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Contents

The Most Four Utilised Medicinal Plants for Anti-Malarial Phytomedicine In Papua and Their Main Chemical Constituents

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Abstract

In Papua, malaria is still a major health problem and one leading dead diseases. Numbers of factor contributes to higher prevalence of this endemic disease, such as undistributed health facilities and skilled workers, misunderstanding of malaria diseases, as well as lack of environmental management and control. This disease is becoming serious, when it has been reported that the two malaria parasites, *plasmodium falcifarum* and *plasmodium vivax*, respectively, were being resistance form anti-malarial drugs recommended and available in the market today. Naturally, it has been widely acknowledged that medicinal plants from surrounding nature are the main sources of natural herbs or phytomedicine for us, and have been playing a key roles in keeping and maintaining our health since the ancient time. This paper highlights that 29 medicinal plants have been identified and used intensively by the indigenous people across Papua for anti-malarial phytomedicine. Amongst those medicinal plants, the most four utilized medicinal plants are Tail kuning (*Tinospora dissitiflora* Diels), Akar kuning (*Arcangelisia flava* (L.) Merr.), Kayu susu (*Alstonia scholaris* Linn.), and Kayu Kuning (*Nauclea orientalis* (L.) L.). Preparation of decoctions from parts of these medicinal plants, such stems, and barks, mostly using medium of hot-water and consumed when anti-malarial phytomedicine are taking place. Yellowish alkaloids, berberine and protoberberine groups represent dominant chemical constitutents both in Tail kuning and Akar kuning, whereas indole alkaloids were the major isolated secondary metabolites of Kayu susu (bark and fruit) and Kayu kuning (bark, wood, and roots). With respect to the complexity of the malarial symptoms, chemical constituents of phytomedicinal decoctions, as well as the successfully implementation of anti-malaria phytomedicine in several African countries, therefore, it is soundly feasible to improve the utilization of these four most utilized medicinal plants for anti-malarial herbal/phytomedicinal products, mainly to develop the standardized products, treatments, and dosages.

Keywords: Four medicinal plants, anti-malarial, chemical constituents, and Papua

Background

Malaria is an endemic and one of several fatality diseases in Papua, covering Papua and West Papua provinces. It has been reported that in 2010 approximately 124 238 the malaria cases were occurred, and it rose to 129 550 malaria case in 2011 (Papua Health Department, 2012). Morbidity of malaria is probably higher than that previously was reported, as there are still un-reported malaria cases across this island, including West Papua province.

A number of factors probably could be addressed to higher prevalence and fatality of malaria in Papua ranging from undistributed health facilities, less number of skilled health workers, unavailability of malarial drugs, bad sanitation, and environmental management and control (Rumbiak, 2006), and resistance of malaria parasite, mainly *Plasmodium falcifarum* and *Plasmodium vivax*. Regardless of those factors mentioned above, traditionally indigenous people of Papua have been using their medicinal plants for treating and alleviating malaria diseases and symptoms. However, it is quite disappointed views that data of anti-plasmodium activities of their medicinal plants are limited or unavailable.

Ethnobotanical studies on medicinal plants in Papua and West Papua provinces have been conducted and reported by students and researchers from the State University of Papua (Sucbu, 2002; Erari, 2005; Rombe, 2006, Lense, 2011; 2012). It can be summarized that 29 species of medicinal plants used for anti-malarial purposes, and among those 29 anti-malaria medicinal plants, the four most dominant medicinal plants used in Papua to alleviate malaria are Tali kuning (*Tinospora dissitiflora* Diels), Akar kuning (*Arcangelisia flava* (L.) Merr.), Kayu kuning (*Nauclea orientalis* (L.) L. and Kayu susu (*Alstonia scholaris* Linn).

This paper is aimed to provide a recent status of ethnobotanical studies on anti-malarial medicinal plants used in Papua and West Papua, mainly the most utilized medicinal plants used by the local ethnics. Diversity of their main chemical constituents of also briefly presented.

Methods

These studies mostly are conducted using literature review. However, the isolation and structural elucidation of berberine in Tali kuning were conducted as described in the previous paper (Wahyudi *et al*., 2012).

Results

Medicinal plant for anti-malaria

Literature reviews indicated that 29 medicinal plants for anti-malarial phytomedicine in Papua were indentified and recorded, and representing 16 plant families. Family Euphorbiaceae consists of 5 plants (17 %), followed by Menispermaceae for 4 plants (14%), Urticaceae (2 medicinal plants (3%), Solonaceae, Meliaceae, Casuarinaceae, and Polypodiaceae of 2 plants each (2%), while the rest families represent 1 plant each (Rutaceae, Apocynaceae, Cariaceae, Liliaceae, Rubiaceae, Acanthaceae, Asteraceae, Goodeniaceae, and Lamiaceae). Different parts of these medicinal plants were used, ranging from leaves, barks, stems/woods, as well as whole plant. In detail, leafs represent the majority (48%) of plant part being used for anti-malarial phytomedicine from Papua, as been illustrated by Figure 1, and followed by barks (24%), stem/wood (17%), and whole plants (11%).

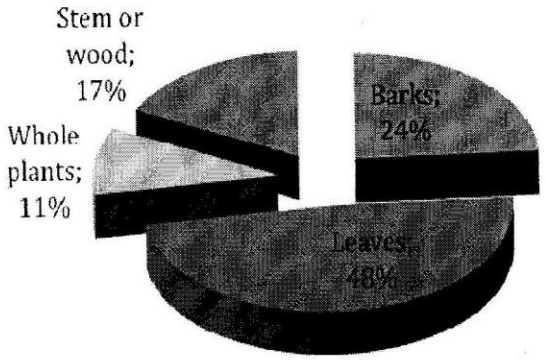


Figure 1. Part of medicinal plants for anti-malarial phytomedicine used by indigenous people in Papua

These 29 plants were compilation of medicinal plants used by the 9 ethnic groups across Papua, representing from low to high land inhabitants, likes Arfak/Manokwari, Wie-khaya, Kanum, Wate, Mooi, Biak, Tepin, Maibrat, and Wondama. Arfak/Manokwari ethic has the highest diversity of anti-malarial phytomedicinal plants (12 plant species), whereas the lowest one is Mooi, Kanum, and Wondama. From those 29 medicinal plants identified, reported and used across Papua, the most utilized medicinal plants are Kayu susu (*A. scholaris* L.R.Br.), Kayu kuning (*N. orientalis* Linn.), Tali kuning (*T. dissitiflora* Diels), and Akar kuning (*A. flava* Merr.), especially at low land or near coastal inhabitants.

Methods of utilization of the medicinal plants

Mostly, anti-malarial phytomedicine from Papua are prepared or used in the form of decoction. Generally, various parts of these medicinal plants are extracted using medium of hot or warm water, and then the cold extracts are filtered and consumed as necessary. This process of preparation can be repeated several times (usually 3-5 times) and when color of the extract is getting changes to clear, the medicinal raw herbs should be replaced with the newest one.

With respect the four most utilized anti-malarial phytomedicine plants, the decoction of Tali kuning and Akar kuning were collected from the whole stems, while Kayu kuning and Kayu susu are collected from their barks.

Main chemical constituents

Summary for main secondary metabolites isolated from the most four utilized anti-malarial phytomedicine plants in Papua were presented in Table 1. This table highlights that the chemical constituents of the two medicinal plants, namely kayu susu (*A. scholaris* L.R.Br.) and Kayu kuning (*N. orientalis* Linn.), respectively, have well investigated and reported. Even though, their barks are mostly used for anti-malarial phytomedicine, the main chemical constituents of other plant parts (leafs, fruits and roots) also have been reported.

Table 1 also highlights that indole alkaloids are dominant compounds isolated and reported from almost all parts of the medicinal plant kayu Susu (*A. scholaris* L.R.Br.), such as barks, leafs and fruits. Similarly, groups of indole alkaloids from dried stems, barks and roots of kayu Kuning (*N. orientalis* Linn.) were also reported and isolated. One alkaloid belonging to protoberberine group, namely berberine, was isolated from the medicinal plant of Tali kuning (*T. dissitiflora* Diels). However, other protoberberine members were isolated from Akar kuning (*A. flava* Merr.). In addition, furanoditerpenes were isolated from this medicinal plant.

Discussion

In Papua, malaria is still becoming one fatality disease to all habitants at any ages, including pregnant women and babies. When the two groups (pregnant women and babies, respectively), are infected, the complexity of treatments and prevalence for dying or being severe are higher, particularly when an appropriate treatments are difficult to achieve or health service even unreachable. This morbidity occurs so frequently at highland /mountainous, or inland areas where the most Papuans live. Even though, 29 medicinal plants utilized for anti-malarial phytomedicine in Papua have been identified and recorded (Suebu, 2002; Erari, 2005; Rombe, 2006, Lense, 2011; 2012). Wahyudi, 2012; Wahyudi et al., 2012), it seems that the roles and applications of their own medicinal plants for anti-malaria phytomedicinal purposes are needed further efforts and encouragements. Also, efficacy of 29 medicinal plants against malaria parasite *Plasmodium* spp either *in vitro* or *in vitro*, have not been clarified yet.

In vitro anti-plasmodium activities of several extracts of medicinal plants from different parts of the world have been investigated and reported by several researches. Bora *et al.* (2007) reported that the people of Northeast India are using 65 medicinal plants belonging to 38 families for curing malaria. They also reported that various plant parts such as root, bark, leaf, fruit and in some cases the whole plants were used for making herbal preparation, which is mostly using water as main medium. Herbal preparations are in the forms of crude extract, juice and decoction or leaf infusion. Sugar or honeys are added occasionally. These indigenous people are using single plant resources for making anti-malarial herbal.

In vitro anti-malarial activities of ethyl acetate and methanol extract of ten medicinal plants from South India against chloroquine (CQ)-sensitive (3D7) and CQ resistant (Dd2) and INDO strain of *Plasmodium falciparum* were conducted by Bagavan *et al.* (2011). They reported that extracts from two of ten medicinal plants showed promising anti-plasmodial activities. Ethyl acetate and methanol extracts from *Phyllanthus emblica* leaf had (IC_{50}) 3D7 of 7.25, and 3.125 µg/mL, respectively, and *Syzygium aromaticum* flower bud had IC_{50} 3D7 of 13 µg/mL and 6.25 µg/mL for ethyl acetate and methanol extract. The other extracts of eight medicinal plants have moderate to low anti-plasmodium activities. On the other hands, Mugangga *et al.* (2010) reported that 5 of 13 medicinal plants used in the treatment of malaria in Rwanda had higher-level activities (IC_{50}<5 µg/mL), ranging from *Zanthoxylum chalybelum, Tithonia diversifolia, Rumex abyssinicus, Fuerstia africana*, and *Microsglossa pyrifolia*.

In vitro assessment for anti-plasmodial activities of two-indole alkaloids, Echitamidine N-dioxide (IC_{50} 63.2 µg/ml) and Nb-demethylalstogustine (IC_{50} 6.75 µg/ml) isolated from bark of Kayu susu (*A. scholaris* L. R.Br) were inactive to promisising level (Salim *et al.*, 2007). Similarly, isolated compounds from Kayu kuning (*N. orientalis* Linn) showed various activities, such as stem had high- moderate activity (He *et al.*, 2005), root had moderate activity (Schicaem *et al.*, 2010), see Table 1. Furthermore, *in vitro* anti-plasmodium activity of protoberberine showed comparable to chloroquine against *P. falcifarum* , but none was active tested *In vivo* against *P. bergei* (Vennerstrom and Klayman (1998). Previous paragraphs indicate that the anti-plasmodium

activity of anti-malarial medicinal plants, whether as single compound or extracts, against malaria parasites are still in clear, mainly the different results among *in vitro* and *in vivo* assessments.

Various reviews on the chemical constituents of antimalarial medicinal plants (Bero *et al.*, 2009; Kaur *et al.*, 200), aditivity and synergism in the anti plasmodial effects of purified compounds from plants extract (Debaro and Ginburg, 2011), whole plant extract versus single compounds (Rosoanaivo *et al.*, 2011), and a reverse pharmacology approaches for developing anti-malarial phytomedicine (Willcox *et al.*, 2011) have been conducted and published. These reviews mainly highlighted that many group of chemical constituents have been reported and isolated recently, and some of those isolated compound have been evaluated for their anti-plasmodium activities. However, there are some disparities or inconsistence results among the antimalarial properties of medicinal plants that have been claimed by local people, tested neither *in vitro* nor *in vivo* assessment. These reviews are also highlighted that anti-plasmodium activities of plant extracts were more active than a single isolated compound against malaria parasites (Rosonaivo et al., 2011). On successful application of standardized anti-malarial medicinal plants in several endemic countries (Willcox *et al.*, 2011), therefore, it is soundly feasible to improve the utilization of anti-malaria medicinal plant into anti-malaria phytomedicine than developing new drugs from these medicinal plants.

Conclusions

Medicinal plants used for treating anti-malarial treatments in Papua are enormous, and the chemical constituents of the most four utilized medicinal plants have been well isolated and reported, and their anti-plasmodium activities against malaria parasites were also well investigated. However, the results indicated that anti-plasmodium activities of most isolated were less than or comparable to chloroquine. With respect to the local capacity and institutional capability in Papua, improving the utilizations of anti-malaria medicinal plants are soundly feasible and workable, than developing new drugs.

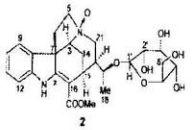
Table

Table 1. Several secondary metabolites isolated from different parts of the most four utilized medicinal plants for anti-malarial phytomedicine in Papua

1. Kayu susu (*A. scholaris* Linn. R.Br.)

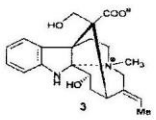
(Indole Alkaloids isolated from barks (Salim *et al.*, 2007)

Akuammiginone



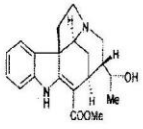
2

Echitamidine-N-okside-

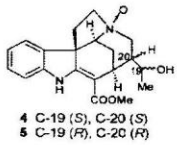


3

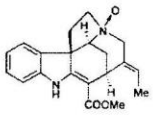
Echitaminic acid



19-O-β-D-glucopyranoside



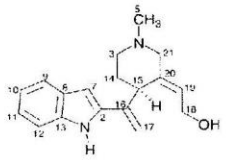
4 C-19 (*S*), C-20 (*S*)
5 C-19 (*R*), C-20 (*R*)



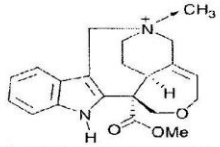
Echitamidine-N-oxide (4) Echitamidine N-dioxide Nb-demethylalstogustine

Nb-demethylalstogustine-N-oxide (5) (IC_{50} 63.2 μg/ml) IC_{50} 6.75 μg/ml)

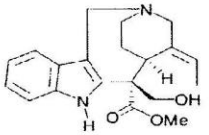
Isolated compounds of leaves from Philippine (Macabeo *et al.*, 2007)



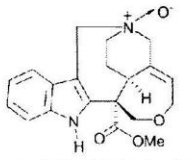
(+)-manilamine (**1**)



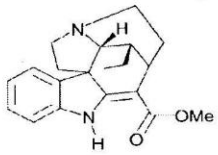
N^4-methyl angusilobine B (**2**)



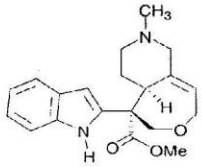
19,20-(*E*)-vallesamine (**3**)



angustilobine B N^4-oxide (**4**)

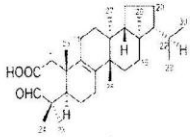


20(*S*)-tubotaiwine (**5**)

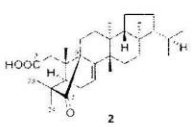


6,7-*seco*-angustilobine (**6**)

Isolated compounds of leaves from Chinese (Wang *et al.*, 2009)



1



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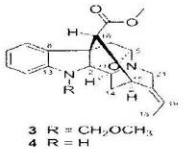


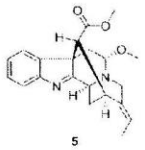
3 R = CH_2OCH_3
4 R = H

Alstonic acid A

Alstonic acid B

N^1-methoymethyl picrinine (3)

Picrinine (4)



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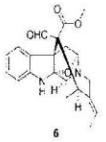

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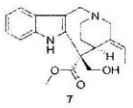

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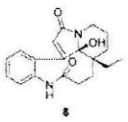

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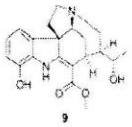

9

5α-methoxystrictamines Picralinal 19.20-(E)-vallesamine Leuconolam Scholaricine

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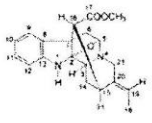
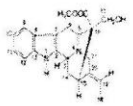
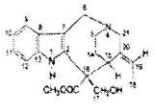
Indole alkaloids of fruits from Thailand (Wongseripipatana *et al.*, 2004)



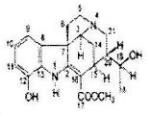
19-*E*-picrinine



19-*E*-akuammidine



19-E-vallesamine



19-scholari...

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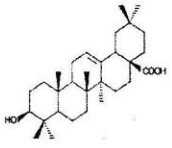
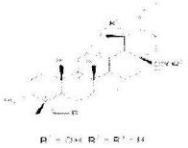
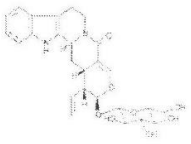
2. Kayu kuning (*Nauclea orientalis* Linn.)

Dried stem of *N. orientalis* Linn. (He et el., 2005)

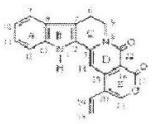
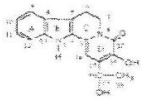
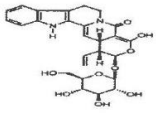
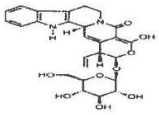
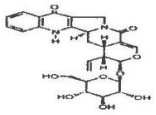




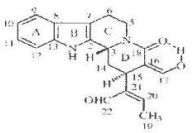
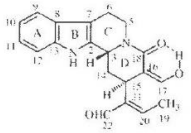
Naucleaorine (IC_{50} 6.9 µg/ml) | Epimmethoxynaucleaorine (IC_{50} 12.4 µg/ml) | Oleanolic acid (IC_{50} 4.9 µg/ml) | 3a.23-dihydroxyurs-12-1n-28-oic acid (IC_{50} 9.7 µg/ml)

Indole alkaloids from the bark (Zhang *et al.*, 2001)

Nauclealines A | Nauclealines B | Naucleosides A | Naucleoside B | Pulmoloside

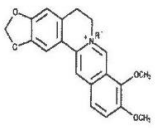
Isomeric indole alkaloids isolated from roots (Shicaem *et al.*, 2010).

Naucleaorals A (IC_{50} >10 µg/ml) | Nauceaorals B (IC_{50} >10 µg/ml)

3. Tali kuning (*Tinospora dissitiflora* Diels).

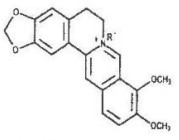
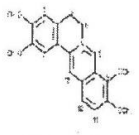
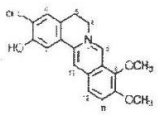
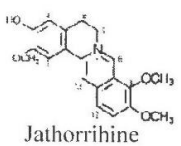
Whole stem (Wahyudi *et al.*, 2012)



Berberin

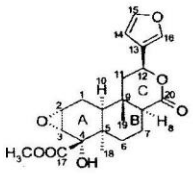
4. Akar kuning (*Arcanglesia falva* Merr.)

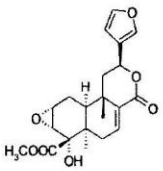
Stem (Subekti et al., 2006)

Berberine | Palmatine | Columbamine | Jathorrihine

Furanoditerpenes from the root (Suzuki *et al*., 2008)





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Question and Answer

Q : How to apply your extract for local people?
A: local people boild the part of the plant then drink the water

Q : the active compound just for preventing or healing too?
A : Based on reference this active compound is preventive and healing too.

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