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ORIGINAL ARTICLE

PROTECTIVE EFFECT OF RESVERATROL ON OXIDATIVE STRESS IN RATS EXPOSED TO ELEVATED DOSES OF SODIUM BENZOATE

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ABSTRACT

Background. Sodium benzoate is a widely used food preservative permitted in Ukraine with an acceptable daily intake of 5 mg/kg body weight. However, exposure to elevated doses may induce oxidative imbalance and metabolic disturbances. Therefore, the search for effective protective agents against sodium benzoate–induced oxidative stress remains relevant. Resveratrol is a natural polyphenolic compound known for its antioxidant, anti-inflammatory, and cytoprotective properties.

Objective. To evaluate the effect of resveratrol on free radical processes and antioxidant defense parameters in rats exposed to elevated doses of sodium benzoate.

Material and Methods. The study was conducted on 42 adult male rats. Sodium benzoate was administered intragastrically at a dose of 30 mg/kg body weight daily for 28 days. Resveratrol was administered intragastrically at a dose of 20 mg/kg body weight. Animals were euthanized on days 14, 21, and 28. Oxidative stress and antioxidant status were assessed by measuring thiobarbituric acid reactive substances (TBARS), products of oxidative modification of proteins, ceruloplasmin content, reduced glutathione levels, and catalase activity in blood serum and liver tissue.

Results. Sodium benzoate exposure resulted in a significant increase in lipid peroxidation and protein oxidative modification, accompanied by a decrease in reduced glutathione levels and catalase activity in both blood serum and liver tissue. By the end of the experiment, TBARS levels increased 5.1-fold in serum and 3.7-fold in liver tissue compared to controls. Resveratrol administration significantly attenuated oxidative damage, restored reduced glutathione levels to near-control values, and increased catalase activity throughout the experimental period ($p \leq 0.05$).

Conclusions. Resveratrol effectively reduces sodium benzoate–induced oxidative stress and restores antioxidant defense mechanisms in rats, indicating its potential protective role against preservative-associated oxidative damage.

Keywords: *lipid peroxidation, resveratrol, sodium benzoate, antioxidant defense system, oxidative stress*

INTRODUCTION

Sodium benzoate (E211), the sodium salt of benzoic acid, is one of the most commonly used preservatives in the food industry. It is widely applied to inhibit microbial growth and prolong the shelf life of beverages, meat and fish products, confectionery, sauces, and fruit-based foods. According to international and national regulations, sodium benzoate is permitted for use only within strictly defined concentrations, and its acceptable daily intake is set at 5 mg/kg body weight. Nevertheless, concerns remain regarding the potential biological effects associated with long-term or excessive intake of this preservative [1, 2].

Experimental and clinical studies indicate that sodium benzoate may exhibit prooxidant activity, leading to the activation of free radical processes and the development of oxidative stress. Excessive generation of reactive oxygen species has been shown to impair mitochondrial function, disrupt cellular metabolism, and induce oxidative damage to lipids and proteins. In addition, sodium benzoate has been reported to interfere with amino acid metabolism, particularly glycine availability, and to exert neuromodulatory effects under certain conditions [3-5].

Of particular concern is the ability of sodium benzoate to participate in benzene formation when combined with ascorbic acid (E300). This reaction may occur during storage and is promoted by exposure to light and elevated temperatures [6]. Benzene is a well-known carcinogen, and chronic exposure has been associated with hematological disorders and an increased risk of leukemia. Although sodium benzoate is generally considered safe within recommended intake limits, combined exposure from

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multiple sources or prolonged intake of elevated doses may pose potential health risks [6, 7].

Sodium benzoate is used not only in food products but also in pharmaceuticals, cosmetics, personal care products, and animal feed, increasing the likelihood of cumulative exposure. Long-term intake may promote its accumulation in organs such as the liver and kidneys, contributing to metabolic disturbances and oxidative imbalance [8, 9]. Therefore, investigating the mechanisms of sodium benzoate–induced toxicity and identifying effective protective strategies remains an important task in food hygiene and public health research [10-12].

Resveratrol is a natural polyphenolic compound widely distributed in grapes, berries, and red wine. It has attracted considerable scientific interest due to its antioxidant, anti-inflammatory, anti-aggregant, and cytoprotective properties [13-15]. Resveratrol is capable of scavenging reactive oxygen species, modulating antioxidant enzyme activity, and supporting endogenous antioxidant defense systems. Previous studies have demonstrated its protective effects against oxidative damage induced by various xenobiotics and environmental stressors [16-18].

Our previous investigations showed that subchronic administration of sodium benzoate at a dose of 30 mg/kg body weight induces pronounced oxidative stress in experimental animals. Based on these findings, the present study aimed to evaluate the ability of resveratrol to attenuate oxidative stress and restore antioxidant defense parameters in rats exposed to elevated doses of sodium benzoate.

MATERIALS AND METHODS

Animals and experimental design

The study was conducted on 42 adult male outbred white rats weighing 170-180 g. Animals were housed under standard vivarium conditions with free access to food and water and maintained on a standard laboratory diet throughout the experiment.

Rats were randomly divided into three experimental groups:

1. intact control group (n = 6);
2. rats receiving sodium benzoate at a dose of 30 mg/kg body weight (n = 18);
3. rats receiving sodium benzoate (30 mg/kg body weight) in combination with resveratrol (20 mg/kg body weight) (n = 18).

All substances were administered intragastrically once daily. The duration of the experiment was 28 days. Animals from the study groups were withdrawn from the experiment in equal numbers on days 14, 21 and 28 after the start of substance administration.

Chemicals and reagents

Sodium benzoate (E211) was used as the toxic agent and administered at a dose of 30 mg/kg body weight. Resveratrol was administered at a dose of 20 mg/kg body weight in the form of the phytocomplex Resverazin, containing resveratrol, red wine extract, and grape seed extract. Thiopental sodium was used for anesthesia during euthanasia procedures.

Sample collection

Animals were euthanized under thiopental sodium anesthesia (60 mg/kg body weight). Blood samples were collected by cardiac puncture and centrifuged at 3000 rpm for 30 min at room temperature (22-24°C) using a CM-6M centrifuge (Elmi Ltd., Riga, Latvia) to obtain serum. Liver tissue samples were excised, perfused with physiological saline, and homogenized (250 mg tissue) using a Silent Crusher S magnetic homogenizer.

Biochemical analysis

Thiobarbituric acid reactive substances (TBARS)

The level of thiobarbituric acid reactive substances (TBARS) was determined according to the method of Ohkawa et al. (1979), based on the reaction of malondialdehyde (MDA) with thiobarbituric acid (TBA) under acidic conditions and high temperature, forming a colored trimethine complex. Briefly, samples were mixed with 0.8% TBA in 1.5% trichloroacetic acid and heated in a boiling water bath (95-100°C) for 60 min. After cooling, the mixture was centrifuged to remove precipitated proteins. The absorbance of the supernatant was measured at 532 nm. A calibration curve was constructed using 1,1,3,3-tetramethoxypropane in the concentration range of 0–10 μmol/L [19].

Oxidative modification of proteins (OMP)

Protein carbonyl content was determined according to Levine et al. (1990), based on the reaction of carbonyl groups with 2,4-dinitrophenylhydrazine (DNPH) to form stable hydrazone derivatives. Samples were incubated with 0.1% DNPH in 2 M HCl for 60 min at room temperature in the dark. Proteins were precipitated with trichloroacetic acid and washed with an ethanol-ethyl acetate mixture. The final precipitate was dissolved in 8 M urea. Optical density was measured at 370 nm (ketone derivatives) and 430 nm (aldehyde derivatives). The calibration range corresponded to 0–5 nmol carbonyl μmol/g protein [20].

Reduced glutathione (GSH)

Reduced glutathione content was determined by the Ellman method (Ellman, 1959), based on the reaction of sulfhydryl groups with 5,5'-dithiobis(2-

nitrobenzoic acid) (DTNB), forming a yellow-colored 5-thio-2-nitrobenzoic acid anion. Samples were mixed with phosphate buffer (pH 7.4) and DTNB reagent and incubated for 10 min at room temperature. Absorbance was measured at 412 nm. A calibration curve was prepared using standard glutathione solutions in the range of 0–100 μmol/L [21].

Catalase activity

Catalase activity was determined spectrophotometrically according to Korolyuk et al. (1988), based on the decomposition of hydrogen peroxide (H_2O_2). The residual hydrogen peroxide forms a stable yellow complex with ammonium molybdate. After incubation of samples with H_2O_2 at 37°C for 10 min, the reaction was stopped by adding 4% ammonium molybdate. Absorbance was measured at 410 nm against a control sample [22].

Ceruloplasmin

Ceruloplasmin concentration was determined by the p-phenylenediamine oxidation method according to Ravin (1961). The reaction mixture was incubated at 37°C for 30 min, and the reaction was stopped with sodium azide. Absorbance was measured at 540 nm [23].

Instrumentation

All spectrophotometric measurements were performed using a ULAB-108UA spectrophotometer (ULAB, Ukraine).

Statistical analysis

Statistical analysis was performed using STATISTICA 13 software (TIBCO Software Inc., Palo Alto, CA, USA). Data are presented as mean ± standard deviation (M ± SD). Differences between independent groups were evaluated using the Mann-Whitney U test. Results were considered statistically significant at $p < 0.05$.

Ethics approval

All experimental procedures involving animals were conducted in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (ETS No. 123) and were approved by the Bioethics Committee of Horbachevsky Ternopil National Medical University (No. 4 25.10.2024). All efforts were made to minimize animal suffering and to reduce the number of animals used.

RESULTS

Exposure of rats to sodium benzoate at a dose of 30 mg/kg body weight resulted in a pronounced activation of lipid peroxidation processes in both blood serum and liver tissue. As shown in Table 1, TBARS levels in blood serum increased significantly throughout the experimental period. On day 14, TBARS concentration was elevated compared to the control group, and a further progressive increase was observed on days 21 and 28. By the end of the experiment, TBARS levels in blood serum exceeded control values by 5.1-fold ($p \leq 0.05$).

In rats exposed with sodium benzoate, a progressive and significant ($p \leq 0.05$) increase in the content of TBARS in the blood serum was observed throughout the study period. On the 28th day of the experiment, this indicator exceeded the level of intact animals by 5.1 times. A similar trend was observed in the liver:

Table 1. TBARS levels in blood serum (μmol/L) and liver tissue (μmol/kg) of rats exposed to sodium benzoate and treated with resveratrol (M ± SD, n = 42)

Animal groups	Research time, days		
	14	21	28
Blood serum			
Control group	2.74 ± 0.14		
Sodium benzoate (30 mg/kg)	11.81 ± 0.42*	13.46 ± 0.36*	14.06 ± 0.31*
Sodium benzoate (30 mg/kg) + resveratrol (20 mg/kg)	11.35 ± 0.21	10.02 ± 0.24**	7.91 ± 0.26**
Liver homogenates			
Control group	1.43 ± 0.09		
Sodium benzoate (30 mg/kg)	3.49 ± 0.19*	4.4 6 ± 0.14*	5.27 ± 0.11*
Sodium benzoate (30 mg/kg) + resveratrol (20 mg/kg)	3.30 ± 0.24	1.97 ± 0.09**	1.57 ± 0.06**

*$p \leq 0.05$ compared to the control group; **$p \leq 0.05$ compared to the sodium benzoate-exposed group

on the 28th day, the content of TBARS was 3.7 times higher compared to the control.

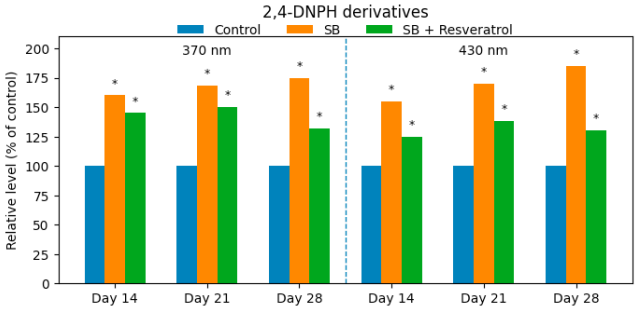
The use of resveratrol was accompanied by a decrease in the level of lipoperoxidation products. On the 14th day, only a tendency to decrease the indicator without statistical significance was noted. A significant decrease ($p \leq 0.05$) in the content of TBARS in the blood serum and liver was observed on the 21st and 28th days of the experiment. At the end of the study, the content of TBARS in the blood serum decreased by 1.8 times, and in the liver - by 3.4 times compared to the group of rats exposed to sodium benzoate.

Activation of free radical oxidation processes leads to the action of reactive oxygen species (ROS) and toxic metabolic products on the protein components of membranes and other proteins of the body, which causes their degradation and changes in structure. Along with the activation of lipoperoxidation processes, processes of oxidative modification of proteins occur.

The results of determining the content of 2,4-dinitrophenylhydrazones (2,4-DNPH) of neutral (370 nm) and basic (430 nm) nature in blood serum are given in Table 2.

In rats after administration of sodium benzoate at a dose of 30 mg/kg body weight, a significant ($p \leq 0.05$) increase in the content of both keto- and aldehyde-derived proteins in blood serum was noted throughout the experiment. The highest values of both fractions of 2,4-DNPH were recorded on the 28th day of the study.

The use of resveratrol led to a decrease in the levels of oxidative modification of proteins. A significant decrease in the content of 2,4-DNPH of a neutral nature was observed only on the 28th day of the experiment,



*$p \leq 0.05$ compared to the control group

Figure 1. Content of oxidative modification products of proteins (2,4-dinitrophenylhydrazones of neutral and basic nature) in liver tissue of rats exposed to sodium benzoate and treated with resveratrol

when this indicator was 1.3 times lower compared to the group of affected animals. The content of 2,4-DNPH of a basic nature was significantly reduced throughout the entire study period.

In the liver of rats after intoxication with sodium benzoate, a significant increase in the content of both fractions of modified proteins was also noted (Figure 1). After the use of resveratrol, their content decreased: on the 28th day, the level of 2,4-DNPH(370) was 49%, and 2,4-DNPH(430) was 43% lower than in the group of affected animals.

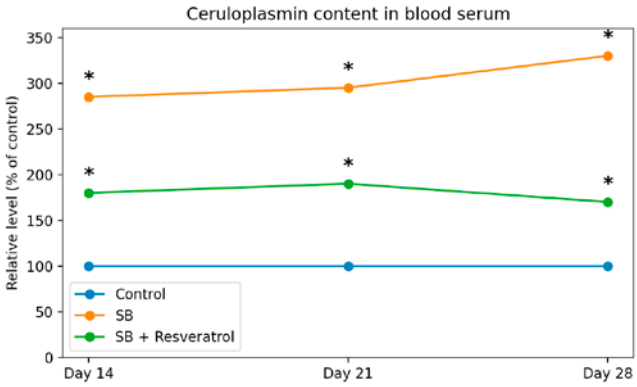
In our experiments, we investigated the content of ceruloplasmin – a protein with enzymatic activity, which is one of the first to enter the body's defense against free radicals (Figure 2).

The content of ceruloplasmin in the blood serum of rats exposed with sodium benzoate significantly ($p \leq 0.05$) increased throughout the experiment (Figure 2). On the 28th day of the study, this indicator

Table 2. Content of oxidative modification products of proteins in blood serum (μmol/g protein) of rats exposed to sodium benzoate and treated with resveratrol (M ± SD, n = 42)

Animal groups	Research time, days		
	14	21	28
2,4-DNPH(370) of neutral nature (keto derivatives)			
Control group	0.118 ± 0.005		
Sodium benzoate (30 mg/kg)	0.217 ± 0.007*	0.235 ± 0.006*	0.275 ± 0.008*
Sodium benzoate (30 mg/kg) + resveratrol (20 mg/kg)	0.211 ± 0.014	0.219 ± 0.005	0.204 ± 0.006**
2,4-DNPH(430) of basic nature (aldehyde derivatives)			
Control group	0.198 ± 0.010		
Sodium benzoate (30 mg/kg)	0.308 ± 0.010	0.333 ± 0.007*	0.380 ± 0.009*
Sodium benzoate (30 mg/kg) + resveratrol (20 mg/kg)	0.243 ± 0.012**	0.277 ± 0.005**	0.247 ± 0.006**

*$p \leq 0.05$ compared to the control group; **$p \leq 0.05$ compared to the sodium benzoate-exposed group



*p ≤ 0.05 compared to the control group

Figure 2. Ceruloplasmin content in blood serum of rats exposed to sodium benzoate and treated with resveratrol

exceeded the control level by 233%. The use of resveratrol contributed to a decrease in the content of ceruloplasmin during all periods of observation, but its values remained higher than the level of intact animals (by 65% on the 28th day).

The content of reduced glutathione in the blood serum and liver of rats exposed with sodium benzoate significantly ($p \leq 0.05$) decreased throughout the experiment (Table 3). By day 28, the content of reduced glutathione decreased by 4.2 times in serum and 1.7 times in liver. The use of resveratrol contributed to the restoration of the level of this indicator, which practically reached the control values.

Catalase activity in blood serum and liver tissue of rats exposed to sodium benzoate was significantly reduced (Table 4). The most pronounced decrease was

Table 3. Reduced glutathione levels in blood serum (μmol/L) and liver tissue (μmol/kg) of rats exposed to sodium benzoate and treated with resveratrol (M ± SD, n = 42)

Animal groups	Research time, days		
	14	21	28
Blood serum			
Control group	1.48 ± 0.06		
Sodium benzoate (30 mg/kg)	0.82 ± 0.03*	0.54 ± 0.03*	0.35 ± 0.03*
Sodium benzoate (30 mg/kg) + resveratrol (20 mg/kg)	1.32 ± 0.09**	1.42 ± 0.09**	1.50 ± 0.08**
Liver homogenates			
Control group	1.77 ± 0.06		
Sodium benzoate (30 mg/kg)	1.52 ± 0.03*	1.29 ± 0.06*	1.03 ± 0.06*
Sodium benzoate (30 mg/kg) + resveratrol (20 mg/kg)	1.60 ± 0.07	1.65 ± 0.09**	1.69 ± 0.10**

*p ≤ 0.05 compared to the control group; **p ≤ 0.05 compared to the sodium benzoate-exposed group

Table 4. Catalase activity in blood serum (μkat/L) and liver tissue (μkat/kg) of rats exposed to sodium benzoate and treated with resveratrol (M ± SD, n = 42)

Animal groups	Research time, days		
	14	21	28
Blood serum			
Control group	1.59±0.16		
Sodium benzoate (30 mg/kg)	1.00±0.06*	0.76±0.06*	0.78±0.07*
Sodium benzoate (30 mg/kg) + resveratrol (20 mg/kg)	1.20±0.07	1.36±0.09**	1.47±0.08**
Liver homogenates			
Control group	2.40±0.14		
Sodium benzoate (30 mg/kg)	1.62±0.07*	0.90±0.09*	0.58±0.05*
Sodium benzoate (30 mg/kg) + resveratrol (20 mg/kg)	2.29±0.17**	2.14±0.20**	2.45±0.17**

*p ≤ 0.05 compared to the control group; **p ≤ 0.05 compared to the sodium benzoate-exposed group

observed on day 28, when catalase activity in blood serum was approximately threefold lower than control values, while in liver tissue it was reduced by 4.1-fold compared to intact animals. Resveratrol administration resulted in a significant increase in catalase activity; in liver tissue, normalization of this parameter was observed as early as day 14 of the experiment.

DISCUSSION

Our results confirm that prolonged administration of sodium benzoate at a dose of 30 mg/kg body weight leads to the development of oxidative stress, which is manifested by the activation of lipoperoxidation processes, increased oxidative modification of proteins and inhibition of enzymatic and non-enzymatic links of the antioxidant system. The established changes are progressive in nature and increase with increasing duration of exposure, which indicates a cumulative effect of the toxicant [3, 4, 8, 9].

Literature data indicate that the effect of sodium benzoate on the prooxidant-antioxidant balance is dose-dependent. Under the conditions of administration of doses close to the permissible daily intake, changes in oxidative stress indicators are moderate or compensatory. At the same time, the use of increased doses (25-50 mg/kg and more) is accompanied by a significant increase in the level of TBARS the accumulation of oxidatively modified proteins and a decrease in catalase activity and glutathione content. Our results are consistent with these observations, since activation of lipoperoxidation was recorded already on the 14th day of the experiment, and maximum depletion of the antioxidant system on the 28th day [17, 18, 24, 25].

The results obtained may be associated with increased generation of reactive oxygen species, impaired mitochondrial respiration, and depletion of the glutathione detoxification pathway. A decrease in catalase activity and reduced glutathione levels indicates insufficient enzymatic neutralization of hydrogen peroxide and other reactive metabolites. An increase in ceruloplasmin levels is likely to be compensatory and reflects activation of the antioxidant defense system in response to excessive production of free radicals [13, 15, 17].

The use of a resveratrol-containing agent led to a significant decrease in the intensity of lipoperoxidation and oxidative modification of proteins, as well as to the restoration of antioxidant system parameters. A significant increase in catalase activity and a decrease in ceruloplasmin content in the studied tissues were observed. The use of resveratrol also contributed to the restoration of the functional activity of the glutathione system by increasing the content of reduced glutathione in the blood serum of rats affected by sodium benzoate [26-28].

Our results are consistent with the data of other researchers who have demonstrated that resveratrol-containing drugs have the ability to repair damage caused by active forms of reactive oxygen species. The regenerative effect of resveratrol is probably due to the combination of its direct antiradical activity and the ability to modulate the endogenous antioxidant system. As a polyphenolic compound, resveratrol is able to neutralize reactive oxygen species and interrupt the chain reactions of lipoperoxidation. This is consistent with our data on the normalization of the glutathione pool and catalase activity under the toxic effects of sodium benzoate.

CONCLUSIONS

Subchronic administration of sodium benzoate at a dose of 30 mg/kg body weight induces significant oxidative stress in rats, as evidenced by enhanced lipid peroxidation, increased oxidative modification of proteins, and disruption of antioxidant defense mechanisms in blood serum and liver tissue.

Resveratrol administration significantly attenuates sodium benzoate–induced oxidative damage by reducing lipid peroxidation and protein oxidation and by restoring reduced glutathione levels and catalase activity. These findings indicate the protective potential of resveratrol-containing formulations against preservative-induced oxidative stress.

Conflict of interest

The authors declare no conflict of interest.

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