The Radioprotective Properties of Imatinib Mesylate-Zinc Complex in Plants

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Abstract: We have studied the radioprotective properties of the Zn Imatinib mesylate complex under model laboratory conditions. The effect of the obtained complex on photosynthetic activity, on morphological, physiological, biochemical parameters, on the activity of the enzyme superoxide dismutase and the yield of malon dialdehyde in seedlings obtained from gamma irradiated wheat seeds at a dose of 220 Gy was studied. It was revealed that treatment of wheat seeds before irradiation with 0.1%; 0.01% and 0.001% aqueous solution of the complex leads to the normalization of the biosynthesis of photosynthetic pigments, has a positive effect on photosynthetic activity, on morphological, physiological and biochemical parameters of seedlings obtained from gamma-irradiated wheat seeds.

Keywords: Imatinib, Radioprotector, Photosynthetic pigments, Fluorescence, Irradiation, Malon dialdehyde.

1. INTRODUCTION

It is known that more effective drugs against the harmful effects of various physical and chemical environmental factors is the most urgent today. Research shows that nitrogen-containing heterocyclic compounds increase the internal defense mechanisms of the body and its detoxifying ability of reactive oxygen species. The presence in its composition of a combination of oxygen and nitrogen atoms, as well as unsaturated bonds, increases the physiological activity of these multifunctional compounds. Benzamide and its derivatives when administered together with antineoplastic agents to suppress tumor growth, increase their effectiveness [1, 2]. Complex compounds of these ligands formed with biogenic metals are also distinguished by their antiradical properties and selectivity. These compounds normalize metabolic processes, increase the longevity of cells during oxygen deficiency, participate in the synthesis of nucleotides, accelerate the regeneration of damaged cells, and increase the activity of enzymes. They are widely used in medicine, in plant growing, in animal husbandry, as well as in the production of pharmaceuticals and dietary supplements. Many trace elements are involved in almost all processes in the plant cell: energy metabolism, primary and secondary metabolism, hormonal regulation, signal transmission, etc. It should be noted that many proteins also (more than 1200) are functionally related to zinc [3-5].

Zinc takes part in all types of metabolism, is present in the composition of 7200 enzymes, is necessary to stabilize the structure of DNA, RNA and ribosomes, it plays an important role in the translation of cell growth and division, participates in the stabilization and permeability of cell and intracellular membranes, membrane transport processes, the formation of antioxidant status as a protector of free radical reactions, has a significant effect on the immune system [6-9].

Recent studies have shown that certain metal ions are most effective as inhibitors of enzymes that enhance the creation of tumor cells. Obtaining and research of such complex compounds that contribute to the neutralization of free radicals created in the body as a result of the influence of a harmful environment is of great practical importance. Based on this, the aim of this work was to study the radioprotective properties of imatinib mesylate- zinc complex in wheat seedlings [11].

2. MATERIALS AND METHODS

The sample of Imatinib mesylate, were purchased from Merck↔Sigma-Aldrich. In experiments with plants were used wheat seeds of the "Bereketli-95" variety. Wheat seeds were irradiated with a dose of 220 gray using the URİ (K-25) device at a dose rate of 13.9 rad / sec, source - ^{60}Co. Vegetation experiments were carried out in vessels 10x20 cm in size, five times repetition during 4 weeks. Morphological parameters and growth dynamics of wheat seedlings was measured every 7 days for a month.

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The amount of chlorophyll pigments, carotenoids, malondialdehyde were measured on a Multiskan GO spectrophotometer. Chlorophyll was extracted from the leaves using 96% ethyl alcohol. Chlorophyll a (665 nm), chlorophyll b (649 nm), and carotenoids (440 nm) were determined by the spectrophotometric method based on their absorption spectra. The pigment content was calculated based on the fresh weight of the leaves (mg/g) using the Wintermans method. The fluorescence of chlorophyll in the leaves was measured with a MINI-PAM (photosynthesis yield analyzer, Germany) device. Using the formulas $F_v = F_m - F_0$ and F_v / F_m, the efficiency of the photochemical conversion of energy in the second photosystem was determined (Maxwell and Johnson, 2000).

To determine the MDA content, the freshly harvested plant leaves were homogenized with 5% trichloroacetic acid, and then for a period of 10 min at 27°C was centrifuged (12000 g).

Next, equal volumes of the supernatant and 0.5% thiobarbituric acid were added to 20% trichloroacetic acid and incubated at 96°Cfor 30 minutes and quickly cooled in an icebath. After centrifugation at 12000 g for 10 min, the optical densityof the superdeposition liquid was determined at 532 and 600 nm.

Data analysis and statistical analysis were conducted using Microsoft Excel. Statistical analysis was performed with the aid of the Stat graphics Plus 5.1 statistical package. The means of values were compared by Duncan's multiple range test (p=0.05).

3. RESULTS AND ITS DISCUSSION

The preparation of the zinc complex of Imatinib mesylate was carried out according to the method described in the literature [10].

Given the fact that it is poorly soluble in water (0.001 g / 100 ml), we took imatinib in the form of mesilate, which is well soluble in water.

The synthesis of the complex was carried out at a temperature of 75-85 ° C in an aqueous-alcoholic medium by intensive mixing for 4 hours. The resulting complex was isolated and washed with hexane. The complex of zinc with imatinib mesylate is a light yellowish amorphous powder. The nature of the diffraction patterns of the synthesized compound and their difference from diffraction patterns of the starting compounds confirmed the individuality selected connections.

The IR spectrum (Figure **1**) of the complex showed the presence of zinc interactions with the mesylate ion. Thus, it can be assumed that, the complex of imatinib mesylate with zinc was formed through the mesylate ion oxygen donor atom [10, 22].

Morphological, physiological and biochemical studies of wheat seedlings were carried out in 11 variants: control, irradiated, treated in three concentrations (0.1%; 0.01%; 0.001%) solutions of the Imatinib mesylate complex. These studies were carried out at different stages of development of wheat seedlings to observe their changes over time. We also studied the effect of the complex on the development of wheat seedlings under normal conditions without seed irradiation. In these experiments, the best results in terms of growth and development were shown by seedling seeds treated with 0.01% and 0.001% solutions of the Zn imatinib mesylate complex.

Based on the results of studies of morphological indicators, it can be concluded that the drug has a positive effect on the growth and development of wheat

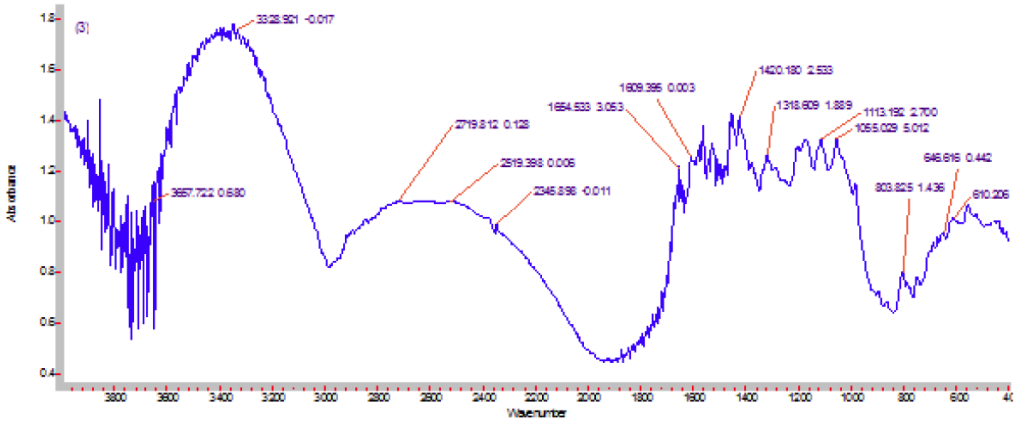

Figure 1: The IR Spectra of the Zn Imatinib Mesylate Complex.

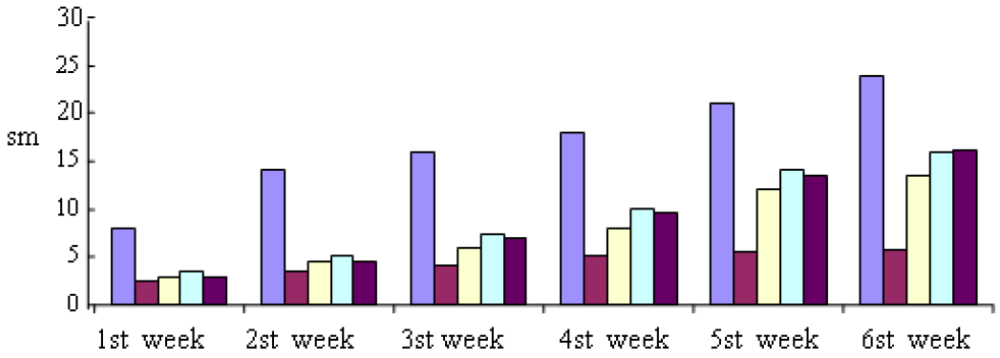

Figure 2: Growth Dynamics of Seedlings in a Gamma of Irradiated Wheat Seeds.

seedlings. At the initial stages of development in the first week, this effect is not noticeable. In the further development in the second week the germination of the irradiated variant rises to the level of the control variant. In the first two weeks, seedlings of gamma-irradiated seeds treated with 0.01% solution of the Zn imatinib mesylate complex showed the best results in growth and development, but at the final stage of experiments seedlings of gamma-irradiated seeds treated with 0.001% solution of the Zn imatinib mesylate complex equaled it and surpassed them in growth (Figure **2**).

Each bar represents mean ± sd (standard deviation) for average of n=3 independent experiments; P = 0,05. It is known that during the pre-sowing treatment of seeds, microelements act as a growth stimulator, increase germination energy and germination. With pre-sowing treatment of seeds with zinc, the photosynthetic activity of plants is improved. The analysis of many years of scientific research by many authors has shown that zinc is an essential element for the normal growth and development of plants. The use of zinc fertilizers increases the yield and quality of spring wheat [12,13].

Studies have shown that pre-sowing treatment of plants with a complex of zinc with lysine not only improves the growth and development of plants, but also protects plants from the toxic effects of cadmium [14].

From left to right - control, irradiated control (220 Gy), a variant with a 0.1% solution of the Zn imatinib mesylate complex + 220 Gy, a variant with a 0.01% solution of the Zn imatinib mesylate complex + 220 Gy, variant with a 0.001% solution of the Zn imatinib mesylate complex + 220 gray.

When the subsequently formed radiation free radicals interacts with the lipids of the cell membranes, lipid peroxidation occurs. Lipid peroxidation reaction causes the formation of several end products. One of them is malon dialdehyde. Malondialdehyde (MDA) accounts for approximately 70% of the total amount of aldehydes formed during membrane lipid peroxidation. The amount of formation of this product determined the degree of damage to the cells. One of the most widespread methods for determining MDA is the thiobarbituric method [15]. We also used this method in experiments to determine the amount of malondialdehyde.

Each bar represents mean ± sd (standard deviation) for average of n=3 independent experiments; P = 0,05.

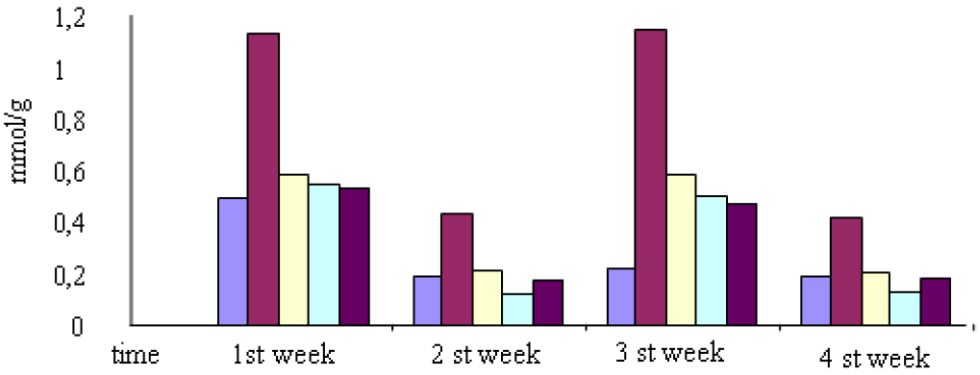

Figure 3: Dynamics of Measuring the Output of Malonic Dialdehyde (mmol/g).

From left to right - control, irradiated control (220 Gy), a variant with a 0.1% solution of the Zn imatinib mesylate complex + 220 Gy, a variant with a 0.01% solution of the Zn imatinib mesylate complex + 220 Gy, variant with a 0.001% solution of the Zn imatinib mesylate complex + 220 Gy.

According to the results of the experiments, it can be said that the obtained complex also has a positive effect on the physiological and biochemical parameters of plants by reducing the yield of the product of lipid peroxidation - malon dialdehyde. This shows the reduction of stress and the regulation of biochemical processes (Figure **3**). It is known that the efficiency of the primary processes of photosynthesis is also an indicator of the state of plants on the impact of the environment. Therefore, to study the radioprotective properties of the complex in experiments, along with the study of morphological parameters, we also investigated the effect of the Zn imatinib mesylate complex on the amount of photosynthetic pigments and on the photosynthetic activity of seedlings of gamma-irradiated wheat seeds. It has been proven that the treatment plants with 0.05-0.1% solutions of iron and zinc complexes leads to an increase in protective and adaptive reactions and leads to an increase in chlorophyll content [16].

Below are the results of experiments to study the effect of the Zn imatinib mesylate complex on the amount of photosynthetic pigments - chlorophylls a and b and carotenoids.

Each bar represents mean ± sd (standard deviation) for average of n=3 independent experiments; P = 0,05.From left to right - control, irradiated control (220 Gy), a variant with a 0.1% solution of the Zn imatinib mesylate complex + 220 Gy, a variant with a 0.01% solution of the Zn imatinib mesylate complex + 220 Gy, variant with a 0.001% solution of the Zn imatinib mesylate complex + 220 Gy.

As can be seen from Figure **4** in the irradiated control variant, a decrease in the amount of photosynthetic pigments of chlorophylls a and b and in the amount of carotenoids is observed, and in the variant with the Zn imatinib mesylate complex treated with a 0.001% solution of the complex, a significant increase in the amount of photosynthetic pigments and carotenoids is observed in comparison with the irradiated control variant and normalization of the amount of carotenoids.

To determine the effect of the complex on photosynthetic activity, we studied the fluorescent characteristics (maximum quantum yield of PS II (photosystem II) - Y) in seedlings of gamma-irradiated wheat seeds. The basis of fluorescent methods is that chlorophyll in photosynthetic membranes serves as a natural indicator of the state of plant cells. When the state of cells is disturbed under the influence of unfavorable conditions, changes in chlorophyll fluorescence occur, which serve as a source of information [17].

Disturbances in the primary processes of photosynthesis are reflected in changes in chlorophyll fluorescence. The index of the maximum quantum efficiency of PS II - Fv/Fm is used to assess the maximum efficiency of PS2 (photosystem II). This indicator provides information about the potential quantum efficiency of PS II. Decrease in this value may indicate the stress state of the plant and partial damage to PS II [18].

Each bar represents mean ± sd (standard deviation) for average of n=3 independent experiments; P = 0,05. In our previous studies, we found the radioprotective effects of complex compounds of various substances of natural origin in wheat seedlings irradiated with different doses [19, 20-21]. The radioprotective effect of the Zn imatinib mesylate complex is similar to the effects of the studied complex compounds of natural origin.

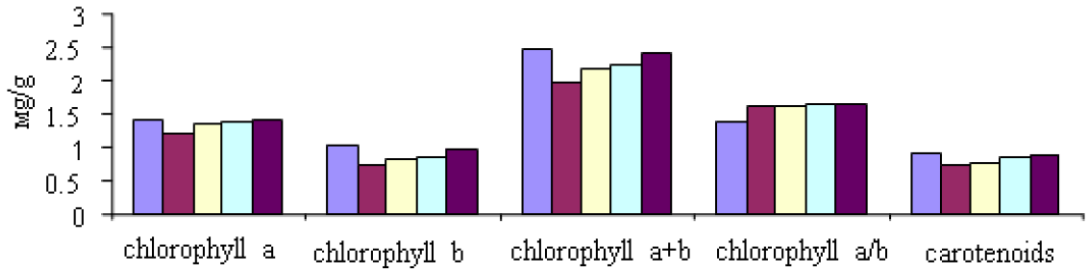

Figure 4: Influence of the Zn Imatinib Mesylate Complex on the Amount of Photosynthetic Pigments of Chlorophylls a and b and the Amount of Carotenoids (mg /g).

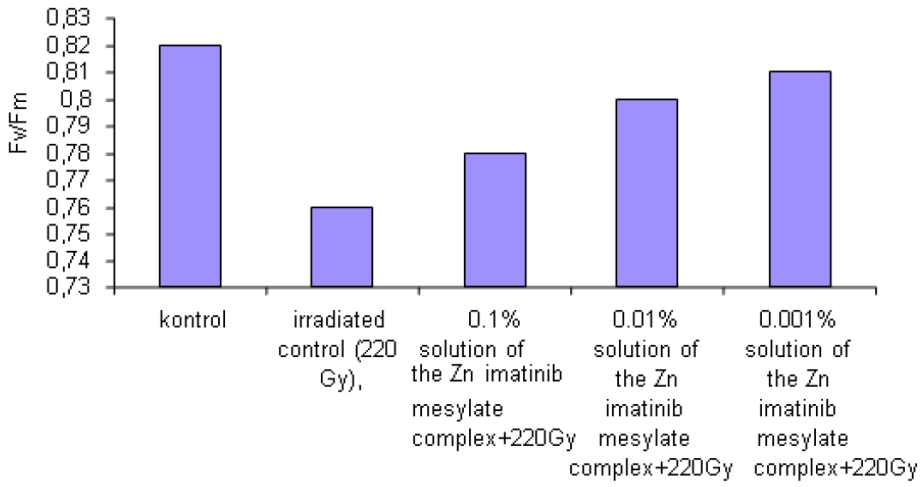

Figure 5: Measurement of the Maximum Quantum Yield of PS II - Fv / Fm.

The results of experiments to study photosynthetic activity showed that when wheat seeds are treated with a 0.01% solution of the Zn imatinib mesylate complex before irradiation at a dose of 220 Gy, an increase in the maximum quantum yield of PS II (Figure **5**).

4. CONCLUSION

Based on the data obtained, it can be concluded that 0.01% and 0,001% solutions of the imatinib mesylate - zinc complex eliminates the harmful effects of gamma radiation, reduces the lipid peroxidation process, normalizes plant growth, the synthesis of photosynthetic pigments in leaves, and the operation of photosystem 2 in chloroplasts. These solutions can be used as radioprotectors.

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