the plant extracts (Abdullah et al., 2017; Khasanah et al., 2021; Nakinchat et al., 2017; Somsak et al.,2017; Zahari et al., 2016; Zin et al., 2020). 4 studies mentioned that the plant extracts have antimalarial activity by having schizonticidal and cytocidal effects causing apoptosis of the parasite at ring and trophozoite stages (Knockleby et al., 2020; Lee et al., 2020; Nutmakul et al., 2020; Syarif et al., 2018). Furthermore, several studies also mentioned the plant extracts have antimalarial activity by inhibiting the formation of hemozoin or polymerization of heme (Ekasari et al., 2019; Somsak et al., 2016; Zahari et al., 2016). Other mechanisms include inhibition of GSK3b (Ali et al., 2017), structure of the compounds (Chumkaew et al., 2016), free radical

scavenging (Dondee et al., 2016; Ounjaijean et al., 2019; Ounjaijean et al., 2020) and inhibition of proinflammatory mechanisms (Leesombun et al., 2019).

4.10 Risk of bias within studies

The risk of bias (RoB) assessment or quality assessment was done using two separate tools for the in vitro and in vivo studies. The in vitro RoB assessment was done using the Checklist for Reporting In-vitro Studies (CRIS) (Krithikadatta et al., 2014) while the in vivo studies were evaluated using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) tool (see section 3.3.1). Table 4.9 and 4.10 shows the summary of RoB assessment for the included in vitro and in vivo studies respectively.

In short, among the in vitro studies, 2 studies had high risk of bias, 14 studies had medium risk of bias while 9 remaining papers had low risk of bias. All papers exhibited meaningful differences between groups and conducted statistical analysis. However, most of the papers lacked in the sample size calculation where only five papers showed said characteristic. In four studies, the allocation sequence, randomization and blinding of the samples were

unclear. The information regarding this aspect was not sufficiently provided in the analysed studies.

On the other hand, for the in vivo studies, eight papers showed medium risk of bias while six papers showed low risk of bias. All studies answered yes for questions 1, 2, 4, 8, 9 and 10 showing that all studies had an adequately generated and applied allocation sequence, similar baseline in the analysis, all the animals housed randomly, incomplete data addresses, all reports of the studies free of selective outcome reporting and free of any other factors that may have resulted in high risk of bias. However, all studies answered no for question 5 which asked if the investigators were blinded from the intervention the animals were receiving. Based on the information from the studies, it was clear that the researchers knew exactly which group of animals were getting the intervention.

Table 4.10: Summary of RoB assessment for in vitro studies.

PAPER	Sample size calculation	Meaningful difference between groups	Sample preparation and handling	Allocation sequence, randomization and blinding	Statistical analysis	Total ROB
Abdulah et al. (2017)	-	+	+	Unclear	+	Medium
Amelia et al. (2019)	-	+	+	-	+	Medium
Auranwiwat et al (2017)	-	+	-	-	+	Medium
Auranwiwat et al (2019)	-	+	-	-	+	Medium
Auranwiwat et al. (2018)	-	+	+	-	+	Medium
Azman et al (2018)	-	+	+	+	+	Low
Chumkaew et al (2016)	-	+	+	-	+	Medium
Ekasari et al. (2019)	-	+	+	-	+	Medium
Kaharudin et al. (2020)	-	+	+	+	+	Low
Khasanah et al. (2021)	-	+	+	-	+	Medium
Knockleby et al. (2020)	-	+	+	+	+	Low
Le Mai et al. (2017)	+	+	+	+	+	Low
Leesombun et al. (2019)	-	+	+	-	+	Medium
Lulan et al. (2020)	-	+	Unclear	-	+	High
Nutmakul et al. (2016)	+	+	+	Unclear	+	Low
Nutmakul et al. (2020)	+	+	+	-	+	Low
Omar et al. (2018)	-	+	-	Unclear	+	Medium
Phuwajaroanpong et al. (2020)	-	+	+	+	+	Low
Promgool et al. (2019)	-	+	-	-	+	High

Syarif et al. (2018)	+	+	+	-	+	Low
Wongsomboon et al. (2021)	-	+	+	Unclear	+	Medium
Zahari et al (2016)a	-	+	+	-	+	Medium
Zahari et al. (2016)b	-	+	+	-	+	Medium
Zin et al. (2020)	+	+	+	+	+	Low

Table 4.11: Summary of RoB assessment for in vivo studies.

PAPER	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total ROB
Ali et al. (2017)	Yes	Similar	Yes	Yes	No	Unclear	No	Yes	Yes	Yes	Medium
Chaniad et al. (2019)	Yes	Similar	Unclear	Yes	No	Unclear	No	Yes	Yes	Yes	Medium
Dondee et al. (2016)	Yes	Similar	Unclear	Yes	No	Yes	Unclear	Yes	Yes	Yes	Medium
Ekasari et al. (2019)	Yes	Similar	Unclear	Yes	No	Yes	Unclear	Yes	Yes	Yes	Low
Fatmawaty et al. (2017)	Yes	Similar	Yes	Yes	No	Unclear	No	Yes	Yes	Yes	Medium
Lee et al. (2020)	Yes	Similar	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Low
Nakinchat & Somsak (2017)	Yes	Similar	Unclear	Yes	No	Yes	Unclear	Yes	Yes	Yes	Medium
Ounjaijean & Somsak (2020)	Yes	Similar	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Low
Ounjaijean (2019)	Yes	Similar	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Low
Phuwajaroanpong et al. (2020)	Yes	Similar	Yes	Yes	No	No	No	Yes	Yes	Yes	Low
Somsak et al. (2016a)	Yes	Similar	Unclear	Yes	No	Yes	Unclear	Yes	Yes	Yes	Medium
Somsak et al. (2016b)	Yes	Similar	Unclear	Yes	No	Yes	Unclear	Yes	Yes	Yes	Medium

Somsak et al. (2017)	Yes	Similar	Unclear	Yes	No	Yes	Unclear	Yes	Yes	Yes	Medium
Widyawaruyanti et al. (2020)	Yes	Similar	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Low

Q1: Was the allocation sequence adequately generated and applied?
Q2: Were the groups similar at baseline or were they adjusted for confounders in the analysis?
Q3: Was the allocation adequately concealed?
Q4: Were the animals randomly housed during the experiment?
Q5: Were the caregivers and /or investigators blinded from knowledge which intervention each animal received during the experiment?
Q6: Were animals selected at random for outcome assessment?
Q7: Was the outcome assessor blinded?
Q8: Were incomplete outcome data adequately addressed?
Q9: Are reports of the study free of selective outcome reporting?
Q10: Was the study apparently free of other problems that could result in high risk of bias?

CHAPTER 5

DISCUSSION

5.1 Interpretation of evidence

This systematic review was conducted to synthesise and analyse existing in vitro and in vivo studies on medicinal plants with antimalarial properties in Southeast Asia. This was done to summarize findings of relevant individual studies and provide a comprehensive overview for an easier access towards information (Ganeshkumar & Gopalakrishnan, 2013). It allows access towards available pre-clinical evidence providing concise answers eliminating the need for further research as well as saving resources (Elsevier, 2019). The analysis was done by looking into the types of plant extracts used and

categorising the activities according to the type of study designs (see section 4.8).

Recent years have shown that malaria still remains a major concern in the SEA region (Gething et al., 2012) (Roy & Khatun, 2015). This is further worsened by the increase in resistance and adverse effects of current treatment of antimalarial drugs. These pose a threat to the global initiative of malaria eradication leading towards the urgency of new antimalarial discovery (WHO, 2020). One of the many approaches used to develop antimalarial drugs is by exploring traditionally used plants and herbs. History has shown that traditional practice of using natural products for medicinal purposes has ushered the discovery and isolation of modern antimalarials (Bourdy et al., 2008; David Phillipson & Wright, 1991; Newman et al., 2000; Tse et al., 2019).

5.1.3 Study designs

For this systematic review, only in vitro, in vivo and studies consisting of both were considered for inclusion. This decision was made as the interest of this systematic review was to look into preclinical data on antimalarial properties of medicinal plants found in Southeast Asia. Preclinical data can provide evidence for the desired

effect of a tested compound and insights on toxicity of the compound (Albers, 2016; Polson & Fuji, 2012). Preclinical research can also identify the active compounds from plant extracts that can lead to isolation for drug development (Koşar, 2019).

Results from the analysis showed that among the 36 identified studies for the systematic review, 22 studies which comprised 61% of the total were in vitro studies. 2 studies were mixed design studies, thus containing the in vitro aspect as well. In vitro was the most preferred method as it is a relatively less expensive approach in discovering new antimalarial drugs (Albers, 2016; Lemma et al., 2017). Other than that, researchers can expose the in vitro parasite cultivation to the desired concentration of plant extracts for any desired amount of time and conduct the assessment in several ways (Trager & Jensen, 1997). However, in vitro studies only act as a preliminary screening and needs to be followed by in vivo testing as in vitro testing is unable to imitate the complexity of a human being (Huxley, 2006; Polson & Fuji, 2012).

5.1.2 Types of bioassays used

Based on the analysis, it was observed that several types of bioassays were used in evaluating the antimalarial properties of the plants. These include Chloroquine sensitive *P.berghei* ANKA (CSPB ANKA) strain, Chloroquine resistant *P.falciparum* FCR3 (CRPF FCR3) strain, Chloroquine resistant *P.falciparum* DD2 (CDPF DD2) strain as well as Chloroquine resistant *P.falciparum* FcB1 (CRPF FcB1) strain, Chloroquine sensitives *P.falciparum* 3D7 (CSPF 3D7) strain, multidrug resistant *P.falciparum* K1 (MRPF K1) strain and Chloroquine resistant *P.falciparum* W2 (CRPF W2) strain (see section 4.4.4). The reason for bioassay selection could be influenced by various factors such as availability, study design and interest of the researchers.

CSPB ANKA was used the most in in vivo studies as is a standard used strain when conducting in vivo malarial investigations and is easily evaluated in the 4 day suppressive test (Peters, 1965). It was also observed that different strains of *P.falciparum* were used in carrying out the in vitro investigations. This is because *P.falciparum* is the most malaria causing species among all (WHO, 2020). Furthermore,

using this strain has been useful in malaria research especially for in vitro evaluation as it provides an accessible form of the target organism (Trager & Jensen, 1997). 31% of studies conducted used more than one type of strain. This is because certain drug sensitive parasites can cause growth and transmission suppression of the drug resistant parasite (Orwa et al., 2019). Thus, using multiple strains of *P. falciparum* can provide a better understanding on the relationship of within host competition and drug resistance (Bushman et al., 2018), resulting in a better assessment of the antimalarial properties of tested medicinal plant extracts. However, the effects of different types of bioassay on the IC_{50} values must be taken into consideration as well (Lemma et al., 2017).

5.1.3 Types of comparison used

It is important for scientific studies to always have a control or standard comparison when carrying out an investigation. This is to ensure the results are reliable and the dosing as well as the toxicity levels are justified (Honek, 2017). In this systematic review, chloroquine was the most reported comparison among the 36 studies. This is

because chloroquine was one of the first drugs produced and most commonly used drug for malarial treatment worldwide (Travassos & Laufer, 2021).

Among the classes of drugs used for comparison, quinoline derivatives were reported as the most. Drugs that belong to this class include chloroquine, mefloquine and lumefantrine. It was then followed by artemisinin derivatives. According to WHO (2015), these drugs were listed as essential medicines for malaria. This factor could have influenced the researcher to choose these drugs as the control for their investigations. However, 6 papers had no comparison or did not mention the comparison of standard drugs used in the studies. A lack of standard drug usage could render the antimalarial potential of the studied plant questionable as no comparison or control was used (Polson & Fuji, 2012).

5.1.4 Medicinal plants with antimalarial properties

From the data analysis, 39 plant species from 19 families were identified through this systematic review (see section 4.5). These plants were chosen due to various reasons such as traditional usage of plant, other proven therapeutic effects of plants, consumption by particular groups (Abdullah et al., 2017; Lee et al., 2020), plants belonging to a certain family (Omar et al., 2018), anti- parasitic properties of plant (Zin et al., 2020) or previously proven antimalarial properties (Somsak et al., 2016). Most plants were chosen based on its ethno pharmacological relevance and other therapeutic effects.

Among these plants, most studies were conducted on plants from the family Annonaceae contributing to 8 studies out of the 36 studies. According to a review by Frausin et al. (2014), plants from the Annonaceae are widely used in treatment for malaria in tropical regions due to its chemical components. In Cameroon 7 species of plants from the Annonaceae family were used to treat malaria while 14 species were used to treat malaria related symptoms (Tsabang et al., 2012). The antimalarial activity of plants from this family could be contributed by

the presence of secondary metabolite alkaloids, acetogenins, sterols and terpenes discovered in different parts of these plants (Ocampo & Ocampo, 2006). Acetogenins were seen to inhibit adenylate translocase on *P.falciparum* in vitro (Rakotomanga et al., 2004) and reduced parasitemia in Plasmodium berghei-infected mice model (Pimenta et al., 2014).

In this family, *Annona* is the most widely explored genera. Several studies have also shown promising antimalarial activities from plants of this genera (Ngbolua et al., 2014; Johns et al., 2011; Leesombun et al., 2019; Somsak et al., 2016). The other genera that was investigated in a few studies from the included studies is the *Uvaria* genus (Auranwiwat et al., 2017; Auranwiwat et al., 2018; Azman et al., 2018). This is in accordance with the findings of Nkunya et al., (1991) in which plants from the genus *Uvaria* have antimalarial properties.

Interestingly, among the 36 studies, 3 studies were conducted using the plant *Moringa oleifera* (Dondee et al., 2016; Nakinchat & Somsak, 2017; Somsak et al., 2016b). This is the plant with the most number of studies conducted among all 39 species. A study conducted

by Obediah & Obi (2020) demonstrated the antiplasmodial activity of *Moringa oleifera* seeds on *Plasmodium berghei* infected albino rats. Furthermore, crude methanol extract of *Moringa oleifera* leaves were seen to suppress the growth of parasites in albino mice (Ogundapo et al., 2015). These findings prove the rationale of using *Moringa oleifera* in antimalarial evaluation and demonstrates the potential of this plant to be further investigated for new antimalarial drug development.

5.1.5 Leaves as plant part of choice

The results from the data analysis showed that various types of plant parts were used for the antimalarial evaluation. This is because different parts of plants can yield different activity and levels of active compounds. For example, a study conducted by Olofssson et al. (2011), showed that the presence of glandular secretory trichomes which are responsible for artemisinin production differs in aerial parts and roots of the plant. Thus, testing different parts of the plant will allow a more thorough evaluation of the plants' antimalarial properties.

Based on the data analysis, it was found that leaves were the most used part of the plant contributing to 32.7% of the total. This includes 10 in vitro studies, 6 in vivo studies and 1 mixed design study. This is in line with previous studies that showed leaves extracts possessing ethno pharmacological relevance and antimalarial activity (Adjanohoun et al., 1996; Andrade-Neto et al., 2004; Goffin et al., 2002; Waako et al., 2005). History has also proven that the drug artemisinin was isolated from the leaves of *Artemisia annua* (Meshnick & Dobson, 2011; Talapko et al., 2019). Factors that could have contributed to the usage of leaves being the highest include the availability of leaves on almost all plants and the high content of bioactive compounds present in leaves (Altemimi et al., 2017).

The second most used part of the plants were bark, stems and twigs which were categorised as one group. This is similar to the usage of *Cinchona* tree bark for malarial treatment (Achan et al., 2011; Meshnick & Dobson, 2011; Talapko et al., 2019). Previously published studies also showed that stem bark extracts of different plants showed high antimalarial activity in in vivo mice models (Kweyamna et al., 2019; Niljan et al., 2014; Obey et al., 2018). These show that leaves and stem barks are widely used in antimalarial investigations.

5.1.6 Methanol as solvent of choice

In an extraction process, different types of solvents can be used for the plants of interest. However, it is important to choose the correct solvent as it affects the yield and the biological activity of the resulting extract (Truong et al., 2019). The suitability of the solvent for the extraction process depends on the particular plant part and compounds of interest as they have different solubility properties in different solvent (Ajanal et al., 2012; Mahdi-Pour et al., 2012). Solvent can be categorised into polar (water, methanol, ethanol), intermediate polar (acetone, dichloromethane) and non-polar (hexane, chloroform) (Abubakar & Haque, 2020).

In this study, methanol was reported as the most used solvent followed by water, ethanol, dichloromethane (DCM), acetone, hexane, ethyl acetate and the least used solvent was chloroform (see section 4.7). Interestingly, it can be observed that the most used solvents were polar and the least used solvent were non polar. Alcohol based solvent (methanol and ethanol) contributed 40.5% of the solvents used which is almost half of the total. This is understandable as alcohols are universal

solvents for phytochemical investigations (Zhang et al., 2018). Studies have shown that alcohol based solvents yielded extraction with the highest bio compound content and biological activity (Dhawan & Gupta, 2017; Do et al., 2014; Truong et al., 2019).

Yet, water was the most used solvent in in vivo studies. This could be because water is the most polar and safest when it comes to administration in animals (Abubakar & Haque, 2020). Other than that, in traditional practices, water is the most commonly used solvent by healers for medicinal plant preparation (P. Tiwari et al., 2011).

5.1.7 Categories of antimalarial activity

The objective of this systematic review was to analyse the available in vitro and in vivo studies on medicinal plants in Southeast Asia that could serve as new antimalarials. The reported plants were then categorised according to highlight the plants with the best antimalarial properties. Due to selective reporting bias present in the literature, in which plants with no or minimal antimalarial activities

were not reported, only a total of 115 plant extracts from 39 plant species were reported. This number only contributed 0.03% of species registered botanically (Botanic Gardens Conservation International 2020). This number is very minute and shows that research for antimalarials originated from natural products need to be increased as current antimalarials are of plant origin (Lemma et al., 2017).

Among these, 6.1% of the extracts were inactive, 23.5% were weak, 41.7% were moderate, 20.9% were good and 7.8% were very good (see section 4.8). The plants were chosen based on its traditional usage, previous antimalarial investigation and phytochemicals present. These reasons are in accordance with the approaches needed for selection of an anti-infectious natural product (Fabricant & Farnsworth, 2001). As previously mentioned, the most studied plants were from the Annonaceae family followed by Zingiberaceae and Menispermaceae families. However, the plant extracts with good and very good antimalarial activity came from other families; Sapindaceae, Zingiberaceae, Simaroubaceae, Lauraceae, Moringaceae, Caricaceae, Cucurbitaceae, Menispermaceae. Moraceae and Asteraceae. Interestingly, most good and very good antimalarial activity came from the families Asteraceae (Ekasari et al., 2019) and Menispermaceae (Le

Mai et al., 2017; Lee et al., 2020; Nutmakiul et al., 2020; Ounjaijean et al., 2019).

Most of the plant extracts showed inactive, weak and moderate activity despites its' traditional usage for generations. This difference could be contributed by host factors such as genetic factors, acquired immunity and social behaviour of the host (Ringwald & Basco, 1999). Other than that, the discrepancy could also be caused by the researchers' reliability on the IC_{50} values and parasitemia inhibition. From the in vitro studies, only plants with mechanisms related to erythrocytic stages of the parasite can be studied using the *P.falciparum* culture (Trager & Jensen, 1997). Since, different cultures of the parasites and different species of mice were used in both the in vitro and in vivo studies, this could have an effect in the results obtained. For example, in a previous study, herbal tea leaves extract of *Artemisia annua* showed different IC_{50} values when tested against chloroquine-sensitive D10 *P. falciparum* and chloroquine-resistant W2 *P. falciparum* clones (De Donno et al., 2012). This can be seen especially in the mixed design studies, where the ethanol extract of *Helianthus annus* seeds gave weak antimalarial activity in vitro but very good activity in in vivo (Ekasari et al., 2019).

Furthermore, it is also important to note that using different extraction methods and solvents can also yield different values for the antimalarial activity (Bacon et al., 2007; Kaddouri et al., 2008; Laufer, 2008). For instance, based on a study by Zin et al. (2020), acetone, methanol, ethanol and aqueous gall extract of *Quercus infectoria* gave IC_{50} values of 5.85, 10, 31, 20 and 30.95 μg/ml respectively. Among these extracts, only the acetone gall extract showed moderate antimalarial activity. Even the usage of polar and non-polar solvents can give different results. This was seen in *Morinda morindoides* which showed IC_{50} values of 1.8 ± 0.2 μg/ml with an ether extract while > 50 μg/ml with ethanolic extract (Tona et al., 2001).

Moreover, when comparing results from in vivo and in vitro, the category of antimalarial activity is different. This discrepancy could be contributed by the drugs' lipophilicity and hydrophobicity that could have increased or decreased the absorption and bioavailability of the tested drug (Pade & Stavchansky, 1998). Therefore using, IC_{50} value and parasitemia inhibition may not be the best procedure to evaluate the antimalarial properties of medicinal plants. However, the plants listed as good and very good should be looked into further as they showed promising potential antimalarial properties. Yet, it is also important to

note that, regardless of the antimalarial activity in in vitro and in vivo studies, the plant extracts may not exhibit the desired effects in clinical trials.

5.2 Risk of bias (RoB) assessment

In this systematic review, only preclinical trials were included for analysis; in vitro and in vivo studies. Thus, only 36 reports were able to be retrieved and analysed. Among these 36 studies, most of them were in vitro studies. The in vitro RoB assessment was done using the Checklist for Reporting In-vitro Studies (CRIS) (Krithikadatta et al., 2014).

Based on the analysis in Table 4.9 (see section 4.10), 9, 13 and 2 studies presented low, medium and high RoB respectively. Studies with high RoB (Lulan et al., 2020; Promgool et al., 2019) possess the risk in which the results may not be able to guide clinical outcomes (Delaney et al., 2019). For the assessment it can be seen that only 5 studies conducted sample size calculation (Le Mai et al., 2017; Nutmakul et al., 2016; Nutmakul et al., 2020; Syarif et al., 2018; Zin et al., 2020). Sample size calculation is needed as it determines the

number of samples needed for the detection of a clinically relevant treatment (Noordzij et al., 2010). Lacking this could have an impact as many studies with inadequate sample size lack clinical relevance (Chander, 2017). Another item, allocation sequence, randomization and blinding was only seen in 6 studies (Azman et al., 2018; Kaharudin et al., 2020; Knockleby et al., 2020; Le Mai et al., 2017; Phuwajaroanpong et al., 2020; Zin et al., 2020) and unclear in 4 studies (Abdulah et al., 2017; Nutmakul et al., 2016; Omar et al., 2018; Wongsomboon et al., 2021). This item aids in minimising selection bias in reporting the results. However, lack of this item could mean that the results were reported to suit the researchers' hypotheses and thus causing selection bias (EDA, 2013; Suresh, 2011).

The RoB analysis for in vivo studies is reported in Table 4.10. It was done using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) tool. 6 studies exhibited low RoB while 8 studies exhibited medium RoB. All studies lacked question 5 (Were the caregivers and /or investigators blinded from knowledge which intervention each animal received during the experiment?), which indicates that in all the studies, the investigators knew which animal group received the treatment. Blinding in an experiment reduces the risk of selection bias. A lack of blinding in these studies

can affect the quality of the study and reduces the reliability of the results (Bespalov et al., 2019; Macleod et al., 2015).

5.3 Study strengths

The main strength of the study is the degree of rigour in conducting the systematic review. The methodology and protocol were conducted in accordance to the updated PRISMA guidelines (Page et al., 2021). Other than that, only in vitro and in vivo studies were included to allow a narrowed and focused review to be conducted. The methodology also included an optimization to limit the search from 20 years to 6 years. This allowed the researcher to obtain newer studies and produce a more focused systematic review. Additionally, the included studies' quality were also accessed to reduce the risk of performance and selection bias.

5.4 Study limitations

This systematic review is subjected to a few limitations. Firstly, meta-analysis was unable to be performed due to the heterogeneity of the data. Other than that, the articles reviewed were only those that could be retrieved online and made accessible to the public. Some studies that were requested from the researchers but had no response were also not included. This could result in a reporting bias due to the incomplete retrieval and assessment of related studies (Lemma et al., 2017). Only articles of the English language were included due to language barrier. Selection bias may also be present due to the inclusion of only studies that showed significant antimalarial results. Publication bias is also a limiting factor because writers frequently choose to patent their findings before publishing their work. As a result, several effective medicinal plants can be discovered as effective but the work is still not published.

CHAPTER 6

CONCLUSION

6.1 Implication for practice

Malaria is a global health issue that affects people all over the world. Despite the great efficiency of currently available antimalarials, due to multiple treatment hurdles and developing resistance, persons around the world are still dying from malaria or being severely impacted by the disease and its complications. Around the world, between 0 to 75% of persons utilise medicinal plants for malaria treatment (Wilcox & Bodeker, 2004). In places where a large ratio of the population has access towards the infrastructure to benefit from improvements in herbal remedies and limited access towards

conventional antimalarials, researches on traditionally used medicinal plants can be very useful in terms evidence base building and supporting better treatment and prevention outcomes (Aracil & Green, 2019).

In this systematic review, a total of 36 studies meeting the inclusion criteria were identified and a total of 115 extracts from 39 plant species were analysed. Different plant extracts such as dichloromethane bark extract of *Alseodaphne corneri Kosterm,* ethanol leaves extract of *Alectryon serratus,* methanol extract of *Tinospora crispa,* aqueous leaves extract of *Gynostemma pentaphyllum* and methanol stem extract of *Artocarpus champeden* showed very good antimalarial activities. Most studied plant family was Annonaceae, yet the most studied plant was *Moringa oleifera* from the family Moringaceae. Furthermore, alcohol based solvent was used in most of the studies and leaves of the plants were the most studied part of the plant. For the risk of bias assessment, most studies showed medium to low risk of bias indicating the results for these studies are valid and the antimalarial activities of these plants can be further investigated.

6.2 Implication for research

Traditional practices in non-Western societies are frequently regarded as useful and vital in attracting research from a global health viewpoint in order to prevent inflicting non-local ideas on local residents (WHO, 2013). The question therefore becomes why, in terms of using traditional medicine in the global fight against malaria, this strategy has been largely overlooked. The promotion of evidence-based medical standards for herbal medicine would complement resources that are in existence in many malaria-endemic areas, where herbal medicine is already deeply ingrained in the souls of many locals. This would also be a long-term, cost-effective, and empowering strategy, because citizens from these countries would have the upper hand to control their own medical production and use through herbal medicine (Aracil & Green, 2019).

In comparison to the huge number of naturally occurring plants, only a minute number of medicinal plant species have been evaluated. Clearly, now is the moment to boost the number of laboratory-based investigations. In addition, additional methodologies such as reverse pharmacology must be

employed to determine the efficacy of antimalarial medicinal plants and extracts that have been historically used (Lemma et al., 2017).

6.3 Future recommendation

For future studies involving medicinal plants for antimalarial properties, randomization, blinding and use of comparator groups should be included in both in vitro and in vivo investigations. More transparent reporting should be practiced as well in future studies to increase the quality of the overall research. Justification of the dosage and extraction methods would be a component that should be included in future studies to allow a better understanding to the readers.

The future studies' quality and the application of important findings will be determined by the collaborative efforts of key stakeholders such as scientists, herbalists, ethnobotanists, traditional healers, policy makers and medical professionals. It is critical to have a balance and properly look into these perspectives in order to develop the most effective solutions.

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APPENDICES

Appendix A: PRISMA 2020 CHECKLIST (Page et al., 2021)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	

	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	

	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Appendix B: Table for Data Extraction.

AUTHOR	TITLE	YEAR	PLANT COLLECTION	PLANT NAME	PLANT PART	EXTRACT USED	ACTIVE COMPOUND	STUDY DESIGN	ANTI-MALARIAL ASSAY / TEST	IC50 DOSES	INHIBITION %	COMPARISON	MOA	OUTCOME

Appendix C: SYRCLE's tool for assessing risk of bias (Hooijmans et al. 2014).

Item	Type of bias	Domain	Description of domain	Review authors judgment
1	Selection bias	Sequence generation	Describe the methods used, if any, to generate the allocation sequence in sufficient detail to allow an assessment whether it should produce comparable groups.	Was the allocation sequence adequately generated and applied?
2	Selection bias	Baseline characteristics	Describe all the possible prognostic factors or animal characteristics, if any, that are compared in order to judge whether or not intervention and control groups were similar at the start of the experiment.	Were the groups similar at baseline or were they adjusted for confounders in the analysis?
3	Selection bias	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment.	Was the allocation adequately concealed?
4	Performance bias	Random housing	Describe all measures used, if any, to house the animals randomly within the animal room.	Were the animals randomly housed during the experiment?
5	Performance bias	Blinding	Describe all measures used, if any, to blind trial caregivers and researchers from knowing which intervention each animal received. Provide any information relating to whether the intended blinding was effective.	Were the caregivers and /or investigators blinded from knowledge which intervention each animal received during the experiment?
6	Detection bias	Random outcome assessment	Describe whether or not animals were selected at random for outcome assessment, and which methods to select the animals, if any, were used.	Were animals selected at random for outcome assessment?
7	Detection bias	Blinding	Describe all measures used, if any, to blind outcome assessors from knowing which intervention each animal received. Provide any information relating to whether the intended blinding was effective.	Was the outcome assessor blinded?
8	Attrition bias	Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized animals), reasons for attrition or exclusions, and any re-inclusions in analyses for the review.	Were incomplete outcome data adequately addressed?
9	Reporting bias	Selective outcome reporting	State how selective outcome reporting was examined and what was found.	Are reports of the study free of selective outcome reporting?
10	Other	Other sources of bias	State any important concerns about bias not covered by other domains in the tool.	Was the study apparently free of other problems that could result in high risk of bias?

Appendix D: Table of excluded studies.

REASON OF EXCLUSION	TITLE	AUTHOR
full text unavailable	Semisynthetic 15-O-Acyl- and 1,15-Di-O-acyleurycomanones from Eurycoma longifolia as potential antimalarials	Chan et al., 2005
	A new family of cystine knot peptides from the seeds of Momordica cochinchinensis	Chan et al., 2013
	Alstoniaphyllines A–C, Unusual Nitrogenous Derivatives from the Bark of Alstonia macrophylla	Cheenpracha et al., 2013
	Antimalarial and cytotoxic activities of pregnene-type steroidal alkaloids from Holarrhena pubescens roots	Cheenpracha et al., 2019
	Screening of Thai medicinal plant extracts and their active constituents for in vitro antimalarial activity	Ichino et al., 2006
	Bioassay-Guided Isolation Of Antiplasmodial Compounds From Two Malaysian Kopsia Species	Ismail et al., 2010
	Ethnobotanical And Ethnopharmacological Documentation Of Antimalarial Plants Used By The Jakun Community In Kg Peta, Endau-Rompin, Johor, Malaysia	Ismail wt al., 2017
	Novel diterpenes with cytotoxic, anti-malarial and anti-tuberculosis activities from a brown alga Dictyota sp.	Jongaramrruong et al., 2007
	New antimalarial bis-dehydroaporphine alkaloids from Polyalthia debilis	Kanokmedhakul et al., 2003
	New bioactive prenylflavonoids and dibenzocycloheptene derivative from roots of Dendrolobium lanceolatum	Kanokmedhakul et al., 2004
	2-Substituted furans from the roots of Polyalthia evecta	Kanokmedhakul et al., 2006
	Bioactive constituents of the roots of Polyalthia cerasoides	Kanokmedhakul et al., 2007
	Kaurane-Type Diterpene Glycoside from the Stem Bark of Acanthopanax trifoliatus	Kiem et al., 2004
	In-vitro response of Plasmodium falciparum to the main alkaloids of Cinchona in northwestern Thailand	Knauer et al., 2003

	Bioactive Lupane and Hopane Triterpenes from Lepisanthes senegalensis	Lomchid et al., 2017
	Antimalarial compounds from Grewia bilamellata	Ma et al., 2006
	Antimalarial and antituberculous poly-O-acylated jatrophane diterpenoids from Pedilanthus tithymaloides	Mongkolvisut et al., 2007
	Antiplasmodial and cytotoxic flavans and diarylpropanes from the stems of Combretum griffithii	Moosophon et al., 2013
	New Bioactive Lupane Triterpene Coumaroyl Esters Isolated from Buxus cochinchinensis	Pan et al., 2015
	Cytotoxic and antimalarial azaphilones from chaetomium longirostre	Panthama et al., 2011
	Cytotoxic coumarins from toddalia asiatica	Phatchana et al., 2014
	Antimalarial Oxoprotoberberine Alkaloids from the Leaves of Miliusa cuneata	Promchai et al., 2016
	(R)-3-(8'-Hydroxyfarnesyl)-indole and other chemical constituents from the flowers of Anomianthus dulcis and their antimalarial and cytotoxic activities	Promchai et al., 2019
	Cassane furanoditerpenoids from the seed kernels of Caesalpinia bonduc from Thailand	Pudhom et al., 2007
	Bioactive galloyl flavans from the stems of Helixanthera parasitica	Rajachan et al., 2020
	Chabamide, a novel piperine dimer from stems of Piper chaba	Rukachaisirikul et al., 2002
	Erythrina alkaloids and a pterocarpan from the bark of Erythrina subumbrans	Rukachaisirikul et al., 2008
	A new antimalarial agent; effects of extracts of Artemisia diffusa against Plasmodium berghei	Rustaiyan et al., 2007
	IN VITRO ANTIMALARIAL ACTIVITY OF THAI PICRASMA JAVANICA Bl STEM EXTRACT	Saiin et al., 2016

	Two new bioactive triterpenoids from the roots of Colubrina asiatica	Sansopha et al., 2020
	Cytotoxic and antiplasmodial compounds from the roots of Strophioblachia fimbricalyx	Seephonkai et al., 2009
	Carbazole alkaloids from the stems of Clausena excavata	Sripisut et al., 2010
	Antioxidant and Antimalarial Activity of Leea indica leaf extract against Malaria-mice Model	Sulistyaningsih et al., 2017
	Inhibitory Activities of Thai Medicinal Plants with Promising Activities Against Malaria and Cholangiocarcinoma on Human Cytochrome P450	Sumsakul et al., 2015
	Diterpenes, sesquiterpenes, and a sesquiterpene-coumarin conjugate from Jatropha integerrima	Suthivaiyakit et al., 2009
	Oxygenated pimarane diterpenes from Kaempferia marginata	Thongnest et al., 2005
	New antimycobacterial and antimalarial 8,9-secokaurane diterpenes from Croton kongensis	Thongtan et al., 2003
	Combretastatins D-3 and D-4, new macrocyclic lactones from Getonia floribunda	Vongvanich et al., 2005
	Antiplasmodial, antimycobacterial, and cytotoxic principles from Camchaya calcarea	Vongvanich et al., 2006
	Antimalarial compounds from Rhaphidophora decursiva	Zhang et al., 2001
not SEA plant	Evaluation of antimalarial, free-radical-scavenging and insecticidal activities of Artemisia scoparia and A. spicigera, Asteraceae	Afshar et al., 2011
	Cajachalcone: An antimalarial compound from Cajanus cajan leaf extract	Ajaiyeoba et al., 2013
	Apigenin inhibits growth of the Plasmodium berghei and disrupts some metabolic pathways in mice.	Amiri et al., 2018
	In-vivo antimalarial activities of crude extract and solvent fractions of the roots of Clematis simensis	Asmare et al., 2017

	Fresen.(Ranunculaceae) in Plasmodium berghei infected mice.	
	In vivo antiplasmodial activity evaluation of the leaves of Balanites rotundifolia (Van Tiegh.) Blatter (Balanitaceae) against Plasmodium berghei	Asrade et al., 2017
	Antiplasmodia Efficacy Of Methanolic Extract Of Leaf Of Morinda Lucida	Ayinla et al., 2013
	In vitro antiplasmodial activity and toxicity assessment of plant extracts used in traditional malaria therapy in the Lake Victoria Region	Ayuko et al., 2009
	In vivo antimalarial extracts and constituents of Prosopis juliflora (Fabaceae)	Batista et al., 2018
	Evaluation of the Antimalarial and Liver Function Potentials of Methanol Extract of Chrysophyllum albidum Stem Bark in Plasmodium berghei - Infected Mice	Umar et al., 2018
	Antimalarial metabolites from Buxus sempervirens	Cai et al., 2015
	Exploring the antimalarial potential of whole Cymbopogon citratus plant therapy	Chukwuocha et al., 2016
	Evaluation of Antimalarial Activity of Methanolic Root Extract of Myrica salicifolia A Rich (Myricaceae) Against Plasmodium berghei-Infected Mice	Kifle et al., 2020
	In vitro and in vivo antimalarial potential of oleoresin obtained from Copaifera reticulata Ducke (Fabaceae) in the Brazilian Amazon rainforest	de Souza et al., 2017
	Determination of effective dose of antimalarial from cassia spectabilis leaf ethanol extract in plasmodium berghei-infected mice	Ekasari et al., 2018
	Methanol extracts of Fagara zanthoxyloides leaves possess antimalarial effects and normalizes haematological and biochemical status of Plasmodium berghei-passaged mice	Enechi et al., 2019
	Antiplasmodial Activity and Amelioration of Altered Haematological Indices by Methanol Extract of Peltophorum pterocarpum in Plasmodium Berghei-Infected Mice Bioactivities and safety profiles of	Enechi et al., 2019

	polyherbal formulations Retailed in Africa View project Prov	
	In vitro antileishmanial, antiplasmodial and cytotoxic activities of phenolics and triterpenoids from Baccharis dracunculifolia DC (Asteraceae)	Filho et al., 2009
	Antimalarial Studies Of The Ethanol Extract Of The Leaves Of Nauclea Latifolia (Rubiaceae)	Fredrick et al., 2015
	Phloroglucinols from the Roots of Garcinia dauphinensis and Their Antiproliferative and Antiplasmodial Activities	Fuentes et al., 2019
	In vivo validation of anti-malarial activity of crude extracts of Terminalia macroptera, a Malian medicinal plant	Haidara et al., 2018
	In Vivo Antimalarial Evaluation of Crude Extract, Solvent Fractions, and TLC-Isolated Compounds from Olea europaea Linn subsp. cuspidata (Oleaceae)	Hailesilase et al., 2020
	In Vitro Therapeutic Value Of Plant Extracts Used In Burkina Faso To Treat Malaria And Pharmacodynamic Studies Of Antimalarial Drugs	Illboudo et al., 2010
	Antiplasmodial and anti-inflammatory activities of Canthium henriquesianum (K. Schum), a plant used in traditional medicine in Burkina Faso	Illboudo et al., 2013
	The Effectiveness of Varying Combination Ratios of A. cordifolia and M. indica against Field and Laboratory Strains of P. falciparum In Vitro	Jibira et al., 2020
	Antimalarial and cytotoxic properties of Chukrasia tabularis A. Juss and Turraea vogelii Hook F. Ex. Benth	Ogbole et al., 2016
	Chemical and bioactivity evaluation of the bark of Neonauclea purpurea	Karaket et al., 2012
	The Antiplasmodial Activity of Isolates from Ajuga remota	Kuria et al., 2002
	In vitro assessment of antiplasmodial activity and cytotoxicity of polyalthia longifolia leaf extracts on plasmodium falciparum strain NF54	Kwansa-Bentum et al., 2019
	Composition and antimalarial activity of extracts of Curcuma longa L. obtained by a combination of extraction	Martinez-Correa et al., 2017

	processes using supercritical CO2, ethanol and water as solvents	
	Anti-malarial activity of leaf-extract of Hydrangea macrophylla, a common Japanese plant	Matsouka et al., 2000
	In Vivo Anti-Malarial Activity of Heracleum persicum Fruit Extract, in Combination with Chloroquine against Chloroquine–Sensitive Strain of Plasmodium	Mazhari et al., 2018
	In vivo antimalarial activity of the crude root and fruit extracts of Croton macrostachyus (Euphorbiaceae) against Plasmodium berghei in mice	Mekonnen et al., 2015
	Antiplasmodial activity of the andiroba (Carapa guianensis Aubl., Meliaceae) oil and its limonoid-rich fraction	Miranda et al., 2012
	Phytochemical investigation of an antimalarial plant: Cochlospermum planchonii	Mischka et al., 2017
	In vitro and in vivo antimalarial evaluations of myrtle extract, a plant traditionally used for treatment of parasitic disorders	Naghibi et al., 2013
	Screening of a library of traditional Chinese medicines to identify anti-malarial compounds and extracts	Nonaka et al., 2018
	ANTIMALARIAL ACTIVITY OF CROTON MACROSTACHYUS EXTRACTS AGAINST PLASMO-DIUM SP	Obey et al., 2015
	Antiplasmodial activity of triterpenes isolated from the methanolic leaf extract of Combretum racemosum P. Beauv	Oluyemi et al., 2020
	Potential antimalarial activity of Coccinia barteri leaf extract and solvent fractions against Plasmodium berghei infected mice	Orabueze et al., 2020
	Spermine alkaloids from Albizia adinocephala with activity against Plasmodium falciparum plasmepsin II	Ovenden et al, 2002
	Design and synthesis of simplified speciophylline analogues and β-carbolines as active molecules against Plasmodium falciparum	Pierrot et al., 2019
	Herbs and herbal combinations used to treat suspected malaria in Bo, Sierra Leone	Ranasinghe et al., 2015

	In vitro antioxidant and antimalarial activities of leaves, pods and bark extracts of Acacia nilotica (L.) Del.	Sadiq et al., 2017
	of the antimalarial effect of Ferulago angulata (Schlecht.) Boiss. extract and suberosin epoxide against plasmodium berghei in comparison with chloroquine \ldots	Sajjadi et al., 2016
	In vitro and in vivo antimalarial activity of the volatile oil of Cyperus articulatus (Cyperaceae)	Silva et al., 2019
	Antimalarial activity and safety assessment of Flueggea virosa leaves and its major constituent with special emphasis on their mode of action	Singh et al., 2017
	Antiplasmodial phloroglucinol derivatives from Syncarpia glomulifera	Su et al., 2016
	Antimalarial activity of Syzygium guineense during early and established Plasmodium infection in rodent models	Tadesse et al., 2017
	Anti-malarial activity of traditional Kampo medicine Coptis rhizome extract and its major active compounds	Teklemichael et al., 2020
	Antimalarial Activity and cytotoxicity profile of the seed extracts of Garcinia kola (GUTTIFERAE)	Ujomu et al., 2019
	In Vivo Antimalarial Activities Of Fractionated Extracts Of Asparagus Africanus In Mice Infected With Plasmodium Berghei	Yared et al., 2012
	In vivo Antiplasmodial and Cytotoxic Activity of Achyranthes aspera and Ficus thoningii in Mice Infected with Plasmodium berghei	Zaruwa et al., 2018
	Anti-malarial property of steroidal alkaloid conessine isolated from the bark of Holarrhena antidysenterica	Dua et al., 2013
cross sectional study	A cross-sectional analysis of traditional medicine use for malaria alongside free antimalarial drugs treatment amongst adults in high-risk malaria endemic provinces of Indonesia	Suswardany et al., 2017
low impact factor	Antimalarial Activity Of 80\% Methanolic Extract Of Brassica Nigra (L.) Koch. (Brassicaceae) Seeds Against Plasmodium Berghei Infection In Mice	Belachew et al., 2015
	Antimalarial Activity of Biflavonoids from Ochna integerrima	Ichino et al., 2005

	The Antimalarial Activity of the Water Extract of Simpur (Dillenia Indica L) Leaves against Plasmodium Berghei in Mice	Riza et al., 2005
method not comprehension	2-Phenylnaphthalenes and a polyoxygenated cyclohexene from the stem and root extracts of Uvaria cherrevensis (Annonaceae)	Auranwiwat et al.,2017
	Part 1: Antiplasmodial, cytotoxic, radical scavenging and antioxidant activities of thai plants in the family acanthaceae	Charoenchai et al., 2010
	Antiplasmodial and other constituents from four Indonesian Garcinia spp.	Elfita et al., 2009
molecular docking studies	Design, synthesis and biological evaluation of 4-aminoquinoline-guanylthiourea derivatives as antimalarial agents	Bhagat et al., 2019
	Identification of novel class of falcipain-2 inhibitors as potential antimalarial agents	Chakka et al., 2015
	Synthesis, antimalarial evaluation and molecular docking studies of some thiolactone derivatives	Sainy et al., 2017
molecular studies	Design, synthesis and in vitro antimalarial evaluation of triazole-linked chalcone and dienone hybrid compounds	Guantai et al., 2010
	New ferrocenic pyrrolo[1,2-a]quinoxaline derivatives: Synthesis, and in vitro antimalarial activity - Part II	Guillon et al., 2011
	New derivatives of quinoline-4-carboxylic acid with antiplasmodial activity	Hochegger et al., 2017
	Synthesis and structure-activity relationships for new 6-fluoroquinoline derivatives with antiplasmodial activity	Hochegger et al., 2019
	Novel inhibitors of Plasmodium falciparum based on 2,5-disubstituted furans	Krake et al., 2017
	Synthesis and antimalarial activities of base-catalyzed adducts of 11- azaartemisinin	Mekonnen et al., 2000
	In vitro antimalarial activity of flavonoid derivatives dehydrosilybin and 8-(1; 1)-DMA-kaempferide	Monbrison et al., 2006

	Broad activity of diphenyleneiodonium analogues against Mycobacterium tuberculosis, malaria parasites and bacterial pathogens	Nguyen et al., 2018
	Structure Activity Refinement of Phenylsulfonyl Piperazines as Antimalarials that Block Erythrocytic Invasion	Nguyen et al. 2021
	Mixed tetraoxanes containing the acetone subunit as antimalarials	Opsenica et al., 2008
	Antiplasmodial activity of targeted zinc(II)-dipicolylamine complexes	Rice et al., 2017
	Synthesis, biological evaluation and mechanistic studies of totarol amino alcohol derivatives as potential antimalarial agents	Tacon et al., 2012
	Synthesis and evaluation of 4-quinazolinone compounds as potential antimalarial agents	Zhu et al., 2010
	Febrifugine analogue compounds: Synthesis and antimalarial evaluation	Zhu et al., 2012
	Synthesis and biological evaluation of febrifugine analogues as potential antimalarial agents	Zhu e al., 2009
no antimalarial activity	New alkaloids from Phoebe grandis (Nees) Merr	Awang et al., 2006
	Roscotanes and roscoranes: Oxygenated abietane and pimarane diterpenoids from Kaempferia roscoeana	Boonsombat et al., 2017
	ent-dioncophylleine A and related dehydrogenated naphthylisoquinoline alkaloids, the first Asian dioncophyllaceae-type alkaloids, from the new" plant species Ancistrocladus benomensis"	Bringmann et al., 2005
	Antioxidant and antimicrobial potential of Garcinia hombroniana Pierre bark	Hofstaetter et al., 2007
	New bioactive clerodane diterpenoids from the bark of Casearia grewiifolia	Kanokmedhakul et al., 2005
	In vitro and in vivo assessment of the anti-malarial activity of Caesalpinia pluviosa	Kayano et al., 2011

	A thermostable lectin from the rhizomes of Kaempferia parviflora	Konkumnerd et al., 2010
	Physicochemical Effects of the Major Quassinoids in a Standardized Eurycoma longifolia Extract (Fr 2) on the Bioavailability and Pharmacokinetic Properties, and their Implications for Oral Antimalarial Activity	Low et al., 2011
	Phytochemicals from Dodonaea viscosa and their antioxidant and anticholinesterase activities with structure–activity relationships	Muhammad et al., 2016
	Constituents of the Indonesian epiphytic medicinal plant Drynaria rigidula	Nugraha et al., 2013
	Alkaloids from the root of Indonesian Annona muricata L	Nugraha et al., 2019
	Two new cytotoxic isomeric indole alkaloids from the roots of Nauclea orientalis	Sichaem et al., 2010
	In vitro reduction of Plasmodium falciparum gametocytes: Artemisia spp. tea infusions vs. artemisinin	Snider et al., 2021
	Antimalarial and Anti-hypoglycemic Properties of Siamese Neem Tree (Azadirachta indica) in Plasmodium berghei Infected Mice Antimalarial activity of Gymnema inodorum extract against Plasmodium berghei infected mice View project Antimalarial of plant extra	Somsak et al., 2015
	Sulfur-containing compounds from Clinacanthus siamensis	Tuntuwachwuttikul et al., 2003
no methodology	Chemical constituents and biological activities from branches of Colubrina asiatica	Sansopha et al., 2018
not comprehensive	Traditional herbal medicine for the control of tropical diseases	Na-Bangchang et al., 2014
	In vivo antiparasitic activity of the Thai traditional medicine plant-Tinospora crispa-against Plasmodium yoelii	Rungruang et al., 2009
	Stage specificity of pasak bumi root (Eurycoma longifolia Jack) isolate on Plasmodium falciparum cycles.	Sholikhah et al., 2008

	Isolation, cytotoxic and antiplasmodial activities of 6-farnesyl-3',4',5,7-tetrahydroxyflavanone from the flower of Macaranga triloba	Zakaria et al., 2011
not medicinal plant	Synthesis and antiplasmodial activity of new heteroaryl derivatives of 7-chloro-4-aminoquinoline	Casagrande et al., 2012
	Anti-malarial activities of two soil actinomycete isolates from sabah via inhibition of glycogen synthase kinase 3β	Dahari et al., 2016
	In vitro antimalarial activity of flavonoid derivatives dehydrosilybin and 8-(1;1)-DMA-kaempferide	Monbrison et al., 2006
	Three New Diketopiperazines from the Previously Uncultivable Marine Bacterium Gallaecimonas mangrovi HK-28 Cultivated by iChip	Ding et al., 2020
	Synthesis of mono-, bis-spiro- and dispiro-β-lactams and evaluation of their antimalarial activities	Jarrahpour et al., 2011
	Seaweed-synthesized silver nanoparticles: an eco-friendly tool in the fight against Plasmodium falciparum and its vector Anopheles stephensi?	Murugan et al., 2015
	Eugenol disrupts Plasmodium falciparum intracellular development during the erythrocytic cycle and protects against cerebral malaria	Pontes et al., 2021
	Bioactive deoxypreussomerins and dimeric naphthoquinones from Diospyros ehretioides fruits: Deoxypreussomerins may not be plant metabolites but may be from fungal epiphytes or endophytes	Prajoubklang et al., 2005
	Metabolite extract of Streptomyces hygroscopicus Hygroscopicus inhibit the growth of Plasmodium berghei through inhibition of ubiquitin - Proteasome system	Rivo et al., 2013
	Isolation and synthesis of falcitidin, a novel myxobacterial-derived acyltetrapeptide with activity against the malaria target falcipain-2	Somanadhan et al., 2013
	The antimalarial natural product symplostatin 4 is a nanomolar inhibitor of the food vacuole falcipains	Stolze et al., 2012
	Structure–Activity Relationship of Anti-malarial Allylpyrocatechol Isolated from Piper betle	Tamura et al., 2020

	Pharmacokinetics and metabolism of the antimalarial piperaquine after intravenous and oral single doses to the rat	Tarning et al., 2008
	Antimalarial Activity of Piperine	Thiengsusuk et al., 2018
not research paper	Bioactive alkaloids from medicinal plants of Lombok	Hadi & Surya, 2002
	In Vivo Antimalarial Activity of Ethanol Extract of Carthamus Tinctorius L. Flowers Against Plasmodium Berghei Strain Anka In Male Mice Balb/C	Hamsidi et al., 2017
	Phytochemical discovery of antifeedant, antimicrobial and antimalarial principles.	Omar, 2001
	Search for bioactive compounds from medicinal plants used as antimalarials : The study of Momordica balsamina L.	Ramalhete et al., 2010
	A new antimalarial candidate	Walawalker, 2004
poor methodology	Evaluation of the inhibitory activities of the extracts of Indonesian traditional medicinal plants against Plasmodium falciparum and Babesia gibsoni	Murnigsih et al., 2005
	AN IN-VIVO EVALUATION OF ANTIPLASMODIAL ACTIVITY OF AQUEOUS AND ETHANOLIC LEAF EXTRACTS OF AZADIRACHTA INDICA IN PLASMODIUM BERGHEI INFECTED BALB/c MICE	Oseni et al., 2012
poor results and discussion	Detection of In Vitro Antimalaria! Activity of Some Myanmar Medicinal	Lai Ei et al., 2008
review paper	Therapeutic Potential of Plant Species Derived from Some Annonaceae Genus	Aziz et al., 2016
	Structurally Diverse Bioflavonoids As Potential Source Of Antimalarial Lead Molecules	Chetia et al., 2016
	The Role of Curcumin as An Antimalarial Agent	Ekawadhani et al., 2020
	In search of cyclooxygenase inhibitors, anti-Mycobacterium tuberculosis and anti-malarial drugs from Thai flora and microbes	Gale et al., 2007

	Biological activities and phytochemicals of Swietenia macrophylla king	Moghadamtousi et al., 2013
	Xanthones as antimalarial agents: discovery, mode of action, and optimization	Riscoe et al., 2005
	Review on in-vitro anti-Malarial activity of Natural β-carboline Alkaloids Design and Synthesis of Novel Therapeutic Agents View project Design, synthesis and biological evaluation of beta-carboline derivatives View project Ashok Penta Send Orders for Rep	Sankaranarayanan et al., 2013
	Robert koch redux: Malaria immunology in papua new guinea	Stanisic et al., 2010
	Phytochemical Constituents and Pharmacological activities of Nyctanthes arbor-tristis	Venkataraman et al., 2019
	Phytochemical Composition Of Agathis Borneensis (Araucariaceae) And Their Biological Activities	Zafirah et al., 2017
structural elucidation studies	Chemical constituents of Avicennia alba. Isolation and structural elucidation of new naphthoquinones and their analogues	Ito e al., 2000
	New Cassane-Type Diterpenes of Caesalpinia crista from Myanmar	Kalauni et al, 2005
	Methyl migrated cassane-type furanoditerpenes of Caesalpinia crista from Myanmar	Kalauni et al, 2005
	Studies on Anti-cancerous and Anti-malarial Substances from Simaroubaceae Plants	Takeya, 2000
	Amalgamating Isatin/Indole/Nitroimidazole with 7-chloroquinolines via azide-alkyne cycloaddition: Synthesis, anti-plasmodial, and cytotoxic evaluation.	Kumar et al., 2020
	Structure-activity relationship of new antimalarial 1-aryl-3-susbtituted propanol derivatives: Synthesis, preliminary toxicity profiling, parasite life cycle stage studies, target exploration, and targeted delivery	Quiliano et al., 2018
	Chemical constituents of the roots of Piper sarmentosum	Tuntuwachwuttikul et al., 2006

survey/questionnaire based design	Ethno-botanical survey of plants used in the traditional treatment of malaria in Sei Kepayang, Asahan of North Sumatera	Abdillah et al., 2014
	The use of antimalarial plants as traditional treatment in Papua Island, Indonesia	Budiarti et al., 2020
	Forest Fevers: traditional treatment of malaria in the southern lowlands of Laos	Elliott et al., 2020
active compound quantification studies	Quantification of the antiplasmodial alkaloid carpaine in papaya (Carica Papaya) leaves	Julianti et al., 2014
article cannot be found	alpha-Glucosidase inhibitory, aromatase inhibitory, and antiplasmodial activities of a biflavonoid gb1 from garcinia kola	Antia et al., 2010
book	Traditional Medicinal Plants and Malaria	Wilcox et al., 2007