IN-VITRO CYTOTOXIC, ANTIMALARIAL AND ANTIAMOEBIC ACTIVITIES OF PROTOBERBERINE ALKALOIDS

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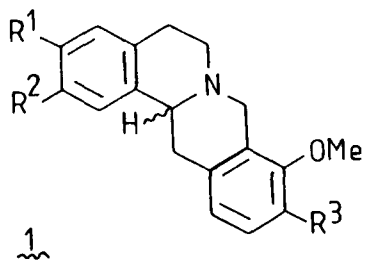
A wide range of plants is used in traditional medicine for the treatment of protozoal diseases (Phillipson and O'Neill, 1987). Some of these plants contain protoberberine alkaloids which may be responsible for their claimed therapeutic effects (Vennerstrom and Klayman, 1988). We have tested five alkaloids dissolved in culture medium for their activities against KB cells as a measure of cytotoxicity to mammalian cells and against two protozoa, Plasmodium falciparum (K1, multi-drug resistant strain) and Entamoeba histolytica (NIH 200). The results are given in Table 1.

Table 1. In vitro cytotoxic, antimalarial and antiamoebic activities of protoberberine alkaloids



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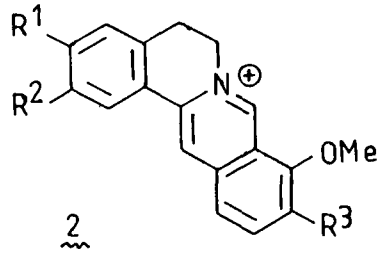

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Alkaloid[a]	R^1	R^2	R^3	KB(A)	IC_{50} values (μM) P. falciparum (B)	E. histolytica	A/B
(±)-canadine 1	$-OCH_2O-$		OMe	>730	>147	126	-
berberine 2	$-OCH_2O-$		OMe	7.3	0.97	111	8
thalifendine 2	$-OCH_2O-$		OH	>698	7.9	115	>88
jatrorrhizine 2	OH	OMe	OMe	>334	3.1	83	>106
columbamine 2	OMe	OH	OMe	78	1.9	156	41

[a]Alkaloids (2) tested as chloride salts

Berberine was the only alkaloid which was toxic to KB cells and the other four alkaloids were non-toxic. Berberine also proved to be the most active alkaloid against P. falciparum and showed marked contrast with the non-active (±)-canadine, the corresponding tetrahydroprotoberberine alkaloid with identical substituents in rings A and D. Thalifendine which differs from berberine in having R^3=OH instead of OMe was approximately ten times less active against P. falciparum. Jatrorrhizine and columbamine were similar to berberine in their activity against P. falciparum and they differ only in the nature of their R^1 and R^2 substituents in ring A (Table 1). None of the alkaloids showed significant activity against E. histolytica and hence showed some selective action. It is surprising that berberine was inactive because it is used in some countries as an amoebicide. In assessing relative in vitro cytotoxicity to antiplasmodial activity, berberine proved to have the least favourable ratio while the closely related jatrorrhizine had a more favourable ratio. These results lend some support to the use of plants containing protoberberine alkaloids for the treatment of malaria but not for the treatment of amoebiasis.

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Phillipson, J.D., O'Neill M.J. (1987) in Biologically Active Natural Products (Hostettmann, K, Lea, P.J. eds). pp 49-64, Clarendon, Oxford
Vennerstrom, J.L., Klayman, D.L. (1988) J. Med. Chem. 31: 1084-1087