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Lipid peroxidation and histological changes in rat thymus tissue after administration of cisplatin and dexamethasone

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The thymus gland plays a crucial role in immune function in both healthy and tumor-bearing organisms and it is particularly sensitive to antitumor drugs, such as cisplatin. It is well known that cisplatin causes significant toxicity, to reduce which, dexamethasone is commonly included in combination chemotherapy regimens. It should be noted that the mechanisms of their combined effects are incompletely studied. The aim of this study was to identify the correlation between the level of lipid peroxidation and histological changes in rat thymus tissue after separate and combined administration of cisplatin and dexamethasone. The experiment was conducted on four groups of animals: a control group, an experimental group with cisplatin injection, an experimental group that received dexamethason and an experimental group that received combined injection of these drugs. In homogenates and supernatants of thymus tissue of rats from all experimental groups quantitative assessment of conjugated dienes was performed by spectrophotometric method after extraction with a mixture of heptane-isopropyl alcohol. The oxidative stress marker malondialdehyde (MDA) was quantified by thiobarbituric acid analysis. Catalase activity was measured by the ammonium molybdate method. Superoxide dismutase (SOD) activity was assessed by the change in the amount of adrenaline autooxidation product. Thymus tissue samples were fixed and processed using standard histological protocols for histological evaluation. The data show that cisplatin and dexamethasone exerted significant increase in the level of conjugated dienes in homogenate of thymus tissue by 113%, 104% and 143% respectively after their separate and combined use. The amount of MDA also increased significantly as a result of both the separate and combined effects of cisplatin and dexamethasone in homogenate and in supernatant of thymus tissue. These quantitative alterations of both conjugated dienes and MDA indicates a promotion of oxidative stress. Catalase and SOD, which are part of the cell's antioxidant system, also exhibit sensitivity to cisplatin and dexamethasone. Following both the separate and combined injection of cisplatin and dexamethasone, a significant reduction in the activity of the antioxidant enzymes in homogenates was registered. At the same time, the quantitative changes in conjugated dienes and MDA level as well as decrease in catalase activity and SOD recorded in the supernatant were more modest. In fact, these drugs induced oxidative stress (OS) via reduction of catalase and SOD activities. In addition, the results of histomorphological analysis indicate the thymotoxic effect of cisplatin and dexamethasone. The finding results confirmed that these drugs demonstrate pro-oxidant and thymotoxic effects, although they act through different molecular mechanisms. The different molecular mechanisms of action of cisplatin and dexamethasone shape the outcome of their combined use. In this case, dexamethasone plays a "preventive" role, likely due to its unique pharmacological properties and mechanisms of action.

Keywords: malondialdehyde; antioxidant enzymes; conjugated dienes; histopathological analysis; thymocyte apoptosis.

Introduction

The thymus gland plays a crucial role in the development and functioning of the immune system. In addition to its immunological functions, it also produces small amounts of hormones that can influence tumor cell biology through both direct and immune-mediated mechanisms (Thapa & Farber, 2019; Savino & Lepletier, 2023). Interestingly, the thymus can exhibit both antitumor and tumor-promoting properties. It contains various types of T-cells with distinct functions: Th1 and Th9 cells act as antitumor effectors, while regulatory T-cells (Tregs) are well-known for their immunosuppressive activity, which can weaken antitumor responses and facilitate tumor progression. Natural killer T (NKT) cells may exhibit either antitumor or immunosuppressive effects, depending on the immunological context. Therefore, the thymus plays an important role in both healthy and tumor-bearing organisms and is likely to respond to chemotherapeutic agents such as cisplatin, which is widely used in cancer treatment (Thapa & Farber, 2019; Savino & Lepletier, 2023).

Cisplatin is currently considered one of the most effective antitumor agents. However, like many chemotherapeutic drugs, it has numerous adverse effects and can induce various toxicities (Tchounwou et al., 2021; Dasari et al., 2022; Kopacz-Bednarska & Król, 2022). These toxicities are largely attributed to the generation of reactive oxygen species (ROS), which are induced by cisplatin (Habtemariam, 2019; Sidharta et al., 2022). ROS can damage key cellular components such as DNA, lipids and proteins, leading to lipid peroxidation (LPO) and other forms of oxidative damage (Romani, 2022; Singh & Manna, 2022; Katanic Stankovic et al., 2023). The generation of ROS and OS is recognized as an additional mechanism underlying cisplatin cytotoxic effects (Aldossary, 2019; Jadon et al., 2019; Sidharta et al., 2022). Elevated ROS levels caused by cisplatin can increase lipid peroxidation, which contributes significantly to the overall cellular damage observed during cisplatin treatment (Ognjanović et al., 2012; Mirzaei et al., 2021; Kopacz-Bednarska & Król, 2022). Due to its strong cytotoxicity and lack of selectivity, cisplatin can also harm normal tissues and immune cells (Li et al., 2025). Its impact on the thymus can lead to thymotoxicity and a reduction in immune function, as the thymus is essential for T-cell development (Byun et al., 2021).

To reduce these undesirable side effects, cisplatin is often administered in combination with other drugs. Among them, dexamethasone holds particular significance because of its anti-inflammatory and immunoregulatory properties (Marchetti et al., 2003, Martin-Sierraa et al., 2019). Dexamethasone is a synthetic glucocorticoid widely used to treat a range of conditions, including cancer, where it helps manage side effects associated with chemotherapy, radiotherapy, and immunotherapy (Martin-Sierraa et al., 2019). However, dexamethasone can also induce thymotoxicity, primarily by triggering apoptosis in thymocytes, the immature T-cells within the thymus. This process

involves complex intracellular signaling that leads to caspase activation – an essential step in the apoptotic pathway (Marchetti et al., 2003).

Studies have demonstrated that both cisplatin and dexamethasone can act as pro-oxidants, promoting ROS production, oxidative stress, and lipid peroxidation (Ognjanović et al., 2012; Cook et al., 2016; Liu et al., 2018). In fact, both drugs are known to induce thymotoxicity and can lead to thymocyte apoptosis (Liu et al., 2018; Li et al., 2025). Despite these effects, they are commonly used together in chemotherapy regimens.

Given these dual effects, it is of scientific interest to investigate oxidative stress and lipid peroxidation levels, the activity of key antioxidant enzymes, and morphological changes in thymic tissue under both separate and combined administration of cisplatin and dexamethasone.

Materials and methods

This study was conducted to identify the correlation between alterations in lipid peroxidation levels and histological changes in thymus tissue. Experiments were conducted according to the "International Recommendations on Carrying out of Biomedical Researches with use of Animals" (CIOMS, 1986, EC, 1986), to the "Human Rights and Biomedicine the Oviedo Convention", to the European Convention for the Protection of Vertebral Animals Used for Experimental and Other Scientific Purposes, and were approved by the National Center of Bioethics (Armenia).

The study was performed on adult Wistar albino female rats (120–150 g weight, 20 rats). Animals were placed in a controlled environment, at a temperature of 25 ± 2 ºC, 12-hour day and night cycle, fed commercial rat feed ad-libitum, and given free access to water in the animal house of the faculty of biology at Yerevan State University.

The animals were divided into 4 groups. Group 1 served as a control group of animals without treatment. Animals in group 2 (n = 5) and group 4 (n = 5) received a single dose of cisplatin (8 mg/kg) by peritoneal injection and were decapitated 24 hours after administration. Group 3 was treated with dexamethasone (4 mg/kg, peritoneal injection) and decapitated 4 hours after administration. Animals in group 4 (n = 5) received the same single dose of dexamethasone within 20 hours after the cisplatin injection (4 hours before decapitation). All animals were euthanized by decapitation at an appropriate time following inhalation ether anesthesia. After the animals were sacrificed the thymus was extracted from each group of animals. The thymus tissue was used for preparation of 10% homogenate in ice-cold 50 mM Tris-HCL buffer, pH 7.4. The homogenates were divided into 2 parts, one of which stored at –20 °C for farther investigation. The other part was used to obtain the supernatant. The homogenates were centrifuged at 1000×g for 10 min at 4 °C (centrifuge Sigma 3-18KS, Osterode am Harz, Germany, 2018). The supernatants were collected and stored at –20 °C. Both the homogenates and supernatants were used for extraction and quantification of lipid peroxidation primary product conjugated dienes (CDs), final product MDA, for estimation of catalase and SOD activities. The samples of thymus glands were used for histopathological examination.

Homogenates and corresponding supernatants from all experimental groups were used to determine the levels of lipid peroxidation primary products conjugated dienes, using a spectrophotometric method (Volchegorskiĭ et al., 1989). The method involves extraction with a heptane-isopropyl alcohol mixture. CDs absorb ultraviolet light at specific wavelengths: 232 nm. Heptane extracts primarily contain neutral lipids, while isopropyl alcohol extracts contain phospholipids. Spectrophotometric measurements were carried out using a BK-UV 1800 Spectrophotometer (Biobase, Jinan (Shandong), China, 2023). The total amount of conjugated dienes was calculated by summing values from both phases. Results for conjugated dienes were expressed in conventional units (Volchegorskiĭ et al., 1989).

MDA levels were measured in 10% thymus homogenates and corresponding supernatants using the method of Buege et al., (1978). This assay is based on the reaction of two molecules of thiobarbituric acid with one molecule of MDA, forming a pink chromogen. The reaction mixture included 30% trichloroacetic acid, 0.6 N HCl, 0.8% thiobarbituric acid solution, and 1 mL of the investigating sample. After heating in a boiling water bath for 20 minutes and cooling, the mixture was centrifuged at 3000 rpm for 10 minutes. The absorbance of the supernatant was measured at 532 nm against a blank solution containing all reagents except the biological sample. MDA concentration was expressed in nmol/mg protein (Buege et al, 1978).

Catalase activity was assessed in both homogenates and supernatants using a colorimetric method (Koroliuk et al., 1988). This method measures the decomposition of hydrogen peroxide (H_2O_2) by catalase, where the residual H_2O_2 forms a stable-colored complex with ammonium molybdate. Absorbance was measured at 410 nm, and enzyme activity was expressed as μmol H_2O_2 decomposed per minute per mg protein (Koroliuk et al., 1988).

SOD activity was determined using the Sirota method (Sirota, 2017). The assay measures the inhibition of adrenaline autooxidation in carbonate buffer. Reaction rate is measured spectrophotometrically from the value of optical density (347 nm) of adrenaline autooxidation product forming within 3–5 minutes of the reaction starting. A 0.1 mL solution of 0.1% adrenaline hydrochloride was added to 3 mL of 0.2 M carbonate buffer, pH 10.5, 0.1 mL sample of homogenate or supernatant and then the optical density of the reaction product was recorded at 347 nm over 3–5 minutes. SOD activity was expressed in conventional units, calculated using the appropriate formula (Sirota, 2017).

Protein concentration was determined spectrophotometrically, after the boiling of samples for 15 minutes in presence of 0.5 N NaOH (Kalb & Bernlohr, 1977).

Thymus tissue samples were fixed in 10% formalin and processed using standard histological protocols (Bancroft & Gamble, 2007). Dehydration was carried out using a Spin Tissue Processor STP-120 (MYR, Italy) followed by paraffin embedding with a Tissue Embedding Center EC-500 (MYR, Italy). Serial paraffin sections of 4–5 μm thickness were prepared using a CUT 5062 microtome (SLEE Medical, Frankfurt am Main, Germany). Six slides were prepared per sample and stained using hematoxylin and eosin, as well as May-Grünwald and Giemsa stains, following Pappenheim's method (Bancroft & Gamble, 2007).

Slides were examined under a trinocular microscope (model B-293), equipped with an Optikam B5 Digital Camera M-114, Via Rigla, Italy. On May-Grünwald and Giemsa-stained slides, mast T-cells were counted in 40 consecutive fields of view at 400× magnification.

Results are expressed as mean ± standard deviation (SD) from five independent experiments. Statistical comparisons between treated and control groups were made using One way ANOVA, with $P < 0.05$ considered statistically significant. Intergroup comparisons were performed using ANOVA Multiple Sample Comparison with Tukey's post-hoc test and Kruskal-Wallis Tests for multiple-group comparison in Statgraphics Centurion 19 Software (Statgraphics Technologies, Inc., Plains, Virginia, USA, 2019). Statistically significant differences were indicated by $P < 0.05$.

Results

The first stage of our research was devoted to identifying quantitative changes in conjugated dienes (CDs) as a result of separate and combined administration of cisplatin and dexamethasone. Quantitative changes in CDs were recorded in all experimental groups and fractions studied.

Compared to the baseline, cisplatin alone treatment increased the amount of CDs by 113%, $P = 6.30 * 10^{-4}$, dexamethasone separate injection by 104%, $P = 6.60 * 10^{-5}$ and the combined use of this drugs elevated the quantity of CDs by 144%, $P = 1.8 * 10^{-3}$ (Table 1, Fig. 1a). The changes in CDs quantity recorded compared to the baseline were reflected in the results of the intergroup comparison of the data. Compared to the cisplatin group, increase in number of CDs by 14%, $P = 1.12 * 10^{-5}$ was revealed in thymus homogenate of rats with cisplatin and dexamethasone combined injection (Table 1, Fig. 1a).

An increase in the amount of CDs by 19%, $P = 1.60 * 10^{-6}$ was also recorded when comparing the results obtained for the thymus homogenate of animals from the cisplatin and dexamethasone co-

injected group with those obtained for the dexamethasone. On the contrary, a decrease in the number of CDs by 12%, $P = 1.18 * 10^{-5}$ and 16%, $P = 1.64 * 10^{-6}$ was registered respectively in the experimental group treated with cisplatin and dexamethasone in comparison with the cisplatin and dexamethasone co-injected group (Table 1, Fig. 1a).

The results confirm that compared to the baseline statistically significant changes of MDA quantity were revealed in all experimental groups. Thus, the amount of MDA in thymus homogenate increased by 84%; $P = 2.47 * 10^{-4}$, by 54%, $P = 2.45 * 10^{-4}$ and by 44%, $P = 4.10 * 10^{-4}$ respectively after cisplatin separate treatment, after separate injection of dexamethasone and after the co-injection of this drugs compared to the baseline (Table 2, Fig. 2a). The changes in MDA quantity recorded compared to the control group were reflected in the results of the intergroup comparison of the data (Table 2, Fig. 2a).

Table 1
The total amount of conjugated dines (CDs) (in conventional units) extracted from thymus tissue of rats at baseline, after separate and combined treatment with cisplatin and dexamethasone

Investigated fractions of thymus tissue	Baseline without treatment	Cisplatin alone treatment	Dexamethasone alone treatment	Cisplatin + dexamethasone
Thymus tissue homogenate	8.65 ± 0.163	18.45 ± 0.85**	17.68 ± 0.76***	21.14 ± 0.38**
Probability	–	$6.30 * 10^{-4}$	$6.60 * 10^{-5}$	$1.80 * 10^{-3}$
Supernatant	9.07 ± 0.39	14.15 ± 0.41***	12.11 ± 0.77****	10.43 ± 0.57
Probability	–	$6.23 * 10^{-5}$	$5.53 * 10^{-6}$	$5.40 * 10^{-3}$

Note: statistically significant differences between experimental groups are indicated as: ** – P < 0.005; *** – P < 0.0005 and **** – P < 0.00005.

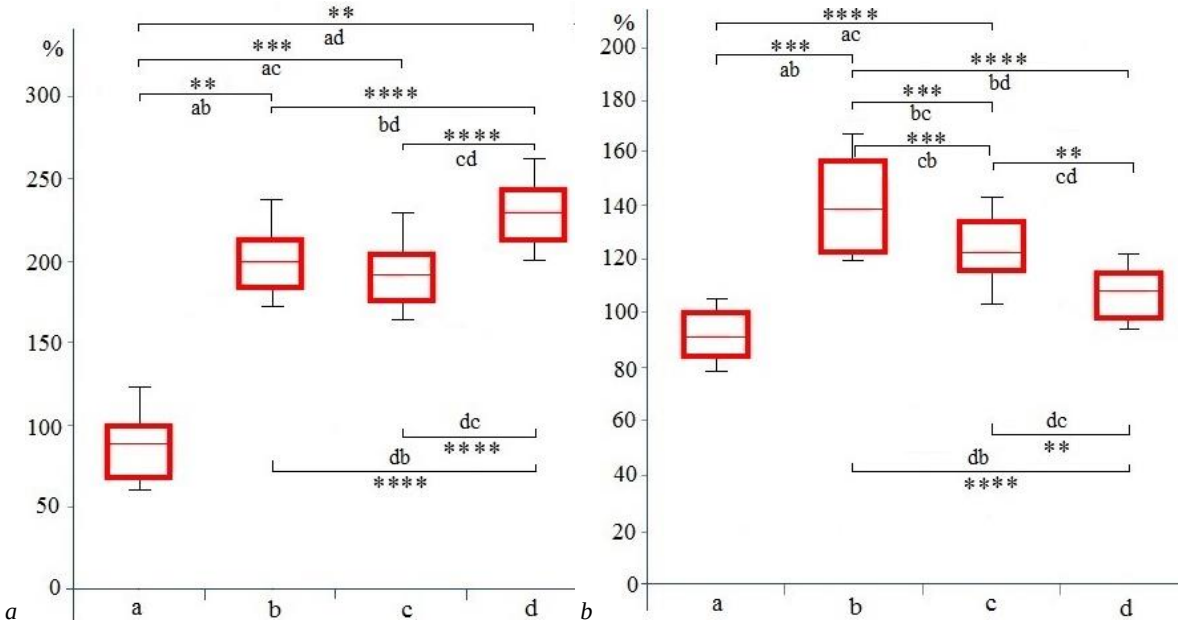

Fig. 1. Changes in the amount of conjugated dienes in homogenate (*a*) and supernatant (*b*) of thymus tissue of rats at baseline and after separate and combined treatment with cisplatin and dexamethasone: *a* – baseline; *b* – after cisplatin separate injection; *c* – after dexamethasone separate injection; *d* – after combined treatment with cisplatin and dexamethasone; statistically significant differences between experimental groups are indicated as: ** – P < 0.005; *** – P < 0.0005 and **** – P < 0.00005

The statistically significant quantitative changes in MDA (decrease by 16%, $P = 3.96 * 10^{-5}$ and by 22%, $P = 2.62 * 10^{-5}$) in the homogenate were revealed when comparing the results of the experimental group with dexamethasone alone treatment and the experimental group co-injected with cisplatin and dexamethasone with group which was injected cisplatin alone. A 20%, $P = 1.45 * 10^{-3}$ increase in MDA level was observed in the group of rats that received a single injection of cisplatin, compared to the experimental group that received only dexamethasone (Table 2, Fig. 2a). In the group of rats with single injection of cisplatin an increase in MDA levels by 28% was detected, $P = 2.62 * 10^{-5}$ in comparison to the experimental group that received a combined injection of cisplatin and dexamethasone (Table 2, Fig. 2a).

The statistically significant changes in the amount of MDA in comparison to the baseline were revealed also in supernatants that formed after the first centrifugation of thymus homogenates. In this case, cisplatin alone injection increased the amount of MDA by 74%, $P = 1.35 * 10^{-6}$, dexamethasone alone treatment by 46%, $P = 1.10 * 10^{-6}$ and the combined use of these drugs by 70%, $P = 3.75 * 10^{-5}$ (Table 2, Fig. 2b). Statistically significant changes in MDA content were also recorded during the intergroup comparison of the data obtained for the supernatant. Compared to the group of animals that received a separate injection of cisplatin, a decrease in MDA content by 16%, $P = 1.36 * 10^{-5}$ was recorded in the group of rats injected with dexamethasone alone.

Compared to the group of animals that received only dexamethasone, an increase in MDA content by 19%, $P = 4.74 * 10^{-5}$ and by 16%, $P = 7.01 * 10^{-6}$ was recorded in the groups that received cisplatin alone and combined with dexamethasone, respectively. At the same time, a statistically significant decrease in MDA content by 14%, $P = 7.01 * 10^{-6}$ was detected in the group of animals, with dexamethasone alone injection compared to the group that received co-injection with cisplatin and dexamethasone (Table 2, Fig. 2b).

Table 2
The amount of MDA (in nmol/mg protein) in 10% homogenate and supernatant of thymus tissue of rats at baseline and after separate and combined treatment with cisplatin and dexamethasone

Investigated fractions of thymus tissue	MDA content (in nmol/mg protein)			
	Baseline without treatment	Cisplatin alone treatment	Dexamethasone alone treatment	Cisplatin + dexamethasone
Homogenate	7.18 ± 0.27	13.20 ± 0.52***	11.05 ± 0.38***	10.35 ± 0.34***
Probability	–	$2.47 * 10^{-4}$	$2.45 * 10^{-4}$	$4.10 * 10^{-4}$
Supernatant	4.03 ± 0.20	7.00 ± 0.24****	5.87 ± 0.26****	6.84 ± 0.30***
Probability	–	$1.35 * 10^{-6}$	$1.10 * 10^{-6}$	$3.75 * 10^{-5}$

Note: statistically significant differences between baseline and each experimental group is indicated as *** – P < 0.0005 and **** – P < 0.00005.

In rat thymus tissue homogenates and supernatants of rats from all experimental groups the activities of antioxidant enzymes catalase and SOD were assessed.

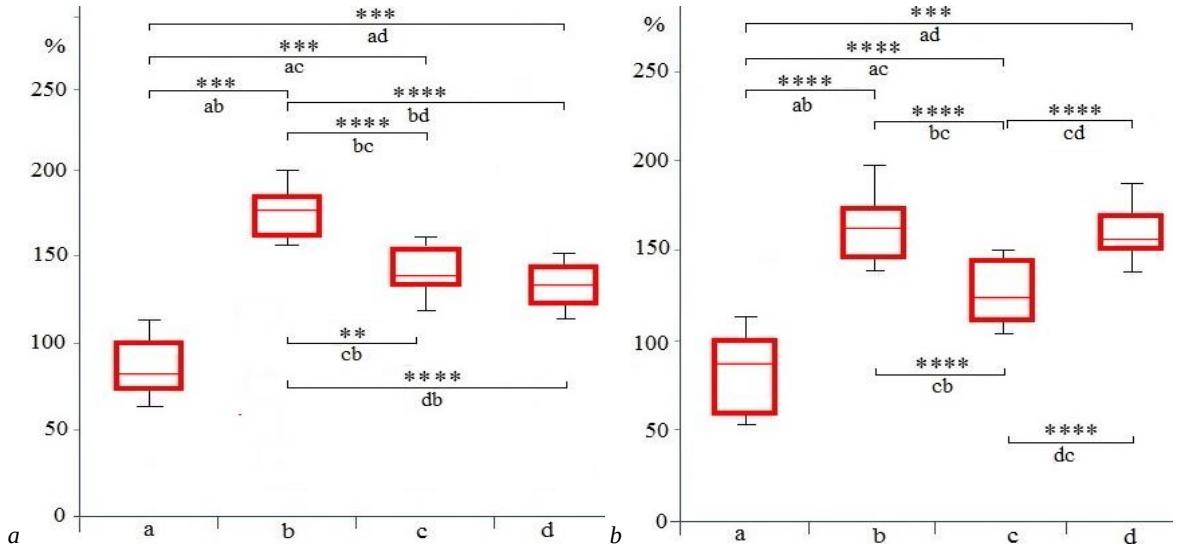

Fig. 2. Changes in the amount of MDA (in %) in 10% homogenate (*a*) and supernatant (*b*) of thymus tissue of rats at baseline and after separate and combined treatment with cisplatin and dexamethasone: *a* – baseline; *b* – after separate cisplatin injection; *c* – after separate injection of dexamethasone; *d* – after combined treatment with cisplatin and dexamethasone; statistically significant differences between experimental groups are indicated as: ** – P < 0.005; *** – P < 0.0005; and **** – P < 0.00005

Table 3
Effect of cisplatin and dexamethasone separate and combined action on catalase activity (in μM/min, mg protein) in homogenates and supernatants of rat thymus tissue

Investigated fractions thymus tissue	Baseline without treatment	Cisplatin alone treatment	Dexamethasone alone treatment	Cisplatin and dexamethasone combined treatment
Homogenate	447.4 ± 19.0	336.0 ± 18.0***	372.3 ± 10.0***	276.0 ± 9.2***
Probability	–	$4.59 * 10^{-5}$	$7.46 * 10^{-4}$	$1.39 * 10^{-6}$
Supernatant	183.0 ± 9.2	135.0 ± 5.4****	146.0 ± 6.3**	140.0 ± 4.5***
Probability	–	$4.88 * 10^{-5}$	$3.00 * 10^{-3}$	$1.26 * 10^{-4}$

Note: statistically significant differences between baseline and each experimental group are indicated as ** – P < 0.005; *** – P < 0.0005 and **** – P < 0.00005.

In thymus tissue homogenates, catalase activity was reduced by 25%, $P = 4.59 * 10^{-5}$, 17%, $P = 7.46 * 10^{-4}$ and 38%, $P = 1.39 * 10^{-6}$ respectively, following both separate and combined injections of cisplatin and dexamethasone compared to the control (Table 3, Fig. 3a). Naturally, these changes affected the results of intergroup comparisons of data. Compared to the group of animals injected with cisplatin alone, catalase activity was increased by 11%, $P = 1.08 * 10^{-5}$ in the variant injected with dexamethasone alone. On the contrary, in comparison with cisplatin alone treatment data, the combined use of cisplatin and dexamethasone reduced catalase activity by 18%, $P = 3.67 * 10^{-5}$ (Table 3, Fig. 3a).

Compared to dexamethasone administered alone, only the group receiving a combined injection of pro-oxidants (cisplatin and dexamethasone) exhibited a statistically significant 26%, $P = 4.12 * 10^{-5}$ decrease in catalase activity (Fig. 3). In the supernatants of thymus tissue of rats from all experimental groups, catalase activity decreased relative to the control. Specifically, catalase activity was reduced by 26%, $P = 4.88 * 10^{-5}$ following cisplatin treatment alone, 20%, $P = 3.00 * 10^{-3}$, after dexamethasone treatment alone, and by 23%, $P = 1.26 * 10^{-4}$ after their combined administration. However, these decreases were comparable across groups, and intergroup analysis did not reveal statistically significant differences in catalase activity (Table 3, Fig. 3b).

Another antioxidant enzyme analyzed in this study was superoxide dismutase (SOD). In thymus tissue homogenates SOD activity was significantly reduced in all treated groups compared to the control. Specifically, cisplatin alone treatment resulted in a 36% decrease, $P = 1.02 * 10^{-3}$ dexamethasone alone injection led to a 23%, decrease $P = 4.10 * 10^{-3}$, and the combined administration of cisplatin and dexamethasone caused a 24% decrease $P = 4.72 * 10^{-5}$ (Table 4, Fig. 4a).

Statistical comparisons of data between experimental groups revealed significant differences in SOD activity. Compared to cisplatin alone treatment, dexamethasone monoinjection increased SOD activity by 19%, $P = 1.01 * 10^{-3}$, while the combined treatment increased it by 22%, $P = 3.96 * 10^{-5}$. Furthermore, cisplatin alone led to a 16% decrease ($P = 1.75 * 10^{-3}$) in SOD activity compared to dexamethasone alone. Cisplatin also caused an 18% decrease ($P < 0.05$) in SOD activity compared to the combined treatment (Table 4, Fig. 4a).

Table 4
Effect of cisplatin and dexamethasone separate and combined action on SOD activity (in conventional units/min, mg protein) in homogenates and supernatants of rat thymus tissue

Investigated fractions thymus tissue	Baseline without treatment	Cisplatin alone treatment	Dexamethasone alone treatment	Cisplatin and dexamethasone combined treatment
Homogenate	83.2 ± 3.6	53.4 ± 2.5**	63.8 ± 2.1***	65.4 ± 2.2****
Probability	–	$1.02 * 10^{-3}$	$4.10 * 10^{-4}$	$2.47 * 10^{-5}$
Supernatant	53.3 ± 2.0	33.6 ± 1.4**	45.3 ± 1.6***	44.8 ± 1.8****
Probability	–	$6.99 * 10^{-6}$	$8.2 * 10^{-6}$	$3.43 * 10^{-6}$

Note: statistically significant differences between baseline and each experimental group are indicated as ** – P < 0.005; *** – P < 0.0005 and **** – P < 0.00005.

Similar patterns were observed in the supernatants. Relative to control values, SOD activity decreased by 37%, $P = 6.99 * 10^{-6}$ f following cisplatin injection, by 15%, $P = 8.2 * 10^{-6}$ after dexamethasone administration and by 16%, $P = 3.43 * 10^{-6}$ after their combined use (Table 4, Fig. 4*b*). Intergroup comparisons revealed that, relative to cisplatin alone use, SOD activity increased by 35%, $P = 2.31 * 10^{-6}$ after dexamethasone mono injection and by 33%, $P = 3.87 * 10^{-7}$ after the combined treatment. When comparing cisplatin to dexamethasone, SOD activity was 26% lower in the cisplatin group, $P = 2.31 * 10^{-6}$, while no significant difference was observed between both dexamethasone alone and the combined group. However, cisplatin alone resulted in a 25% decrease, $P = 3.87 * 10^{-7}$ in SOD activity compared to the combined treatment (Table 4, Fig. 4a).

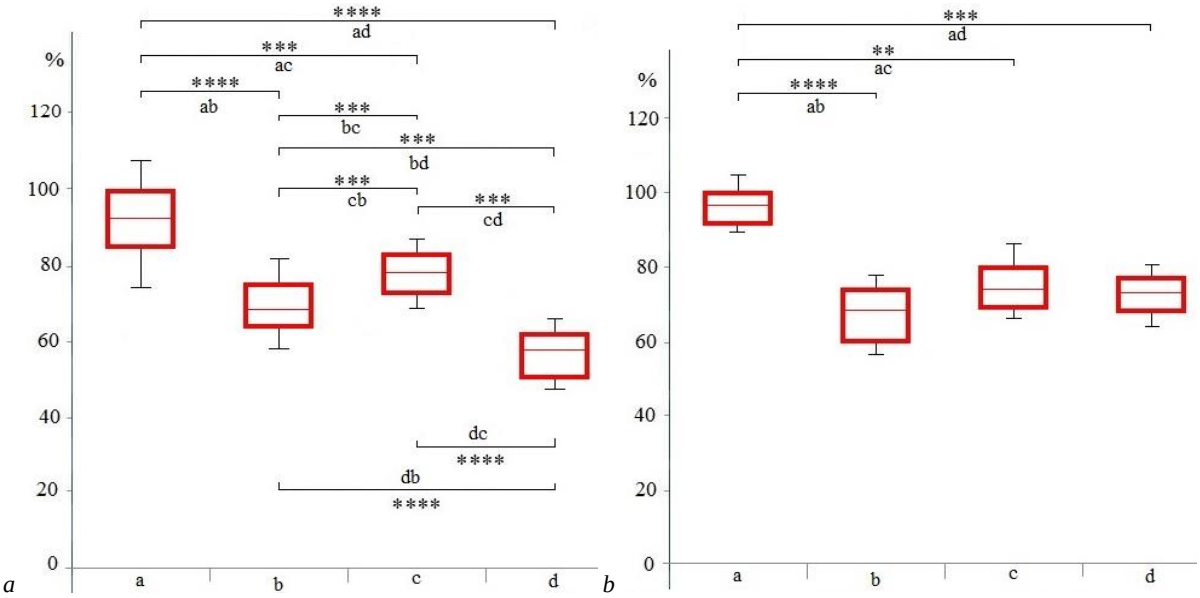

Fig. 3. Effect of separate and combined action of cisplatin and dexamethasone on catalase activity in homogenates (*a*) and supernatants (*b*) of thymus tissue: *a* – baseline; *b* – after cisplatin separate injection; *c* – after dexamethasone separate injection; *d* – after combined treatment with cisplatin and dexamethasone; statistically significant differences between baseline and each experimental group are indicated as ** – P < 0.005; *** – P < 0.0005 and **** – P < 0.00005

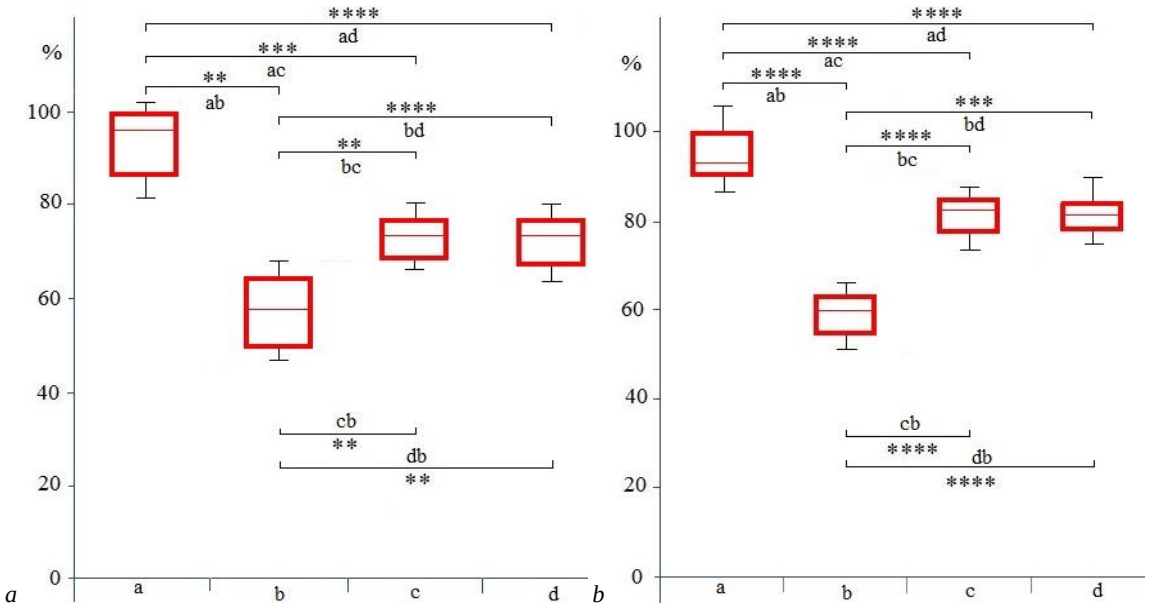

Fig. 4. Effect of separate and combined action of cisplatin and dexamethasone on SOD activity in homogenates (*a*) and supernatants (*b*) of thymus tissue: *a* – baseline; *b* – after cisplatin separate injection; *c* – after dexamethasone separate injection; *d* – after combined treatment with cisplatin and dexamethasone; statistically significant differences between baseline and each experimental group are indicated as ** – P < 0.005; *** – P < 0.0005 and **** – P < 0.00005

Histomorphological changes in the thymus from the experimental groups studied were revealed on the hematoxylin and eosin-stained slides. The obtained results showed that cisplatin separate injection induced apoptosis of thymocytes that were actively proliferating (Fig. 5d, 5e, 6f). The cisplatin treatment seems associated with an increase in the size and number of Hassall's corpuscles (Fig. 5f), interpreted as a response to enhanced apoptotic turnover and thymic degeneration.

The cisplatin treated thymus showed altered cytological architecture, reduced thymocyte density compared to control in the medullar part (Fig. 5d, 5e, 5f). Dexamethasone alone treatment caused thymic involution through profound cortical lymphocyte apoptosis, possible necrosis, architectural disruption (Fig. 6g, 6h, 6i). Connective tissue proliferation is observed around blood vessels (Fig. 6h, 6i). The vascular endothelium is enlarged, the surrounding perivascular connective tissue appears edematous (Fig. 6h, 6i).

Combined injection of cisplatin and dexamethasone produced an effect similar to that of cisplatin. In this case, too, a large number of Hassall's corpuscles are observed; the connective tissue is enlarged like fibrosis, in thymus cells (Fig. 7j, 7k, 7l).

Mast cells and their quantitative changes after separate and combined injections of cisplatin and dexamethasone were examined by staining thymus tissue using the Pappenheim method.

The studies revealed an increase in the number of these cells in all the studied experimental groups. There was an increase in the number of mast cells and their accumulation both in the lobular parenchyma and in the perivascular and interlobular connective tissues. Clusters of mast cells are found in the perivascular connective tissue, along with signs of their degranulation (Fig. 8). Mast cells are also detected in the medulla of the lobules (Fig. 8) in the subcapsular zone (Fig. 8) and in the interlobular connective tissue (Fig. 8c). The appearance of numerous mast cells in all compartments of the organ is noted in all experimental groups. In all experimental groups, the number of mast cells is higher than in the control group (Table 5 and Fig. 8d, 8e, 8f, 8g, 8h, 8i).

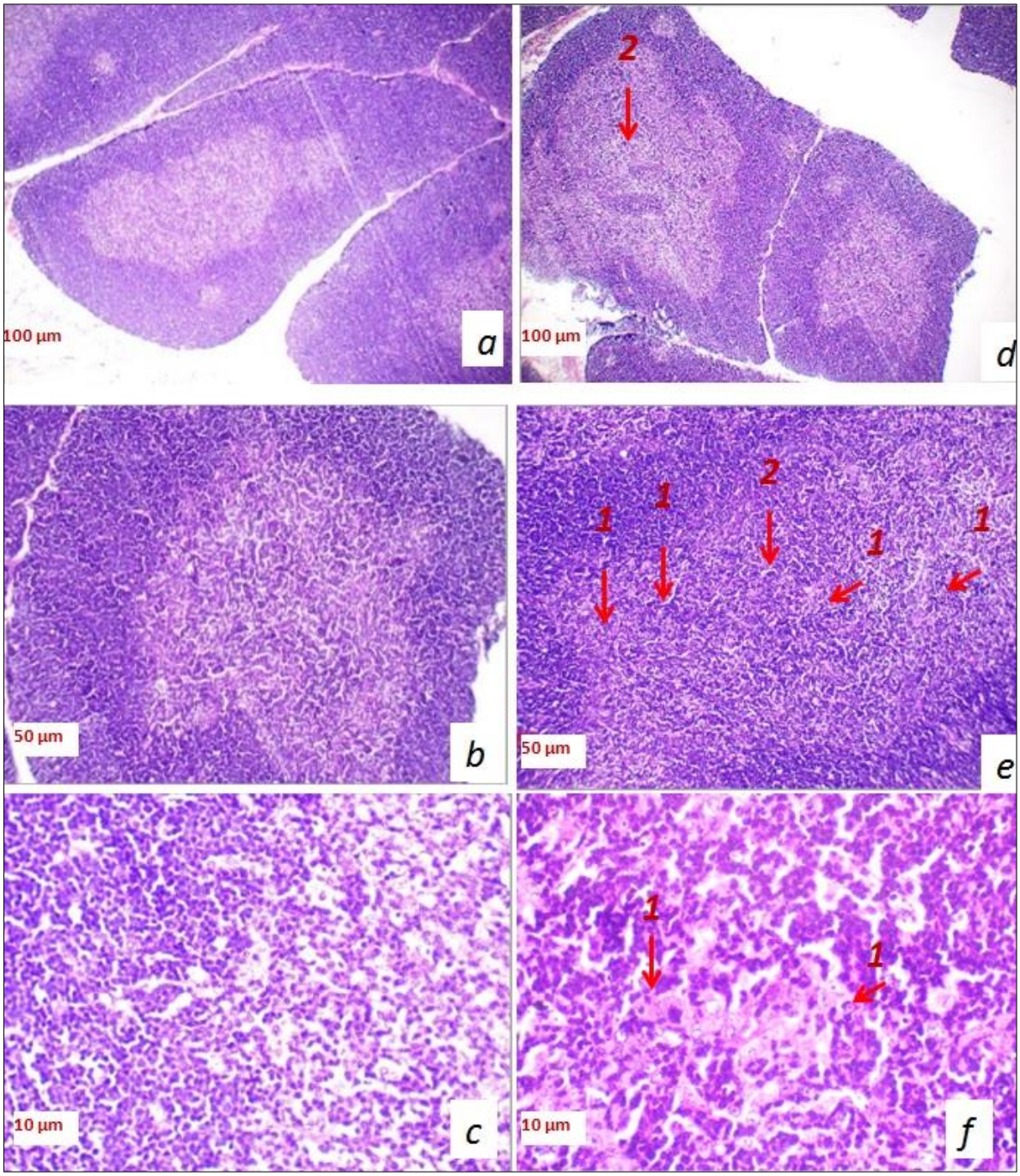

Fig. 5. Microphotographs of thymus tissues: staining with hematoxylin and eosin; *a, b, c* – thymus of rats of control group; *d, e, f* – thymus of rats treated with cisplatin alone; *1* – thymocyte apoptosis; *2* – Hassall's corpuscles

Table 5
The amount of mast cells counted in 40 successive fields of view per section at 400x magnification

Baseline without treatment	Cisplatin alone treatment	Dexamethasone alone treatment	Cisplatin and dexamethasone combined treatment
2.82 ± 0.342	3.95 ± 0.44	5.20 ± 0.84	4.85 ± 0.55
Probability	0.01	0.025	0.025

Discussion

The intensity of lipid peroxidation depends on the amount of ROS and free radicals present in the cell. The level of LPO is judged based on the number of products formed as a result of this process (Ayala et al., 2014; Hauck & Bernlohr, 2016). It is known that unsaturated fatty acids, both free and incorporated into various lipids, serve as substrates for lipid peroxidation (Ayala et al., 2014; Hauck & Bernlohr, 2016, Valgimigli, 2023). The process of lipid peroxidation begins with the attack of oxidizers (ROS, free radicals) on unsaturated fatty acids. As a result, primary products of lipid peroxidation conjugated dienes (CDs) are formed, which are subsequently cleaved to form MDA and other aldehydes (Ayala et al., 2014; Hauck & Bernlohr, 2016; Valgimigli, 2023).

The results of quantitative analysis of conjugated dienes showed that there were statistically significant changes in the amount of CDs in all preparations studied (Table 1). The effect of cisplatin is stronger than that of dexamethasone, and the result of their combined effect is not the mathematical sum of their individual effects. The activation of lipid peroxidation processes is evidenced by an increase in the number of conjugated dienes in the studied thymus homogenates by about 2.0–2.5 times (Table 1, Fig. 1). These significant changes have affected the results of intergroup comparisons of data. In this case, changes of varying magnitude are recorded.

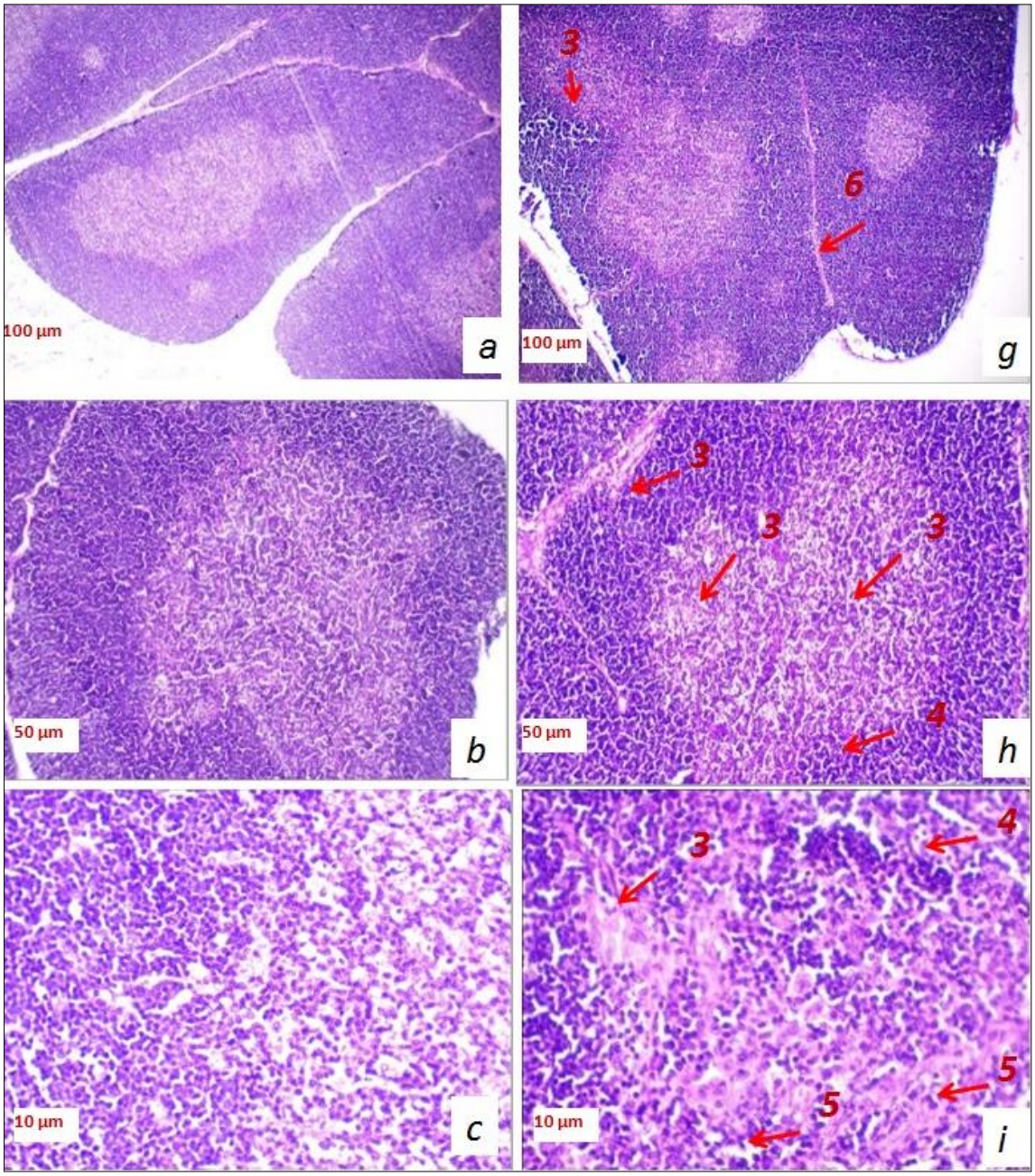

Fig. 6. Microphotographs of thymus tissues: staining with hematoxylin and eosin; *a*, *b*, *c* – thymus of rats of control group; *g*, *h*, *i* – thymus of rats treated with dexamethasone; *3* – cortical lymphocyte apoptosis; *4* – architectural disruption; *5* – necrosis; *6* – connective tissue proliferation

The intergroup comparison of lipid peroxidation product data allows us to identify the difference in the intensity of the effect of cisplatin and dexamethasone when used separately and in combination.

At the same time, in the supernatant obtained from thymus tissue, the quantitative changes in conjugated dienes recorded in the case of separate and combined exposure to cisplatin and dexamethasone compared to the control are more modest. As in the homogenate, the increase in the number of conjugated dienes in the supernatant compared to the control was greater after exposure to cisplatin than the effect of dexamethasone.

Quantitative changes in conjugated dienes after cisplatin and dexamethasone action in different tissues were also documented in our early works and by other authors (Cui et al., 2018; Yavroyan et al., 2024, 2025).

Since conjugated dienes are primary products of the lipid peroxidation, the increase in their amount after the cisplatin and dexamethasone separate and combined injection is sufficient to conclude that these drugs stimulated peroxidation of lipids. Moreover, some researchers believe that CDs, should serve as a marker of lipid peroxidation levels, rather than MDA (Cui et al., 2018; Yavroyan et al., 2021, 2025). Considering that MDA is still an accepted marker of oxidative stress and LPO levels (Ayala et al., 2014; Hauck & Bernlohr, 2016; Jadoon et al., 2017), we preferred to determine the amount of MDA. An increase in the amount of MDA was recorded as a result of separate and co-injection of cisplatin and dexamethasone (Table 2). The data obtained indicate that certain patterns are observed in the changes in the amount of MDA: first, the effect caused by cisplatin alone injections is stronger than that caused by dexamethasone in both the homogenates and supernatants studied. The MDA levels recorded in the supernatants are about 2 times lower than in the homogenates. In addition, the result of the combined application of these prooxidants is not the sum of the results of their separate injection.

As in the case of conjugated dienes, revealed changes in MDA levels compared to the control following separate and combined injections of cisplatin and dexamethasone have an impact on the intergroup comparison data. Changes in the amount of MDA after exposure to the cisplatin and steroids were also recorded in liver, kidney and other tissues of rats (Ayala et al., 2014; Yavroyan et al., 2021; Sidharta et al., 2022; Yavroyan et al., 2024).

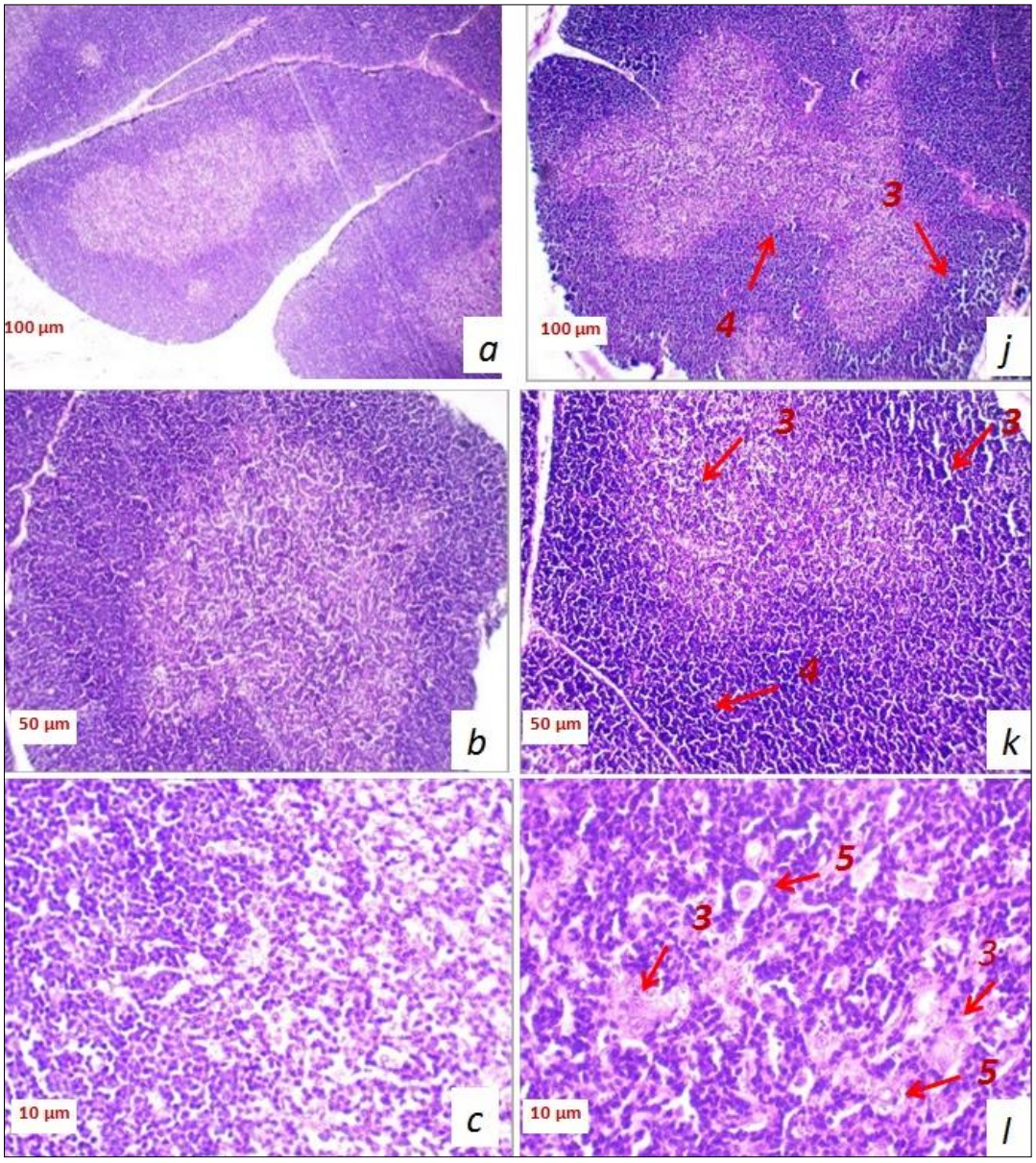

Fig. 7. Microphotographs of thymus tissues: staining with hematoxylin and eosin: *a, b, c* – thymus of rats of the control group; *j, k, l* – thymus of rats treated with cisplatin and dexamethasone; *3* – cortical lymphocyte apoptosis; *4* – architectural disruption; *5* – necrosis

It is known that the main components of cellular antioxidant defense are antioxidant enzymes, such as SOD, catalase, glutathione peroxidase, and others, which neutralize ROS and maintain cellular homeostasis (Hauck & Bernlohr, 2016; Valgimigli, 2023). The pro-oxidant properties of cisplatin and dexamethasone are also evidenced by the changes in the activity of the antioxidant enzyme catalase as a result of the separate and combined effects of these drugs (Yavroyan et al., 2024, 2025). In the homogenate of thymus tissue, separate injection of cisplatin and dexamethasone reduced catalase activity by 25% and 17% respectively. But in the case of combined injection, the enzyme activity reduction was greater (38%) than the effect caused by both cisplatin and dexamethasone. The same trend is observed in the supernatant, where catalase activity is lower compared to the homogenate. A reduction in catalase enzyme activity as a result of both cisplatin and dexamethasone exposure has also been reported in our early works and by other researchers (Yang et al., 2018; Yavroyan et al., 2024, 2025).

SOD is also a key enzyme in the cell's anti-oxidant defense system. It helps neutralize harmful superoxide radicals, converting them into less harmful substances. Cisplatin is able to interact with human SOD. Cisplatin can suppress SOD activity, contributing to oxidative stress and possibly impairing the function of the thymus and other tissues (Yang et al., 2018).

Our results confirm that separate and combined injection of cisplatin and dexamethasone have a significant suppressive effect on SOD activity. Moreover, both in the homogenate and supernatant, the suppressive effect of cisplatin is the strongest. And the result of combined injection of these drugs is similar to the effect caused by dexamethasone. Other authors also note the pro-oxidant properties of cisplatin and dexamethasone (Banci et al., 2012; Yang et al., 2018).

The different magnitudes of effects caused by pro-oxidants are likely due to their different molecular mechanisms of action in terms of oxidative stress stimulation and ROS formation.

It is known that although the main target of cisplatin is DNA, only 5–10% of the amount of imported cisplatin is covalently bound to DNA. The remaining 75–85% of it binds to non-DNA targets, containing nucleophilic groups (Tchounwou et al., 2021; Dasari et al., 2022).

Cisplatin may exert its cytotoxicity by interacting with sulfur atoms in glutathione and other proteins. The resulting functionally damaged proteins may also contribute to the biochemical mechanism of cisplatin cytotoxicity (Aldossary, 2019; Dasari et al., 2022). The cisplatin also impairs mitochondrial function by binding to mitochondrial DNA (mtDNA) (Aldossary, 2019, Dasari et al., 2022, Romani, 2022). Due to this, the impairment of mtDNA and ensuing mitochondrial dysfunction give rise to the generation of unbound ROS and trigger oxidative stress-mediated reactions (Kopacz-Bednarska &

Król, 2022, Romani, 2022). Dexamethasone is a synthetic glucocorticoid, which exerts its effects through receptor-mediated regulation of genetic activity. The glucocorticoid receptor is a ligand activated transcription factor that controls gene expression in a complex with hormone (Patil et al., 2018; Reichardt et al., 2021). It is known that dexamethasone exhibits strong antiinflammatory and immunomodulatory effects. Dexamethasone can both up regulate and down regulate expressions of the genes, which facilitates antiinflammatory and immunosuppressant effects (Patil et al., 2018; Reichardt et al., 2021). It has been shown that dexamethasone induced increases in ROS production and this process is also dependent on binding of the hormone-receptor complex to the glucocorticoid response elements. Glucocorticoids can contribute to oxidative stress and ROS formation by suppressing the expression of various antioxidant enzymes (Patil et al., 2018; Reichardt et al., 2021).

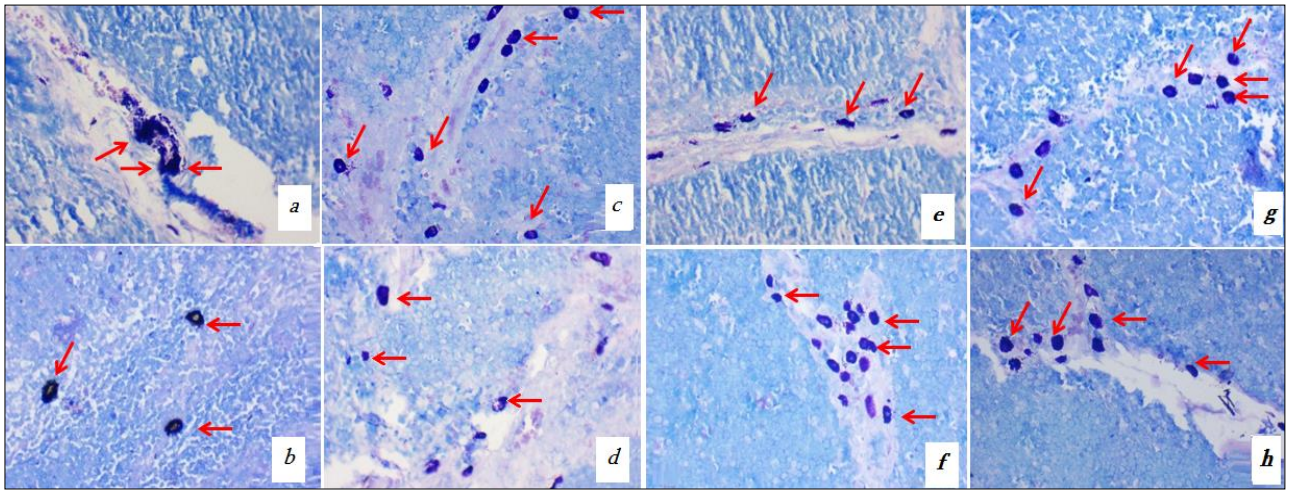

Fig. 8. Mast cells in thymus tissues from different experimental groups after the staining: May-Grünwald and Giemsa according to Pappenheim; *a*, *b* – thymus of rats of control group; *c*, *d* – thymus of rats treated with cisplatin; *e*, *f* – thymus of rats treated with dexamethasone; *g*, *h* – thymus of rats with cisplatin and dexamethasone combined treatment; red arrows – mast cells

The histological observation of the thymus tissue of animals from the control group revealed normal structures (Fig. 5a, 5b, 5c). Histopathology examination of thymus slices from rats treated with cisplatin alone showed different alterations. (Fig. 5d, 5e, 5f). Cisplatin monoinjection induced apoptosis of thymocytes. Cisplatin treated thymus showed altered cytological architecture, reduced thymocyte density compared to control in the medullar part. Hassall's corpuscles are special and specific bodies present in the thymic medulla. The Hassall's corpuscles are specific to the thymus. The number of Hassall's corpuscles increases or decreases with different diseases and their histopathological importance (Hassan et al., 2014).

Cisplatin treatment seems associated with an increase in the size and number of Hassall's corpuscles, interpreted as a response to enhanced apoptotic turnover and thymic degeneration. Chemotherapy-induced thymic changes are mentioned by other investigators (Hassan et al., 2014; Hou et al., 2021). Dexamethasone alone treatment caused thymic involution through profound cortical lymphocyte apoptosis, and architectural disruption of the thymus. Dexamethasone also causes changes in the connective tissue of thymocytes. The vascular endothelium is enlarged; the surrounding perivascular connective tissue appears swollen. Investigations showed that there was a direct and significant relationship between the dosage of dexamethasone and the level of apoptosis (Marchetti et al., 2003; Dustar et al., 2016). Moreover, there is an opinion that thymocyte apoptosis induction by dexamethasone is one of the best characterized experimental models of programmed cell death (Ortiz et al., 2001; Dustar et al., 2016).

Combined injection of cisplatin and dexamethasone produces an effect similar to that of cisplatin. In this case, too, a large number of Hassall's corpuscles are observed, the connective tissue is enlarged like fibrosis, in thymus cells. This suggests that in this case the effect of cisplatin predominates.

An essential component of the thymic microenvironment is mast cells. Through the production of various cytokines, they influence intercellular interactions and the permeability of the blood-thymus barrier. Mast cells are extremely important for neuro-immune communication as well as their mutual control on local defense reactions and mucosa conditions. It is assumed that the thymus serves as a site for the formation and deposition of mast cells. Being under complex neuroendocrine control, mast cells may play an important role in the temporary transformation of the thymus during stress responses, including their influence on extrathymic cell migration (Thapa & Farber, 2019; Artashyan & Khramtsova, 2023). The studies revealed an increase in the number of mast cells in all the studied experimental groups.

Thus, pro-oxidants cisplatin and dexamethasone manifest their own abilities in different ways, which is due to the different molecular mechanisms of their action. It is likely that different molecular mechanisms of action also determine the outcome of the "negotiation" between cisplatin and dexamethasone at the molecular level and the "deterrent" role of dexamethasone in the case of their combined use.

Conclusions

The observed increases in lipid peroxdation products – namely, conjugated dienes, MDA- along with decreased activities of the antioxidant enzymes catalase and SOD, confirm the pro-oxidant nature of both cisplatin and dexamethasone. When administered separately, cisplatin demonstrates a significantly stronger oxidative effect than dexamethasone. However, during combined treatment, dexamethasone appears to exert a buffering effect, partially mitigating the oxidative stress induced by cisplatin.

Histological analysis further supports the differential effects of these pro-oxidants. Although both cisplatin and dexamethasone promote oxidative stress and apoptosis, they produce distinct histological alterations in thymus tissue when used individually. Cisplatin primarily causes severe architectural disruption and thymocyte apoptosis, while dexamethasone leads to thymic involution and connective tissue changes. When administered together, the resulting histological changes resemble those caused by cisplatin alone, but are notably less severe – suggesting that dexamethasone plays a protective role.

The differences in both the nature and severity of effects are likely attributable to the distinct molecular mechanisms through which cisplatin and dexamethasone stimulate oxidative stress and generate ROS. Furthermore, the moderating influence of dexamethasone during co-administration may stem not only from these mechanistic differences but also from its strong anti-inflammatory and immunomodulatory properties. Together, these characteristics allow dexametha-

sone to attenuate some of the cytotoxic effects of cisplatin when these two drugs are used in combination.

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