Biol. Stud. 2026, 20(2), 125–136 • https://doi.org/10.30970/sbi.2002.879
www.https://publications.lnu.edu.ua/journals/index.php/biology

UDC: 577.21:616.36-008.6

BIOCHEMICAL INDICATORS OF LIVER FUNCTIONAL STATE IN RATS UNDER EXPOSURE TO THE CYTOTOXIC XENOBIOTIC DIETHYL PHTHALATE

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Ketsa, O., Rakhmatova, K., & Voloschuk, O. (2026). Biochemical indicators of liver functional state in rats under exposure to the cytotoxic xenobiotic diethyl phthalate. *Studia Biologica*, 20(2), 125–136. doi:10.30970/sbi.2002.879

Background. The widespread use of phthalates, including diethyl phthalate (DEP), in industrial and household products raises concerns about their potential hepatotoxic effects. The liver, as the central organ of detoxification and metabolism, is particularly vulnerable to the toxic effects of xenobiotics, especially DEP. **Objective**: this study aimed to assess the indicators of liver functional state in rats under exposure to the cytotoxic xenobiotic diethyl phthalate.

Materials and Methods. The experiment was conducted on adult white rats, which were divided into three groups: the control group and two experimental groups that received DEP orally at doses of 2.5 mg/kg and 5 mg/kg for 21 days. Biochemical markers of hepatocyte damage and cholestasis, including the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), the levels of total and direct bilirubin, as well as the albumin-to-globulin ratio, were analyzed in blood serum using standard spectrophotometric and automated methods.

Results and Discussion. It was found that administration of DEP led to dose- and time-dependent changes in markers of liver functional state. At a dose of 5 mg/kg, DEP caused a significant increase in ALT and AST activity as early as on day 14 of xenobiotic exposure, indicating hepatocyte damage. By day 21 of the experiment, both doses of the xenobiotic induced a marked elevation in all studied serum markers of liver function. At the same time, increased GGT and ALP activity, along with elevated levels of total and direct bilirubin, indicated the development of cholestatic dysfunction. In addition, a decrease in the albumin-to-globulin ratio in both DEP-treated groups over three weeks indicated impaired protein-synthesizing function of the liver.

Conclusion. The xenobiotic DEP induces a combined hepatocellular and cholestatic liver dysfunction in a dose- and time-dependent manner. The observed biochemical changes indicate oxidative stress and disrupted energy metabolism as key mechanisms underlying DEP-induced hepatotoxicity. The obtained results highlight the importance of further research into the molecular pathways of phthalate-induced liver injury and support the development of biocompatible materials and early diagnostic tools for hepatotoxicity.

Keywords: diethyl phthalate, liver function, hepatotoxicity, cholestasis, biochemical markers

INTRODUCTION

In the modern context of a rapid increase in chemical load on the environment, the problem of toxic effects of xenobiotics on human and animal organisms is becoming increasingly relevant. Over the past decades, there has been a steady rise in the amount of chemical substances entering the environment due to intensive development of industry, agriculture, and household consumption (Thacharodi *et al*., 2023). A significant portion of these substances are xenobiotics – chemical compounds foreign to living organisms, which can exert negative effects on metabolism, cellular structures, and the functioning of internal organs (Bhatt *et al*., 2021; Štefanac *et al*., 2021).

Among the most common groups of harmful compounds are phthalates – esters of phthalic acid widely used as plasticizers in the production of polymeric materials, as well as components of cosmetics, perfumes, food packaging, medical devices, pharmaceutical products, and household goods (Arrigo *et al*., 2023; Mariana & Cairrao, 2023). Among them, particular attention is drawn to the most widespread phthalate – diethyl phthalate (DEP), characterized by high chemical stability, lipophilicity, and the ability to penetrate the body through various routes – via the skin, respiratory tract, or food intake (Weaver *et al*., 2020). Numerous studies have demonstrated that prolonged or excessive exposure to DEP can lead to the development of various pathological changes, including reproductive dysfunction (Hasan *et al*., 2024), immunosuppression (Fan *et al*., 2025), neurotoxicity (Tran *et al*., 2021; Chen *et al*., 2024), cardiotoxicity (Mariana *et al*., 2023), and hepatotoxicity (Zhao *et al*., 2025).

Particular attention among these effects is given to its negative impact on the liver – a key organ of detoxification and metabolism, which is the first to respond to the entry of xenobiotics and bears the greatest burden during their neutralization (Feng *et al*., 2024). The liver plays a primary role in the metabolism of DEP, as a result of which it undergoes structural and functional changes that may serve as early markers of toxicity and predictors of subsequent systemic disorders (Chen *et al*., 2024; Ketsa *et al*., 2024).

Since the liver is the primary target of xenobiotic action, the toxic effect of DEP on the liver may manifest as impaired permeability of cell membranes, activation of free radical oxidation processes of biomolecules, imbalance of the antioxidant system, and disturbances in protein, carbohydrate, and lipid metabolism. In this regard, studying biochemical markers of the liver's functional state – such as the activity of serum transaminases (alanine aminotransferase (ALT), aspartate aminotransferase (AST)), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), levels of various bilirubin fractions, and other blood parameters – is of particular importance, as they allow for an objective assessment of the degree of toxic liver injury.

This study addresses the need for an in-depth investigation of the mechanisms of DEP's toxic effects on the liver, with the aim of timely diagnosis and prevention of potential adverse consequences of its exposure. Furthermore, the obtained results may serve as a basis for the further development of measures for the prevention and correction of toxic liver damage.

The aim of the work is to assess the indicators of liver functional state in rats under the influence of the cytotoxic xenobiotic diethyl phthalate.

MATERIALS AND METHODS

Experimental studies were conducted on sexually mature white outbred rats weighing 160–200 g. The animals were kept under standard vivarium conditions in accordance with the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (1986) and the guidelines of the VII National Congress on Bioethics "General Ethical Principles for Experiments on Animals" (Kyiv, 2019) (the Minutes of the meeting of bioethics commission of ES Institute of Biology, Chemistry and Bioresources, Yuriy Fedkovich Chernivtsi National University No 3 dated October 1, 2024). The rats were randomly divided into three groups of 18 animals each: Group I – control group (intact animals); Group II – animals receiving DEP at a dose of 2.5 mg/kg body weight; Group III – animals receiving DEP at a dose of 5 mg/kg body weight.

DEP was administered orally to the rats once daily by gavage for 21 days in the form of a commercial preparation, as a pure, oil-like liquid, without any additional solvents. The doses were selected based on literature data regarding phthalate toxicity (Mondal *et al*., 2020) and were adjusted according to the conditions of the experiment.

The animals were anesthetized using ether, after which the carotid artery was transected to collect arterial blood, resulting in the euthanasia of the animals. Euthanasia of laboratory animals was performed on the 21st day after the start of DEP administration. Blood samples were collected from the carotid artery into glass centrifuge tubes. To obtain serum, the samples were centrifuged at 1500 rpm for 10 min.

The main biochemical indicators characterizing the functional state of the hepatobiliary system were determined in the blood serum, namely the activities of ALT, AST, GGT, ALP, as well as the levels of total and direct bilirubin, and the results of the thymol turbidity test. Biochemical analyses were conducted using an automatic analyzer HTI BioChem FC-120 (USA).

ALT activity was estimated by the amount of pyruvate formed, which, in the presence of lactate dehydrogenase, was reduced to lactate with the simultaneous oxidation of NADH to NAD^+. The rate of NADH oxidation is directly proportional to ALT activity in the sample. AST activity was determined enzymatically based on the conversion of aspartate and α-ketoglutarate to glutamate and oxaloacetate. Oxaloacetate, in the presence of malate dehydrogenase, was reduced to malate with the simultaneous oxidation of NADH to NAD^+. The enzyme activity was measured photometrically by the rate of decrease in NADH concentration, which is directly proportional to AST activity in the sample. (Thomas, 1998). GGT activity was determined by the rate of formation of 2-nitro-5-aminobenzoic acid, and the result was expressed in units per liter (U/L) (Schumann, 2002). The enzymatic activity of ALP was assessed by the rate of formation of p-nitrophenol. The determination of total bilirubin was based on its ability to be oxidized in an acidic medium in the presence of vanadate and detergent, forming a yellow product whose

concentration is directly proportional to the bilirubin content. The principle of the method for determining direct bilirubin was based on its reaction with diazotized sulfanilic acid to form azobilirubin, which had an absorption maximum at 560 nm. The color intensity was directly proportional to the concentration of direct bilirubin in the sample (Simmons, 1968).

The protein-synthesizing function of the liver was evaluated by measuring the albumin-to-globulin ratio (A/G ratio). Serum protein fractions were analyzed using phosphate buffer kits (Filicit-Diagnostics, Ukraine).

Statistical analysis was performed using the open-source software R (version 4.x). For each time point (day 14 and day 21), one-way ANOVA was applied to evaluate the effect of DEP dose on the measured biochemical parameters. For pairwise comparisons between groups, Tukey's multiple comparison post-hoc test was performed using the TukeyHSD() function in R. Differences were considered statistically significant at $P \leq 0.05$. Data are presented as mean ± standard deviation (SD).

RESULTS AND DISCUSSION

The assessment of biochemical indicators of the liver functional status showed that exposure to DEP causes dose-dependent changes in the activity of key enzymes associated with hepatocellular damage and cholestasis.

The results of the study demonstrated that on the 14th day of the experiment, in animals receiving DEP at a dose of 2.5 mg/kg body weight, the enzymatic activities of ALT and AST did not differ from those of the control group, indicating the absence of significant hepatocyte membrane disruption at an early stage under conditions of low toxicant exposure (**Fig.1**), indicating preservation of hepatocyte integrity and the liver's compensatory capacity under minimal toxic load.

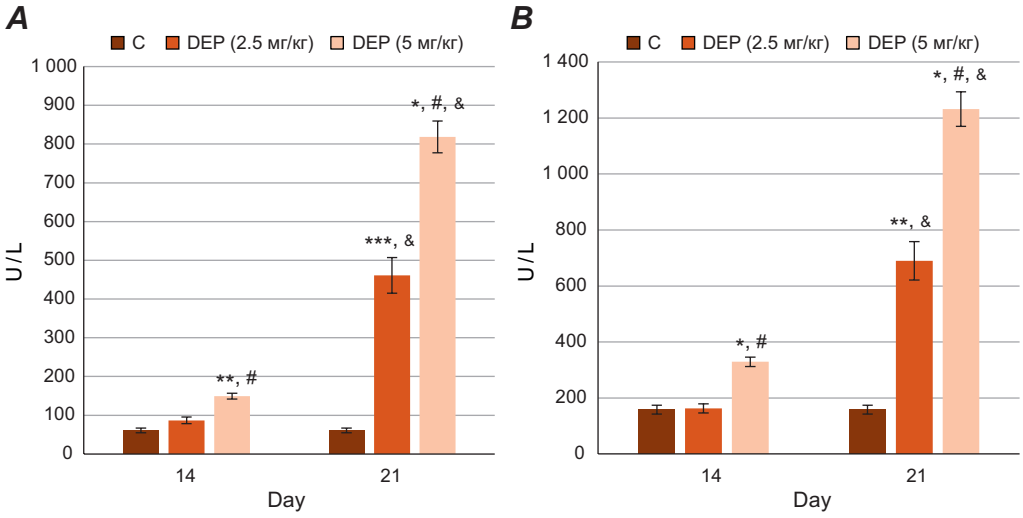

Fig. 1. Alanine aminotransferase (***A***) and aspartate aminotransferase (***B***) activities in the blood serum of rats under diethyl phthalate administration

Note (abbreviations used): C – control group (intact animals) (M ± m, n = 18); Group II – rats administered diethyl phthalate at 2.5 mg/kg body weight (M ± m, n = 18); Group III – rats administered diethyl phthalate at 5.0 mg/kg body weight (M ± m, n = 18). Symbols indicate statistical significance: * – $P < 0.05$; ** – $P < 0.01$; *** – $P < 0.001$ compared with the control group; # – significant difference between Group III and Group II; & – significant difference compared with day 14 within the same group

In contrast, animals administered DEP at a dose of 5 mg/kg showed a significant increase in ALT activity by 2.5 times (**Fig. 1*A***) and AST activity by 2.1 times (**Fig. 1*B***) compared to intact animals (P ≤ 0.05). The elevated levels of these transaminases indicate early manifestations of hepatocyte cytolysis caused by the toxic effect of the xenobiotic.

On day 21 of the study, more pronounced impairments were observed in animals of both experimental groups. In the group receiving the lower dose of DEP, ALT activity increased by 7.6 times (**Fig. 1*A***), and AST activity increased by 2.1 times (**Fig. 1*B***) compared to the control (P ≤ 0.05), indicating an escalation of toxic liver damage under prolonged exposure to DEP even at a lower dose. In Group III, these parameters were even higher: ALT activity increased by 13.5 times, and AST by 7.8 times relative to the control group (P ≤ 0.05) (**Fig. 1**). This dynamic confirms the presence of dose-dependent hepatocellular damage, likely due to oxidative stress, disruption of energy metabolism, and mitochondrial membrane damage, which are characteristic effects of phthalates (Zhao *et al*., 2024).

The study of GGT enzymatic activity, which reflects the state of the biliary system and serves as an indicator of cholestasis, showed that on the 14th day, this parameter in the group of animals receiving DEP at a dose of 2.5 mg/kg body weight did not differ from the control values. Meanwhile, in the group of rats administered DEP at a dose of 5 mg/kg, a moderate but significant increase in GGT activity by 2.1 times compared to the control was observed (P ≤ 0.05) (**Fig. 2**). This indicates the onset of biliary dysfunction under the influence of a higher dose of the toxicant.

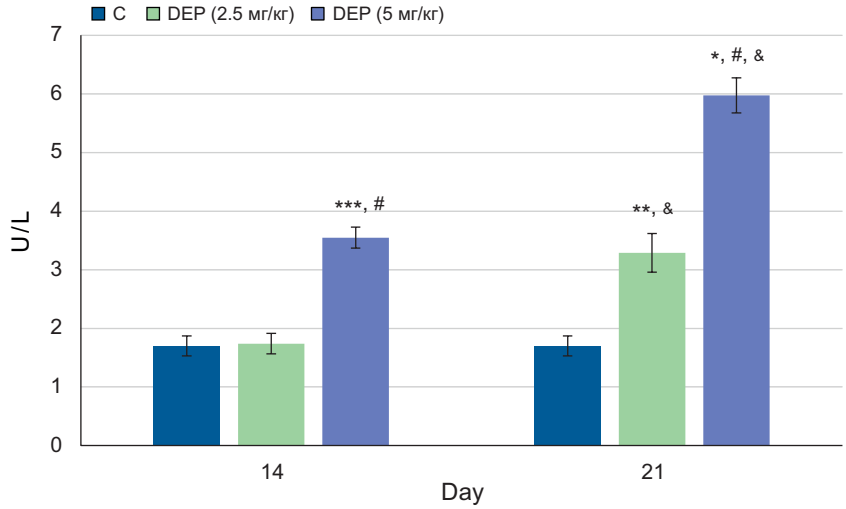

Fig. 2. γ-Glutamyltransferase enzymatic activity in the blood serum of rats under diethyl phthalate administration

On the 21st day, a clear increase in GGT activity was observed in all experimental groups. Thus, in animals that received DEP at a dose of 2.5 mg/kg, the enzyme activity increased by 1.9 times, while in animals receiving 5 mg/kg, it increased by 3.5 times compared to control values (P ≤ 0.05). The increase in GGT may be associated with both the impaired bile duct function and with the activation of the enzymatic antioxidant system in response to oxidative stress, induced by DEP (Ketsa *et al*., 2024).

The obtained results regarding the activity of transaminases and GGT indicate the development of dose-dependent hepatocellular damage and the formation of signs of bile duct dysfunction under the influence of DEP. For a comprehensive assessment of liver functional status, changes in ALP activity, which is an important marker of cholestasis and reflects the integrity disruption of the bile ducts, were also analyzed.

Analysis of the study results showed that on the 14th day of the experiment, in rats that received DEP at a dose of 2.5 mg/kg body weight, ALP activity did not significantly differ from the control group values, indicating the preservation of functional capacity of the biliary system at an early stage under conditions of lower toxic load. At the same time, in the group of animals administered DEP at a dose of 5 mg/kg, a statistically significant increase in ALP activity by 1.6 times compared to the control was observed ($P \leq 0.05$), which may indicate initial manifestations of intrahepatic cholestasis and compensatory enhancement of enzyme synthesis.

Three weeks of administration of the lower DEP dose contributed to an increase in ALP activity by 1.6 times relative to control values ($P \leq 0.05$), confirming the gradual deepening of hepatobiliary system dysfunction with prolonged exposure even to low doses of the toxicant. In animals that received the higher DEP dose, a more pronounced increase in ALP activity was observed – 3.4 times compared to intact animals ($P \leq 0.05$). Such dynamics are characteristic of the development of progressive cholestasis against the background of oxidative stress induced by phthalate exposure.

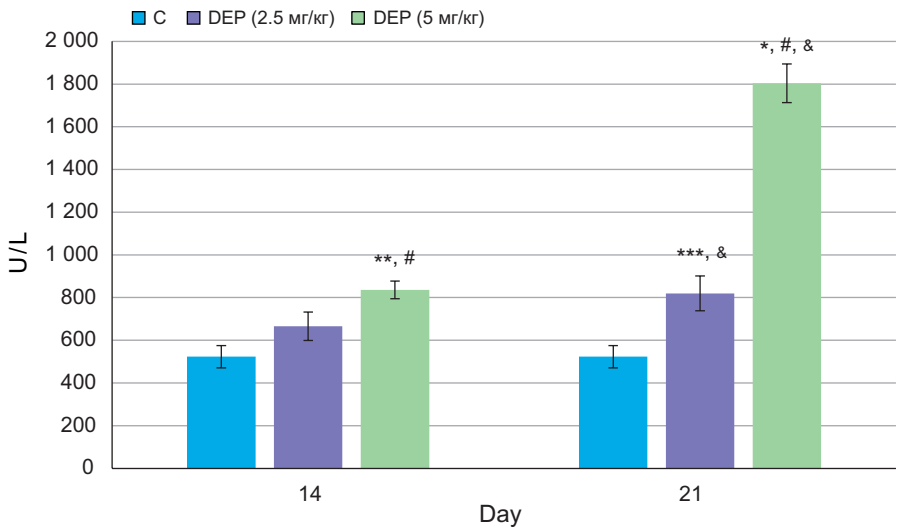

Fig. 3. Alkaline phosphatase enzyme activity in the serum of rats under diethyl phthalate administration

For a more detailed assessment of hepatobiliary system impairments, levels of total and direct bilirubin were examined. After two weeks of xenobiotic administration, significant changes in total bilirubin concentration were observed in animals receiving DEP at a dose of 5 mg/kg, with an average increase of 50 % compared to the control ($P \leq 0.05$) (**Fig. 4*A***).

The level of direct bilirubin in this group also showed a tendency to increase in the blood serum – 1.6 times compared to the intact animals (**Fig. 4*B***), which may indicate the onset of impaired conjugation and release of bilirubin into the bloodstream.

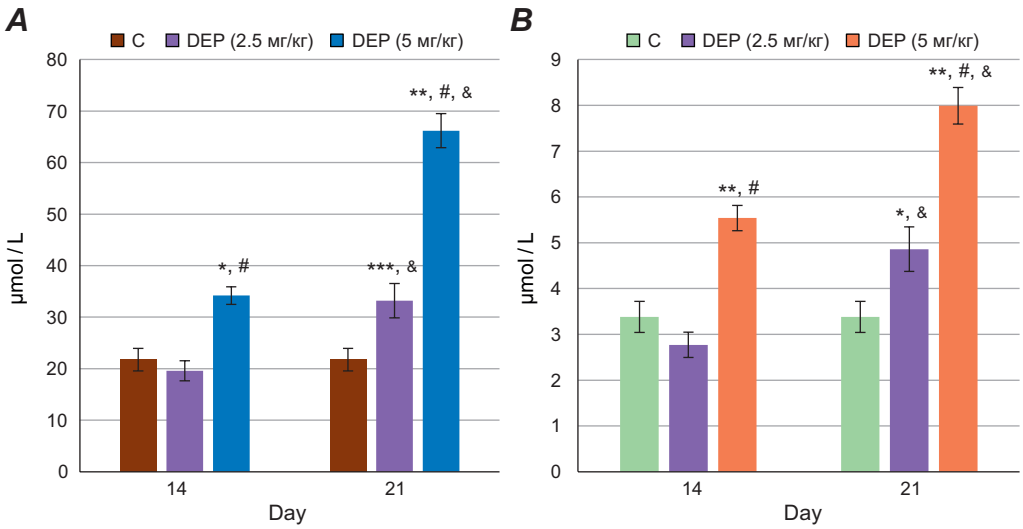

Fig. 4. Levels of total (***A***) and direct (***B***) bilirubin in the serum of rats under diethyl phthalate administration

More pronounced changes were observed on the 21st day of the study. In the group of rats receiving DEP at a dose of 2.5 mg/kg, total bilirubin increased by 1.6 times, and direct bilirubin by 1.4 times compared to the control ($P \leq 0.05$) (**Fig. 4**).

In the group of animals administered the higher dose of the toxicant, the increase was more significant: total bilirubin levels exceeded control values by 3 times, and direct bilirubin by 2.4 times compared to the control ($P \leq 0.05$) (**Fig. 4**).

The obtained results indicate that DEP exposure leads not only to hepatocyte damage and activation of cytolytic enzymes but also to the development of pronounced cholestatic manifestations and disturbances in pigment metabolism, which are dose-dependent. The increase in direct bilirubin levels alongside elevated ALP and GGT activities confirms injury to both the liver parenchyma and bile ducts, likely caused by the toxic effects of DEP through mechanisms involving oxidative stress, mitochondrial dysfunction, and damage to hepatocyte membrane structures (Ketsa *et al*., 2024; de Tymowski *et al*., 2019).

Considering the obtained results on changes in total and direct bilirubin levels, which indicate the development of cholestatic disorders and progressive hepatocyte damage, the albumin-to-globulin ratio (A/G ratio) was evaluated for a more in-depth assessment of the liver's synthetic function. This indicator reflects the balance between albumin, which is synthesized in hepatocytes, and globulins, a relative increase of which may occur in response to inflammatory processes and impaired protein metabolism. The A/G ratio allows assessment of dysproteinemia and disturbances in protein-synthetic liver function associated with parenchymal damage.

The study results showed that on the 14th day of the experiment, in animals receiving DEP at a dose of 2.5 mg/kg, the albumin-to-globulin ratio did not differ from control values, indicating the preservation of the liver's protein-synthetic function at the early stage of toxic exposure (**Fig. 5**). At the same time, in the group of animals administered DEP at a dose of 5 mg/kg, there was a tendency toward a decrease in the A/G ratio – on average by 38 % compared to the control (**Fig. 5**), which may reflect the development of dysproteinemia, a relative decrease in albumin synthesis, and impairment of the liver's synthetic function.

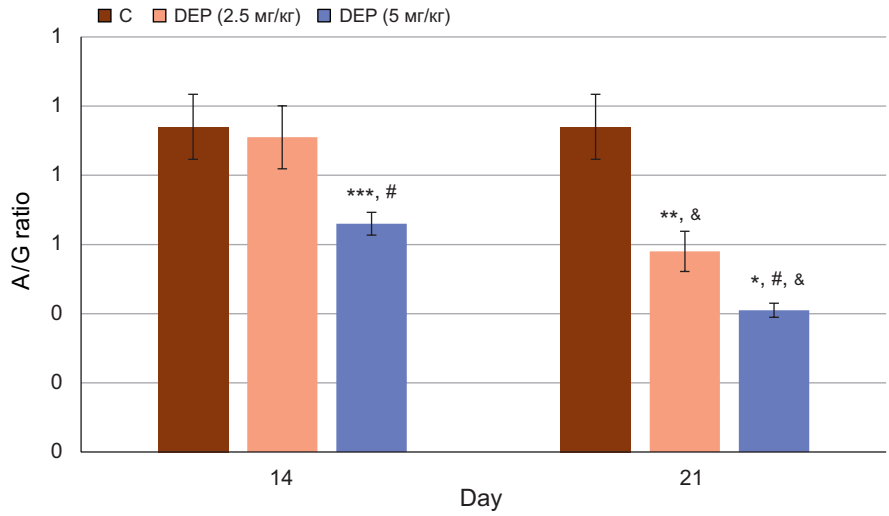

Fig. 5. Albumin-to-globulin ratio in the blood of rats under diethyl phthalate administration

More pronounced changes were observed on the 21st day of the study. In the group of animals receiving the lower dose of DEP, the albumin-to-globulin ratio decreased by 1.6 times compared to the control ($P \leq 0.05$), indicating the development of significant impairments in the synthetic function of hepatocytes and the onset of dysproteinemia. In rats administered DEP at a dose of 5 mg/kg, the A/G ratio decreased by 2.3 times relative to control values ($P \leq 0.05$), confirming pronounced disturbances in protein metabolism, a reduction in albumin synthesis, and a substantial decline in liver functional activity (**Fig. 5**).

Thus, changes in the albumin-to-globulin ratio are consistent with the dynamics of hepatic enzyme activity and bilirubin levels, indicating complex hepatocellular damage and the gradual development of hepatobiliary system dysfunction under dose-dependent DEP exposure.

Furthermore, the experimental results support the important role of oxidative stress in the pathogenesis of hepatobiliary injury. Although oxidative stress parameters were not directly assessed in the present study, the observed biochemical changes are consistent with our previous findings demonstrating activation of lipid peroxidation and mitochondrial dysfunction under DEP exposure (Ketsa *et al*., 2024).

The toxic effects of DEP are likely associated with excessive formation of reactive oxygen species (ROS) and depletion of the antioxidant defense system (Zhao *et al*., 2025; Ketsa *et al*., 2024), leading to peroxidative damage of hepatocyte membrane lipids, increased membrane permeability, and disruption of cellular structural integrity.

The initiation of these processes may contribute to suppression of the liver's protein-synthetic function, as evidenced by alterations in the albumin-to-globulin ratio at the later stages of the experiment. These findings indicate the involvement of mitochondria-related mechanisms in DEP toxicity (Ketsa *et al*., 2024), combining membrane injury in hepatocytes with functional metabolic disturbances.

Thus, the study revealed novel aspects of DEP's toxic effects, including: 1) the establishment of a combined (cytolytic–cholestatic) nature of hepatotoxicity; 2) confirmation of the dose- and time-dependence of biochemical changes; 3) substantiation of

the role of oxidative stress and mitochondrial dysfunction as key mechanisms of liver injury based on both current results and our previous studies; and 4) demonstration of preserved compensatory capacity of the liver at early stages of intoxication, which has prognostic significance for early detection of toxic effects.

The obtained data not only confirm the hepatotoxic potential of DEP but also expand current understanding of its pathogenic mechanisms, which is crucial for the development of diagnostic markers for early liver injury and the prevention of potential consequences of chronic phthalate exposure. The study results demonstrate that DEP induces impairments in hepatocellular and bile excretory liver functions, with the nature of these changes depending on both the dose of the xenobiotic and the duration of its administration.

CONCLUSION

The impact of DEP on the animal organism causes dose-dependent impairments in liver functional status, as the main homeostatic organ, manifested by combined cytolytic and cholestatic alterations. Increased aminotransferase activity indicates hepatocyte damage and activation of cytolytic processes, while elevated GGT, ALP activities, and direct bilirubin levels serve as markers of developing bile excretory dysfunction. The observed changes are likely associated with disturbances in protein metabolism and hepatic synthetic function induced by DEP exposure, as evidenced by alterations in the albumin-to-globulin ratio at later stages of the experiment following administration of both studied doses of the xenobiotic. The identified liver lesions exhibit a combined nature – from initial manifestations of cytolysis to pronounced cholestasis during prolonged xenobiotic exposure. These findings deepen the understanding of the molecular mechanisms underlying the hepatotoxic effects of phthalates and highlight the potential risks of prolonged DEP exposure on the hepatobiliary system. Given the widespread use of phthalates in industry and everyday life, the results of this study may be valuable for bioengineering detoxification systems, developing novel biosensor approaches for early diagnosis of hepatotoxicity, creating biocompatible materials with minimal toxic impact, and designing innovative bioengineering strategies for the prevention and correction of toxic liver injuries.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Human Rights: this article does not contain any studies with human subjects performed by any of the authors.

Animal Studies: all international, national and institutional guidelines for the care and use of laboratory animals were followed.

AUTHOR CONTRIBUTIONS

Conceptualization, [O.V.; O.M.]; methodology, [O.V.; K.V.]; validation, [O.V.; O.M.]; formal analysis, [O.V.; K.V.; O.M.].; investigation, [O.V.; K.V.]; resources, [O.V.; K.V.; O.M.]; data curation, [O.V.; K.V.; O.M.]; writing – original draft preparation, [O.V.; K.V.; O.M.]; writing – review and editing, [O.V.; O.M.]; visualization, [O.V.; K.V.; O.M.] supervision, [O.V.; K.V.; O.M.]; project administration, [O.V.]; funding acquisition, [-].

All authors have read and agreed to the published version of the manuscript.

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МОЛЕКУЛЯРНІ МАРКЕРИ ФУНКЦІОНАЛЬНОГО СТАНУ ПЕЧІНКИ ЩУРІВ ЗА ДІЇ ЦИТОТОКСИЧНОГО КСЕНОБІОТИКА ДІЕТИЛФТАЛАТУ

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Обґрунтування. Широке використання фталатів, включаючи діетилфталат (ДЕФ), у промислових і побутових виробах викликає занепокоєння щодо їхнього потенційного гепатотоксичного впливу. Печінка, будучи центральним органом детоксикації та метаболізму, особливо вразлива до токсичного впливу ксенобіотиків, зокрема, ДЕФ. Мета дослідження – оцінити показники функціонального стану печінки щурів за впливу цитотоксичного ксенобіотика діетилфталату.

Матеріали та методи. Експеримент проводили на дорослих білих щурах, яких розділили на три групи: контрольну та дві експериментальні групи, що отримували ДЕФ перорально в дозах 2,5 мг/кг і 5 мг/кг протягом 21 дня. Біохімічні маркери

пошкодження гепатоцитів і холестазу, включаючи активності аланінамінотрансферази (АЛТ), аспартатамінотрансферази (АСТ), γ-глутамілтрансферази (ГГТ), лужної фосфатази (ЛФ), рівнів загального та прямого білірубіну, а також співвідношення альбумінів до глобулінів, аналізували в сироватці крові за допомогою стандартних спектрофотометричних і автоматизованих методів.

Результати. Встановлено, що введення ДЕФ призвело до дозо- та часозалежних змін маркерів функціонального стану печінки. За введення ДЕФ у дозі 5 мг/кг спостерігали значне підвищення активності АЛТ і АСТ вже на 14-й день надходження ксенобіотика в організм, що свідчить про пошкодження гепатоцитів. На 21-шу добу експерименту обидві дози ксенобіотика викликали помітне підвищення вмісту в сироватці крові всіх досліджуваних маркерів функціонального стану печінки. Водночас підвищена активність ГГТ і ЛФ, разом із підвищеними рівнями загального та прямого білірубіну, вказувала на розвиток холестатичної дисфункції. Окрім того, зниження співвідношення альбумінів до глобулінів в обох групах, які отримували ДЕФ протягом трьох тижнів, свідчило про порушення білоксинтезуючої функції печінки.

Висновки. Ксенобіотик ДЕФ викликає комбіновану гепатоцелюлярну та холестатичну дисфункцію печінки дозо- і часозалежним чином. Виявлені біохімічні зміни свідчать про оксидативний стрес і порушення енергетичного обміну як ключові механізми, що лежать в основі гепатотоксичності ДЕФ. Отримані результати підкреслюють важливість подальших досліджень молекулярних шляхів пошкодження печінки, викликаного фталатом, і підтримують розробку біобезпечних матеріалів та ранніх діагностичних інструментів для гепатотоксичності.

Ключові слова: діетилфталат, функція печінки, гепатотоксичність, холестаз, біохімічні маркери

Received / Одержано 02 December, 2025 | Revision / Доопрацьовано 02 April, 2026 | Accepted / Прийнято 22 June, 2026 | Published / Опубліковано 25 June, 2026