

# ANALYSIS OF PLANT INGREDIENTS IN REMEDIAL FORMULATIONS OF MALARIA IN MALAY MEDICAL MANUSCRIPTS

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## ABSTRACT

**Introduction:** Malaria is an infectious disease caused by *Plasmodium* spp. The main treatment is artemisinin which was discovered after a massive study on Chinese medical manuscripts. However, artemisinin monotherapy is now challenged by antimalarial drug resistance and there are issues of relapse and failure when using artemisinin-based combination therapy (ACTs). Interestingly, traditional Malay medicine also provides numerous remedies to treat malaria, of which can be obtained from Malay medical manuscripts (MMM). Hence, this study aims to extract and analyse the formulations in MMM. **Methods:** Several terms referring to malaria were scanned throughout 10 MMM. The formulations were then extracted, and the ingredients were identified and compared to contemporary studies. **Results:** A total of 17 formulations were identified, comprising of 37 ingredients. Twenty-five of them were plant-based ingredients and were further analysed. The analysis revealed that 10 of the ingredients have been empirically demonstrated to possess pharmacological actions against malaria such as *Alpinia galanga*, *Syzygium aromaticum* and *Myristica fragrans*. Those plants had been shown to eliminate *Plasmodium* spp. in in vitro or in vivo experiments. Thirteen of the ingredients had been shown to have pharmacological actions that help relieve symptoms of malaria such as *Tabernaemontana corymbosa* that has anti-pyretic effect while the other two ingredients have not been reported in pharmacological studies. **Conclusion:** In short, the formulations mentioned in MMM have potential to be developed into accessible and affordable alternative malaria treatments due to its inhibitory and anti-plasmodial activity against *Plasmodium* spp.

**KEYWORDS:** Malay medical manuscript, malaria, demam kura, *Plasmodium*

## INTRODUCTION

Malay manuscripts are written documents that originate from the Malay Archipelago that show information found by the populace in the past. The majority of the text has been passed down through the centuries and covers various disciplines including literature, medicine, religious texts, laws and legislation, and history. The Malay Archipelago is rich with its own knowledge of traditional medicine and it is recorded in the Malay medical manuscripts (MMM). Malay medical manuscripts are manuscripts containing information on medicinal practices and knowledge from the Malay Archipelago population that can be dated back to the 16<sup>th</sup> to the 18<sup>th</sup> century (Mohd Shafri, 2018a). In Malaysia, National Library of Malaysia has the highest collection of Malay manuscripts with approximately 4,884 copies as of in 2018 (National Library of Malaysia, 2018) and more than 100 copies are MMM (Mohd Shafri et al., 2021a).

Malay traditional medicine has the possibility to be a developed and recognised pharmacopeia considering that there is a significant number of MMM available. The current generation in Southeast Asia should be proud and make efforts to retrieve the valuable knowledge contained in MMM. Currently there are a few studies that have been done on the medical texts such as the works of Maidin & Mamat (2014), Mat Piah (2015) and Mohd Shafri (2021b). In MMM, various diseases are mentioned such as typhoid fever, tuberculosis, sinus, psoriasis and malaria.

Malaria is a disease that is frequently mentioned in MMM and it is still prevalent in hyper endemic countries. The disease is still considered as one of the most infectious vector-borne diseases worldwide caused by the parasitic *Plasmodium* protozoa and transmitted by the bites of female *Anopheles* mosquitoes (Talapko et al., 2019). It can present in complicated presentations that can progress to death within days or even hours (Buck & Finnigan, 2021). The discovery of artemisinin from *Artemisia Annua* tree that was recorded in a medical manuscript in 2<sup>nd</sup> Century BC China by Tu Youyou has led to development of antimalarial drug. The use of artemisinin in combination therapy, the Artemisinin-Combination Therapy (ACT), give rise to malarial treatment that could efficiently eliminate the *Plasmodium* parasite (Tse et al., 2019). However, due to the reports of treatment failure and the increasing antimalarial resistance such as the case reported in the Great Mekong (World Health Organization, 2021), there are initiatives for researchers to find another approach in combating antimalarial infection. Therefore, the objective of the study is to gather remedial formulations for malaria disease from MMM and conduct a comparative analysis with the contemporary studies on the herbs extracted from the MMM to identify the scientific evidence supporting the herbs' uses in treating Malaria.

## METHODOLOGY

### Selection of Manuscripts

The transliterated manuscripts were chosen if it contains any information on malaria. Keywords or term used for the screening of manuscripts are malaria, *demam kura*, *demam*, *hummā al-nāfid*, *humma al-thani*, *humma al-ghibb* or *hummā al-rib'* (Mohd. Shafri, 2018b).

### Extraction & Classification of Data

The data extraction process was done by extracting information of several categorisation that include name of manuscripts, malaria term used in manuscripts, formulation number, formulation type, and materials from the formulation in the manuscripts.

Formulation number was assigned to formulations with no designated formulation number in the format of "YYYY.XX.YY", for which:

YYYY indicates the manuscript designated catalogue number.

XX indicates the order of the formulation was found in the manuscript.

YY indicates the page number the formulation was stated in the manuscript or transliterated book.

If there is no designated catalogue number, the first letter of the first and second words of the book title were utilised instead. Example of the first formulation number from the manuscript of *Rumah Ubat Di Pulau Penyengat* would be presented as RU.01.41. Plant-based materials from the formulations were further classified and scientific names were searched in various sources, i.e., Dewan Bahasa dan Pustaka (2017), Mat Piah & Mustapha (2019), Mamat et al. (2015), and online resources for botany, i.e., <https://www.nparks.gov.sg/>, <https://mybis.gov.my/one/>, and <https://www.kew.org/>.

### **Comparative Analysis of Manuscript Content**

The extracted contents were analysed by comparing with contemporary studies on the treatment formulations and natural products. The search was carried out using Google Scholar using specific keywords. The keywords used for literature search were the scientific/vernacular name of plant, malaria, antimalaria, antimalarial resistance, *Plasmodium*, medicinal uses and pharmacology, any combination together with the use of Boolean operators, i.e., AND, OR, NOT.

The pharmacological actions that were screened in the studies to determine if a particular ingredient has any relation to treating malaria, are anti-plasmodial, antimalarial, anti-parasite, antioxidant and antipyretic. Any mention of treatment of fever and jaundice were also noted as symptoms reliever for malaria. If there was any scientific evidence in the literature in treating malaria, the article would be chosen for further reading.

## **RESULTS AND DISCUSSIONS**

Malay medical manuscripts are the world heritage and not only the physical manuscript is valuable, what is more important is the content inside them. They can be sources for drug development especially in the current era where new diseases emerge and even some of the existing diseases are still not having effective treatment or at the risk of facing antimicrobial resistance. The latter is true for malaria where resistance is currently reported for the ART. Therefore, there is a need to look back into ancient medicine, specifically MMM, to find potential alternative treatment for malaria.

### **Selection of Manuscripts**

Nine manuscripts and transliterated manuscripts were screened in the initial stage and only six contain the keywords and hence, were selected; *Al-Rahmah Fi al-Tibb wa al-Hikmah* (transliterated edition by Mohd Shafri & Muhammad Yahya, 2017), *Rumah Ubat Pulau Penyengat* (transliterated edition by Mohd Shafri, 2018a), *Tayyib al-Insan Fi Tibb al-Insan* (transliterated edition by Mohd Shafri, 2018b), *Kitab Tib MSS 2515* (transliterated edition by Mat Piah & Baba, 2014), and *Warisan Perubatan Melayu* (transliterated edition by Ahmad, 2005) and MSS 4837 (unpublished).

### **Extraction of Data**

From the transliterated manuscripts, 17 remedial formulations for malaria were extracted. The information extracted are the name of manuscripts, malaria term used in manuscripts, formulation number, formulation type, and materials from the formulation in the manuscripts. The extracted data is presented in the Table 1.

**Table 1: Extracted information of Malaria formulations in Malay medical manuscript.**

Manuscript	Term used in Manuscript (Malay/ English)	Formulation Number	Formulation (Malay/ English)	Materials (Malay/ English/ Scientific name)
MSS 4837	Demam Kura Spleen fever	4837.042.068	<p><i>Daun terung asam, Garam siam sedikit. giling lumat-lumat, perah, ambil airnya dan minum pagi sebelum basuh muka. Baiknya kita minum itu seruas jari manis kita. Buat demikian tiga pagi. Kalau muntah juga, jangan berhenti di dalam tiga pagi.</i></p> <p>Borneo sour eggplant leaves, a little bit of Siamese salt, grind well, squeeze the paste to get the liquid part. Drink in the morning before washing the face. The best is to drink about one phalanx of our ring finger for three mornings. If the patient vomits, do not stop at least for three mornings.</p>	<p><i>Daun terung asam</i> Borneo sour eggplant <i>Solanum lasiocarpum</i></p> <hr/> <p><i>Garam siam</i> Siamese salt</p>
MSS 2515	Sehari demam sehari tiada sebab bertambah penyakit safrawi Intermittent fever because increased safrawi disease.	2515.01.98	<p><i>Akan ubatnya minum air limau hantu dan sakar pagi belum makan nasi; maka ia muntah setelah itu maka makan tepung jerubah yang direndamkan dan tepung gandum yang direndamkan dengan sakar; maka makan tiga pagi; jika tiada baik maka makan pecahar yang menghilangkan penyakit itu; maka afiat.</i></p> <p>The remedy is to drink the squeezed juice of key lime and sugar in the morning before eating rice. After the patient vomits, then eat rice flour and wheat flour that have been soaked with sugar. Eat it for three mornings. If there is no improvement, then eat the laxative that will remove the disease. Then you will recover.</p>	<p><i>Air limau hantu</i> Key lime squeeze <i>Citrus aurantiifolia</i></p> <hr/> <p><i>Sakar</i> Sugar</p> <hr/> <p><i>Tepung jerubah</i> Rice flour <i>Oryza sativa</i></p> <hr/> <p><i>Tepung gandum</i> Wheat flour <i>Triticum spp.</i></p> <hr/> <p><i>Pecahar</i> Laxative</p>
Al-Rahmah fi al-Tibb wa al-Hikmah	Humma Al- ghabb Tertian fever	AF.01.171	<p><i>Diminum air buah limo, ertinya air buah mentul daripada sukkar pada pagi- pagi qadar tiga hari. Tiap kali diminum akan dimuntah akan dia. Bermula makanan tatkala dimakan ubat ini roti tepung jagung dan sukkar, dan roti tepung gandum yang sudah terkhamir, dimakan dia dengan kuah daging anak hayam.</i></p> <p>Drink key lime squeeze with sugar for about three mornings. The patient will vomit after every drink. At the beginning of the treatment, eat this formulation: bread</p>	<p><i>Air buah limo mentul</i> Key lime <i>Citrus aurantifolia</i></p> <hr/> <p><i>Sukkar</i> Sugar</p> <hr/> <p><i>Roti tepung jagung</i> Bread made from corn flour <i>Zea mays</i></p>

			made from corn flour and sugar, and bread made from fermented wheat flour, eat it with the gravy chick curry.	<i>Roti tepung gandum yang terkhamir</i> Bread made from fermented wheat flour <i>Triticum spp.</i>
				<i>Kuah daging anak hayam</i> Gravy of chick curry <i>Gallus gallus</i>
	<i>Humma al-thani</i> Intermittent fever (every 24 hours and subsides with a full body chill)	AF.02.172	<i>Cuka pagi-pagi, minum qadar three hari jua.</i> Vinegar in the morning, drink for around three days.	<i>Cuka</i> Vinegar
	<i>Humma al-rib'</i> Quartan fever	AF.03.173	<i>Air susu lembu atau kerbau yang baharu diperah dicampur dengan minyak sapi yang sudah ditanak dan air madu yang sudah ditanak hingga hilang kubohnya.</i> Take fresh cow or buffalo milk, mix with cooked ghee and honey water that has been cooked until the foam disappears.	<i>Air susu lembu</i> Cow milk <i>Air susu kerbau</i> Buffalo milk <i>Minyak sapi</i> Ghee <i>Air madu</i> Honey water
		AF.04.174	<i>Diminum minyak lenga yang baharu diperah pagi-pagi qadar tiga hari, dan tiap-tiap hari diminum qadar (teks hilang) wiqyah atau empat wiqyah nescaya hilang lerai.</i> Drink cold-pressed sesame oil for about three mornings. Drink it every day of the amount about (missing text) <i>wiqyah</i> or four <i>wiqyah</i> , then the fever will go away.	<i>Minyak lenga</i> Sesame oil <i>Sesamum indicum</i>
Rumah Ubat Di Pulau Penyengat	<i>Demam Kura</i> Spleen fever	RU.01.35	<i>Minyak halia. Satu camca minyak halia dan satu camca air panas.</i> Ginger oil. One tablespoon of ginger oil and one tablespoon of hot water.	<i>Minyak halia</i> Ginger oil <i>Zingiber officinale</i>
		RU.02.41	<i>Rebus Qaranful (Cengkih). Bungkus direbus dengan air sejuk satu gelas setengah, bila susut setengah gelas angkat. Sejukkan, minum itu air pagi dengan petang.</i> Boil cloves. Wrap the cloves and boil with one and half cups of water until the water decreases to half a cup. Cool it down, drink it in the morning and evening.	<i>Cengkih</i> Clove <i>Syzygium aromaticum</i>

		RU.03.43	<i>Buah halia. Tiga butir pagi dan tiga butir petang. Ginger ma'jun. Eat three ma'jun in the morning and evening.</i>	<i>Ma'jun Halia Ginger electuary Zingiber officinale</i>
Tayyib al-Ihsan fi Tibb al-Insan	<i>Humma al-ghibb</i> Tertian fever	TA.01.145	<i>Diminum air limau lima (limau nipis) dengan sukkar pada pagi-pagi dan muntah ia dan makanannya sagun-sagun dhurah dan tepung gandum yang dimasak dan kuah anak ayam tiga hari maka jika tiada hilang maka hendaklah diminum pecahar (ubat pencuci perut) safra (hempedu). Drink key lime squeeze with sugar in the morning and the patient will vomit. Then eat sagun-sagun (a type of delicacy) made from sorghum and made from fermented wheat flour and gravy of chick dish for three days. If there is no improvement, then drink laxative for safra (remedy for cleaning the bowel).</i>	<i>Air limau nipis Key lime squeeze Citrus aurantiifolia Sukkar Sugar Dhurah Sorghum Sorghum bicolor Tepung gandum Wheat flour Triticum spp. Pecahar safra Laxative for safra</i>
		TA.02.146	<i>Minum air limau lima tujuh biji besar dengan sukkar bagi orang yang kuasa atas minumannya. Drink the squeeze of approximately 5-7 big-sized key limes with sugar, only for those who can bear the formulations.</i>	<i>Air limau Key lime squeeze Citrus aurantiifolia Sukkar Sugar</i>
	<i>Humma al-thani</i> Intermittent fever (every 24 hours and subsides with a full body chill)	TA.03.146	<i>Diminum cuka tiap-tiap hari pagi-pagi dan makanannya muzawwarat (makanan berasaskan tumbuh-tumbuhan untuk orang sakit, lebih mudah dihadam) tiga hari. Drink vinegar every morning and the food is muzawwarat (vegetarian dishes for sick people, easier to digest) for three days.</i>	<i>Cuka Vinegar</i>
	<i>Humma al-rib</i> Quartan fever	TA.04.147	<i>Diminum air susu lembu serta minyak sapi dan manisan lebah dan meninggal ia akan yang lainnya mujarrab. Drink cow milk with ghee and honey and it will be significantly effective.</i>	<i>Air susu lembu Cow milk Minyak sapi Ghee Manisan lebah Honey</i>
	<i>Humma al-nafid</i>	TA.05.147	<i>Muntah ia dengan cuka dan manisan lebah tiga hari atau tujuh hari pada pagi-pagi kemudian isti'mal ia akan sharab asali iaitu</i>	<i>Cuka Vinegar</i>

Fever with symptoms of ague fit or fever paroxysm	<p><i>diambil manisan lebah yang suci daripada buihnya dan dibubuh di dalam tiap-tiap seratl daripadanya satu dirham mustaki dan satu dirham lada hitam dan satu dirham halia dan disejukkan dia dan diisti'malkan dia dan makanannya tepung gandum yang halus bersih dan kuah daging kibash yang dimasukkan dengan baharat.</i></p> <p>Drink vinegar and honey for three or seven mornings and the patient will vomit. Then take pure honey without foam and place every one <i>ratl</i> of honey with one <i>dirham</i> of terebinth tree bark, one <i>dirham</i> of peppercorn, one <i>dirham</i> of ginger. Cooled it down and use it and eat it with fined wheat flour and sheep broth that has allspice mixed in with.</p>	<p>Manisan lebah Honey</p> <hr/> <p>Mustaki (getah kayu) Terebinth tree bark Terebinthe pistache</p> <hr/> <p>Lada hitam Black pepper Piper nigrum</p> <hr/> <p>Halia Ginger Zingiber officinale</p> <hr/> <p>Tepung gandum Wheat flour Triticum spp.</p> <hr/> <p>Daging kibash /kambing biri-biri Sheep flesh</p> <hr/> <p>Baharat Allspice</p> <ul style="list-style-type: none"> <li>- Lada hitam, buah pelaga, kulit kayu manis, cengkik, ketumbar, jintan putih, buah pala, paprika</li> <li>- Black pepper, cardamom, cinnamon, clove, coriander, cumin, nutmeg, paprika.</li> <li>- Piper nigrum, Amomum spp., Cinnamon zeylanicum, Syzygium aromaticum, Corriandrum sativum, Foeniculum vulgare, Myristica fragrans, Capsicum annuum.</li> </ul>		
Warisan Perubatan Melayu	Demam Kura Spleen fever	WP.01.27	<p><i>Ambil akar susun kelapa berat tiga timbang, lempoyang berat dua timbang, lengkuas berat setimbang, bawang putih berat setimbang, lada sulah berat setimbang, kapur batu berat setimbang, dan cabai berat setimbang; maka sekalian ramuan itu giling lumat-lumat dengan air limau nipis. Maka rebus dengan air tiga bahagi, beri tinggal sebahagi, hingga hendak</i></p>	<p>Akar susun kelapa Rosebay root Tabernaemontana corymbosa</p> <hr/> <p>Lempoyang Bitter ginger Zingiber zerumbet</p>

	<p><i>menghancurkan ubat yang digiling itu sekadar dapat diminum jua. Sudah itu ambil besi tiga bilah, bakar pada api; kemudian celupkan pada ubat itu yang sudah diisi dalam cawan. Beri minum orang sakit itu berulang-ulang.</i></p> <p>Take Rosebay root (three portions), bitter ginger (two), galangal (one), garlic (one), white pepper (one), limestone (one) and chilli pepper (one), grind everything into a paste with key lime squeeze. Boil with three parts of water until left with one part of the water and the formulation is dissolved and palatable to drink. Take three metal blade and heat it on fire, then dip the hot metal into the medicine mixture that has been filled into a cup.</p>	<p>Lengkuas Galangal <i>Alpinia galanga</i> Bawang putih Garlic <i>Allium sativum</i> Lada sulah White pepper <i>Piper nigrum</i> Kapur batu Limestone <i>Calcium carbonate</i> Cabai Chilli pepper <i>Capsicum frutescens</i> Air limau nipis Key lime squeeze <i>Citrus aurantiifolia</i></p>
WP.02.27	<p><i>Ambil buah lakum yang masak, makan sebiji-sebiji pagi petang setiap hari, selama tiga hari.</i></p> <p>Take ripe threeleaf cayratia fruits, take one fruit in the morning and in the evening every day for three days.</p>	<p>Buah lakum Threeleaf cayratia <i>Cayratia trifolia</i></p>
WP.03.27	<p><i>Ambil daun keduduk segenggam erat, daun gandarusa segenggam erat, bawang putih seulas, dan lada tujuh butir; sekalian itu pipis lumat-lumat, airnya cuka; beri minum sebanyak dua ruas jari selama tiga pagi; hampasnya ditempelkan betul-betul pada tempat kura itu.</i></p> <p>A handful of strait rhododendron's leaves, a handful of leaves of willow-leaved justicia, a clove of garlic, seven black peppers. Grind everything with vinegar. Drink an amount of about two phalanges for three mornings. Take the residual paste and fix it at the area of the swollen spleen.</p>	<p>Daun keduduk Stratis rhododendron <i>Melastoma malabathricum</i> Daun gandarusa Willow-leaved justicia <i>Justicia gendarussa</i> Bawang putih Garlic <i>Allium sativum</i> Lada Black pepper <i>Piper nigrum</i> Cuka Vinegar</p>

## Classification of Data

Thirty-seven materials were identified from the extracted remedial formulations, of which 25 are plant-based materials. These materials are tabulated in Table 2. The table also includes the scientific names, plant parts used in the formulations, formulation number, and the frequency of mentions in manuscripts and formulations. The results show that key lime has been frequented the most in terms of number of manuscripts (four mentions) followed by clove, ginger, black/white pepper and wheat flour (two each). Key lime is also the most repeated ingredient in terms of number of formulations (five times) and followed by black/white pepper (four); ginger and wheat flour (3 each), and garlic and clove (two each).

**Table 2: List of Identified Plant-Based Materials.**

Plant Name	Scientific Name	Parts of Materials Used	Formulation Number	Frequency	
				Manuscript	Formulation
<i>Air limau nipis, Air limau hantu</i>	<i>Citrus aurantiifolia</i>	Fruit/ Juice	2515.01.98, AF.01.171, TA.01.145, TA.02.146, WP.01.27	4	5
<i>Akar susun kelapa</i>	<i>Tabernaemontana corymbosa</i>	Root	WP.01.27	1	1
<i>Bawang putih</i>	<i>Allium sativum</i>	Bulb	WP.01.27	1	2
<i>Biji jintan</i>	<i>Foeniculum vulgare</i>	Seeds	TA.05.147	1	1
<i>Buah keduduk</i>	<i>Melastoma malabathricum</i>	Leaf	WP.03.27	1	1
<i>Buah lakum</i>	<i>Cayratia trifolia</i>	Fruit	WP.02.27	1	1
<i>Buah pala</i>	<i>Myristica fragrans</i>	Seeds	TA.05.147	1	1
<i>Buah pelaga</i>	<i>Amomum spp.</i>	Seeds	TA.05.147	1	1
<i>Cabai</i>	<i>Capsicum frutescens</i>	Fruit	WP.01.27	1	1
<i>Cengkih</i>	<i>Syzygium aromaticum</i>	Flower	RU.02.41, TA.05.147	2	2
<i>Daun gandarusa</i>	<i>Justicia gendarussa</i>	Leaf	WP.03.27	1	1
<i>Daun terung asam</i>	<i>Solanum lasiocarpum.</i>	Leaf	4837.042.068	1	1
<i>Dhurah</i>	<i>Sorghum bicolor</i>	Seeds/ Grain	TA.01.145	1	1
<i>Halia</i>	<i>Zingiber officinale</i>	Not specified - Possibly Rhizome, Oil	TA.05.147, RU.01.35, RU.03.43	2	3
<i>Ketumbar</i>	<i>Corriandrum sativum</i>	Seeds	TA.05.147	1	1
<i>Kulit kayu manis</i>	<i>Cinnamon zeylanicum</i>	Bark	TA.05.147	1	1

Lada, Lada hitam, Lada sulah	<i>Piper nigrum</i>	Seeds	TA.05.147	2	4
Lempoyang	<i>Zingiber zerumbet</i>	Fruit	WP.01.27	1	1
Lengkuas	<i>Alpinia galanga</i>	Fruit	WP.01.27	1	1
Minyak lenga	<i>Sesamum indicum</i>	Oil	AF.04.174	1	1
Mustaki (getah kayu)	<i>Terebinthe pistache</i>	Wood latex/resin	TA.05.147	1	1
Paprika	<i>Capsicum annuum</i>	Fruits	TA.05.147	1	1
Roti tepung jagung	<i>Zea mays</i>	Root	AF.01.171	1	1
Tepung gandum	<i>Triticum spp.</i>	Grain	TA.01.145, TA.05.147, 2515.01.98,	2	3
Tepung jerubah	<i>Oryza sativa</i>	Grain	2515.01.98	1	1

### Comparative Analysis

Comparative analysis was performed by comparing the plant-based materia medica from the remedial formulations with contemporary scientific literature. The analysis shows that 11 or 44% of the plants-based materials play significant roles in relation to reduce, eradicate or manage the malaria infections in patients while 12 either have antipyretic and/or antioxidant pharmacological properties that can help reduce the symptoms, and 2 did not have any scientific evidence. The comparative analysis is presented in Table 3.

**Table 3: Table of Comparative Analysis of Plant-based Materials.**

Formulation Number	Vernacular Name	Scientific Name	Scientific Literature Evidence
TA.05.147	Cinnamon bark ( <i>Kulit kayu manis</i> )	<i>Cinnamomum zeylanicum</i>	Antiparasitic effect by inhibition of heme bio-crystallization (Attieh et al., 2015) and enoyl-ACP reductase anzyme activity (Nkanwen et al., 2013).
TA.05.147, RU.01.35, RU.03.43	Ginger ( <i>Halia</i> )	<i>Zingiber officinale</i>	Exhibit inhibitory effects on the malarial parasite's replication. (Biruksew et al., 2018).
WP.01.27	Garlic ( <i>Bawang putih</i> )	<i>Allium sativum</i>	Contain allicin that inhibits the CAC1 cysteine proteases falcipain 2, rhodesain, cathepsin B and L in the low micromolar range. Potent antiparasitic activity (Coppi et al., 2006).
WP.01.27	Galangal ( <i>Lengkuas</i> )	<i>Alpinia galanga</i>	Contain anti-plasmodial components and antioxidant activity that contribute to the antimalarial activity (Al-Adhroey et al., 2010).
TA.05.147	Nutmeg ( <i>Buah pala</i> )	<i>Myristica fragrans</i>	Exhibit antioxidant properties. Potent antimalarial activity against <i>Plasmodium</i> . (Thiengsusuk et al., 2013)
TA.05.147	Cardamom ( <i>Buah pelaga</i> )	<i>Amomum spp.</i>	Contain terpene endoperoxide, specifically cardamom peroxide, which exhibited strong inhibition of <i>Plasmodium falciparum</i> . (Hu et al., 2018)
WP.01.27	Chilli Pepper ( <i>Cabai</i> )	<i>Capsicum frutescens</i>	Anti-plasmodial and antioxidant activity (Habte & Assefa, 2020).
RU.02.41, TA.05.147	Clove ( <i>Cengkih</i> )	<i>Syzygium aromaticum</i>	Inhibitory effects against <i>P. falciparum</i> (Batiha et al., 2020a, Dantata & Hotoro, 2020).
TA.05.147	Black pepper/ peppercorn ( <i>Lada hitam</i> )	<i>Piper nigrum</i>	Antimalarial Activity of Piperine cause changes in parasite morphology (Thiengsusuk et al., 2018).
WP.01.27	Bitter Ginger ( <i>Lempoyang</i> )	<i>Zingiber zerumbet</i>	Antimalarial activity and cytotoxicity by inhibiting <i>Plasmodium</i> propagation (Sriphana et al., 2013, Yob, et al., 2010).
WP.02.27	Threeleaf cayratia ( <i>Buah lakum</i> )	<i>Cayratia trifolia</i>	Antimalarial activity on <i>P. berghei</i> (Alkandahri et al., 2020)

2515.01.98, AF.01.171, TA.01.145, TA.02.146, WP.01.27 WP.03.27	Key lime ( <i>Limau nipis</i> ,)	<i>Citrus aurantiifolia</i>	Enhance malarial clearance but does not have antimalarial effect on its own. (Adegoke et al., 2011; Shija et al., 2020).
WP.03.27	Willow-leave Justica ( <i>Daun gandarusa</i> )	<i>Justicia gendarussa</i>	No study on anti-plasmodial activity found. Relieves fever and contain high antioxidant properties (Shinwari et al., 2020).
WP.01.27	Great Rosebay ( <i>Akar susun kelapa</i> )	<i>Tabernaemontana corymbosa</i>	No study on anti-plasmodial activity found but have antiparasitic properties. Treat ailments such as fever, and jaundice (Abubakar & Loh, 2016).
4837.042.068	Borneo sour eggplant ( <i>Daun terung asam</i> )	<i>Solanum lasiocarpum</i> .	No study on anti-plasmodial activity found. Contain high antioxidant activity (Soon & Ding, 2021).
TA.01.145	Grain sorghum ( <i>Dhurah</i> )	<i>Sorghum bicolor</i>	No study on anti-plasmodial activity found.
WP.03.27	Straits Rhododendron ( <i>Buah keduduk</i> )	<i>Melastoma malabathricum</i>	No study on anti-plasmodial activity found. Relieve fever and have antioxidant properties (Joffry et al., 2012).
TA.05.147	Cumin/ fennel seeds ( <i>Biji jintan</i> )	<i>Foeniculum vulgare</i>	No study on anti-plasmodial activity found. Antipyretic and antioxidant properties (Badgujar et al., 2014).
AF.04.174	Sesame oil ( <i>Minyak lenga</i> )	<i>Sesamum indicum</i>	No study on anti-plasmodial activity found. Sesamol contain anti-inflammatory and antioxidant properties (Wu et al., 2019).
TA.05.147	Terebinth tree ( <i>Mustaki</i> )	<i>Terebinthe pistache</i>	No study on anti-plasmodial activity found. Compounds in resin used to treat fever due to its antipyretic activity (Bozorgi, et al., 2013).
TA.05.147	Cayenne ( <i>Paprika</i> )	<i>Capsicum annum</i>	No study on anti-plasmodial activity found. Capsicum has antioxidant properties (Batiha et al., 2020b, Sanati et al., 2018).
AF.01.171	Corn flour ( <i>Tepung jagung</i> )	<i>Zea mays</i>	No study on anti-plasmodial activity found. Contains highly antioxidant secondary metabolites (Okokon et al., 2017).
TA.01.145, TA.05.147, 2515.01.98,	Wheat ( <i>Tepung gandum</i> )	<i>Triticum spp.</i>	Not found
2515.01.98	Fermented Rice Flour ( <i>Tepung jerubah</i> )	<i>Oryza sativa</i>	Not found

In a study by Al-Adhroey et al. (2010), the extract of *A. galanga* rhizome was demonstrated to suppress the activity of early infection of *Plasmodium* parasite and cure the infected mice up to 65-67% effectiveness at a dose of 400 mg/kg when compared to the negative control. It is postulated the antiplasmodial activity is contributed by terpenoid and flavonoid. Meanwhile, Thiengsusuk et al. (2018) reported that the exposure of piperine (alkaloid that can be found in *P. nigrum*) to *P. falciparum* in vitro showed a morphological change of the parasite that affects and slows down its growth until it undergoes death after eight-hour exposure. Other than that, *M. fragrans* was reported by the same research group, Thiengsusuk et al. (2013), to exhibit potent antimalarial activity in an in vitro experiment using parasite culture, with an IC<sub>50</sub> of less than 10 mg/ml.

As for *Amomum spp.*, Hu et al. (2018) mentioned that cardamom contains cardamom peroxide which is a terpene endoperoxide that exhibits a strong inhibitory activity towards *P. falciparum*, however the pharmacological mechanism is unclear. Besides, Habte & Assefa (2020) revealed that *C. frutescens* extract suppresses the percentage of parasitaemia in infected up to 93.29% when. On the other hand, *S. aromaticum* was shown to possess inhibitory effect on *P. falciparum* at 50 mg/ml concentration (Dantata & Hatoro (2020). *Z. officinale* or ginger has been revealed by Biruksew et al. (2018) that its extract displays a notable chemo-suppression and suggested that it has an inhibitory effect on *Plasmodium* parasite replication, which may be due to the evenly spread active compounds found in the ginger extracts.

As for cinnamon, Nkanwen et al. (2013) discovered that the dichloromethane/methanol extract can inhibit the activity of *P. falciparum* enoyl-ACP reductase enzyme in vitro up to 33%. The enzyme is found in the parasite and it synthesises fatty acids which are crucial for membrane formation and survival. By inhibiting the enzyme, it may inhibit the growth of the parasite. Apart from that, the invasion of the parasite causes haemolysis, releasing free iron that is toxic towards *Plasmodium*. The parasite avoids this by detoxifying the free iron by bio-crystallisation into  $\beta$ -hematin. Hence, the inhibition of hematin bio-crystallisation by cinnamon water may result in toxicity to the parasite and this action is similar to chloroquine (Attieh et al., 2015).

*Z. zerumbet* essential oil contains a bioactive compound called zerumbone (Yob et al., 2011). Based on the study done by Sriphana et al. (2012), zerumbone was shown to exhibit antimalarial activity against *P. falciparum*. However, it also shows a high cytotoxicity towards cancer cell line. Thus, zerumbone could cause harm towards the human cells but the compound shows a potential alternative antimalarial drug. Lastly, *A. sativum* extract contains a compound allicin that is produced when the cloves is crushed. Coppi et al. (2006) reported that allicin is a cysteine protein inhibitor which can inhibit the erythrocytic stage and sporozoites invasions of the *Plasmodium*, which subsequently decreases parasitaemia. Based on the previous contemporary studies on these 11 plants and frequency of mentions of the ingredients, these four plants shall be prioritised in the effort of searching for potential therapeutic plants for malaria. They are ginger (mentioned in two manuscripts and three formulations), garlic (one manuscript and two formulations), clove (two manuscripts and two formulations), and black/white pepper (2 manuscripts and four formulations)

From the 25 plant-based material identified, 56% or 14 of the materials were found to not have any literature evidence on its pharmacological actions against the parasite. However, this does not mean the plant's medicinal values is dismissed. This may be attributed to low priority, low interest or lack of awareness regarding the plant. Further research should be done on the plant's pharmacological action against the *Plasmodium* parasite to ascertain whether it will truly aid in treating patients with malaria. In addition, not all materials in a formulation can be assumed to have therapeutic effects towards malaria. In modern pharmacology, some excipients are added with active ingredient to make a dosage form. Similarly, some materials in the formulations function as stabilisers for the formulation, e.g., lime juice maybe added to control the pH, sugar maybe added to mask bitter or sour taste, and flour maybe added to increase viscosity of a formulation.

Despite the lack of scientific literature evidence of not possessing any anti-plasmodial activity, 12 out of 25 plant-based materials were observed to have antioxidant properties and/or antipyretic properties. The plants stated to have antioxidant properties in literature were implied to have anti-plasmodial

activity as it can counteract the oxidative damages caused by the parasite (Builders et al., 2014). Meanwhile antipyretics are properties that can help to relieve fever, which is a clinical manifestation of malaria (Buck & Finnigan, 2021).

## CONCLUSION

Malaria is a disease that has existed in the Malay Archipelago since the 16<sup>th</sup> century. In several Malay medical manuscripts, the remedial formulations for antimalarial drugs used during the olden times were able to be found. Seventeen formulations of remedies with 37 unique materials were extracted from the manuscripts and compared to contemporary literature. Eleven have supportive evidence while 14 are yet to be researched with regards to their scientific evidence of their antimalarial use. The plants that have the most potential to be developed for antimalaria are *Z. officinale*, *A. sativum*, *S. aromaticum*, and *P. nigrum*.

## REFERENCES

- Abdullah, H. (2017). Khazinat al-Insan. Akademi Jawi Malaysia Sdn. Bhd.
- Abubakar, I. B., & Loh, H. S. (2016). A review on ethnobotany, pharmacology and phytochemistry of *Tabernaemontana corymbosa*. *Journal of Pharmacy and Pharmacology*, 68(4), 423–432.
- Adegoke, S. A., Oyelami, O. A., Olatunya, O. S., & Adeyemi, L. A. (2011). Effects of lime juice on malaria parasite clearance. *Phytotherapy Research*, 25(10), 1547–1550.
- Ahmad, A. S. (2005). Warisan Perubatan Melayu. Dewan Bahasa dan Pustaka, Kuala Lumpur.
- Al-Adhroey, A. H., Nor, Z. M., Al-Mekhlafi, H. M., & Mahmud, R. (2010). Median lethal dose, antimalarial activity, phytochemical screening and radical scavenging of methanolic *Languas galanga* rhizome extract. *Molecules*, 15(11), 8366–8376.
- Alkandahri, M. Y., Maulana, Y. E., Subarnas, A., Kwarteng, A. & Berbudi, A. (2020). Antimalarial activity of extract and fractions of *Cayratia trifolia* (L.) Domin. *International Journal of Pharmaceutical Research, Supplementary Issue(1)*, 1435-1441.
- Attieh, H. A., Abu Lafi, S., Jaber, S., Abu-Remeleh, Q., Lutgen, P. & Akkawi, M. (2015). Cinnamon bark water-infusion as an in-vitro inhibitor of  $\beta$ -hematin formation. *Journal of Medicinal Plants Research*, 9(38), 998-1005.
- Badgular, S. B., Patel, V. V., & Bandivdekar, A. H. (2014). *Foeniculum vulgare* Mill: A review of its botany, phytochemistry, pharmacology, contemporary application, and toxicology. *BioMed Research International*, 2014, 842674.
- Batiha, G. E. S., Alkazmi, L. M., Wasef, L. G., Beshbishy, A. M., Nadwa, E. H., & Rashwan, E. K. (2020a). *Syzygium aromaticum* L. (myrtaceae): Traditional uses, bioactive chemical constituents, pharmacological and toxicological activities. *Biomolecules*, 10(2), 202.
- Batiha, G. E. S., Alqahtani, A., Ojo, O. A., Shaheen, H. M., Wasef, L., Elzeiny, M., Ismail, M., Shalaby, M., Murata, T., Zaragoza-Bastida, A., Rivero-Perez, N., Beshbishy, A. M., Kasozi, K. I., Jeandet, P., & Hetta, H. F. (2020b). Biological properties, bioactive constituents, and pharmacokinetics of some *Capsicum* spp. and capsaicinoids. *International Journal of Molecular Sciences*, 21(15), 1–35.
- Biruksew, A., Zeynudin, A., Alemu, Y., Golassa, L., Yohannes, M., Debella, A., Urge, G., De Spiegeleer, B., & Suleman, S. (2018). *Zingiber officinale* Roscoe and *Echinops kebericho* Mesfin showed antiplasmodial activities against *Plasmodium Berghei* in a dose-dependent manner in Ethiopia. *Ethiopian Journal of Health Sciences*, 28(5), 655–664.

Bozorgi, M., Memariani, Z., Mobli, M., Salehi Surmaghi, M. H., Shams-Ardekani, M. R., & Rahimi, R. (2013). Five pistacia species (*P. vera*, *P. atlantica*, *P. terebinthus*, *P. khinjuk*, and *P. lentiscus*): A review of their traditional uses, phytochemistry, and pharmacology. *The Scientific World Journal*, 2013, 219815.

Buck, E., & Finnigan, N. A. (2021). *StatPearls* [Internet]. <https://www.ncbi.nlm.nih.gov/books/NBK551711/>

Builders, M., Alemika, T., & Aguiyi, J. (2014). Antimalarial activity and isolation of phenolic compound from *Parkia biglobosa*. *IOSR Journal of Pharmacy and Biological Sciences*, 9(3), 78–85.

Coppi, A., Cabinian, M., Mirelman, D., & Sinnis, P. (2006). Antimalarial activity of allicin, a biologically active compound from garlic cloves. *Antimicrobial Agents and Chemotherapy*, 50(5), 1731–1737.

Dantata, A. A., & Hotoro, A. S. (2020). Anti-Plasmodial Activity of the aqueous *Syzygium aromaticum* (clove) flower bud extract against *Plasmodium falciparum*. *Dutse Journal of Pure and Applied Sciences*, 6(2), 207–216.

Dewan Bahasa dan Pustaka (2017). Pusat Rujukan Persuratan Melayu. Retrieved September 21, 2023, from <https://prpm.dbp.gov.my/>

Habte, G., & Assefa, S. (2020). In vivo antimalarial activity of crude fruit extract of *Capsicum frutescens* var. *minima* (Solanaceae) against *Plasmodium berghei*-infected mice. *BioMed Research International*, 2020, 1320952.

Hajlaoui, H., Arraouadi, S., Noumi, E., Aouadi, K., Adnan, M., Khan, M. A., Kadri, A., & Snoussi, M. (2021). Antimicrobial, antioxidant, anti-acetylcholinesterase, antidiabetic, and pharmacokinetic properties of *Carum carvi* L. and *Coriandrum sativum* L. Essential Oils Alone and in Combination. *Molecules*, 26(12), 3625.

Hu, X., Lim, P., Fairhurst, R. M., & Malmone, T. J. (2018). Synthesis and study of the antimalarial cardamom peroxide xirui. *Tetrahedron*, 74(26), 3358–3369.

Joffry, S. M., Yob, N. J., Rofiee, M. S., Affandi, M. M. R. M. M., Suhaili, Z., Othman, F., Akim, A. M., Desa, M. N. M., & Zakaria, Z. A. (2012). *Melastoma malabathricum* (L.) Smith ethnomedicinal uses, chemical constituents, and pharmacological properties: A review. *Evidence-Based Complementary and Alternative Medicine*, 2012(Table 1), 6–20.

Maidin, P., & Mamat, M. N. (2014). Daripada falsafah menjadi sains: Doktrin perubatan melayu dalam kitab bustan Al-Salatin. *Perpustakaan Negara Malaysia*, 1, 1–12.

Mat Piah, H. (2015). Ilmu Perubatan Melayu Tradisional dari Naskhah-Naskhah Lama. *Jurnal Antarabangsa Alam Dan Tamadun Melayu*, 3(3), 3–17.

Mat Piah, H. & Baba, Z. (2014). *Kitab Tib MSS 2515*. UKM Press.

Mat Piah, H. & Mustapha, N. M. (2019). *Kitab Tib MSS1292*. Institut Penyelidikan Perhutanan Malaysia.

Mamat, H., Tan, K. K. & Mohamed Arifin, Y. (2015, January). *Malaysia Biodiversity Information System (MyBIS)*. Retrieved September 21, 2023, from <https://www.mybis.gov.my/art/15>.

Mohd Shafri, M. A. (2018a). *Rumah Ubat di Pulau Penyengat*. Akademi Jawi Malaysia Sdn. Bhd.

Mohd Shafri, M. A. (2018b). *Tayyib al-Insan Fi Tibb al-Insan*. Akademi Jawi Malaysia Sdn. Bhd.

Mohd Shafri, M. A., Jamil, A. M., Zamli, Z., Mohammad, M. & Ahmad Nadzirin, I. (2021a). Malay medical knowledge on a nipah-leaf (*Nypa fruticans*) manuscript: A descriptive study. *International Journal of Allied Health Sciences*, 5(5), 2386-2395.

- Mohd Shafri, M. A. (2021b). Treatments of eye diseases in Malay medical manuscript ramuan obat eap153/9/4. *Journal of Al-Tamaddun*, 16(1), 27–45.
- Mohd Shafri, M. A. & Muhammad Yahya, H. (2017). *Kitab Perubatan Melayu: Al-Rahmah Fi Al-Tibb Wa Al-Hikmah*. Akademi Jawi Malaysia Sdn. Bhd.
- National Library of Malaysia. (2018). Annual Report of National Library of Malaysia 2018.
- Ngadeni, N. (2018). *Perubatan Melayu Berdasarkan Manuskrip Kitab Tibb Melayu*. Baytul Hikma.
- Nkanwen, E. R. S., Awouafack, M. D., Bankeu, J. J. K., Wabo, H. K., Mustafa, S. A. A., Ali, M. S., Lamshoft, M., Choudhary, M. I., Spiteller, M. & Tane, P. (2013). Constituents from the stem bark of *Cinnamomum zeylanicum* Welw. (Lauraceae) and their inhibitory activity toward *Plasmodium falciparum* enoyl-ACP reductase enzyme. *Record of Natural Products*, 7(4), 296-301.
- Okokon, J. E., Antia, B. S., Mohanakrishnan, D., & Sahal, D. (2017). Antimalarial and antiplasmodial activity of husk extract and fractions of *Zea mays*. *Pharmaceutical Biology*, 55(1), 1394–1400.
- Sanati, S., Razavi, B. M., & Hosseinzadeh, H. (2018). A review of the effects of *Capsicum annuum* L. and its constituent, capsaicin, in metabolic syndrome. *Iranian Journal of Basic Medical Sciences*, 21(5), 439–448.
- Shija, K. M., Nondo, R. S. O., Mloka, D., Sangeda, R. Z., & Bwire, G. M. (2020). Effects of lemon decoction on malaria parasite clearance and selected hematological parameters in *Plasmodium berghei* ANKA infected mice. *BMC Complementary Medicine and Therapies*, 20(1), 1–12.
- Shinwari, Z. K., Ahmad, I., Ahmad, N., Fozia, Akhlaq, M., Baharullah, & Wahab, A. (2020). Investigation of phytochemical, antimicrobial activities of *Justicia gendarussa* and *Justicia adhatoda*. *Pakistan Journal of Botany*, 52(5), 1745–1749.
- Soon, A. T. K., & Ding, P. (2021). A review on wild indigenous eggplant, terung asam sarawak (*Solanum lasiocarpum* Dunal.). *Sains Malaysiana*, 50(3), 595–603.
- Sriphana, U., Pitchuanom, S., Kongsaree, P., & Yenjai, C. (2013). Antimalarial activity and cytotoxicity of zerumbone derivatives. *ScienceAsia*, 39(1), 95–99.
- Sriti, J., Wannes, W. A., Talou, T., Vilarem, G., & Marzouk, B. (2011). Chemical composition and antioxidant activities of Tunisian and Canadian coriander (*Coriandrum sativum* L.) Fruit. *Journal of Essential Oil Research*, 23(4), 7–15.
- Talapko, J., Škrlec, I., Alebić, T., Jukić, M., & Včev, A. (2019). Malaria: The past and the present. *Microorganisms*, 7(6), 179.
- Thiengsusuk, A., Chaijaroenkul, W. & Na-Bangchang, K. (2013). Antimalarial activities of medicinal plants and herbal formulations used in Thai traditional medicine. *Parasitology Research*. 112, 1475-1481.
- Thiengsusuk, A., Muhamad, P., Chaijaroenkul, W., & Na-Bangchang, K. (2018). Antimalarial activity of piperine. *Journal of Tropical Medicine*, 2018, 9486905.
- Tse, E. G., Korsik, M., & Todd, M. H. (2019). The past, present and future of anti-malarial medicines. *Malaria Journal*, 18(1), 1–21.
- World Health Organization (WHO). (2021). Malaria: Antimalarial drug resistance in the Greater Mekong subregion. <https://www.who.int/news-room/q-a-detail/malaria-antimalarial-drug-resistance-in-the-greater-mekong-subregion> (Accessed on 13 February 2021).
- Wu, M., Aquino, L. B. B., Barbaza, M. Y. U., & Hsieh, C. (2019). Anti-inflammatory and anticancer properties of bioactive compounds from *Sesamum indicum*. *Molecules*. 24(1), 1–28.

Yob, N. J., Zakaria, Z. A., Jofrry, S. M., Affandi, M. M. R. M. M., Teh, L. K., & Salleh, M. Z. (2011). *Zingiber zerumbet* (L.) Smith: A review of its ethnomedicinal, chemical, and pharmacological uses. *Evidence-Based Complementary and Alternative Medicine*, 2011, 543216.