Role of Single-Electron Oxidation Potential and Lipophilicity in the Antiplasmodial *in vitro* Activity of Polyphenols: Comparison to Mammalian Cells

Philippe Grellier[a], Aušra Nemeikaitė-Čėnienė[b], Jonas Šarlauskas[c], and Narimantas Čėnas[c,d,*]

[a] Museum National d'Histoire Naturelle, 61 rue Buffon, F-75231 Paris Cedex 05, France
[b] Institute of Immunology of Vilnius University, Molėtų Pl. 29, LT-08409 Vilnius, Lithuania
[c] Institute of Biochemistry, Mokslininkų 12, LT-08662 Vilnius, Lithuania. Fax: 370-5-2721 96. E-mail: ncenas@bchi.lt
[d] Vilnius Pedagogical University, Studentų 39, LT-08106 Vilnius, Lithuania

* Author for correspondence and reprint requests

Z. Naturforsch. **63c**, 445–450 (2008); received November 8/December 13, 2007

In spite of extensive studies, the structure-activity relationships in the action of polyphenols against the malaria parasite *Plasmodium falciparum* are poorly understood so far. As the mammalian cell cytotoxicity of polyphenols shows a negative dependence on the potential of the phenoxyl radical/phenol redox couple (E_7^2), due to the involvement of prooxidant events, and a positive dependence on the octanol/water distribution coefficient at pH 7.0 (log D), we examined the role of these parameters in their antiplasmodial *in vitro* activity. We found that the concentrations of hydroxybenzenes causing 50% inhibition of the growth of *P. falciparum* strain FcB1 (IC_{50}) are described by the regression log IC_{50} (μM) = 0.36 + 1.81 E_7^2 (V) – 0.10 log D [n = 11, r^2 = 0.760, $F(2.8)$ = 12.03]. The IC_{50} values of flavonoids (n = 5), comprising a separate less active series, did not depend on their E_7^2 values, 0.33 V–0.75 V. These findings were similar to the mammalian cell cytotoxicity data. However, the mammalian cell cytotoxicity of hydroxybenzenes showed more pronounced dependence on their E_7^2 values [$\Delta\log CL_{50}/\Delta E_7^2 = (6.9 - 5.1)\ V^{-1}$, where CL_{50} is the compound concentration for 50% cell survival] than on their antiplasmodial activity. Although it is unclear whether the prooxidant action is the main factor in the antiplasmodial action of polyphenols or not, our data showed that the ease of their oxidation (decrease in E_7^2) may enhance their activity. On the other hand, the different sensitivity of the mammalian cell cytotoxicity and the antiplasmodial activity of the hydroxybenzenes to their E_7^2 values implied that compounds with high oxidation potential may be used as relatively efficient antiplasmodial agents with low mammalian cell cytotoxicity.

Key words: Plasmodium falciparum, Flavonoids, Phenols