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IN-VITRO AND IN-VIVO ANTIMALARIAL ACTIVITIES OF SOME QUASSINOIDS FROM BRUCEA JAVANICA FRUITS

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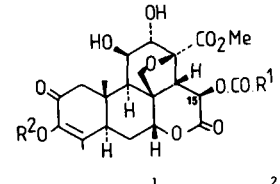
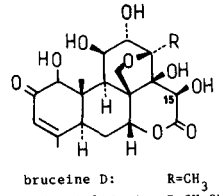
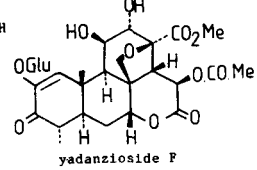
Brucea javanica L. (Merr.) Simaroubaceae fruits are used throughout Asia in traditional medicine as a treatment for malaria. We demonstrated earlier (O'Neill et al 1985a,b) the in vitro antimalarial activities of some chloroform-soluble quassinoids of the fruit and of its chloroform-insoluble, butanol-soluble extract. This butanol extract has now been purified by TLC and reverse phase HPLC and has yielded a series of quassinoids, 4 of which have been characterised by ^{1}H NMR and MS as bruceine D (1), yadanziolide A (2) and the quassinoid glycosides yadanziosides F (3) and I (4). Each of these compounds was assessed for in vitro antimalarial activity against chloroquine resistant P. falciparum by a standard technique (Desjardins et al, 1979) which measures inhibition of uptake of ^{3}H-hypoxanthine into the plasmodium. The results (Table 1) show that the non-glycosidic polar quassinoids (1) and (2) are highly active, having IC_{50} values of 0.015 and 0.050 $\mu g ml^{-1}$ respectively. This order of activity is similar to that of some more lipophilic chloroform-soluble quassinoids, eg (5) and (7). However, the quassinoid glycosides (3) and (4) are much less active, having IC_{50} values of 5.0 and 25.0 $\mu g ml^{-1}$ respectively. In fact, the 3-O-glucoside (4) is over 2000 times less active in vitro than its aglycone (7). The in vitro activity of the butanol extract is almost certainly attributable to highly active non-glycosidic quassinoids diluted with relatively inactive glycosides. The butanol extract and quassinoids (5) and (6) were tested for in vivo antimalarial activity against P. berghei infections in mice, using a standard 4-day test (Peters, 1984). The samples were administered orally each at 4 concentrations between 10-300 $mgKg^{-1}.day^{-1}$ for the butanol extract and between 0.1-3 $mg.Kg^{-1}.day^{-1}$ for the quassinoids. 5 Mice were used at each dose. Reduction in parasitaemia to 50% that in control mice, served as the index of antimalarial activity. Death which occurred before sacrifice on the 4th day was 'toxic death'. In this test chloroquine has an ED_{50} = 1.90 $mg.Kg^{-1}.day^{-1}$. (5) And (6) reduced parasitaemia in the mice, having ED_{50} values of 2.30 and 1.40 $mg.Kg^{-1}.day^{-1}$ respectively. No toxic deaths occurred with either compound at 3 $mg.Kg^{-1}.day^{-1}$, the highest concentration tested. The butanol extract was also highly active in vivo, having an ED_{50} of 43 $mg.Kg^{-1}.day^{-1}$. 9 Toxic deaths were produced at the highest dose levels (300 and 100 $mg.Kg^{-1}.day^{-1}$), which were well above the ED_{50} values. Clearly the value of quassinoids from B. javanica fruits as future antimalarials deserves further study.



bruceine A: R^1=$CH_2CH(Me)_2$, R^2=H
brusatol: R^1=CH=C(Me)$_2$, R^2=H
yadanzioside I: R^1=Me, R^2=Glucose
bruceine B: R^1=Me, R^2=H



bruceine D: R=CH_3
yadanziolide A: R=CH_2OH



yadanzioside F

Table 1. In vitro antimalarial activities of some quassinoids and extract from Brucea javanica fruit

		In vitro antimalarial activity against P. falciparum (K-1) IC_{50} $\mu g\ ml^{-1}$*
1.	bruceine D	0.015
2.	yadanziolide A	0.050
3.	yadanzioside F	5.0
4.	yadanzioside I	25.0
5.	bruceine A	0.011
6.	brusatol	0.003
7.	bruceine B	0.011
	B. javanica fruit butanol extract	0.50
	chloroquine	0.210

*based upon 2 fold dilutions in duplicate

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