Reversal of Chloroquine and Mefloquine Resistance in *Plasmodium falciparum* by the Two Monoindole Alkaloids, Icajine and Isoretuline

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The chloroquine-potentiating activities of the *Strychnos myrtoides* alkaloids strychnobrasiline and malagashanine has been demonstrated *in vitro and in vivo* by Rasoanaivo et al. in 1994 [1]. In the continuation of our search for new antiplasmodial indole alkaloids [2] and with the aim of finding new resistance-modifiers agents, eight naturally occurring monoindole alkaloids (icajine, strychnobrasiline, isoretuline, retuline, novacine, holstine and dolichantoside) were evaluated *in vitro* for their ability to inhibit *Plasmodium falciparum* growth and, in drug combination, to reverse the resistance of a chloroquine-resistant strain of *Plasmodium falciparum*. None of these indole alkaloids has significant intrinsic antiplasmodial activity (IC₅₀ > 10 μM or 5 μg/ml). Nevertheless, three alkaloids (icajine, isoretuline and strychnobrasiline) reverse chloroquine resistance at concentrations between 2.5 and 25 μg/ml (IF of 12.82 for isoretuline on W2 strain). The Interaction Factor (IF) equals 2, <2, or >2 for additive, antagonistic or synergistic effects of alkaloids on chloroquine inhibition, respectively. Icajine and isoretuline were also assessed *in vitro* for their mefloquine potentiating activity on a mefloquine-resistant strain of *Plasmodium falciparum*. Only icajine proved to be synergistic with mefloquine (IF = 15.38).

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