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CELL BIOPHYSICS

The Radioprotective Effect of Chlorophyll-Based Drugs

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Abstract—This paper summarizes the relevant data on the use of chlorophyll derivatives as radioprotectors, which have been previously presented (partially and without analysis) in other works. We present and discuss findings from experiments that have shown an increase in the survival rate of chlorophyll-treated mice after γ-irradiation. Intramuscular injection of chlorophyll has been shown to lead to a pronounced decrease in leukopenia syndrome in irradiated animals. A reduction in malondialdehyde concentration in the blood and liver of irradiated animals treated with chlorophyll compared to the control group has been also found. These data suggest that suppression of the process of lipid peroxidation may be a molecular mechanism for the radioprotective effect of chlorophyll preparations. This has been confirmed by the experiments on registration of chemiluminescence accompanying lipid peroxidation in the presence of chlorophyllin (a water-soluble hydrolysis product of chlorophyll) at various concentrations. The effect of the studied drug has led to a decrease in the intensity of chemiluminescence, thus indicating a decrease in the intensity of the lipid oxidation under the action of free radicals in the sample.

Keywords: radiation sickness, lipid peroxidation, chlorophyll, antioxidant, radioprotector, ionizing radiation

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CHLOROPHYLL AMONG OTHER RADIOPROTECTIVE DRUGS

The danger of radiation contamination of the environment in the modern world remains quite high. It comes not only from the testing of nuclear weapons or the possibility of their use but also from possible accidents at radiation industry facilities and an ever-growing amount of radioactive waste. Therefore, the risk of radiation damage to both humans and farm animals increases every year. One of the main tasks of radiobiology is the development of effective drugs that can prevent the negative effect of ionizing radiation on a living organism. Not only is the effectiveness of these drugs important but also the safety of their use, i.e., the absence of toxicity. However, many currently used radioprotectors have a toxic effect [1]. One area of great interest is the development of nontoxic radioprotective preparations based on chlorophyll. In 1990, the authors of [2] showed the radioprotective effect of chlorophyllin, a water-soluble product of chlorophyll saponification, on *Drosophila melanogaster* flies. This conclusion was made based on a decrease in the number of spots on the wings of chlorophyllin-treated flies, which were considered as markers of the damage of the genome under the action of γ-radiation at a dose of 20 Gy. Further, more detailed studies of the radioprotective properties of chlorophyllin were carried out [3–6].

The radioprotective properties of chlorophyll were described in the works of the 21st century that were performed in the Scriabin Moscow State Academy of Veterinary Medicine and Biotechnology under the guidance of Prof. N.P. Lysenko [7–12]. The use of chlorophyll contributes to a sharp increase in the survival of laboratory animals exposed to a superlethal dose of γ-radiation [7, 12]. In this case, the value of the dose change factor of γ-radiation (the ratio of the radiation doses causing the death of half of the individuals that received and did not receive the drug) was in the range of 2–4 for different radiation doses. This indicator may be quite good. The authors [13], who studied the radioprotective effects of genistein, mexidol, litane, and cytochrome c under X-ray radiation, showed that the values of the dose change factor did not exceed the value of 1.7 for all these substances.

Before analyzing the works devoted to the radioprotective effect of chlorophyll-based drugs, we consider it necessary to classify radioprotective drugs. A successful classification was given by M.V. Vasin in the review [14]. Depending on the mechanisms of radioprotective action the author divides these substances into five groups.

Group 1 includes radioprotectors that are effective at superlethal doses of radiation (up to 15 Gy) and neutralize the effects of ionizing radiation at the stage

Abbreviations: IL, interleukin.

of radiation-chemical reactions (mainly due to the neutralization of free radicals and reactive oxygen species). The review [14] emphasized the prevention of the consequences of DNA radiolysis. However, we note that the biological effect of radiation is mainly the radiolysis of water, followed by the lipid peroxidation process with the use of hydroxyl and peroxyl radicals [15, 16]. As examples of radioprotectors, M.V. Vasin cited sulfur-containing compounds (β-mercaptoethylamines, aminoalkylthiosulfates, thiazolidines, etc.) and substances that cause hypoxia in tissues through cellular receptors (phenylalkylamines, histamine, acetylcholine, quinoline derivatives, purine nucleotides, etc.) or otherwise (*n*-aminopropiophenone, nitrites, cyanides, phenols, and other alcohols, etc.).

Group 2 includes radiomitigators that accelerate the post-radiation recovery of tissues through the activation of proinflammatory signaling pathways and increase of secretion of hematopoietic growth factors. These compounds include steroid hormones and their analogs, adjuvants (enhancers) of immunological reactions (peptidoglycans, polynucleotides, etc.), and various cytokines (interferons, proinflammatory interleukins (IL): IL-1, IL-8, IL-12, tumor necrosis factor, etc.).

Group 3 includes radio modulators that increase the nonspecific resistance of the body. These compounds include antioxidants, antimutagens, and anti-inflammatory substances. M.V. Vasin also attributes to this group vitamins A, C, and E, bee products, trace elements, and ω-unsaturated fatty acids (the latter should be used with caution because they are a good substrate for lipid peroxidation [17]). The action of radiomodulators is often directly opposite to the action of radio transmitters.

Group 4 includes means of prevention or relief of primary reactions to radiation (antiemetic and antidiarrheal drugs).

Group 5 includes sorbents for adsorption of radionuclides in the intestine and complexes for their binding in the blood [14].

Elements-antagonists of radionuclides that compete for a place in metabolic pathways, should probably also be classified as radioprotective drugs. They include, for example, iodine, calcium, and potassium preparations for the prevention and therapy of the action of radioactive iodine [14, 18, 19], strontium, and cesium isotopes [19], respectively, etc.

It should be noted that the same substance can be assigned to several groups described above. As an example, indralin can be attributed to both radioprotectors and radiomitigators; radioprotector aminofostin, which can stimulate the antioxidant system of the body, simultaneously acts as the radiomodulator [14]. Chlorophyll and its derivatives most likely also exhibit the properties of both a radioprotector and radiomodulator; in our opinion, the molecular mechanism of its action in both cases may be the same, i.e., inhibition of the process of lipid peroxidation.

As the main light-trapping pigment of plants, chlorophyll is not found in animal cells. However, once there, it may exhibit an antioxidant function due to the presence of aromatic systems in its molecule similar to many classical antioxidants [20]. It should be pointed out that chlorophyll is not a water-soluble substance because of the presence of a phytol alcohol residue in its molecule. Therefore, some studies have used a chlorophyll saponification product, i.e., water-soluble chlorophyllin. The formula of chlorophyll with an indication of the atomic groups that are removed during the saponification of chlorophyll, is shown in Fig. 1. Higher plants, which are the main raw materials for the production of chlorophyll and chlorophyllin, contain two forms of chlorophyll, i.e., chlorophyll a and chlorophyll b, whose ratio can be different and depends on many factors [21]. However, we do not believe that the effects of chlorophylls or chlorophyllins a and b on lipid peroxidation processes are different.

THE RADIOPROTECTIVE EFFECT OF CHLOROPHYLL AND ITS DERIVATIVES AND ITS PROPOSED MECHANISMS

Studies of the radioprotective effect of chlorophyllin were performed at the turn of the 20th–21st centuries. The authors of [3] observed a decrease in the number of micronuclear polychromatic erythrocytes in mice, which were formed under the action of γ-radiation at a dose of 1.15 Gy, after oral administration of chlorophyllin at concentrations from 50 to 200 μg/g of animal weight. At about the same time, the radioprotective effect of chlorophyllin was studied by the criterion of reducing chromosomal abnormalities in bone marrow cells [5] and spermogonia [6] of mice exposed to γ-radiation at a dose of 1.00 and 0.75 Gy, respectively. Both studies evaluated the effect of chlorophyllin on reducing the number of sister chromatid exchanges. Their significant decrease in bone marrow cells was observed at doses of the drug of 50 and 100 μg/g of animal weight. A dose of 10 μg/g had no effect.

The authors of [5] noted that at a dose of 50 μg/g of animal weight, chlorophyllin protects the bone marrow by less than half and the dose of 100 μg/g of animal weight completely protects mice from γ-radiation at a dose of 1.00 Gy. At the same time, chlorophyllin at all three doses returned the values of the mitotic index in irradiated animals to the values corresponding to nonirradiated mice. The authors did not observe an increase in the mitotic index of bone marrow cells in nonirradiated mice treated with chlorophyllin in comparison with that in the control group [5]. The authors of a similar study [6] evaluated sister chromatid exchanges in spermatogonia using chlorophyllin at doses of 100 and 200 μg/g of animal weight. They

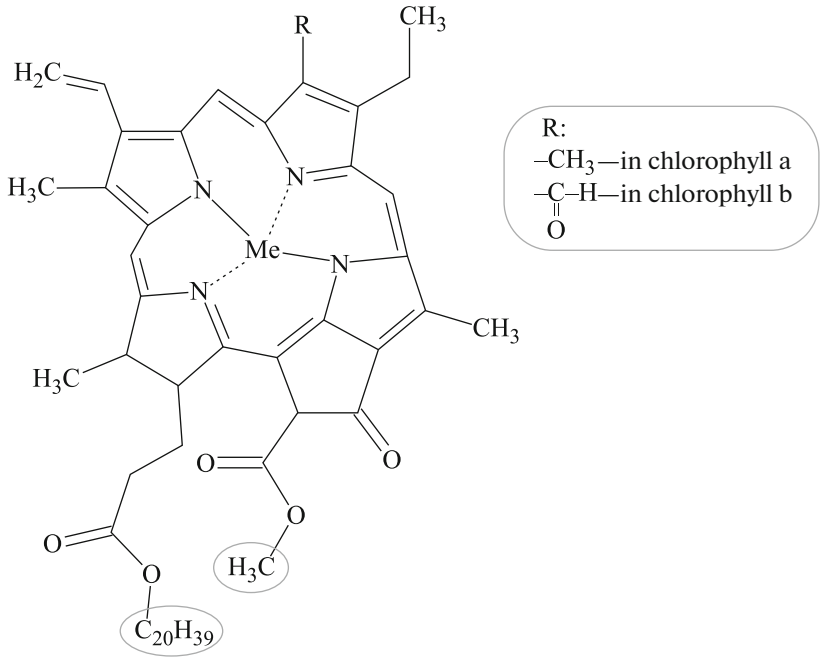

Fig. 1. The formula of chlorophyll of higher plants. The gray oval marks the residues of alcohols that are cleaved off during saponification of chlorophyll for the chlorophyllin preparation. Me is Mg^{2+} ion in the chlorophyll molecule or Cu^{2+} in the copper chlorophyllin molecule.

obtained reliable data about a dose-dependent effect of chlorophyllin, which led to a decrease in the number of sister chromatid exchanges caused by γ-radiation at a dose of 0.75 Gy in spermogonies. The authors noted that only chlorophyllin at a dose of 200 μg/g of animal weight provided full protection because only in this case did the number of sister chromatid exchanges decrease to the value observed in nonirradiated animals.

We believe that the radioprotective effects of chlorophyll derivatives are based on their antioxidant properties, which have been stated in the literature from the second half of the last century [22] to the present [23]. The authors of [4] described in 2004 the antioxidant effect of chlorophyllin, which reduced the content of reactive oxygen species in mouse lymphocytes and protects cells from radiation-induced apoptosis. The control time points in the described experiment were 24, 48, and 72 h after irradiation. At a dose of γ-radiation of 2 Gy, the action of chlorophyllin at a dose of 200 μg/g of animal weight led to a decrease in the proportion of dead cells (although it was still higher than in the control group). The interesting result of the authors of [4] concerning the apoptosis caused by γ-radiation at a dose of 1 Gy should be noted. After irradiation for 48 h, the percentage of the cell apoptosis in the chlorophyllin-treated group was higher than in the untreated group, although it was also lower for this group after irradiation for 24 and 72 h.

A similar result is presented for the activity of superoxide dismutase, catalase, and glutathione peroxidase. A decrease in this value was observed in the chlorophyllin-treated group but the activity of the latter two enzymes at other control points was higher for the chlorophyllin-treated group. The activity of superoxide dismutase after irradiation for 24 and 72 h did not differ for the groups that received and did not receive chlorophyllin. This rather strange effect was not observed in all other experiments on the study of the radioprotective effect of chlorophyllin that we analyzed. The authors of [4] also studied the effect of chlorophyllin on the intensity of lipid peroxidation, which was evaluated by spectrophotometric measurement of the content of thiobarbiturate-reactive substances induced by γ-radiation dose of 5 Gy. Chlorophyllin significantly reduced the intensity of lipid peroxidation in irradiated animals but still did not return its value to that for the control group. At the same time, a significant decrease in the intensity of lipid peroxidation was observed in the groups of nonirradiated animals for the control point of 24 h compared with the control group [4].

The proof that chlorophyll derivatives can act by suppressing lipid peroxidation was obtained using a molecular model [24]. Using the chemiluminescence method that is most suitable for real-time study of free radical processes [25, 26], the authors of [24] evaluated the dose-dependent effect of chlorophyllin on the suppression of lipid peroxidation, which was triggered by a quasi-hypoxygenase reaction catalyzed by the

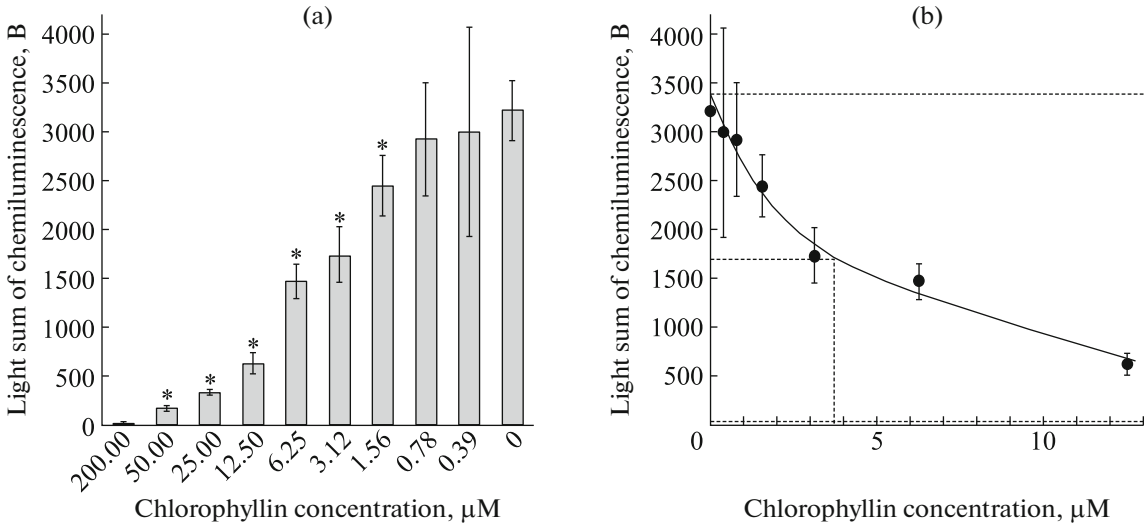

Fig. 2. (a) The light sum of chemiluminescence of the system that contains 10 μM cytochrome c, 300 μM tetraoleoyl cardiolipin, 25 μM coumarin-334, and 150 μM lipoperoxides, in the presence of various concentrations of chlorophyllin for 5 min of the reaction. Asterisk (*) designates a significant difference from the control value at $P = 99\%$ [24]. (b) Graphical determination of the chlorophyllin concentration that causes half quenching of chemiluminescence in the system (3.7 μM). The lower dotted line is the light sum value for a sample that contains no cytochrome c (peroxidase control) [24].

cytochrome c complex with tetraoleoylcardiolipin. The results of these experiments are shown in Fig. 2.

It should be noted that the authors of [24] used a glycerol-containing food additive "Chlorophyll liquid" (Nature's Sunshine Products Inc., United States) as the chlorophyllin preparation. Glycerol can quench chemiluminescence [26] without suppressing the intensity of the lipid peroxidation process. The decrease in chemiluminescence is caused by intercepting the energy of electronic excitation from lipid peroxidation products without further radiation in the form of photons through the mechanisms described in [27]. There are possible errors in determining the concentration of chlorophyllin that caused half inhibition of lipid peroxidation, and its minimal active concentrations. However, these inaccuracies do not negate the conclusions from [24] that chlorophyll derivatives suppress lipid peroxidation, which is the mechanism of their radioprotective action.

N.P. Lysenko et al. [8, 10, 11] studied the change in various clinical parameters under the action of chlorophyll in laboratory animals exposed to external ionizing radiation.

The paper [10] provided data on a decrease in the cortisol content in irradiated animals either treated or not treated with chlorophyll preparation. An increase in the concentration of cortisol indicates that the body is in a stressful state [28, 29]. Therefore, a decrease in the content of this hormone in the serum of irradiated animals treated with chlorophyll preparation can indicate a decrease in the severity of radiation syndrome [30]. The results presented in [8, 11] and illustrated in Fig. 3 also support this statement.

Malondialdehyde is one of the stable final products of lipid peroxidation, and thus is its biochemical marker [31, 32]. The results that show a decrease in the content of malondialdehyde in the blood (Fig. 3a) and liver (Fig. 3b) of irradiated mice under the action of chlorophyll preparation in combination with the data presented in [24] allow us to say with confidence that the mechanism of radioprotective action of chlorophyll preparations is the suppression of lipid peroxidation. In the described experiment, mice were subjected to a single external exposure to γ-radiation at a dose of 5 Gy. The experimental groups were injected with chlorophyll at a concentration of ~5.5 mM in a volume of 0.2 mL/mouse before or immediately after irradiation. The result is fully consistent with the conclusions of the authors of [4], who evaluated the effect of chlorophyllin on the content of malondialdehyde after γ-radiation. In this case, the use of the drug before irradiation is more effective than after irradiation (Fig. 3). We also note that a dose of 5 Gy did not cause significant erythrocytopenia (Fig. 3c) but caused leukopenia (Fig. 3d), whose severity was reduced by the use of a chlorophyll preparation, although the level of leukocytes in the blood in the first week of the experiment did not return to the value observed in nonirradiated animals.

Thus, the use of chlorophyll preparations can effectively mitigate the clinical manifestations of radiation sickness. Therefore, comprehensive studies of the radioprotective properties of chlorophyll with the determination of the most effective method of their clinical use seem appropriate.

As mentioned, the biological effect of radiation is primarily the radiolysis of water (although there is also

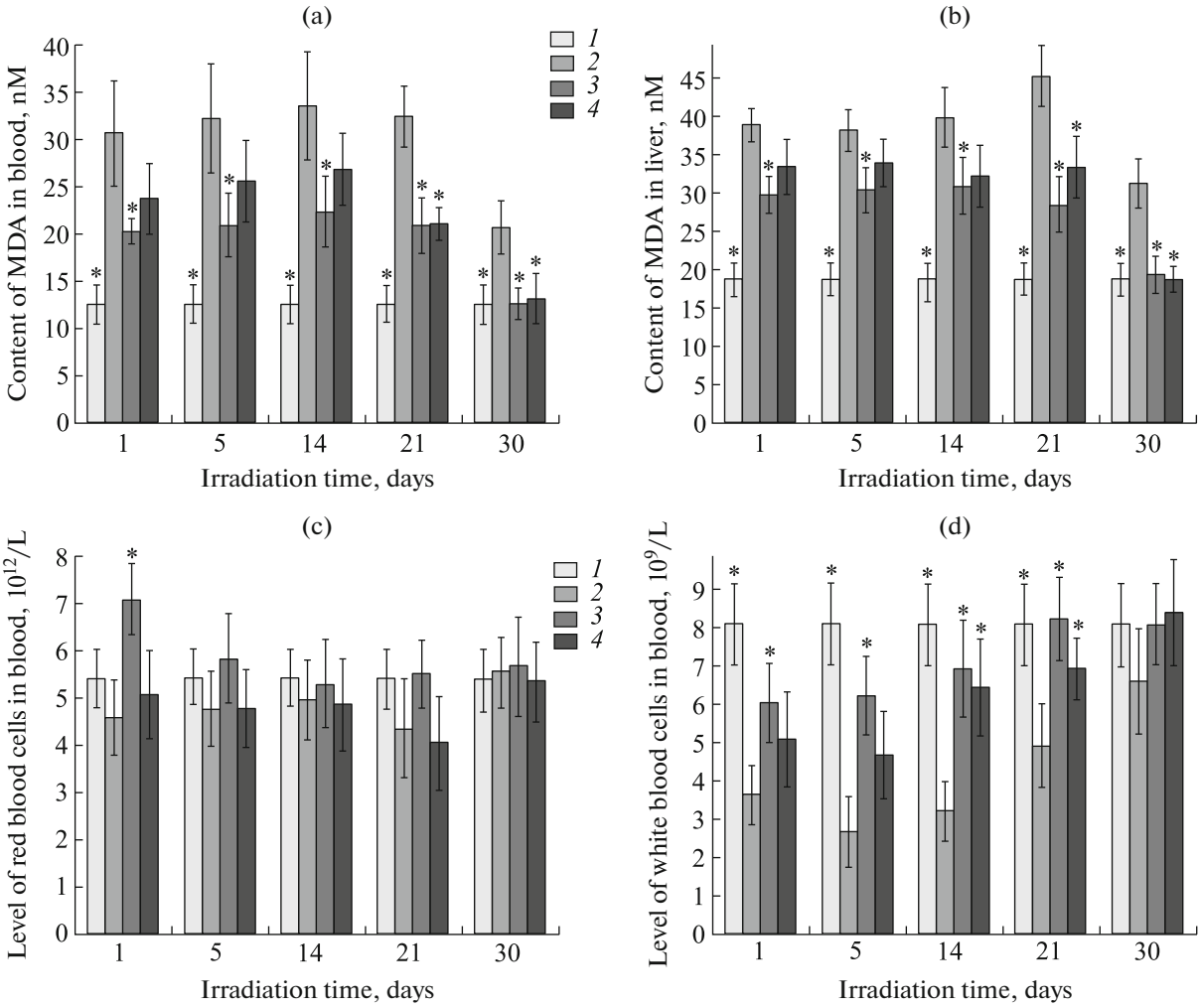

Fig. 3. The radioprotective effect of chlorophyll (single intramuscular injection, 0.2 mL, ~5.5 mM) under a single action of γ-radiation (5 Gy; radiation power, 4.3 R/min). The effect on the content of malondialdehyde in the blood (a), malondialdehyde in the liver (b), red blood cells (c), and leukocytes in the blood (d). The numbers indicate the experimental groups of mice that did not receive the drug and were not irradiated (*1*), were irradiated without receiving the drug (*2*), received the drug before irradiation (*3*), and received the drug after irradiation (*4*). Asterisk (*) designates a significant difference ($P = 95$, $n = 12$) from the value in the group exposed to γ-radiation without receiving the drug (group 2). The graphs are based on the data presented in [8, 11].

direct radiolysis of biomolecules), followed by further attack of its products on biological molecules [16]. The formation of so-called lipid radiotoxins is of special significance in this process. These products are involved in the lipid peroxidation triggered by the products of water radiolysis [15]. We believe that the mechanism of the radioprotective effect of chlorophyll preparations is associated with the suppression of this process (Fig. 4).

However, the neutralization of lipid radicals by chlorophyll derivatives does not negate the possible ability of these drugs to neutralize both hydroxyl and peroxyl radicals and radical radiolysis products of proteins and nucleic acids. This aspect of their action should be examined in future studies. The blocking of lipid peroxidation because of radiation through both the neutralization of the products of water radiolysis and the direct neutralization of lipid radicals will prevent cell death by the mechanism of apoptosis [33], necrosis-like death by the mechanism of ferroptosis [34], and the induced necroptosis of neighboring cells [35]. Thus, the blocking of lipid peroxidation will greatly facilitate the course of radiation sickness. At the same time, the use of chlorophyll even after exposure to ionizing radiation significantly reduces the clinical manifestations of radiation damage (Fig. 3, and data [8, 11]).

CLINICAL FORMS OF CHLOROPHYLL-BASED DRUGS

For the greatest effectiveness of the clinical use of chlorophyll-based drugs, it is necessary to determine whether chlorophyll or water-soluble chlorophyll will

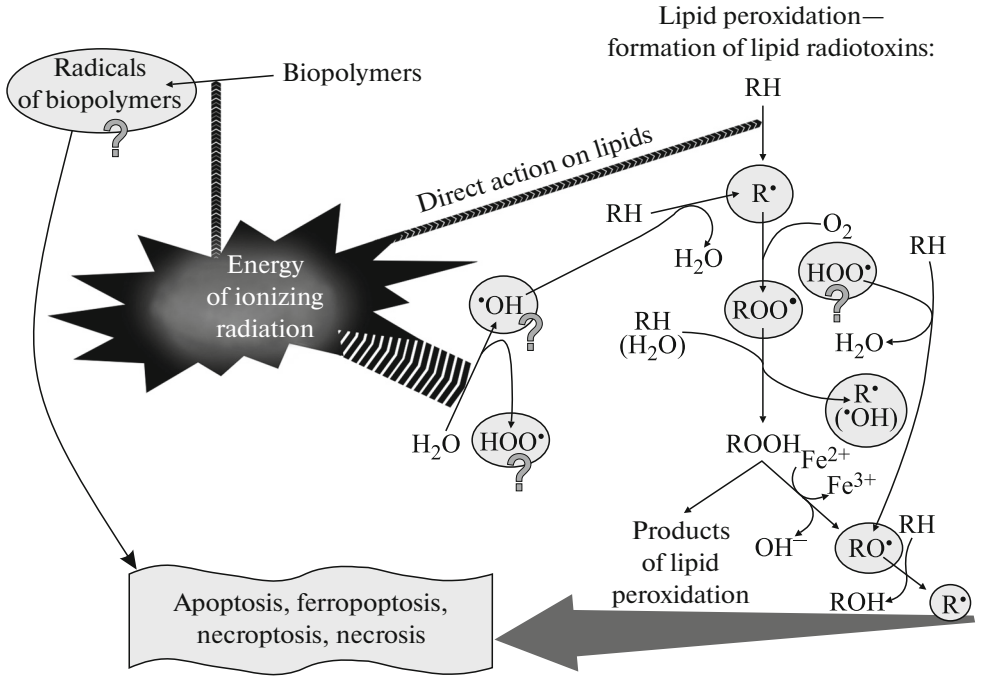

Fig. 4. The mechanism of radioprotective action of chlorophyll-based drugs. The gray oval marks the radicals that are neutralized by chlorophyll derivatives. The question mark indicates an assumption that has not been tested on a molecular model that chlorophyll neutralizes the corresponding radical.

be used and to choose the optimal way of using the drug in clinical practice.

Some commercial companies offer preparations based on chlorophyll. Most often, these drugs are various dietary chlorophyllin-containing supplements, such as the one used in [24]. However, all of them are registered as biologically active substances but not medicinal preparations. In addition, the manufacturer's protocol for taking these drugs in no way can provide concentrations of chlorophyllin in the body that would guarantee at least some effect according to scientific research [3–8, 10–12, 24]. Thus, it is still impossible to say that there are any chlorophyll-based drugs on the market that have been developed for both the prevention and therapy of radiation sickness in particular and stabilizing free radical processes in the body in general.

Water-soluble substances are much more easily absorbed in the intestine and transported by blood. However, in the absence of special carriers, their passage through cell membranes is difficult. At the same time, water-soluble compounds also act more effectively in the cellular cytoplasm. The authors of [7, 8, 10–12] injected chlorophyll into experimental animals intramuscularly. The authors of [2–6] studied the effect of water-soluble chlorophyllin.

The form of the drug and the method of its administration are extremely important. In addition to the classical oral and intravenous administration, inhaled delivery methods are currently being developed for radioprotective drugs [1].

To increase the effectiveness of oral administration of drugs, some researchers suggest using liposomes with certain properties [36–39]. In our opinion, it is necessary to use water-soluble chlorophyllin in liposomes, which contain surface-bound ligands to specific receptors of the target cells in the most radiosensitive tissues. It is necessary to perform a multifaceted study of the radioprotective effect of various clinical forms of chlorophyll and chlorophyllin, e.g., in the form of solutions or suspensions of free molecules and in the composition with liposomes including large liposomes that contain liposome/chlorophyll (or chlorophyllin) compositions.

In conclusion, we also note that for greater efficiency it is possible to use a combination of the chlorophyll-based drugs with other radioprotectors and radiomodulators. The effect of a combined agent consisting of chlorophyll, curcumin, and DNA from fish milk on the cortisol content in the blood of irradiated animals was studied [10]. The authors of [40] reported a radioprotective effect of honey in combination with a chlorophyll preparation. The radiomodulatory properties of bee products were also mentioned in the review [14].

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflicts of interest. This article does not contain any studies with the use of humans and animals as objects of research.

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