CHEMIJA. 2011. Vol. 22. No. 4. P. 229–233

Antiplasmodial *in vitro* activity of chysanthemoyl-substituted quinones: roles of single-electron reduction potential and glutathione reductase inhibition

Philippe Grellier[1],

Audronė Marozienė[2],

Henrikas Nivinskas[2],

Avtandil Dolidze[3],

Roin Chedia[3],

Nino Kavtaradze[3],

Narimantas Čėnas[2]*

[1] *Museum National d'Histoire Naturelle, UMR 7245 CNRS, 61 rue Buffon, F-75231 Paris Cedex 05, France*

[2] *Institute of Biochemistry of Vilnius University, Mokslininkų 12, LT-08662 Vilnius, Lithuania*

[3] *P. Melikishvili Institute of Physical and Organic Chemistry of Tbilisi University, Politkovskaia 5, 0186 Tbilisi, Georgia*

Although quinones have been a subject of great interest as possible antimalarial agents, their mechanisms of action against the malaria parasite *Plasmodium falciparum* are vaguely understood. Flavoenzyme electrontransferase-catalyzed single-electron reduction with the subsequent redox cycling and oxidative stress that accelerates with an increasing the the quinone / semiquinone redox couple (single-electron reduction potential, E^1_7), and the inhibition of the antioxidant flavoenzyme glutathione reductase (GR, EC 1.8.1.7) have been proposed, among several possible mechanisms. Here, we examined the *in vitro* activity against the *P. falciparum* strain FcB1 and the inhibition activity of *P. falciparum* GR several previously uninvestigated hydroxynaphtho- and hydroxyanthraquinones and their esters of chrysanthemic acid. Taken together with our previous results, the obtained data point to a less pronounced role of E^1_7 in the antiplasmodial activity of quinones as compared with their mammalian cell cytotoxicity, and to a modest role of GR inhibition underlying the other dominant mechanisms of quinone action. However, it also implies that quinones with a low reduction potential may be used as relatively efficient antiplasmodial agents with a low mammalian cell cytotoxicity.

Key words: *Plasmodium falciparum*, quinones, glutathione reductase

Abbreviations: E^1_7, potential of quinone / semiquinone redox couple at pH 7.0; IC_{50}, the compound concentration causing 50% parasite growth inhibition; cL_{50}, the compound concentration for 50% survival of mammalian cells; GR, glutathione reductase; K_i, inhibition constant; k_{cat}, catalytic constant; k_{cat} / K_m, bimolecular enzymatic reaction rate constant

INTRODUCTION

The antimalarial action of quinones has been a subject of intensive studies leading to the identification of a number of compounds that were active at micromolar or lower concentrations against the malarial parasite *Plasmodium falciparum* [1–8]. The action of quinones in *P. falciparum* is attributed to several posible mechanisms: i) flavoenzyme electrontransferase-catalyzed single-electron reduction with subsequent redox cycling and oxidative stress [1], ii) inhibition of mitochondrial electron-transport chain [7], iii) inhibition of dihydroorotate dehydrogenase which participates in pyrimidine *de novo* synthesis in *P. falciparum* [7], and iv) inhibition of the antioxidant flavoenzyme glutathione reductase (GR, EC 1.8.1.7) [4, 6]. However, except the specific inhibition of mitochondrial bc_1 complex of *P. falciparum* by atovaquone, the clinically used representative of 2-hydroxy-3-alkyl-1,4-naphthoquinones, and its analogues [7], and the

* Corresponding author. E-mail: narimantas.cenas@bchi.vu.lt

formation of alkylating products of two-electron reduction of aziridinyl-substituted quinones [8], the importance of other mechanisms in the antiplasmodial activity of quinones remains unclear. Using a multiparameter regression analysis, a positive correlation between the antipasmodial activity of quinones and their potency as *P. falciparum* GR inhibitors was also revealed [8].

The cytotoxicity of quinones in mammalian cells frequently increases with an increase in the potential of quinone / semiquinone redox couple (single-electron reduction potential, E_7^1) with the $\Delta\log cL_{50} / \Delta E_7^1 \sim -10\ V^{-1}$ relationship in which cL_{50} is compound concentration for 50% cell survival ([9] and references therein). This points to the oxidative stress as the main factor of their cytotoxicity, because, as a rule, the single-electron reduction of quinones by flavoenzymes-electrontransferases initiating redox cycling is characterized by $\Delta\log$ (rate constant) / $\Delta E_7^1 \sim 10\ V^{-1}$ relationship ([9, 10], and references therein). However, the role of E_7^1 of quinones in their antiplasmodial activity remains unclear, because previous studies involved either quinones with uncharacterized reduction potentials [3–7] or were focused mainly on aziridinyl-substituted quinones which are known to exhibit several modes of action [2, 8].

Here, we have examined the antiplasmodial *in vitro* activity and interaction with *P. falciparum* GR of several previously uncharacterized chrysanthemoyl-substituted quinones and their analogues. Taken together with our previous observations [8], these data indicate a less significant role of E_7^1 in the antiplasmodial activity of quinones as compared with their mammalian cell cytotoxicity, and an uncertain role of GR inhibition.

EXPERIMENTAL

Chrysanthemic acid (3-(1-isobutenyl)-2,2-dimethylcyclopanecarboxylic acid) and its methyl ester (the ratio of cis- and trans-isomers 1 : 1.7), 2,3-dihydroxy-1,4-naphthoquinone, 5-acetyloxy-1,4-naphthoquinone, 2-chrysanthemoyloxy-1,4-naphthoquinone, 2-chrysanthemoyloxy-3-hydroxy-1,4-naphthoquinone, and 1-hydroxy-2-chrysanthemoyloxy-9,10-anthraquinone (trans-isomers), 5-chrysanthemoyloxy-1,4-naphthoquinone the ratio of cis- and trans-isomers, 1 : 2) were obtained as described [11, 12]. The structure of the compounds was identified by elemental analysis, NMR (Bruker AMX-400), IR (UR-20), and m/s (Finnigan CQ). All other compounds were obtained from Sigma and used without further purification.

Recombinant GR from *P. falciparum* was prepared as described [13] and was a generous gift of Dr. Elisabeth Davioud-Charvet (Biochemie-Zentrum der Universität Heidelberg, Germany). The concentration of GR was measured according to $\varepsilon_{461} = 11.7\ mM^{-1}cm^{-1}$. All kinetic experiments were carried out spectrophotometrically, using a Perkin Elmer Lambda 25 UV–VIS spectrophotometer in 0.1 M K-phosphate buffer (pH 7.0) containing 1 mM EDTA at 25 °C. Steady-state rates of enzymatic NADPH oxidation were determined using $\Delta\varepsilon_{340} = 6.2\ mM^{-1}cm^{-1}$. At the saturating concentrations of substrates, 100 μM NADPH and 1 mM GSSG, the catalytic constant (k_{cat}, or moles of NADPH oxidized per mole of enzyme active center per second) of GR was 145 s^{-1}. In reversible inhibition studies, the reaction rates were determined at a fixed NADPH concentration (100 μM) and at varying GSSG concentrations (1.0–0.13 mM) in both the presence and absence of 4–5 different concentrations of the inhibitor. The inhibition constants K_i were obtained from the dependence of $1/k_{cat}$ on the inhibitor concentration [I]. In the case of incomplete inhibition, i. e. nonlinear dependence of $1/k_{cat}$ on [I], the K_i corresponds to the inhibitor concentration causing a 50% enzyme inhibition, and was calculated from the plot 1/inhibition degree *vs.* 1/[I]. The quinone reductase activity of GR was calculated according to the rates of quinone-mediated reduction of cytochrome *c* (50 μM) in the presence of 50 μM NADPH, using $\Delta\varepsilon_{550} = 20\ mM^{-1}\,cm^{-1}$.

The chloroquine-resistant *Plasmodium falciparum* strain FcB1 from Colombia was kindly provided by Dr. H. D. Heidrich (Max-Planck Institut für Biochemie, Martinsried bei München, Germany) and is deposited in the Protist collection of Musée National d'Histoire Naturelle, Paris, France. *P. falciparum* FcB1 strain was maintained in continuous culture on human erythrocytes. *In vitro* antiplasmodial activity was determined using a modified semiautomatic microdilution technique according to the extent of [^{3}H]hypoxanthine incorporation [8, 14]. Stock solutions of test compounds in DMSO were serially diluted with culture medium and added to asynchronous parasite cultures (1% parasite-infected cells and 1% final hematocrit) for 24 h, at 37 °C, prior to the addition of [^{3}H]hypoxanthine, for 24 h. The experiments were repeated in triplicate. The statistical and multiparameter regression analyses were performed using Statistica (version 4.3) (Statsoft Inc., 1993).

RESULTS AND DISCUSSION

Since the previous studies of the antiplasmodial activity involved a limited number of aziridinyl-unsubstituted quinones with available E_7^1 values, we aimed to extend their number. Thus, we studied the activity of chrysanthemoyl-substituted quinones and several analogues (compounds 7, 9–11, 14, 16, and 17 (Table)) with the E_7^1 values determined in our previous work [15]. The values of IC_{50} (the compound concentration causing a 50% *P. falciparum* growth inhibition) of compounds and their E_7^1 values are given in Table together with data on the activity of other quinones towards the same *P. falciparum* strain [8]. The antiplasmodial activity of all examined quinones (Table) exhibited a scattered and poorly expressed dependence on their E_7^1 (Fig. 1) with the coefficient $\Delta\log IC_{50} / \Delta E_7^1 = -3.114 \pm 1.001\ V^{-1}$ ($r^2 = 0.362$, $F(1,17) = 9.67$). Because partly-substituted quinones may undergo side-reactions with reduced glutathione (GSH) and other nucleophiles, we limited our

data set by including only fully-substituted quinones and low-potential 2-hydroxy-1,4-naphthoquinones which react with GSH at negligibly low rates [17] (compounds 4, 14–19 (Table)). However, it did not improve the correlation, giving $r^2 = 0.227$ (data not shown).

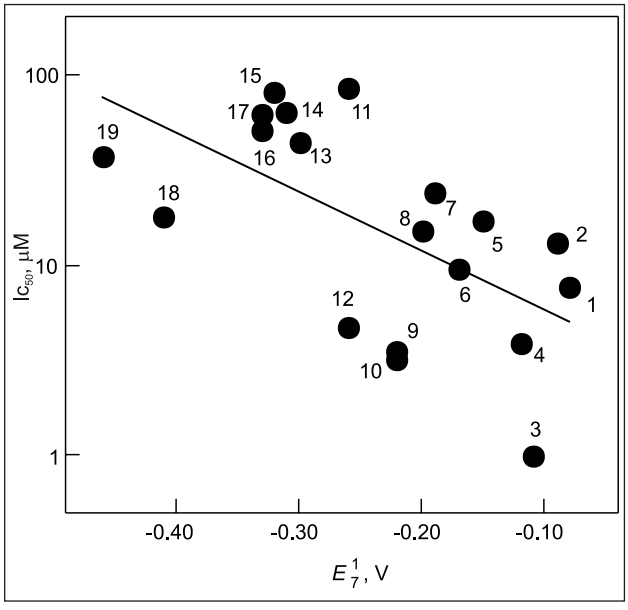

Fig. 1. Relationship between the E^1_7 values of quinones and their IC_{50} against *P. falciparum*. The numbers of compounds as in Table

Prooxidant events may take place during the action of quinones against *P. falciparum* due to their redox cycling in parasitized erythrocytes [2]. However, unlike what was observed in mammalian cell cytotoxicity studies, we were unable to test the possible protective effects of desferroxamine and the antioxidant *N,N'*-diphenyl-*p*-phenylene diamine [9, 17], because these compounds inhibited the growth of FcB1 *P. falciparum* with the IC_{50} close to 10 μM [18]. It has also been reported that 0.4 mM mannitol, a scavenger of OH· radical, protected against the presumably prooxidant antiplasmodial activity of curcumin [19]. In our hands, 0.4 mM mannitol did not inhibit the growth of FcB1 *P. falciparum,* neither did it protect against the activity of the several quinones examined.

Another suggested mechanism of the antiplasmodial activity of quinones and other redox active aromatic compounds, such as methylene blue, is the inhibition of flavoenzyme glutathione reductase (GR) [4, 6, 8, 13]. GR, which contains FAD and a redox-active catalytic disulfide in the active center, catalyzes the reduction of glutathione disulfide (GSSG) at the expense of NADPH. It is assumed that *P. falciparum* GR plays an important role during the intraerythrocyte growth of the parasite, protecting it from oxidative stress [20]. By analogy with previous observations [4, 8], we showed that quinones acted on GR as noncompetitive inhibitors *vs.* GSSG at a fixed NADPH concentration (Fig. 2), thus suggesting that they bind at the interface domain of the two GR

Table. **The values of single-electron reduction potentials of quinones (E^1_7) [10, 16], their concentrations causing 50% inhibition of *Plasmodium falciparum* strain FcB1 (IC_{50}), their inhibition constants of *P. falciparum* glutathione reductase (K_i, the maximal inhibition degree shown in parentheses), and their catalytic (k_{cat}) and bimolecular (k_{cat}/K_m) rate constants of reduction by *P. falciparum* GR**

No.	Quinone	E^1_7 (V)	IC_{50} (μM)	K_i (μM)	k_{cat} (s^{-1})	k_{cat}/K_m ($M^{-1}s^{-1}$)
1.	2,6-Dimethyl-1,4-benzoquinone	–0.08	7.6 ± 0.5[b]	2.80 ± 0.30 (74)[b]	2.2 ± 0.4[b]	(1.3 ± 0.2) × 10^{4}[b]
2.	5-Hydroxy-1,4-naphthoquinone	–0.09	13.0 ± 2.3[b]	0.15 ± 0.05 (65)[b]	11.4 ± 1.0[b]	(8.0 ± 1.8) ×10^{5}[b]
3.	5,8-Dihydroxy-1,4-naphthoquinone	–0.11	1.0 ± 0.1[b]	0.60 ± 0.20 (5.8)[b]	14.0 ± 1.8[b]	(8.6 ± 1.4) × 10^{5}[b]
4.	9,10-Phenanthrene quinone	–0.12	3.9 ± 0.2[b]	2.50 ± 0.50[b]	0.44 ± 0.1[b]	(8.4 ± 1.8)× 10^{3}[b]
5.	1,4-Naphthoquinone	–0.15	17.0 ± 1.3[b]	2.50 ± 0.30[b]	2.2 ± 0.2[b]	(1.1 ± 0.1) × 10^{4}[b]
6.	Trimethyl-1,4-benzoquinone	–0.17	9.6 ± 0.7[b]	16.2 ± 2.8[b]	≥0.40[b]	≥1.4 × 10^{3}[b]
7.	2-Chrysanthemoyloxy-1,4-naphthoquinone	–0.19[a]	24.0 ± 9.8	0.61 ± 0.12 (80)	0.29 ± 0.04	(4.9 ± 0.9) × 10^{3}
8.	2-Methyl-1,4-naphthoquinone	–0.20	15.0 ± 1.0[b]	39.0 ± 7.0[b]	0.28 ± 0.10[b]	(4.0 ± 0.6) × 10^{3}[b]
9.	5-Chrysanthemoyloxy-1,4-naphthoquinone	–0.22[a]	3.5 ± 0.4	5.90 ± 0.80 (63)	0.25 ± 0.05	(2.1 ± 0.5) × 10^{4}
10.	5-Acetyloxy-1,4-naphthoquinone	–0.22[a]	3.2 ± 0.6	0.55 ± 0.13 (73)	0.16 ± 0.03	(1.0 ± 0.3) × 10^{4}
11.	2,3-Dihydroxy-1,4-naphthoquinone	–0.26[a]	85.0 ± 20	50.0 ± 11.0	≥0.07	(7.0 ± 1.5) × 10^{3}
12.	Tetramethyl-1,4-benzoquinone	–0.26	4.7 ± 0.4[b]	160.0 ± 20[b]	0.6 ± 0.10[b]	(2.0 ± 0.4) × 10^{3}[b]
13.	1,8-Dihydroxy-9,10-anthraquinone	–0.30	44.0 ± 4.9[b]	90.0 ± 10[b]	≥0.20[b]	(7.4 ± 1.4) × 10^{2}[b]
14.	2-Chrysanthemoyloxy-3-hydroxy-1,4-naphthoquinone	–0.31[a]	63.0 ± 3.0	50.0 ± 8.0	≥0.03	(1.4 ± 0.4) × 10^{3}
15.	1,2-Dihydroxy-9,10-anthraquinone	–0.32	81.3 ± 3.5	≥200	0.14 ± 0.05	(5.0 ± 0.5) × 10^{3}
16.	1,4-Dihydroxy-9,10-anthraquinone	–0.33[a]	50.7 ± 3.0[b]	170.0 ± 20	0.22 ± 0.08[b]	(6.0 ± 1.2) × 10^{3}[b]
17.	1-Hydroxy-2-chrysanthemoyloxy-9,10-anthraquinone	–0.33[a]	61.3 ± 9.0	31.0 ± 5.0	≥0.5	(6.0 ± 0.7) × 10^{3}
18.	2-Hydroxy-1,4-naphthoquinone	–0.41	18.0 ± 0.8[b]	≥500[b]	–	–
19.	2-Hydroxy-3-methyl-1,4-naphthoquinone	–0.46	37.0 ± 6.1[b]	≥500[b]	–	–
20.	Chrysanthemic acid	–	747 ± 56	≥500	–	–
21	Ethylchrysanthemate	–	217 ± 67	240.0 ± 20	–	–

[a] From Ref. [15]. [b] From Ref. [8].

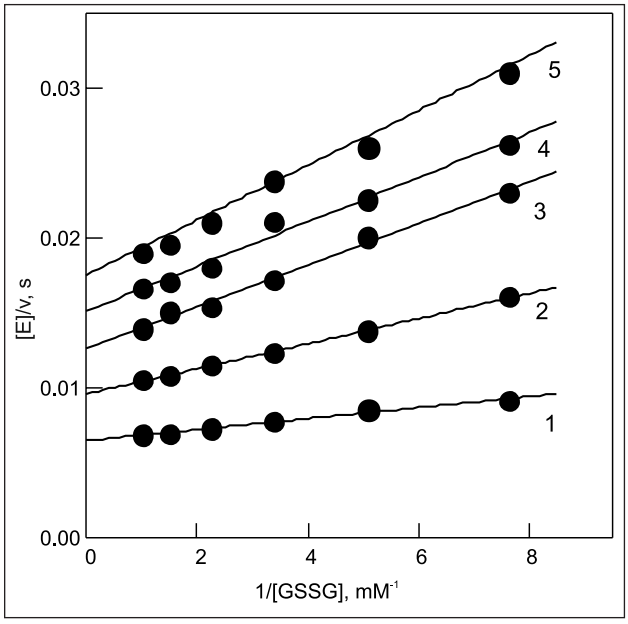

Fig. 2. Inhibition of *P. falciparum* GR by 2-chrysanthemoyloxy-1,4-naphthoquinone. Inhibitor concentration: 0 (1), 0.25 μM (2), 0.5 μM (3), 0.75 μM (4), and 1.0 μM (5); NADPH concentration: 100 μM

subunits [13, 20]. This domain is distant from both NADP(H) and GSSG-binding sites. We found that the antiplasmodial activity of quinones exhibited a weak positive dependence on their GR inhibition constant, K_i (Table), with the coefficient $\Delta\log IC_{50} / \Delta\log K_i = 0.289 \pm 0.101$ ($r^2 = 0.324$, $F(1,17) = 8.16$, data not shown). Neither a two-parameter regression analysis using E_7^1 and $\log K_i$ as independent variables did improve the correlation, giving $\Delta\log IC_{50} / \Delta E_7^1 = -2.183 \pm 1.90\ V^{-1}$ and an uncertain relationship between IC_{50} and K_i ($\Delta\log IC_{50} / \Delta\log K_i = 0.109 \pm 0.187$, $r^2 = 0.376$, data not shown). However, this may be explained by a general decrease of K_i of quinones upon an increase in their E_7^1 (Table), which is described by a relatively well expressed linear relationship with the ratio $\Delta\log K_i / \Delta E_7^1 = -8.583 \pm 1.327\ V^{-1}$ ($r^2 = 0.711$, data not shown). Thus, in fact, E_7^1 and $\log K_i$ may not be considered as truly independent parameters. Overall, the current results of regression analysis are similar to our previous ones [8], except the less pronounced role of GR inhibition. This discrepancy may be explained by the use of aziridinyl-substituted quinones in our previous study [8], as they possess an additional antiplasmodial action mechanism. One may also note that, although chrysanthemic acid and its methyl ester do inhibit GR, chrysanthemoyl-substituted quinones do not exhibit a high affinity for GR, acting as its inhibitors (Table). In addition, quinones undergo GR-catalyzed redox cycling and convert the antioxidant functions of GR into prooxidant ones [4, 6, 8]. The rate constants of quinone reduction by GR (Table) show that the reactivity of the currently investigated compounds 7, 9–11, 14, 16, and 17 is similar to that of previously investigated quinones with similar E_7^1 values [8]. However, the reduction of quinones by GR may not be considered as an important factor in their antiplasmodial activity, because GR reduces quinones by 1–2 orders of magnitude slower than does ferredoxin : $NADP^+$ reductase, another recently characterized source of quinone free radicals in *P. falciparum*.

Our findings show that the link between the antiplasmodial activity of quinones and their E_7^1 values or their efficiency in inhibiting GR is vague. It contrasts with the pronounced influence of E_7^1 on the antiplasmodial activity of other redox cycling compounds – nitrobenzenes and nitrofurans – which are characterized by $\Delta\log IC_{50} / \Delta E_7^1 = -8.295 \pm \pm 1.771\ V^{-1}$ and with the mammalian cell cytotoxicity of quinones [9]. It points to some other dominant mechanisms of action of quinones on *P. falciparum*, such as an inhibition of the mitochondrial respiratory chain or pyrimidine *de novo* biosynthesis [7]. Nevertheless, the different sensitivity of the mammalian cell cytotoxicity and the antiplasmodial activity of quinones to their E_7^1 values implies that compounds with a low reduction potential may be used as relatively efficient antiplasmodial agents with a low mammalian cell cytotoxicity.

CONCLUSIONS

Data of this work show that the presence of a chrysanthemate substituent does not significantly influence the antiplasmodial activity of quinones and their inhibition of glutathione reductase. The link between the antiplasmodial activity of quinones and their E_7^1 values or their efficiency to inhibit GR is not well expressed. It indicates the dominant role of the other mechanisms of action. However, the low sensitivity of antiplasmodial activity of quinones to their E_7^1 values implies that compounds with a low reduction potential may be used as relatively efficient antiplasmodial agents with a low mammalian cell cytotoxicity.

ACKNOWLEDGEMENTS

We thank Dr. Elisabeth Davioud-Charvet (Biochemie-Zentrum der Universität Heidelberg, Germany) for her generous gift of recombinant GR from *P. falciparum*.

Received 2 June 2011
Accepted 26 June 2011

References

1. J. L. Vennerstrom, J. W. Eaton, *J. Med. Chem.*, **31**, 1269 (1988).
2. T.-S. Lin, L.-Y. Zhu, S.-P. Xu, A. A. Divo, A. C. Sartorelli, *J. Med. Chem.*, **34**, 1634 (1991).
3. C. L. Zani, E. Chiari, A. U. Krettli, S. M. F. Murta, M. L. Cuningham, A. H. Fairlamb, A. J. Romanha, *Bioorg. Med. Chem.*, **5**, 2185 (1997).
4. C. Biot, H. Bauer, R. H. Schirmer, E. Davioud-Charvet, *J. Med. Chem.*, **47**, 5972 (2004).
5. E. Perez-Sacau, A. Estevez-Braun, A. G. Ravelo, D. Gutierrez Yapu, A. Gimenez Turba, *Chem. Biodivers.*, **2**, 264 (2005).

6. H. Bauer, K. Fritz-Wolf, A. Winzer, S. Kühner, S. Little, V. Yardley, B. Palfey, R. H. Schirmer, E. Davioud-Charvet, *J. Am. Chem. Soc.*, **126**, 10784 (2006).
7. T. Rodriguez, F. Lopez, R. Moreira, *Curr. Med. Chem.*, **17**, 929 (2010).
8. P. Grellier, A. Marozienė, H. Nivinskas, J. Šarlauskas, A. Aliverti, N. Čėnas, *Arch. Biochem. Biophys.*, **494**, 32 (2010).
9. A. Nemeikaitė-Čėnienė, J. Šarlauskas, Ž. Anusevičius, H. Nivinskas, N. Čėnas, *Arch. Biochem. Biophys.*, **416**, 110 (2003).
10. N. Čėnas, Ž. Anusevičius, H. Nivinskas, L. Misevičienė, J. Šarlauskas, *Methods Enzymol.*, **382B**, 258 (2004).
11. N. Kavtaradze, T. Kurtskhalia, T. Korkia, T. Shatakishvili, R. Chedia, A. Dolidze, *Georgia Chem. J.*, **5**, 561 (2005).
12. I. Jinikashvili, N. Kavtaradze, A. Dolidze, R. Chedia, *Georgian Engineer. News*, **1**, 251 (2006).
13. P. M. Färber, L. D. Arscott, C. H. Williams, Jr., K. Becker, R. H. Schirmer, *FEBS Lett.*, **422**, 311 (1998).
14. P. Grellier, J. Šarlauskas, Ž. Anusevičius, A. Marozienė, C. Houee-Levin, J. Schrevel, N. Čėnas, *Arch. Biochem. Biophys.*, **393**, 199 (2001).
15. A. Marozienė, A. Nemeikaitė-Čėnienė, N. Čėnas, *Chemija*, **22**, 162 (2011).
16. P. Wardman, *J. Phys. Chem. Ref. Data*, **18**, 1637 (1989).
17. K. Öllinger, A. Brunmark, *J. Biol. Chem.*, **266**, 21496 (1991).
18. P. Grellier, A. Nemeikaitė-Čėnienė, J. Šarlauskas, N. Čėnas, *Z. Naturforsch.*, **63c**, 445 (2008).
19. L. Cui, J. Miao, L. Cui, *Antimicrob. Agents Chemother.*, **51**, 488 (2007).
20. K. Becker, L. Tilley, J. L. Vennerstrom, D. Roberts, S. Rogerson, H. Ginsburg, *Int. J. Parasitol.*, **61**, 1509 (2004).

Philippe Grellier, Audronė Marozienė, Henrikas Nivinskas, Avtandil Dolidze, Roin Chedia, Nino Kavtaradze, Narimantas Čėnas

CHRIZANTEMOIL-PAVADUOTŲ CHINONŲ ANTIPLAZMODINIS AKTYVUMAS *IN VITRO*: VIENELEKTRONINĖS REDUKCIJOS POTENCIALO IR GLIUTATIONREDUKTAZĖS INHIBICIJOS ĮTAKA

S a n t r a u k a

Nors chinonai yra nuolat tiriami kaip potencialūs antimaliariniai agentai, jų poveikio mechanizmai maliarijos parazitui *Plasmodium falciparum* nėra pakankamai suprasti. Greta kitų galimų mechanizmų nagrinėjami ir flavininių fermentų elektrontransferazių sukeliami chinonų cikliniai redoks virsmai, kurie turėtų suintensyvėti didėjant chinono / semichinono redoks poros potencialui (vienelektroninės redukcijos potencialui, E_7^1), ir antioksidacinio flavininio fermento gliutationreduktazės (GR, FK 1.8.1.7) inhibicija chinonais. Šiame darbe ištirtas kelių anksčiau netirtų hidroksinafto- ir hidroksiantrachinonų bei jų chrizantemų rūgšties esterių poveikis *P. falciparum* kamienui FcB1 ir jų inhibuojantis poveikis GR iš *P. falciparum.* Gautieji duomenys ir ankstesnių tyrimų rezultatai leidžia teigti, kad chinonų E_7^1 įtaka jų antiplazmodiniam aktyvumui yra daug menkesnė, palyginus su potencialo įtaka chinonų citotoksiškumui žinduolių ląstelėse, o GR inhibicijos įtaka taip pat menka. Tai reiškia, kad vyrauja kiti chinonų veikimo mechanizmai. Antra vertus, galima teigti, kad mažo redukcijos potencialo chinonai gali būti naudojami kaip santykinai efektyvūs antiplazmodiniai agentai, pasižymintys mažu citotoksiškumu žinduolių ląstelėms.