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The role of oil solutions of thiosulfonates in the modulation of antioxidant parameters in rat kidneys

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This study investigated the influence of thiosulfonate esters, specifically S-ethyl-4-aminobenzenethiosulfonate (ETS), S-allyl-4-aminobenzenethiosulfonate (ATS), and S-allyl-4-acetylaminobenzenethiosulfonate (AATS), at a dose of 50 mg/kg body weight on the antioxidant defense system in rat kidneys. The kidneys are essential organs involved in maintaining metabolic homeostasis and they are constantly exposed to reactive oxygen species (ROS) and oxidative stress. The effectiveness of the antioxidant defense system was evaluated by measuring oxidative stress markers, including lipid peroxidation (LPO), as well as the activity of key antioxidant enzymes, such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GP), glutathione reductase (GR), and the level of reduced glutathione (GSH). Dysfunction of oxidant protection was observed with an oily diet, characterized by an increase in lipid hydroperoxide levels, a decrease in the SOD and catalase activity, and a decrease in the antioxidant activity of the entire glutathione chain. Administration of thiosulfonates, especially ETS and AATS, helped stabilize antioxidant protection. The beneficial antioxidant effects of thiosulfonates can be partially explained by their ability to prevent the formation of free radicals, can intercept, neutralize reactive oxygen species and other harmful substances that can damage body cells.

Key words: S-ethyl-4-aminobenzenethiosulfonate, S-allyl-4-aminobenzenethiosulfonate, S-allyl-4-acetylaminobenzenethiosulfonate, kidneys, antioxidant system

Introduction

Organosulfur compounds (OSCs) are natural compounds found in various *Allium* species, known for their diverse biological activities such as antimicrobial, antioxidant, anti-inflammatory, antidiabetic, anticarcinogenic, and antispasmodic effects. These compounds have gained attention in the agri-food industry as potential alternatives to synthetic preservatives. However, before their widespread use in the food industry, it is essential to assess their safety according to the guidelines provided by the European Food Safety Authority (EFSA).

Thiosulfonates are a class of chemical compounds that contain a sulfonate group ($–SO_3$) and a thiosulfonate group ($–S–SO_3$). These compounds have potential applications in various fields, including:

• *Industry.* Thiosulfonates are used in industrial processes as stabilizers, antioxidants, pH regulators, corrosion inhibitors, and more. They can be employed in the production of plastics, paints, detergents, pharmaceuticals, and other products [24].

• *Agrochemistry.* Some thiosulfonates have potential applications in agriculture as fungicides, insecticides, and herbicides. They can be used to control harmful organisms such as fungi, insects, and weeds, and improve crop yield [12].

• *Medicine.* Certain studies have indicated potential medical applications of thiosulfonates. For instance,

some thiosulfonates are being investigated as antitumor agents due to their ability to impact the growth and proliferation of cancer cells. Additionally, some thiosulfonates have demonstrated anti-inflammatory and antioxidant activities, which could be beneficial in treating oxidative stress-related diseases [2, 22].

• *Electrochemistry.* Thiosulfonates can also find applications in the field of electrochemistry. They are used as electrolytes in batteries, electrolytic processes, and other electrochemical applications [7].

Considering the potential applications of thiosulfonates, it is important to also consider their toxicity, environmental impact, and safety of use [14, 23].

The kidneys play a crucial role in toxin elimination and are involved in the regulation of water and electrolyte balance, as well as blood filtration. Studying the antioxidant system of the kidneys in the context of thiosulfonate research is essential because the antioxidant system is a key defense mechanism against oxidative stress, which can be induced by certain chemical substances, including thiosulfonates [8, 16].

Oxidative stress occurs when the level of free radicals and other reactive oxygen species exceeds the capacity of the antioxidant system to neutralize them. This can lead to cell and tissue damage, including in the kidneys. Thiosulfonates not only inhibit oxidative processes within cells but also stimulate the expression of genes that produce enzymes involved in the antioxidant defense system. One important target within cells for these compounds is redox-sensitive transcription factors, specifically antioxidant-responsive elements (ARE). By modulating the expression of genes regulated by ARE, thiosulfonic acid esters can exert cytoprotective effects.

In thiosulfonate studies, investigating the antioxidant system of the kidneys and spleen allows for an assessment of whether these compounds can induce oxidative stress and cellular damage in these organs. Research may involve measuring the levels of antioxidants such as glutathione, superoxide dismutase (SOD), catalase, and other antioxidant enzymes, as well as evaluating the levels of oxidative markers such as malondialdehyde (MDA) [17] or reactive oxygen species (ROS). In our study, we investigated the radical scavenging and antiradical activities of S-ethyl-4-aminobenzenethiosulfonate (ETS), S-allyl-4-aminobenzenethiosulfonate (ATS), and S-allyl-4-acetylaminobenzenethiosulfonate (AATS) *in vivo* to establish the relationship between their structure and activity.

Based on the aforementioned information, the objective of our study was to investigate the impact of various sulfur-containing compounds, specifically ETS, ATS, and AATS, on the antioxidant defense system in the kidneys of rats.

Materials and Methods

Our study focused on investigating the biological effects of S-ethyl-4-aminobenzenethiosulfonate (ETS), S-allyl-4-aminobenzenethiosulfonate (ATS), and S-allyl-4-acetylaminobenzenethiosulfonate (AATS). These compounds were synthesized at the Department of Technology of Biologically Active Compounds, Pharmacy, and Biotechnology of the Lviv Polytechnic National University following a previously described protocol. The dosage and duration of administration were determined based on our previous studies [12]. The selected doses of thiosulfonates was 50mg/kg of body weight, administered orally for a period of 21 days to white male Wistar rats weighing between 190 and 210 g. The research was conducted at the Laboratory of Biochemistry of Animal Adaptation and Ontogeny, Institute of Animal Biology NAAS (Lviv, Ukraine). The study was conducted following the general ethical principles of animal experiments established by the First National Congress on Bioethics (Kyiv, Ukraine, 2001) and in accordance with the provisions of the "European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes" (Strasbourg, France, 1986). Permission to conduct the study was obtained from the Bioethics Committee of the Institute of Animal Biology NAAS (Protocol no. 128 from February 27, 2023). The animals were housed in a vivarium with suitable lighting and temperature conditions.

Each experiment involved dividing the animals into four groups, each consisting of 5 rats: I group served as the control; II, III, IV, and V groups were experimental. The control group (I) did not receive any substances, while the experimental groups (II, III, IV, and V) were administered either oil or an oil solution of thiosulfonates.

Both the control and experimental groups were provided with standard pelleted food for laboratory rats. The animals in the experimental groups were given 500 µL of either oil or an oil solution of thiosulfonates.

The activity of superoxide dismutase (SOD) was measured by the reduction of nitrotetrazolium blue by superoxide radicals. The results were expressed in arbitrary units per 1 mg of protein.

To determine the activity of catalase (CAT), the ability of hydrogen peroxide to form a stable colored complex with molybdenum salts was utilized. The CAT activity was expressed as the reduction in hydrogen peroxide content.

The activity of glutathione peroxidase (GP) was determined by the rate of glutathione oxidation during its interaction with tert-butyl hydroperoxide. The GP activity was expressed in nmol of glutathione per minute per 1 mg of protein.

The activity of glutathione reductase (GR) was measured by the decrease in oxidized glutathione content during its interaction with NADPH. The GR activity was expressed in µmol of oxidized NADP per min per 1 mg of protein.

To determine the level of free glutathione (GSH), the reaction of GSH with 5,5'-dithiobis-2-nitrobenzoic acid was employed, resulting in the formation of a colored product. The GSH content was expressed in millimoles per gram of tissue [11].

After conducting the experiments, the data were statistically analyzed using the *Microsoft Excel* software, employing the one-way method.

The statistical analysis was performed using *Microsoft Excel 2013*. The results were presented as the Mean±Standard Error of the Mean (M±SEM). To assess the significance of the differences between groups, one-way analysis of variance (ANOVA) was conducted, followed by the Tukey-Kramer test. Significance levels were categorized into three gradations: * or $^{\#}$ for P≤0.1, ** or $^{\#\#}$ for P≤0.05, and *** or $^{\#\#\#}$ for P≤0.01. Differences were considered statistically significant at a significance level of P≤0.1, which spoke about the existence of a 10% probability that the relationship found between the variables in the samples is just a random feature of the given samples.

Results and Discussion

Lipid peroxidation and oxidative stress play a significant role in the pathophysiology of kidney damage. Reactive oxygen species (ROS) can induce oxidative damage to cellular components, including lipids, proteins, and DNA, leading to dysfunction and injury of renal cells [8].

One of the key mechanisms involved in lipid peroxidation is the generation of lipid hydroperoxides, which are highly reactive and can initiate a chain reaction of oxidative damage in the kidneys [15]. The accumulation of lipid hydroperoxides can lead to cellular dysfunction and contribute to the development of kidney diseases.

The antioxidant defense system in the kidneys plays a crucial role in maintaining the redox balance and protecting against oxidative stress. This system involves various antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), as well as non-enzymatic antioxidants like reduced glutathione (GSH) [1, 9].

Studies have shown that increased ROS production and impaired antioxidant defense mechanisms can disrupt the pro/antioxidant balance in the kidneys, leading to oxidative stress and tissue damage [5, 9].

The results of the research show that the level of lipid hydroperoxides in the kidney homogenate of rats in IV and V groups likely increased under the influence of thiosulfonates compared to the control (table), by 61.4% and 29.5%, respectively, with a probability of 1 and 10 percent. However, it should be noted that the relationship between the variables observed in the samples may be a random feature of the specific sample (table, fig. 1). This increasing trend is also observed when comparing with the group of rats that received oil. Therefore, the thiosulfonates ATS and AATS may contribute to the elevation of lipid hydroperoxide levels in the rat kidney homogenate, indicating a potential induction of oxidative stress in the animal's body. Lipid hydroperoxides are products of lipid peroxidation, which occurs when there is an excessive presence of free oxygen radicals or insufficient activity of antioxidant systems.

On the contrary, a probable decrease in the content of TBC (thiobarbituric acid reactive substances)-active products was observed in the kidney homogenate of rats that received both oil and thiosulfonates compared to the control group. This suggests that the oil, as a solvent, may also provide protection against free radical damage to the kidneys (table, fig. 2).

When there is an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system, oxidative stress can occur, leading to lipid peroxidation. Lipid peroxidation is a process in which reactive oxygen species attack polyunsaturated fatty acids in cell membranes, resulting in the formation of lipid hydroperoxides. These hydroperoxides can then decompose into various byproducts, including TBARS (thiobarbituric acid reactive substances). Therefore, increased levels of TBARS indicate higher levels of lipid peroxidation and oxidative damage to cellular membranes [6].

Reducing oxidative stress would be expected to lead to a decrease in lipid peroxidation and consequently lower levels of TBARS. By maintaining a balance between ROS production and antioxidant defenses, it is possible to mitigate the harmful consequences of oxidative stress on cellular structures and functions.

In contrast to the level of lipid hydroperoxides in the kidney homogenate of rats that received both oil and thiosulfonates, a significant decrease in the content of TBARS (thiobarbituric acid reactive substances)-active products was observed compared to the control group.

Table. Indicators of antioxidant parameters of rat kidney homogenate (M±S.E.M., n=5)

Indicator	I — Control	II — oil	III — ETS	IV — ATS	V — AATS
SOD, U/mg of protein	28,00±0,61	18,55±0,23↓***	22,82±0,60↓**↑###	22,57±0,60↓**↑###	19,89±1,26↓***
CAT, mmol/min×mg of protein	17,76±0,27	15,18±1,32↓	17,34±0,22↑#	16,86±0,48↓*	13,56±0,84↓**
GPx, nmol GSH/min×mg of protein	83,46±2,51	52,97±3,95↓***	64,20±3,78↓**↑#	58,44±4,27↓***	77,78±2,91↓**↑###
GR, nmol NADPH/min×mg of protein	1,40±0,06	1,25±0,31	2,00±0,48↑**↑#	0,88±0,11↓**↓#	1,44±0,03
GSH (*10^{-1}), mmol/g	3,36±0,11	2,83±0,15↓**	3,36±0,21↑##	2,15±0,10↓***↓###	4,39±0,07↑*↑###
TBARS, nmol/g tissue	6,34±0,81	4,18±0,21↓**	4,72±0,13↓**↑#	4,46±0,23↓**↑	3,63± 0,22↓***↓#
LHP, CU/g tissue	0,44±0,02	0,48±0,04	0,48±0,05	0,71±0,05↑***↑###	0,57±0,04↑*↑#

Note. here and further *–*** — P ≤,1; 0,05; 0,001 — the statistically significant difference in III, IV, V, VI, VII groups compared to I group (control); #–### — P≤ 0,1; 0,05; 0,001 — the statistically significant difference in III, IV, V groups compared to II group.

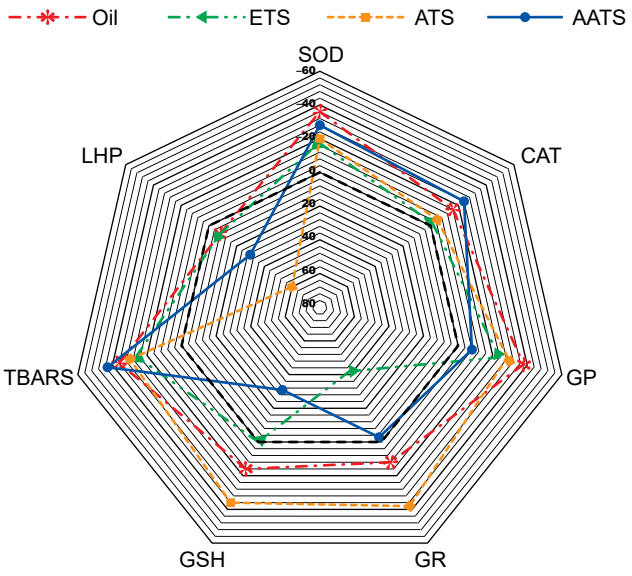

Fig. 1. Relative percentage deviation of the experimental groups relative to the control, which we took as the zero reference

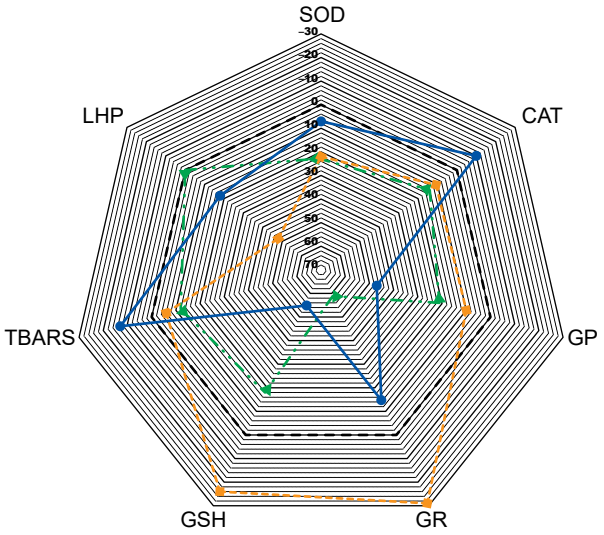

Fig. 2. The relative percentage deviation of the experimental groups relative to the group that was fed pure oil, which we took as the zero reference

This suggests that the oil, as a solvent, may introduce and reduce the content of TBARS by 34% compared to the control (see fig. 1). However, when comparing the effects of esters on the kidney homogenate relative to the oil group, it was found that feeding rats ATS resulted in a statistically insignificant increase in TBARS, while feeding rats ETS led to a statistically significant increase. On the other hand, feeding rats AATS resulted in a statistically significant reduction of 13.16% compared to the oil group, with a significance level of P≤0.1. This suggests that despite the increase in the level of lipid hydroperoxides in the rat kidney homogenate after the introduction of thiosulfonates into the diet, the antioxidant system neutralizes the appearance of free radicals and subsequent oxidation, thereby minimizing oxidative stress and reducing the TBARS level. By maintaining a balance between the production of reactive oxygen species (ROS) and antioxidant defences, it is possible to mitigate the harmful consequences of oxidative stress on cellular structures and functions.

Interesting patterns were also observed in the glutathione antioxidant chain of free radical oxidation. Specifically, a decrease in the activity of superoxide dismutase (SOD) was observed in all experimental groups compared to the control group (see table, fig. 1). This reduction in SOD activity can disrupt the balance between ROS production and antioxidant defences, resulting in an accumulation of superoxide radicals and subsequent oxidative damage to cellular structures. The reduction in SOD activity was 33.75% in the oil group, 18.5% in the ETS group, 19.39% in the ATS group, and 28.96% in the AATS group. However, comparing the effects of thiosulfonates with oil, it can be observed that all thiosulfonates mitigate the reduction in SOD activity (see fig. 2) and enhance antioxidant protection compared to the oil group. Specifically, SOD activity increases by 23% in the ETS group, by 21.67% in the ATS group, and by 7.22% in the AATS group. This is consistent with other studies, as thiosulfonates have been reported to have varied effects on SOD activity. Some studies suggest that thiosulfonates can enhance SOD activity, while others indicate a decrease in SOD levels. The specific impact may depend on the experimental conditions, dosage, and the specific system being investigated [4, 6].

A decrease or increase in catalase levels can provide insights into the oxidative status and the efficiency of the antioxidant defence system in the body. Catalase is an enzyme that plays a crucial role in breaking down hydrogen peroxide into water and oxygen, thereby protecting cells from oxidative damage. Changes in catalase levels can indicate alterations in oxidative stress levels and the overall balance between reactive oxygen species (ROS) production and antioxidant defence.

In this case, all groups showed decreased catalase levels compared to the control. The largest decrease of 23.64% was observed in the AATS group, while the use of oil led to a decrease of 14.52% in catalase levels. The use of ETS and ATS resulted in a decrease of approximately 5% in catalase levels. These reductions in catalase levels suggest a potential disruption in the antioxidant defence system and an imbalance between ROS production and antioxidant protection in the kidney homogenate of rats treated with thiosulfonates or oil [1, 18].

A decrease in catalase levels can indicate a compromised antioxidant defense system, which may lead to an accumulation of hydrogen peroxide and other reactive oxygen species (ROS). This reduction in catalase activity can result in an impaired ability to neutralize oxidative stress and may suggest an imbalance between ROS production and antioxidant capacity. Additionally, decreased catalase levels may indicate a higher susceptibility to oxidative damage and an increased risk of oxidative stress-related diseases [3, 10]. Since oil and oil solutions reduce the level of catalase, we can conclude that the main influence on this indicator is exerted by oil as an independent substance and a solvent for thiosulfonates.

At the same time, thiosulfonates such as ETS and ATS neutralize this oil effect, and an increase in catalase levels when using these ethers relative to the oil group can indicate an upregulation of the antioxidant defense system in response to oxidative stress [13]. This upregulation of catalase activity serves as a protective mechanism to mitigate the harmful effects of reactive oxygen species (ROS) and maintain redox balance within cells, which is caused by thiosulfonates compared to oil (see fig. 2).

A decrease in glutathione peroxidase (includes both catalase and glutathione links) levels can indicate a compromised antioxidant defense system, particularly in the context of the cellular antioxidant enzyme network. Glutathione peroxidase is responsible for the reduction of hydrogen peroxide and organic hydroperoxides, utilizing glutathione as a co-substrate. Therefore, a reduction in its levels may suggest an impaired ability to neutralize peroxides and mitigate oxidative stress.

Oil solutions led to a decrease in the level of glutathione peroxidase in all groups (see fig. 1) compared to the control group. A decrease in glutathione peroxidase was observed by 36.5% in the oil group ($P<0.001$), 29.97% in the ATS group ($P<0.001$), 23.07% in the ETS group ($P<0.05$), and 6.8% in the AATS group ($P<0.05$).

A decrease in glutathione peroxidase activity can lead to an accumulation of peroxides and reactive oxygen species (ROS), which can contribute to oxidative damage and disrupt cellular redox balance. This reduction may also indicate a decreased capacity to protect against oxidative stress-related diseases and conditions. However, a direct comparison with the oil group allows us to draw conclusions about the antioxidant protection caused by thiosulfonates. All thiosulfonates increase the glutathione peroxidase level relative to the oil group by 10.32% (ETS), 21.2% (ATS), and 46.83% (AATS) (see fig. 2).

Glutathione reductase is a key enzyme involved in maintaining the reduced form of glutathione, which is crucial for neutralizing reactive oxygen species (ROS) and detoxifying harmful substances. In the oil group, there is an insignificant decrease by 10.31% in the level of this enzyme relative to the control, but unlike the previous results, ATS does not exhibit antioxidant properties. On the contrary, it further enhances the effect of oxidative damage relative to the control group. The decrease in the level of glutathione reductase in ATS is 37.4% relative to the control group, which is 29.6% relative to the oil group (see fig. 1). A reduction in glutathione reductase levels can lead to an accumulation of oxidized glutathione and a diminished capacity to regenerate reduced glutathione. This imbalance can disrupt the antioxidant capacity of cells, resulting in increased oxidative stress and heightened vulnerability to oxidative damage.

Other thiosulfonates showed an antioxidant effect, and this effect was so great that it completely compensated for the oxidizing effect of the oil, increasing the content of glutathione reductase by 2.8% in the AATS group and by 42.87% in the ETS group relative to the control group, which was an increase of 15.2% and 60% compared to the oil group, respectively.

The last of the glutathione chain is reduced glutathione. In the groups of animals that consumed oil and ATS in the kidney homogenate, the level of GSH was reduced relative to the control group by 15.77% and 36.01%, respectively. A decrease in the content of reduced glutathione (GSH) can indicate a disruption in the antioxidant defense system and redox balance within cells. Here are some characteristics associated with a decrease in GSH levels.

Impaired antioxidant capacity: GSH plays a crucial role in cellular antioxidant defense by taking part in the reactive oxygen species (ROS) reduction and neutralizing free radicals. A decrease in GSH content can result in reduced antioxidant capacity, making cells more susceptible to oxidative damage.

Oxidative stress: Decreased GSH levels are often associated with increased oxidative stress. GSH acts as a critical cellular redox buffer, and its depletion can disrupt the balance between pro-oxidants and antioxidants, leading to an ROS accumulation and oxidative damage to cellular components.

Imbalanced redox status: GSH serves as a critical regulator of the cellular redox status, maintaining a reducing environment inside cells. A decrease in GSH content can disturb the redox balance and affect cellular signaling pathways and redox-sensitive processes.

Impaired detoxification: GSH is involved in the detoxification of xenobiotics and harmful substances. Reduced GSH levels can hinder proper detoxification processes, leading to the accumulation of toxic compounds and increased susceptibility to cellular damage.

It should be noted that ETS and AATS stabilized the level of GSH. We did not observe differences in the level of GSH between the ETS group and the control group. The indicators in these groups differed only by mathematical expectation. However, AATS led to an increase in the GSH indicator by 30% relative to the control group and by 55.12% relative to the oil group [20].

Our data are consistent with the results of research by other authors and indicate that oil, as a solvent, causes a decrease in GSH content and may be the cause of disturbances in the functioning of the glutathione link of antioxidant protection. At the same time, thiosulfonates at different stages, depending on the type, act as antioxidants, restore antioxidant protection, and normalize oxidative processes.

Studies have reported a decrease in activity of the antioxidant system following an oil diet. This reduction in activity of the antioxidant system may be associated with oxidative stress and the generation of ROS. It is important to note that excessive consumption of certain types of oils, particularly those high in omega-6 fatty acids, can lead to an imbalance between pro-oxidants and antioxidants, thereby affecting the activity of the antioxidant system and other antioxidant enzymes. At the same time, thiosulfonates to varying degrees improved antioxidant indicators. Thiosulfonates can react with reactive oxygen species, donating their electrons and forming stable, less reactive compounds. This reduces oxidative stress and prevents cell damage. In addition, some thiosulfonates can activate enzymatic antioxidant defense systems, particularly glutathione-S-transferase, which plays an important role in the detoxification of harmful compounds.

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Роль олійних розчинів тіосульфонатів у модуляції антиоксидантних показників у нирках щурів

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Досліджували вплив естерів тіосульфонатів, зокрема S-етил-4-амінобензентіосульфонату (ЕТС), S-аліл-4-амінобензентіосульфонату (АТС) та S-аліл-4-ацетил-амінобензентіосульфонату (ААТС), у дозі 50 мг/кг маси тіла на систему антиоксидантного захисту в нирках щурів. Нирки є важливим органом у підтримці метаболічного гомеостазу і постійно зазнають впливу активних форм кисню (АФК) та оксидативного стресу. Ефективність системи антиоксидантного захисту оцінювали вимірюванням маркерів оксидативного стресу, зокрема показників пероксидного окиснення ліпідів (ПОЛ) та активності ключових ензимів антиоксидантної системи — таких, як каталаза (КАТ), супероксиддисмутаза (СОД), глутатіонпероксидаза (ГП), глутатіонредуктаза (ГР), та рівень відновленого глутатіону (ВГ). Дисфункцію системи антиоксидантного захисту спостерігали в нирках тварин, які споживали з кормом олію, про що свідчать показники підвищеного вмісту гідропероксидів ліпідів, зниження активності СОД і каталази, ензимів глутатіонової ланки та знижений вміст відновленого глутатіону. Споживання тіосульфонатів, особливо ЕТС та ААТС, сприяло стабілізації системи антиоксидантного захисту. Позитивний антиоксидантний ефект тіосульфонатів можна частково пояснити їхньою здатністю запобігати утворенню вільних радикалів, перехоплювати і нейтралізувати активні форми оксигену та інші шкідливі речовини, здатні пошкоджувати клітини організму.

Ключові слова: S-етил-4-амінобензентіосульфонат, S-аліл-4-амінобензентіосульфонат, S-аліл-4-ацетиламіно-бензентіосульфонат, нирки, антиоксидантна система

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