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On possible role of hydrogen peroxide molecules in ion beam therapy of cancer cells

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The possible role of molecular products of cell radiolysis, in particular, hydrogen peroxide molecules, in blocking DNA activity in cancer cells during irradiation with heavy ions is investigated. It is supposed that hydrogen peroxide molecules can form long-lived molecular complexes with DNA atomic groups and, thus, prevent the realization of genetic information in the biological cells. Using the quantum-mechanical approach based on density functional method and implicitly taking into account the aqueous medium, the competitive interactions of water and hydrogen peroxide molecules with DNA nucleic bases have been analyzed. Estimates of the characteristic lifetimes of complexes of water molecules and hydrogen peroxide with atomic groups of DNA allow showing the possibility to block the genetic activity of DNA by hydrogen peroxide in biological cells after their irradiation with ion beams. The effect of DNA blocking in cancer cells could be enhanced by a decrease in the cell temperature.

Keywords: ion beam therapy, DNA blocking, hydrogen peroxide, computational studies.

1. Introduction

Radiation therapy is one of the most promising treatments of cancer diseases today. In this approach, the tumor is irradiated with a beam of particles (protons, electrons, neutrons, ions, etc.), which leads to its destruction. Irradiation with protons and heavy ions is the most effective since these particles have the Bragg effect, which means that a particle passing through a medium loses most of its energy in a certain small area inside the body (under it stopping at the Bragg peak) [1–4]. The location of the peak is strictly determined by beam energy and the type of ions. Thus, there is the possibility of precise alignment of the beam energy peak with the position of the cancerous tumor, and transfer most of the beam energy directly to the tumor, minimally damaging adjacent healthy tissue. Other types of radiation, such as electrons or photons, do not have this effect and transfer energy to the tissue sequentially during the whole path from the body surface to the tumor. In this case, healthy tissues are significantly damaged also, especially if the tumor is deep enough. Therefore, heavy ion irradiation is considered the most effective and safe method of treating cancer with radiation therapy.

The processes leading to the deactivation of cancer cells during ion therapy are still insufficiently studied. It is considered that the key mechanism of cancer treatment should be connected with DNA termination of execution of their functions, but the mechanisms of these effects still need to be studied. It have been considered the action on DNA macromolecules of secondary electrons, free radicals, charged particles, and even shock waves that can be formed during cell irradiation [5–8]. At the same time, it is now known that defects in the DNA structure that can occur in these cases have a relatively short lifetime, and the macromolecule can be effectively restored in a cell due to repair processes [9]. Thus, the mechanisms of ion beam action on a DNA macromolecule in a living cell require careful consideration. An experimental studies show that a significant role here can be played by products of radiolysis of water, which make up most of the content of the cell nucleus [10, 11]. However, the role of some water molecular products (such as hydrogen peroxide) is practically not taken into account when considering the effects of ion irradiation.

This article discusses the possible mechanisms of action of hydrogen peroxide (H_2O_2) molecules on DNA activity in the biological cell compared to the action of water molecules (H_2O), which usually stabilize the state of the macromolecules. In Sec. 2, the various products of water radiolysis of the biological cell are considered and the possible role of H_2O_2 is discussed. A hypothesis is formulated about the possibility of reducing the activity of a DNA recognition sites due to interaction with H_2O_2. The formation of

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the complexes of DNA with H_2O_2 allows blocking the genetic activity of the macromolecule as a whole. In Sec. 3, the results of modeling of molecular complexes consisting from a DNA nucleic base, molecules H_2O_2 and H_2O are under consideration. The study leads to an understanding of the role of hydrogen peroxide in ion beam therapy of a cancer cell. The estimations of the lifetimes of considered complexes are done in Sec. 4. The effect could have the definite interest for development of the methods and tactics of cancer treatment. The discussion of the results obtained and the conclusions are presented in Sec. 5.

2. Radiolysis products of biological cell: H_2O_2 and H_2O molecules

Under physiological conditions, the processes of functioning of the genetic apparatus of a biological cell strongly depends on the content and state of water molecules [10, 11]. Due to radiolysis processes, the substance of the cell nucleus is changed sufficiently and can remain changed due to large time. After radiolysis, the water medium in the cell is transformed mostly into the following products: radicals, charged particles, and molecules [5–8, 10–13]. The latter are H_2 (hydrogen) and H_2O_2 molecules. The results of the water radiolysis study show that the radicals and ions are not long-living products. They can be active on some short time scale, up to 10^{-6} s during the physic-chemical stages of radiolysis [7, 12, 13]. It should be noted also that H_2 molecules are not so active in chemical reactions and, therefore, don't take place in the formation of the content of the irradiated cell nucleus. The definite attention is attracting by the peroxide molecules. Under now time, the role of H_2O_2 molecules in the cell radiolysis is not completely clear. It is known that when a tumor is irradiated with an ion beam, the concentration of H_2O_2 molecules in a cell medium significantly increases and without external intervention remains stable for a relatively long time [7, 12, 13]. The long lifetime of H_2O_2 (more than a month after irradiation) in an aqueous medium was noticed also in the special experiments during industrial production and use of peroxide [14].

The participation of H_2O_2 molecules in the functioning of a biological cell has been studied experimentally [15, 16]. In these studies, the sensitivity of cancer cells and even their death with an increase in the concentration of H_2O_2 molecules are shown. These data show that H_2O_2 molecules take part in the regulation of the biological cell activity and can influence the work of the cell genetic apparatus. But the mechanism of such action of H_2O_2 is not determined yet.

It should be noted that water molecules exist in the cell nucleus in a sufficiently large amount [10, 11]. In turn, peroxide molecules are formed thereafter cell irradiation [7, 12, 13]. That is, at the physic-chemical stage of radiolysis, reactions between radicals $HO^{\bullet}$ lead to the formation of peroxide molecules:

$$HO^{\bullet} + HO^{\bullet} \rightarrow H_2O_2. \qquad (1)$$

The biological processes connected with the transfer of genetic information in the cell should begin 10^{-6} s after radiolysis. At this stage, which can be called "biological", the medium of the cell and its nucleus are mainly composed of H_2O and H_2O_2 molecules. The competition of these molecules in the irradiated cell will determine the course of all following biological processes. It should be noted also that the H_2O_2 and H_2O molecules are consisted of the same atoms, have a similar atomic structure, and closed in the size to each other (Fig. 1).

The formation of peroxide molecules in a water environment should lead to some definite consequences in the cell medium. First, on a "biological" time scale, H_2O_2 molecules have a larger concentration in the cell solution than other radiolytic products, and the probability of their "meeting" with the atomic groups of DNA becomes higher. Second, the H_2O_2 molecule is similar to the H_2O molecule, however, the peroxide molecules have an additional oxygen atom and could form another environment around the active centers of DNA. In turn, another environment of the DNA sites should lead to the blocking of DNA genetic information from the different bindings necessary for the normal functioning of the cell. And thirdly, H_2O_2 and H_2O molecules have one important difference. This is the ability to the conformational transformation of H_2O_2, in contrast to the stability of H_2O structure under physiological conditions. In fact, H_2O_2 can rearrange the mutual position of the O–H bonds by rotating around O–O bond. This transformation changes the dihedral angle (θ) and the conformation of the molecule (Fig. 1). The ability of the H_2O_2 molecule to undergo conformational transformations should lead to its more efficient (than H_2O) binding to the atomic groups of DNA macromolecule and can promote more stable structure of the complex with DNA.

To understand how important these properties are for the functioning of the molecule in the cell, a comparative analysis of the interaction of H_2O_2 and H_2O molecules with the atomic groups of a DNA macromolecule in an aqueous solution was carried out. The most energetically advantageous complexes of DNA bases with H_2O_2 and H_2O molecules have been identified. When choosing mo-

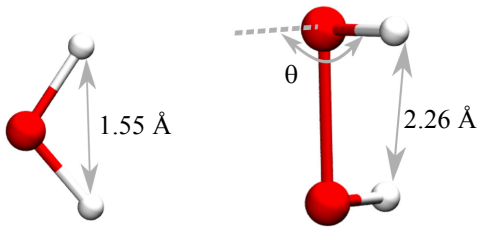

Fig. 1. (Color online) Spatial structure of H_2O (left) and H_2O_2 (right) molecules. The oxygen and hydrogen atoms are marked in red and white, respectively. The distances between the hydrogen atoms in the molecules are indicated by arrows. In H_2O_2 structure, there is a definite dihedral angle (θ) between the O–H bonds.

lecular complexes, it is assumed that only complexes with at least two bonds of non-valent interactions between different atomic groups of medium molecules and atomic groups of DNA should be considered. It is supposed that the molecular complexes are formed by hydrogen bonds as well as by ionic and van der Waals interactions.

The formation of at least two non-valent bonds between different molecular groups ensures the stability of molecular complexes and the accuracy of information transfer in genetic processes. Note that a similar condition about the need of two hydrogen (or non-valent) bonds formation has been formulated for the process of nucleic acid sites recognition by cell molecules [17, 18].

It should be noted that at physiological temperatures and below, the structure of the molecular complexes under consideration will not change significantly, only the amplitudes of conformational vibrations and their frequency values will decrease. This will be due to the effective change in the masses of the structural elements of the double helix, such as nucleic bases, the mass of which can increase due to the effective attachment of the peroxide molecules.

3. Blocking of DNA atomic groups of specific recognition

To understand the possibility of the formation of the stable complexes of H_2O_2 and H_2O molecules with atomic groups of DNA nucleic bases (specific recognition sites), the structure and energy formation of the complexes are studied in this section. In Fig. 2 the recognition sites of the nucleic bases are marked by Roman numerals. For most of these sites, it is possible form a stable molecular complexes between atomic groups of nucleic bases and H_2O_2, or H_2O molecules with the help of two H bonds in accordance with peculiarities of the process of nucleic acid sites recognition [17, 18].

In the study of molecular complexes, the structures of the atomic groups of DNA double helix interacting with H_2O_2 or H_2O were considered as unchanged. At the same time, the peroxide molecule has been considered as a structure with a conformational degree of freedom due to the rotation of the O–H bonds around the O–O axis in the molecule in accordance with the data of [19–21]. The calculations of interaction energies of the complexes and determination of the positions of molecules in them were performed in our work [22] by the quantum-mechanical method using density functional approach in B3LYP/6-311+G(d,p) basis and taking into account the implicit water environment in the PCM (polarizable continuum model) approximation. It was shown that the quantum-mechanical approach and the method of atom-atomic potential functions used in our work [23] give similar results, testifying about the importance of considering the participation of H_2O_2 in the mechanism of ion therapy.

The configurations of all stable complexes of nucleic bases with H_2O_2 and H_2O molecules shown in Fig. 2, and

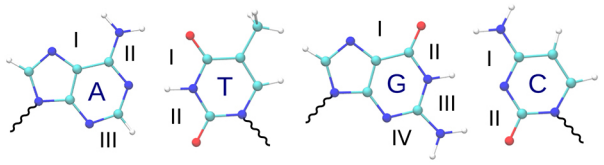

Fig. 2. (Color online) The interactions sites (marked by Roman numerals) of DNA nucleic bases with H_2O_2 and H_2O molecules. The carbon, nitrogen, oxygen, and hydrogen atoms are marked in green, blue, red, and white, respectively. The binding of the nucleic bases to the DNA backbone are indicated by wavy lines.

the calculation results of their interaction energies are presented in Table 1 (third column). As seen, the interaction energies between the atomic groups of nucleic bases with H_2O_2 molecules can differ significantly (the average value is 1.9 kcal/mol, or 3.05 k_BT). These differences are mainly associated with the configuration of the atomic sites themselves and the type of connection of the molecules within the complexes. Based on the obtained results, it can be concluded that in all complexes the participation of H_2O_2

Table 1. The interaction energy values of the complexes consisting of a nucleic base and H_2O_2 molecule (E_p, kcal/mol), classified by their possible interaction sites around the nucleic bases

Nucleic base	Interaction site	$-E_p$ (ΔE)	α	θ, deg
Adenine	I	10.8 (1.2)	6.5	109
	II	11.2 (2.2)	34.2	111
	III	(--)	(--)	(--)
Thymine	I	10.4 (1.8)	16.8	117
	II	11.2 (1.9)	20.7	117
Guanine	I	11.0 (2.5)	59.3	72
	II	13.4 (1.8)	18.6	103
	III	(--)	(--)	(--)
	IV	9.8 (2.0)	25.3	112
Cytosine	I	12.9 (1.8)	18.6	105
	II*	10.4 (--)	(--)	57
	III	(--)	(--)	(--)

Notes: In brackets the values of energy difference with respect to the complexes with H_2O (E_w) are given: $\Delta E = |E_p| - |E_w|$. The energy values for 3d column are calculated in [22] using B3LYP-PCM method. The complexes with only two H bonds are under consideration (see text for details). The designation (--) means that there is no minimum with two H bonds in this complex. In 4th column, the calculation results for parameter $\alpha = \exp(\Delta E/k_BT)$ are given for each interaction sites. In column 5, the values of dihedral angles (in degrees) of peroxide molecules in considered complexes are done.

*In position II of Cytosine, the minimum for the interaction energy of nucleic base with water molecule by two H bonds in the complex is not observed.

molecules leads to the advantage in the stabilization energy in comparison with the corresponding complexes that include H_2O molecules.

The reason of such differences is clearly seen on the configuration of complexes with Thymine base (Fig. 3). Indeed, at each interaction site (the position I and II), the H_2O_2 and H_2O molecules can form two H bonds, and the corresponding bond lengths are very close. But, as seen, the hydrogen bonds in a complex with H_2O_2 have a straightened form (Fig. 3). At the same time, the H bonds between the water molecule and the nucleic base in I and II sites of Thymine are sufficiently bent (see Fig. 3) and therefore weakened. The bending of H bonds means a decrease in the binding energy between the molecules in the complex. The effect of more weak binding for a water molecule to Thymine base is clearly seen in the results of Table 1. Thus, we can consider that, due to the conformational features of the H_2O_2 molecule (the possibility to change the torsion angle), the corresponding complexes are more stable and, therefore, should exist for a longer time in the bound state. That is, it can be concluded that hydrogen peroxide molecules are more "suitable" than water molecules for the formation of complexes with Thymine nucleic bases.

As seen from Table 1**,** the most likely sites for the formation of complexes between nucleic base and peroxide molecule are sites I and IV of Guanine and site II of Adenine. But if it will be considered the interaction of "closed" base pairs with H_2O_2 or H_2O, then only sites of Guanine can be considered active in such recognition. The site I of Adenine has a small value of the α parameter. The other sites can be considered open for interaction only after disclosing of the base pairs. It should be noted that, in all cases, the differences in complex formation energies for different nucleic base interaction sites show an advantage in the formation of complexes with peroxide molecules as compared with complexes with water.

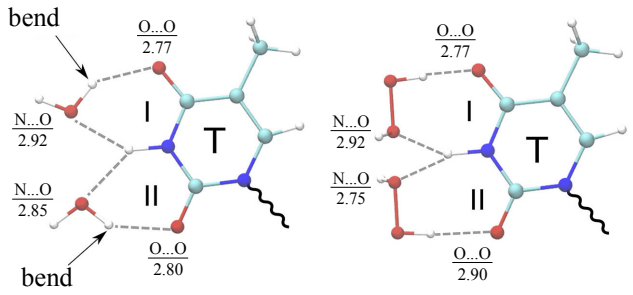

Fig. 3. (Color online) Spatial configurations of the complexes of H_2O (left) and H_2O_2 (right) with Thymine nucleic base for I and II possible positions of water or peroxide molecules. The H bonds are indicated by the dotted lines. The bends in the hydrogen bonds for the complexes of Thymine with water molecules are marked by the arrows. The distances between heavy atoms (O…O and N…O) of the nucleic base and H_2O or H_2O_2 molecules are given in Å. The binding of the nucleic bases to the DNA backbone is indicated by wavy lines.

It is important to emphasize that the difference in the energies of complex formation, in addition to differences in the formation of hydrogen bonds, is associated with the conformation of H_2O_2 molecule itself. An additional study of the shape of the peroxide molecule has shown that at all binding sites the dihedral angle θ changes its value to form the most advantageous structure of the complex (Table 1, 5th column). The most significant is the changes in H_2O_2 conformation during the formation of a complex with Guanine (site I) at about 70° and Cytosine (site II) at about 60°. Note that the middle meaning of the dihedral angle in H_2O_2 is about 120°. Such a large change in the value of the torsion angle may mean the transition of the molecule to another, more favorable for interaction with DNA, conformational state. It should be noted that the effect of a significant change in the peroxide dihedral angle values is observed for the nucleotides in the G•C base pair, but not for A•T.

4. Lifetimes of complexes of H_2O_2 molecules with DNA atomic groups

To understand the possibility of complex formation of H_2O_2 with the DNA atomic group, the rate constant of such complex is considered in comparison with the corresponding value for the complex with H_2O. Having data about the formation energy of the molecular complexes (3d column of Table 1), the value of its rate constant (K) can be estimated by the Arrhenius-type formula as

$$K = A\exp\left(-E/k_BT\right), \tag{2}$$

where A (s^{-1}) is the rate constant of complex formation at zero energy. The E is the energy of complex formation of DNA atomic group with H_2O_2 (E_p) or H_2O (E_w) molecules, k_BT reflects the value of heating energy of the environment. Note that the energy values E in Eq. (2) are already known from our calculations for the set of considered complexes (Table 1). These data give the possibility to compare the lifetimes of the bound states of the complexes consisting of a nucleic base with H_2O_2 and H_2O molecules.

As can be seen, the reversing of formula (2) gives the expression for the estimation of lifetime ($t \sim K^{-1}$) of the complexes of DNA atomic group with H_2O_2 or H_2O molecules. Really, after inverting the formula, one can obtain

$$t \sim \omega^{-1}\exp\left(E/k_BT\right), \tag{3}$$

where ω (s^{-1}) is the frequency of the structural transformations of the molecular complex with DNA atomic group on the pathway to the barrier between the bound and unbound states of the complex. The observation of the frequency ω would mean the formation of the bound state of the complex. The expression for the frequency ω can be written as

$$\omega \sim \sqrt{k/m}. \tag{4}$$

In expression (4) k is the force constant of the complex formation and m is the reduced mass of the complex struc-

ture mobility. Due to the same quantity (two) of H bonds in the complexes with H_2O_2 and H_2O, the force constants k for these complexes should be close to each other in its value.

Let us take into account also that the masses of nucleic bases are larger in an order than the masses of H_2O_2 (m_p) or H_2O (m_w) molecules. Therefore, considering the structural dynamics of the complexes, it is sufficient to consider the movements of m_p or m_w relatively to the DNA nucleic base in the complex only. In addition, when estimating the frequency ω, it is also necessary to take into account that the H_2O_2 molecule has a mass almost twice as much as the H_2O molecule, i.e., $m_p > m_w$. Thus, according to expression (4), the value of ω_p for the complex with H_2O_2 should be lower than the same as ω_w for the complex with H_2O. So, it is valid to assume

$$\omega_w/\omega_p \sim \sqrt{m_p / m_w} \geq 1. \tag{5}$$

The performed estimations can be used for the comparison of the lifetime of the complexes of DNA atomic groups with H_2O_2 and H_2O molecules. From expression (3) the lifetime for H_2O_2 molecule in the complex compared with H_2O molecule can be written as

$$t_p \sim \frac{\omega_w}{\omega_p} \alpha t_w, \tag{6}$$

where $\alpha = \exp(\Delta E / k_B T)$ and $\Delta E = |E_p| - |E_w|$ is the difference between the energy of complexation of the nucleic base with molecules of peroxide or water.

The expression (6) determines the relative lifetime of the complex of the DNA nucleic base with a peroxide molecule (t_p) in comparison with the lifetime for the same complex but with a water molecule (t_w). Evaluating expressions (5) and (6), we can obtain

$$t_p > \alpha t_w. \tag{7}$$

For quantitative estimates of the lifetimes ratio (7), the values of the parameter α for each interaction site are calculated and presented in the 4th column of Table 1. Besides, from the data given in Table 1 (3d column), it can be assumed that for all complexes the following ratio is valid: $\Delta E / k_B T > 1.9$. So, accounting relation (5) and the value of α for the site I of Adenine, the estimation of t_p by the expression (6) gives $t_p > 6.5\ t_w$. Note that this α value is the lowest value for the related complexes lifetimes. The same estimations for the site I of Guanine give $t_p > 59\ t_w$, for the site II of Adenine $t_p > 34\ t_w$, and for the site IV of Guanine $t_p > 25\ t_w$.

As follows from the calculated lifetimes of the complexes, the H_2O_2 molecules can block the atomic groups of DNA bases for a relatively longer time (compared to water). This conclusion is consistent with the results of computer simulations [7], which indicate the existence of H_2O_2 for a long time at a sufficiently high concentration in a physiological solution after irradiation with heavy ions.

Comparing the lifetime values of H_2O_2 near the DNA PO_4 group obtained in [22, 23] (about 2.4 time more of water) with the shortest expected lifetime of H_2O_2 near DNA nucleic base (the site I of Adenine), we can conclude that the atomic groups of nucleic bases are more attractive sites for the binding of H_2O_2 to DNA macromolecule.

It is important to emphasize that parameter α is very sensitive to the temperature of the environment. Note that our estimations and obtained results are valid for the some time interval of the residence of the cell at physiological temperature. Really, under decreasing the temperature value in the cell medium, parameter α will increase and the lifetime of peroxide molecules near DNA will grow. In this case, the time of the blocking of DNA sites will be increased, and as a result, DNA can be deactivated.

And in the case of the opposite process, when the temperature in the cellular environment increases, the parameter α will decrease, and the lifetime of peroxide molecules near the DNA helix in the cell will also decrease. That is, in this case, an increase in the temperature of the cell environment will prevent the treatment of the disease.

It should be noted that the presence of H_2O_2 molecules near DNA atomic groups can be observed by the appearance of an absorption band in the macromolecule vibration spectra about 370 cm^{-1} [20], where the torsion oscillations around the O–O bond in the peroxide molecule can be observed. In this case, the low-temperature condition can be important since, because the vibration will be realized against the background of a large number of fluctuations of both the macromolecule itself and its aqueous environment. Note that, in low-temperature conditions, the torsion vibrations of peroxide molecules can be unfrozen in DNA grooves and occur directly near the surface of the double helix in a small layers of water molecules. So, under the low temperature, the vibrations of peroxide molecules could be visible in DNA vibrational spectra.

5. Conclusions

The mechanisms of inactivation of cancer cells under the influence of beams of high-energy ions in the method of ion therapy are being studied. The work draws attention to the possible role of molecular products of water radiolysis, in particular, hydrogen peroxide molecules, in blocking the activity of DNA in cancer cells. Using the quantum-mechanical approach, the competitive interactions of water and hydrogen peroxide molecules with DNA recognition sites are studied and the advantage of hydrogen peroxide molecules in the complexation with DNA nucleic bases is shown. Analyzing the interactions of radiolysis products with DNA macromolecule, it is concluded that hydrogen peroxide molecules can form long-lived complexes with atomic groups of DNA sites of specific recognition — nucleic bases.

Estimates of the characteristic lifetimes of the complexes of peroxide molecules with DNA atomic groups allow formulating the hypothesis about the mechanism of hydrogen peroxide blocking of DNA genetic activity in cancer cells. As follows from the analysis of experimental data, as a result of irradiation in the nucleus of a biological cell, a large number of hydrogen peroxide molecules can be formed. According to our hypothesis, these molecules compete with water molecules for interaction with DNA and can form long-lived molecular complexes with nucleic bases of the macromolecule. Thus, hydrogen peroxide molecules, through the formation of stable complexes can block the processes of DNA unzipping and the genetic activity of the DNA macromolecule as a whole [24].

It is important to underline that the action of peroxide molecules on cell DNA can be observed at low temperatures. At these conditions, torsion vibrations of peroxide molecules can occur against the background of a static (frozen) macromolecule and so should be sufficiently visible in vibration spectra DNA.

The obtained results are important for understanding the mechanisms of cancer cell neutralization, in particular, with the help of the ion therapy method, and allow formulating the holistic mechanism for the influence of H_2O_2 molecules on the processes of genetic information transmission in biological cells.

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Про можливу роль молекул перекису водню в іонно-променевій терапії ракових клітин

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Досліджено можливу роль молекулярних продуктів радіолізу клітин, зокрема молекул перекису водню, у блокуванні активності ДНК у ракових клітинах під час опромінення важкими іонами. Припускається, що молекули перекису водню можуть утворювати довготривалі молекулярні комплекси з атомними групами ДНК і, таким чином, перешкоджати реалізації генетичної інформації в біологічних клітинах. За допомогою квантово-механічного підходу, заснованого на використанні метода функціонала густини та неявного урахування водного середовища, проаналізовано конкурентні взаємодії молекул води та перекису водню з нуклеїновими основами ДНК. Оцінки характерних часів життя комплексів молекул води та перекису водню з атомними групами ДНК дозволяють показати можливість блокування генетичної активності ДНК молекулами перекису водню в біологічних клітинах після їх опромінення пучками іонів. Ефект блокування ДНК в ракових клітинах може бути посилений зниженням клітинної температури.

Ключові слова: іонно-променева терапія, блокування ДНК, перекис водню, обчислювальні дослідження.