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Prooxidant cytotoxicity of polyphenolic compounds in primary mice splenocytes: the role of redox potential and lipophilicity

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Flavonoids and other polyphenolic antioxidants frequently exhibit the prooxidant cytotoxicity in malignant mammalian cells, which increases with an ease of their oxidation (decrease in the redox potential of the phenoxyl radical / phenol couple, $E_7(Q^{\cdot-}/QH_2)$), and an increase in their lipophilicity (log *P* or log *D*). However, little is known about their cytotoxicity in primary cells, although it may help to understand their side effects, and the possible selectivity of their particular structures towards the malignant cells. We found that the 24 h-action of flavonoids (n = 10) and hydroxybenzenes (n = 13) in primary mice splenocytes was described by two separate although scattered quantitative structure-activity relationships (QSARs), each showing the negative dependence of cytotoxicity on the $E_7(Q^{\cdot-}/QH_2)$ of compounds, and a positive dependence on their log *D*. The cytotoxicity of polyphenols was decreased by antioxidants and inhibitors of cytochromes P-450, α-naphthoflavone and isoniazide, and increased by an inhibitor of catechol-*O*-methyltransferase, 3,5-dinitrocatechol. Taken together with the QSARs of flavonoids and hydroxybenzenes in several malignant (cancer or virus-transformed) cells, our data point to a limited importance of flavonoids and other polyphenols as possible anticancer agents because their action in primary and transformed (cancer) cells follows the similar trends.

Key words: flavonoids, polyphenols, antioxidants, cytotoxicity, oxidative stress

Abbreviations: BCNU – 1,3-bis(2-chloroethyl)-1-nitrosourea; cL_{50} – concentration of agent for 50% cell death; COMT – catechol-*O*-methyltransferase; *D* – octanol / water distribution coefficient of compound at pH 7.0; DPPD – *N,N*'-diphenyl-*p*-phenylene diamine; $E_7(Q^{\cdot-}/QH_2)$ – redox potential of semiquinone / hydroquinone (phenoxyl radical / phenol) couple at pH 7.0; $E_7(Q^{\cdot-}/QH_2)_{(calc.)}$ – calculated redox potential of semiquinone / hydroquinone (phenoxyl radical / phenol) couple at pH 7.0; QSAR – quantitative structure-activity relationship; ROS – reactive oxygen species.

INTRODUCTION

Flavonoids and other polyphenols, e. g. the derivatives of gallic and caffeic acid (Fig. 1), are commonly regarded as the antioxidants which protect the cell from the reactive oxygen species (ROS), e. g. superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH\cdot$) [1]. On the other hand, high concentrations of polyphenols are cytotoxic, causing an increase in the mitochondrial permeability, cytochrome *c* release, the inhibition of topoisomerases and kinases, the activation of signal-transducing proteins, induction of apoptosis (a programmed cell death), and a necrotic cell death [2–7]. Importantly, these phenomena take place together with the oxidative stress (enhanced ROS production) exerted by the polyphenols. The latter arises from the prooxidant action of their quinone- and / or quinomethide (auto)oxidation products [8–11], which may participate in the redox cycling catalyzed by single-electron transferring flavoenzymes with the concomitant production of ROS, and / or deplete the cellular –SH antioxidants. In the cell, polyphenols can be oxidized by the transition metals, mitochondrial bc_1 complex and cytochrome *c*, and during the reductive Fe^{2+} mobilization from ferritin [12–14]. Polyphenols also autooxidize in the cell growth medium with the production of extracellular H_2O_2 [15].

Importantly, several studies have shown that the cytotoxicity of polyphenols increased with an ease of their (auto) oxidation (decrease in the redox potential of the phenoxyl

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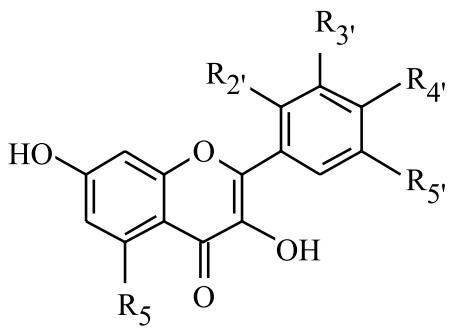
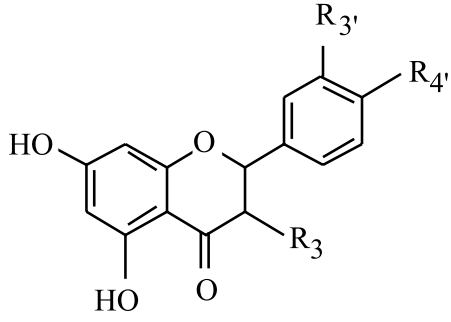


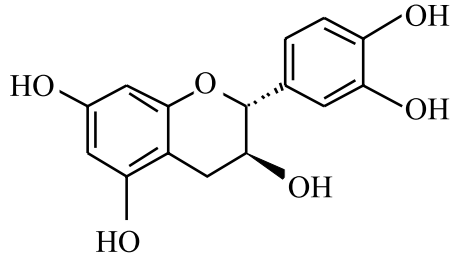
Flavonols

$R_5 = R_{3'} = R_{4'} = R_{5'} = OH$; $R_{2'} = H$	Myricetin
$R_5 = R_{3'} = R_{4'} = OH$; $R_{2'} = R_{5'} = H$	Quercetin
$R_5 = R_{2'} = R_{4'} = OH$; $R_{3'} = R_{5'} = H$	Morin
$R_5 = R_{4'} = OH$; $R_{2'} = R_{3'} = R_{5'} = H$	Kaempferol
$R_5 = OH$; $R_{2'} = R_{3'} = R_{4'} = R_{5'} = H$	Galangin
$R_5 = R_{2'} = R_{5'} = H$; $R_{3'} = R_{4'} = OH$	Fisetin

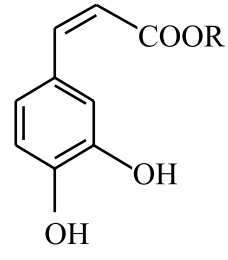


Flavonols

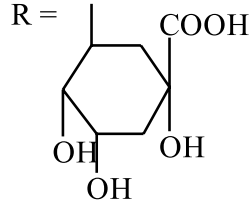
$R_3 = R_{3'} = R_{4'} = OH$	Taxifolin
$R_3 = R_{3'} = H$; $R_{4'} = OH$	Naringenin
$R_3 = H$; $R_{3'} = OH$; $R_{4'} = OCH_3$	Hesperetin



Flavan-3-ol
Catechin

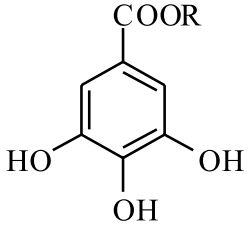


R = H Caffeic acid



Chlorogenic acid

Derivatives of gallic acid



a) R = H
b) R = CH_3
c) R = C_2H_5
d) R = C_4H_9
e) R = C_8H_{17}

Fig. 1. The structures of nontrivial polyphenolic antioxidants studied in this work

radical / phenol couple, $E_7(Q^{-\cdot}/QH_2)$), and an increase in their lipophilicity [11, 16, 17, 18]. Taken together with the antioxidant protection, these data show that the formation of the prooxidant products of polyphenol (auto)oxidation may be a major or a rate-determining factor in their cytotoxicity.

One may note that the majority of the cytotoxicity studies of polyphenols were performed in malignant (tumour or virus-transformed) mammalian cells ([2–8, 11, 16, 17], and references therein), with an emphasis on their potential anticancer action. However, their parallel studies in the primary (nontransformed) cells were scarce although they may be useful in the elucidation of the side-effects of polyphenols, and their selectivity towards the cancer cells. These studies were mainly confined to the short time, 2–4 h, experiments in primary rat hepatocytes ([10, 18, 19], and references therein). In our opinion, the primary mice splenocytes may be a more advantageous and novel cellular model because they enable to perform longer, 24 h, cytotoxicity tests [20]. The importance of

their studies may be attributed to a more adequate reflection of the long term organism exposure effects to polyphenols, i. e. their chronic cytotoxicity, as well as to the development of the quantitative structure-activity relationships (QSARs) for polyphenols. In this work, we examined the cytotoxicity of a series of flavonoids and hydroxybenzenes in primary mice splenocytes and obtained important information on the role of redox potential and lipophilicity in their cytotoxicity.

EXPERIMENTAL

Flavonoids and other polyphenols used in this study (Fig. 1), desferrioxamine, *N,N*'-diphenyl-*p*-phenylene diamine (DPPD), 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), 3,5-dinitrocatechol, dicumarol, α-naphthoflavone, and izoniazide were obtained from Sigma-Aldrich and were used as received.

In the studies of the primary mice splenocytes, 4- to 8-week old male and female BALB/c mice (24 ± 2.0 g) were kept under standard conditions and were given food and water *ad libitum*. The mice were sacrificed by decapitation, their spleen was removed according to an established procedure [20]. These experiments were approved by the Lithuanian Veterinary and Food Service (License No. 0215, 2011). For each experiment, spleens of 3–5 mice were used as a source of splenocytes. Erythrocytes were lysed by 5 min exposure in lysis solution (0.155 M NH_4Cl, 10 mM KCl, 0.1 mM EDTA). After washing the cells twice with RPMI 1640 medium, they were resuspended at the concentration of 10^6 cells/ml in RPMI 1640 medium with 5% fetal bovine serum and antibiotics, and were used for the further experiments. Cell viability was determined after 24 h of incubation of splenocytes with the examined compounds in 96-well cell culture plates (200 µl suspension per well) according to a Trypan blue exclusion test.

Statistical and multiparameter regression analysis was performed using Statistica (version 4.3, StatSoft Inc., 1993).

RESULTS AND DISCUSSION

We studied the 24 h cytotoxicity of flavonoids ($n = 10$) and hydroxybenzenes ($n = 13$) (Fig. 2) in primary mice splenocytes, determining their concentrations causing 50% cell death, cL_{50} (Table1). As in the previous studies in several malignant cell lines ([11, 16, 17], Table2), we found that the cytotoxicity of hydroxybenzenes and flavonoids in primary splenocytes were described by two separate equations. The cytotoxicity of hydroxybenzenes is described by two-parameter Eq. (1):

Table 1. **The redox potentials of phenoxyl radical / phenol couple of polyphenols determined by pulse-radiolysis ($E_7(Q^-/QH_2$, standard error of estimate, ±0.015 V) [21, 22], their redox potential values calculated from the reactivity towards the single-electron oxidants ($E_7(Q^-/QH_{2\ (calc.)}$, standard error of estimate, ±0.04 V) [17], the calculated octanol / water (pH 7.0) distribution coefficients (D) [11, 17], and the concentrations for 50% cell survival (cL_{50}) of flavonoids and hydroxybenzenes in 24 h cytotoxicity tests in primary mice splenocytes**

No.	Compound	$E_7(Q^-/QH_2$, V[a]	$E_7(Q^-/QH_{2\ (calc.)}$, V	log *D*	cL_{50}, µM
			Hydroxybenzenes		
1.	Di-3,5-*t*-butylcatechol	0.39		4.26	56 ± 5.0
2.	*t*-Butylhydroquinone	0.46	0.50	2.30	98 ± 8.0
3.	4-Methylcatechol	0.46		1.34	28 ± 4.0
4.	Hydroquinone	0.48	0.48	0.64	58 ± 7.0
5.	Catechol	0.53	0.54	0.88	58 ± 8.0
6.	Caffeic acid	0.54		–0.08	188 ± 20
7.	Chlorogenic acid	0.54		–2.36	1 400 ± 160
8.	Gallic acid	0.56		–1.76	880 ± 90
9.	Methylgallate	0.56		1.54	315 ± 30
10.	Ethylgallate	0.56	0.49	2.07	139 ± 20
11.	Butylgallate	0.56		3.13	139 ± 18
12.	Octylgallate	0.56		5.26	41 ± 6.0
13.	*p*-Methoxyphenol	0.73	0.73	1.30	≥1 000
			Flavonoids		
14.	Quercetin	0.33	0.36	2.74	150 ± 17
15.	Fisetin	(0.33)	0.36	1.78	100 ± 19
16.	Myricetin	(0.36)	0.31	2.83	34 ± 4.0
17.	Taxifolin	0.50	0.56	1.22	875 ± 90
18.	Catechin	0.57	0.55	0.45	119 ± 15
19.	Morin	(0.60)	0.40	1.97	180 ± 20
20.	Galangin	(0.62)	0.72	2.68	312 ± 25
21.	Hesperetin	0.72	0.75	2.30	925 ± 75
22.	Kaempferol	(0.75)	0.39	2.69	300 ± 25
23.	Naringenin	–	0.79	2.59	550 ± 60

[a] The redox potential values for flavonoids calculated in Ref. [22] are shown in parentheses.

$$\log cL_{50} = (0.477 \pm 0.699) + (3.599 \pm 1.269)\, E_7(Q^-/QH_2) - (0.145 \pm 0.048) \log D \ (r^2 = 0.683), \quad (1)$$

where the $E_7(Q^-/QH_2)$ (V) is the redox potential of the semiquinone / hydroquinone couple, and D is the octanol / water (pH 7.0) distribution coefficient of the compound.

The analysis of the cytotoxicity of flavonoids is more complex because, according to our best knowledge, only several flavonoids were characterized by the $E_7(Q^-/QH_2)$ values determined directly by the pulse-radiolysis experiments ([22], Table 1). The same study [22] also provided the $E_7(Q^-/QH_2)$ values for several other flavonoids, which were calculated according to the electronic effects of the substituents (Table1). However, in our opinion, these values were overestimated because they did not reflect the charge delocalization effects in the stabilization of the anion-radicals of flavonols morin and kaempferol [17]. Alternatively, we calculated the $E_7(Q^-/QH_2)$ values for flavonoids and other polyphenols from the rates of their oxidation by single-electron oxidants, ferricyanide and cytochrome *c* [17], ($E_7(Q^-/QH_{2\ (calc.)}$, Table1). They show a modest deviation from the directly determined $E_7(Q^-/QH_2)$ values, ≤0.07 V (Table1), and provide the reasonable values for the redox potentials of morin and kaempherol (Table1). Thus, the cytotoxicity of flavonoids in splenocytes is described by Eq. (2) using the $E_7(Q^-/QH_2)_{\ (calc.)}$ as the correlation parameter:

$$\log cL_{50} = (1.447 \pm 0.475) + (1.836 \pm 0.634)\, E_7(Q^-/QH_2)_{\ (calc.)} - (0.015 \pm 0.147) \log D \ (r^2 = 0.547). \quad (2)$$

Although being more scattered than Eq. (1), Eq. (2) shows that the cytotoxicity of flavonoids in primary splenocytes also follows a similar trend as in the malignant mammalian cells (Table2, Fig. 2B). The cytotoxicity of quercetin in splenocytes was partly protected by the antioxidant DPPD (*N,N'*-diphenyl-*p*-phenylene diamine), which protects the cell from the membrane lipid peroxidation, by the Fe-ion chelator desferrioxamine, which protects from the Fenton reaction, and was potentiated by the prooxidant BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea), which inactivates the antioxidant enzyme glutathione reductase, and depletes the intracellular antioxidant, reduced glutathione [23] (Fig. 3). These data point to an involvement of the ROS and the oxidative stress in the cytotoxicity of quercetin. Besides, the cytotoxicity of quercetin was partly protected by the inhibitors of cytochromes P-450 1A1/A2 and 2E1, α-naphthoflavone and izoniazide, and potentiated by an inhibitor of catechol-*O*-methyltransferase (COMT), 3,5-dinitrocatechol (Fig. 3) [24–27]. Analogous modulation effects were also observed in the cytotoxicity of naringenin and caffeic acid (data not shown). The effects of inhibitors point to an important role of the intracellular metabolism of polyphenols under the action of cytochromes P-450 and COMT, which modulates their cytotoxicity, as it was observed in the previous studies [11, 16–18]. In this case, COMT performs *O*-methylation of catechol groups, which decreases the cytotoxicity of the parent compounds [26, 27], and cytochromes P-450 perform their hydroxylation and / or oxidative demethylation, which increases their cytotoxicity [24, 25]. Because flavonoids are *O*-methylated much faster than catechols [27], the action of COMT may decrease their cytotoxicity more efficiently than the cytotoxicity of hydroxybenzenes. For this reason flavonoids comprise a separate series of compounds with lower cytotoxicity (Fig. 2A, B). The more rapid interconversion of flavonoids, i. e. their methylation by COMT and

Table 2. **The comparison of QSARs describing the 24 h cytotoxicity of flavonoids and hydroxybenzenes in malignant mammalian cells, primary mice splenocytes, and primary rat hepatocytes. The QSARs are presented as log cL_{50} (μM) = a + b $E_7(Q^-/QH_2)$ (V) + c log D, where cL_{50} is compound concentration causing 50% cell death, $E_7(Q^-/QH_2)$ is the redox potential of phenoxyl radical / phenol couple, and D is the octanol / water distribution coefficient of compound at pH 7.0. In the case of flavonoids, $E_7(Q^-/QH_{2\ (calc.)}$ were used instead of $E_7(Q^-/QH_2)$**

No.	Cell line	Group of compounds	*a*	*b*	*c*	r^2	Reference
1.	Primary mice splenocytes	Hydroxybenzenes	0.48 ± 0.70	3.60 ± 1.27	–0.14 ± 0.05	0.683	This work
2.	Primary mice splenocytes	Flavonoids	1.45 ± 0.48	1.84 ± 0.63	–0.02 ± 0.15	0.547	This work
3.	Primary rat hepatocytes	Hydroxybenzenes[a]	2.81 ± 0.59	2.08 ± 0.89	–0.53 ± 0.14	0.561	[18]
4.	Mice hepatoma (MH-22a)	Hydroxybenzenes	–0.33 ± 0.68	5.10 ± 1.21	–0.07 ± 0.05	0.783	[16]
5.	Mice hepatoma (MH-22a)	Flavonoids	1.84 ± 0.20	2.10 ± 0.26	–0.18 ± 0.06	0.916	[17]
6.	Human promyelocytic leukemia cells (HL-60)	Hydroxybenzenes	–1.39 ± 0.8	6.90 ± 1.45	–0.20 ± 0.05	0.817	[11]
7.	Human promyelocytic leukemia cells (HL-60)	Flavonoids	2.22 ± 0.62	2.01 ± 0.59	–0.48 ± 0.20	0.832	[17]
8.	Lamb embryo kidney fibroblasts transformed by bovine leukemia virus (FLK)	Hydroxybenzenes	–0.67 ± 0.64	5.46 ± 1.17	–0.16 ± 0.04	0.817	[11]
9.	Lamb embryo kidney fibroblasts transformed by bovine leukemia virus (FLK)	Flavonoids	2.06 ± 0.35	1.80 ± 0.46	–0.29 ± 0.11	0.769	[17]

[a] 2 h cytotoxicity [18].

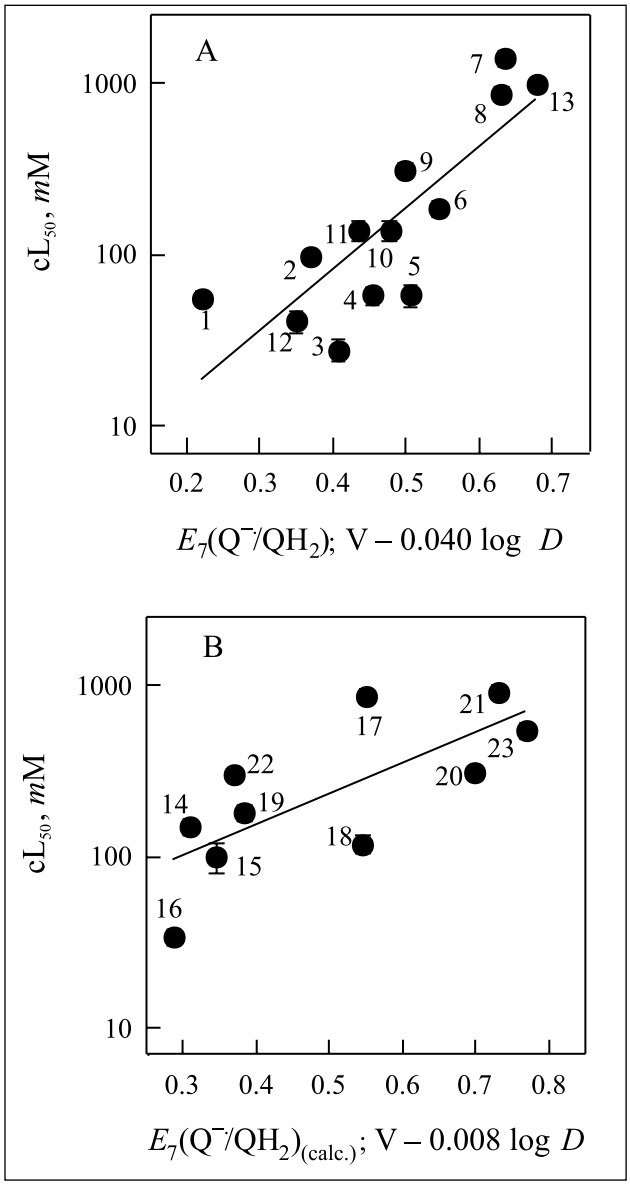


Fig. 2. QSARs in the cytotoxicity of polyphenols in primary mice splenocytes. The QSARs show the dependence of cL_{50} of hydroxybenzenes on their $E_7(Q^-/QH_2)$ values and log *D* according to Eq. (1) (A), and the dependence of cL_{50} of flavonoids on their $E_7(Q^-/QH_2)_{(calc.)}$ values [17] and log *D* according to Eq. (2) (B). The numbers of compounds are taken from Table 1

hydroxylation / oxidative demethylation by cytochromes P-450 also may explain a less pronounced role of redox potential of flavonoids in their cytotoxicity as compared to that of hydroxybenzenes (Table2).

Finally, the obtained QSARs in the cytotoxicity of polyphenols in primary splenocytes (Eqs. 1, 2) although being scattered, are similar to those observed in malignant cell lines (Table2). The similar trend, i. e. an increase in the cytotoxicity of hydroxybenzenes with an increase in their oxidation rate and lipophilicity, was also observed in primary rat hepatocytes [18] (Table2). However, one may note that some reported values of cL_{50} may be too high, being close to the limits of polyphenol solubility. On the other hand, the quantitative characterization of the cytotoxicity of flavonoids in hepatocytes was insufficient because of the problematic use of voltammetric redox potentials in the QSARs [19]. However, taken together, these data challenge the usefulness of flavonoids and other redox active polyphenols as the potential antitumour agents because of the nonspecific character of their cytotoxicity, i. e. its dependence on the redox properties and lipophilicity of the compounds, which is similarly manifested both in primary and malignant cell lines.

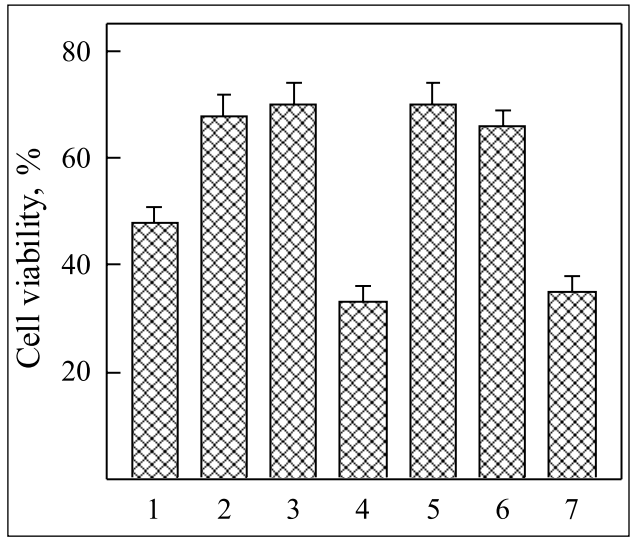


Fig. 3. The modulation of the cytoxicity of 150 μM quercetin in mice splenocytes. Additions: quercetin (1), quercetin + 3.0 μM DPPD (2), quercetin + 300 μM desferrioxamine (3), quercetin + 20 μM BCNU (4), quercetin + 5.0 μM α-naphthoflavone (5), quercetin + 1.0 mM izoniazide (6), and quercetin + 5.0 μM 3,5-dinitrocatechol (7), n = 3, $p < 0.02$ for 2–7 against 1. The addition of the above concentrations of DPPD, desferrioxamine, BCNU, α-naphthoflavone, izoniazide, and 3,5-dinitrocatechol in the absence of quercetin did not decrease the cell viability below 97 ± 2%

CONCLUSIONS

Our data show that the cytotoxicity of polyphenolic antioxidants in primary mice splenocytes is prooxidant and it follows the trends observed in several malignant cell lines, i. e. the increase in the cytotoxicity upon the ease of oxidation of polyphenols, and an increase in their lipophilicity. Being partly supported by the cytotoxicity studies in other primary cell lines, our data challenge the usefulness of flavonoids and other redox active polyphenols as the potential antitumour agents because of the absence of their specificity.

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POLIFENOLIŲ PROOKSIDACINIS CITOTOKSIŠKUMAS PIRMINIUOSE PELŲ SPLENOCITUOSE: REDOKSO POTENCIALO IR LIPOFILIŠKUMO VAIDMUO

S a n t r a u k a

Flavonoidų ir kitų polifenolinių antioksidantų citotoksiškumas piktybinėse ląstelėse dažnai yra prooksidacinis. Jis auga didėjant oksidacijos lengvumui (mažėjant fenoksilo radikalo / fenolio poros redokso potencialui ($E_7(Q^-/QH_2)$) ir didėjant jų lipofiliškumui (log *P* arba log *D*). Tačiau mažai žinoma apie jų citotoksiškumą pirminėse (netransformuotose) žinduolių ląstelėse, nors šie duomenys būtų vertingi siekiant išsiaiškinti jų pašalinį poveikį ar įvertinant tam tikrų struktūrų selektyvumą navikinėms ląstelėms. Nustatėme, kad flavonoidų (n = 10) ir hidroksibenzenų (n = 13) 24 val. citotoksiškumas pirminiuose pelių splenocituose yra aprašomas atskirais kiekybiniais struktūros-aktyvumo ryšiais (QSAR), kur kiekvienai yra būdinga neigiama toksiškumo priklausomybė nuo junginių $E_7(Q^-/QH_2)$ ir teigiama priklausomybė nuo jų log *D*. Antioksidantai ir citochromų P-450 inhibitoriai α-naftoflavonas ir izoniazidas mažino polifenolių citotoksiškumą, o katechol-*O*-metiltransferazės inhibitorius 3,5-dinitrokatecholis didino jų citotoksiškumą. Palyginus šio darbo duomenis su flavonoidų ir hidroksibenzenų poveikiu keliose piktybinėse (navikinėse ar virusų transformuotose) ląstelių linijose, galima teigti apie ribotą flavonoidų ir kitų polifenolių kaip potencialių priešnavikinių agentų svarbą, nes jų poveikis pirminėms ir navikinėms ląstelėms yra aprašomas panašiomis QSAR.