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Antimalarial Herbal Plants in Kupang, Indonesia

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Abstract

Malaria is an infectious disease caused by Plasmodium parasite transmitted through female Anopheles mosquito bite. This disease is harmful because Plasmodium is known to be resistant to antimalarial drugs. The emergence of malaria resistance has raised concerns among researchers to look for any alternative antimalarial drugs. There are some plants potentially used as antimalarial drugs that should be-well-documented through scientific research. This study aimed to get to know plant species that has antimalarial activity in Kupang region. Method: This research applied qualitative descriptive method while using exploration method specifically in the sampling process. Every sample is then taken for preservation as herbarium and identified based on its morphological features using determination key handbook. The result showed that there are 17 species of antimalarial plant in 10 observational sites. Those species of antimalarial plants i.e. *Tithonia diversifolia*, *Momordica charantia*, *Cyperus rotundus*, *Strychnos lingustrina*, *Andrographis paniculata*, *Callicarpa longifolia*, *Tinospora crispa*, *Piper betle*, *Plectranthus scutellarioides*, *Alstonia scholaris*, *Carica papaya*, *Amaranthus spinosus*, *Artocarpus champeden*, *Cassia siamea*, *Azadirachta indica*, *Helianthus annuus* and *Blumea balsamifera*. Therefore, the availability of the plant species with antimalarial activity in Kupang needs to be explored and developed as an alternative approach for the society in treating Malarial diseases.

How to Cite

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INTRODUCTION

Malaria is an infectious disease caused by *Plasmodium falciparum*, *P. vivax*, *P. malariae*, *P. ovale* (Depkes RI, 2008a) and *P. knowlesi* (Singh et al., 2004) parasites, which reside and reproduce inside human blood cells and is transmitted through female Anopheles mosquito bite. The most abundant species found in Indonesia are *P. falciparum* and *P. vivax* (Depkes RI, 2008b). Up until now, malaria has still become a harmful disease which causes high morbidity and mortality (WHO, 2011). One reason is the resistance of *P. falciparum* towards chloroquine (Gunawan, 2010), sulfadoxine-pyrimethamine (SP) (Kemenkes RI, 2011), and even against antermisin in areas between Cambodia and Thailand border (Noedl et al., 2008), Thailand, Myanmar, Cambodia and Vietnam (WHO, 2012). Therefore, new alternative of antimalarial drugs is needed to anticipate the resistance toward artemisinin.

Cases on Plasmodium resistance and no effective antimalarial drugs available has become the obstacles for researchers, and therefore through the use of natural substances will certainly become a solution for this case. Indonesia is rich with natural resources. There are around 30.000 plant species in Indonesia's tropical forest. Among 9.600 species of them is known to have medicinal properties, however, only 200 of them has been used as traditional medicine including the use as antimalaria drugs. Traditional medicinal plant is a plant used by traditional society, either its roots, stems, or leaves, to treat a disease because it is believed to cure the disease or that least o put out from its misery (Noorhidyah and Sidiyasa, 2006). Commonly, the medicinal plants used are taken from around their own neighborhood.

Previous studies showed that the plants used by the society as antimalarial drugs, have been scientifically proven to contain antimalarial compounds and have antimalarial activity. Some of those antimalarial herbal plants are brotowali (*Tinospora crispa*) (Adnan et al., 2001) & (Ihwan et al., 2014), Sambiloto (*Andrographis paniculata*-Nees) (Zein et al., 2013), Papaya (*Carica papaya*) (Falah et al., 2013) and Talikuning (*Anamirta cocculus*) (Muti'ah et al., 2010).

Efforts done by the society and researchers to develop medicine from natural materials has since grown rapidly and prospectively, that is supported by the availability of biological resources. Besides that, around 370 native ethnic groups with local wisdom (include in medicine) have also enriched the enthno-medicine treasure and nation's culture. An understanding of sickness and health related with the use of local plants as traditional medicine is obtained from socialization which is trusted and believed to be true and also in herited from generation to generation (Rahayu et al., 2006). The same situation also occurs in Kupang city and Kupang regency of East of Nusa Tenggara province.

Society knowledge, especially in traditional medicine must be documented properly and scientifically. The delivery of information about the use of traditional medicine hereditarily until now is still by oral. Using plants to cure a disease by making a traditional herb is customary for Indonesian people. Various types of traditional herbal plants are formulated in Indonesia, either as a trademark for commercial or home made. Based on the description above, the necessity to conducta research on antimalarial herbal plants is needed in Kupang City and Kupang Regency.

This study aimed to get to know the number and species of plants that has antimalarial activity in Kupang City and Kupang Regency. Therefore, the availability of natural resources (plant species with antimalarial potencies) in Kupang needs to be explored and developed, as a useful source of information for the society as an alternative approach in treating Malarial disease.

METHODS

This research was conducted from May to October 2015, in Kupang city (district of Alak, Maulafa, and Kelapa Lima) and Kupang regency (district of Amarasi, West Amarasi, West Kupang and East Kupang). Materials used in this research were a digital camera, a set of tools for herbarium (dry preservation) process (Murni et al, 2015), GPS (Global Positioning System), determination key handbook, and other relevant textbooks (Falah et al., 2013, Kinho et al., 2011).

The steps in this research were observation, determining the sampling locations, preparing apparatus and materials, and then sampling. Sampling was done through exploration method, i.e. by exploring every sampling area. Every plant species with antimalarial potencies or containing antimalarial compounds was documented by using digital camera. The obtained data on kinds of plants with antimalarial drug potentials or containing antimalarial compounds were then identified and described based on its morphological features and other related-literature studies.

Method for Herbarium Preparation

The process of making a dry herbarium is

done through these following steps (Murni et al, 2015):

1. Preparation of the Tools and Materials Needed: a) Tools for observing, measuring and taking notes: utensils, labelling card and camera; b) Tools for collecting specimen : knife or garden scissors; c) Preservatives and materials for storage: alcohol, news paper, plastic bags, hand sprayer; d) Tools for pressing (Plant Press) : thick card board or plywood and raffia ribbon; e) Tools formounting, herbarium sheets (manila paper) of size 29-31 x 39-42 cm, strings, sewing needle, andglue or adhesive.
2. Collection and Preservation during Sampling. a) Samples were taken with the size of 30 - 40 cm with also considering important organs or parts that should not be separated or cut-off as the specimen have to be in complete form.Terms for certain habitus :1) Small-sized plants like grasses, herbs and bushes would be collected completely as one individual. 2) Trees, large bushes and lianas were collected limited to the size determined above starting from the bud; b) Samples were then pressed in newspaper folding, stacked, tied, stored inside plastic bags and sprayed with alcohol. It will then be enclosed firmly to make it air-tight.
3. Pressing and Drying. Before drying the samples, it would be preceded with alcohol spraying, then each was placed in news paper foldings. It would then be pressed by using 32 x 42 cm sized cardboard or plywood on each side, with the máximum number of 50 specimens. The labeling card was made sure that it was clearly printed or written during this process. After pressing, specimens weretied and dried under sunlight for 46 - 48 hours.
4. Mounting. Dried specimens were mounted or sewed on a 28 - 30 cm x 39 - 42 cm herbarium sheet (manila paper). After mounting, each specimen was grouped according to its level of taxonomic classification.
5. Labelling

Specimens mounted were each labelled permanently using a herbarium label listing important information on the specimen and was placed on the bottom-right side of the specimen.

RESULT AND DISCUSSION

Data on antimalarial herbal plants in Kupang in 10 observational sites is presented in Table 1. Ten of the observational sites on antimalarial herbal plants in Kupang is presented in Figure 1.

The result showed that there are 17 antimalarial herbs found in 10 observation sites. They were *T.diversifolia, M.charantia, C.rotundus, S.lingustrina, A.paniculata* Nees, *C.longifolia, T.crispa* (L) Miers, *P.betle* L., *P.scutellarioides* L., *A.scholaris* (L.) R.Br, *C.papaya* L. *A.spinosus* L., *A.champeden, C.siamea* Lamk., *A.indica, H.annuus* L. and *B.balsamifera.* Some of these species were found in all of the observational sites while others were found in certain sites only. The data of this herbal distribution location is presented in Table 2.

Based on Table 2, certain species were found in all observational sites, but other types that were found in certain locations only. The 17 of antimalarial herbal plants are presented in these following figures (Figure 2).

The result showed that both of Kupang City and Kupang Regency have natural resources potentially capable to be developed and utilized for public welfare, notably in handling malarial diseases. These potencies are shown by the num-

Tabel 1. 10 observational sites of antimalarial herbal plants in Kupang

Location Site	District	Village	Coordinate Points	
			Latitude (S)	Longitude (E)
Kupang Regency	West Kupang	Tesabela	10.17'41.80°	123°29'30.03°
		Tablolong	10°18'59.14°	123°28'50.62°
	Amarasi	Tesbatan	10°05'42.06°	123°56'09.92°
	West Amarasi	Teunbaun	10°18'16.71°	123°42'33.50°
	East Kupang	Oesao	10°05'52.47°	123°51'11.31°
Kupang City	Alak	Nunhila	10°09'51.87°	123°34'49.68°
		Alak	10°11'02.14°	123°33'23.91°
	Maulafa	Maulafa	10°11'35.66°	123°37'53.95°
		Sikumana	10°12'30.61°	123°36'09.11°
	Kelapa Lima	Lasiana	10°08'15.19°	123°40'02.13°

Figure 1. Location of research and the observation point

Tabel 2. Antimalarial herbal plants distribution in 10 observationalsites.

Species	Site									
	A	B	C	D	E	F	G	H	I	J
Tithonia diversifolia	-	-	√	√	-	-	-	-	-	-
Momordica charantia	√	√	√	-	√	√	√	√	-	√
Cyperus rotundus	-	-	√	√	-	-	-	-	√	-
Strychnos lingustrina	√	√	-	-	-	-	-	-	-	-
Andrographis paniculata Nees	-	√	-	-	-	√	√	√	√	√
Callicarpa longifolia	-	-	-	√	-	-	-	-	-	-
Tinospora crispa (L) Miers	-	-	-	-	-	√	-	-	√	√
Piper betle L.	-	√	√	√	√	√	√	√	√	√
Plectranthus scutellarioides L.	-	√	-	-	-	-	-	-	-	√
Alstonia scholaris (L.) R.Br	√	√	√	√	-	√	√	√	√	√
Carica papaya L.	√	√	√	√	√	√	√	√	√	√
Amaranthus spinosus L.	√	√	√	√	√	√	√	√	√	√
Artocarpus champeden	√	√	√	√	√	√	√	√	√	√
Cassia siamea Lamk	√	√	√	√	√	√	√	√	√	√
Azadirachta indica	√	√	√	√	√	√	√	√	√	√
Helianthus annuus L.	-	-	-	-	-	-	-	-	-	√
Blumea balsamifera	-	-	-	√	√	√	-	√	√	√

Description: A. TesabelaVillage; B. Tablolong Village; C. Tesbatan Village; D. Teunbaun Village; E. OesaoVillage; I. Sikumana Village; F. Nunhila Village; J. Lasiana Village; G. Alak Village; H. Maulafa Village

ber of plants species as antimalarial drugs that are either grown in the wild or planted in the garden or in the home yard.

Literature studies gave information that these antimalarial herbal plants which are found in Kupang city and Kupang regency and that have been identified and tested in the laboratory, do have antimalarial activities. Moreover, the antimalarial active compounds with each of its parasite inhibition mechanism have also been identified (Table 3).

Table 2 shows 17 antimalarial activity of medicinal plants based on laboratory tests. Kembang bulan leaves (*T. diversifolia*) contain *sesquiter-*

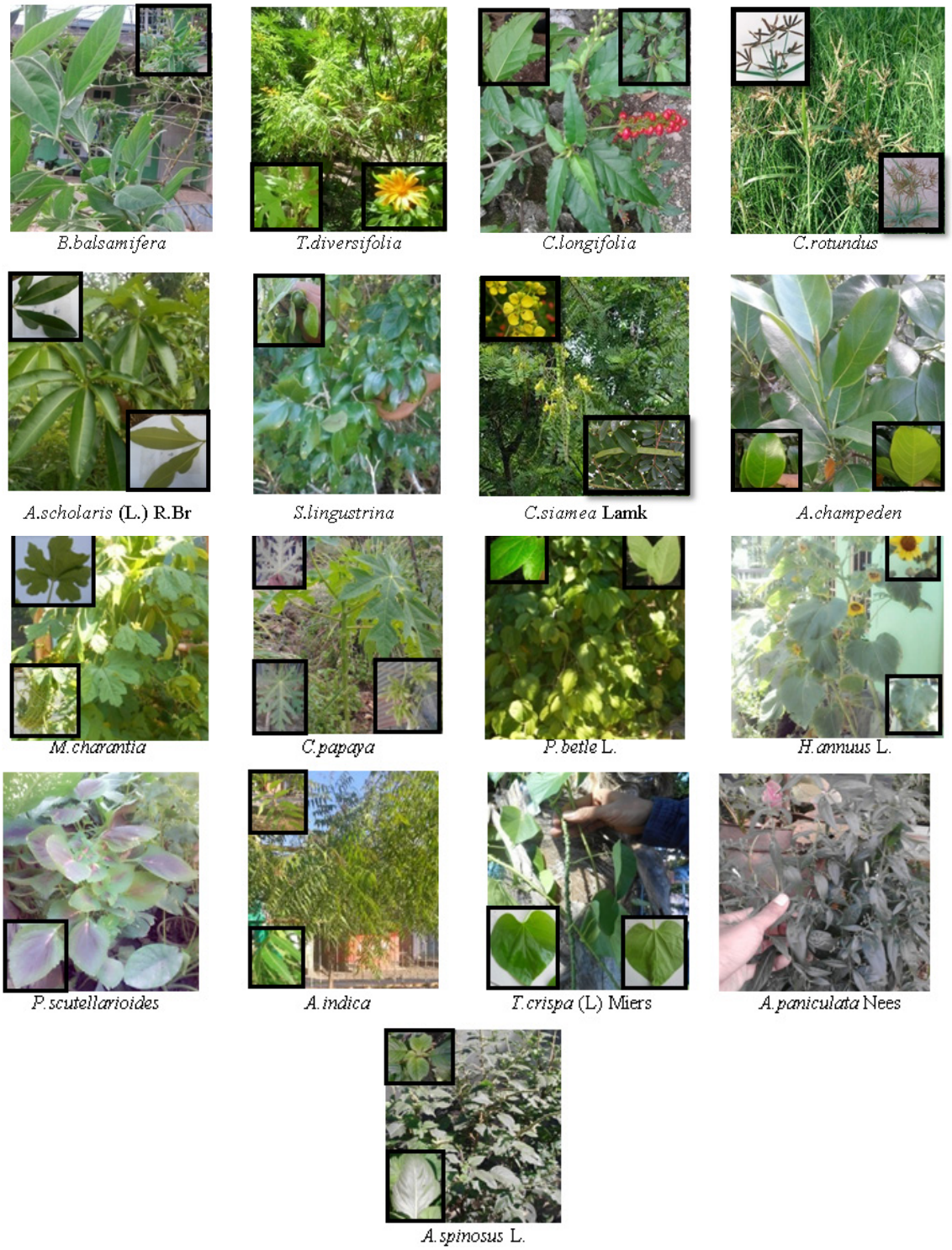

Figure 2. Antimalarial herbal species in 10 observational sites

pene lactonetaginin compound (Syarif, 2012; Utami & Armiyanti, 2012), which have inhibition effect to *P.berghei* growth with its ED_{50} value of 114 mg/kgbw (Budiati, 2011). Its inhibition mechanism is by inhibiting the polymerization of heme (Afiyah, 2007). Besides that, kembang bulan also has effective digestive toxic effect and contact toxic effect as biolarvacide to *C. bezziana* larvae, that can cause death, decrease pupa weight and inhibit the pupa formation and its hatch ability to become imago (Wahdana, 2014).

Pare fruit (*M. charantia*) contains many compounds, i.e. momordicin, momordine, quarantine, hydroxtrytamine, resin, saponin, alkaloid, flavonoid (Kurniawan & Ginanjar, 2005). However, its inhibition pathway is still unknown. Teki

Table 3. The antimalarial potencies of medicinal plants

Scientific Name	Local Name (Indonesian)	Plant Organ(s) used	Antimalarial compound	References
Tithonia diversifolia	Kembang Bulan	Leaf	sesquiterpene lactone taginin C	(Syarif et al., n.d.), (Utami & Armiyanti, 2012)
Momordica charantia	Pare / Paria	Fruit	momordicin, momordin, quarantine, hydroxtrytamine, resins, saponins, alkaloids, flavonoids	(Kurniawan dan Ginanjar, 2005)
Cyperus rotundus	Teki		α-*cyperon*	(Nuri et al., 2010)
Strychnos lingustrina	Bidara Laut	Root, Stem, and Leaf	strychnine, loganin, tannin andbrusin	(Setiawan et al., 2014) (Kemenkes RI, 2011)
Andrographis paniculata Nees	Sambiloto	Leaf	andrographolide	(Zein et al., 2013)
Callicarpa longifolia	Tabar Besi	Stem, Leaf	flavonoids and flavonols	(Pasaribu, 2014), (Falah et al., 2013) (Dewi et al., 2007)
Tinospora crispa (L) Miers	Brotowali	Root, Stem and Leaf	tinokrisposid, berberine, palmatine	(Adnanet al., 2001), (Ihwanet al., 2014)
Piper betle L.	Sirih	Leaf	antymicin,piperaquine	(Nugroho, 2011)
Plectranthus scutellarioides L.	Miyana	Leaf	Essential oil, tannin, catechut tannin and flavonoids	(Nugroho, 2011)
Alstonia scholaris (L.) R.Br	Kayu Susu	Stem, Leaf	Echitamine, tubotaiwine, akuamicine, picrinine, echitamidine, strictamine	(Pankti et al., 2012)
Carica papaya L.	Pepaya	Root, Stem and Leaf	Alkaloids, karpain, caricaxantine, violaxantine, papain, saponins, flavonoids, polyphenol.	(Rehena, 2010)
Amaranthus spinosus L.	Bayam Duri	Root, Stem and Leaf	betalain, betaninandamarantin	(Susantiningsih, 2013)
Artocarpus champeden	Cempedak	Bark and Leaf	flavonoids artoindonesianin E, heteroflavonon C, artoindonesianin R, heterophyline, artoindonesianin A-2, cycloheterophyline, artonin A, artokarpon A, artokarpon B	(Widyawaruyanti et al., 2011), (Hafid dkk., 2011)
Cassia siamea Lamk	Johar	Leaf	blumealakton	Muis, 2015
Azadirachta indica	Nimba	Leaf	azadirachtin, nimbolide	(Aini et al., 2004), (Deshpande, et al., 2014)
Helianthus annuus L.	Bunga Matahari	Leaf	sesquiterpenelaktones	(Hayati, 2011)
Blumea balsamifera	Sembung	Leaf	flavanoids, terpenes, lactones, cineol, borneol, kamper, tannin, limonene, palmitine acid, myristine, alcohol, sesquiterpene, dimethyl ether chloracetophenone, pyrocatechin, glycosides andsaponins,	(Falah et al., 2013) (Hani, 2008)

grass (*C. rotundus*) has compound with antimalarial activity, i.e. α-cyperon (Nuri et al., 2010)), and it growth inhibition mechanism of parasite is through the reaction between unsaturated carbonyl groupα, βcontained inside α-cyperon compound (Nuri et al., 2010).

Bidara Laut fruit (*S. lingustrina*) contains striknin, loganin, tannin, steroid and brucine (Setiawan et al., 2014; Suhada, 2013; Erlinda, 2013) Even though there are still no references explaining its inhibition pathway, Lubis (2008) noted that ethyl acetate fraction from *S.lingustrina* stem at the dose of 2,30 mh/kg bwhas antimalarial activity towards *Plasmodium berghei*-infected mice. Moreover, Huda (2006) explained that water extract of *S.lingustrina* stem at effective dose of 50% (ED50) 0,45 mg/ kg bw have antimalarial potencies.

Sambiloto (*A. paniculata* Ness) contains andrographolide compound and have an *in vitro* antimalarial effect to *P. falciparum* (Zein et al., 2013) but still no reference describing its inhibition pathway towards parasite growth.

Tabar Besi (*C. longifolia*) contains flavonoids compound, and the flavonol isolated from ethyl acetate fraction, has high toxicity activity to shrimp larvae of *Artemiasalina* Leach (Pasaribu, 2014). According to Dewi et al., (2007), Tabar besi is an antimalarial herbonce used by the Kutai community.

Brotowali (*Tinosporacrispa* (L) Miers) contains compounds such as tinokrisposide, berberine, palmatine (Adnan et al., 2001; Ihwan et al., 2014). Berberine is a quartenary alkaloids compound containing quartenary nitrogen in its structure, which has been known to have inhibition activity towards Plasmodium growth by blocking the Colin intracellular transport (Ancelin & Vial, 1986). Colin is required for phospholipid biosynthesis in cellular membrane formation of parasite to cover up the parasitophorous vacuole, cytosol and other subcellular compartments that will consequently inhibit the formation of new parasites. Blocking of Colin transport has been used as one strategy in treating malaria (Rosenthal, 2003).

Berberine is an in vitro biosynthesis inhibitor of nucleic acid and protein of *P. falciparum* that shows strong interaction with DNA (Birdsall & Kelly, 1997). Compounds such as berberine and palmatineare also a quartenary alkaloid and quinolin compound that only differ in its methoxyl and hydroxyl groups (Simanjuntak, 1995) also have the same type of activity, mechanism and inhibition target.

Adnan et al., (2001) explained that tinokrisposide compound is a compound with furanoditerpene glycoside structure. This structure is identic with nimbolid structure with antimalarial activity. however, the inhibition mechanism of those compound has still not been found yet. However, based on the resembling chemical structure we could imply that both have the same inhibition mechanism towards plasmodium growth.

Sirih (*P.betlle* L.) contains artemisin piperaquine compound. Miyana (*P.scutellarioides* L.) contains essensial oil, tannin, cathecin tannin, and flavonoid compounds (Nugroho, 2011). Unfortunately, their antimalarial compound and its inhibition mechanism has still not been found yet, however, according to Nugroho (2011), by mixing sirih fruit, miyana leaves, yolk, and honey, it is able to decrease parasitemia level in *P.bergei*-infected mice.

Kayu susu (*A.scholaris* (L) R.Br) contains echitamin, tubotaiwin, akuammisin, pikrinin, echitamidin and striktamin compounds (Pankti et al., 2012). Although its inhibition mechanism is still unexplained, this plant has been known for itspotencies as antimalarial drugs (Rezeki et al., 2012). Papaya (*C.papaya* L.) contains carpain alkaloids, caricaksantin, violaksantin, papain, saponin, flavonoids, polythenol and saponins (Rehena, 2010). Nuri (2005) highlighted that flavonoid compounds have pharmacologic activity and possesses different chemical structure with other antimalarial drugs. Drugs with different structure would probably have different targets of inhibition.

Bayam duri (*A.spinosus* L.) contains betalain, betanin and amaranthin compounds. Its inhibition mechanism is probably by its ability for chelating metal ions required for parasite metabolism, obstructsheme polymerization and its ability to increase mice hemoglobin (Susantiningsih, 2013). Besides that, bayam duri also has antioxidant activity that prevents the peroxidation of lipidand endothelial cells which playscrucial part in systemic complication mechanism of malaria (Percario et al., 2012). Cyclic amine in betalain that resembles thoxyquine, is a reactive group that with only one phenolic group or acyclic amine, betacyanine and betaxhantine could become electron donor that stabilizes free radicals (Mastuti, 2010).

Cempedak (*A.champeden* Spreng) contains isoprenil flavon, flavonoid, artoindonesianin E, heteroflavonon C, artoindonesianin R, heterofilin, artoindonesianin A-2, cycloheterofilin, artonin A, artokarpon A, artokarpon B. Isoprenilflavoncan inhibit lymphocyte proliferation because theisoprenil chain in isoprenil flavon undergoes substitution at its carbon atom (C-8). Moreover,

A. champeden Spreng also contains cycloheterofilin which is able to inhibit the growth stadium of *P. falciparum* malarial parasite from the ring stadium to trofozoit stadium andcauses abnormal morphology growth of the skizon stadium. Cycloheterofilinis also able to inhibit globin degradation in food vacuole of malarial parasites (Widyawaruyanti et al., 2011). Combination therapy of cempedak ethanol extract and artesunat is more effective as an *in vivo* antimalarial drug. This shows that cempedak is more effective if used as a part of a combination therapy (Hafid et al., 2011).

Johar (*C.siamea* Lamk) contains alkaloids, saponin, flavonoid, tannin, and triterpenoid which shows significant antiplasmodium activity with 31.44% of inhibition percentage (Fitrianingsih et al., 2010). Rahardjo et al., (2014) also concluded that water extract of johar leaves have inhibition ability to P. berghei growth *in vitro* in mice with ED_{50} value of 83.77412 mg/kg BW, but its inhibition mechanism is still unknown.

Nimba (*A.indica*) contains azadirachtin and nimbolide. The inhibition mechanism of nimba seed extract or the antimalarial compound contained inside of it is supposedly related to the immune response of the parasite (Aini et al., 2004) and having antimalarial activity (Deshpande et al., 2014).

Sunflower (*H.annuus* L.) contains sesquiterpen, lactone, diterpene, monoterpenoids and phenol compounds. Sesquiterpene has been known to possess antimalarial activity (Hayati and Muti'ah, 2011) through the formation of free radicals that will deteriorate vital components of the parasite that will have fatal effect (Nurrachma & Putrianti, 2005).

Sembung (*B.balsamifera*) contains flavonoid, terpene, lactones, cineol, borneol, camper, tannin, limonene, palmitine acid, myristine, alcohol, sesquiterpene, dimethyl ether chloroacetophenon, pyrocatechin, glycoside and saponin (Hani, 2008; Falah et al., 2013), ethyl acetate fraction contains polyphenol, tannin, flavonoid, and monoterpene, sesquiterpene, and Quinone compound. Characterization result by uv spectrophotometry and infrared spectrophotometry for ethyl acetate active fraction have identified sesquiterpene lactone compound (*blumealactone*) that possesses anti-plasmodium activity at dose of 118 mg/kg BW with inhibit percentage of 17,53% (Muis, 2015).

CONCLUSION

There are 17 antimalarial herbal plants species which are distributed in 10 observational sites in Kupang City and Kupang Regency. These plant species are *T.diversifolia, M.charantia, C.rotundus, S.lingustrina, A.paniculata* Nees, *C.longifolia, T.crispa* (L) Miers, *P.betle* L., *P.scutellarioides* L., *A.scholaris* (L.) R.Br, *C.papaya* L., *A.spinosus* L., *A.champeden, C.siamea* Lamk., *A.indica, H.annuus*L. and *B.balsamifera.*

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