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Revealing indigenous Indonesian traditional medicine: anti-infective agents

Paul A. Keller

University of Wollongong, keller@uow.edu.au

Ari Satia Nugraha

University of Wollongong, asn559@uow.edu.au

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Abstract

Indonesia is rich in medicinal plants which the population has used traditionally from generation to generation for curing diseases. Our interest in the treatment of infectious diseases has lead to the investigation of traditional Indonesian treatments. In this review, we present a comprehensive review of ethnopharmacologically directed screening in Indonesian medicinal plants to search for new anti-viral, antimalarial, anti-bacterial and anti-fungal agents. Some potent drug leads have been isolated from Indonesian medicinal plants. Further research is still required for the lead development as well as the search for new bioactive compounds from the enormous medicinal plant resources.

Keywords

Revealing, indigenous, Indonesian, traditional, medicine, anti, infective, agents, CMMB

Disciplines

Life Sciences | Physical Sciences and Mathematics | Social and Behavioral Sciences

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Revealing Indigenous Indonesian Traditional Medicine: Anti-infective Agents

Ari S. Nugraha^{a,b,*} and Paul A. Keller^a

^a*School of Chemistry, Faculty of Science, University of Wollongong, Wollongong, New South Wales, Australia 2522*

^b*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Jember, Jember, Indonesia 68212*

asn559@uowmail.edu.au

Indonesia is rich in medicinal plants which the population has used traditionally from generation to generation for curing diseases. Our interest in the treatment of infectious diseases has led to the investigation of traditional Indonesian treatments. In this review, we present a comprehensive review of ethnopharmacologically directed screening in Indonesian medicinal plants to search for new anti-viral, anti-malarial, anti-bacterial and anti-fungal agents. Some potent drug leads have been isolated from Indonesian medicinal plants. Further research is still required for the lead development as well as the search for new bioactive compounds from the enormous medicinal plant resources.

Keywords: Indonesian medicinal plants, anti-viral, anti-malaria, anti-bacteria, anti-fungi.

Indonesia is an archipelago consisting of approximately 17,508 islands and is covered by tropical rain forest, seasonal forest, mountain vegetation, subalpine shrub vegetation, swamp and coastal vegetation. With its reflective mixture of Asian and Australian native species, Indonesia is said to possess the second largest biodiversity in the world, with around 40,000 endemic plant species including 6,000 medicinal plants [1-5].

Medicinal plants have accompanied the development of indigenous Indonesian traditional treatments which is a combination of physical and spiritual aspects to form a holistic medication. This is heavily influenced by the Indian Ayurveda, ever since the early civilization in Indonesia when Hinduism spread from India to Asia [6,7]. Conversely, the incorporation of indigenous medicinal plants not found in India enhanced the development of local Indonesian traditional medication [6] which has been further enriched by influences from Chinese and Arabian traders [8]. The long indigenous history and the variety of geographical conditions have created a variety of unique Indonesian cultures, of which only a few have recorded their traditional medication; these include the indigenous people of Sumatra, Java and Bali [9-13]. Much of this knowledge was not recorded and was verbally passed from generation to generation, which is common in tribes living in remote areas [14]. The knowledge is commonly practiced which leads to most of the population still relying upon medicinal plants [15, 16].

The settlement of Europeans in Indonesia in the early 17th century intervened with the local medication [17]. The lack of knowledge of European physicians of the unique

tropical diseases and the limited western medication forced the Western scientists to explore the Indonesian medicinal plants [17]. They subsequently used and published indigenous Indonesian traditional herbal medicine treatments showing them to be understandable and legitimate [8,17]. Findings were published in notable books, including “De medicina Indorum” by Bontius in 1642 [18], “the Ambonese herbal” by Rumphius in 1741 [19], “Materia Indica” by van der Burg in 1885 [17], “De nuttige planten van Nederlansch Indie” by Heyne in 1927 [20] and “select Indonesian medicinal plants” by Steenis-Kruseman in 1953 [21]. The outcomes were also reported in the Medical Journal of the Dutch East-Indies (1894-1925) [17].

Common infectious diseases occurring in traditional circumstances were able to be correlated with the then modern clinical pathology [19]. This made it easier for investigators, when reading ancient texts and listening to local informers (healers), to re-collect the knowledge through expedition which now helps scientists to perform narrowed pharmacochemical screening in finding new anti-infectious drug leads [22]. Since the 1970’s, with the use of laboratory based experiments and the development of analytical technology, many bioactive compounds from Indonesian medicinal plants have been revealed. These include anti-viral, anti-malarial, anti-bacterial and anti-fungal agents. This review examines these anti-infective natural products and lists plants extracts that require further analysis.

Anti-Viral Agents: Traditional knowledge was clearly unable to describe a viral pathology, however

ethnopharmacological studies show the Indigenous people could diagnose viral infections and could cure them by using specific plant preparations [27]. Common viral infections known in Indonesian traditional circumstances include human herpes and rhino virus [12, 28]. Later diseases such as poliovirus, human immunodeficiency virus, and avian myeloblastosis virus have resulted in extensive screening of Indonesian medicinal plants for activities against these viruses. This section will consider developments in targeting herpes simplex virus (HSV), poliovirus, rhinovirus, human immunodeficiency virus (HIV) and avian myeloblastosis virus-reverse transcriptase (AMV-RT).

Table 1: Extracts of selected Indonesian medicinal plants which have potential anti-HSV-1 and poliovirus activity [33, 34].

Plant	Part of plant	Virus type	
		HSV-1 EC ₅₀ , µg/mL	Poliovirus IC ₅₀ , µg/mL
Guttiferae			
<i>Garcinia griffithii</i> T. A.	-	781	600
<i>Garcinia mangostana</i> L.	LF	40*	
Melastomataceae			
<i>Melastoma malabathricum</i> L.	LF	192	111
Loranthaceae			
<i>Elytranthe globosa</i> B.	LF	336	217
<i>Elytranthe maingayi</i> V.T.	LF	233	41
<i>Elytranthe tubaeflora</i> R.	LF	176	56
<i>Scurrula ferruginea</i> D.	LF	i	62
Meliaceae			
<i>Toona sureni</i> (Bl.) Merr	LF	37*	
Piperaceae			
<i>Piper aduncum</i> L.	FL	344	105
<i>Piper aduncum</i> L.	LF	720	105
Punicaceae			
<i>Punica granatum</i> L.	PR	64*	
Sapindanaceae			
<i>Filicium decipiens</i> T.	SB	68*	
<i>Nephelium lappaceum</i> L.	PR	70*	
Simaroubaceae			
<i>Eurycoma longifolia</i> Jack.	ST	62*	
Verbanaceae			
<i>Vitex pubescens</i> V.	BK	i	i

LF: Leaf; SB: Stem bark; FL: Flower; PR: Pericarp; ST: Stem; HSV-1: Herpes simplex virus type-1; i: inactive. All the samples are methanol extracts. EC₅₀: 50% effective concentration *Expressed as IC₅₀: concentration that inhibits 50%.

Anti-HSV and anti-poliovirus: Selected Indonesian medicinal plant extracts have been tested against HSV-1 and poliovirus (Table 1) [29]. Quassionoid compounds might be responsible for the anti-HSV-1 activity although a drawback to further development is their cytotoxicity [30]. Another study proposed the essential oil and tannin constituents were responsible for the anti-HSV-1 activity [31, 32]. This was based on data suggesting plants that do not contain essential oils or tannins, e.g. *Garcinia* sp, have lower activity against HSV-1 than high essential oil containing plants, e.g. Sapindanaceae plants.

Anti-Rhinovirus: Ginger rhizome is commonly prepared into a traditional hot drink for common cold relief which can be correlated with rhinovirus infection. Many rhino anti-virals from natural products have been found from higher plants including lipophilic flavonoid type molecules (i.e flavan **1** and 4',6-dichloroflavan **2**) [35]. An investigation into the Indonesian ginger rhizome resulted

in the isolation of four lipophilic sesquiterpenes, ar-curcumene **3**, β -sesquiphellandrene **4**, α -zingiberene **5**, β -bisabolene **6** (Figure 1). These compounds possessed rhinovirus IB inhibitor activity at an ED₅₀ of 20.4, 0.9, 1.90, 14.3 µg/10 mL, respectively. The most active is the β -sesquiphellandrene **4** with IC₅₀ of 0.44 µM. A structure analysis would suggest that the sesquiterpene and flavan compounds are equal in size and polarity [36]. However, a minor change in structure results in a significant difference in bioactivity and further studies are therefore required to determine the target of the flavan and the sesquiterpenes molecules.

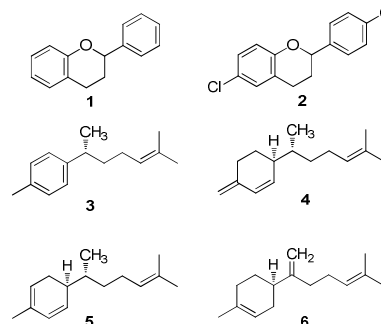


Figure 1: Rhino anti-viral sesquiterpenes (**3-6**) isolated from *Zingiber officinale* [36].

Anti-HIV agents: Although HIV is an imported disease to Indonesia, it is highly prevalent. While there are no specific traditional medicines to treat HIV, traditional anti-viral concoctions may lead to new potential anti-HIV leads. Therefore at least twenty one Indonesian medicinal plants were screened against HIV-1 protease and HIV-1 replication (Table 2) [37-39].

The methanol extracts of some medicinal plants are more active against HIV-1 protease while the more polar water extracts are more active against HIV-1 replication. There are four methanol extracts of *Terminalia belerica* Roxb, *Swietenia mahagoni* L., *Woodfordia floribunda* Salisb. and *Garcinia mangostana* L. which may contain potential anti-HIV-1 protease inhibitors with IC₅₀ values of 50, 40, 40, 50 µg/mL, respectively [37]. However, there was no further exploration of these plants except *Garcinia mangostana* L. This study isolated mangostin **7** and γ -mangostin **8** (Figure 2) which showed non-competitive inhibition against HIV-1 protease with IC₅₀ values of 5.12 and 4.81 mM, respectively [40].

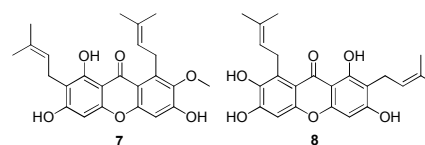


Figure 2: Mangostins isolated from *Garcinia mangostana* [40].

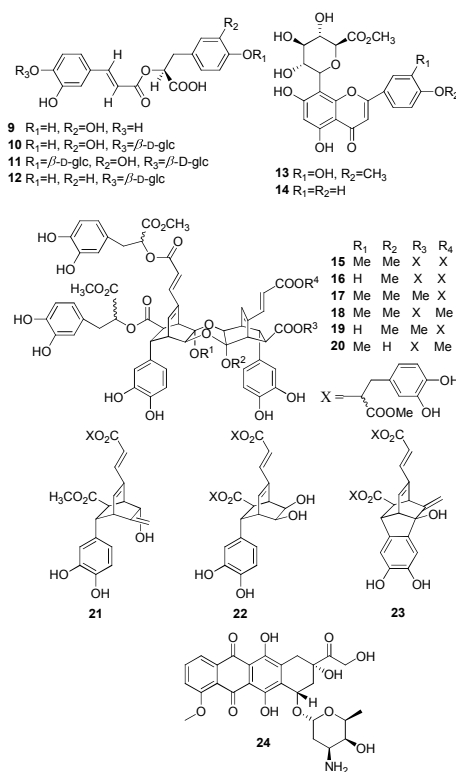
Table 2: Extracts of selected Indonesian medicinal plants which show anti-HIV-1 protease and replicase activity [37, 38].

Plant	Part of plant	HIV-1 protease IC ₅₀ , µg/mL		HIV-1 rep. IC ₅₀ , µg/mL
		MeOH ext.	H ₂ O ext.	
Acanthaceae				
<i>Andrographis paniculata</i> Nees.	LF	500	500	≥170*
Apiaceae				
<i>Foeniculum vulgare</i> Mill	SD	100	>500	
Apocynaceae				
<i>Parameria laevigata</i> Moldenke.	BK	100	>500	
Clusiaceae				
<i>Garcinia mangostana</i> L.	PL	50	100	
Combretaceae				
<i>Terminalia bellerica</i> Roxb.	FR	50	220	
Compositae				
<i>Elephantopus scaber</i> L.	WP	500	>500	
Elaeocarpaceae				
<i>Elaeocarpus grandiflorus</i> Smith	FL	100	100	
Fabaceae				
<i>Caesalpinia sappan</i> L.	BK	280	320	
<i>Sindora sumatrana</i> Miq.	FR	260	360	≥134*
Hypoxidaceae				
<i>Curculigo orchidioides</i> Gaertn.	FR	400	400	
Lauraceae				
<i>Cinnamomum sintok</i> Bl.	BK	220	320	
Loganiaceae				
<i>Strychnos nux-vomica</i> L.	BK	500	>500	
Loranthaceae				
<i>Loranthus parasiticus</i> (L.) Merr	ST	100	260	≥79.4*
Lythraceae				
<i>Woodfordia floribunda</i> Salisb.	FL	50	50	
Malvaceae				
<i>Helicteres isora</i> L.	FL	380	>500	≥65*
Meliaceae				
<i>Swietenia mahagoni</i> L.	BK	40	100	≥28.4**
Parmeliaceae				
<i>Usnea misaminensis</i> Vain.	WP	220	>500	
Poaceae				
<i>Andropogon zizanioides</i> (L.) Urban	RT	500	>500	
Solanaceae				
<i>Physalis angulata</i> L.	AP	340	>500	
Zingiberaceae				
<i>Curcuma aeruginosa</i> Roxb.	RZ	500	>500	≥323*
<i>Curcuma xanthorrhiza</i> Roxb.	RZ	300	>500	

RT:Root; SD:Seed; FL:Flower; LF: Leaf; AP:Aerial part; BK: Bark; WP:Whole plant; ST: Stem; HSV-1: Herpes simplex virus type 1. * H₂O extract. ** MeOH extract. IC₅₀: concentration that inhibits 50%

Anti-AMV-RT: The fruit of the Indonesian medicinal plant *Helicteres isora* L., was screened for potential anti-AMV-RT activity. From these four secondary metabolites were reported: rosmarinic acid **9**, 4'-O-D-glucopyranosil rosmarinic acid **10**, 4,4'-O-di-β-D-glucopyranosyl rosmarinic acid **11** and 4'-O-D-glucopyranosil isorinic acid **12**, which exhibited xanthine oxidase inhibition [41]. Additional work revealed the flavonoid glucuronides, 3',5,7,8-tetrahydroxy-4'-methoxyflavone 8-O-β-D-glucopyranosiduronic acid methyl ester **13**, 4',5,7,8-tetrahydroxyflavone 8-O-β-D-glucopyranosiduronic acid methyl ester **14** and the first neolignans, helicterins A-F (**15-20**), helisterculin A **21**, helisterculin B **22** and helisorin **23**, isolated from *Helicteres isora* L obtained from Indonesia (Figure 3) [42-43].

The helicterins were tested against avian myeloblastosis virus-reverse transcriptase (AMV-RT) and presented weak

**Figure 3:** Glycosidic and non glycosidic metabolites isolated from *Helicteres isora* [41-43].**Table 3:** Bioactivity of helicterins A-F **15-20**, helisterculin A **21**, helisterculin B **22**, helisorin **23** and adriamycin **24** against AMV-RT [42,43].

Compounds	AMV-RT, IC ₅₀ µM
15	66
16	172
17	417
18	372
19	120
20	226
21	1600
22	1000
23	460
24	66

activity (Table 3). However, compared to the standard drug for AMV infection, adriamycin **24**, and helicterins A **15** possessed equal activity [43]. There is no specific information regarding the mechanism of inhibition of this compound.

**Figure 4:** Map of Indonesia [46]. * The sites of ethnopharmacological field trips in endemic malaria regions in some islands. Each region is discussed separately in the following sections.

Anti-malarial agents: Ethnopharmacological studies revealed particular medicinal plants were used for malarial

fever therapy in some regions (Figure 4). Further experiments produced extracts responsible for the claimed activity (Table 4) with only a small number investigated further to reveal individual compounds [44-45].

Table 4: Anti-malarial activity of extracts of some Indonesian medicinal plants [44-45].

Plants	Part of plant	Inhibition rates against <i>Plasmodium falciparum</i> , %
Apocynaceae		
<i>Catharanthus roseus</i> L.	AP	52
<i>Rauwolfia serpentina</i> (L.) Benth.	BK	66
Asteraceae		
<i>Achillea millefolium</i> L.	WP	98
<i>Ageratum conyzoides</i> L.	WP	62
Euphorbiaceae		
<i>Phyllanthus niruri</i> L.	WP	50*
Loganiaceae		
<i>Strychnos lucida</i> R.Br.	WD	100
Meliaceae		
<i>Azadirachta indica</i> Juss	LF	60
<i>Lansium domesticum</i> Corr.	BK	66
<i>Swietenia macrophylla</i> King.	SD	98
Myrtaceae		
<i>Baeckea frutescens</i> L.	LF	90
Rubiaceae		
<i>Morinda citrifolia</i> L.	FR	56
Zingiberaceae		
<i>Curcuma xanthorrhiza</i> Roxb.	RZ	100

AP: Aerial part; BK: Bark; WP: Whole plant; WD: Wood; LF: leaf; SD: Seed; FR: Fruit; RZ: Rhizome. All materials were prepared as a water extract. Concentration for assay, 1 mg/mL. *50% of inhibition at 3.5 µg/mL.

Sumatra Island: An expedition in Sumatra Island revealed *Anthocephalus chinensis*, *Beilschmiedia madang* BL. and *Brucea javanica* L. Merr to be used in malarial therapy [3].

Anthocephalus chinensis (Rubiaceae). The people in Indragiri Hulu area, Riau Province have used the bark, root and leaf of *Anthocephalus chinensis* in malaria therapy. Fourteen compounds were successfully isolated including glycosides, 3'-*O*-caffeoylsveroside **25**, sweroside **26**, loganic acid **27**, loganin **28**, loganol **29**, kelampayoside A (derived from "kelampayan", the local species' name) **30**, 8-epikingiside **31**, kelampayoside B **32** (Figure 5), and alkaloids vallesiachotamine **33**, isovallesiachotamine **34**, cadambine **35**, strictosidine lactam **36**, desoxycordifoline **37**, 5 α -carboxystrictosidine **38** (Figure 6) [47]. Compounds **26-29**, **31**, **33-37** were previously identified from various Rubiaceae species of different origins [48-52].

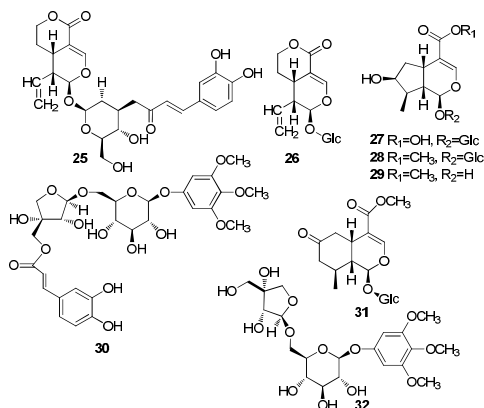


Figure 5: Glycosides isolated from the bark of *Anthocephalus chinensis* [47].

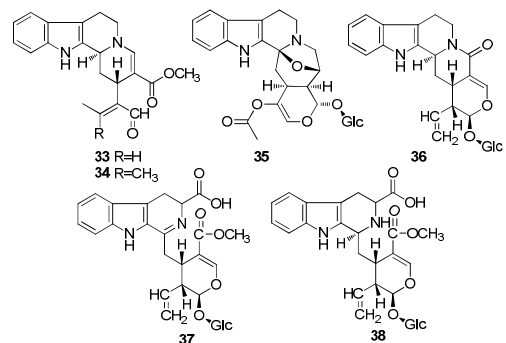


Figure 6: Alkaloids isolated from the bark of *Anthocephalus chinensis* [47].

Among the fourteen compounds (Figures 5 and 6), only eight were subjected to *in vitro* testing against the *Plasmodium falciparum* K1 strain. The results indicated no anti-malarial activity except the indole type compound cadambine **35**, which showed a moderate inhibitory activity at IC₅₀ of 6.77 µM and IC₉₀ 9.85 µM [47].

Beilschmiedia madang BL. (Lauraceae). The decocted wood of *B. madang* (locally called as 'medang kohat') has been used by people in Kepahiang to treat malaria fever [53]. From this was isolated dehatrine **39** (Figure 7) which was found to have anti-malarial activity with an IC₅₀ of 0.17 µM against the *Plasmodium falciparum* K1 strain, a chloroquine resistant strain [53].

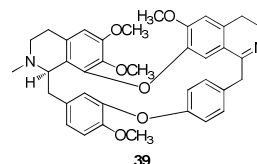


Figure 7: Molecular structure of dehatrine [53].

Brucea javanica L. Merr. (Simaroubaceae). This species was found through an expedition to Rejang Lebong where the plant has been traditionally used to treat malaria. The same species is used by the Bugisse, 'people of Makassar' for the same purpose. Successfully identified were eleven triterpenoids including, bruceajavanin A **40**, dihydrobruceajavanin A **41**, bruceajavanin B **42**, bruceantanol **43**, bruceantanol B **44**, bruceine A **45**, bruceine B **46**, bruceine C **47**, bruceine D **48**, bruceine J **49**, yandaziolide A **50** [54] and five alkaloids including 11-hydroxy-canthine-6-one **51**, 11-hydroxy-1-methoxy-canthine-6-one **52**, canthine-6-one **53**, canthine-6-one-3-*N*-oxide **54** and bruceacanthinoside **55** (Figure 8) [55], of which the last four compounds **51-54** were previously reported from non-Indonesian Simaroubaceae medicinal plants [56-58].

Compounds **40** and **42** possessed moderate anti-malarial activity, e.g. IC₅₀ 1.1 µM and 4.4 µM against the *Plasmodium falciparum* K1 strain, respectively [55]. On the other hand, compound **43** presented only modest anti-malarial activity (IC₅₀, 25 µM) [55]. Some of the

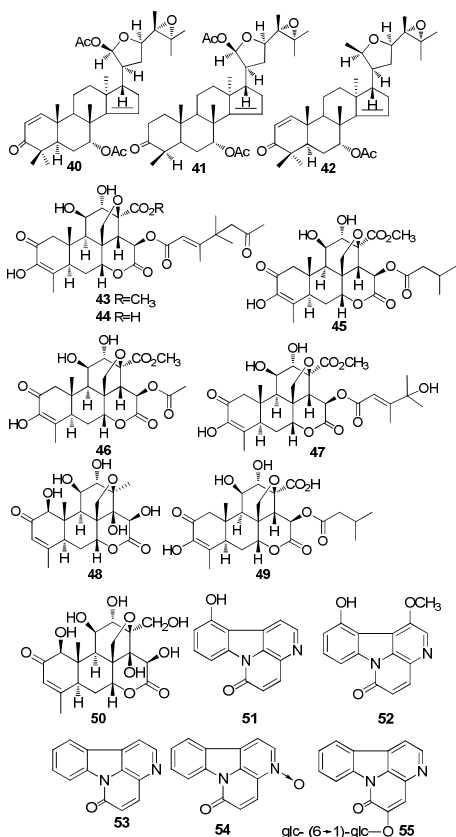


Figure 8: Metabolites isolated from *Brucea javanica* [55].

compounds were also tested against *Babesia gibsoni* parasite of dogs which brucein A **45**, bruceinthinol **43** and B **44** possessed potent activities with IC_{50} values of 4, 12 and 12 ng/mL, respectively [54].

Java and Lombok Islands: The Javanese and Lomboknese native people have been infected with malarial fever for centuries. However, they survive by consuming young leaves of *Alstonia scholaris* [59]. Investigation on samples taken from Java and Lombok Island, isolated 21 alkaloids, including, picraline **56**, N_1 -methylburnamine **57**, akuammidina **58**, φ -akuammigine **59**, akuammiline **60**, akuammiline N_4 -oxide **61**, deacetyluammiline **62**, 5 α -methoxy-akuammiline **63**, tubotaiwinine **64**, tubotaiwinine N_4 -oxide **65**, scholaricine **66**, N_4 -methylscholaricine **67**, vallesamine **68**, alstonamine **69**, 6,7-*seco*-alstonamine **70**, 6,7-*seco*-19,20 α -epoxyalstonamine **71**, leuconolam **72**, mataranine A **73**, mataranine B **74**, kotarajine **75** and (15*S*, 16*S*)-losbamine **76** (Figure 9) [59, 60]. Tubotaiwine **64** and mataranine A **73** and B were claimed to be responsible for the anti-malarial activity (Table 5) [60, 61].

Flores Island: An ethnopharmacological expedition reported that the people of Flores Island have used *Fagara rhetza* (Roxb.) DC, locally named as Haleza, to treat malarial fever. Eleven compounds were isolated in this study. The bark contains rutaecarpine **77**, evodiamine **78**, skimmianine **79**, zanthobungeanine **80**, *O*-geranyl sinapyl

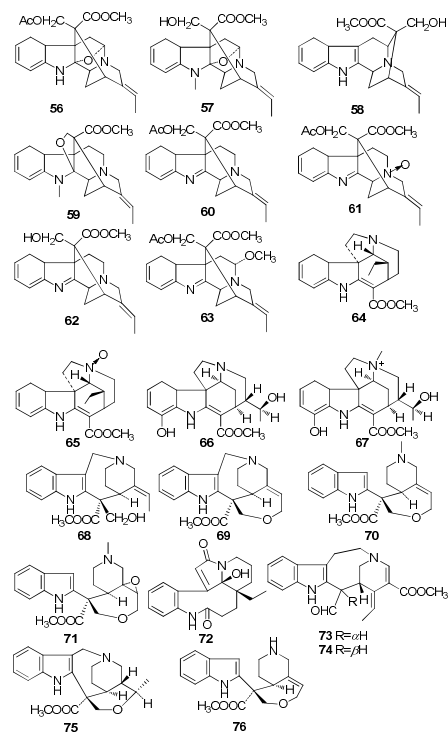


Figure 9 : Alkaloids isolated from *Alstonia scholaris* [59, 60].

Table 5: Anti-malarial activity of several alkaloids isolated from *Alstonia scholaris* [60,61].

Alkaloids	EC_{50} , μ M
60	18
62	36
63	7
64	^a
69	24
70	17
73	7.4 ^b
74	9.7 ^c

^aNo potency. ^bBioactivity against *Plasmodium falciparum* K1 (an antifolate resistant parasite strain). ^cAgainst *Plasmodium falciparum* TM4 (an anti-folate sensitive parasite strain)

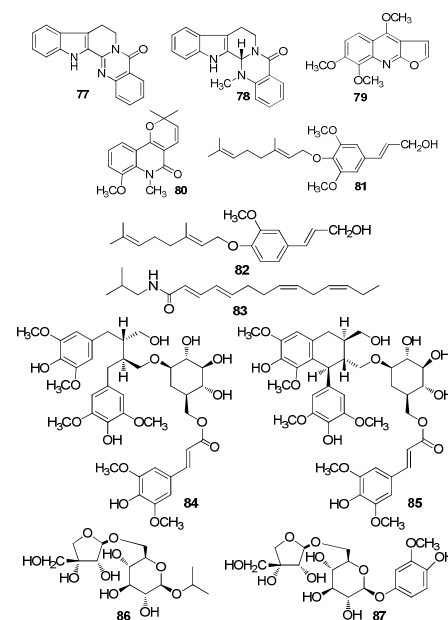


Figure 10: Metabolites isolated from *Fagara rhetza* [62-67].

alcohol **81**, *O*-geranylconiferyl alcohol **82**, hazaleamide **83**, hazaleanin A **84**, hazaleanin B **85**, isopropyl apioglucoiside **86** and 4-hydroxyguaiacol apioglucoiside **87**, of which compounds **77-80** were previously identified from other plants however no bioactivity data was reported (Figure 10) [62-67]. In this study, only hazaleamide **83** showed a moderate activity against *Plasmodium falciparum* with an IC₅₀ value of 43 μM [62-67].

Kalimantan (Borneo) Island: Malarial fever is a long lasting health problem of Dayak tribes that inhabit the isolated rainforests of Kalimantan Island. An expedition found two plants species, *Eurycoma longifolia* Jack. and *Lansium domesticum* Corr. Ser. have been intensively used for malarial fever treatment [68-69].

Eurycoma longifolia Jack. (Simaroubaceae). This plant is locally called “pasak bumi” by people of Borneo Island where it has been used to treat malaria, dysentery, glandular swelling and persisten fever [68]. Eleven molecules, 9-methoxycanthin-6-one **88**, 9-hydroxycanthin-6-one **89**, 9-methoxycanthin-6-one-*N*-oxide **90**, 9-hydroxycanthin-6-one-*N*-oxide **91**, β-carboline-1-propionic acid **92**, 7-methoxy-β-carboline-1-propionic acid **93**, eurycomanone **94**, 13,21-dihydroeurycomanone **95**, 13β,21-dihydroeurycomanone **96**, eurycomanol **97** and longilactone **98**, were isolated of which only the compounds **93** and **94** were shown to have weak anti plasmodium activity [68].

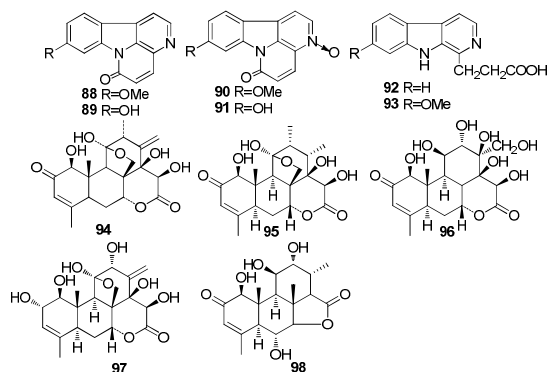


Figure 11: Alkaloids and terpenes isolated from *Eurycoma longifolia* [68].

Lansium domesticum Corr. Ser. (Meliaceae). Isolation revealed five compounds, 3-keto-22-hydroxynoceradiene **99**, onoceradienedione **100**, methyl lansiolate **101**, methyl lansiolate A **102** and methyl 15-acetoxylansiolate **103** (Figure 12) [69]. The anti-malarial activity of the isolates were tested against *Plasmodium berghei* (Table 6).

Table 6: Anti malarial activity of isolates from *Lansium domesticum* Corr. Ser [69].

Quassinoids	IC ₅₀ , μM
99	2.41
100	1.66
101	0.65
102	0.69
103	0.17

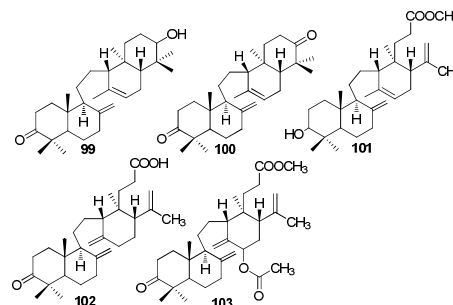


Figure 12: Anti-malarial agents isolated from *Lansium domesticum* [69].

The most active compound isolated was the methyl ester 15-acetoxylansiolate **103**. This *in vitro* test result agreed with the *in vivo* test by using infected *Plasmodium berghei* mice where **103** possessed 44% parasitemia inhibition at 50 mg/kg daily doses [69].

Sulawesi Island: There are two traditionally prepared medicines for malarial therapy; the seed kernel of *Caesalpinia crista* species (called ‘Bakor’) and decocted root bark and stem of *Quassia indica* (Gaertn.) Nooteboom, named ‘Tobello’ by central Sulawesi people.

Caesalpinia crista (Fabaceae). From this species were isolated at least 24 cassane and norcassane type compounds. The quassinoids are caesalpinins C-P **104-117**, norcaesalpinins A-F **118-123**, caesalmin B **124**, E **125** and G **126**, caesalpin F **127**, 14(17)-dehydrocaesalpin F **128**, caesaldekarin E **129**, 2-acetoxy-3-deacetoxycaesaldekarin E **130**, 1-deacetoxy-1-oxocaesalmin C **131**, 3-deacetoxy-6-acetoxycaesaldekarin E **132**, 2-acetoxycaesaldekarin E **133**, bonducellpins A-C **134-136** and 7-acetoxybonducellpin C **137** (Figure 13) [70-73].

The preliminary anti-malarial testing in mice infected with chloroquinene-resistant *Plasmodium berghei*, showed that norcaesalpinin A **118** suppressed the parasitemia by 48.0, 40.9 and 33.0% at doses of 10, 1 and 0.1 mg/kg, respectively [70].

Most of the isolates were also tested against *Plasmodium falciparum* culture (see Table 7) with **122** as the most active quassinoid with an IC₅₀ value of 0.09 μM [74].

A QSAR study on the cassane and norcassane-type diterpenes observed that the presence of an acetoxy group resulted in a higher anti-malarial activity than when a hydroxyl substituent was present. On the other hand, any additional functional group on the C-ring in 17-norcassane-type diterpenes reduced the activity [74].

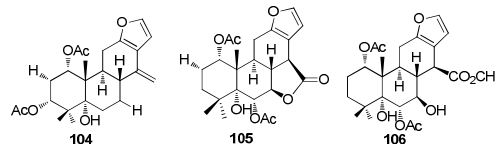


Figure 13: Quassinoids isolated from *Caesalpinia crista* [70-73].

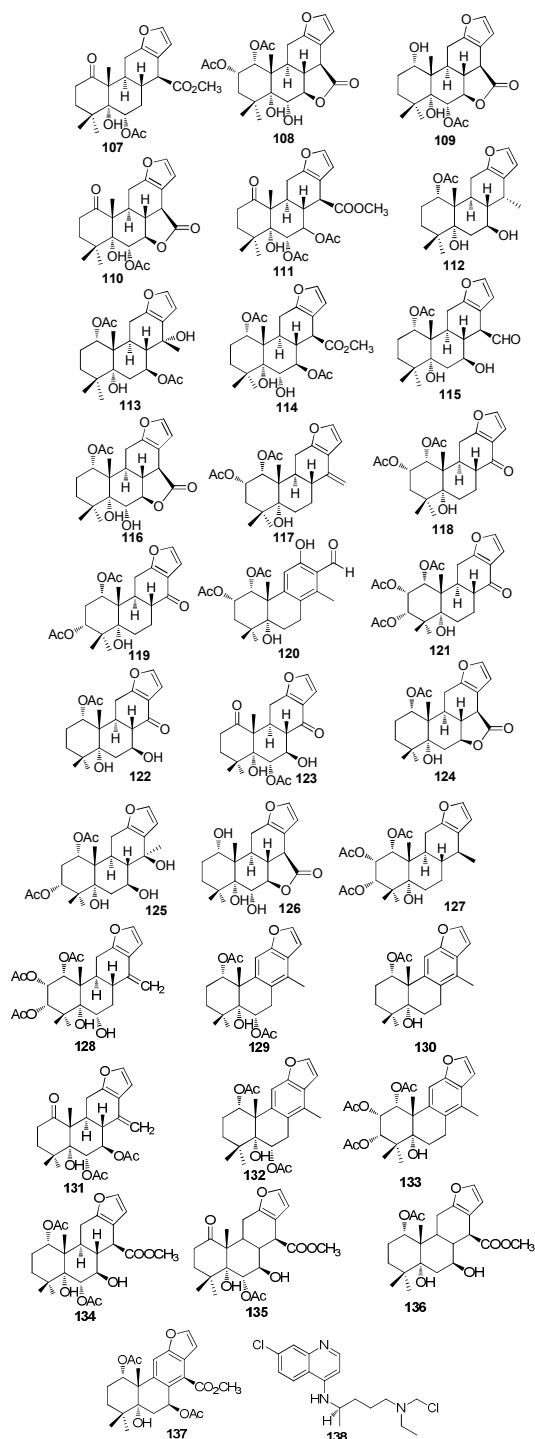


Figure 13 (continued): Quassinoids isolated from *Caesalpinia crista* [70-73].

Quassia indica (Gaertn.) Nooteboom. (Simaroubaceae). The chemical screening of the species isolated eight quassinoids, samaderine B-C, E, X-Z, **139-144**, indaquassin C, X **145-146**, samarinolide **147** and 2-*O*-glucosylsamaderine C **148** (Figure 14). Compounds **139-141**, **145**, **147** were previously isolated from other simaroubaceous [76]. Four of the isolates were tested for anti-malarial activity against *Plasmodium falciparum* K1 (Table 8) which showed that samaderine **142** was the most active compound [76].

Table 7: Isolated quassinoids activity against *Plasmodium falciparum* [73, 74].

Quassinoids	IC ₅₀ μM	Quassinoids	IC ₅₀ μM
104	0.76	121	2.0
105	0.80	122	0.09
106	6.50	123	0.14
107	0.65	124	0.80
109	>10	125	>10
110	>10	126	>10
111	1.00	128	0.20
112	0.4	129	4.0
113	0.65	130	0.098
114	>10	131	2.9
115	0.12	133	6.5
116	>10	135	0.24
117	1.7	136	0.12
118	0.80	137	0.60
119	0.26	138*	0.29
120	5.0		

* Chloroquine **138**, positive control, was discovered in 1934 and it has been used as anti-malarial agent which also shows anti-viral effects [75].

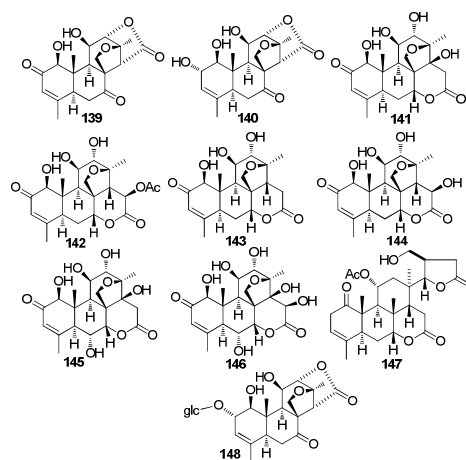


Figure 14 : Quassinoids isolated from *Quassia indica* [76].

Table 8: Anti-malarial activity of isolates from *Quassia indica* (Gaertn.) Nooteboom [76].

Quassinoids	IC ₅₀ , nM
139	210
141	56
142	14
144	71

Anti-bacterial agents: Indigenous Indonesian people has treated diarrhea, swelling, redness and fever with medicinal plant preparations [11,77] in which these symptoms have modern clinical correlation with bacteria causing diseases. Most of the anti-bacterial outcomes were preliminary studies of extracts (see Table 9), which only gave indications of activity. Several extracts such as those from *Terminalia catappa*, *Swietenia mahagoni* Jacq., *Phyllanthus acuminatus*, *Ipomoea spp.*, *Tylopora asmathica* and *Hyptis brevipes* possessed high activity which might provide a stimulus for further research [78]. Additional work was performed on a few species resulting in the following:

Clerodendron calamisotum L. and *Clerodendron paniculatum* L. (Verbenaceae): At least five alkaloids were present in *Clerodendron calamisotum* L. and *Clerodendron paniculatum* L. however the alkaloids were not responsible for the anti-bacterial activity [61].

Table 9: Anti-bacterial activities of extracts of Indonesian medicinal plants [24, 78].

Plant	Part of plant	Anti-microbial activities**					
		BS	SA	EC	SC	FO	XC
Acanthaceae							
<i>Gendarusa vulgaris</i> Nees	LF, RT, ST		+				
<i>Graptophyllum pictum</i> (L.) Griff.*							DG
<i>Staurogyne sp</i>	LF, RT, ST		+		+	+	
Amaranthaceae							
<i>Celosia argentea</i> L. fma	FR, LF, ST		++	+		+	
<i>Celosia plumose</i> (Voss) Back	FR, LF, ST		++	+		+	
Amaryllidaceae							
<i>Crinum asiaticum</i>	LF		++	+	+		
<i>Crinum lineare</i> L.	LF				++		
<i>Curculigo sp.</i>	LF, RT, ST		++	+			
Anarcadiaceae							
<i>Mangifera foetida</i> Lour.	LF		+				
<i>Mangifera indica</i> L.	BK		++				
Apocynaceae							
<i>Alstonia scholaris</i> (L) R. Br.	LF, ST		++				
<i>Cantharanthus roseus</i> (L.) G. Don*			+				
Araceae							
<i>Acorus calamis</i> L.	LF, RT,RZ		+	+			
Araliaceae							
<i>Aralidium pinnatifidum</i> Miq.	LF		++	+			
Balsaminaceae							
<i>Impatiens balsamina</i> L.	LF, ST		+				
Begoniaceae							
<i>Begonia isopera</i> Bl.	LF, ST		+		+	+	
Bombacaceae							
<i>Ceiba petandra</i> (L.) Gaertn.	LF, ST		++				
Bromeliaceae							
<i>Ananas comosus</i> (L.) Merr.	LF		+	+		+	
Capparaceae							
<i>Crateva religiosa</i> Forst.	LF, ST		+	+			
Clusiaceae							
<i>Cratoxylon formosum</i> (Jack) Griff.	BK		+				
<i>Garcinia atroviridis</i> Griff.	LF, ST		++	+			
<i>Garcinia mangostana</i> L.	BK		+				
<i>Garcinia parvifolia</i> Miq.	LF, ST		++	+			
Compositae							
<i>Blumea balsamifera</i> DC.	LF, RT, ST		+	+		+	
<i>Plucea indica</i> (L.) Less.	LF, ST		++	+		+	
Connaraceae							
<i>Rourea mimosoides</i> (Vahl)	LF, ST		+	+			
Convolvaceae							
<i>Ipomoea batatas</i> (L.) Lamk.	LF, ST		+				
<i>Merremia umbellata</i> (L.) Hall.	LF, ST		+				
Cyperaceae							
<i>Scleria purpurascens</i> Steud.	LF, ST		+				
Dilleniaceae							
<i>Dillenia meliosmifolia</i> Hook.	LF		+				
<i>Tetracaria asiatica</i> (Lour.)	LF		+		+		
<i>Tetracera sp.</i>	LF		+				
Ebenaceae							
<i>Diospyros sp.</i>	LF, ST		++	+			
Euphorbiaceae							
<i>Breynia racemosa</i> M.	LF, ST		+				
<i>Croton cf. caudatus</i> Geisel.	LF, ST, BK		++				
<i>Galearia filiformis</i> Boerl.	LF				+		
<i>Galearia sp.</i>	LF, ST		++	+	+	+	
<i>Jatropha curcas</i> L.	LF				+		
Euphorbiaceae							
<i>Macaranga gigantea</i> M.	LF		++	+			
<i>Macaranga gigantea</i> M.	BK		+	+	+		
<i>Macaranga triloba</i> M.	LF		+	+		+	
<i>Mallotus ricinoides</i> M.	LF		+				
Euphorbiaceae							
<i>Phyllanthus emblica</i> L.	LF, ST		+	+			
<i>Pimelioidendron papaveroides</i>	LF, ST		+	+			

Table 9 (continued): Anti-bacterial activities of extracts of Indonesian medicinal plants [24, 78].

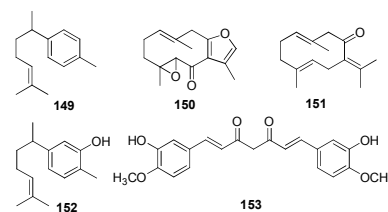
Plant	Part of plant	Anti-microbial activities**					
		BS	SA	EC	SC	FO	XC
Gnetaceae							
<i>Gnetum latifolium</i> Bl.	LF, ST		+				+
Hanguanaceae							
<i>Hanguana malayana</i> (Jack) Merr.	LF, ST		++				
Labiatae							
<i>Coleus scutellarioides</i> (L.) Bth.	LF, ST		++				+
<i>Hyptis brevipes</i> *			+++	+			+
<i>Ocimum basilicum</i> L.	FL, LF, ST		+	+			
<i>Ocimum tenuiflorum</i> L.	FL, LF, ST		+	+			
<i>Orthosiphon aristatus</i> (Bl.) Miq.	LF, ST		+				
Lauraceae							
<i>Litsea elliptica</i> Bl.	LF		+				
<i>Litsea robusta</i> Bl.	LF		++				
Lecythidaceae							
<i>Barringtonia lanceolata</i> (Bl.)	LF		++				
<i>Barringtonia sp.</i>	BK		++				
Leguminosae							
<i>Bauhinia sp</i>	LF, ST						+
<i>Crotalaria juncea</i> L.*		DG					
<i>Cassia cf. nodosa</i> Buch. Ham.	BK		++	++			+
<i>Flemingia strobilifera</i> (R.Br.)	FR, LF, ST		+				
<i>Mimosa pigra</i> L.	LF, ST		+				
<i>Sesbania aculeate</i> Poir.	LF, RT, ST		++				
<i>Tamarindus indica</i> L.	LF, ST		++	++			
Longaniaceae							
<i>Fagraea cf. auriculata</i> Jack	LF		+	+	+		
Lythraceae							
<i>Lagerstromia speciosa</i> (L.)	LF, ST		++	++			
Malvaceae							
<i>Abelmoschus ficulneus</i> W. et H.	LF, ST		++			++	
<i>Abelmoschus moschatus</i> Medik.	LF, ST		+				
<i>Gossypium barbadense</i> L. var.	LF, ST		++				
<i>Hibiscus x archeri</i> Wats.	LF, ST		++				
<i>Hibiscus sabdariffa</i> L.	LF, ST		++				
<i>Hibiscus tiliaceus</i> L.	BK		++				
	LF, ST		+				
Melastomataceae							
<i>Dissochaeta gracilis</i> (jack) Bl.	LF, ST		+				+
<i>Melastoma affine</i> D.Don	LF, ST		++	+	+		
<i>Melastoma malabathricum</i> L.	FL,ST,LF		++	+	+	+	
<i>Phyllagathis rotundifolia</i> (Jack) Bl.	LF, ST		+	+	+		
Meliaceae							
<i>Aglaiia eximia</i> Miq.	BK		+	+			+
<i>Swietenia mahagoni</i> Jcq.*			+	++	DG		+
			+				+
<i>Swietenia mahagoni</i> L. *	PC		+	+			
Menispermaceae							
<i>Arcangelisia flava</i> (L.) Merr.	LF, RT, ST		++		++		+
<i>Tinomisium petiolare</i> Hook. F. et Thoms.	BK		+				
Moraceae							
<i>Artocarpus elasticus</i> Reinw. Ex Bel.	BK		++				+
<i>Artocarpus nitidus</i> Trec.	BK				+		+
<i>Ficus grossularioides</i> Burm. f.	LF, ST		+	+			
<i>Ficus macrocarpa</i> Kurz	LF, ST		++	+			
<i>Ficus pandana</i> Burm. f.	LF, ST		++	+			
Myristicaceae							
<i>Horsfieldia glabra</i> (Bl.) Warb.	BK		+				
<i>Horsfieldia wallichii</i> (Hook. F. et Thunb.) Warb.	BK		++				
Myrtaceae							
<i>Eugenia polyantha</i> Wight	LF, ST		+				+

Table 9 (continued): Anti-bacterial activities of extracts of Indonesian medicinal plants [24, 78].

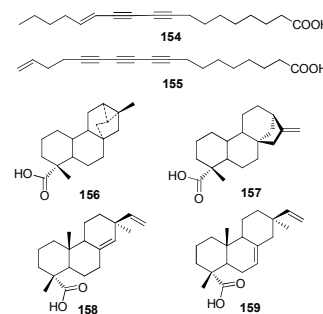
Plant	Part of plant	Anti-microbial activities**					
		BS	SA	EC	SC	FO	XC
Myrtaceae							
<i>Psidium guajava</i> L.	LF, ST		++	+			
<i>Rhodmania cinerea</i> Jack	LF, ST		++	+			
Pandanaceae							
<i>Pandanus</i> sp.	LF		+				
Passifloraceae							
<i>Adenia cordifolia</i> ENgl.	LF, ST		++	+			
Rhamnaceae							
<i>Gouania lepostachya</i> DC.	LF, ST		++		+	+	
Rhizophoraceae							
<i>Anisophyllea disticha</i> (Jack) Baill.	LF, ST		+		+		
Rubiaceae							
<i>Hedyotis capitellata</i> Wall.	LF, ST		+				
<i>Hedyotis leucocarpa</i> Elm.	LF, ST		+				
<i>Mussaenda frondosa</i> L.	LF, ST		+				
<i>Uncaria gambir</i> (Hunt.) Roxb.	LF, ST		++			+	
Rutaceae							
<i>Citrus aurantifolia</i> Swingle	FR		++	++			
Simaroubaceae							
<i>Brucea javanica</i> (L.) Merr.	LF, ST		++		+		
Staphyleaceae							
<i>Turpinia sphaerocarpa</i> Hassk.	LF, ST		++	++			
Symplocaceae							
<i>Symplocos cochinchinensis</i> (Lour.) Moore	LF, ST		+	+	++	+	
Theaceae							
<i>Eurya acuminata</i> DC.	LF, ST		+				
Thymelaeaceae							
<i>Aquilaria malaccensis</i> Lamk.	LF, ST		+				
Tiliaceae							
<i>Elaeocarpus cf. mastersii</i> King	LF, ST, BK		++	++			
<i>Grewia acuminata</i> Juss.	BK		++			+	
Ulmaceae							
<i>Trema tomentose</i> (Roxb.) Hara	LF, ST		+				
Urticaceae							
<i>Dendrocnide stimulans</i> (L.f.) Chew	RT		++				
Violaceae							
<i>Rinorea anguifera</i> (lour.) O.K.	BK		+	+			
Zingiberaceae							
<i>Boesenbergia rotunda</i> (L.) Mansf.	LF, RZ, ST		+				
<i>Costus</i> sp.	LF, ST		+				
<i>Curcuma cf. heyneana</i> Val. Et v. Zijp	RZ					+	
<i>Curcuma</i> sp.	RZ		+		+		
<i>Zingiber purpureum</i> Roxb.	RZ		+		+		

LF: Leaf, ST: Stem, BK: Bark, PC: Pericarp, RZ: Rhizome, BS: *Bacillus subtilis*, SA: *Staphylococcus aureus*, EC: *Escherichia coli*, SC: *Saccharomyces cerevisiae*, FO: *Fusarium oxysporum*, XC: *Xanthomonas campestris*. All samples are methanol extracts except indicated by * extract of DCM. ** + is 25% or less than control; ++, equal to the control; +++, 25-50% more than the control; +++++, 50% and more than the control

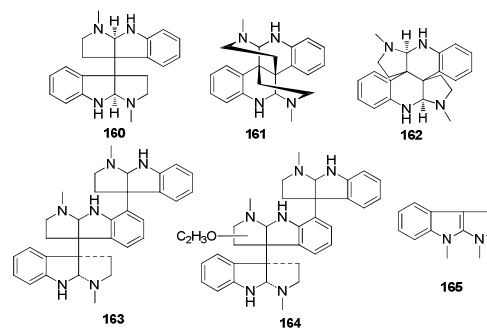
Curcuma xanthorrhiza Roxb.: The species sample collected from Yogyakarta contains sesquiterpenes, α -curcumene **149**, germacrone **150**, zederone **151**, xanthorrhizol **152** and curcumin **153** (Figure 15). The crude extracts possessed moderate antibacterial activity (MRSA) while the isolated curcumene showed less activity [79]. The extract has potential against *Staphylococcus* mutants for dental caries prevention [80].

**Figure 15:** Sesquiterpenes isolated from *Curcuma xanthorrhiza* [79].

Mitrephora celebica (Annonaceae): Two oropheic acid and four diterpenes were isolated from the bark of the species, oropheic acid **154**, 13,14-dihydrooropheic acid **155**, *ent*-trachyloban-19-oic acid **156**, *ent*-kaur-16-en-19-oic acid **157**, 8(14),15-pimaradien-18-oic acid **158** and 7,15-pimaradien-18-oic acid **159** (Figure 16) [81, 82]. These compounds are proposed to be responsible for the antibacterial activities of the stem bark extracts against methicillin-resistant *Staphylococcus aureus* and *Mycobacterium smegmatis*.

**Figure 16:** Oropheic acids and diterpenes isolated from *Mitrephora celebica* [81, 82].

Among the compounds, **154**, **155**, **156** and **157** exhibited significant inhibitory activity with an MIC of 25, 12.5, 6.25, 6.25 $\mu\text{g/mL}$, respectively while the others showed an MIC of more than 100 $\mu\text{g/mL}$ [81, 82]. This difference might be correlated with the existence of an extra bridged ring in ring C of the structure.

**Figure 17:** Alkaloids isolated from *Psychotria malayana* [61].

Psychotria malayana Jack (Rubiaceae): The aqueous extracts of the leaves or bark of the species has been used traditionally to treat infections on open wounds by the Lomboknese. Chemical investigation on the locally named as "lolon jalun" plant successfully identified six alkaloids, *meso*-chimonanthine **160**, calcycanthine **161**, *iso*-calcycanthine **162** and hodgkinsine **163** and two

probable new alkaloids named LPM-574 **164** and LMP-186 **165** (Figure 17) [61]. Hodgkinsine **163** presents the major alkaloid while *meso*-chimonanthine **160** exists as a minor alkaloid constituent along with two others which were still under investigation [59]. Further chemical investigation on their activities are discontinued [59]. However, initial bacterial testing (Table 10) revealed that isolate **164** can caused bacteriolysis at 1.0 mg/mL but suppressed the growth at 0.5 mg/mL [61].

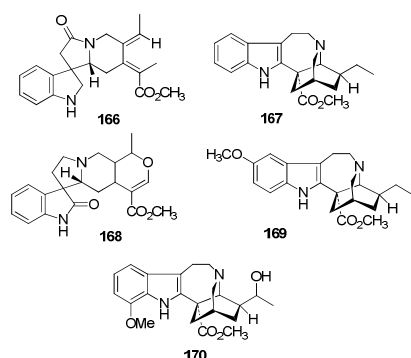


Figure 18: Alkaloids isolated from *Voacanga foetida* [84].

Voacanga foetida (Bl.) Rolfe (Apocynaceae): A phytochemical study on a Lombok Island sample isolated seven alkaloids, lombine **166** and coronaridine **167** [84], uncarine **168** voacangine **169**, voacristine **170**, mataranine A **73** and B **74** (Figure 18). The latter two compounds also exist in *Alstonia scholaris* collected from the same region.

Table 10: Bacteriostatic activity of alkaloids isolated from *Psychotria malayana* Jack [61].

Sample	C, mg/mL	Bacteriostatic activity	
		SA	EC
163	1.0	-	-
	0.5	-	-
164	1.0	++	++
	0.5	+	+

Note: C : Concentration ; SA: *Staphylococcus aureus*; EC: *Eschericia coli*.

Lombine **166** is responsible for the antibacterial activity of the original extract as this alkaloid exhibited bactericidal activity against *Staphylococcus aureus* and *Escherichia coli* resulting in 94% and 95% cell death, respectively at a concentration of 0.5 mg/mL compared to crude extracts which only partially inhibited at the same concentration [83]. Voacristine **170** showed lower activity with 87% of bacterial cell death at 1.0 mg/mL [61].

Anti fungal agents: Indonesian medicinal plants have also been prepared traditionally for fungi caused diseases [84, 85]. Investigations resulted in several species extracts showing significant activities (see Tables 11 and 12) [86, 87]. For example, the extracts of *Tylophora asthmatica*, *Phyllanthus acuminatus* Vahl. and *Swietenia mahogany* Jacq. contain potent compounds against *Phytium ultimum*. On the other hand, extracts of *Ipomoea spp* and *Swietenia mahogany* Jacq. gave significant inhibition against *Scleretonium rolfsii*. Other anti-fungal studies showed *Wangiellia dermatitidis* and *Microsporum gypseum* are more sensitive against Zingiberacea extracts.

In summary, this review has highlighted the investigations which studied 181 of around six thousand Indonesian medicinal plants which revealed 165 isolates. Some potent drug leads were isolated, eg β -sesquiphellandrene as an anti-rhinoviral agent, dehatrine, mataranine A and B as anti-malarial agents and lombine and LPM-574 as anti-bacterial agents. The remaining preliminary studies on these Indonesian medicinal plants indicate that they are prospective sources of potent anti-microbial constituents and require further studies to establish these outcomes.

Acknowledgments: ASN would like to thank the AusAID program and the University of Wollongong, Australia for ADS and HDR scholarships.

Table 11: Anti-yeast like fungal activity of extracts of medicinal plants [87].

Plants	Part of plant	Yeast like fungal species				
		CN	SC	CA	WD	AA
Zingiberaceae						
<i>Alpinia galanga</i>	ST				11.9± 0.8	
<i>Alpinia galanga</i>	RZ	10.2±0.7			27.3 ±7.5	9.5 ±0.0
<i>Alpinia mutica</i>	ST				8.2 ±0.7	
<i>Curcuma zedoaria</i>	RZ	14.8±2.1	13.3±0.2	13.5± 0.0	11.5 ±1.0	
<i>Zingiber purpureum</i>	RZ	11.4±0.5		9.3± 0.9	11.3± 1.2	11.1± 0.4
<i>Zingiber officinale</i>	RZ			11.5± 0.0		

CN: *Cryptococcus neoformans*; SC: *Sacharomyces cerevisiae*; CA: *Candida albicans*; WD: *Wangiellia dermatitidis*; AA: *Alternaria alternate*; ST: Stalk; RZ: Rhizome. All sample are ethanolic extracts; Antifungal activity showed by mean diameter (mean ± SE, mm) of fungal growth inhibition zones. Sterile paper disc (7.5 mm diameter) was impregnated into 0.2 mg/ μ L ethanolic extract for disk diffusion assays.

Table 12: Anti-filamentous fungal activity of extracts of medicinal plants [78, 87].

Plants	Filamentous like fungal species									
	PU	RS	SR	AF	PP	FO	MG	PB	Rh	TM
Acanthaceae										
<i>Graptophyllum pictum</i> (L.) Griff.*	+	++	+		+					
<i>Graptophyllum pictum</i> (L.) Griff.**			+							
Apocynaceae										
<i>Alstonia scholaris</i> (L.) R.Br.**	+		+							
<i>Cantharanthus roseus</i> (L.) G. Don**	+		+							
Asclepiadaceae										
<i>Tylophora asthmatica</i> *						DG				

Table 12 (Continued): Anti-filamentous fungal activity of extracts of medicinal plants [78, 87].

Plants	Filamentous like fungal species									
	PU	RS	SR	AF	PP	FO	MG	PB	Rh	TM
<i>Tylophora asthmatica</i> **	+++									
Convolvulaceae										
<i>Ipomoea</i> spp.*	++	+	+							
<i>Ipomoea</i> spp.**	++	++	++++							
Combretaceae										
<i>Terminalia catappa</i> L.*	+	+	+	+						
<i>Terminalia catappa</i> L.**	++++				++					
Elaeocarpaceae										
<i>Elaeocarpus grandiflorus</i> S.*			+	+						
<i>Elaeocarpus grandiflorus</i> S.**	++									
Euphrobiaceae										
<i>Phyllanthus acuminatus</i> Vahl.*	++		+	++						
<i>Phyllanthus acuminatus</i> Vahl.**	+++	+								
Fabaceae										
<i>Erythrina variegata</i> L.*	+	+		+						
<i>Antidesma bunius</i> (L.) Spreng*		+	+	+						
Fibaceae										
<i>Sesbania grandiflora</i> Pers*	++			+						
Labiatae										
<i>Hyptis brevipes</i> *	+	+	+	+	++					
Leguminosae										
<i>Crotalaria juncea</i> L.*		+			+					
<i>Crotalaria juncea</i> L.**	+									
Meliaceae										
<i>Swietenia mahagoni</i> Jacq.*	+++	++	+++							
<i>Swietenia mahagoni</i> L. (leaf)*				++	+					
<i>Swietenia mahagoni</i> L. (Pericarp)*	++	+	+	+						
<i>Swietenia mahagoni</i> L. (Pericarp)**		+		+						
Moringaceae										
<i>Moringa oleifera</i> Lam.**	+									
Rubiaceae										
<i>Mussaenda pubescens</i> Ait. f.**	+	++		+						
<i>Morinda citrifolia</i> L.*		+								
<i>Morinda citrifolia</i> L.**	++	+	+	+						
Zingiberaceae										
<i>Alpinia galanga</i> (ST)***								8.2		
<i>Alpinia galanga</i> ***				14.4		11.9	20.6	31.1	12.2	16.6
<i>Curcuma globosus</i> ***				9.5			25.3	9.5	14.2	9.5
<i>Curcuma zedoaria</i> ***							27.9	8.2		26.4
<i>Etilingera elatior</i> ***							9.5			
<i>Etilingera littoralis</i> ***				8.8						
<i>Zingiber purpureum</i> ***				14.2		9.5	27.3	17.1	11.5	20.6
<i>Zingiber officinale</i> ***							20.8	12.2	8.8	18.2

PU: *Phytium ultimum*; RS: *Rhizoctonia solani*; SR: *Sclerotium rolfsii*; AF: *Aspergillus fumigatus*; PP: *Phytophthora parasitica*; FO: *Fusarium oxysporum*; MG: *Microsporium gypseum*; PB: *Pseudallescheria*; RH: *Rhizopus* sp; TM: *Trichophyton mentagrophytes*; DG: Decrease growth. All extracts were obtained from the aerial part of plants except, *S. Mahogany*, whose seed was used and the Zingiberaceae, whose rhizome was used unless stated as ST (stalk). * DCM extract; **MeOH extract; ***EtOH extract. Activity shown as symbol + 25% less than control, ++ equal to the control, +++, 25-50% more than control, ++++ 50% than control. In case of Zingiberaceae extracts, result was showed as mean diameter (in mm) of fungal growth inhibition zones. Sterile paper disc (7.5 mm diameter) was impregnated into 0.2 mg/ μ L ethanolic extract for disk diffusion assays.

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