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The Effectiveness of Local Plants from Lom and Sawang Ethnics as Antimalarial Medicine

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Abstract

Native people or ethnic societies that live in endemic malaria islands such as in Bangka Island and Belitung Island have used many medicinal plants to cure malaria. Leaves of *kesembung* (*Scaevola taccada* (Gaertn Roxb), roots of *kebentak* (*Wikstroemia androsaemofolia* Decne), and roots of medang *mencena* (*Dapniphyllum laurinum* (Benth) are the examples. This research was aimed to investigate the present of some biochemical compound and evaluate the antimalarial activity of ethanol extract of the plants against *Plasmodium falciparum* 3D7 in vitro. The IC50 level was determined through visual observation under microscope over 5000 of giemsa-stained erythrocytes then analyzed by probit analysis. Results showed that kebentak root ethanol extract was effective to inhibit P. falciparum 3D7 with level 0.485 µg/mL. Furthermore, the IC50 level of *kesembung* leaves and *medang* root were 44.352 µg/mL and 1486.678 µg/mL respectively. Phytochemical test result showed that *kebentak* leaf ethanol crude extract contained triterpenoid, *kesembung* root contained phenol and tannins; moreover, *medang* root contained alkaloid, saponin, and triterpenoid.

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INTRODUCTION

Indonesia as one of developing countries embraces the local wisdom in people daily activities such as the utilization of medicinal plant to cure disease. In Indonesia, medicinal use of natural materials has been done by the ancestors and it has been passed down from one generation to the next generation. Every society in every region has been using a variety of useful plants in their environment (Ifandi et al., 2016). Sawang ethnic is native society that inhabits Belitung Island, while Lom ethnic inhabits Bangka Island. The study about plant utilization in medical treatment by local people in both islands has been delivered by *Tim penulis Ristoja* (2013a, 2013b).

Bangka and Belitung islands are the endemic area of malaria. The number of people suffering for malaria increase twofold in the last two decades due to resistance of new *Plasmodium falciparum* strain to chloroquine and its derivatives (Trape et al., 2002). The efforts in order to explore new potential antimalarial plants are needed to overcome the resistance of malarial parasites (Bankole et al., 2016). Historical records show that mostly antimalarial drugs are derived from medicinal plants, namely Artemisin derived from *Artemisia annua*. This plant has been used by society in China. Previous study about extract of belilik fruit and root (*Brucea javanica* Merr.) origin from Bangka showed optimal inhibition to *Plasmodium falciparum* growth with IC_{50}< 0.01 µg/mL (Helmi & Susanti, 2013b).

Lom and Sawang ethnics as native inhabitants of Bangka and Belitung Islands should have traditional knowledge in malaria treatment. Sawang ethnic hereditary utilize the leaf of *kesembung laut* (*Scaevola taccada* Gaertn Roxb) or also called as *benak* or *kumak* for malarial treatment. In addition, Lom ethnic utilize *kebentak* (*Wikstroemia androsaemofolia* Decne) root and *medang mencena* (*Daphnipyllum laurinum* (Benth) Ballon root (*Tim Penulis Ristoja*, 2013a, 2013b).

Kesembung lives in beach ecosystem, where it will not disrupted by the waves and will get optimum sun-light. This plant is herbaceous with widened upper, shiny green yellowish colour, curvy edge, wax-coated surface, spherical to elliptical shape, and rounded tip leaves. Size of these leaves is around 16.5-30 x 7.5-9.5 cm (Kontz et al*.,* 1996). According to Meijin (2009), *Scaevola* genus contains several active compounds such as coumarins, terpenoids, iridoids, alkaloids, and flavonoids. Plants in this genus have shown biological activities such as antiviral, antitumor, and antibacterial. Taxonomically, this plant is classified in *Goodneciae* family (Heywood (1993 in Koontz et al*.,* 1996).

Kebentak that found in Bangka or Belitung Islands are able to grow in biome with sandy soil structure or heathland with watery red yellowish soil structure. According to Heyne (1987), this plant is classified in family *Thymalaceae*. It has various content of flavonoids, biflavanoids, coumarin, atsiri oil, and polysaccharides (Huang et al*.,* 2010; Lu et al*.,* 2011; Li et al*.,* 2012; Lu et al*.,* 2012; Ko et al*.,* 2013). Based on traditional knowledge in medicine, *Wikstroemia* can be applied as antioxidant, antimicrobial, anti-inflammatory, antivirus, antitumor, anticancer, anti-browning, and antifertility. Helmi & Susanti (2013a) stated that ethanol extract of *kebentak* leaf and fruit is not effective to cure malaria, but there is possibility its root has the potential. Belitung people utilize this plant fruit as antimalarial drug (Fakhrurrozi, 2001). Lom ethnic used the root of *kebentak* as antimalarial drug (*Tim Penulis Ristoja*, 2013a).

Medang mencena plant is shrubs that commonly used as cure for malaria, joint pain, and neck pain by Lom ethnic people (Tim Penulis Ristoja, 2013a). This plant has not been optimally explored yet, but it has been reported that plants in genus *Daphniphyllum* contain alkaloid (Padwa et al., 2009). Lee et al. (1998) stated that family *Daphnyphylaceae* has antioxidant activity.

This study was aimed to detect biochemical content in *kesembung* leaf, *kebentak* root, and *medang mencana* root qualitatively and to investigate antimalarial activity of these plants against *P. falcifarum* 3D7.

METHODS

Extraction

Root of *medang mencena* and *kebentak* were obtained from Air Abik village, Belinyu subdistrict, Bangka. Furthermore, *kesembung* leaf was obtained from Matras Beach area, Bangka. The extraction was conducted in Mathematics and Natural Sciences Laboratory, Bangka Belitung University. Extraction was conducted through maceration with ethanol absolute 96% with proportion 1:3 of plant and ethanol. Maceration was conducted for 3 days in room temperature. Filtrates were evaporated with vacuum rotary evaporator.

Phytochemical Test

Phytochemical test were conducted in Mathematics and Natural Sciences Laboratory, Bangka Belitung Universiy. In this study, qualitative test of phytochemical was conducted. The

material used were sulfuric acid, alcohol, acetic acid glacial, diethyl eter, Dragendorff (mix $Bi(NO_3)_2 \cdot 5H_2O$ in nictric acid and Ki solution), ethanol, $FeCl_3$ 1%, H_2SO_4, HCL, kloroform, and ammonia. The analysis were including alkaloid test by Robinson method (1995). The other active compounds that detected were saponin, triterpenoid, steroid, flavonoid, and phenol through Harborne method (1996).

***In vitro* Antimalarial Activity Test**

The equipment that used in this study was *eppendorf* tube, laminar air flow, vortex, candle jar, centrifuge, CO_2 incubator, and autoclave. Materials that used were *P. falciparum* (strain 3D7, HEPES, RPMI 1640 (Rosewell Parla Memorial Institute), sodium bicarbonate ($NaHCO_3$), hypoxanthine, gentamycin, demineralized water, dimethyl sulfoxide (DMSO), immersion oil, 20% giemsa staining, sterile water. The anti-parasite test was conducted in Pharmacognosy and Phytochemistry laboratory, Faculty of Pharmacy, Airlangga University.

Firstly, master solution was made in DMSO and diluted into series of concentration with medium RPMI 1640 enriched with 10% plasma, 25 mM HEPES, and 25 mM $NaHCO_3$ until the concentration in culture wells were 100. 10, 1. 0.1, and 0.01 µg/ml. Cells were cultured with 5% of hematocrit and 1% of parasitemia. Cultures were harvested after 48 hours of incubation then smeared into object glass with 20% of giemsa staining. Furthermore, IC_{50} level was determined after the percentage of parasitemia and probit analysis result were obtained (Fidock et al., 2004, Ekasari et al., 2009).

Data Analysis

Smear preparates were observed using microscope with 1000X of magnification after addition of immersion oil. Parasitemia and parasite growth inhibition number were calculated from the number of infected erythrocyte for each 5000 observed erythrocyte using the formula below.

1. Percentage of parasitemia = (infected erythrocytes/5000 erythrocytes) x 100%;
2. Percentage of growth = % parasitemia of parasite (48 hour - 0 hour);
3. Percentage of inhibition = 100% - (Xp/Xk) x 100%,

Xp = tested parasitemia dan Xk = control parasitemia (-).

RESULTS AND DISCUSSION

Three species (*kesembung, medang mencena, kebentak*) were used in this research (Figure 1). The methanol extraction of *kesembung* leaf, *medang mencena* root, and *kebentak* root through maceration with ethanol yielded 7.85%, 4.97%, and 4.64% of extract respectively (Table 1).

Phytochemical compounds are substances that can protect plant from diseases. Naturally, plants produce these compounds to protect their self from damage, but human explore and use them in diseases prevention (Builder et al., 2014). Several secondary metabolites have antiplasmodic activity (Saxena et al., 2010). Qualitative test through colorimetry showed that *kesembung* leaf contain phenol, tannins, and triterpenoids. In addition, *medang mencana* root contained alkaloids, saponins, and triterpenoids, while *kebentak* root contained only triterpenoid (Table 2). Therefore the three plants have different kind of active compound contents, but they all have triterpenoids. According to Harborne (1996), triterpenoids are consisted of long hydrocarbon chain C_{30} that cause non-polarity. This compound has cyclic structure that mostly consisted of alcohol, aldehyde, or carboxylic acid. Normally, it has no co-

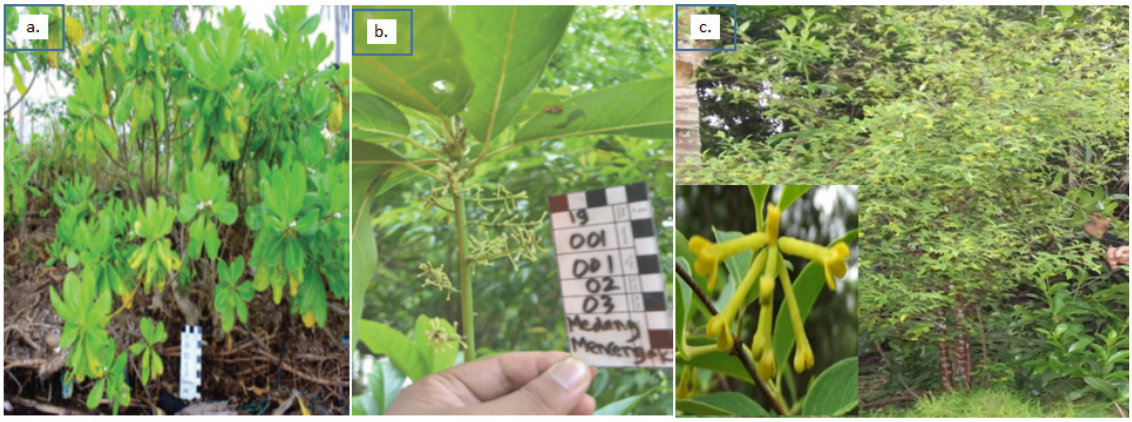

Figure 1. The plants in this study: a. *kesembung* (source: Tim Penulis Ristoja 2013b), b. *medang mencena* (source: Tim Penulis Ristoja 2013a), c. *kebentak* (source: Idha Susanti 2013)

Table 1. Yield of plant extraction

Type of plant and its part	Initial Weight (g)	Final Weight (g)	Yield (%)
Kesembung Leaf	63.7	5	7.85
Medang Root	72.5	3.6	4.97
Kebentak Root	34.5	1.6	4.64

lour in crystal form with high melting point and optical active.

Table 2. Phytochemical components of each plant

Compounds	*Kesembung* Leaf	*Medang* Root	*Kebentak* Root
Alkaloid	-	+	-
Flavonoid	-	-	-
Phenol	+	-	-
Saponin	-	+	-
Steroid	-	-	-
Tanin	+	-	-
Triterpenoid	+	+	+

Note: (+) detected, (-). Not detected

Numbers of active compounds have been isolated; their antiplasmodic activity has been proven through *in vitro* and *in vivo*. For example, quinine from *Cinchona ledgeriana* is one of antimalarial drug that has been used until these days (Bell, 2005). According to Bero et al., (2009), most compounds that show positive result in phytochemical test are antimalarial substances. Commonly, those compounds are alkaloids, terpens, quassinoids, flavonoids, limonoids, calcons, peptides, xanthones, quinones, coumarines, and the other antimalarial substances (Kaur et al., 2009). Fidock et al. (2004) stated that six targets of antimalarial agents are cytosol (folic metabolism, glycolysis, protein synthesis, gluthatione metabolism in cytosol, and signal transduction), parasites membrane (phospolipids metabolism and membrane transport), food vacuole (hem polymerization, haemoglobin hydrolysis, free radical releasing), mitochondria (electron transports), apicoplast (protein synthesis, DNA synthesis, transcription, type II fatty acid biosynthesis, isoprenoid synthesis, and protein famesilation),and extracellular (erythrocyte invasion).

Antimalarial test result shows that *kesembung* has IC_{50} 44.352 µg/mL (Table 3). According to Pouplin et al (2007), an extract could be classified as active parasitemia reducer if it can reduce more than 30% of parasitemia. Therefore, *kesembung* can be utilized to reduce parasitemia with concentration 10 µg/mL.

Phytochemically showed that *kesembung* leaf extract contained phenol, tannin, and triterpenoids. Previous researchers reported that those compound having antimalarial activity. Table 3 showed that this extract could inhibit the plasmodium. It was assumed that phenol, tannin and triterpenoid in this extract could inhibit the para-

Table 3. Percentage of *P. falciparum* 3D7 growth and the inhibition of *Kesembung* leaf extract

Concentration (µg/mL)	Repetition	% Parasitemia 0 hour	% Parasitemia 48 hour	% Growth	Average % Growth	Average % Inhibition	IC_{50} (µg/mL)
Control (-)	1	1.16	3.83	2.67	2.76	-	44.352
	2	1.16	4	2.84			
100	1	1.16	2.14	0.98	1.11	59.78	
	2	1.16	2.4	1.24			
10	1	1.16	2.96	1.8	1.84	33.33	
	2	1.16	3.05	1.89			
1	1	1.16	3.27	2.11	2.13	22.83	
	2	1.16	3.31	2.15			
0,1	1	1.16	3.4	2.24	2.27	17.75	
	2	1.16	3.46	2.3			
0,01	1	1.16	3.73	2.57	2.63	4.71	
	2	1.16	3.85	2.69			

sit. It was supported by Laphookhieo et al. (2009) and Kusch et al. (2011) who explained that phenol increase cellular oxidation in red blood cell and inhibit protein synthesis of parasite when act as antimalarial agent. Builder (2010) taked that these processes will lead to oxidative damage by malaria parasite induction. Because of that, antioxidant activity of phenol increases the effectiveness of antimalarial activity (Builder et al., 2014). In addition, Syarif (2007) stated that phenol takes role in inhibition of hem polymerization.

Triterpenoid has also been reported as antimalarial agent. A study showed that triterpenoid that isolated from *Lansium domesticum* had antimalarial activity with IC_{50} 5.9 µg/mL (Saewan, 2006). Betulinic acid (pentacyclic triterpens) can fuse with erythrocyte membrane then enter into the cell through lipid bilayer, as a result growth and invasion of malaria parasite are inhibited (Ziegler 2004). There is correlation between the increasing of IC level with malaria parasite proliferation; therefore the alterations of erythrocyte membrane and parasite vacuolization are the acts of triterpenoids in antimalarial. Pouplin et al., (2007) stated that triterpenoids inhibit parasites growth by hampering protein synthesis inside parasite cells. Fidock (2004) taked that saponin, flavonoid, and tannin as antioxidant will scavenge free radicals due to damage of parasite invasion.

Medang mencana antimalarial activity test show that it had IC_{50} 1486.68µg/mL (Table 4), it could be categorized not effective to be used as antimalarial drugs. Although, it was not effective as antimalarial drug but this extract could inhibit the *P. falcifarum* (table 4). This plant has not optimally studied yet, but it had been proven that it had alkaloids contents such as daphnyphyllin (Hirata, 1975). Alkaloids have been known as natural resources that can be utilized as drug. Quinine is one of alkaloids that has been utilized as antimalarial drug, it is produced by *Cinchona succiroba* (Kaur et al., 2009). This compound will block the intracellular choline transport that can inhibit parasite growth (Hilou et al., 2006). Besides alkaloid, medang mencena leaf extract contained saponin. Saponin could inhibit parasite growth by inducing the erythrocyte lysis (Widodo & Rahayu, 2010). Perhaps, the increase of concentration and suitable solvent usage in extraction will allow the plant to perform better antimalarial activity.

Kebentak root extract has level of IC_{50} 0.485 µg/mL (Table 5). Triterpenoid in kebentak root is expected can effectively inhibit *P. falcifarum* growth. This plant is classified in family *Thymelaceae*, that is to say that alkaloid is commonly found compound in plants of this family. Phytochemically showed that kebentak root extract contained triterpenoid. Quassinoid is one of triterpens that found abundant in plant of family *Simaroubaceae*. Several active quassinoid are isolated from Indonesian herbal such as pasakbumin B, pasakbumin C, and eurikumanondari from *Eurycoma longifolia* Jack. The other quassinoids are bruseajavanin A, dihidrobruseajavanin A, and bruseakantinosid that isolated from *Brucea javanica* Jack were effective to inhibit the *P. falciparum*.

Wikstromia has been reported not only contains triterpenoid, but also contains several

Table 4. Percentage of *P. falciparum* 3D7 growth and the inhibition of *Medang* root extract

Concentration (µg/mL)	Repetition	% Parasitemia 0 hour	% Parasitemia 48 hour	% Growth	Average % Growth	Average % Inhibition	IC_{50} (µg/mL)
Control (-)	1	1.16	3.55	2.39	2.48	-	1486.68
	2	1.16	3.73	2.57			
100	1	1.16	0.83	0	0	100	
	2	1.16	0.62	0			
10	1	1.16	2.94	1.78	1.75	29.44	
	2	1.16	2.88	1.72			
1	1	1.16	3.01	1.85	1.82	26.61	
	2	1.16	2.94	1.78			
0,1	1	1.16	3.24	2.08	1.98	20.16	
	2	1.16	3.04	1.88			
0,01	1	1.16	3.53	2.37	2.21	10.89	
	2	1.16	3.21	2.05			

Table 5. Percentage of *P. falciparum* 3D7 growth and the inhibition of *Kebentak* root extract

Concentration	Repetition	% Parasitemia		% Growth	Average	Average	IC_{50}
(µg/mL)		0 hour	48 hour		% Growth	% Inhibition	(µg/mL)
Control (-)	1	1.16	3.81	2.65	2.78	-	0.485
	2	1.16	4.07	2.91			
100	1	1.16	0.5	0	0	100	
	2	1.16	0.42	0			
10	1	1.16	1.88	0.72	0.73	73.74	
	2	1.16	1.9	0.74			
1	1	1.16	2.35	1.19	1.25	55.04	
	2	1.16	2.47	1.31			
0.1	1	1.16	2.86	1.7	1.76	36.69	
	2	1.16	2.98	1.82			
0.01	1	1.16	3.24	2.08	2.16	22.3	
	2	1.16	3.41	2.25			

types of flavonoid, biflavanoid, coumarin, atsiri oil, lignin, polysaccharide, and the other active compounds (Huang et al., 2010; Li et al*.,* 2010; Li et al., 2012; Ko et al., 2013; Lu et al., 2011; Lu et al., 2012). *Wikstromia* contained some flavonoid/ biflavonoid such as Naringin,5,6,7-Trihydroxy-4'-methoxy-dihydroflavonol,kaempferol-3-O-b-D-glucopyranoside, kaempferol-3-robinoside-7-rhamnoside, wikstrol A, wikstrol B, chamaejasmin, neochamaejasmin, isochamaejasmin, chamaechromone,genkwanin, quercetin, quercitrin, sikokianin B, sikokianin C, sikokianin D, stelleranol, genkwanol C, genkwanol B, tricin, 4'-methoxydaphnodorin (Li et al*.,* 2005; Huang et al*.,* 2010; Chen et al*.,* 2012; Li et al*.,* 2012; Yongqin et al., 2012; Ko et al., 2013).

Besides, the other compounds that have also been isolated from this plant are organic acid, namely 4-hydroxybenzoic acid, dibutyl phthalate, benzoic acid, coumarin (umbdheforne, daphnogitin, aphnogitin, daphnoretin, daphnoretin-7-O-β-D-glucoside, wikstrosin, umbelliferone, 6'-hydroxy, 7-O-7'-dicoumarin), steroid (daucosterol dan β-sitosterol), lignan (lirioresinol B, bis-5,5-nortrachelogenin, dan bis-5,5'-nortrachelogenin), atsiri oil, phenol (chrysophanol), glycoside (daucosterol; beta-sitosterol), and lignan (tricin) (Geng et al., 2006a, 2006b; Lu et al. 2011; Ko et al. 2013; Wang et al. 2005; Li & Li 2010; Li et al. 2012; Yongqin et al. 2012)

According to Wang, *Wikstromia indica* and *W. ovate* (Salago) in Philippine are known containing saponin, resin, and glycoside. Alkaloid is not identified in those plants. Helmi and Susanti (2013a) reported that leaf and fruit extract of *kebentak* contain steroid, triterpenoid, flavonoid, and phenol. Furthermore, saponin is only found in benta fruit. Next study by Helmi & Susanti (2013a) shows that both extracts and fruit were not effective in *P. falcifarum* growth inhibition. The optimum dose of the extract that can inhibit 50% of parasite growth was >100 µg/mL. In spite of this study, it has been revealed that benta root can inhibit parasitemia for more than 30% of *P. falciparum* parasites with concentration 0.1 µg/mL.

A research about antimalarial study of *W. indica*, plant that share the same genus with kebentak has been conducted. Root of this plant was extracted with BuOH solvent. The solution was fractionized to flavonoids; specifically sikokianin B dan sikokianin C. Sikokianin B and sikokianin C perform excellent inhibition over the growth of *P. falciparum* with IC_{50} yaitu 0.54 µg/mL and 0.56 µg/mL respectively (Nunome et al., 2004). On the other hand, there was no flavonoid detected in *kebentak* root.

The lowest inhibition of parasite was performed by *kebentak* root (Table 6). The IC_{50} level of *kebentak* crude extract was 0.485 µg/mL. Another key point stated by Fidock et al. (2004) explains that antimalarial compounds will effective if their IC_{50} level around 1-5 µg/mL. According to this, *kebentak* extract was the only effective plant that can be used as antimalarial drug. The active compounds contained in kebentak could be fractionized and purified in order to increase its effectiveness against malaria parasites. In further, this

extract potential as a new source for malaria cure.

Table 6. The IC_{50} level of three tested plants

Extracts	IC_{50} (µg/mL)
Kesembung leaf	44.352
Kebentak root	0.485
Medang root	1486.68

CONCLUSIONS

Ethanol crude extract of *Kebentak* root had the highest effectiveness against *P. falciparum* 3D7 with IC_{50} level was 0.485 µg/mL. The IC_{50} levels of *Kesembung* leaf and *medang mencena* root were 44.352 µg/mL and 1486.678 µg/mL respectively. Phytochemical test results show that ethanol crude extract of *Kebentak* root contains triterpenoid, *Kesembung* leaf contains phenol, tannins, and triterpenoids, while *Medang Mencana* root contains alkaloid, saponin, and triterpenoid.

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