CHAPTER II

LITERATURE REVIEW

***Picrasma javanica* Bl.**

Picrasma javanica Bl. is a medium-sized tree belonging to family Simaroubaceae. It is commonly found in rain forests in New Guinea and Southeast Asia. Its bark was widely used in traditional medicine as an effective anti-malarial remedy. Its chemical constituents have been investigated (Table 2.1). Pavanand *et al* (1988) demonstrated that the crude chloroform extract and isolated fractions of the bark possessed the *in vitro* antimalarial activity using a morphological screening test (Tables 2.2 and 2.3). Further purification resulted in the identification of the pure alkaloids, 1-vinyl-4-methoxy-β-carboline and 1-vinyl-4-methoxy-1-vinyl-β-carboline. Both compounds could inhibit the growth of *Plasmodium falciparum* using microdilution radioisotope technique (Table 2.4).

Table 2.1 Chemical constituents of *Picrasma javanica* Bl.

Compounds	**Parts**	**Sources**	**Yield** (%)	**References**
Indole alkaloid				
1. Canthin-6-one	Bark	Indonesia	-	Ohmoto *et al*., 1987
2. 1-Acetyl-4-methoxy-β-carboline	Bark	Indonesia	0.00052	Yoshikawa *et al.*, 1993
3. 1-Ethyl-4-methoxy-β-carboline	Bark	Indonesia	0.01075	Yoshikawa *et al.*, 1993
4. 1-Ethyl-β-carboline	Bark	Indonesia	-	Ohmoto *et al*., 1987
5. 4-Methoxy-1-vinyl-β-carboline	Bark	Australia	-	Johns *et al.*, 1970
	Bark	Indonesia	0.00593	Yoshikawa *et al.*, 1993
	Stembark	Thailand	0.012	Pavanand *et al.*, 1988
6. 6-Hydroxy-4-methoxy-1-vinyl-β- carboline	Stembark	Thailand	-	Pavanand *et al.*, 1988
7. Crenatidine	Bark	Indonesia	-	Ohmoto *et al*., 1987
8. Crenatine	Bark	Indonesia	0.00016	Arbain and Sargent, 1987
9. 5-Hydroxycrenatin	Bark	Indonesia	0.00036	Arbain and Sargent, 1987
10. Dehydrocrenatine	Bark	Indonesia	0.00131	Arbain and Sargent, 1987
11. 5-Hydroxy dehydrocrenatin	Bark	Indonesia	0.00749	Arbain and Sargent, 1987
12. Javacarboline	Stem	Indonesia	0.00021	Koike *et al.*, 1994
13. Picarsidine J	Bark	Indonesia	-	Ohmoto *et al*., 1987
14. Picarsidine G	Bark	Indonesia	0.06	Yoshikawa *et al.*, 1993
15. Picarsidine I	Bark	Indonesia	-	Ohmoto *et al*., 1987
16. Picarsidine T	Bark	Indonesia	-	Ohmoto *et al*., 1987
Coumarin				
17. 6-methoxy-7,8-methylenedioxy coumarin	Bark	Indonesia	0.00053	Yoshikawa *et al.*, 1993

Table 2.1 Chemical constituents of *Picrasma javanica* Bl. (continued)

Compounds	**Parts**	**Sources**	**Yield** (%)	**References**
Sesquiterpene				
18. Picrasinoside B	Bark	Indonesia	0.00027	Koike and Ohmoto, 1990
19. Picrasma sesquiterpene lactone I	Leaf	-	-	Fujimoto *et al.,* 1989
20. Picrasma sesquiterpene lactone II	Leaf	-	-	Fujimoto *et al.,* 1989
Triterpene				
21. Hispidal A	Stembark	Indonesia	0.00405	Ishii *et al.*, 1991
22. Javanicin A	Bark	Indonesia	0.00416	Ohmoto *et al.*, 1989
23. Javanicin B	Bark	Indonesia	0.00011	Koike and Ohmoto, 1990
24. Javanicin C	Bark	Indonesia	0.00038	Ohmoto *et al.*, 1989
25. Javanicin D	Bark	Indonesia	0.00094	Ohmoto *et al.*, 1989
26. Javanicin E	Bark	Indonesia	-	Koike and Ohmoto, 1990
27. Javanicin F	Bark	Indonesia	-	Koike and Ohmoto, 1990
28. Javanicin G	Bark	Indonesia	-	Koike and Ohmoto, 1990
29. Javanicin H	Leaf	Indonesia	0.00156	Koike *et al.*, 1991a
30. Javanicin I	Leaf	Indonesia	0.00031	Koike *et al.*, 1991a
31. Javanicin J	Leaf	Indonesia	0.00078	Koike *et al.*, 1991a
32. Javanicin K	Leaf	Indonesia	0.00078	Koike *et al.*, 1991b
33. Javanicin L	Leaf	Indonesia	0.00078	Koike *et al.*, 1991a
34. Javanicin M	Bark	Indonesia	-	Koike *et al.*, 1990
35. Javanicin N	Stem	Indonesia	0.00081	Koike *et al.*, 1991c
36. Javanicin O	Leaf	Indonesia	0.00078	Koike *et al.*, 1991b
37. Javanicin P	Leaf	Indonesia	-	Koike *et al.*, 1991c
38. Javanicin Q	Leaf	Indonesia	-	Koike *et al.*, 1991c
39. Javanicin R	Leaf	Indonesia	0.00012	Koike *et al.*, 1991b

Table 2.1 Chemical constituents of *Picrasma javanica* Bl. (continued)

Compounds	**Parts**	**Sources**	**Yield** (%)	**References**
40. Javanicin S	Leaf	Indonesia	0.00014	Koike *et al.*, 1991b
41. Javanicin T	Stem	Indonesia	0.00216	Koike *et al.*, 1991b
42. Javanicin U	Stem	Indonesia	0.00078.0	Koike *et al.*, 1991d
43. Javanicin V	Stem	Indonesia	0.00075	Koike *et al.*, 1991d
44. Javanicin W	Stem	Indonesia	0.00027	Koike *et al.*, 1991d
45. Javanicin X	Bark	Indonesia	0.0005	Koike *et al.*, 1991d
46. Javanicin Y	Bark	Indonesia	0.00044	Koike *et al.*, 1991d
47. Javanicin Z	Bark	Indonesia	0.00222	Koike *et al.*, 1995
48. Dihydro javanicin z	Bark	Indonesia	0.00155	Koike *et al.*, 1995
49. Hemiacetal javanicin z	Bark	Indonesia	0.0025	Koike *et al.*, 1995
50. Javanicinoside A	Bark	Indonesia	0.00194	Ohmoto *et al.*, 1989
51. Javanicinoside B	Bark	Indonesia	0.08333	Koike and Ohmoto, 1990
52. Javanicinoside C	Bark	Indonesia	0.00088	Koike and Ohmoto, 1990
53. Javanicinoside D	Bark	Indonesia	0.00466	Ishii *et al.*, 1991
54. Javanicinoside E	Stem	Indonesia	0.00008	Ishii *et al.*, 1991
55. Javanicinoside F	Bark	Indonesia	0.00166	Ishii *et al.*, 1991
56. Javanicinoside G	Stem	Indonesia	0.000108	Ishii *et al.*, 1991
57. Javanicinoside H	Bark	Indonesia	0.00444	Ishii *et al.*, 1991
58. Javanicinoside I	Stem	Indonesia	0.00162	Koike and Ohmoto, 1992
59. Javanicinoside J	Stem	Indonesia	0.00029	Koike and Ohmoto, 1992
60. Javanicinoside K	Stem	Indonesia	0.000108	Koike and Ohmoto, 1992
61. Javanicinoside L	Stem	Indonesia	0.000054	Koike and Ohmoto, 1992
62. Lanosta-7,24-dien-3-one	Stem	Indonesia	0.00297	Ishii *et al.*, 1991
63. Picarsin A	Stem	Indonesia	0.0075	Koike *et al.*, 1994
64. Picrajavanin A	Bark	Indonesia	0.00348	Yoshikawa *et al.*, 1993
65. Picrajavanin B	Bark	Indonesia	0.00192	Yoshikawa *et al.*, 1993

Table 2.1 Chemical constituents of *Picrasma javanica* Bl. (continued)

Compounds	**Parts**	**Sources**	**Yield** (%)	**References**
66. Picrasin A	Stem	Indonesia	0.00075	Ishii *et al.*, 1991
67. Picrasinoside F	Bark	Indonesia	0.00055	Koike and Ohmoto, 1990
68. Quassin	Bark	Indonesia	0.00027	Koike *et al.*, 1990
69. Neoquassin	Stem	Indonesia	0.00027	Ishii *et al.*, 1991

Table 2.2 Minimal inhibitory concentrations (MICs) of crude solvent extracts of *Picrasma javanica* Bl. for antimalarial activity against fresh isolates of *Plasmodium falciparum* determined by a morphological screening test

Solvents extracts	**MICs** (μg / ml)
Chloroform	24
Ethanol	64
Water	no inhibition ($\geq$127.3)

Table 2.3 Minimal inhibitory concentrations (MICs) of the fractions isolated from *Picrasma javanica* Bl. for antimalarial activity against fresh isolates of *Plasmodium falciparum* determined by a morphological screening test

Fractions	**MICs** (μg / ml)
Non-alkaloidal part	No inhibition > 49.5
Alkaloidal part	13.2
F-I	No inhibition > 15
F-II	11.24
F-III	No inhibition > 15
F-IV	6.0
F-V	No inhibition > 15
F-VI	8.44

Table 2.4 Minimal inhibitory concentrations (MICs) of pure alkaloids isolated from *Picrasma javanica* Bl. for antimalarial activity against *Plasmodium falciparum* determined by microdilution radioisotope technique

***P. falciparum* isolated**	**MICs** (ng / ml)		
	Alkaloid A[a]	Alkaloid B[b]	mefloquine
313	1921.3	3587.9	ND
Y-6	2486.5	2236.8	10.3
129	2615.9	3653.0	7.4
S-3	2705.5	3644.3	29.0
Mean ± SEM	2432.3 ± 176.2	3280.5 ± 348.2	15.6 ± 6.8

[a]Alkaloid A = 4-methoxy-1-vinyl-β -carboline

[b]Alkaloid B = 6-hydroxy-4-methoxy-1-vinyl-β-carboline

Antimalarial activity of β-carboline alkaloids

Numerous of β-carboline alkaloids showed interesting antimalarial activities. The β-carboline alkaloids (Figure 2.1) isolated from *Strychnos usambarensis* Gilg (Loganiaceae), showed antimalarial activity against *P. falciparum* (Table 2.5). This tree has been used traditionally by people of the Banyambo tribe who live along the Akagera river on the border between Rwanda and Tanzania. The leaves and roots are used as the main ingredient of a curarizing arrow poison (Wright *et al*., 1991).

Table 2.5 *In vitro* activities of the alkaloids against *Plasmodium falciparum*

Alkaloids	IC_{50} (95% C.I.) μg/ml against *P. falciparum*
a. Usambarensine type	
Usambarensine	0.38 (0.261-0.549)
3′,4′-Dihydrousambarensine	0.01 (0.008-0.019)
N_b-methylusambarensine chloride	2.39 (1.43-4.99)
b. Usambarine type	
Usambarine	≈1.85
18,19-Dihydrousambarine oxalate	1.07 (0.86-1.33)
c. Strychnopentamine	
Strychnopentamine	0.09 (0.051-0.180)
Strychnopentamine methanesulphonate	0.09 (0.057-0.143)
d. Akagerine and Tubulosine	
Akagerine	6.98 (3.80-12.77)
Tubulosine	0.020 (0.019-0.021)

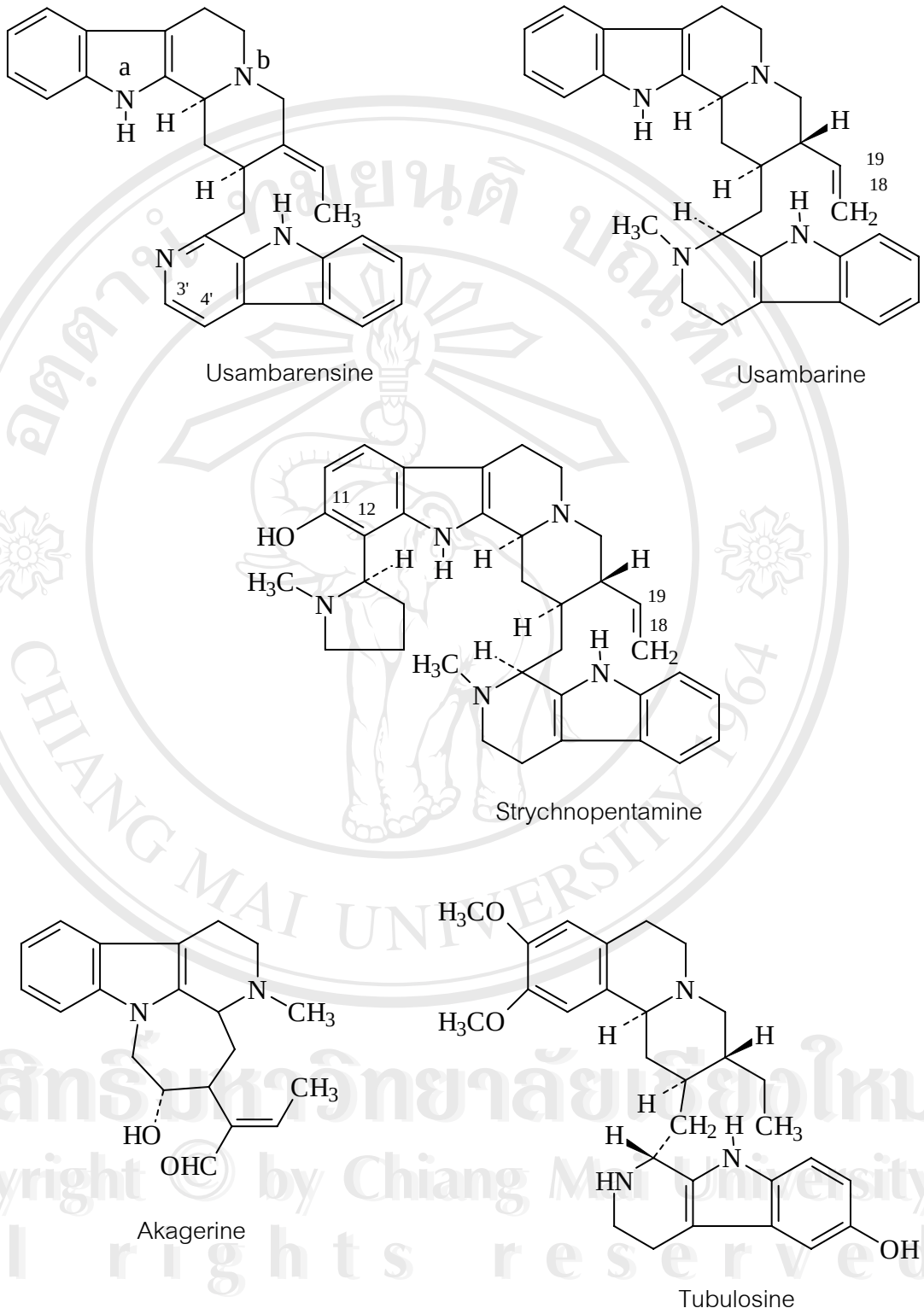
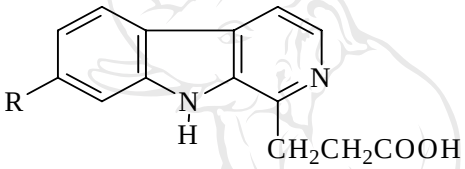


Figure 2.1 The β-carboline alkaloids isolated from *Strychnos usambarensis* Gilg

Two isolates from the roots of *Eurycoma longifolia* Jack (Simaroubaceae) collected in Kalimantan, Indonesia, the β-carboline alkaloids; β-carboline-1-propionic acid and 7-methoxy-β-carboline-1-propionic acid (Figure 2.2) were not significantly active with a panel of human cancer i.e. breast, colon, fibrosarcoma, lung, melanoma, KB, and KB-V1 (a multi-drug resistant cell line derived from KB) and murine lymphocytic leukemia (P-388). However, 7-methoxy-β-carboline-1-propionic acid demonstrated significantly active antimalarial activity as judged by studies conducted with cultured *P. falciparum* strains D-6 and W-2 with IC_{50} of 3144 and 2978 ng/ml respectively (Kardono *et al*., 1991).



1-propionic acid-β -carboline; R = H

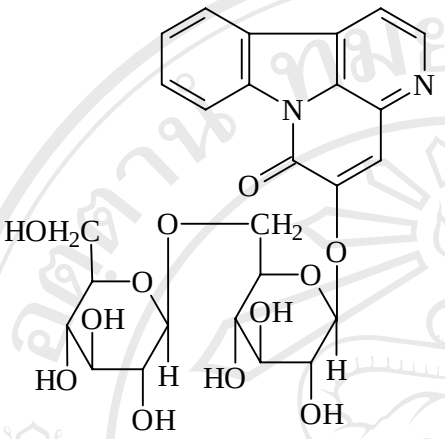
1-propionic acid-7-methoxy-β-carboline-; R = OMe

Figure 2.2 The β-carboline alkaloids isolated from the roots of *Eurycoma longifolia* Jack

A β-carboline alkaloidal glycoside, bruceacanthinoside (Figure 2.3) was isolated from the stem of *Brucea javanica* (L.) Merr. (Simaroubaceae), a traditional medicine used to treat malaria in the Bengkulu area, Sumatra, Indonesia. Bruceacanthinoside was shown to inhibit the growth of the cultured chloroquine-resistant *P. falciparum* K1 (IC_{50} 25 μM, IC_{90} 43 μM) (Kitagawa *et al*., 1994).

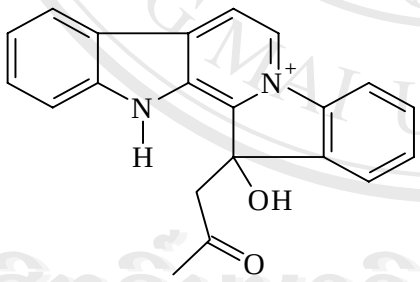
From the CH_2Cl_2 extract of the sponge *Hyrtios* cf. *erecta* (Thorectidae), collected from Fiji, the known compounds Homofascaplysin A and Fascaplysin were isolated (Figure 2.4). Homofascaplysin A was shown to be potent *in vitro* inhibitors of chloroquine-susceptible (NF54) [IC_{50} 24 ng/ml] and chloroquine-resistant *P. falciparum* (K1) [IC_{50} 14 ng/ml]. The cytotoxicity

against rat skeletal muscle myoblast (L-6) cells and mouse peritoneal macrophages was reported as MICs of 1.1 and 30 μg/ml, respectively (Kirsch *et al*., 2000).

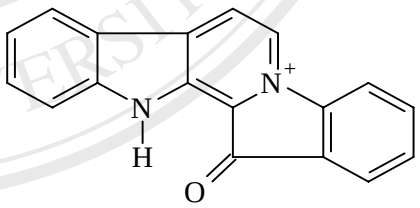


Bruceacanthinoside

Figure 2.3 Bruceacanthinoside isolated from the stem of *Brucea javanica* (L.) Merr.



Homofascaplysin A



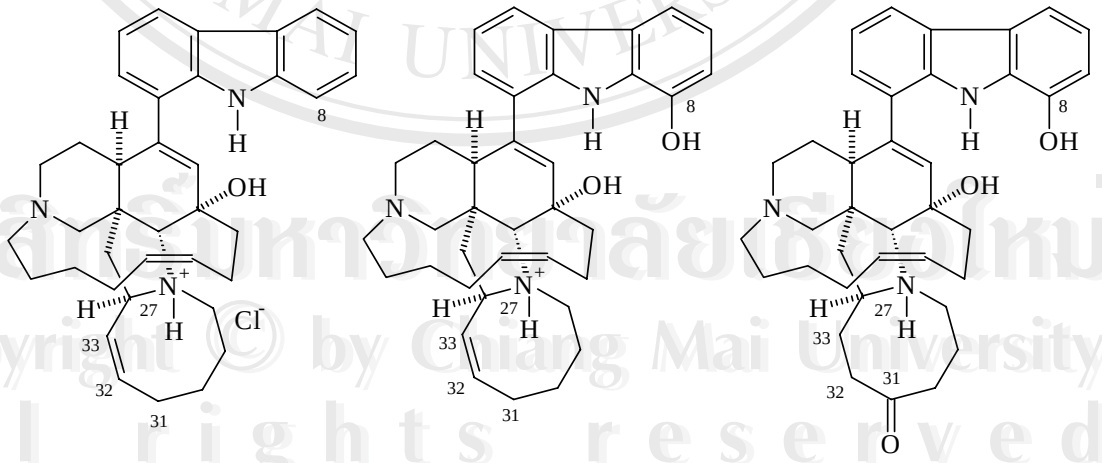
Fascaplysin

Figure 2.4 The β-carboline alkaloids isolated from the sponge *Hyrtios* cf. *erecta*

Manzamines (Figure 2.5) are a structurally unique group of β-carboline alkaloides isolated from several marine sponge species found in the Indian Ocean and the Pacific Ocean. Manzamine A was initially isolated from a *Haliclona* sp. but has been subsequently found in other genera of marine sponges, including *Pellina*, *Pachypellina*, *Xestospongia*, *Ircinia*, and

Amphimedon. In addition, more than 30 other compounds structurally related to manzamine A have been isolated from sponges and characterized; these include 8-hydroxymanzamine A and the ketone derivative manzamine F.

The survival over time (60 days posttreatment) of mice infected with the erythrocytic stages of *P. berghei* was compared to survival after treatment with a single intraperitoneal injection of either manzamine A, (-)-8-hydroxymanzamine A, manzamine F, chloroquine, or artemisinin. All control mice and mice treated with manzamine F died within 4 days posttreatment. In contrast, a single intraperitoneal administration of manzamine A (50 or 100 μmol/Kg) or (-)-8-hydroxymanzamine A (100 μmol/Kg) prolonged the survival of *P. berghei*-infected mice for more than 10 days, with 40% of mice treated with 100 μmol of manzamine A per Kg surviving for more than 60 days and recovering with no detectable parasitemia. Similarly, oral administration of an oil suspension of manzamine A or (-)-8-hydroxymanzamine A significantly prolonged the survival of infected mice. The ability of manzamine A and its hydroxyl derivative to extend the lives of infected mice far exceeded that of chloroquine and artemisinin, two of the most important human therapeutic antimalarial drugs. Manzamine A was toxic to mice at 500 μmol/Kg, but it showed more slowly acting toxicity than chloroquine, which caused almost instantaneous death of the treated mice at 500 μmol/Kg (Ang *et al*., 2000)



Manzamine A (-)-8-Hydroxymanzamine A Manzamine F

Figure 2.5 Structures of manzamines tested for antimalarial activity