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ANAEROBIC GLYCOLYSIS AND OXIDATIVE STRESS INTERRELATION IN ERYTHROCYTES UNDER ADMINISTRATION OF *CORNUS MAS* L. FRUIT EXTRACTS TO RATS WITH STREPTOZOTOCIN-INDUCED DIABETES MELLITUS

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Background. In diabetes mellitus (DM), analysis of changes in the biochemical profile of erythrocytes is the important stage of complex scientific research to clarify the mechanism of action of medicinal products based on plant raw materials. The fruits of *Cornus mas* L. are widely known. The biologically active compounds of these fruits show multiple biological effects. However, the effect of the fruit extracts of cornelian cherry on the functional state of erythrocytes in diabetes has not been sufficiently studied. The high glucose concentration in erythrocytes induces various structural and functional changes, which lead to numerous disturbances in their metabolism. Glucose transported into erythrocytes by facilitated diffusion via GLUT2 undergoes catabolic breakdown in anaerobic glycolysis (90 % of all glucose) and pentose phosphate pathway (the rest 10 %). ATP and reduced coenzymes of NADH + H^+ and NADPH + H^+ formed due to metabolism participate in maintaining the structure of hemoglobin. Enzymes of the antioxidant defense system, which prevent hemoglobin oxidation into methemoglobin, are especially important. Hyperglycemia and the development of oxidative stress in diabetes are the cause of a decrease in the activity of antioxidant enzymes and the accumulation of ligand forms of hemoglobin ($HbCO_2$, MetHb, HbA1*c*). Therefore, the work aimed to investigate the effect of extracts of red and yellow fruits of *Cornus mas* L. on the content of end products of the glycolytic breakdown of glucose in erythrocytes and biochemical markers of the antioxidant status of these blood cells in rats with streptozotocin-induced diabetes.

Materials and Methods. DM 1 type in animals was induced by intraperitoneal injection of streptozotocin. Experiments were performed on male Wistar rats, who, from the 10th day after diabetes induction, were administered *per os* extracts of red and yellow fruits of the cornelian cherry and loganic acid obtained from yellow fruits at a dose of 20 mg/kg of body weight for 14 days. On the 24th day of the experiment, the rats were decapitated under ether anesthesia, and blood was taken. The content of pyruvate and lactate (as the end products of anaerobic glycolysis) and L-lactate dehydrogenase activity were determined in plasma and erythrocytes, as well as biochemical markers of the antioxidant status of erythrocytes (activity of superoxide dismutase, catalase and glutathione peroxidase, level of reduced glutathione, TBA-reactive substances, concentration of oxidative modifications of proteins and advanced oxidation protein products).

Results. The activity of catalase, superoxide dismutase, glutathione peroxidase and the concentration of reduced glutathione significantly increased against the decrease in the content of oxidative modifications of proteins, advanced oxidation protein products, TBA-reactive substances, pyruvate, L-lactate, and lactate dehydrogenase in rats with DM after administration of the fruit extracts of the cornelian cherry. Noteworthy, these biochemical indicators made it possible to assess the intensity of anaerobic glycolysis and the antioxidant status of blood erythrocytes in streptozotocin diabetes.

Conclusions. Extracts of *Cornus mas* L. fruits might be potential natural drugs for the treatment of metabolic disorders in diabetes, as they have a corrective effect on the catabolic breakdown of glucose and the antioxidant defense system of erythrocytes, preventing the development of oxidative stress. It should be pointed out that the extract of red fruits of cornelian cherry showed the best effect among the studied extracts in normalizing these indicators.

Keywords: diabetes mellitus, erythrocytes, extracts of *Cornus mas* L. fruit, pyruvate, lactate, antioxidant enzymes

INTRODUCTION

Type 1 diabetes mellitus (DM) is the most common autoimmune chronic disease caused by the destruction of β-cells of the islets of Langerhans in the pancreas, which is characterized by insulin deficiency and, as a result, hyperglycemia (Kuchurka *et al.*, 2022; DiMeglio *et al.*, 2018). The morbidity of type 1 DM has been exponentially increasing by 2–5% annually worldwide (Rodrigues Oliveira *et al.*, 2023). In diabetes, a chronic increase in the level of glucose activates the biochemical reactions of reactive oxygen species (ROS) formation, so their excessive generation is an important factor in the development of diabetic complications, such as diabetic nephropathy and retinopathy, vascular thrombosis, also cardiovascular and vascular diseases as a whole (Buko *et al.*, 2018).

Erythrocytes are highly specialized blood cells that perform several important functions in the body. These cells are implemented in the vascular bed which they normally never leave (Wang *et al.*, 2021). They transport oxygen, carbon dioxide, amino acids, and medicinal substances, adsorbed to the surface of the plasma membrane, maintain the acid-alkaline, ion balance of blood and are involved in water-salt exchange. Erythrocytes play an important role in regulating the activity of the hemostasis system and execute many protective functions (Herance *et al.*, 2023; Kuhn *et al.*, 2017).

Under DM, erythrocytes undergo biochemical alterations, particularly, their aggregation ability intensifies, structural deformations and changes in the composition of membrane phospholipids, and disturbances in energy metabolism with depletion of adenosine triphosphate (ATP) levels occur (Herance *et al.*, 2023). Glucose transport, the concentration of which increases in the blood due to diabetes, is enhanced by facilitated diffusion via GLUT2 into erythrocytes with a subsequent involvement in metabolic transformations. This monosaccharide undergoes catabolism in anaerobic glycolysis (90% glucose) and pentose phosphate pathway (the rest 10%). ATP and reduced coenzymes of NADH + H^+ and NADPH + H^+ formed as a result of metabolism are involved in maintaining the structure of hemoglobin. Due to the absence of mitochondria, anaerobic glycolytic breakdown of glucose is the main energy source for erythrocytes. ATP, as a product of glycolysis, is a necessary energy substance for various biochemical reactions in erythrocytes to support their physiological functions, in particular, the transmembrane exchange of ions and organic metabolites (Wang *et al.*, 2021).

Every day about 1400 mmol of lactate is formed in the human body. The main sources of lactate are skin, erythrocytes, brain, muscles and intestines. The amount of lactate increases in the body when it is needed for rapid resynthesis of ATP, which causes a sharp rise in the rate of glycolysis. Under such conditions, pyruvate, the final product of glycolysis, is reduced to L-lactate. This reaction is catalyzed by lactate dehydrogenase (LDH, EC 1.1.1.27), which oxidizes the NADH + H^+ to NAD^+ and is again involved in glycolysis processes. If this does not happen, glycolysis will stop due to a deficiency of oxidized NAD^+. Accumulation of lactate affects the glucose breakdown, as it slows the overall rate of glycolysis, reduces the affinity of phosphofructokinase enzyme (EC 2.7.1.11) for ATP and fructose-6-phosphate and causes the dissociation of the active tetrameric form of phosphofructokinase into less active dimers (Boretsky *et al.*, 2023).

In the conditions of intracellular hyperglycemia, not only intensive catabolic glycolysis occurs, but also autooxidation of glucose, which is one of the main mechanisms of the formation of free radicals in erythrocytes. Oxidative stress, which develops against the increased glucose concentration, is characterized by an imbalance between the formation of ROS and antioxidant defense mechanisms and plays a significant role in the pathophysiology of erythrocytes. These blood cells are the first ones negatively affected by endogenous and exogenous oxidants (Orrico *et al.*, 2023).

DM refers to a group of diseases that are difficult to treat, despite significant progress in medical and biological technologies and extensive research on this pathology (Wang *et al.*, 2021). This necessitates the search for more effective schemes of therapy for this endocrine disease. Besides, new antidiabetic drugs are worthy to create based on plant raw materials, which would prevent the development of complications and improve the quality of life in diabetic patients (Kuznetsova *et al.*, 2016). The fruits of cornelian cherry are widely known. They are used in a number of medical practices due to the presence of biologically active compounds in them (Dzydzan *et al.*, 2019; 2020; Klymenko *et al.*, 2021). These compounds show multiple biological effects, e.g. antioxidant, anti-inflammatory, antibacterial activity and especially significant antidiabetic properties (Dzydzan *et al.*, 2022; Brodyak *et al.*, 2023). However, the effect of the fruit extracts of the cornelian cherry on the functional state of erythrocytes in diabetes has not been sufficiently studied. Therefore, the work aimed to investigate the effect of extracts of red and yellow fruits of cornelian cherry (*Cornus mas* L.) and the iridoid

glycoside of these fruits – loganic acid on the content of end products of the glycolytic breakdown of glucose in erythrocytes and biochemical markers of the antioxidant status of these blood cells in rats with streptozotocin-induced diabetes.

MATERIALS AND METHODS

Animal experiments. The research was conducted on male Wistar rats. The animals were kept in a vivarium and had free access to food and water. All experiments were performed according to international bioethical requirements (Directive 2010/63/EC of the European Parliament of October 22, 2010 on the protection of animals used in scientific research and the National Institutes of Health Guide for the care and use of laboratory animals, 1978). The bioethical examination of the experiments carried out at the Biological Faculty of the Ivan Franko National University of Lviv was executed in the form of a protocol No. 43-03-2024 of March 20, 2024.

Type 1 diabetes in animals was induced by intraperitoneal injection of streptozotocin (STZ) (Sigma-Aldrich, St. Louis, MO, USA) at a dose of 55 mg/kg rat weight. Glucose concentration was determined by the glucose oxidase method using the analytical kit "Filisit-Diagnostika" (Dnipro, Ukraine). Animals with a glucose level of over than 12 mmol/L were used in the experiment. The rats were divided into 5 groups: the first group – control; the second group – animals with streptozotocin-induced DM; the third, fourth, and fifth groups – rats with STZ-induced DM that were administered the extract of red fruits ("Podolski" cultivar – BDPA 10462, ripe fruits of red color), extract of yellow fruits ("Yantarnyi" – BDPA 14131 and "Flava" cultivars – BDPA 8795, ripe fruits of yellow color) of *C. mas* L., and loganic acid (extracted from the yellow fruits of the cornelian cherry), respectively, in a dose of 20 mg/kg of body weight. The amount and duration of extracts administration were based on previous studies (Dzydzan *et al.*, 2019; 2020). Ripe fruits (*C. mas* L.) were collected at the Arboretum and Institute of Physiography in Bolestraszyce (Przemyśl, Poland). The extracts were obtained by prof. Alicja Kucharska at the Department of Fruit, Vegetable, and Plant Nutraceutical Technology at the Wrocław University of Environmental and Life Sciences (Wroclaw, Poland). Methods of preparation of the extracts of cornelian cherry, their identification, and determination of bioactive compounds of extracts by UPLC-qTOF-MS/MS and HPLC-PDA methods are described by Dzydzan *et al.* (Dzydzan *et al.*, 2019; 2020).

Blood collection. On the 24th day of the experiment, rats of all experimental groups were decapitated under ether anesthesia, and blood sampling was performed. Blood was collected with the addition of heparin, centrifuged to obtain plasma, and erythrocytes were washed three times with phosphate-buffered saline (137.0 mM NaCl, 2.7 mM KCl, 10.0 mM $Na_2HPO_4 \cdot 7H_2O$, 1.8 mM KH_2PO_4; pH 7.4). The following indicators were studied in erythrocytes: catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), reduced glutathione (GSH), oxidative modifications of proteins of a basic (OMP_{430}) and neutral (OMP_{370}) character, advanced oxidation protein products (AOPPs), TBA-reactive substances (TBARS). The content of pyruvate, L-lactate, lactate/pyruvate ratio was determined in plasma and erythrocytes, and LDH activity only in plasma.

Determination of the metabolites of anaerobic glycolysis. The concentration of pyruvate was determined in hemolysates of erythrocytes and plasma using the analytical kit "Filisit-Diagnostika" (Dnipro, Ukraine). The optical density of the test samples was determined spectrophotometrically at λ = 540 nm (Katsuki *et al.*, 1961). To obtain

protein-free blood samples to determine the L-lactate content, 50% trichloroacetic acid was added to plasma or erythrocytes to a final concentration of 10%, the samples were centrifuged for 5 minutes at 10000 rpm. The supernatant was neutralized with 0.5 mol/L NaOH (to pH 7.0). The determination of L-lactate in protein-free blood samples was carried out according to the enzymatic-chemical method with the formation of Prussian blue. The concentration of the colored product was measured spectrophotometrically at λ = 680 nm. The brightness of the color correlates with the concentration of L-lactate in the sample (Demkiv *et al.*, 2023). The total activity of LDH isoforms in blood plasma was determined using the commercial kit "Filisit-Diagnostika" (Dnipro, Ukraine) by the kinetic ultraviolet method and detected at λ = 340 nm.

Antioxidant enzymes and metabolites of oxidative stress assays. The activity of SOD was evaluated by the amount of nitro formazan formed and determined by the method described by P. Kakkar *et al.* (Kakkar *et al.*, 1984). Results were expressed as c.u./mg of protein. The activity of CAT was evaluated by the decrease in the color intensity of the H_2O_2 complex with molybdenum salt (Góth *et al.*, 1991). One unit of enzyme activity was expressed as nmol H_2O_2/min · mg of protein. The activity of GPx was determined by the rate of oxidation of GSH by tertiary butyl hydroperoxide and expressed in μmol/min · mg of protein (Melekh *et al.*, 2017). The level of GSH was measured according to the method based on the property of glutathione to reduce 5,5′-dithiobis-2-nitrobenzoic acid (Ellman's reagent) with formation a colored yellow product (Chakravarty & Rizvi, 2011). The analysis of the level of OMP of neutral and basic characters is based on the spectrophotometric detection of hydrazones formed in the reaction of aldehyde and ketone groups of aliphatic amino acid residues with 2,4-dinitrophenylhydrazine, which absorb at λ = 370 nm and λ = 430 nm, respectively (Strugała *et al.*, 2019). The determination of AOPPs formed as a result of the reaction of proteins with chlorinated oxidants, such as chloramines, was carried out using spectrophotometric detection (Taylor *et al.*, 2015). The level of TBARS lipid peroxidation products was expressed in pmol/mg hemoglobin using the molar absorption coefficient (156000 $M^{-1} \cdot cm^{-1}$) and detected on a spectrophotometer at λ = 532 nm (Strugała *et al.*, 2019).

Statistical analysis. Statistical processing of the results was carried out using Microsoft Excel 2013. The main statistical indicators were calculated based on direct quantitative data obtained as a result of research (mean – M; standard error of the mean – m). To assess the probability of the difference between the statistical characteristics of two alternative data sets, a univariate analysis of variance (ANOVA 1) was performed. A difference with a probability of $p \geq 0.95$ (significance level $P < 0.05$), calculated using StatPlus software with post-hoc analysis, was considered significant.

RESULTS AND DISCUSSION

Despite the fact that erythrocytes provide oxygen transport for oxidative reactions in the body, metabolism in these cells is oxygen-independent since there is no mitochondria in the cytoplasm. Erythrocytes metabolize glucose intensively. The glucose transporter GLUT2 mediates its transmembrane transfer by facilitated diffusion into these cells. Since the concentration of glucose in the blood increases under diabetes, it is transported into erythrocytes, escalates and, accordingly, raises involvement in metabolism. The main catabolic process in erythrocytes is glycolysis, which concludes with the formation of two molecules of pyruvate (Wang *et al.*, 2021). According to the results of our experiments, the content of pyruvate increases 1.3-fold in erythrocytes

under diabetes (**Table 1**). Pyruvate, the end product of glycolysis, is converted into lactate in erythrocytes with the enzyme LDH_2 (Boretsky *et al.*, 2023). We detected a 2.9-fold increase in lactate concentration in rats' erythrocytes in diabetes mellitus (**Table 1**). Such changes might be caused by the activation of anaerobic glycolysis. A significant increase in the ratio between these metabolites in erythrocytes of animals with experimental diabetes confirms this assumption (**Table 1**).

The administration of extracts of red and yellow fruits of *C. mas* L. and loganic acid to rats with streptozotocin-induced diabetes for 14 days caused a significant decrease of these metabolites and the reduction in lactate/pyruvate (L/P) ratio to the values of the control group (**Table 1**). The discovered changes can be explained precisely by the anti-hyperglycemic properties of the extracts (Dzydzan *et al.*, 2019; 2020; 2022). A decrease in the concentration of glucose in the blood plasma after the administration of extracts to animals with DM leads to a decline in the intensity of glucose transport into erythrocytes and, as a result, a restoration of the balance of catabolic breakdown of glucose in glycolysis. On the other hand, the obtained results, such as a significant decrease in the concentration of metabolites (**Table 1**), complement and confirm the effect of biologically active compounds in the extracts on carbohydrate metabolism in diabetes (Dzydzan *et al.*, 2019; 2020).

Table 1. **Concentration of substances of carbohydrate metabolism in erythrocytes of rats with streptozotocin-induced DM after treatment with extracts of red (ERF), yellow (EYF) cornelian cherry fruits and loganic acid (LA)**

Substances / Groups of animals	Pyruvate, mM	L-lactate, mM	L/P ratio, c.u.
Control	0.16 ± 0.01	3.70 ± 0.16	22.5 ± 0.5
DM	0.20 ± 0.01 ***	10.71 ± 0.21 ***	52.7 ± 1.1 ***
DM + ERF	0.17 ± 0.01 ***, ###	3.82 ± 0.13 ###	21.8 ± 0.4 ###
DM + EYF	0.18 ± 0.01 ***, ###	4.61 ± 0.17 **, ###	25.9 ± 0.5 **, ###
DM + LA	0.16 ± 0.01 ###	3.70 ± 0.25 ###	23.0 ± 0.4 ###

Designations. Compared to the control group: ** – P <0.01; *** – P <0.001; compared to the DM group: ### – P <0.001

In the body, pyruvate undergoes further catabolism – in aerobic conditions to acetyl-CoA, or in anaerobic conditions to lactate (Kuchurka *et al.*, 2022). Since the glycolytic process is characteristic of all cells of the human and mammalian body, pyruvate and lactate are present in all organs and tissues, particularly in the blood. Determining the content of these metabolites in clinical and scientific practice is one of the traditional biochemical markers for conformity assessment of the adequacy of tissue oxygenation to their metabolic, oxidizing processes (Chaudhry, Varacallo, 2024). Thus, considering the mentioned above and the changes detected in erythrocytes, we determined the content of these metabolites in the blood plasma (**Table 2**).

Analyzing the results of the level of pyruvate in the blood plasma, we established that its content increased 1.7-fold in diabetes compared to the control (**Table 2**). It should be noted that pyruvate accumulation in plasma might be due to a decrease in

the amount or allosteric inhibition of pyruvate dehydrogenase activity (catalyzes the conversion of pyruvate to acetyl-CoA in aerobic conditions). It is worth paying attention to the fact that pyruvate metabolism violation in DM impedes the functioning of β-cells of pancreatic islets. It was established in diabetic mice and rat models that the activity of pyruvate dehydrogenase, disturbed in β-cells of the islets of Langerhans, is due to an increase in the activity of pyruvate dehydrogenase kinase. In addition, the activity of pyruvate carboxylase, which involves pyruvate in gluconeogenesis, is also reduced in β-cells of diabetic mice (Gray *et al.*, 2014).

Table 2. **Effect of cornelian cherry fruit extracts on the total level of intermediate products of glucose metabolism and lactate dehydrogenase (LDH) activity in plasma of rats with diabetes**

Substances / Groups of animals	Pyruvate, mM	L-lactate, mM	L/P ratio, c.u.	LDH, mU/L
Control	0.20 ± 0.01	4.60 ± 0.23	22.5 ± 0.5	353.0 ± 7.7
DM	0.34 ± 0.01 ***	13.61 ±0.64 ***	38.9 ± 2.2 ***	659.9 ± 33.1 ***
DM + ERF	0.22 ± 0.01 ###	4.41 ± 0.20 ###	18.9 ± 1.2 **, ###	398.9 ± 22.2 ###
DM + EYF	0.19 ± 0.01 ###	4.02 ± 0.27 *, ###	20.8 ± 0.4 ###	346.1 ± 18.7 ###
DM + LA	0.16 ± 0.01 **, ###	3.90 ± 0.19 *, ###	23.1 ± 1.6 **, #	408.4 ± 19.8 *, ###

Designations. Compared to the control group: * – P <0.05; ** –P < 0.01; *** – P <0.001; compared to the DM group: ### – P <0.001

It is worth noting that in type 1 DM, due to insulin insufficiency, cells cannot efficiently transport glucose utilizing insulin-dependent transporters. β-Oxidation of fatty acids compensatory increases in the liver, and acetyl-CoA, which is involved in ketogenesis, accumulates. Ketone bodies are an alternative source of energy in extrahepatic tissues. Acetyl-CoA formed from β-hydroxybutyrate or acetoacetate is an allosteric inhibitor of the pyruvate dehydrogenase and provokes the accumulation of pyruvate (Kolb *et al.*, 2021; Gray *et al.*, 2014). In addition, under diabetes, erythrocytes are also an important source of pyruvate, transporting it into the plasma by monocarboxylate transporters (MCT) (Boretsky *et al.*, 2023; Halestrap, 2012).

There was a significant decrease in pyruvate content in the blood plasma after the administration of extracts of red and yellow fruits of the *C. mas* L. and loganic acid to diabetic animals: 1.5-, 1.8-, and 2.1-fold, respectively (**Table 2**). Such changes can be explained by the restoration of the oxygen transport function of erythrocytes, the functional activity of pyruvate carboxylase, enzymes of the Krebs cycle, and the electron transport chain in cells with intensive oxidative metabolism (Chaudhry, Varacallo, 2024).

Glucose and lactate metabolism are closely related because these compounds can be converted into each other. Glucose is a major source of lactate and, accordingly, lactate is the main substrate for the synthesis of endogenous glucose in the liver or kidneys. In the case of changes in glucose metabolism (obesity, diabetes, etc.), lactate homeostasis is disturbed. Lactate is also considered a regulator of energy homeostasis (Wu *et al.*, 2016). The present study showed an almost three-fold increase in the content of lactate

in the blood plasma of rats with experimental DM (**Table 2**). An elevated blood lactate concentration (hyperlactatemia) is indicated by both an increase in the processes of glycolysis and insufficient oxidation of the products of intermediate carbohydrate metabolism (Kuchurka *et al.*, 2022). The administration of all studied extracts led to a significant decrease in the concentration of lactate. It should be noted that the biggest difference in the change of its content in plasma was observed in yellow cornelian cherry-treated and loganic acid-treated diabetic rats (**Table 2**).

The imbalance of metabolites of carbohydrate metabolism was definitely reflected in the ratio between these acids, which led to an increase in the L/P ratio in the plasma of rats with diabetes. One of the main markers of the development of myocardial hypertrophy and heart failure is the violation of the lactate-to-pyruvate balance, which is accompanied by a decrease in the intensity of pyruvate oxidation in the mitochondria of cardiomyocytes and an increase in lactate export (Boretsky *et al.*, 2023).

A significant decrease in the L/P ratio in the blood plasma of diabetic animals was observed when the extracts were administered to rats. The extract of red fruits of the cornelian cherry decreases this indicator by 2.1 times, the extract of yellow fruits of *C. mas* L. – by 1.9 times, and the loganic acid obtained from the yellow fruits of *C. mas* L. – by 1.7 times compared to the STZ-treated group (**Table 2**). In clinical practice, the determination of the level of pyruvate and lactate is one of the traditional biochemical markers for assessing the compliance of tissue oxygenation of their metabolic and oxidizing processes. So, we can affirm that the cornelian cherry extracts correct such metabolic processes both in erythrocytes and in blood plasma.

As is well known, the cytoplasmic enzyme LDH catalyzes the last reaction of anaerobic glycolysis. Normally, LDH is present in all cells of the body and blood plasma. During the research, an increase in the activity of LDH in the plasma of rats with diabetes was found to be 1.9 times higher compared to control animals (**Table 2**). An increase in the activity of this enzyme in plasma is a bad prognostic feature for pathological processes in the body, in particular under hemolysis of erythrocytes, dystrophy of muscle fibers, myocardial infarction, thromboembolism of the pulmonary artery, hepatitis and other disorders (Farhana & Lappin, 2023). After the oral administration of extracts of fruits of *C. mas* L., the activity of LDH significantly decreased compared to the diabetic group of animals, which reached the same values as in the control group (**Table 2**). The obtained results regarding changes in LDH activity in blood plasma might be due to the protective effect of bioactive compounds contained in the studied extracts at the level of the whole organism. The extracts of *C. mas* L. fruit may exhibit anti-inflammatory, antidiabetic, hepatoprotective, antioxidative, and anti-osteoporotic effects (Klymenko *et al.*, 2021).

In diabetes, hyperglycemia provokes the development of oxidative stress, during which more free radicals are formed in the body than can be neutralized by antioxidant defense systems. Erythrocytes are negatively affected by oxidative stress and are sensitive to them because the oxidation of structural (membrane proteins) and functional proteins (enzymes) instigates an imbalance of carbohydrate metabolism and disruption of erythrocyte functions (Wang *et al.*, 2021). Spontaneous oxidation of Fe^{2+} in the heme of hemoglobin is a constant source of superoxide anion in erythrocytes, which with the SOD enzyme turns into hydrogen peroxide, which one, in turn, undergoes break down by CAT and GPx enzymes (Rocha *et al.*, 2015).

Taking into account the fact that the administration of the fruit extracts of the cornelian cherry results in the restoration of impaired glucose metabolism, we investigated

the biochemical markers of the antioxidant status of blood erythrocytes. Enzymes of antioxidant protection are peculiarly important. In DM, we observed a decrease in the activity of SOD, CAT, and GPx in blood erythrocytes compared to control (**Fig. 1*A,B,C***). That sort of effect can be explained by inhibition of the functional activity of enzymes, which is a result of their excessive oxidation and change in conformational state (Asmat *et al.*, 2016). Oral administration of the extract of red fruits of the cornelian cherry and loganic acid led to an increase in the activity of SOD compared to rats with diabetes. At the same time, a significant increase in the activity of CAT and GPx was observed after the administration of fruit extracts of the *Cornus mas* L. (**Fig. 1*A,B,C***).

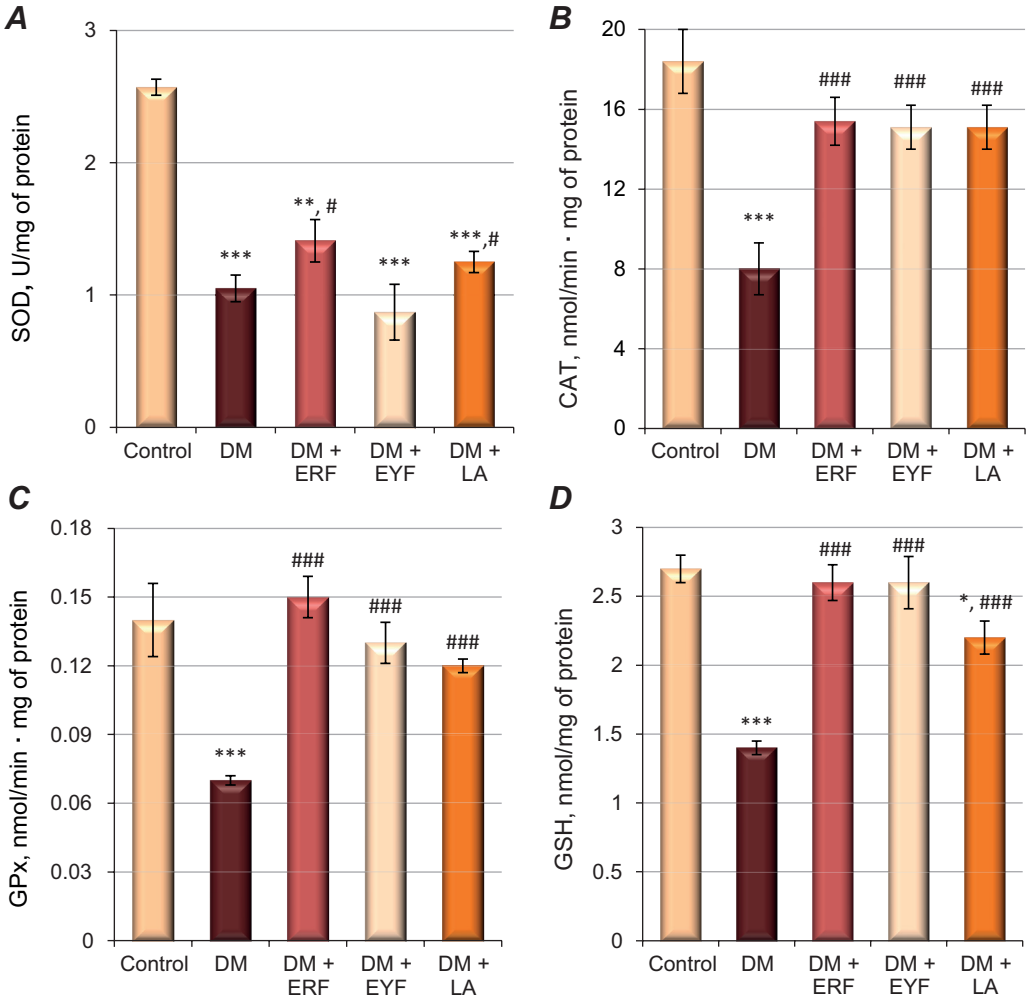

Fig. 1. Activity of enzymes of antioxidant defense system: (A) superoxide dismutase; (***B***) catalase; (***C***) glutathione peroxidase and level of reduced glutathione (***D***) in erythrocytes of animals with DM under administration of extracts of red (ERF) and yellow (EYF) fruits of *C. mas* L. and loganic acid (LA) extracted from yellow fruits of cornelian cherry

Designations. Compared to the control group: * – P <0.05; ** – P <0.01; *** – P <0.001; compared to the DM group: # – P <0.05; ### – P <0.001

Reduced glutathione (GSH) plays an important role in the regulation of the redox state of the cell and is one of the indicators that characterize the intensity of oxidative stress (Vašková *et al.*, 2023). We established a decrease in the content of GSH in erythrocytes of blood in diabetes, and an increase in its content after cornelian cherry extracts treatment to diabetic animals (**Fig. 1*D***). The increase in the activity of the enzymes of the antioxidant defense system and the endogenous antioxidant – GSH under the administration of extracts of *C. mas* L. is due to the presence of a significant amount of iridoids and anthocyanins in them (Dzydzan *et al.*, 2019; 2020).

The antioxidant properties of cornelian cherry fruit extracts are based on the ability to scavenge free radicals, regulate enzyme-mediated (SOD, CAT, GPx) and non-enzymatic (GSH) antioxidant protection of the body (Dzydzan *et al.*, 2019; 2020; Seniv *et al.,* 2021). Moreover, biologically active substances, present in the extracts of fruits of *C. mas* L. are capable of modulating numerous signaling pathways (for example, quercetin inhibits the activities of xanthine oxidoreductase, inducible nitric oxide synthase), maintaining the redox balance of the whole organism (Dzydzan *et al.*, 2019; 2020; 2022; Xu *et al., 2019*).

Proteins, as the main bioorganic polymers of cells, tissues, and body fluids, are the main targets of oxidation. Besides, oxidative stress provokes autoxidation of carbohydrates and peroxidation of lipids with the formation of highly active intermediate products that also attack functional groups of proteins. Reversible oxidative modifications are important in physiological processes, while irreversible modifications cause pathological changes and promote disease progression (Kehm *et al.*, 2021).

It was determined that under DM, the concentration of OMPs of neutral and basic characters increases in erythrocytes (**Fig. 2*A*,*B***). The administration of extracts of red and yellow fruits of *C. mas* L. and loganic acid causes a significant decrease in the level of OMPs (**Fig. 2*A*,*B***).

The markers of oxidative damage of proteins are AOPPs which formed and accumulated under diabetes as a result of increased carbonyl oxidation processes, as well as disruption of the prooxidant-antioxidant balance (Strugała *et al.*, 2019). Confirmation of all these changes in DM is an increase in the level of AOPPs in erythrocytes compared to control rats (**Fig. 2*C***). The administration of extracts of the cornelian cherry fruits to STZ-induced rats shows a significant decrease in this parameter compared to a group of diabetic animals that did not receive the extracts (**Fig. 2*C***).

Since diabetes-induced oxidative stress increases lipid peroxidation (Satriyasa, 2016), we investigated the content of TBARS. A significant decrease in the TBARS level in erythrocytes was observed after the administration of the extract of red fruits of the cornelian cherry and loganic acid to rats with diabetes (**Fig. 2*D***). The ability of *C. mas* L. fruit extracts to reduce the manifestations of oxidative stress might be a consequence of the synergistic effect of bioactive substances (Dzydzan *et al.*, 2019; 2020).

Under hyperglycemia, glucose autoxidation combined with other metabolic changes is the main mechanism of excessive ROS formation in erythrocytes (**Fig. 3**). Oxidative stress leads to an imbalance between oxidative processes and antioxidant defense in erythrocytes with a shift in the balance towards oxidation (Wang *et al.*, 2021). The main changes in erythrocytes of the cornelian cherry-treated diabetic groups are summarized in the scheme (**Fig. 3**). These results emphasize that anaerobic glycolysis (restoring

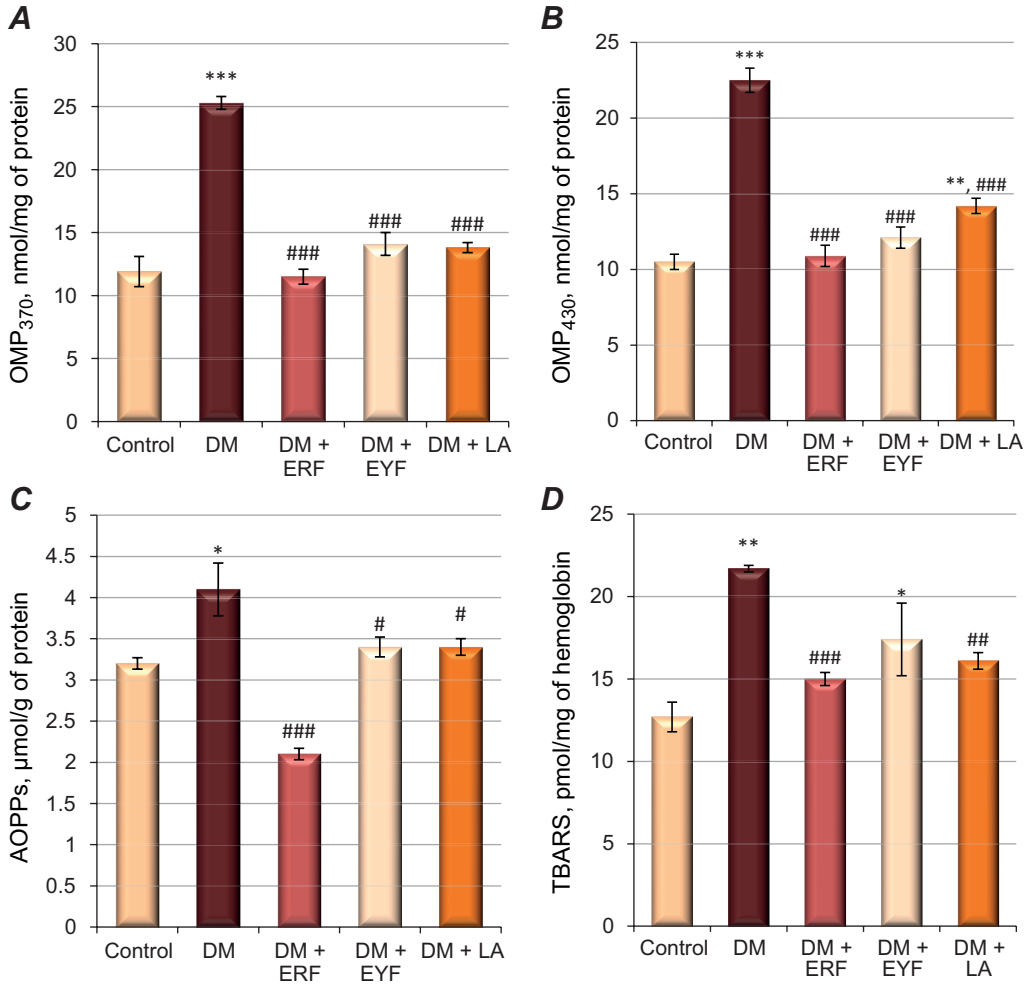

Fig. 2. Effects of the extracts of *Cornus mas* L. fruits on the content of oxidative modifications of proteins of neutral (***A***) and basic (***B***) characters, advanced oxidation protein products (***C***) and TBA-reactive substances (***D***) in rats' erythrocytes under diabetes mellitus (DM)
Designations. Compared to the control group: * – P <0.05; ** – P <0.01; *** – P <0.001; compared to the DM group: # – P <0.05; ## – P <0.01; ### – P <0.001

the balance of metabolites of glycolytic breakdown of glucose) and antioxidant status of erythrocytes are normalized under administration of the extracts of *C. mas* L. fruits.

Although devoid of organelles, mature erythrocytes contain cytosolic and membrane-associated molecules that could be DM biomarkers or drug targets offering timely and accurate prediction. Alternative therapeutic schemes can also be tested based on these cells. Additionally, erythrocytes could be used as delivery systems with the potential to increase the bioavailability of the active drug agent (Anastasiadi *et al.*, 2024).

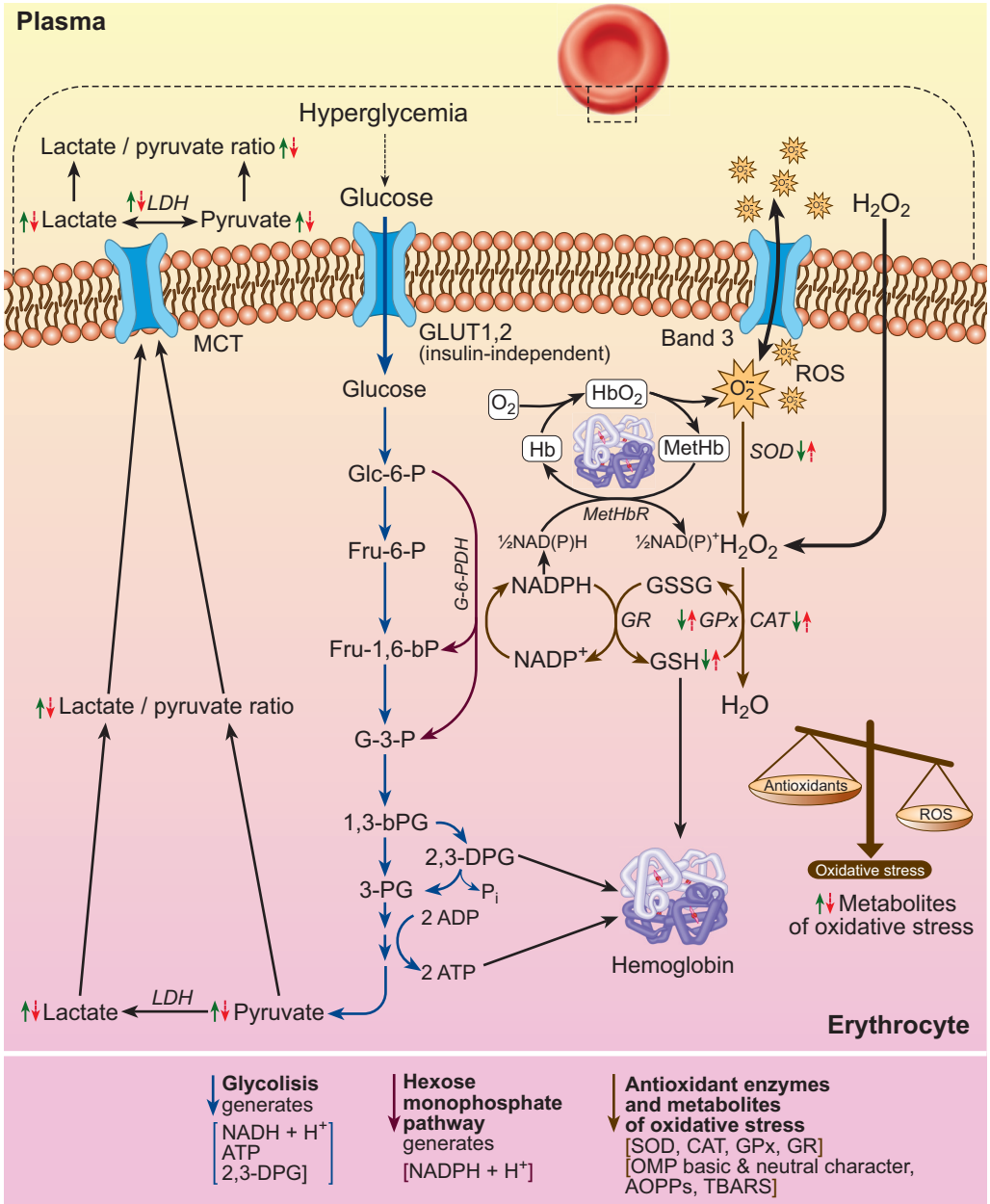

Fig. 3. The extracts of the cornelian cherry fruits restore carbohydrate metabolism and antioxidant balance in the blood erythrocytes of rats with streptozotocin-induced DM. Diabetes mellitus – ↑ (increase) or ↓ (decrease); extracts of red, yellow fruits of *Cornus mas* L. and loganic acid, extracted from the yellow fruits of cornelian cherry – ↑ (increase) or ↓ (decrease); AOPPs – advanced oxidation protein products; MCT – monocarboxylate transporter; CAT – catalase, 2,3-DPG – 2,3-diphosphoglycerate; Hb – hemoglobin; GR – glutathione reductase; GPx – glutathione peroxidase; GSH – reduced glutathione; LDH – lactate dehydrogenase; MetHbR – methemoglobin reductase; OMP – oxidative modifications of proteins; ROS – reactive oxygen species; SOD – superoxide dismutase; TBARS – TBA-reactive substances

CONCLUSIONS

Extracts of red and yellow fruits of *C. mas* L. and the main iridoid glycoside isolated from yellow fruits – loganic acid – can be natural drugs for correcting disorders in erythrocytes in diabetes. The positive effect of the extracts is realized by preventing the development of metabolic disorders and oxidative stress in these blood cells. It is noteworthy to mention that the extract of red fruits of *C. mas* L. showed the best effect among the studied extracts.

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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, [I.B.; A.M.]; methodology, [A.Z.C.; A.M.]; validation, [A.M.; I.B.]; formal analysis, [I.B.; A.M.]; investigation, [A.Z.C.; A.M.]; resources, [A.Z.C.]; writing – original draft preparation, [A.M.]; writing – review and editing, [I.B.]; visualization, [I.B.] supervision, [I.B.]; project administration, [A.Z.C.; N.S.]; funding acquisition, [–].

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

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ВЗАЄМОЗВ'ЯЗОК АНАЕРОБНОГО ГЛІКОЛІЗУ Й ОКСИДАТИВНОГО СТРЕСУ В ЕРИТРОЦИТАХ ЗА ВВЕДЕННЯ ЕКСТРАКТІВ ПЛОДІВ ДЕРЕНУ СПРАВЖНЬОГО (*CORNUS MAS* L.) ЩУРАМ ЗІ СТРЕПТОЗОТОЦИН-ІНДУКОВАНИМ ДІАБЕТОМ

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Вступ. За цукрового діабету (ЦД) важливим етапом комплексних наукових досліджень задля з'ясування механізму дії лікарських препаратів на основі рослинної сировини є аналіз змін у біохімічному профілі еритроцитів. Плоди *Cornus mas* L. мають широкий спектр застосування, адже біологічно активні сполуки цих плодів виявляють різноманітні біологічні ефекти. Однак вплив екстрактів плодів дерену справжнього на функціональний стан еритроцитів за ЦД вивчено недостатньо. На тлі високої концентрації глюкози в еритроцитах відбуваються різноманітні структурно-функціональні зміни, які призводять до численних порушень у їхньому метаболізмі. Глюкоза, яка транспортується в еритроцити полегшеною дифузією через GLUT2, зазнає катаболічного розщеплення в анаеробному гліколізі (90 % глюкози) та пентозофосфатному шунті (решта 10 %). Утворені в результаті метаболізму АТФ і відновні еквіваленти $НАД^+$ і $НАДФ^+$ беруть участь у підтриманні структури гемоглобіну. Особливо важливе значення мають ензими антиоксидантного захисту, які запобігають його окисненню в метгемоглобін. Гіперглікемія та розвиток оксидативного стресу за діабету є причиною зниження активності антиоксидантних ензимів і накопичення лігандних форм гемоглобіну ($HbCO_2$, MetHb, $HbA1_c$). Тому метою роботи було дослідити вплив екстрактів червоних і жовтих плодів дерену справжнього (*Cornus mas* L.) на вміст кінцевих метаболітів гліколітичного розщеплення глюкози в еритроцитах і біохімічні маркерні показники антиоксидантного статусу цих клітин крові у щурів зі стрептозотоцин-індукованим ЦД.

Матеріали та методи. ЦД 1 типу у тварин індукували внутрішньоочеревинним введенням стрептозотоцину. Експерименти проводили на щурах-самцях лінії Wistar, яким з 10-го дня від моменту індукції діабету *per os* упродовж 14 днів вводили екстракти червоних, жовтих плодів дерену справжнього та логанову кислоту, отриману із жовтих плодів, у дозі 20 мг/кг маси тіла. На 24-й день експерименту щурів декапітували під ефірним наркозом, проводили забір крові. У плазмі й еритроцитах визначали вміст піруват і лактату (як кінцевих метаболітів анаеробного гліколізу), активність лактатдегідрогенази, а також досліджували біохімічні маркерні показники антиоксидантного статусу еритроцитів (активність супероксиддисмутази, каталази і глутатіонпероксидази, відновлений глутатіон, ТБК-позитивні продукти, концентрацію окисно модифікованих білків і кінцевих продуктів оксидації білків).

Результати. За введення екстрактів плодів дерену справжнього щурам із ЦД спостерігали достовірне підвищення активності каталази, супероксиддисмутази, глутатіонпероксидази, концентрації відновленого глутатіону на тлі зниження вмісту окисно модифікованих білків, кінцевих продуктів оксидації білків, ТБК-позитивних

продуктів, піруват, L-лактату й лактатдегідрогенази. Ці біохімічні показники дали змогу схарактеризувати інтенсивність анаеробного гліколізу й антиоксидантний статус еритроцитів крові за стрептозотоцинового діабету.

Висновки. Екстракти плодів *Cornus mas* L. можуть бути потенційними природними засобами для лікування метаболічних порушень за ЦД, оскільки проявляють коригувальний вплив на катаболічне розщеплення глюкози й антиоксидантну систему захисту еритроцитів, запобігаючи розвиткові оксидативного стресу. Варто зазначити, що серед досліджуваних екстрактів найкращий ефект у нормалізації цих показників виявив екстракт червоних плодів дерену.

Ключові слова: цукровий діабет, еритроцити, екстракти плодів *Cornus mas* L., піруват, лактат, ензими антиоксидантного захисту

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