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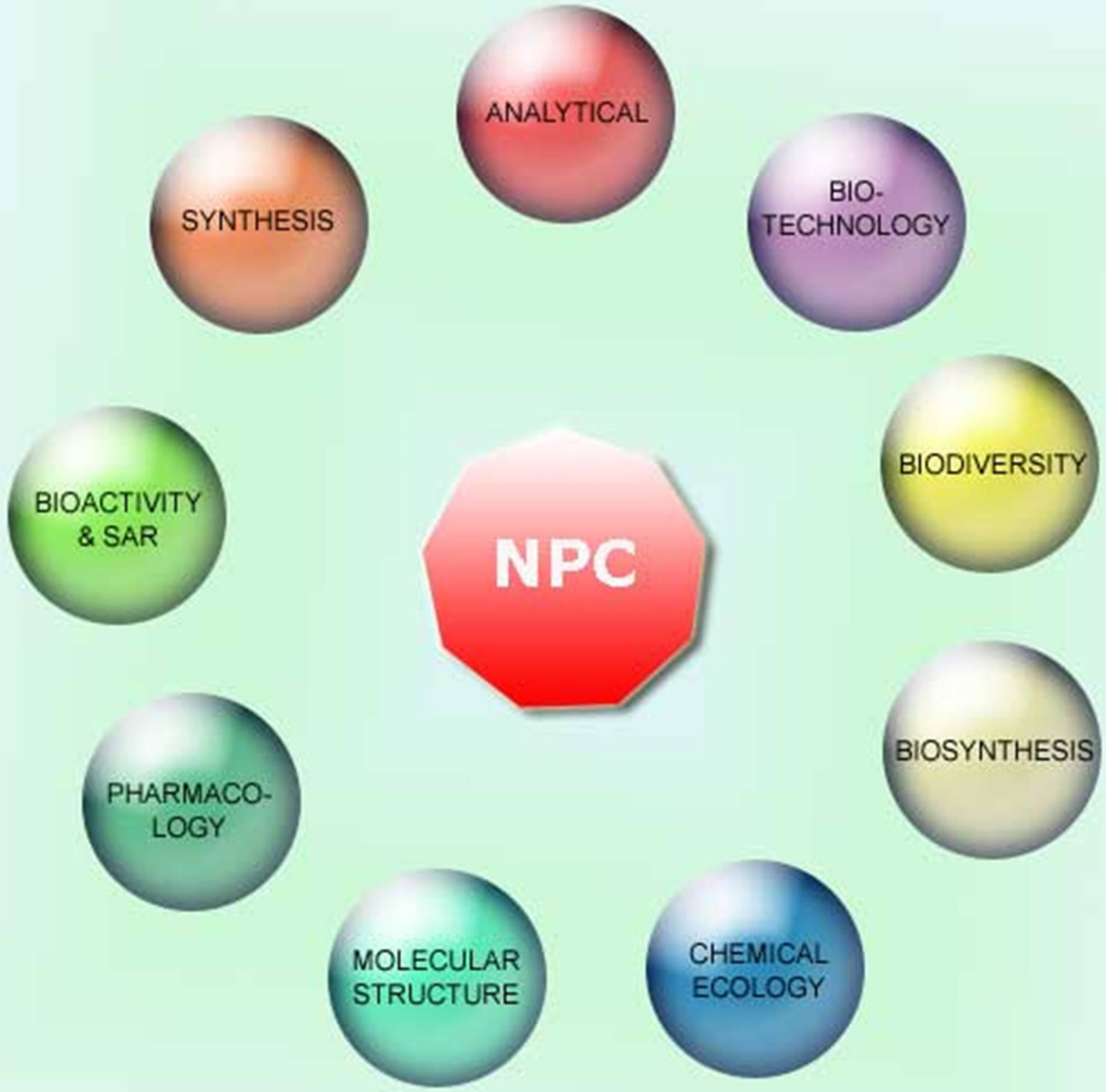

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Revealing Indigenous Indonesian Traditional Medicine: Anti-infective Agents

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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, 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 occuring 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 [22-26]. 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 plant 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 myeoblastosis 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 myeoblastosis 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			
Garcinia griffithii T. A.	-	781	600
Garcinia mangostana L.	LF	40*	
Melastomataceae			
Melastoma malabathricum L.	LF	192	111
Loranthaceae			
Elytranthe globosa B.	LF	336	217
Elytranthe maingayi V.T.	LF	233	41
Elytranthe tubaeflora R.	LF	176	56
Scurrula ferruginea D.	LF	i	62
Meliaceae			
Toona sureni (Bl.) Merr	LF	37*	
Piperaceae			
Piper aduncum L.	FL	344	105
Piper aduncum L.	LF	720	105
Punicaceae			
Punica granatum L.	PR	64*	
Sapindanaceae			
Filicium decipiens T.	SB	68*	
Nephelium lappaceum L.	PR	70*	
Simaroubaceae			
Eurycoma longifolia Jack.	ST	62*	
Verbaneceae			
Vitex pubescens 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. EC_{50}: 50% effective concentration *Expressed as IC_{50}: 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-sesquiphelandrene **4**, α-zingiberene **5**, β-bisabolene **6** (Figure 1). These compounds possessed rhinovirus IB inhibitor activity at an ED_{50} of 20.4, 0.9, 1.90, 14.3 µg/10 mL, respectively. The most active is the β-sesquiphellandrene **4** with IC_{50} 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.

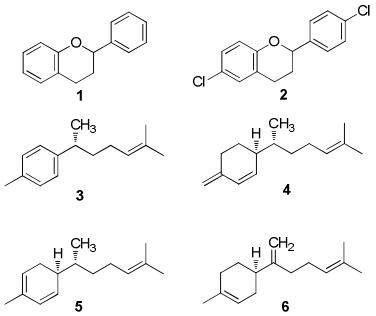

Figure 1: Rhino anti-viral sesquiterpenes (**3**-**6**) isolated from *Zingiber officinale* [36].

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, *Swiettenia mahagoni L.*, *Woodfordia floribunda* Salisb. and *Garcinia mangostana* L. which may contain potential anti-HIV-1 protease inhibitors with IC_{50} 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 IC_{50} values of 5.12 and 4.81 mM, respectively [40].

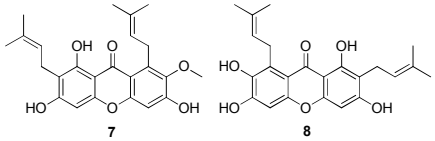

Figure 2: Mangostins isolated from Garcinia mangostana [40].

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_2O ext.	
Acanthaceae				
Andrographis paniculata Nees.	LF	500	500	≥170*
Apiaceae				
Foeniculum vulgare Mill	SD	100	>500	
Apocynaceae				
Parameria laevigata Moldenke.	BK	100	>500	
Clusiaceae				
Garcinia mangostana L	PL	50	100	
Combretaceae				
Terminalia belerica Roxb.	FR	50	220	
Compositae				
Elephantopus scaber L.	WP	500	>500	
Elaeocarpaceae				
Elaeocarpus grandiflorus Smith	FL	100	100	
Fabaceae				
Caesalpinia sappan L.	BK	280	320	
Sindora sumatrana Miq.	FR	260	360	≥134*
Hypoxidaceae				
Curculigo orchioides Gaertn.	FR	400	400	
Lauraceae				
Cinnamomum sintok Bl.	BK	220	320	
Loganiaceae				
Strychnos nux-vomica L.	BK	500	>500	
Loranthaceae				
Loranthus parasiticus (L.) Merr	ST	100	260	≥79.4*
Lythraceae				
Woodfordia floribunda Salisb.	FL	50	50	
Malvaceae				
Helicteres isora L.	FL	380	>500	≥65*
Meliaceae				
Swietenia mahagoni L.	BK	40	100	≥28.4**
Parmeliaceae				
Usnea misaminensis Vain.	WP	220	>500	
Poaceae				
Andropogon zizanioides (L.) Urban	RT	500	>500	
Solanaceae				
Physalis angulata L.	AP	340	>500	
Zingiberaceae				
Curcuma aeruginosa Roxb.	RZ	500	>500	≥323*
Curcuma xanthorriza 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. * H_2O extract. ** MeOH extract. IC_{50}: 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-glucopyranosyl rosmarinic **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 glucoronides, 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 myeoblastosis virus-reverse transcriptase (AMV-RT) and presented weak

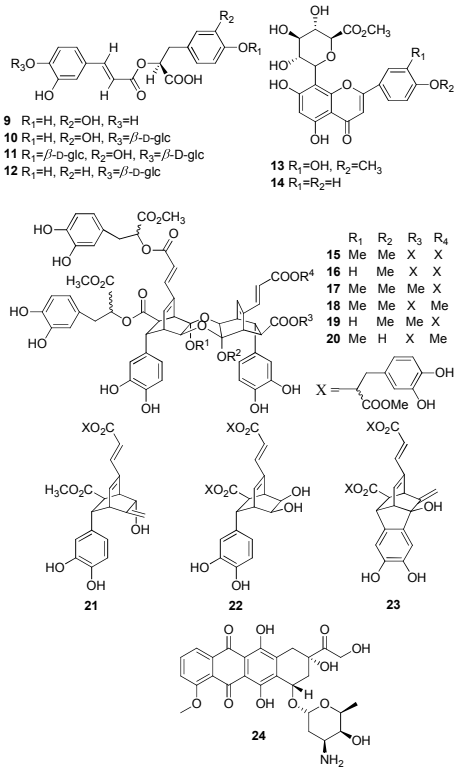

Figure 3: Glycosidic and non glycosidic metabolites isolated from *Helicteres isora* [41-43].

Table 3: Bioactivity of helicterins A-F **15**-**20**, helisterculin A **21**, helisterculin B **22**, helisorin **23** and adriamicyn **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 ethnophamarcological 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 the 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 *Plasmodium falciparum*, %
Apocynaceae		
Catharanthus roseus L.	AP	52
Rauvolfia serpentine (L.) Benth.	BK	66
Asteraceae		
Achillea millefolium L.	WP	98
Ageratum conyzoides L	WP	62
Euphorbiaceae		
Phyllanthus niruri L.	WP	50*
Loganiaceae		
Strycthnos lucida R.Br.	WD	100
Meliaceae		
Azadirachta indica Juss	LF	60
Lansium domesticum Corr.	BK	66
Swietenia macrophylla King.	SD	98
Myrtaceae		
Baeckea frutenscen L.	LF	90
Rubiaceae		
Morinda citrifolia L.	FR	56
Zingiberaceae		
Curcuma xanthorrhiza 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*-caffeoylsweroside **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**, 5α-carboxystrictosidine **38** (Figure 6) [47]. Compounds **26**-**29**, **31**, **33**-**37** were previously identified from various Rubiaceous species of different origins [48-52].

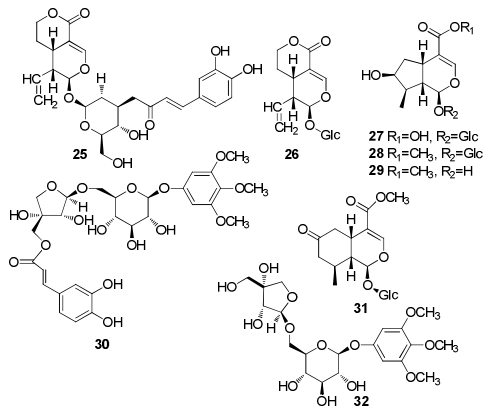

Figure 5: Glycosides isolated from the bark of *Anthocephalus chinensis* [47].

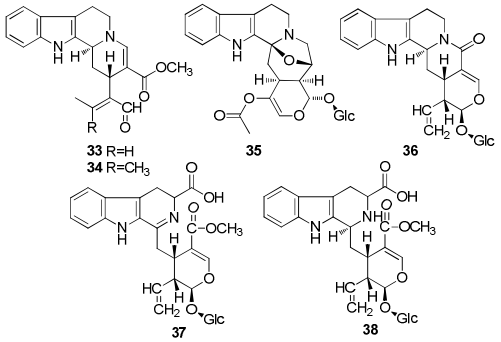

Figure 6: Alkaloids isolated from the bark of *Anthocephalus chinensis* [47].

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 IC_{50} of 6.77 µM and IC_{90} 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 IC_{50} of 0.17 µM against the *Plasmodium falciparum* K1 strain, a chloroquine resistant strain [53].

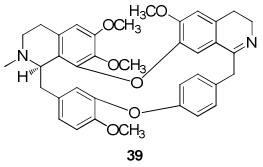

Figure 7: Molecular structure of dehatrine [53].

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 Makasasar' for the same pupose. Successfully identified were eleven triterpenoids including, bruceajavanin A **40**, dihydrobrucejavanin A **41**, bruceajavanin B **42**, bruceantinol **43**, bruceantinol 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-canthin-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 Simaroubaceous medicinal plants [56-58].

Compounds **40** and **42** possessed moderate anti-malarial activity, e.g. IC_{50} 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 (IC_{50}, 25 µM) [55]. Some of the

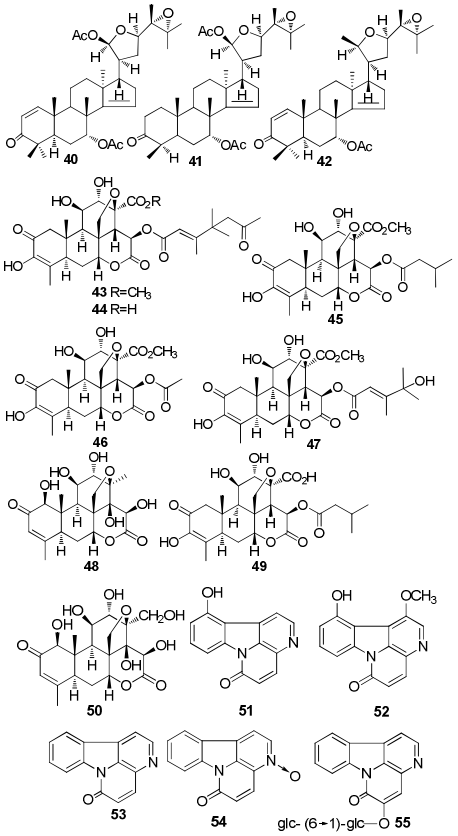

Figure 8: Metabolites isolated from *Brucea javanica* [55].

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 Lomboknesse 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**, deacetylakuammiline **62**, 5α-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*-epoxy-alstonamine **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*-geranylsinapyl

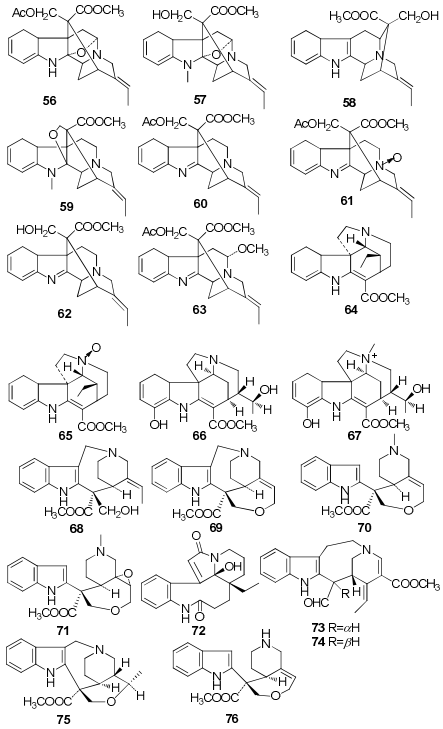

Figure 9: Alkaloids isolated from *Alstonia scholaris* [59, 60].

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

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

[a]No potency. [b]Bioactivity against *Plasmodium falciparum* K1 (an antifolate resistant parasite strain). [c] Against *Plasmodium falciparum* TM4 (an anti-folate sensitive parasite strain)

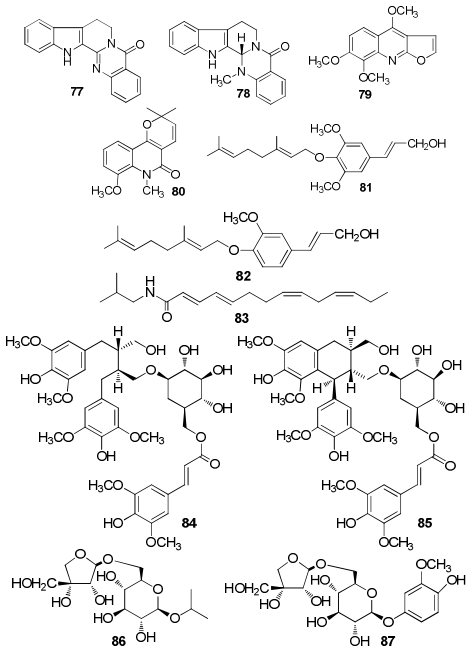

Figure 10: Metabolites isolated from *Fagara rhetza* [62-67].

alcohol **81**, *O*-geranylconiferyl alcohol **82**, hazaleamide **83**, hazaleanin A **84**, hazaleanin B **85**, isopropyl apioglucoside **86** and 4-hydroxyguaiacol apioglucoside **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 IC_{50} 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**, 13*β*,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].

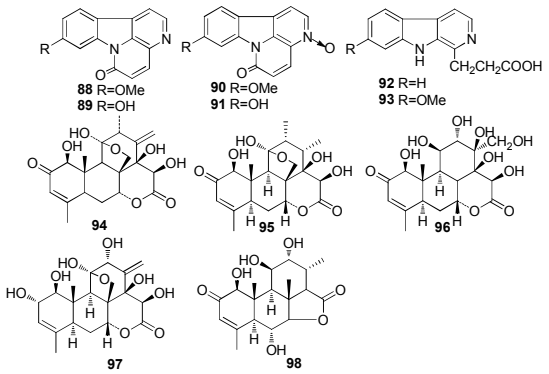

Figure 11: Alakaloids and terpenes isolated from *Eurycoma longifolia* [68].

Lansium domesticum Corr. Ser. (Meliaceae). Isolation revealed five compounds, 3-keto-22-hydroxyonoceradiene **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

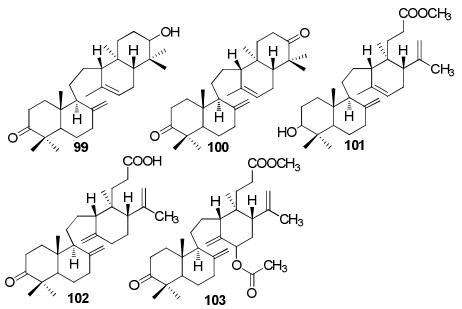

Figure 12: Anti-malarial agents isolated from *Lansium domesticum* [69].

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% parasetimia 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 'Bagor') 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 norcasssane type compounds. The quassionoids 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-oxocaesalminin 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 IC_{50} 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].

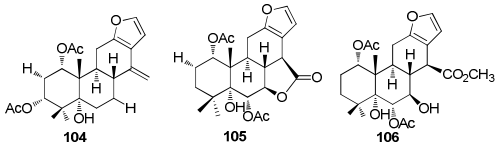

Figure 13: Quassionoids isolated from *Caesalpinia crista* [70-73].

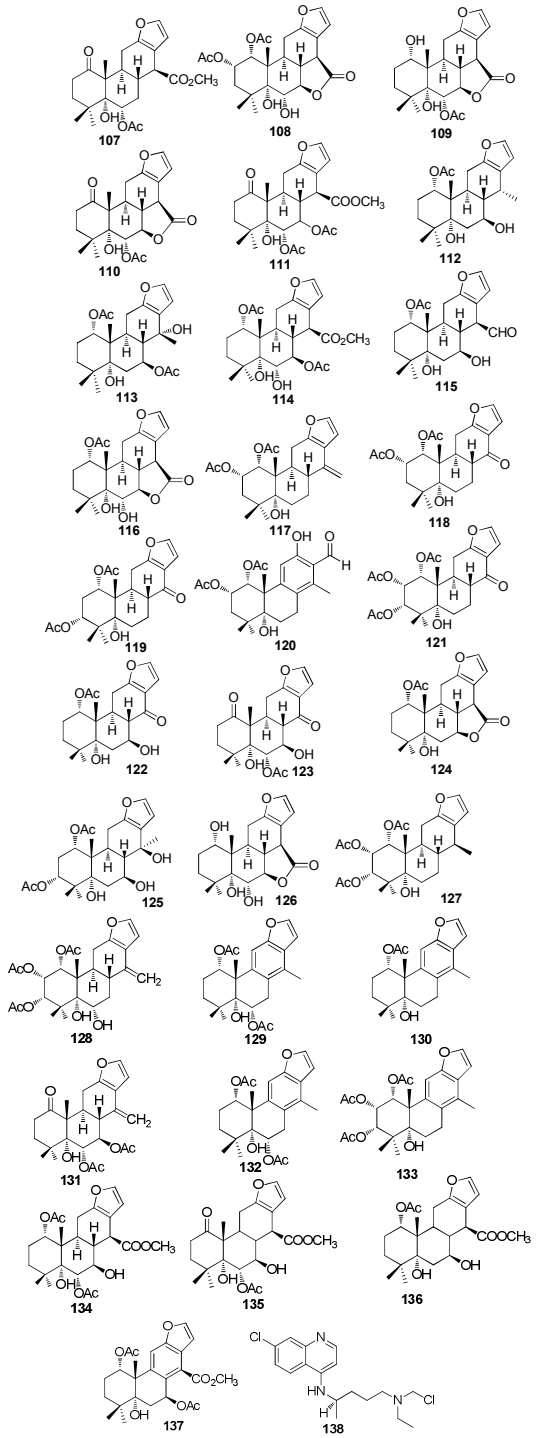

Figure 13 (*continued*): Quassionoids isolated from *Caesalpinia crista* [70-73].

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**, simarinolide **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].

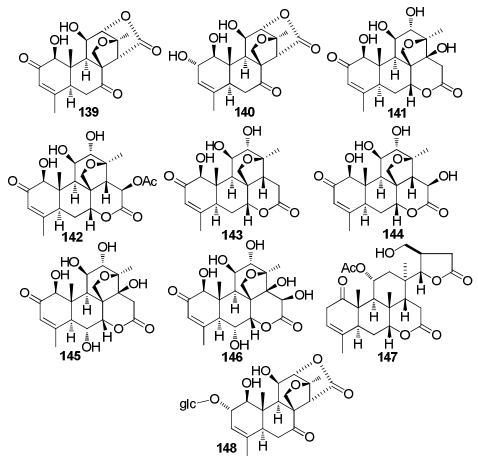

Figure 14 : Quassionoids isolated from *Quassia indica* [76].

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 correlations 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							
Gendarusa vulgaris Nees	LF, RT, ST		+				
Graptophyllum pictum (L.) Griff.*							DG
Staurogyne sp	LF, RT, ST		+		+	+	
Amaranthecеae							
Celosia argentea L. fma	FR, LF, ST		++	+		+	
Celosia plumose (Voss) Back	FR, LF, ST		++	+		+	
Amaryllidaceae							
Crinium asiaticum	LF		++	+	+		
Crinium lineare L.	LF				++		
Curculigo sp.	LF, RT, ST		++	+			
Anarcadiaceae							
Mangifera foetida Lour.	LF		+				
Mangifera indica L.	BK		++				
Apocynaceae							
Alstonia scholaris (L) R. Br.	LF, ST		++				
Cantharanthus roseus (L.) G. Don*			+				
Araceae							
Acorus calamis L.	LF, RT,RZ		+	+			
Araliaceae							
Aralidium pinnatifidum Miq.	LF		++	+			
Balsaminaceae							
Impatiens balsamina L.	LF, ST		+				
Begoniaceae							
Begonia isopera Bl.	LF, ST		+		+	+	
Bombaceae							
Ceiba petandra (L.) Gaertn.	LF, ST		++				
Bromeliaceae							
Ananas comosus (L.) Merr.	LF		+	+		+	
Capparaceae							
Crateva religiosa Forst.	LF, ST		+	+			
Clusiceae							
Cratoxylon formosum (Jack)	BK		+				
Garcinia atroviridis Griff.	LF, ST		++	+			
				+			
Garcinia mangostana L.	BK		+				
Garcinia parvifolia Miq.	LF, ST		++	+			
				+			
Compositae							
Blumea balsamifera DC.	LF, RT, ST		+	+		+	
Plucea indica (L.) Less.	LF, ST		++	+		+	
Connaraceae							
Rourea mimosoides (Vahl)	LF, ST		+	+			
Convulaceae							
Ipomoea batatas (L.) Lamk.	LF, ST		+				
Merremia umbellata (L.) Hall.	LF, ST		+				
Cyperaceae							
Scleria purpurascens Steud.	LF, ST		+				
Dillenaceae							
Dillenia meliosmifolia Hook.	LF		+				
Tetracia asiatica (Lour.)	LF		+		+		
Tetracera sp.	LF		+				
Ebenaceae							
Diospyros sp.	LF, ST		++	+			
Euphorbiaceae							
Breynia racemosa M.	LF, ST		+				
Croton cf. caudatus Geisel.	LF, ST, BK		++				
Galearia filiformis Boerl.	LF				+		
	BK		++	+	+		
Galearia sp.	LF, ST		++		+	+	
Jatropha curcas L.	LF				+		
Euphorbiaceae							
Macaranga gigantea M.	LF		++	+			
Macaranga gigantea M.	BK		+	+	+		
Macaranga triloba M.	LF		+	+		+	
Mallotus ricinoides M.	LF		+				
Euphorbiaceae							
Phyllanthus emblica L.	LF, ST		+	+			
Pimeliodendron papaveriodes	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							
Gnetum latifolium Bl.	LF, ST		+			+	
Hanguanaceae							
Hanguana malayana (Jack) Merr.	LF, ST		++				
Labiatae							
Coleus scutellarioides (L.) Bth.	LF, ST		++			+	
*Hyptis brevipes**			+++	+			+
Ocimum basilicium L.	FL, LF, ST		+	+			
Ocimum tenuiflorum L.	FL, LF, ST		+	+			
Orthosiphon aristatus (Bl.) Miq.	LF, ST		+				
Lauraceae							
Litsea elliptica Bl.	LF		+				
Litsea robusta Bl.	LF		++				
Lecythidaceae							
Barringtonia lanceolata (Bl.)	LF		++				
Barringtonia sp.	BK		++				
Leguminosae							
Bauhinia sp	LF, ST				+		
Crotalaria juncea L.*		DG					
Cassia cf. nodosa Buch. Ham.	BK		++	++		+	
Flemingia strobilifera (R.Br.)	FR, LF, ST		+				
Mimosa pigra L.	LF, ST		+				
Sesbania aculeate Poir.	LF, RT, ST		++				
Tamarindus indica L.	LF, ST		++	++			
Longaniaceae							
Fagraea cfrf. auriculata Jack	LF		+	+	+		
Lythraceae							
Lagerstromia speciosa (L.)	LF, ST		++	++			
Malvaceae							
Abelmoschus ficulneus W. et H.	LF, ST		++		++		
Abelmoschus moschatus Medik.	LF, ST		+				
Gossypium barbadense L. var.	LF, ST		++				
Hibiscus x archeri Wats.	LF, ST		++				
Hibiscus sabdariffa L.	LF, ST		++				
Hibiscus tiliaceus L.	BK		++				
	LF, ST		+				
Melastomataceae							
Dissochaeta gracilis (jack) Bl.	LF, ST		+			+	
Melastoma affine D.Don	LF, ST		++	+	+		
Melastoma malabathricum L.	FL,ST,LF		++		+	+	
Phyllagathis rotundifolia (Jack) Bl.	LF, ST		+	+	+		
Meliaceae							
Aglaia eximia Miq.	BK		+	+		+	
Swietenia mahagoni Jcq.*		+	++	DG			+
		+					+
*Swietenia mahagoni*L. *	PC	+	+				
Menispermaceae							
Arcangelisia flava (L.) Merr.	LF, RT, ST		++		++	+	
Tinomiscium petiolare Hook. F. et Thoms.	BK		+				
Moraceae							
Artocarpuis elasticus Reinw. Ex Bel.	BK		++			+	
						+	
Artocarpus nitidus Trec.	BK			+			
Ficus grossularioides Burm. f.	LF, ST		+	+			
Ficus macrocarpa Kurz	LF, ST		++	+			
Ficus pandana Burm. f.	LF, ST		++	+			
Myristicaceae							
Horsfieldia glabra (Bl.) Warb.	BK		+				
Horsfieldia wallichii (Hook. F. et Thunb.) Warb.	BK		++				
Myrtaceae							
Eugenia polyantha 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							
Psidium guajava L.	LF, ST		++	+			
Rhodmania cinerea Jack	LF, ST		++	+			
Pandanaceae							
Pandanus sp.	LF		+				
Passifloraceae							
Adenia cordifolia ENgl.	LF, ST		++	+			
Rhamnaceae							
Gouania lepostachya DC.	LF, ST		++		+	+	
Rhizophoraceae							
Anisophyllea disticha (Jack) Baill.	LF, ST		+		+		
Rubiaceae							
Hedyotis capitellata Wall.	LF, ST		+				
Hedyotis leucocarpa Elm.	LF, ST		+				
Mussaenda frondosa L.	LF, ST		+				
Uncaria gambir (Hunt.) Roxb.	LF, ST		++			+	
Rutaceae							
Citrus aurantifolia Swingle	FR		++	++			
Simaroubaceae							
Brucea javanica (L.) Merr.	LF, ST		++		+		
Staphylaceae							
Turpinia sphaerocarpa Hassk.	LF, ST		++	++			
Symplocaceae							
Symplocos cochinchinensis (Lour.) Moore	LF, ST		+	+	++	+	
Theaceae							
Eurya acuminata DC.	LF, ST		+				
Thymelaeceae							
Aqularia malaccensis Lamk.	LF, ST		+				
Tiliaceae							
Elaeocarpus cf. mastersii King	LF, ST, BK		++	++			
Grewia acuminata Juss.	BK		++			+	
Ulmaceae							
Trema tomentose (Roxb.) Hara	LF, ST		+				
Urticaceae							
Dendrocnide stimulans (L.f.) Chew	RT		++				
Violaceae							
Rinorea anguifera (lour.) O.K.	BK		+	+			
Zingiberaceae							
Boesenbergia rotunda (L.) Mansf.	LF, RZ, ST		+				
Costus sp.	LF, ST		+				
Curcuma cf. heyneana Val. Et v. Zijp	RZ					+	
Curcuma sp.	RZ		+		+		
Zingiber purpureum 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**, xanthorrizol **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* mutans for dental caries prevention [80].

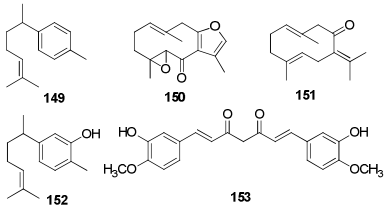

Figure 15: Sesquiterpenes isolated from Curcuma xanthorrhiza [79].

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*.

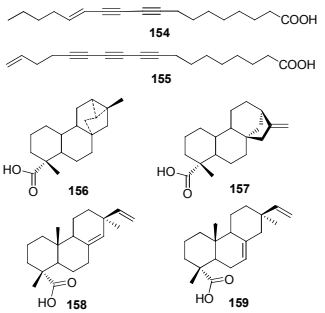

Figure 16: Oropheic acids and diterpenes isolated from *Mitrephora celebica* [81,82].

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

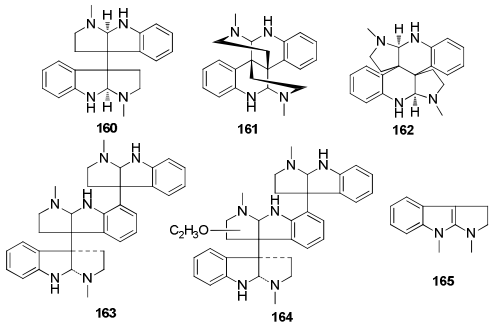

Figure 17: Alakloids isolated from *Psychotria malayana* [61].

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 Lomboknesse. 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].

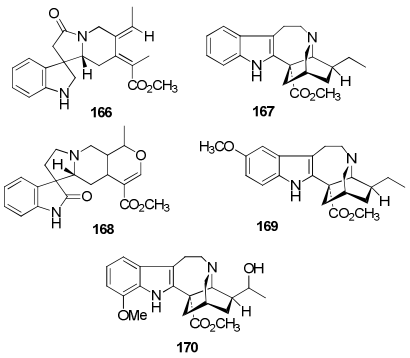

Figure 18: Alkaloids isolated from *Voacanga foetida* [84].

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: *Eschiricia 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].

Antifungal 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						
Alpinia galanga	ST				11.9± 0.8	
Alpinia galanga	RZ	10.2±0.7			27.3 ±7.5	9.5 ±0.0
Alpinia mutica	ST				8.2 ±0.7	
Curcuma zedoaria	RZ	14.8±2.1	13.3±0.2	13.5± 0.0	11.5 ±1.0	
Zingiber purpureum	RZ	11.4±0.5		9.3± 0.9	11.3± 1.2	11.1± 0.4
Zingiber officinale	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/µL 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										
Graptophyllum pictum (L.) Griff.*	+	++	+		+					
Graptophyllum pictum (L.) Griff.**			+							
Apoctnaceae										
Alstonia scholaris (L.) R.Br.**	+		+							
Cantharanthus roseus (L.) G. Don**	+		+							
Asclepiadaceae										
*Tylophora asthmatica**					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**
*Tylophora asthmatica***	+++									
Convolvulaceae										
*Ipomoea spp.**	++	+	+							
*Ipomoea spp.***	++	++	++++							
Combreatceae										
Terminalia catappa L.*	+	+	+	+						
Terminalia catappa L.**	++++				++					
Elaeocarpaceae										
Elaeocarpus grandiflorus S.*			+	+						
Elaeocarpus grandiflorus S.**	++									
Euphrobiaceae										
Phyllanthus acuminatus Vahl.*	++		+	++						
Phyllanthus acuminatus Vahl.**	+++	+								
Fabaceae										
Erythrina variegata L.*	+	+		+						
Antidesma bunius (L.) Spreng*		+	+	+						
Fibaceae										
Sesbania grandiflora Pers*	++			+						
Labiatae										
*Hyptis brevipes**	+	+	+	+	++					
Leguminosae										
Crotalaria juncea L.*		+			+					
Crotalaria juncea L.**	+									
Meliaceae										
Swietenia mahagoni Jacq.*	+++	++	+++							
Swietenia mahagoni L. (leaf)*				++	+					
Swietenia mahagoni L. (Pericarp)*	++	+	+	+						
Swietenia mahagoni L. (Pericarp)**		+		+						
Moringaceae										
Moringa oleifera Lam.**	+									
Rubiaceae										
Mussaenda pubescens Ait. f.**	+	++		+						
Morinda citrifolia L.*		+								
Morinda citrifolia L.**	++	+	+	+						
Zingiberaceae										
Alpinia galanga (ST)***								8.2		
*Alpinia galanga****				14.4		11.9	20.6	31.1	12.2	16.6
*Curcuma globosus****				9.5			25.3	9.5	14.2	9.5
*Curcuma zedoaria****							27.9	8.2		26.4
*Etlingera elatior ****							9.5			
*Etlingera littoralis****				8.8						
*Zingiber purpureum****				14.2		9.5	27.3	17.1	11.5	20.6
*Zingiber officinale****							20.8	12.2	8.8	18.2

PU: *Phytium ultimum*; RS: *Rhizoctonia solani*; SR: *Scleretonium rolfsii*; AF: *Aspergillus fumigatus*; PP: *Phytophthora parasitica*; FO: *Fusarium oxyporum*; MG: *Microsporum gypseum*; PB: *Pseudallescheria*; RH: *Rhizopus s*p; 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/µL ethanolic extract for disk diffusion assays.

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