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COMPLEX SYSTEMS BIOPHYSICS

A Study of the Antioxidative and Radioprotective Properties of Isobornylphenols during X-Ray Irradiation at a Low Dose

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Abstract—The inhibitory efficiency and radioprotective properties of two isobornylphenols were studied during their administration 30 minutes before X-ray irradiation of outbreed mice (females) at a dose of 50 sGy. It was found that 1,3-dihydroxy-4,6-diisopropylbenzene exhibited high efficiency due to its interaction with peroxy radicals. The spleen index and the content of the lipid peroxidation products in blood plasma, which were previously suggested as tests for the assessment of the radioprotective properties of substances during the irradiation of animals at low doses, returned to the norm with the prophylactic administration of 2-isobornyloxyphenols. An aqueous solution of ethanol was found to be unfavorable as a solvent for the administration of hydrophobic substances under the effects of weak radiation. The data we obtained and the literature analysis allow us to propose isobornylphenols as radioprotective agents during radiation at different doses.

Keywords: isobornylphenols, antioxidant activity, lipid peroxidation, X-ray, radioprotective properties

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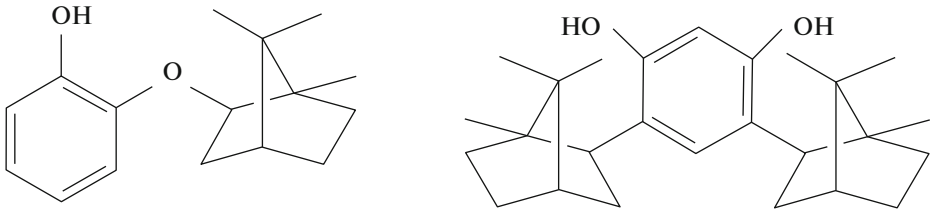
The differences in the main molecular mechanisms in the development of the effects of ionizing radiation on the body [1, 2] result in the lack of universal radioprotective agents that protect biological objects from damage due to ionizing radiation in all dose ranges [3, 4]. This follows from the idea from the 1970s that the membrane, as well as DNA, is also a target during ionizing radiation on biological objects. Processes of lipid peroxidation (LP) that occur at the membrane, cellular, and organ levels are among the most ancient regulatory mechanisms in evolutionary terms. These can be considered as a normal physiological process [5, 6] and the intensification of the oxidation processes caused by activation of reactive oxygen species is the main cause of the development of oxidative stress, which plays an important role as a mediator in the destruction of membranes, lipids, proteins, DNA, and other cellular components [7, 8]. The system of the redox homeostasis plays an important role in the formation of radiation-induced instability of the genome [9].

Synthetic compounds and cytokines are more effective in the system that protects the body against the acute radiation at the sublethal and lethal doses, but agents of a natural origin have an advantage during irradiation at low doses [4, 10–14]. The search for methods for protection against ionizing radiation at low doses is now becoming increasingly important because of the widespread use of ionizing radiation sources in medical practice and everyday life. This is due to the necessity of searching for effective, nontoxic, and inexpensive radioprotective methods, among which a large group of compounds are preparations that have the ability to inhibit LP processes with injection into the body. In recent years, research has focused on the search for new semi-synthetic antioxidants (AOs) which have lower toxicity compared to synthetic compounds. Isobornylphenols (IBPs) are considered promising and are actively studied; their kinetic characteristics and physicochemical properties were generalized in [15].

The aim of the work was to evaluate the inhibitory efficiency and to study the radioprotective properties of two IBPs with their administration to mice 30 min before X-ray irradiation at a dose of 50 cGy.

MATERIALS AND METHODS

The objects of this study were white outbreed mice (females) weighing 20.5–25 g; the total number of animals was 80 and the age at the time of irradiation was 10–11 weeks. The animals were kept under standard



Isobornylphenol 2 1,3-Dihydroxy-4,6-diisopropylbenzene

Fig. 1. The structural formulas of the studied compounds.

vivarium conditions in accordance with the rules developed by the European Convention for the Protection of Animals used for experimental purposes.

First, 2-isobornyloxyphenol (IBP **1**) and 1,3-dihydroxy-4,6-diisopropylbenzene (IBP **2**) were dissolved in 9.5% aqueous ethanol and injected intraperitoneally at doses of 7.8 and 5 mg/kg, respectively (10^{-5} M). Synthesis of the studied IBPs, which was presented in detail in [16, 17], was carried out by the alkylation of dihydrophenols by camphene in the presence of the various homogeneous and heterogeneous catalysts: the effective catalyst used to obtain IBP **1** was sulphocationite Fiban K1 [16], while for IBP **2** it was aluminium isopropylate [17]. The structural formulas of studied IBPs are given in Fig. 1.

The inhibitory effect of IBP **2** was studied in a model reaction of ethylbenzene oxidation initiated by azobisisobutironitrile. The kinetics of oxygen uptake during oxidation were recorded using a highly sensitive volumetric setting at 333 K and the initiation rate of $W_i = (5–10) \times 10^{-8}$ M s^{-1}. Ethylbenzene with a dissolved initiator was held in a thermostat and the substance was then added. From the kinetics of the oxygen uptake curves the value of the induction period (τ) by the method in [18] and the initial rate of oxygen absorption were determined.

The antioxidant properties of IBP **2** were studied during autooxidation of methyl oleate in a thin layer with free access of air (323 K). For methyl oleate the substance was introduced in ethyl alcohol. The initial share of alcohol in the total volume of the reaction mixture in all experiments was constant at 4%. The course of oxidation was followed by the accumulation of hydroperoxides (ROOH), whose concentration was determined by iodometric titration (*GOST 26593-85*). The effectiveness of the inhibitory action of additives was determined by the duration of the induction period (τ_1). The time interval from zero to a perpendicular dropped onto the X axis from the point of intersections of the linear plots of the kinetic curves of ROOH accumulation, which corresponded to the initial oxidation rate in the induction period and the maximum rates of the peroxide accumulation was taken as τ_1 [19].

Mice (their food was removed from the cages the previous night) were irradiated in special containers in groups of ten individuals, placing each in a separate cell with freedom of movement. The X-irradiation was performed using a RUM-17 apparatus (Mosrentgen, Russia) at a total dose of 50 cGy (the dose rate was 16 cGy/min; the filter was 0.5 mm Al + Cu) from 11.05 to 11.25 h to exclude the influence of daily fluctuations on the values of the antioxidant activity (AOA) of lipids in tissues [20]. The mice were previously divided into eight groups with similar body weights:

K – the initial control group;

1—the mice received a 9.5% aqueous solution of ethanol;

2—the mice received a 9.5% aqueous solution of ethanol 30 minutes before irradiation at a dose of 50 cGy;

3—the mice received the IBP **1** solution in a 9.5% aqueous solution of ethanol;

4—the mice received the IBP **2** solution in a 9.5% aqueous solution of ethanol;

5—the mice received the IBP **1** solution in 9.5% aqueous solution of ethanol 30 minutes before irradiation at a dose of 50 cGy;

6—the mice received the IBP **2** solution in a 9.5% aqueous solution of ethanol 30 minutes before irradiation at a dose of 50 cGy;

7—the intact age control group.

Slaughter of the mice, whose food was previously removed, was done by decapitation. Blood was collected in test tubes treated with a 5% solution of sodium citrate. The blood plasma was separated using an OPn-3 laboratory clinical centrifuge (AO TNK Dastan (Kirgiz Republic) at 1500 rpm for 5 min. Immediately after decapitation the liver and spleen were placed on ice. The content of the oxidation products that reacted with 2-thiobarbituric acid (TBA-RS) was determined by the method described in [21]. Protein concentration was analyzed via the modified microbiuretic method [22], using bovine serum albumin as a standard in the concentration range from 0.09 to 0.76 mg/mL The correlation coefficients of calibration lines R were within 0.99–1.0. The analysis of the

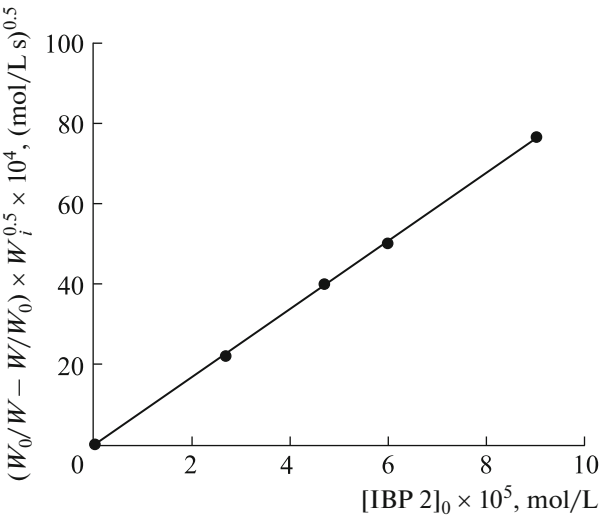


Fig. 2. The dependence of the initial rate of the ethylbenzene inhibited oxidation on the initial concentration of isobornylphenol 2 in coordinates of $(W_0/W - W/W_0)W_i^{0.5} = fk_7[\text{IBP 2}]_0/k_6^{0.5}$. The temperature was 333 K.

level of TBA-RS and protein in each sample was carried out in three parallel measurements.

To determine the initial biochemical parameters for this group of mice the decapitation of animals of group **K** was carried out at the beginning of the experiment. To assess the remote effects of the treatments all other groups of mice were decapitated within 30 days after the treatments simultaneously, including the age control group. We determined both the absolute and relative weight (index) of the spleen and liver, which is the ratio of the weight of the organ in mg to the body weigh in g. All studied parameters were determined individually for each animal at the time of decapitation.

The data were processed with a commonly used statistical variation method, the significance of the differences was evaluated using the *t*- student criterion [23]. The experimental data are presented in the form of the average arithmetic means with their mean square errors ($M \pm m$).

RESULTS

When introduced into animals, AOs are effective regulators of the oxidation processes that play an important role in cellular metabolism both in the norm and during the actions of damaging factors. As well, the radioprotective efficiency of AOs substantially depends on the value of their constant rate of reaction with peroxide radicals (k_7), while the initial antioxidant status of the tissues plays an important role in the manifestation of the radioprotective properties of both synthetic and natural AOs [13]. This is due to the fact that the efficiency of the inhibitory effect of AOs in complex systems is determined not only by the ability to react with the main oxidation chains of peroxy radicals, but also by their participation in side reactions.

It has been experimentally shown that all enzymes of the antioxidant defense are substrate induced, which results in the participant of AOs at the first stages of protection due to their interaction with reactive oxygen species, whose concentration increases under ionizing irradiation. This makes it necessary to evaluate the ability of newly synthesized compounds to inhibit the oxidation processes in model systems at the beginning. Therefore, the first stage of the work was a study of the antiradical activity of IBP 2, in which the OH-groups are located in the *m*-position relative to one other and have two isobornyl substituents (Fig. 1). To determine the value of the inhibition parameter, that is, fk_7, where k_7 is the rate constant of the interaction of IBP 2 with peroxy radicals and f is a stoichiometric coefficient of inhibition, the initial oxidation rate in the presence of IBF 2 was represented in the coordinates of the equation $(W_0/W - W/W_0) \times W_i^{0.5} = fk_7[\text{IBP 2}]_0/k_6^{0.5}$, where W_0 is the oxidation rate in the absence of additives and k_6 is the rate constant of the square chain termination of $RO_2^{\bullet}$ radicals (Fig. 2). From the tangent of the obtained curve (Fig.2) the calculated value of the inhibition parameter is $fk_7 = 3.7 \times 10^5$ (M s)$^{-1}$. To calculate the value of the constant k_7 the value of the stoichiometric coefficient of inhibition was obtained from the dependence $\tau W_i = f[\text{IBP 2}]$ (Fig. 3) which was found to be $f = 2.3$. This value is more than $f = 2$ for monophenols and substituted catecol and hydroquinone, in which only one of the free radicals interacts with the OH-group due to the formation of the energetically favorable quinonoid structure. Considering the obtained value $f = 2.3$, the value of the rate constant for the reaction of IBP 2 with peroxy radicals of ethylbenzene is equal $k_7 = 1.6 \times 10^5$ M s^{-1}, which indicates its rather high antiradical activity towards peroxy radicals. Earlier, the rather low inhibitory activity for IBP 1 was revealed**,** which is due to an intramolecular hydrogen bond in its molecule [24].

The antioxidant activity of IBP 2 was studied in a model system of methyl oleate autooxidation, i.e., under conditions where side reactions involving AOs can manifest themselves, resulting in deviation from the linear dependence of the induction period on the initial concentration compound and due to reduction of its efficiency. The kinetic curves of the peroxide accumulation of methyl oleate at the different concentrations of IBP 2 are shown in Fig. 4. As can be seen from presented data, an increase in the amount of the administrated preparation results in an increase in the inhibition period of the oxidation processes. As well, the magnitude of the inhibition period increases lin-

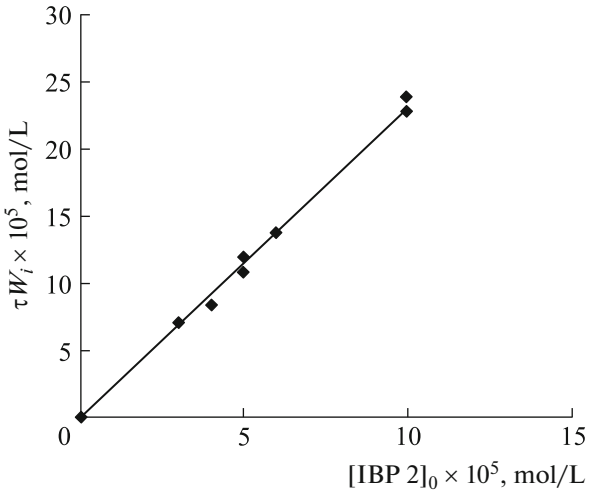


Fig. 3. The dependence of the induction period τ, calculated from the kinetic curves of the oxygen uptake during the initiated oxidation of ethylbenzene, on the initial concentration of isobornylphenol **2**. The temperature was 333 K.

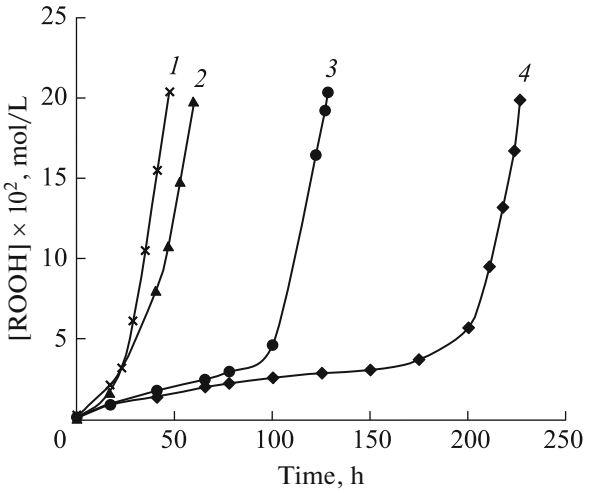


Fig. 4. Kinetic curves of the accumulation of peroxides during the autoxidation of methyl oleate in the thin layer (333 K) in the absence (*1*) and presence of isobornylphenol **2** at concentrations 1×10^{-4} (*2*), 5×10^{-4} (*3*) and 1×10^{-3} (*4*) mol/L.

early with an increase in its initial concentration (Fig. 5).

The linear dependence τ_1 on the IBP 2 concentration indicates the insignificant effect of the side reactions on the mechanism of its inhibition of autooxidation process in the studied concentration range.

Since the antioxidant (AO) status of a biological object has substantial seasonal and daily variability and the AOA level of lipids in tissues is one of the important factors by which one can evaluate the efficiency of the radioprotecive properties of preparations [13, 20], the next stage was the estimation of the initial antioxidant status of mice in group K before the experiment. In complex biological systems, LP intensity is usually evaluated by the contents of TBA-reactive substances in tissues of mice [25]. It was found that the concentrations of the TBA-reactive substances were 0.244 ± 0.0255 and 0.0131 ± 0.0011 nmol/mg protein for the blood plasma and liver respectively. This indicates the low intensity of the LP processes in tissues of mice and is consistent with the literature data about the high AO status of laboratory rodents in the winter [20].

Morphometric parameters, which are indicators of physiological state and allow us to determine the intensity of the exchange balance, are usually used in ecological investigations to estimate the biological effects of technogenic pollution of the environment [26, 27]. Nevertheless, as shown in [28, 29], the spleen index and the TBA-RS content in the blood plasma also are sensitive tests for estimating biological effects under ionizing radiation at low doses in laboratory experiments. This led to the choice of these indicators to evaluate the radioprotective properties of the studied compounds. The results of the analysis of the spleen index (SI) within 30 days after peritoneal administration of the preparations are presented in Table 1.

As can be seen from the presented data, the administration of both the 9.5% aqueous solution of ethanol (group 1) and the IBP 1 solution at a dose of 5 mg/kg in a 9.5% aqueous solution of ethanol (group 3) within 1 month after the treatment did not have a significant

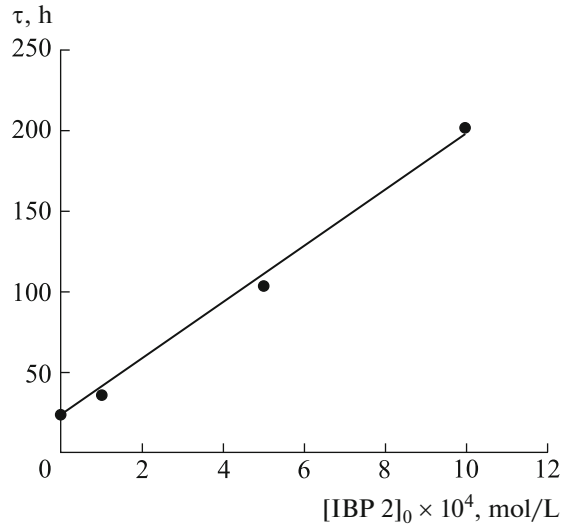


Fig. 5. The dependence of the induction period, as determined from the kinetic curves of the accumulation of peroxides during the autooxidation of methyl oleate in the thin layer, on the initial concentration of isobornylphenol **2**. The temperature was 323 K.

Table 1. The values of the relative weight (index) of the spleen in the control and experimental groups of outbreed mice (females)

Experimental conditions (group of mice)	Index of spleen, ‰
Initial control (group K)	3.58 ± 0.21
Age control (group 7)	4.20 ± 0.26
30 days after the administration of the 9.5% aqueous solution of ethanol (group 1)	4.30 ± 0.30
30 days after the administration of a 9.5% aqueous solution of ethanol 30 min before irradiation at a dose of 50 cGy (group 2)	3.94 ± 0.33
30 days after the administration of IBP 1 in a 9.5% aqueous solution of ethanol (group 3)	4.20 ± 0.29
30 days after the administration of IBP 2 in a 9.5% aqueous solution of ethanol (group 4)	4.70 ± 0.36
30 days after the administration of IBP 1 in a 9.5% aqueous solution of ethanol 30 min before irradiation at a dose of 50 cGy (group 5)	4.4 4 ± 0.33
30 days after the administration of IBP 2 in a 9.5% aqueous solution of ethanol 30 min before irradiation at a dose of 50 cGy (group 6)	4.8 0 ± 0.50

effect on the SI values (the value of the indicator corresponds to its value in the age control and in group 1). IBP 2 administration at a dose of 7.8 mg/kg of the same solution (group 4) within 1 month after the treatment caused a slight (by 12%) but significant increase of this indicator relative to its value in the age control group ($p < 0.001$) and also compared with the values in the mice of group 1 ($p < 0.01$) during the administration of only the 9.5% aqueous solution of ethanol.

A slightly different picture was revealed within 1 month after the combined action of the IBPs and acute X-radiation at a relatively low dose of 50 cGy (Table 1). First, it should be noted that the administration of the 9.5% aqueous solution of ethanol caused a decrease in the average SI value (group 2), although it indicates only a tendency to that change. Within 30 days after the combined action of X-rays and IBPs administrated 30 min before irradiation an SI increase was detected in both cases compared with the value of this parameter in the group 2, mice that received only the aqueous ethanol solution (Table 1). However, a significant ($p < 0.01$) increase in SI only occurred up to the value in the age control group in the case of IBP **1.** In the experiment with IBP 2 a significant increase by 11.7% ($p < 0.01$) and 21.8% ($p < 0.001$) occurred compared with the similar value in groups 7 and 2, respectively (Table 1).

It is necessary to note that the administration of the 9.5% aqueous solution of only ethanol 30 min before irradiation at a dose of 50 cGy led to an insignificant reduction of the TBA-RS content in the blood plasma within 30 days (Table 2). As well, the studied IBP had a different influence on the LP intensity in the blood plasma. Thus, within 1 month after IBP 2 administration in the aqueous solution of ethanol the contents of TBA-reactive substances in the blood plasma of mice were practically the same as the value in the age control and exceeded the value in group 1 by 13% ($p < 0.02$). Within 1 month after IBP 1 administration in an aqueous solution of ethanol the TBA-reactive substances content in the blood plasma of mice significantly decreased by 1.3 ($p < 0.001$) and 1.5 ($p < 0.001$) times compared with the values of the indices in the age control group and on group of mice with the administration only of an aqueous solution of ethanol, respectively (Table 2).

A different picture of the effects is observed after the combined action of the IBP and X-ray irradiation. Thus, the LP intensity in the blood plasma of mice with the administration of IBP 1 in the aqueous solution of ethanol 30 min before irradiation (group 5) does not significantly differ from the value in the age control group and is only higher than in group 2 by 21.1% ($p < 0.1$) (Table 2). A significant increase of the LP intensity in the blood plasma was detected within 1 month after IBP **2** administration in the aqueous solution of ethanol relative to the age control by 28.6% ($p < 0.01$) and to the group mice 2 by 1.5 times ($p < 0.001$) (Table 2).

DISCUSSION

These data show that within 1 month the biological effects were substantial but differed in their dependence on the chemical structure of IBP, both with the administration of the studied IBP in mice and the combined action of preparations and X-ray irradiation of animals at a dose of 50 cGy. Thus, IBP 1 normalized the LP intensity in the blood plasma of the irradiated mice and also maintained the SI value at the level of the parameter in the age control group. IBP 2 administration and/or use with the combined action with X-ray irradiation results in significant differences in the SI and the LP intensity in the blood plasma of mice relative to the similar parameters in the age control and experimental groups of mice when only the administration of an aqueous solution of ethanol was performed.

In addition, the following issue should be noted. Within 1 month after administration to mice of only the 9.5% aqueous solution of ethanol no significant differences in the spleen indices (Table 1) and liver

Table 2. The content of the TBA-reactive substances in the blood plasma in the control and experimental groups of outbred mice (females)

Experimental conditions (group of mice)	[TBA-RS], nmol/mg of protein
Age control (group 7)	0.0748 ± 0.0089
30 days after the of administration a 9.5% aqueous solution of ethanol (group 1)	0.0656 ± 0.0066
30 days after the administration of a 9.5% aqueous solution of ethanol 30 min before irradiation at a dose of 50 cGy (group 2)	0.0624 ± 0.0084
30 days after the administration of IBP **1** in a 9.5% aqueous solution of ethanol (group 3)	0.0489 ± 0.0066
30 days after the administration of IBP **2** in a 9.5% aqueous solution of ethanol (group 4)	0.0739 ± 0.0047
30 days after the administration of IBP **1** in a 9.5% aqueous solution of ethanol 30 min before irradiation at a dose of 50 cGy (group 5)	0.0755 ± 0.0100
30 days after the administration of IBP **2** in a 9.5% aqueous solution of ethanol 30 min before irradiation at a dose of 50 cGy (group 6)	0.0960 ± 0.0190

indices (LI = 42.2 ± 1.0 in group 1) as well as the contents of TBA-reactive substances in the blood plasma (Table 2) occurred compared with the values of these parameters in the age control group (LI = 45.1 ± 2.1). However, with the combined action of the 9.5% aqueous solution of ethanol and X-ray irradiation at a dose of 50 cGy a clear heterogeneity in the liver index (LI) was revealed: for one-half of the mice in group 2 the LI significantly increased, reaching the value of 47.7 ± 1.25 ($n = 5$), while the other half of the mice had a significantly decreased LI to a value of 37.1 ± 1.7 ($n = 5$). These data indicate that an aqueous solution of ethanol is unfavorable as a solvent for the administration of hydrophobic substances during investigation of their influence on the development of the biological effects of ionizing radiation at low doses.

CONCLUSIONS

Analysis of these experimental data shows that the kinetic characteristics of semi-synthetic AOs have a significant influence on the development of effects with radiation at a low dose. Thus, the rather high value of the rate constant of the IBP 2 interaction with peroxy radicals, together with its ability to modify the parameters of the physicochemical LP regulatory system in tissues with their administration, allow us to consider IBP **2** as a perspective radioprotective agent during acute irradiation at sublethal and the minimal lethal doses. This assumption is based on a previously obtained direct correlation between the radioprotective properties of synthetic antioxidants during acute irradiation of Balb/c mice at a lethal dose of 6 cGy and the AOA of the studied substances [30]. The higher value of the stoichiometric inhibition parameter for IBP 2 compared with substituted catechol and hydroquinone allows us to propose that polyphenol, with the *m*-position of the OH-group, can act independently on each one. The value of the stoichiometric inhibition parameter could then be $f = 4$. The cause of the noticeable decrease in f for IBP 2 to 2.3 compared with the expected value is still unclear and requires further investigation.

These data make it possible to consider IBP **1** as a promising radioprotective agent during radiation exposure at low and/or relatively low doses. This assumption also agrees with the results that were obtained earlier on the increase in the inhibitory efficiency of IBP **1** in polar media [31, 32], despite its rather low antiradical activity in the reactions of ethylbenzene initiated oxidation, i.e., during the oxidation of a non-polar substrate [24].

These data suggest the need to carry out further studies for selection of the most promising compounds among terpenephenols (semi-synthetic antioxidants) as potential radioprotective agents.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

COMPLIANCE WITH ETHICAL STANDARDS

All applicable international, national and institutional principles for the care and use of animals in the performance of work have been observed.

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