A221 *In vitro* and *in vivo* activities of various *Strychnos* alkaloids against *Plasmodium falciparum*

M. Frédérich [a,b], M.J. Jacquier [c], P. Thépenier [c], P. De Mol [b], M. Tits [a], G. Philippe [a], C. Delaude [a], L. Angenot [a], M. Zèches-Hanrot [c]

[a] University of Liège, Natural and Synthetic Drug Research Center, Laboratoire de Pharmacognosie, Avenue de l'Hôpital 1, B36, 4000-Liège, Belgium. [b] University of Liège, Laboratoire de Microbiologie Médicale, 4000-Liège, Belgium. [c] Laboratoire de Pharmacognosie, UMR 6013 CNRS, 51687 Reims, France.

Malaria is the major parasitic infection in many tropical and subtropical regions, leading to more than one million deaths (principally young African children) out of 400 million cases each year (1). The *in vitro* antiplasmodial, antiamoebic and cytotoxic activities of indolic alkaloids, more particularly isolated from various *Strychnos* species have been previously investigated (2,3). In this work, the *in vitro* antiplasmodial activities of 69 further alkaloids from various *Strychnos* species were evaluated against chloroquine-resistant and chloroquine-sensitive lines of *Plasmodium falciparum*. The compounds, mainly indolomonoterpenic alkaloids, exhibited a wide range of biological potencies in antiplasmodial assays. The most active alkaloids were also tested for cytotoxicity against HCT-116 cells to determine their antiplasmodial selectivity. As a result of these studies, structure – activity relationships of these alkaloids begin to emerge. Four types of bisindole skeletons exhibited high and selective activities against *Plasmodium*: They are: sungucine type (IC_{50} ranging from 80 nM to 10 µM), longicaudatine type (IC_{50} ranging from 0.5 µM to 10 µM), matopensine type (IC_{50} ranging from 150 nM to 10 µM) and usambarine type alkaloids. In the last structural type, we found isostrychnopentamine and ochrolifuanine A active against chloroquine-sensitive and -resistant strains (IC_{50} respectively of 100-150 nM and 100–500 nM) and dihydrousambarensine which exhibited a 30-fold higher activity against the chloroquine-resistant strain (IC_{50} = 32 nM). *In vivo*, isostrychnopentamine has been found to be partially active against blood stages of *P. berghei* in mice after subcutaneous administration.

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A222 Evaluation of sage phenolics for their antileishmanial activity and modulatory effects on interleukin-6, interferon and tumour necrosis factor-α-release in RAW 264.7 cells

O.A. Radtke [a], L.Y. Foo [b], Y. Lu [b], A.F. Kiderlen [c] and H. Kolodziej [a]

[a] Institut für Pharmazie, Pharmazeutische Biologie, Freie Universität Berlin, Königin-Luise-Str. 2+4, D-14195 Berlin, Germany. [b] New Zealand Institute for Industrial Research, Gracefield Road, Lower Hutt, New Zealand. [c] RobertKoch-Insttut, Department of Infectious Diseases, Nordufer 20, D-13353 Berlin, Germany.

Leishmaniasis is a major worldwide health problem with many clinical manifestations in humans. Species of the parasitic protozoa *Leishmania* are estimated to threaten some 350 million people world-wide (1). In previous studies, we have shown that tannins have favourable antileishmanial activity *in vitro* and might be considered as beneficial immunological response modifiers (2, 3). Continuing our research program to identify novel antileishmanial compounds, a series of seven structurally related sage phenolics including caffeic acid (**1**), rosmarinic acid (**2**), salvianolic acid I (**3**), K (**4**) and L (**5**), the methyl ester of 4 (**6**), and sagerinic acid (**7**) was tested for activity against both promastigotes and amastigotes of *L. major*, *L. donovani*, *L. guyanensis*, and *L. killicki* as well as immunomodulatory effects on macrophage functions.

None of the test samples revealed marked activity against the extracellular *Leishmania* forms (IC_{50} > 25 nM). In contrast, compounds **1**, **3**, **5** and **6** significantly reduced the intracellular survival of *Leishmania* amastigotes within RAW 264.7 cells (IC_{50} 3-23 nM) when compared with the reference Pentostam® (IC_{50} 10.6 nM). The *in vitro* TNF-inducing potential of the compounds producing 50% lysis in murine L929 cells ranged from 19 – 117 U/ ml. Furthermore, some test compounds showed appreciable IL-6 inducing potentials as reflected by increased proliferation rates of B9 cells (EC_{50} 3-40 U/ml). Only negligible interferon-like activities were induced as observed in a virus protection assay performed with culture supernatants from RAW cells treated with these sage phenolics.

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