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Review

Review of the chemical structures and antimalarial activities of indole alkaloids isolated from *Picrasma javanica* Bl.

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ABSTRACT

Picrasma javanica Bl. is a critical natural source to develop the new antimalarial drugs having novel mode of action. It was found that fourteen indole alkaloids were purified from *P. javanica* that was growing in Indonesia, New Guinea and Thailand. However, only two purified compound of Thai *P. javanica*, 4-methoxy-1-vinyl-β-carboline (dehydrocrenatine) and 6-hydroxy-4-methoxy-1-vinyl-β-carboline, were tested for antimalarial activities. In addition, crenatine (1-ethyl-4-methoxy-β-carboline) and dehydrocrenatine were synthesized and evaluated for antimalarial activity and selective toxicity. Therefore, it is valuable to study the structure-activity relationship of these fourteen indole alkaloids of *P. javanica* as the potential antimalarial drugs. Importantly, Thai *P. javanica* shall be reserved as medicinal plant for malaria disease treatment.

Keywords: Indole alkaloids, β-carboline, chemical structure, *Picrasma javanica* Bl, antimalarial activity.

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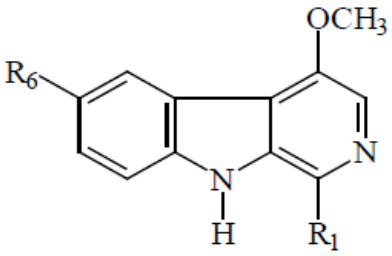
INTRODUCTION

Picrasma javanica Bl. is a medium size tree, up to 20 m high. Leaves imparipinnat, alternate; leaflets 3 to 7, elliptic-oblong, 1.5 to 2.5 cm wind, 4.5 to 7 cm long. Inflorescence is axillary panicle, unisexual, monoecious; flowers white, yellow or green; calyx persistent. Fruit drupaceous, compressed-globose or ovoid, turned pale yellow when ripe (Chuakul et al., 1997). The bark of this medicinal plant was reputedly used for the treatment of malaria in the traditional medicine in Myanmar, Indonesia and Thailand (Old Style Doctor Association, 1962). In 1942, during the 2nd World War, 36 recipes of Thai Folk Medicine included *P. javanica* were used for treatment of either *Plasmodium faciparum* or *P. vivax* infected soldiers by Ketusinh (1948). Recently, Tangjitman et al. (2013) studied to compare traditional medicinal knowledge in 14 Karen villages in northern Thailand and determined culturally important medicinal plant in each Karen villages. In total 379 medicinal plant species were used. It was found that *P. javanica* showed cultural important index (CI) of 0.96. Therefore, it is valuable to reinvestigate the chemical constituents of *P. javanica* and evaluate their antimalarial activities.

Previously, Saiin et al. (2003) reported that the *in vitro* antimalarial activities against *P. falciparum* K1 of four extracts from the stem bark of *P. javanica*; for example water, methanol, chloroform and hexane extracts were studied using a modification of the [^{3}H]hypoxanthine incorporation method. It was found that the hexane extract showed *in vitro* antimalarial activity with IC_{50} of 3.3 μg/ml. The extract was further fractionated using quick column chromatography, resulting in ten fractions. Fraction V was the most effective against *P. falciparum* K1 with IC_{50} of 4.4 μg/ml. Further isolation of fraction V using a column chromatographic technique provided six fractions. According to ^{1}H- and ^{13}C-NMR spectra, it could be concluded that the major compound in fraction V-3 was β-sitosterol. Unfortunately, the antimalarial activity of β-sitosterol could not be determined because of its low solubility in dimethyl sulfoxide.

Recently, Saiin et al. (2016) reported the results of

isolation and *in vitro* antimalarial activity against *P. falciparum* K1 of chloroform extract from Thai *P. javanica* stem bark. It was found that 4-methoxy-1-vinyl-β-carboline (Figure 1) and its derivative 1-ethyl-4-methoxy-β-carboline play a role for antimalarial activity of *P. javanica*. The literature review data suggested that the further study should be focus on the antimalarial activity of sixteen indo-type-alkaloids reported for this medicinal plant. Moreover, Saiin et al. (2016) reported that the chloroform and hexane extracts of *P. javanica* stem showed *in vitro* antimalarial activity against *P. falciparum* K1 with IC_{50} of 21.6 and 33.2 μg/ml, respectively. The indole alkaloid, Javacarboline, may respond for the antimalarial activity of the stem of *P. javanica*.



(2); 1-ethyl-4-methoxy-β-carboline (crenatine): $R_1 = CH_2CH_3$, $R_6 = H$

(13); 4-methoxy-1-vinyl-β-carboline (dehydrocrenatine): $R_1 = CH{=}CH_2$, $R_6 = H$

(14); 6-hydroxy-4-methoxy-1-vinyl-β-carboline: $R_1 = CH{=}CH_2$, $R_6 = OH$

Figure 1. Chemical structure of β-carbolines found in Thai *P. javanica.*

SCOPE OF REVIEW

The objectives of this review were: (i) to determine the chemical structures of the indole alkaloids isolated from *P. javanica*; (ii) to determine the antimalarial activity of the purified compounds of *P. javanica*; and (iii) to provide the perspective to study *P. javanica* as potential antimalarial drugs resource. The review was complied by performing the PubMed®, SCOPUS and Web of Science (ISI) searches for all years using the term *Picrasma javanica*. Only the original articles that reported about indole alkaloids were discussed in this paper.

RESULTS AND DISCUSSION

Determined of the chemical structure of Indole alkaloids of *P. javanica*

The authors extracted and determined the ^{1}H-NMR spectra data of the indole alkaloids of *P. javanica* that were published (Table 1). According to the review data, Crenatine and dehydrocrenatine are 1-ethyl-4-methoxy-β-carboline and 4-methoxy-1-vinyl-β-carboline, respectively. In summary, there are fourteen indole alkaloids were purified from *P. javanica* (Figures 1 to 3). Of fourteen compounds, seven compounds were reported by Ohmoto et al. (1987).

In vitro antimalarial activities of indole alkaloids of *P. javanica*

Fourteen indole alkaloids were purified from *P. javanica* collected from Indonesia, New Guinea and Thailand. Only two compounds from Thai *P. javanica* that were tested for antimalarial activity. Pavanand et al. (1988) reported that 4-methoxy-1-vinyl-β-carboline was effective against *P. falciparum* isolates with mean inhibitory dose 50 (ID_{50}) of 2.4 μg/ml, while 6-hydroxy-4-methoxy-1-vinyl-β-carboline showed mean ID_{50} of 3.2 μg/ml. In addition, several β-carbolines including naturally occurring substances and their corresponding cationic derivatives were synthesized and evaluated for antiplasmodial activity. It was found that dehydrocrenatine (4-methoxy-1-vinyl-β-carboline) was effective against *P. falciparun* chloroquine sensitive strain (FCR-3) with EC_{50} (M) 5.0×10^{-6} (cal. 1.1 μg/ml), while crenatine (1-ethyl-4-methoxy-β-carboline) EC_{50} (M) of 1.6×10^{-5} (cal. 3.6 μg/ml) (Takasu et al., 2004, 2005). Importantly, their salts; quaternary carbolinium cations not only showed much higher potencies than neutral β-carbolines, but also they could

Table 1. The ^{1}H-NMR spectra data extracted from the literature papers.

Compounds	References	^{1}H-NMR spectra data
Canthin-6-one (6)	Ohmoto et al., 1987	^{1}H-NMR (400 MHz, δ in DMSO-d_6): 6.65 (1H, d, *J* =9.7 Hz, H-5), 7.28 (1H, t, *J*=7.7 Hz, H-10), 7.45 (1H, t, *J*=7.7 Hz, H-9), 7.59 (1H, d, *J*=5.0 Hz, H-1), 7.73 (1H, d, *J*=7.7 Hz, H-11), 7.77 (1H, d, *J*=9.7 Hz, H-5), 8.28 (1H, d, *J*=7.7, H-8), 8.58 (1H, d, *J*=5.0 Hz, H-2).
1-Acetyl-4-methoxy-β-carboline (8)	Yoshikawa et al., 1993	No data Refer to B. S. Joshi, V. N. Kamat, and D. H. Gawad, Heterocycles, 7, 193 (1977).
1-Ethyl-4-methoxy-β-carboline (2)	Yoshikawa et al., 1993	No data Refer to Johns et al., 1970
1-Ethyl-β-carboline (1)	Ohmoto et al., 1987	^{1}H-NMR (400 MHz, δ in DMSO-d_6): 1.42 (3H, t, *J*=8.0 Hz, –CH_3), 3.18 (2H, q, *J*=8.0 Hz, –CH_2–), 7.23 (1H, t, *J*=8.0 Hz, H-6), 7.53 (1H, t, *J*=8.0 Hz, H-7), 7.64 (1H, d, *J*=8.0 Hz, H-8), 7.88 (1H, d, *J*=5.0 Hz, H-4), 8.16 (1H, d, *J*=8.0 Hz, H-5), 8.28 (1H, d, *J*=5.0 Hz, H-3), 11.53 (1H, s, –NH, disappeared with D_2O)
4-Methoxy-1-vinyl-β-carboline (13)	Johns et al., 1970	^{1}H-NMR (100 MHz, δ in $CDCl_3$): 4.08 (3H, s, 4-OCH_3), 5.50, 6.21, 7.20 (3H, AMX-system, J_{AM}=1.5 Hz, J_{AX}=10.5, J_{XM}=17.2 Hz, –CH=CH_2), 7.2-7.5 (3H, m, H-6, 7, 8), 8.34 (1H, q, *J*=7.2 Hz, H-5), 8.08 (1H, s, H-3),
	Yoshikawa et al., 1993	No data Refer to Johns et al. (1970) and Ohmoto et al. (1987)
	Pavanand et al., 1988	^{1}H-NMR (MHz (no data),δ in DMSO-d_6): 4.14 (3H, s, 4-OCH_3), 5.39, 6.32, 7.35 (3H, AMX-system, J_{AM}=2.2 Hz, J_{AX}=12.0, J_{MX}=19.0 Hz, –CH=CH_2), 7.56-8.24 (4H, m, phenyl group protons), 8.07 (1H, s, H-3).
6-Hydroxy-4-methoxy-1-vinyl-β-carboline (14)	Pavanand et al., 1988	^{1}H-NMR (MHz (no data), δ in DMSO-d_6): 4.10 (3H, s, 4-OCH_3), 5.4, 6.24, 6.96 (3H, AMX-system, J_{AM}=1.5 Hz, J_{AX}=12.0, J_{MX}=13.0 Hz, –CH=CH_2), 7.5 (1H, d, $J_{7,8}$ =10.8 Hz, H-8), 7.69 (1H, dd, $J_{7,8}$ =10.8 Hz, $J_{5,7}$ =0.9 Hz, H-7), 7.69 (1H, d, $J_{5,7}$ =0.9 Hz, H-5), 8.05 (1H, s, H-3).

Table 1. Continues.

Crenatidine (5)	Ohmoto et al., 1987	^{1}H-NMR (400 MHz, δ in $CDCl_3$): 1.37 (3H, t, *J*=8.0 Hz, –CH_3), 3.10 (2H, q, *J*=8.0 Hz, –CH_2–), 3.85 (3H, s, 8-OCH_3), 4.02 (3H, s, 4-OCH_3), 6.83 (1H, d, *J*=8.0 Hz, H-7), 7.14 (1H, t, *J*=8.0 Hz, H-6), 7.90 (1H, d, *J*=8.0 Hz, H-5), 7.95 (1H, s, H-3), 9.64 (1H, s, –NH, disappeared with D_2O)
Crenatine (2)	Arbain and Sargent, 1987	No data
	Ohmoto et al., 1987	^{1}H-NMR (400 MHz, δ in $CDCl_3$): 1.37 (3H, t, *J*=8.0 Hz, –CH_3), 3.13 (2H, q, *J*=8.0 Hz, –CH_2–), 4.07, (3H, s, 4-OCH_3), 7.15-7.50 (3H, m, H-6,7,8), 8.00 (1H, s, H-3), 8.35 (1H, d, *J*=8.0 Hz, H-5)
	Johns *et al*., 1970	^{1}H-NMR (100 MHz, δ in $CDCl_3$): No data ……. (3H, t, *J*=…. Hz, –CH_3), No data ……. (2H, q, *J*=….. Hz, –CH_2–), No data ……, (3H, s, 4-OCH_3), 7.2-7.6 (3H, m, H-6, 7, 8), 8.00 (1H, s, H-3), 8.1 (1H, q, *J*=7.3 Hz, H-5). Refer to Sanchez, E., and Comin, J., An. Asoc. Quim. Argent., 1969, 57, 57.
5-Hydroxycrenatine (10)	Arbain and Sargent, 1987	^{1}H-NMR (80 MHz, δ in CD_3COCD_3): 1.37 (3H, t, *J*=7 Hz, Me), 3.16 (2H, q (partly obscured by HOD signal), *J*=7 Hz, CH_2), 4.12 (3H, s, OMe), 6.94 (1H, dd, *J*=7 Hz, H-6), 7.06 (1H, t, *J*=7 Hz, H-7), 7.76 (1H, dd, *J*=7 Hz, H-8), 7.95 (1H, s, H-3).
Dehydrocrenatine (13)	Arbain and Sargent, 1987	No data Refer to Johns et al. (1970)
5-Hydroxy dehydrocrenatine (9)	Arbain and Sargent, 1987	^{1}H-NMR (300 MHz, δ in CD_3OD): 4.05 (3H, s, OCH_3), 5.47 (1H, dd, *J*=11, 2 Hz, H_A), 6.18 (1H, dd, *J*=17, 2 Hz, H_M), 7.26 (1H, dd, *J*=17, 11 Hz, H_X), 6.86 (1H, dd, $J_{6,7}$ =8 Hz, $J_{6,8}$ =1 Hz, H-6), 6.96 (1H, t, $J_{7,6} = J_{7,8}$ = 8 Hz, H-7), 7.66 (1H, dd, $J_{8,7}$ = 8 Hz, $J_{8,6}$ = 1Hz, H-8), 7.82 (1H, s, H-3), 7.84 (1H, s, OH or NH), 80 Hz, δ in DMSO-d_6), inter al., 10.00, br s, 1H, D_2O-exchangeable OH or NH; 11.50, br s, 1H, D_2O-exchangeable OH or NH.

Table 1. Continues.

Javacarboline (11)	Koike *et al*., 1994	^{1}H-NMR (500 MHz, δ in DMSO-d_6): 5.89 (1H, dd, *J*=6.1, 1.2 Hz, H-3), 3.84 (1H, dd, *J*=16.8, 1.2 Hz, H-4a), 3.55 (1H, dd, *J*=16.8, 6.1 Hz, H-4b), 7.74 (1H, br d, *J*=8.0 Hz, H-5), 7.17 (1H, ddd, *J*=8.0, 7.1, 0.9 Hz, H-6), 7.34 (1H, ddd, *J*=8.2, 7.1, 0.7 Hz, H-7), 7.64 (1H, dt, *J*=8.2, 0.9 Hz, H-8), 11.75 (1H, 9-NH, disappeared with D_2O), 8.84 (1H, s, H-17), 2.84 (1H, s, H-19), 2.96 (1H, q, *J*=7.6 Hz, H-20), 1.21 (1H, t, *J*=7.6 Hz, H-21), 2.47 (1H, s, H-22).
Picrasidine I (3)	Ohmoto et al., 1987	^{1}H-NMR (400 MHz, δ in DMSO-d_6): 4.11 (1H, s, 4-OCH_3), 5.10, 6.30, 7.61 (3H, AMX-system, J_{AM}=16.9 Hz, J_{AX}=10.6, J_{MX}=2.2 Hz, –CH=CH_2), 6.95 (1H, dd, *J*=7.7, 1.0 Hz, H-7), 7.06 (1H, t, *J*=7.7 Hz, H-6), 7.65 (1H, dd, *J*=7.7, 1.0 Hz, H-5), 8.07 (1H, s, H-3), 10.03 (1H, s, 8-OH, disappeared with D_2O), 11.53 (1H, s, –NH, disappeared with D_2O)
Picrasidine J (4)	Ohmoto *et al*., 1987	^{1}H-NMR (400 MHz, δ in DMSO-d_6): 1.30 (3H, t, *J*=7.7 Hz, –CH_3), 3.10 (2H, q, *J*=7.7 Hz, –CH_2–), 4.05 (3H, s, 4-OCH_3), 6.91 (1H, dd, *J*=7.7, 1.0 Hz, H-7), 7.02 (1H, t, *J*=7.7Hz, H-6), 7.63 (1H, dd, *J*=7.7, 1.0 Hz, H-5), 7.91 (1H, s, H-3), 9.95 (1H, s, 8-OH, disappeared with D_2O), 11.33 (1H, s, –NH, disappeared with D_2O)
Picrasidine T Hydrochloride (7)	Ohmoto et al., 1987	^{1}H-NMR (400 MHz, δ in DMSO-d_6): 1.85 (1H, dddd, *J*=15.0, 12.0, 10.0, 7.0, 4.0 Hz, H-15a), 1.99 (1H, dddd, *J*=15.0, 8.0, 3.0, 2.0, 1.0 Hz, H-15b), 2.60 (1H, dddd, *J*=16.0, 4.0, 2.0, 1.0 Hz, H-16a), 2.65 (1H, dddd, *J*=16.0, 12.0, 4.0, 3.0 Hz, H-16b), 3.59 (1H, ddd, *J*=18.0, 10.0, 8.0 Hz, H-14a), 3.79 (1H, ddd, *J*=18.0, 7.0, 2.0 Hz, H-14b), 3.98 (1H, s, 4-OCH_3), 4.04 (3H, s,4'-OCH_3), 7.02 (1H, dd, *J*=8.0, 1.0 Hz, H-7'), 6.94 (1H, dd, *J*=4.0, 2.0 Hz, H-17), 7.10 (1H, td, *J*=8.0, 1.0 Hz, H-6'), 7.16 (1H, dd, *J*=8.0, 1.0 Hz, H-7), 7.25 (1H, t, *J*=8.0 Hz, H-6), 7.69 (1H, dd, *J*=8.0, 1.0 Hz, H-5'), 7.77 (1H, dd, *J*=8.0, 1.0 Hz, H-5),

Table 1. Continues.

		7.80 (1H, s, H-3'), 8.08 (1H, s, H-3), 9.96 (1H, s, 8-OH, disappeared with D_2O), 10.29 (1H, s, 8'-OH, disappeared with D_2O), 11.84 (1H, s, 9'-NH, disappeared with D_2O), 12.83 (1H, s, 9-NH, disappeared with D_2O).
Picrasidine G (12)	Yoshikawa et al., 1993	No data Refer to K. Koike, T. Ohmoto, Chem. Pharm. Bull., 35, 3305 (1987) Compared with Picrasidine-G hydrochloride from *Picrasma quassioides*

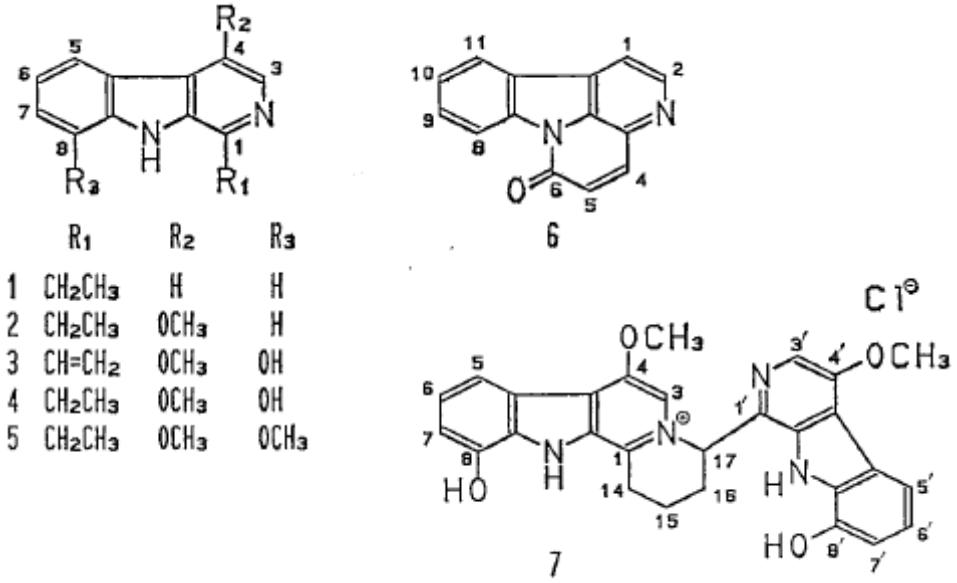


Figure 2. The chemical structure of seven indole alkaloids of *P. javanica* reported by Ohmoto et al. (1987). (1); 1-Ethyl-β-carboline, (2); Crenatine, (3); Picrasidine-I, (4); Picrasidine-J, (5); Crenatidine, (6) ; Canthin-6-one, (7) ; Picrasidine-T hydrochloride.

increase selective toxicity (Selective toxicity = EC_{50} value for Mouse mammary tumor FM3A cells/ EC_{50} for *P. falciparum*).

The perspective to study Thai *P. javanica* as potential antimalarial drugs resource

The indole alkaloids of *P. javanica* should be purified and determined their chemical structure again. Thai *P. javanica* shall be confirmed its chemical constituents. Further study shall be focus on the structure-activity relationship of these fourteen indole alkaloids of *P. javanica* as the potential antimalarial drugs. Also, the synthesis method for these indole alkaloids shall be investigated.

CONCLUSION

P. javanica is a critical natural source to develop the new antimalarial drugs having novel mode of action. Importantly, Thai *P. javanica* shall be reserved as medicinal plant for malaria disease treatment.

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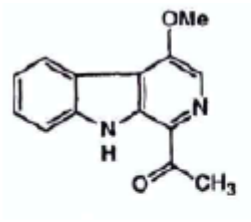
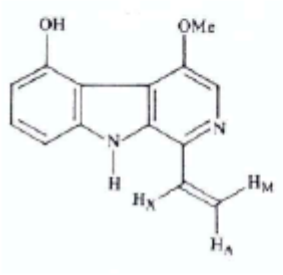
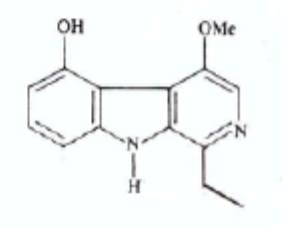


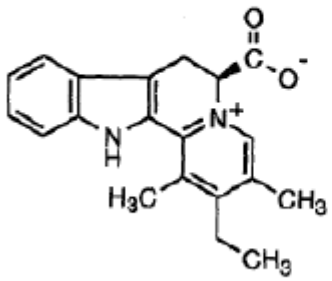
1-Acetyl-4-methoxy-β-carboline (8)



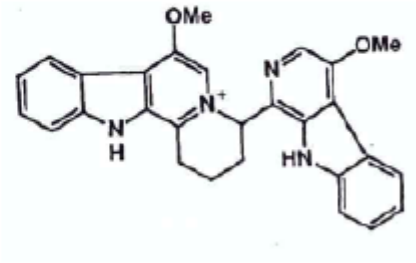
5-Hydroxy dehydrocrenatine (9)



5-Hydroxycrenatine (10)



Javacarboline (11)



Picrasidine G (12)

Figure 3. Others five chemical structure of indole alkaloids of *P. javanica*.

kind supervises at Tohoku University that was supporting by Japanese government scholarship.

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