MALARIA JOURNAL

ORAL PRESENTATION Open Access

Antimalarial activity of ulein and proof of its action on the *Plasmodium falciparum* digestive vacuole

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From Parasite to Prevention: Advances in the understanding of malaria
Edinburgh, UK. 20-22 October 2010

Background

For thousands of years, plants have formed the basis of traditional medicine systems. The first drug to be used against malaria was quinine, which was isolated from South American *Cinchona* spp., in 1820. More recently, artemisinin, isolated in China from *Artemisia annua* L. and derivatives have been used successfully against malaria that has become resistant to chloroquine. We have been investigating plants traditionally used in Brazil to treat malaria and fevers.

Materials and methods

Screening of plant extracts for inhibition of *Plasmodium falciparum* growth was assayed by the [^{3}H]-hypoxanthine methodology. EtOH extract from *Aspidosperma parvifolium* was shown to be active (W2: IC_{50} = 42.51 ± 6.33 μg/ml) and has afforded the alkaloid ulein, which has shown a good antiplasmodial activity (W2: IC_{50} = 0.98 ± 0.20 μg/ml). Possible targets for ulein have been investigated by confocal microscopy using a proton fluorescent probe (BCECF-AM) in *P. falciparum* synchronous culture of W2-infected red blood cells by comparison with mefloquine (MQ) and bafilomycin A1 (BAF). Dynamic imaging was performed with the LSM 510 laser-scanning microscope (Carl Zeiss), using LSM 510 software (version 2.5), in the Axiovert 100 M microscope equipped with a 63xoil immersion objective. Software-based analysis of data allowed fluorescence imaging in a selected cell as a function of time.

Results

Dynamic images have shown that ulein (5 ng/ml), was able to mobilize protons altering the pH gradient in the digestive vacuole (DV), like MQ, a weak-base antimalarial quinoline. However, after the addition of ulein, BAF (4 μM), an inhibitor of the H+ pump from acidic compartments of eukaryotic cells, had no action on the DV suggesting that it is a target for ulein action.

Conclusions

This work shows that ulein is able to act on the DV, probably due to its alkaloid structure. Whether there is a participation of PfCRT, PfMDR1, and PfATPase6 in ulein action is still an open question. Its action on calcium homeostasis needs to be further investigated. These data disclose ulein as a potential antimalarial drug.

Acknowledgements
Funding was provided by FAPEMIG, CNPq, MS, Brazil.

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Published: 20 October 2010

doi:10.1186/1475-2875-9-S2-O9
Cite this article as: de Oliveira *et al.*: Antimalarial activity of ulein and proof of its action on the *Plasmodium falciparum* digestive vacuole. *Malaria Journal* 2010 **9**(Suppl 2):O9.

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