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RESTORING REDOX HOMEOSTASIS IN BRAIN AND COLON TISSUES IN A DMH-INDUCED COLON ADENOCARCINOMA MODEL THROUGH THE APPLICATION OF METAL NANOPARTICLES COMPOSITION

Introduction. *The process of free radical oxidation that prevails over the body's antioxidant defense system leads to the acceleration of cancer progression. Metal nanoparticles (NPs) have become a central focus of contemporary discussions within the field of oncology. The application of metal nanoparticles to balance redox homeostasis is currently a highly prominent topic in modern scientific research in oncology.*

The aim of the study *– to explore the potential benefits of Au/Ag/Fe NPs usage as a novel intervention for the correction of redox imbalance and restoring of antioxidant system functioning, particularly in the context of DMH-induced colon adenocarcinoma.*

Research Methods. *The study was performed on 125 outbred white male rats. Animals were divided into groups: I – control intact group (35 individuals); II – experimental group (70 individuals) with N,N-dimethylhydrazine hydrochloride administration once a week for 30 weeks; III – an experimental group (20 animals) with daily intragastric administration of Au/Ag/Fe NPs for 21 days. To evaluate oxidative stress manifestations in brain and colon tissues, the concentration of TBARS, diene (DC), and triene conjugates (TC), Schiff base (OSH) was determined. The activity of the antioxidant system was evaluated by catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GR), glutathione peroxidase (GPx), and reduced glutathione (GSH).*

Results and Discussion. *This article demonstrates the multifaceted relationship between development of oxidative stress and carcinogenesis, highlighting its significance in cancer progression prognosis. It was confirmed that DMG-induced colon adenocarcinoma in situ leads to an increase in levels of oxidative stress markers and a decrease in the activity of antioxidant factors. In addition, it was verified that Au/Ag/Fe NPs use caused a decrease in the concentration of TBARS, diene, triene conjugates, and Schiff bases. These led to the reduction of manifestations of oxidative stress and restoration of enzymes of the antioxidant system and its biological mediators of a non-enzymatic nature. The activities of catalase, superoxide dismutase, glutathione peroxidase, and the concentrations of reduced glutathione were restored to control indicators.*

Conclusion. *The use of Au/Ag/Fe NPs leads to the restoration of the redox homeostasis, improving the antioxidant system in terms of induced adenocarcinoma of the large intestine.*

KEY WORDS: **colon adenocarcinoma; brain tissue; colon tissue; oxidative stress; antioxidant system; metal nanoparticles.**

INTRODUCTION. Nowadays, scientists have discovered a direct connection between oncological diseases and oxidative stress. The processes of free radical oxidation, which have gone out of the control of the antioxidant protection system, can lead to the rapid development of carcinogenesis. Antioxidants, free radical reaction inhibitors, play a significant role in regulating lipid peroxidation (LPO). The antioxidant system (AOS) provides the adaptive resistance of the organism and regulates the reactions of lipids due to the functioning of the system of enzymatic and non-enzymatic mechanisms to control the content of active forms of oxygen (AFO) and free radicals [1]. Violations of the antioxidant system lead to the development of various pathologies caused by polyunsaturated fatty acid oxidation by AFO in the lipids of cells [2]. The proliferative activity of tumor tissues increases with a high level of antioxidants. The tumor intensively accumulates bio-antioxidants from the blood during its malignant growth, thus providing the conditions for further malignancy progression. At the same time, physiological AOS resources are depleted, and the body's antitumor reactivity decreases, leading to further neoplasm development [3].

The brain is especially vulnerable to lipid peroxidation and the consequent pathological sequences due to its high metabolic rate, lipid-rich composition, limited antioxidant defenses, and unique physiolog-

ical properties [4]. Scientists have already proven the critical role of lipid peroxidation in different neurodegenerative disorders [5, 6]. However, the influence of redox balance and antioxidant response violations caused by neoplastic lesion development and progression are still insufficiently studied. An increase of reactive oxygen species because of oxidative stress progression leads to elevated levels of lipid peroxidation, protein oxidation along with DNA injury. Lipid peroxidation results in the generation of harmful substances, which subsequently have the potential to induce neuronal apoptosis [7, 8]. The central nervous system has a relatively lower antioxidant protection system in comparesment with other organs. An imbalance between ROS production and antioxidant defenses contributes to the high vulnerability of brain tissue to oxidative stress. Even slight disruptions in brain function can have significant neurological consequences. Oxidative damage different brain regions can lead to cognitive decline, memory impairment, and various neurological disorders. It's important to mention that although the above-described mechanisms provide a potential link between DMH-induced cancer and oxidative stress influence on the brain, more research is crucial to establish these relationships with greater certainty.

Although traditional treatments like chemotherapy, radiation therapy, and surgery interventions remain essential, researchers are continuously working on the development of new approaches that can improve survival rates, reduce side effects, and target cancer cells more efficiently. Nanoparticles have shown promising potential in the field of cancer treatment [9, 10]. Nanoparticles have multifunctional properties. It`s scientifically proven that metal nanoparticles demonstrate antimicrobial, antifungal, antiviral, catalytic/photocatalytic, antioxidant/antiradical, and other properties [11–13]. Physical-chemical, biological, and physiological aspects of the influence of metal nanoparticles are currently being actively studied. Considering the convincing positive results of applying certain classes of metal nanoparticles, we have decided to focus our attention on studying the mechanisms of the impact of their combination. In our previous research, we established a pronounced positive effect of using Au/Ag/Fe NPs composition on hematological indicators under conditions of DMH-induced carcinogenesis.

It was established that the introduction of this composition of NPs led to normalizing the blood cell homeostasis in experimental animals with modeled non-metastatic colon adenocarcinoma. The positive impact of such NPs composition manifested in an increase in RBC count and the HGB rate in nano-treated rats, and a decrease in MCV, MCH, and MCHC to normal references. Moreover, the administration of NPs normalized the neutrophils rate, and LMR, and lead to the restoration of the PLT rate. Taking into account, the previously studied biosafety of gold, silver, and iron composition further amplification of scientific studies on this nanoparticle composition is highly needed, as it might be possibly used in the future in protocols of non-metastatic forms of colon cancer treatment [14].

In recent years, numerous studies have been conducted on silver nanoparticles (AgNPs) for their potential use in various biomedical applications, including cancer therapy. The specific physicochemical characteristics of AgNPs, such as their high ratio of surface area to volume with optical features influenced by size and potential antibacterial action, are well recognized [15–17]. AgNPs can cause cell death in breast, lung, colon, and liver cancer cells, according to in vitro studies. According to reports, AgNPs cause cancer cells to undergo apoptosis, oxidative stress, and DNA damage, which causes cell death [18, 19]. The application of AgNPs in cancer treatment remains a matter of contention, demanding additional research to gain a deeper understanding of the possible advantages and disadvantages involved. One of the concerns is the potential toxicity of AgNPs, as they can accumulate in the body and cause cellular damage, particularly in the liver and kidneys. Furthermore, the size and shape of AgNPs can also affect their toxicity and efficacy. Smaller AgNPs are more likely to penetrate cell membranes and cause cytotoxicity. AgNPs have a variety of interesting biological properties. They have a variety of uses, including biomedical products. In addition, further expansion of their therapeutic use as antiviral and antitumor drugs is expected [20, 21].

Gold nanoparticles (AuNPs) are very common in the biomedical field. AuNPs have many unique properties such as ease of synthesis, tunable size, ease of surface modification, surface plasmon resonance (SPR), and X-ray attenuation [22]. This makes them the center of attention in many applications, including the growing field of nanomedicine, biosensors, targeted drug delivery, radiation therapy, photothermal therapy, biomedical imaging, and cancer diagnostics and therapeutics [23].

Metabolomics is used in several studies to assess the cytotoxicity of AuNPs and reveal their molecular information. Au nanorods (AuNRs) are one example of AuNPs that have strong absorption in the near-infrared spectral region and can be used in tumor thermal therapy (hyperthermia), and in targeted tumor therapy. It was observed, using conventional assays, that AuNRs have a unique influence on cell viability by causing the death of

cancer cells (A549 cell line), while having a negligible effect on normal cells (16HBE and MSC cell lines). The authors showed that AuNRs were released from the lysosome of cancer cells, and then translocated into the mitochondria, causing oxidative stress by the production of ROS. Alternatively, the normal cells had more intact lysosomes, and thus the AuNRs were not released in the cell cytoplasm [24, 25].

Ferrum (Fe) is an integral element of a living organism, which is part of many iron-containing proteins and enzymes, such as cytochrome, peroxidase, oxidase, catalase, hemoglobin, myoglobin, etc. The more macroscopic Fe is crushed, the larger its surface area becomes and the more it is prone to oxidation with the formation of oxides (NPOFe), which act as nanoparticles of Ferrum (NPFe) [26]. The structural composition of many macroorganisms contains NPOFe, and in some bacteria, they are synthesis products. Physical, and biological, respectively, the pharmacological properties of NPFe and NPOFe depend on their size: larger particles are better admire macrophages, but smaller ones tend to be longer circulate in the bloodstream, and penetrate well through the capillary wall.

NPOFe physicochemical properties indicate the potential for their use in the detoxification of biological fluids, antimicrobial therapy, tissue regeneration, etc., but their qualitatively new properties determine significant biodegradation of ferum with the release of its ions. Therefore, these nanoparticles' biological activity or toxic effect depends on their size and a physicochemical state that requires further study [27, 28].

The antioxidant/antiradical properties of metal nanoparticles are especially interesting and the least studied simultaneously. Despite some scientific studies concerning the search and synthesis of compounds with antioxidant/antiradical effects, there is still a need for additional experimental data about the antiradical properties of metal nanoparticles, especially nanodispersions of Ag, Au, Fe NPs combination [29, 30].

Thus, our experimental study aimed to study redox balance and antioxidant response violations in brain and colon tissue, as well as to evaluate the possibility of Au/Ag/Fe NPs application to correct redox balance disorders as well as to normalize altered antioxidant system functioning in terms of DMH-induced colon adenocarcinoma.

RESEARCH METHODS. *Animals.* The study was carried out on 125 mature outbred white male rats with a body weight of (175.0±4.2) g, which were kept in standard vivarium conditions. The survival and weight of animals were monitored throughout the experiment. The animals had free access to drinking water and the primary food ration *ad libitum*. Experimental animals were randomly divided into the following groups: 1 – control group (35 animals); 2 – animals with DMH administration (70 animals), and 3 – 20 animals, with a modeled colon adenocarcinoma *in situ,* received a composition of Au/Ag/Fe metal nanoparticles intragastrically daily for 21 days after the end of DMH administration.

Large intestine neoplastic lesion modeling. The dimethylhydrazine model (DMH-model) is one of the most widely used in experimental oncology and a 100% reproducible model of colon neoplastic lesions, one of most similar to sporadic colorectal cancer (CRC) in humans [31]. The neoplastic lesion was modeled using N, N-dimethylhydrazine dihydrochloride (DMH) (Sigma-Aldrich Chemie, Japan; D161802 series) prediluted with isotonic sodium chloride solution. The carcinogen was injected subcutaneously into the interscapular area with a dose of 7.9 mg/kg of the animal's body weight once a week for 30 weeks. Control group animals were subcutaneously injected with a saline solution at the rate of 0.1 ml per 100 g of body weight every week in a similar area of the body to simulate possible stress effects. As modeling of adenocarcinoma *in situ* of the colon lasts for 30 weeks and animals of each experimental group were removed from the experiment to collect materials every 30 days, we divided the terms of the experiment into 7 stages (each step refers to 30 days of the experiment) for the convenience of the presentation of the results. The same number of rats from each experimental group were deeply sedated with thiopental (50 mg/kg, intraperitoneally, Arterium, NUA/3916/01/02) 24 hours after the last DMH injection every 30 days, and then sacrificed with cervical displacement and exsanguination.

Colon adenocarcinoma *in situ* was histologically confirmed in all animals of the 2nd group after 30 weeks of DMH administration.

Algorithm of metal nanoparticles composition application. Au/Ag/Fe nanoparticles (NPs) composition, which was used in this study, was obtained by mechanical mixing silver, gold, and iron NPs aqueous dispersions. Size of nanoparticles: Au – 30 nm, Ag – 30 nm, Fe – 40 nm. The concentration of metals in 1 ml of the original aqueous solution: Au – 3.1 μg, Ag – 1.6 mg, Fe – 0.1 mg.

Experimental animals received an aqueous dispersion of Au/Ag/Fe NPs intragastrically once a day for 21 days at a dose of 0.842 mg Ag / 0.0526 mg Fe / 1.625 μg Au per 1 kg of animal body weight. The original aqueous solution of NPs was diluted with distilled water in a ratio of 1:10 before usage.

Animals of this group were removed from the experiment according to the above-mentioned method 72 hours after the last introduction of NPs.

Algorithm of conducted manipulations with experimental animals. Carcinogen injection, corrective factor administration, and sampling for biochemical studies were carried out at the same time of the day (10:00–12:00) in a specific room with an air temperature of 18–20 °C. All manipulations with experimental animals were carried out in compliance with the rules "European Convention for the protection of vertebrate animals used for experimental and other scientific purposes" as well as according to "Scientific and practical recommendations for keeping laboratory animals and working with them" [32] and the Law of Ukraine "On the Protection of Animals from Cruelty" No. 3447-IV, 2006.

Preparation of Tissue Homogenate

10% tissue homogenate was used in the research: 100 mg of brain and colon tissue was taken, and 1 ml of 0.9 % physiological solution was added. Each specimen was homogenized separately with a SilentCrusher S magnetic homogenizer with a speed range of up to 75,000 rpm. The resultant supernatant was used for the different estimations.

Malondialdehyde (MDA) Determination

Lipid structure can be transformed by oxidizing agents with the production of lipid peroxides, leading to the formation of malondialdehyde (MDA). MDA can be measured as thiobarbituric acid reactive substances (TBARS). The concentration of MDA was studied colorimetric test method at 535 nm using the thiobarbituric acid [33].

Diene and triene conjugates (DC, TC) Determination

The concentration of DC and TC was determined according to the method, which is based on the fact that hydroperoxides extracted with a heptane-isopropyl mixture have a corresponding absorption maximum of DC and TC at a wavelength of 232 nm [34].

Schiff bases (OSH) Determination

The content of Schiff bases was determined by the spectrophotometric method, the principle of which is because the process of lipid peroxidation is accompanied by the reorientation of double bonds with the appearance of specific optical properties. Moreover, Schiff bases have an absorption maximum at 400 nm [35].

Catalase (CAT) Determination

Catalase activity was measured in homogenates with 1 % Triton X-100. The decrease in absorbance of hydrogen peroxide at 240 nm was measured. The rates were determined at 25 °C using 10 mmol/L hydrogen peroxide. The activity was expressed in universal units [36].

Superoxide dismutase (SOD) Determination

Superoxide dismutase activity was measured after homogenization of the initial supernatant and centrifugation at 10 000 g for 30 min at 40 °C as described by Sykes *et al* [37].

Reduced Glutathione (GSH) Determination

The concentration of GSH was measured with colorimetric test method based on the reaction of GSH from the blood sample with 5,5′-dithiobis-2-nitrobenzoic acid at 412 nm [38].

Glutathione Peroxidase (GPx) Activity Determination

Reduction of organic peroxides in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and sodium azide was used to analyze the activity of GPx with the colorimetric method at 340 nm [39].

Glutathione Reductase Activity Determination

The decrease in NADPH was used to measure the activity of glutathione reductase (GR) with the colorimetric method at 340 nm. One unit of GR activity was identified as the quantity of GR that catalyzes the oxidation of 1 μmol of NADPH per 1 minute [40].

Statistical processing of the obtained results was performed using the computer program Microsoft Excel XP (USA). The obtained results were processed by the method of variational statistics using one-factor analysis of variance ANOVA with the Originpro 7.5 program. The differences between the average values were reliable for the probability of the alternative hypothesis of at least 0.95. The differences were considered significant if $p \leq 0.05$.

RESULTS AND DISCUSSION. The formation of oxidative stress markers is a normal consequence of a variety of essential biochemical reactions which accompany both physiological and pathological processes. In particular, is also known that oxygen radicals could be formed in excess neoplastic lesion development. Oxidative stress parameters such as lipoperoxidation products, TBARS, the activity of antioxidant enzymes, and non-enzymatic antioxidant mediators showed that the oxidative stress parameters of DMH-injured animals were significantly modified compared to the controls.

The analysis of the obtained data showed that 30 weeks after modeling-induced adenocarcinoma started diene and triene conjugates are formed in amounts much more significant than TBARS and decay very quickly. Diene and triene conjugates decay leads to toxic products' appearance (TBARS, Schiff's bases, aldehydes, and ketones).

The final product of LPO is TBARS, which can form polymer molecules with proteins and phos-

pholipids, which leads to a decrease in membrane permeability, reduces the activity of membrane enzymes, and decreases the speed of phospholipid metabolism. An increase in the concentration of TBARS in animals with induced adenocarcinoma was observed by 7.3 times ($p<0.001$) in the homogenate of colon tissue and by 4.2 times ($p<0,001$) in the brain homogenates, compared to the same indicators in the group of control animals (Figure 1).

A significant increase in the concentration of diene and triene conjugates was found by 8.3 and 7.1 times ($p<0.001$), respectively, in the homogenate of the colon tissue compared to similar indicators of the control group of animals. The concentration of diene and triene conjugates also grew in the brain tissue of injured animals by 2.8 times and 2.9 times ($p<0.001$), respectively, compared to the identical indicators of the control group animals (Figure 1).

The concentration of OSH under the conditions of DMH-induced carcinogenesis significantly increased by 3.9 times ($p<0.001$) in the colon tissue homogenate and by 2.7 times ($p<0.001$) in the brain tissue homogenate compared to the same indicators of the control group (Figure 1).

The above-described increase in oxidative stress violates the redox balance and inactivates antioxidant enzymes. It was experimentally proved that the activity of SOD decreases by 2.0 times ($p<0.001$) in colon tissue and by 2.4 times ($p<0.001$) in brain tissue during the development of colon adenocarcinoma (Figure 2).

Under the conditions of DMH-induced carcinogenesis, the activity of CAT decreased statistically significantly both in the large intestine and in the brain tissues by 1.5 times ($p<0.001$) and 1.8 times ($p<0.001$), respectively, compared to the same indicator in the group of control animals (Figure 2). It is known that catalase is sensitive to AFO, particularly hydrogen peroxide and superoxide anion radicals, which can cause inhibition of enzyme activity.

The mechanism of the antioxidant activity of the glutathione system is related to the ability of glutathione to reduce H_2O_2, organic peroxides – hydroperoxides (R-O-O-H), alkyl peroxides (R-O-O-R) with the use of the selenium-containing enzyme GPx. At the same time, harmless organic alcohols (R-OH) are formed, which are undergo further oxidation, and GS-SG is restored to the original level with the help of NADPH-dependent GR. The second important component of the glutathione protective system is glutathione conjugation, which detoxifies xenobiotics and endogenous metabolites [41, 42].

We observed a reduction in the concentration of G-SH (by 1.8 times), as well as the decrease in activity of GPx enzymes (by 2.5 times) and GR (by 2.6 times) ($p<0.001$) under the conditions of induced oncogenesis in the tissue of the large intestine, which display a high affinity for G-SH. The same regularity was observed while investigating the activity of identical substances in brain tissue homogenates of DMH-injured animals: activity of GPx enzymes and GR decreased by 2.5 times ($p<0.001$) and by 2.0 times ($p<0.001$) respectively; reduction of G-SH concentration by 1.7 times compared to same indicators of the control group (Figure 2).

Low GPx activity is possible only if the optimal level of intracellular GSH is reduced, which is not

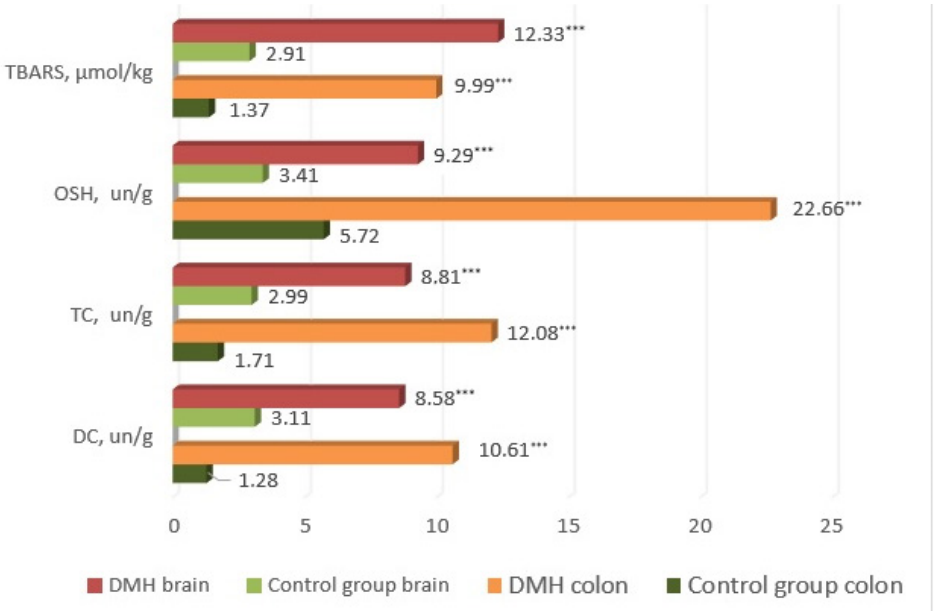

Figure 1. Effect of DMH-induced CRC on levels of oxidative stress markers in brain and colon tissues.
Note. *** – significant changes between the indexes of control and DMH-affected animal group ($p<0.001$).

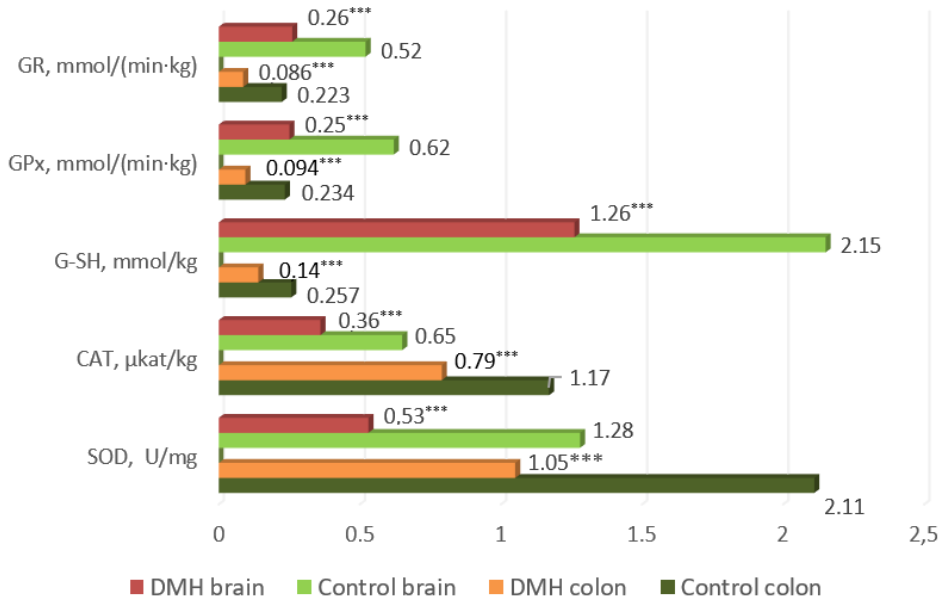

Figure 2. Effect of DMH-induced CRC on levels of antioxidants in brain and colon tissues: activity of antioxidative enzymes. Note. *** – significant changes between the indexes of control and DMH-affected animal group (p<0.001).

only needed as a substrate for reactions but also as a factor necessary for the constant restoration of selenol groups located in the catalytic center of the enzyme, which are oxidized in the reaction. The intracellular activity of GR decreases with the accumulation of the oxidized form of NADH.

The intensification of glutathione oxidation processes, as well as the slowing down of its recovery due to the low activity of GR and inhibition of the activity of the critical antioxidant enzyme – GPx, causes the decompensation of the glutathione system.

Earlier mentioned changes in the levels of GP and GR indicate that their synthesis in the endoplasmic reticulum was significantly disrupted, suppressing the functional activity of the glutathione-dependent part of the antioxidant system on the background of oxidative stress development.

The Au/Ag/Fe NPs composition has been investigated for its potential positive impact on oxidative stress indicators. Such metallic NPs maintain unique properties, making them promising correction methods for various applications, including antioxidant therapy.

The application of this correction method led to a significant decrease in the diene and triene conjugates concentration in the colon tissue by 4.6 and 5.7 times (p<0.001), as well as in the brain tissues – by 1.5 and 1.4 times, respectively, compared to the same indicators in the group of animals without correction (Figure 3).

It was established that with metal NPs usage, the OSH concentration in the large intestine tissue of injured animals was reliably reduced by 1.5 times (p<0.001) compared to the same indicator in the animals without a corrective effect of NPs. OSH concentration in the brain tissue also decreased by 1.7 times with such metal NPs composition application. The use of Au/Ag/Fe NPs led to a significant decrease in TBARS level by 4.4 times in the colon tissue and 2.2 times in the brain tissue, compared to a similar indicator in the animals where nanoparticles were not used (Figure 3).

All mentioned above indicate that the use of Au/Ag/Fe nanoparticles as a correction method of modeled carcinogenesis in experimental animals leads to a decrease in AFO formation, as well as a decrease in the activity of free radical processes, which leads to a reduction in the manifestations of oxidative stress.

A similar positive effect of metal NPs use was established during the antioxidant system markers levels investigation. Thus the activity of SOD in the colon tissue of experimental animals increased significantly by 2.0 times (p<0.001) with the use of NPs relative to the same indicator in the group of animals with modeled adenocarcinoma (Figure 4). The same tendency was observed with concentration of SOD in the brain tissue – it increased by 1.7 times compared with DMH-injured animals (Figure 4). Our research also demonstrated a reliably significant increase in the catalase activity (Figure 4) by 1.3 times (p<0.001) in the colon tissue and by 1.5 times in the brain tissue under the conditions of Au/Ag/Fe nanoparticles use as a correction method compared to animals of the DMH-injured group.

The use of Au/Ag/Fe NPs resulted in a significant increase in the G-SH level of the colon tissue (1.9 times), as well as in the rise of such selenium-dependent AOS enzyme activity as GPx (2.01 times)

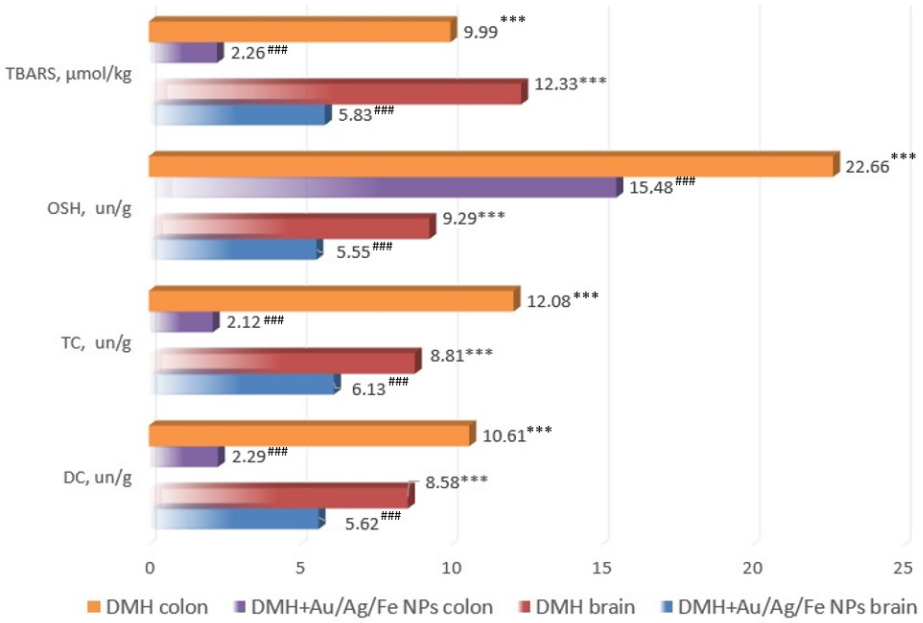

Figure 3. Effect of Au/Ag/Fe metal nanoparticles composition application on levels of antioxidants in brain and colon tissues of animals with DMH-induced colon adenocarcinoma

Note. *** – significant changes between the indexes of control and DMH-affected animal group ($p<0.001$).

– significant changes between the indexes of DMH-affected animal group and group of injured animals treated with metal NPs composition ($p<0.001$).

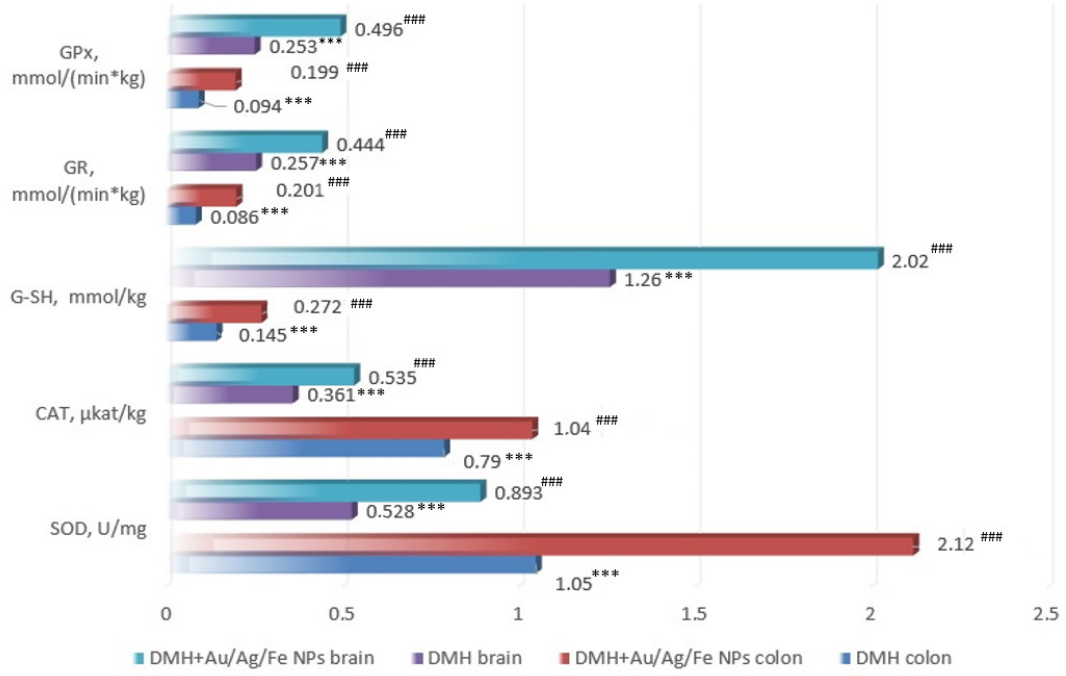

Figure 4. Effect of Au/Ag/Fe metal nanoparticles composition use on levels of antioxidants in brain and colon tissues of animals with DMH-induced colon adenocarcinoma: activity of antioxidative system markers.

Note. *** – significant changes between the indexes of control and DMH-affected animal group ($p<0.001$).

– significant changes between the indexes of DMH-affected animal group and group of injured animals treated with metal NPs composition ($p<0.001$).

and GR (by 2.3 times) ($p<0.001$) relative to the same indicators in the group of animals with modeled DMH-carcinogenesis. The same regularity was observed while investigating the activity of identical substances in brain tissue homogenates of DMH-injured animals: G-SH level increased by 1.6 times, the activity of GPx and GR both increased by 2.0 times and by 1.7 times, respectively (Figure 4).

The application of Au/Ag/Fe NPs composition has been observed to reduce oxidative stress

manifestations in experimental animals with DMH-induced carcinogenesis, as described above. Such a correction method leads to the recovery of antioxidant system enzymes' functional capacity and their non-enzymatic biological mediators.

CONCLUSION. In conclusion, our research indicates that oxidative stress markers are significantly associated with CRC. Insufficient antioxidant defense mechanisms contribute to the development and progression of CRC. Oxidative stress markers were identified as potential indicators of CRC severity and progression. With our research, we also proved the mediated effect of DMH-induced adenocarcinoma development on the brain, which was proven by significant deviations in redox balance markers. Moreover, new methods for reducing oxidative stress, such as Au/Ag/Fe NPs composition, demonstrate promise in mitigating oxidative stress manifestations in experimental animals with DMH-induced carcinogenesis. Application of such metal NPs composition leads to the normalization of pro- and antioxidant balance indicators. Glutathione system activity increased cellular protection against free radicals and antiperoxidases. All mentioned above led to oxidative activity inhibition, especially LPO activity. Overall, the Au/Ag/Fe NPs composition application reveals the potential of reducing oxidative stress manifestations in experimental animals. Further research in this area is needed to develop new therapeutic approaches for managing oxidative stress-related conditions, including cancer.

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ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ

ВІДНОВЛЕННЯ РЕДОКС-ГОМЕОСТАЗУ В ТКАНИНАХ ГОЛОВНОГО МОЗКУ І ТОВСТОЇ КИШКИ ЗА УМОВ ДМГ-ІНДУКОВАНОЇ АДЕНОКАРЦИНОМИ ТОВСТОЇ КИШКИ ІЗ ЗАСТОСУВАННЯМ КОМПОЗИЦІЇ НАНОЧАСТИНОК МЕТАЛІВ

Резюме

Вступ. *Процеси вільнорадикального окиснення, які переважають над системою антиоксидантного захисту організму, ініціюють прискорення та прогресування канцерогенезу. Застосування наночастинок металів у галузі онкології активно вивчають науковці. Оцінка ефективності використання композицій наночастинок металів для корекції проявів оксидативного стресу є важливою темою сучасних наукових досліджень.*

Мета дослідження *– вивчити потенційні переваги використання композиції наночастинок Au/Ag/Fe (НЧ Au/Ag/Fe) як нового методу корекції проявів оксидативного стресу та покращення функціонування антиоксидантної системи за умов розвитку ДМГ-індукованої аденокарциноми товстої кишки.*

Методи дослідження. *Дослідження проведено на 125 безпородних білих щурах-самцях. Тварин поділили на групи: 1-ша – контрольна (35 особин); 2-га – 70 щурів, яким 1 раз на тиждень протягом 30 тижнів вводили N,N-диметилгідразину гідрохлорид; 3-тя – 20 тварин, яким після закінчення моделювання неопластичного ураження товстої кишки щоденно впродовж 21 доби внутрішньошлунково вводили НЧ Au/Ag/Fe. Для оцінки проявів оксидативного стресу в тканинах головного мозку і товстої кишки визначали концентрацію ТБК-активних продуктів, дієнових і трієнових кон'югатів, основ Шиффа. Активність антиоксидантної системи оцінювали за каталазною, супероксиддисмутазною, глутатіонредуктазною, глутатіонпероксидазною активністю і вмістом відновленого глутатіону.*

Результати й обговорення. *У статті продемонстровано багатогранний зв'язок між розвитком оксидативного стресу та канцерогенезом, підкреслено його значення в прогнозуванні прогресування раку. Підтверджено, що ДМГ-індукована аденокарцинома товстої кишки in situ супроводжувалася підвищенням рівня маркерів оксидативного стресу та зниженням активності антиоксидантних факторів. Крім того, підтверджено, що використання НЧ Au/Ag/Fe сприяло зменшенню проявів оксидативного стресу і відновленню активності ензимів антиоксидантної системи та її біологічних медіаторів неензимної природи. Каталазна, супероксиддисмутазна, глутатіонпероксидазна, глутатіонредуктазна активність і вміст відновленого глутатіону в групі тварин, в яких застосовували композицію наночастинок металів, відповідали контрольним показникам.*

Висновки. *Використання композиції наночастинок Au/Ag/Fe призводить до відновлення окисно-відновного гомеостазу при індукованій аденокарциномі товстої кишки.*

КЛЮЧОВІ СЛОВА: **аденокарцинома товстої кишки; тканина мозку; тканина кишки; оксидативний стрес; антиоксидантна система; наночастинки металів.**