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EFFECT OF BIOACTIVE COMPOUNDS FROM *CORNUS MAS* L. FRUITS ON THE LEVEL OF ADVANCED GLYCATION END-PRODUCTS (AGEs) AND RECEPTORS FOR AGEs IN BLOOD PLASMA AND LEUKOCYTES OF RATS WITH STREPTOZOTOCIN-INDUCED DIABETES MELLITUS

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Background. Metabolic distortions mediated by chronic hyperglycemia lead to pathophysiological alterations in diabetes mellitus. Persistent elevation of blood glucose promotes non-enzymatic glycation of proteins and lipids, leading to the accumulation of advanced glycation end-products (AGEs). Accumulation of AGEs reflects impaired metabolic clearance and/or excretion and is therefore considered a marker of both long-term glycemic control and oxidative-carbonyl stress in tissues. The biological effects of AGEs are largely mediated through their interaction with the receptor for advanced glycation end products (RAGE), triggering pro-inflammatory signaling pathways. Accordingly, this study investigated the effects of bioactive compounds extracted from cornelian cherry fruits (*Cornus mas* L.) on AGE and RAGE levels in plasma and blood leukocytes of rats with experimental diabetes mellitus.

Materials and Methods. Experiments were conducted in streptozotocin-induced diabetic rats divided into three experimental groups. Starting on day 10 after diabetes induction, animals received oral administration of fruit extracts from the ‘Podolski’ and ‘Yantarnyi‘ & ‘Flava‘cultivars of the cornelian cherry, as well as the iridoid glycoside loganic acid isolated from these fruits, at a dose of 20 mg/kg body weight for 14 consecutive days. Control and untreated diabetic rats received distilled water (1 mL per rat) by oral gavage. On day 24 of the experiment, blood samples were collected. Levels of fluorescent and non-fluorescent AGEs were determined in plasma and leukocytes. Full-length receptor for AGEs (flRAGE) expression in leukocyte membranes was assessed using an indirect immunoperoxidase assay, while plasma concentrations of the soluble form of RAGE (sRAGE) were measured by immunoblotting.

Results. One of the mechanisms of the deleterious effect of high glucose levels, in particular its ability to react non-enzymatically with proteins with the formation of AGEs, has been studied. An increase in AGE levels in blood plasma of rats with diabetes was found. At the same time, a decrease in the fluorescent and non-fluorescent AGE levels in leukocytes was observed. This is likely due to impaired leukocyte glucose uptake under the condition of diabetic hypoinsulinemia. There was a significant increase in the number of $RAGE^+$ leukocytes and the level of sRAGEs in plasma of rats with diabetes. It was found that the content of the fluorescent and non-fluorescent AGEs significantly increased in leukocytes of rats with DM after administration of the extracts from the 'Podolski' and 'Yantarnyi' & 'Flava' cultivars of the cornelian cherry, and the loganic acid. It is worth noting that the extract from the fruits of *Cornus mas* L. 'Podolski' cultivar showed the best effect among all studied extracts and led to a reduction in the level of AGEs in the blood plasma and receptors to them.

Conclusions. The fruit extract from the 'Podolski' cultivar of *Cornus mas* L. demonstrates therapeutic potential in the correction of impaired glucose metabolism in diabetes mellitus. The beneficial effects of the extract's bioactive compounds are associated with the inhibition of glycation, the formation of AGEs, and normalization of RAGE levels in blood plasma and leukocytes.

Keywords: experimental diabetes mellitus, fruit extracts of cornelian cherry, loganic acid, leukocytes, blood plasma, markers of oxidative-carbonyl stress, AGEs, RAGEs

INTRODUCTION

In diabetes mellitus (DM), chronic hyperglycemia promotes the intensification of macromolecular glycation processes, alterations in metabolic pathway activity, and the development of oxidative and carbonyl stress accompanied by multiple metabolic disturbances (Kato *et al*., 2024; Rhee & Kim, 2018; Wang *et al*., 2025).

Carbonyl stress is characterized by the accumulation of reactive carbonyl compounds (RCOs), which arise as intermediates of carbohydrate and lipid metabolism as well as from the modification of proteins by these metabolites. Several RCOs – including glyoxal, methylglyoxal, arabinose, glycoaldehyde, 3-deoxyglucosone, and dehydroascorbate – are generated from carbohydrates and can non-enzymatically react with amino groups of proteins, leading to the formation of advanced glycation end-products (AGEs). These include carboxymethyllysine, pentosidine, imidazolone, glyoxal-lysine dimer, and methylglyoxal-lysine dimer. In addition, certain RCOs, such as glyoxal, malondialdehyde, hydroxynonenal, and acrolein, are produced during lipid peroxidation of polyunsaturated fatty acids. Moreover, glyoxal, methylglyoxal, acrolein, and glycoaldehyde may also arise from amino acid metabolism mediated by leukocyte myeloperoxidase (Kato *et al*., 2024; Lamprea-Montealegre *et al*., 2022). The relationships between RCOs and AGEs are complex. Individual AGEs, such as carboxymethyllysine, may originate from multiple precursors, whereas a single RCO can generate several different AGE structures (Khalid *et al*., 2022). Consequently, AGEs represent a heterogeneous group of compounds formed through non-enzymatic reactions between proteins, lipids, nucleic acids, and reducing sugars in the Maillard glycation reaction. Accumulation of AGEs is widely considered a major contributor to the development and progression of diabetic complications (Kato *et al*., 2024; Nomi *et al*., 2020; Twarda-Clapa *et al*., 2022).

From a physicochemical perspective, AGEs are heterogeneous heterocyclic yellow-brown compounds that can be either fluorescent or non-fluorescent. Fluorescent AGEs include pentosidine and methylglyoxal-derived hydroimidazolone, whereas non-fluorescent AGEs comprise N-ε-carboxymethyllysine, carboxyethyllysine, and carboxymethylhydroxylysine. These compounds promote protein aggregation and cross-linking, resulting in increased resistance to proteolytic degradation. Consequently, elevated AGE levels disrupt protein function and intracellular signaling pathways (Dariya & Nagaraju, 2020).

Furthermore, AGEs stimulate the generation of free radicals, particularly reactive oxygen species (ROS), in addition to those produced during autoxidation reactions. This process impairs antioxidant defense systems and induces both carbonyl and oxidative stress within cells, ultimately leading to excessive free radical production that damages DNA, proteins, and lipids and disrupts fundamental biological processes (Wang *et al*., 2025).

Attenuation of oxidative–carbonyl stress through various therapeutic strategies – including antioxidant administration, inhibition of ROS generation, modulation of oxidative protein modifications, detoxification of ROS, suppression of AGE formation, application of carbonyl scavengers, and induction of carbonyl-metabolizing enzymes – has been shown to alleviate the progression of this endocrine disorder (Khangholi *et al*., 2015; Shen *et al*., 2020; Yeh *et al*., 2017). Accordingly, the development of antioxidant-based strategies aimed at mitigating oxidative–carbonyl stress associated with diabetes relies on monitoring changes in relevant biochemical biomarkers.

The rate of glycation reactions depends on several factors, including glucose concentration, the reactivity of protein amino groups, protein half-life, and total protein concentration (Khalid *et al*., 2022; Luo *et al*., 2016). Consequently, AGEs formed on plasma proteins represent diagnostically important biomarkers of glycation processes. Enhanced glycation of plasma proteins leads to the formation of atypical intermolecular cross-links, disruption of receptor–ligand interactions, decreased enzymatic activity, and alterations in the circulating half-life of proteins (Thornalley & Rabbani, 2011; Wang *et al*., 2025).

AGEs were the first identified ligands of the receptor for advanced glycation end-products (RAGE), a member of the immunoglobulin superfamily that functions as a type I transmembrane pattern-recognition receptor (PRR) and serves as a key mediator of innate immune responses. Unlike many other PRRs, RAGE recognizes structurally diverse ligands, including damage-associated molecular patterns (DAMPs), AGEs, amyloid-β (Aβ), and fibrillar protein structures. The full-length form of RAGE (flRAGE) consists of three main domains: an extracellular ligand-binding domain, a transmembrane α-helix, and a short unstructured C-terminal cytoplasmic domain involved in intracellular signaling. Binding of AGEs to RAGE on the cell surface, including that of leukocytes, triggers the release of pro-inflammatory cytokines such as IL-6, CXCL8, and IL-12, as well as inflammatory mediators including TNF, IL-1, and CCL2 (Dong *et al*., 2022; Khalid *et al*., 2022).

Among the numerous RAGE isoforms, particular attention has been paid to those lacking transmembrane and cytoplasmic domains. These variants include truncated or soluble RAGE (sRAGE) and endogenous secretory RAGE (esRAGE), which are generated through alternative mRNA splicing. Owing to the absence of transmembrane and cytoplasmic regions, these soluble isoforms function as circulating decoy receptors that attenuate the interaction between membrane-bound flRAGE and its ligands (Erusalimsky, 2021; Khalid *et al*., 2022; Ruiz *et al*., 2020). Elevated plasma levels of sRAGE have been reported in type 1 DM, where they are thought to exert protective effects by limiting AGE-mediated cellular damage. Notably, circulating sRAGE concentrations positively

correlate with AGE levels in the peripheral blood (Challier *et al*., 2005; Thomas *et al*., 2011; Wang *et al*., 2025).

In diabetes, increased intravascular AGE accumulation enhances the expression of RAGEs in vascular wall cells, including endothelial cells and smooth muscle cells, as well as in leukocytes. Activation of intracellular signaling pathways mediated by AGE–RAGE complexes promotes leukocyte diapedesis from the bloodstream into tissues and inflammatory areas (Rhee & Kim, 2018; Wang *et al*., 2025).

Leukocytes in diabetic conditions undergo complex alterations in biochemical and morphofunctional parameters, which are often interrelated and mutually reinforcing. Impaired glucose transport in leukocytes suppresses glycolytic metabolism. In particular, reduced phosphofructokinase activity leads to increased levels of glucose-6-phosphate, fructose-6-phosphate, hydrogen ions, and lactate (Alba-Loureiro *et al*., 2007). Furthermore, leukocytes in diabetes exhibit a decreased activity of key antioxidant enzymes, including superoxide dismutase and glutathione peroxidase. The latter enzyme is particularly susceptible to nonenzymatic glycation and may become inactivated under conditions of pronounced oxidative stress (Cecerska-Heryć *et al*., 2025). These alterations impair the functional capacity of leukocytes and, thereby, contribute to the development of diabetic complications and associated comorbidities.

Type 1 DM represents the most life-threatening form of the disease due to its autoimmune etiology. Currently, this condition cannot be prevented, halted, or reversed (Rodrigues Oliveira *et al*., 2023). Therefore, the identification of therapeutic approaches capable of alleviating disease manifestations and slowing its progression remains an important research priority. A growing body of evidence indicates that bioactive antioxidant compounds may mitigate oxidative–carbonyl stress associated with diabetes. Plant-derived materials represent an important source of such compounds (Anwar *et al*., 2021; Holst & Williamson, 2008; Khangholi *et al*., 2015; Yeh *et al*., 2017). In particular, plants of the Cornaceae family are characterized by a high content of natural antioxidants, including phenolic compounds (anthocyanins, phenolic acids, and flavonols) and iridoids, especially in the fruits of the cornelian cherry (*Cornus mas* L.) (Bayram & Arda Ozturkcan, 2020; Brodyak *et al*., 2025; Dzydzan *et al*., 2020). The abundance of these compounds depends on plant genotype, cultivation practices, environmental growth conditions, as well as fruit maturity and coloration (Brodyak *et al*., 2025). Bioactive constituents of *C. mas* fruits have been reported to exert multiple biological effects, including antidiabetic, antioxidant, and anti-inflammatory activities (Brodyak *et al*., 2025; Dzydzan *et al*., 2020). Therefore, the work aimed to investigate the effect of extracts from the fruits of the ‘Podolski’ and ‘Yantarnyi‘ & ‘Flava‘ cultivars of the cornelian cherry (*Cornus mas* L.), and the iridoid glycoside of these fruits – loganic acid on the content of AGEs and RAGEs in leukocytes and blood plasma of rats with streptozotocin-induced diabetes.

MATERIALS AND METHODS

Animal Study. The animal experiments were approved by the Ethics Committee of the Department of Biochemistry of the Faculty of Biology (Protocol 57-02-2026 dated 16 February, 2026), Ivan Franko National University of Lviv, Ukraine. Experiments were performed in accordance with international standards of humane treatment of laboratory rats and the requirements of Article 26 of the Law of Ukraine “On the Protection of Animals from Cruelty”, the Directive 2010/63/EU of the European Parliament and the Council of 22 October 2010 on the protection of animals used for scientific purposes and

the National Institutes of Health guide for the care and use of laboratory animals (NIH publications no. 8023, revised 1978). Experimental procedures and handling of the animals were carried out as stipulated by the guidelines for the humane use of animals.

Induction of DM in rats. Male Wistar strain rats weighing 140 ± 10 g were used in the experiments. The rats were kept in standard vivarium conditions (free access to water and standard chow, 12/12 h light/dark cycle). The room temperature and humidity were maintained at about 22 ± 2 °C and 60 ± 5 %, respectively. After one week of adaptation, DM was induced in rats by intra-peritoneal injection of streptozotocin (STZ) (Sigma-Aldrich, St Louis, MO, USA), dissolved in 10 mM citrate buffer (pH 4.5), at a dosage of 55 mg/kg of body weight (b.w.). The development of DM was monitored by measuring blood glucose levels. This was done 72 hours after and on the 10th day following the administration of STZ using the glucose oxidase method (Filicit-Diagnostics kit, Dnipro, Ukraine). In the subsequent experiments, rats with glucose levels exceeding 12 mM were used. The animals of the control group were selected among intact animals, which had a glucose concentration in the range of 3.7–5.0 mM.

Rats were randomly divided into five groups containing eight animals each: group 1 – control rats (healthy animals), group 2 (DM) – rats with STZ-induced DM, group 3 (DM + extract 'Podolski') – diabetic rats treated with the extract from the fruits of the 'Podolski' cultivar of *C. mas*, group 4 (DM + extract 'Yantarnyi' & 'Flava') – diabetic rats treated with the extract from the fruits of the 'Yantarnyi' & 'Flava' cultivars of *C. mas*, group 5 (DM + loganic acid) – diabetic rats treated with loganic acid. Loganic acid is represented by a mixture of three isomers of loganic acid extracted from fruits of the cornelian cherry 'Yantarnyi' & 'Flava' cultivars.

On the 10th day following the induction of diabetes, the rats with DM from the third to fifth groups were orally administered the extracts of the different cultivars of the cornelian cherry for 14 days at a dose of 20 mg per 1 kg of b.w. The extracts were dissolved in water and administered in the amount of 1 mL per rat. The amount and duration of extract administration were based on previous studies (Dzydzan *et al.*, 2020). Once daily for 14 days, rats of the control and DM groups received 1 mL per rat of water by gavage.

Methods of preparation of the extracts from the cornelian cherry fruits, their identification, and determination of bioactive compounds of extracts by UPLC-qTOF-MS/MS and HPLC-PDA methods are described by A. Z. Kucharska in O. Dzydzan *et al.* (2020).

The object of study and blood collection. The study focused on blood leukocytes and plasma obtained from rats. On the last day of the experiment (24 days after STZ administration), rats of all groups were decapitated under ether anesthesia. Blood samples were collected with the addition of heparin (heparin : blood ratio of 1 : 100). Blood was centrifuged for 15 min at 960 g in an Eppendorf 5417 R centrifuge to obtain plasma. Plasma was frozen and stored at -20 °C for further measurements.

Isolation of blood leukocytes. Leukocytes were isolated from blood by centrifugation over a gradient of ficoll-triombrast density (r = 1.076–1.078). Then, the cells were washed three times with cold (4 °C) phosphate-buffered saline (PBS: 137 мМ NaCl, 2.7 мМ KCl, 10 мМ $Na_2HPO_4 \cdot 7H_2O$, 1.8 мМ KH_2PO_4, pH 7.4). Leukocytes ($2.5 \cdot 10^6$) were lysed in 150 µL of the buffer composed of 0.5 % Triton X-100, 100 mM KCl, 5 mM $MgCl_2$, 2 mM EGTA, 25 mM Tris (pH 7.5), and a protease inhibitor cocktail (Sigma, USA). The lysates of leukocytes were centrifuged at 10,600 g for 10 min at 4 °C to remove cell debris. Supernatants were collected and used for separation in SDS-PAAG, followed by the immunoblot analysis of RAGE antibodies. The protein content in lysates of leukocytes and plasma was determined according to Lowry's method (Lowry *et al.*, 1951).

Assay of the content of fluorescent AGEs. AGE levels in blood plasma and in leukocytes were determined according to the method described by Putta and Kilari (Putta & Kilari, 2015). Plasma was diluted with PBS (pH 7.4) in a ratio 1 : 50. AGE levels in leukocytes and in plasma were determined by measuring the fluorescence at an excitation wavelength of λ = 370 nm and an emission wavelength of λ = 440 nm. Solution of BSA (bovine serum albumin) was used as a standard (1 mg/mL), and its fluorescence intensity was defined as one unit of fluorescence. The fluorescence intensity was expressed in arbitrary units (AU) per mg of protein.

Immunocytochemical assay of the content of non-fluorescent AGEs and RAGEs. Non-fluorescent AGEs in leukocytes and flRAGEs on the leukocyte membrane were detected and visualized in blood leukocytes by indirect immunoperoxidase method. Leukocytes (150.000/μL) were applied on a microscope glass slide, fixed with methanol solution (10 min, -4 °C) and then with chilled acetone for two min. Cells were permeabilized with 0.1 % Triton X-100 in PBS (PBS-T). Preparations were incubated for 5 min with 0.3 % H_2O_2 solution to block endogenous cell peroxidase and exposed to blocking buffer (1 % BSA in PBS for 1 h for blocking binding sites. The cells were incubated with Rabbit AGE Antibody (orb10064, Biorbyt, Great Britain) or Rabbit RAGE Antibody (16346-1-AP, Proteintech, США), diluted in blocking buffer in a ratio 1 : 300, for 2 h at room temperature, washed with PBS containing 0.05 % Triton X-100, and then incubated with secondary antibody LSAB®2 Biotinylated Link for Streptavidin HRP/AP (DAKO, USA), diluted in blocking buffer in a ratio 1 : 500, for 1 h at room temperature. After washing in 0.05 % PBS-T, a color reaction was performed to detect positive signals using 3,3′-diaminobenzidine (DAB) and 0.015 % H_2O_2. The content of AGEs or RAGEs in the studied cells was analyzed by light microscopy using a ×40 objective of the MICROmedXS-5520 microscope and a video camera for the microscope (DCM310) with software (ScopePhoto). The specificity of binding was confirmed using negative controls (cell samples without the use of primary and secondary antibodies). The binding of antibodies to AGEs or RAGEs of leukocytes was characterized by the activity of the peroxidase reaction, which was detected by brown deposits of oxidative polymerization products of DAB in the mode of digitizing microphotographs of leukocytes (500 cells were differentiated on the preparation). The intensity of antibody binding was assessed on a scale of «+» and «–». The content of AGE^+ leukocytes and $RAGE^+$ leukocytes was calculated by the proportion.

Immunoblotting. The lysates of leukocytes were subjected to 10 % SDS–PAGE, transferred onto nitrocellulose sheets and immunoblotted essentially. The membranes were probed with Rabbit RAGE Antibody (16346-1-AP, Proteintech, USA) followed by goat anti-rabbit IgG-HRP conjugate (AP308P, Millipore, USA). The immunoreactive bands visualized by chemiluminescence (Pierce, Rockford, Illinois) were analyzed densitometrically using GelPro32.

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

Differential effects of diabetes and cornelian cherry fruit extracts on AGEs accumulation in plasma and leukocytes. AGEs are important diagnostic markers used to assess treatment efficacy under hyperglycemic conditions. Strategies aimed at preventing AGE formation or reducing their accumulation have therapeutic potential for delaying the progression of diabetic complications. According to our findings, DM was associated with a 1.5-fold increase in plasma AGE levels compared with control rats (**Fig. 1*A***). This increase is consistent with previously reported elevations in blood glucose and glycated hemoglobin levels in diabetic rats (Dzydzan *et al.*, 2020), indicating sustained hyperglycemia.

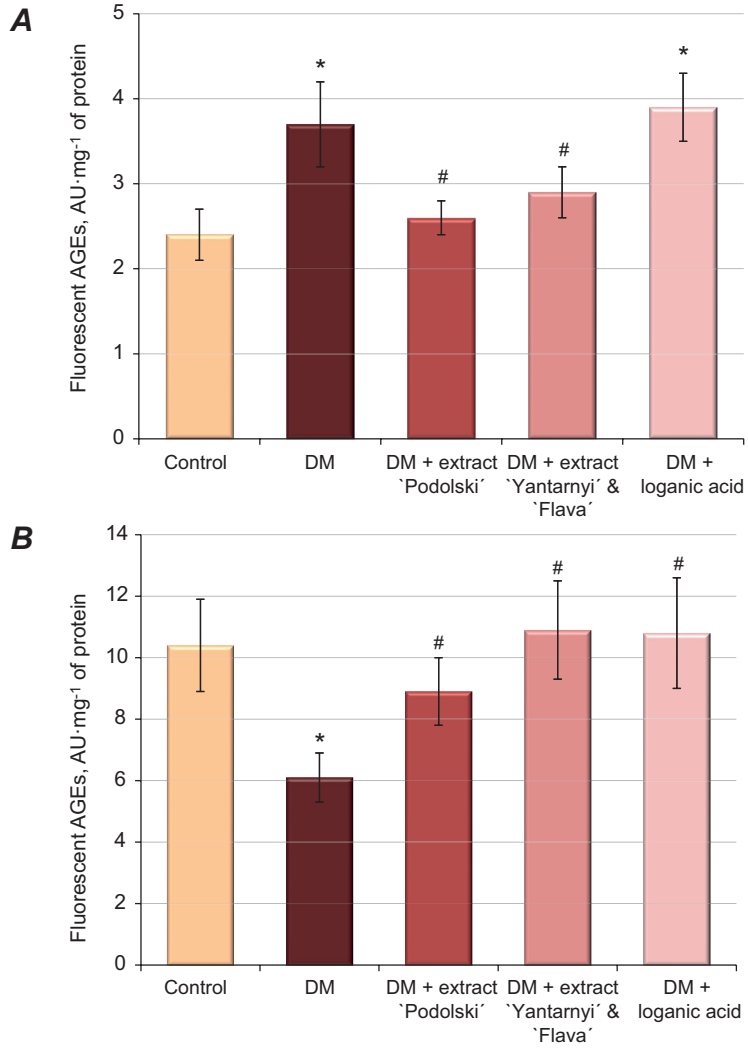

Fig. 1. The content of fluorescent AGEs in plasma (***A***) and in leukocytes (***B***) of control rats, with DM and diabetic rats treated with the extracts from the fruits of *C. mas* `Podolski´ cultivar, `Yantarnyi´ & `Flava´ cultivars, and loganic acid. *Designations*. Compared to the control group: * – $P < 0.05$; compared to the DM group: # – $P < 0.05$

Analysis of both fluorescent and non-fluorescent AGEs in plasma and blood leukocytes of diabetic rats (**Fig. 1** and **2**) allowed us to evaluate the effects of *C. mas* fruit extracts from different cultivars on oxidative–carbonyl stress, for which these compounds serve as biomarkers. Oral administration of fruit extracts from the 'Podolski' cultivar, characterized by red-colored ripe fruits, as well as the 'Yantarnyi' & 'Flava' cultivars, which produce yellow-colored ripe fruits, resulted in a significant reduction in plasma fluorescent AGE levels by 24 % and 22 %, respectively, in diabetic rats. The observed decrease in AGE content may be attributed to the hypoglycemic and antioxidant properties of these extracts, as previously demonstrated (Brodyak *et al.*, 2025). In contrast, administration of loganic acid to diabetic rats did not exert a hypoglycemic effect (Dzydzan *et al.*, 2020). Consequently, protein glycation in plasma persisted, which likely accounted for the elevated AGE levels observed in this group (**Fig. 1*A***).

In DM, chronic hyperglycemia resulted in a marked increase in plasma AGE levels (**Fig. 1*A***). In contrast, leukocytes isolated from blood of diabetic rats exhibited a significant reduction in fluorescent AGE content, which was 1.7-fold lower than that observed in control animals (**Fig. 1*B***). Immunocytochemical analysis of non-fluorescent AGEs in leukocytes, classified as AGE-positive (AGE^+) and AGE-negative (AGE^-) cells (**Fig. 2*A***), further confirmed a decrease in intracellular AGE accumulation under diabetic conditions (**Fig. 2*B***). Specifically, AGE^+ leukocytes accounted for 59 % in the control group and only 47 % in diabetic rats (**Fig. 2*B***).

These findings may be explained by the non-enzymatic and spontaneous nature of protein glycation, which depends on protein half-life, the degree and duration of hyperglycemia, and tissue or cellular permeability to free glucose (Lang *et al.*, 2020). In leukocytes, impaired glucose transport due to dysfunction of insulin-dependent glucose transporters under hypoinsulinemic conditions likely contributes to the observed reduction in intracellular AGE formation. Indeed, glucose uptake in leukocytes is mediated by specific glucose transporter (GLUT) isoforms. GLUT3 and GLUT4, which are expressed in leukocytes and translocate to the plasma membrane upon activation by insulin and other stimuli, exhibit a higher affinity for glucose than the insulin-independent GLUT1 isoform. GLUT1 primarily transports reduced sugars, including glucose, mannose, galactose, and glucosamine (Maratou *et al.*, 2007; Vrhovac *et al.*, 2014). Accordingly, reduced translocation of GLUT3 and GLUT4 to the leukocyte plasma membrane under hypoinsulinemic conditions likely leads to decreased intracellular glucose availability and, consequently, attenuated AGE formation.

In contrast, administration of fruit extracts from *C. mas* cultivars 'Podolski', 'Yantarnyi' & 'Flava' and loganic acid to diabetic rats resulted in a significant increase in fluorescent AGE levels in leukocytes by 1.45-, 1.74-, and 1.77 times, respectively, compared with untreated diabetic animals (**Fig. 1*B***). Similarly, the content of non-fluorescent AGEs in leukocytes increased by 19 % following treatment with the 'Podolski' cultivar extract, by 21 % after administration of the 'Yantarnyi' & 'Flava' cultivars extract, and by 63 % in response to loganic acid (**Fig. 2*B***).

The hypoglycemic and antioxidant activities of cornelian cherry fruit extracts (Brodyak *et al.*, 2025; Dzydzan *et al.*, 2020) likely enhance glucose uptake by leukocytes, thereby restoring intracellular glucose availability and normalizing AGE formation to levels comparable with those observed in control animals (**Fig. 1*B*** and **2**). Endogenous AGE formation represents an integral component of normal metabolic processes and occurs physiologically in all tissues and body fluids, both intracellularly and extracellularly, through non-enzymatic reactions between carbonyl groups of reducing sugars and free amino groups of proteins (Chen *et al.*, 2018).

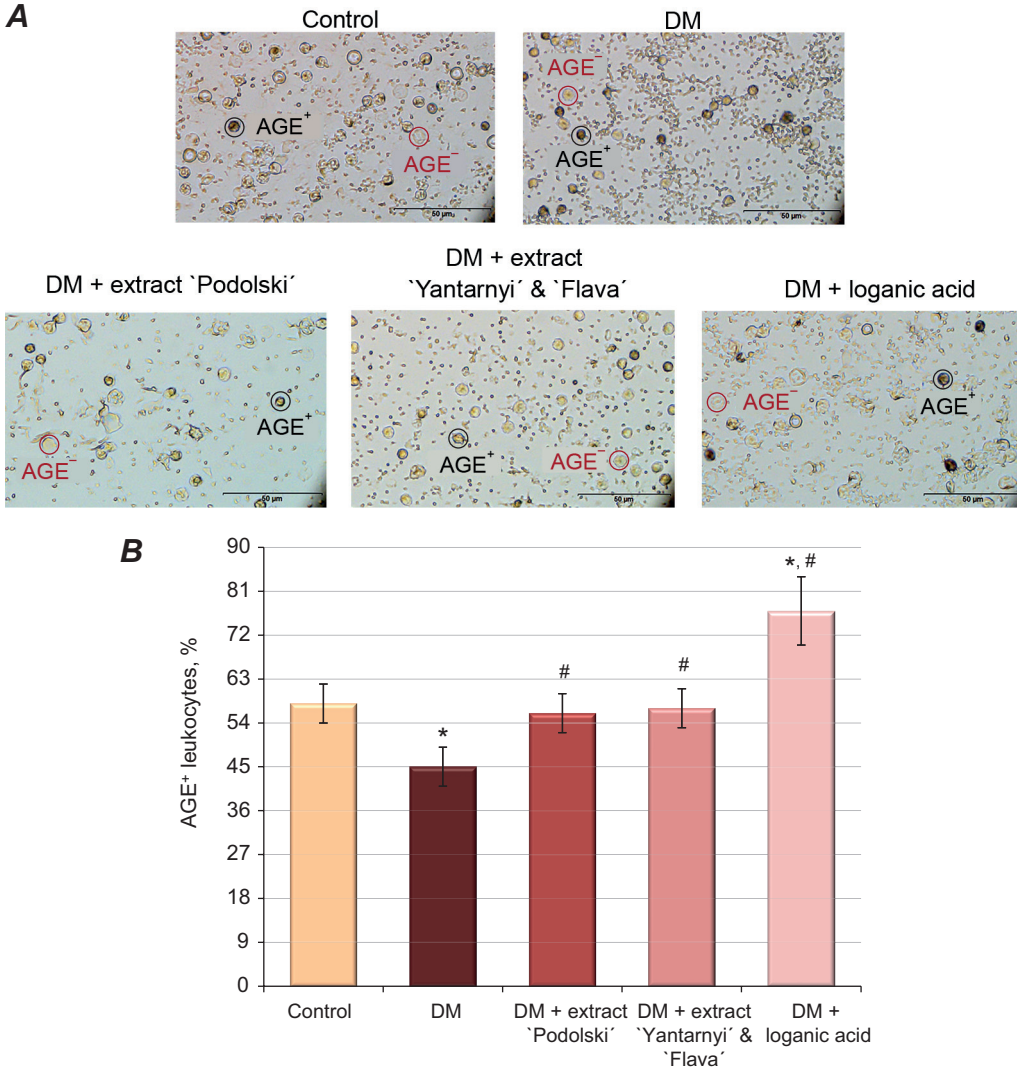

Fig. 2. Representative micrographs of immunocytochemical staining of blood leukocytes using antibodies against AGEs (**A**), and quantitative analysis of AGE-positive (AGE^+) and AGE-negative (AGE^+) leukocytes (%) in control rats, STZ-induced diabetic rats, and diabetic rats treated with fruit extracts from different *C. mas* cultivars. *Designations*. Compared to the control group: * – $P < 0.05$; compared to the DM group: # – $P < 0.05$

Notably, loganic acid induced the most pronounced increase in non-fluorescent AGE levels in leukocytes (**Fig. 2**). This effect may be attributed to its ability to enhance glucose uptake by leukocytes despite the absence of a systemic hypoglycemic effect in diabetic conditions, thereby promoting intracellular glycation processes (Dzydzan *et al.*, 2020).

Effects of cornelian cherry fruit extracts on leukocyte RAGE expression and plasma sRAGE levels in experimental DM. The biological effects of AGEs are primarily mediated through their interaction with cell-surface receptors for AGEs (RAGEs), which activate pro-inflammatory signaling pathways (Khalid *et al.*, 2022). Under physiological

conditions, RAGE is expressed at low levels in various cell types, including cardiomyocytes, neurons, endothelial cells, dendritic cells, neutrophils, monocytes/macrophages, and lymphocytes. However, RAGE expression is markedly upregulated in multiple pathological states. The AGE–RAGE axis plays a critical role in the pathogenesis of both type 1 and type 2 DM and their associated complications (Goh & Cooper, 2008).

To assess membrane-bound RAGE expression in blood leukocytes, immunocytochemical analysis was performed. During image analysis, leukocytes were classified as RAGE-positive (RAGE$^+$) or RAGE-negative (RAGE$^-$) cells (**Fig. 3*A***).

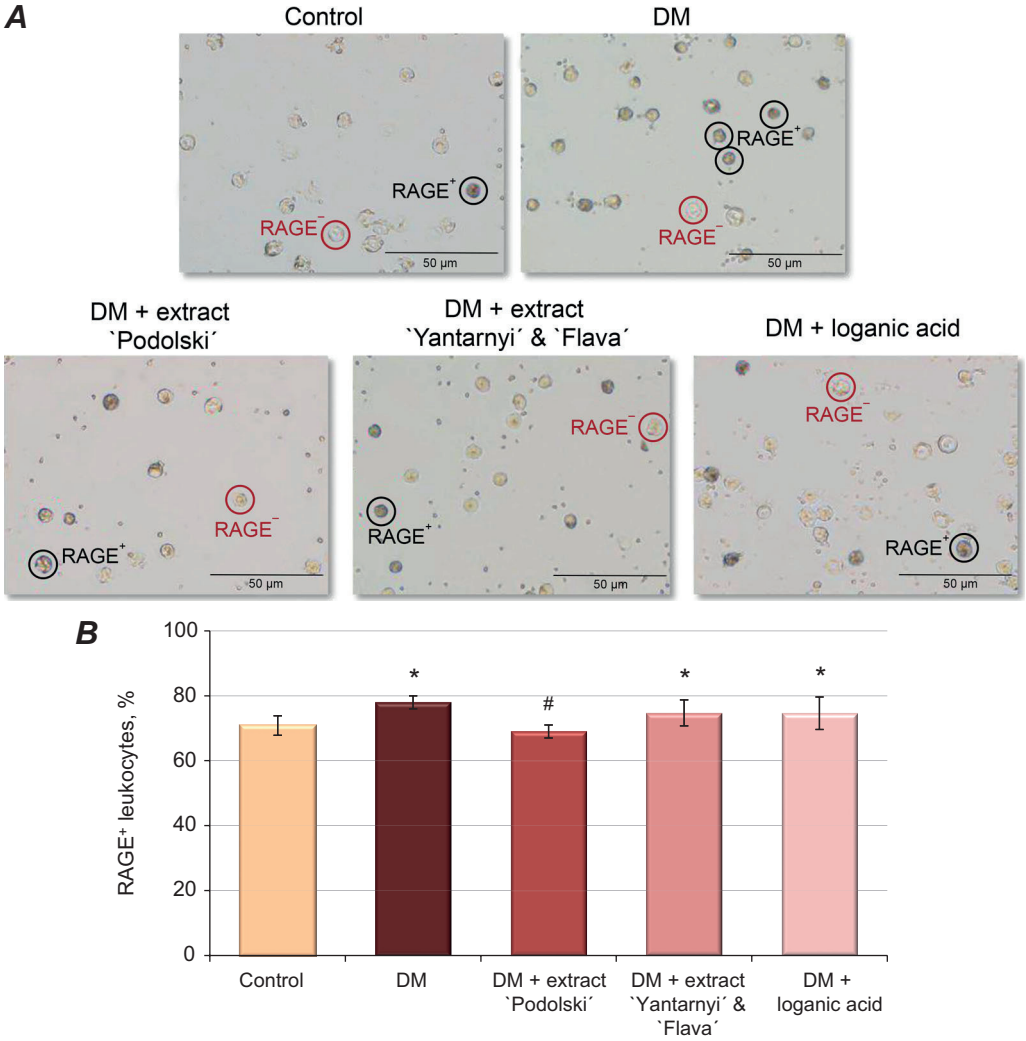

Fig. 3. Immunocytochemical analysis of blood leukocytes using antibodies against the receptor for AGEs (***A***), and quantitative analysis of the proportion of RAGE-positive (RAGE$^+$) leukocytes (%) in control rats, STZ-induced diabetic rats, and diabetic rats treated with fruit extracts from different *C. mas* cultivars (***B***). *Designations*. Compared to the control group: * – $P < 0.05$; compared to the DM group: $^{\#}$ – $P < 0.05$

Based on the obtained data, a modest but statistically significant increase (approximately 10 %) in the proportion of RAGE$^+$ leukocytes was observed in diabetic rats com-

pared with controls (**Fig. 3*B***). It is well established that increased circulating AGE levels enhance RAGE gene expression and translation, thereby creating a positive feedback loop that promotes leukocyte activation (Gallucci, 2016). Accordingly, the elevated plasma AGE levels detected under diabetic conditions (**Fig. 1*A***) were associated with enhanced RAGE expression on leukocyte membranes (**Fig. 3**).

RAGE exists in several isoforms, including a soluble extracellular form, which lacks the C-terminal cytoplasmic domain but retains all immunoglobulin-like domains present in flRAGE (Heier *et al.*, 2015). According to our results, plasma sRAGE levels were significantly increased in diabetic rats (**Fig. 4**). Soluble RAGE can be generated either by proteolytic shedding of the extracellular domain of flRAGE mediated by metalloproteinases or through alternative splicing. We hypothesize that the elevated sRAGE levels observed in diabetes result primarily from enhanced proteolytic cleavage of flRAGE, whose membrane expression in leukocytes was increased under diabetic conditions (**Fig. 3**).

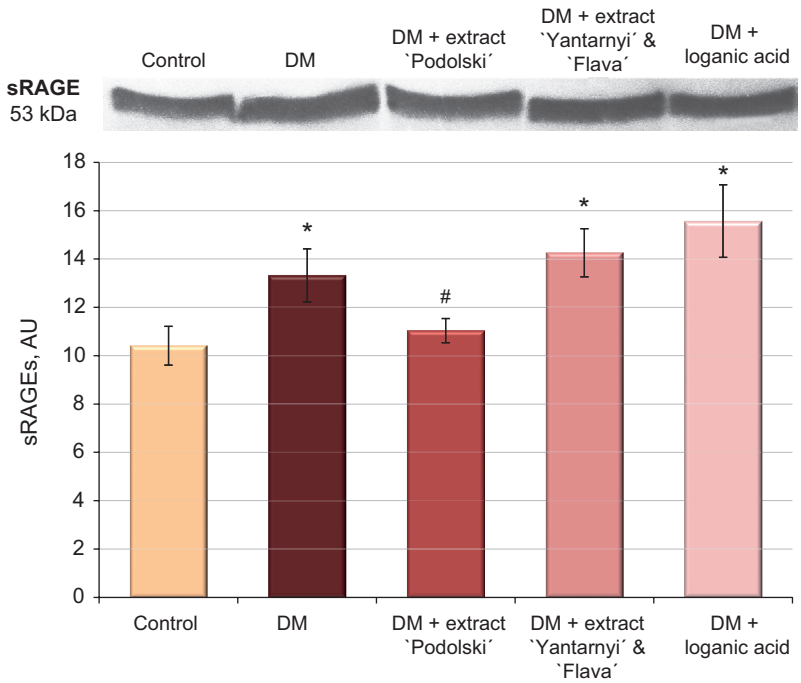

Fig. 4. Plasma levels of soluble RAGE (sRAGE) in control rats, STZ-induced diabetic rats, and diabetic rats treated with fruit extracts from *C. mas* 'Podolski' cultivar, 'Yantarnyi' & 'Flava' cultivars, and loganic acid. sRAGE content was assessed by immunoblotting and quantified using GelPro32 software. The amount of protein loaded into each well and its transfer to the membrane were monitored by Ponceau staining and analyzed using GelPro 32. *Designations*. Compared to the control group: * – $P < 0.001$; compared to the DM group: # – $P < 0.01$

Notably, only administration of *C. mas* fruit extract from the 'Podolski' cultivar resulted in a reduction of both membrane-bound RAGE expression in leukocytes and plasma sRAGE levels to values comparable with those of control animals (**Fig. 3** and **4**). These changes in plasma sRAGE concentration are likely associated with the ability of the 'Podolski' cultivar extract to modulate plasma AGE levels (**Fig. 1**) and reduce the proportion of $RAGE^+$ leukocytes (**Fig. 3**), suggesting a coordinated regulatory effect on the AGE–RAGE axis.

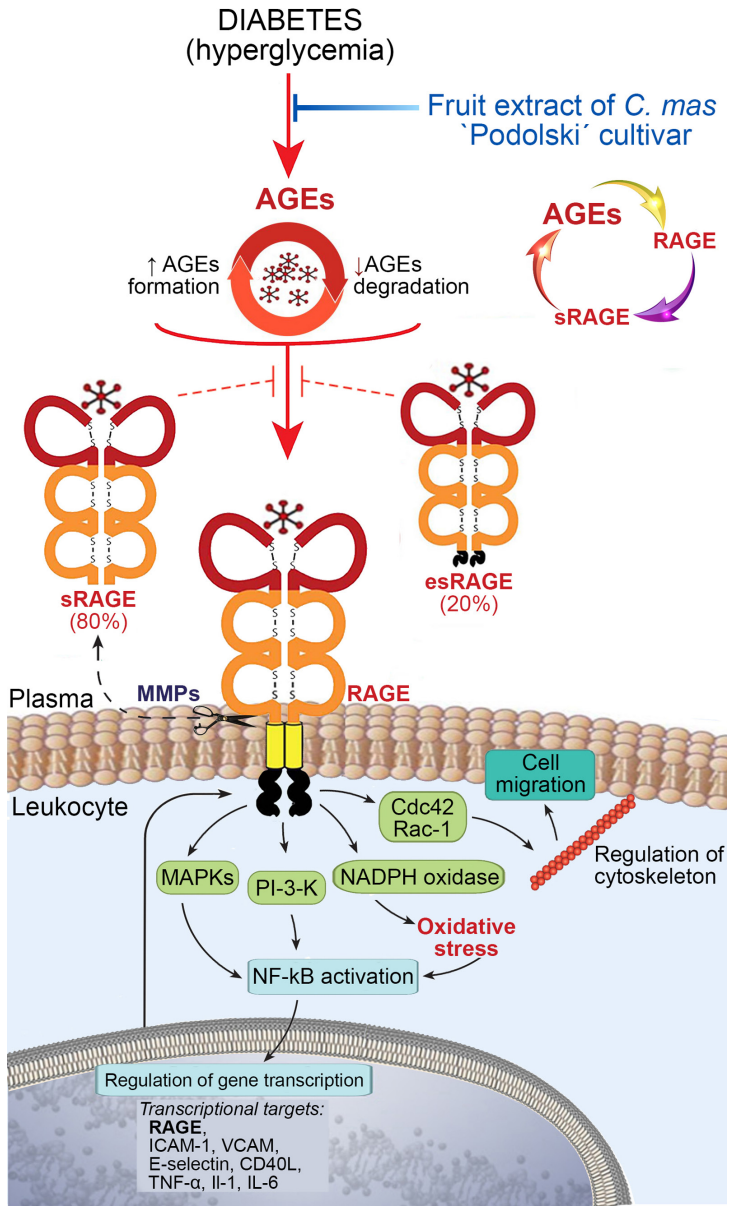

Fig. 5. The effects of AGEs, formed under hyperglycemic conditions, on circulating sRAGE in plasma and membrane-bound RAGEs expression in blood leukocytes. AGEs positively regulate RAGE expression in leukocytes, while sRAGE can be generated through proteolytic shedding of membrane-bound RAGE mediated by matrix metalloproteinases (MMPs); therefore, sRAGE levels may positively correlate with circulating AGEs. The fruit extract of *Cornus mas* L. 'Podolski' cultivar reduces AGE levels and disrupts the positive feedback loop AGEs → RAGE → sRAGE

Abbreviation: CD40L, CD40 ligand; CDC42, cell division cycle 42; esRAGE, endogenous secretory RAGE; *ICAM1,* Intercellular adhesion molecule; 1IL, Interleukin; MAPKs, Mitogen-activated protein kinases; NF-κB, Nuclear factor kappa B; PI-3-K, Phosphoinositide 3-kinase; Rac1, Ras-related C3 botulinum toxin substrate 1; TNFα, Tumor necrosis factor; VCAM1, Vascular cell adhesion molecule 1

The effects of the cornelian cherry fruit extracts on AGE levels in plasma and leukocytes, as well as on different RAGE isoforms under diabetic conditions, are summarized schematically in **Fig. 5**. Enhanced plasma protein glycation represents a direct pathological consequence of DM, as it promotes the formation of intermolecular cross-links, alters protein half-life, disrupts enzymatic activity, and impairs ligand-binding affinity. In addition, activation of the AGE–RAGE axis triggers multiple intracellular signaling pathways, including the stimulation of ROS generation via NADPH-oxidases. These processes may contribute to the development of oxidative-carbonyl stress in blood leukocytes of rats under the experimental conditions examined in this study (**Fig. 5**).

It is worth noting that among the tested extracts, only the fruit extract of *C. mas* 'Podolski' cultivar, which exhibits the most pronounced hypoglycemic effect (Brodyak *et al.*, 2025), was associated with a reduction in both membrane-bound flRAGE and sRAGE isoforms. This extract significantly lowered circulating AGE levels in plasma, which likely resulted in a concomitant decrease in sRAGE concentration (**Fig. 4**).

Considering the AGE–RAGE interaction at the cellular level and the ability of the 'Podolski' cultivar extract to disrupt the positive feedback loop (AGEs → RAGE → sRAGE) in plasma and in leukocytes, it can be hypothesized that this molecular mechanism underlies the inhibitory effects of the extract's bioactive compounds on stress-induced signaling pathways (**Fig. 5**). Collectively, these findings suggest that the fruit extract of *C. mas* 'Podolski' cultivar may represent a promising candidate for adjunctive strategies aimed at mitigating metabolic and inflammatory disturbances associated with DM.

CONCLUSIONS

An increase in plasma levels of AGEs and sRAGE was observed in rats with experimental DM. In contrast, blood leukocytes from diabetic animals exhibited reduced levels of both fluorescent and non-fluorescent AGEs accompanied by increased expression of flRAGE compared with control animals. These alterations in intracellular AGE content may be associated with impaired glucose transport into leukocytes under diabetic conditions.

Importantly, only the fruit extract of *C. mas* 'Podolski' cultivar reduced plasma AGE levels as well as RAGE isoforms involved in pro-inflammatory signaling. These findings highlight the potential of this extract to modulate the AGE–RAGE axis and support its further investigation as a biologically relevant approach for improving metabolic and inflammatory status in DM.

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

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REFERENCES

Alba-Loureiro, T. C., Munhoz, C. D., Martins, J. O., Cerchiaro, G. A., Scavone, C., Curi, R., & Sannomiya, P. (2007). Neutrophil function and metabolism in individuals with diabetes mellitus. *Brazilian Journal of Medical and Biological Research*, 40(8), 1037–1044. doi:10.1590/s0100-879x2006005000143
Crossref ● PubMed ● Google Scholar

Anwar, S., Khan, S., Almatroudi, A., Khan, A. A., Alsahli, M. A., Almatroodi, S. A., & Rahmani, A. H. (2021). A review on mechanism of inhibition of advanced glycation end products formation by plant derived polyphenolic compounds. *Molecular Biology Reports*, 48(1), 787–805. doi:10.1007/s11033-020-06084-0
Crossref ● PubMed ● Google Scholar

Bayram, H. M., & Arda Ozturkcan, S. (2020). Bioactive components and biological properties of cornelian cherry (*Cornus mas* L.): a comprehensive review. *Journal of Functional Foods*, 75, 104252. doi:10.1016/j.jff.2020.104252
Crossref ● Google Scholar

Brodyak, I., Moroz, A., Bernacka, K., Kucharska, A. Z., & Sybirna, N. (2025). Alleviation of hyperglycaemia and oxidative stress by fruit extracts of different cultivars of the cornelian cherry (*Cornus mas* L. and *Cornus mas* × *Cornus officinalis*) in rats with diabetes mellitus. *Food & Function*, 16(5), 2136–2155. doi:10.1039/d4fo05426a
Crossref ● PubMed ● Google Scholar

Cecerska-Heryć, E., Engwert, W., Michałów, J., Marciniak, J., Birger, R., Serwin, N., Heryć, R., Polikowska, A., Goszka, M., Wojciuk, B., Wiśniewska, M., & Dołęgowska, B. (2025). Oxidative stress markers and inflammation in type 1 and 2 diabetes are affected by BMI, treatment type, and complications. *Scientific Reports*, 15(1), 23605. doi:10.1038/s41598-025-05818-z
Crossref ● PubMed ● PMC ● Google Scholar

Challier, M., Jacqueminet, S., Benabdesselam, O., Grimaldi, A., & Beaudeux, J.-L. (2005). Increased serum concentrations of soluble receptor for advanced glycation end products in patients with type 1 diabetes. *Clinical Chemistry,* 51(9), 1749–1750. doi:10.1373/clinchem.2005.051961
Crossref ● PubMed ● Google Scholar

Chen, J.-H., Lin, X., Bu, C., & Zhang, X. (2018). Role of advanced glycation end products in mobility and considerations in possible dietary and nutritional intervention strategies. *Nutrition & Metabolism*, 15(1), 72. doi:10.1186/s12986-018-0306-7
Crossref ● PubMed ● PMC ● Google Scholar

Dariya, B., & Nagaraju, G. P. (2020). Advanced glycation end products in diabetes, cancer and phytochemical therapy. *Drug Discovery Today*, 25(9), 1614–1623. doi:10.1016/j.drudis.2020.07.003
Crossref ● PubMed ● Google Scholar

Dong, H., Zhang, Y., Huang, Y., & Deng, H. (2022). Pathophysiology of RAGE in inflammatory diseases. *Frontiers in Immunology*, 13, 931473. doi:10.3389/fimmu.2022.931473
Crossref ● PubMed ● PMC ● Google Scholar

Dzydzan, O., Brodyak, I., Sokół-Łętowska, A., Kucharska, A. Z., & Sybirna, N. (2020). Loganic acid, an iridoid glycoside extracted from *Cornus mas* L. fruits, reduces of carbonyl/oxidative stress biomarkers in plasma and restores antioxidant balance in leukocytes of rats with streptozotocin-induced diabetes mellitus. *Life*, 10(12), 349. doi:10.3390/life10120349
Crossref ● PubMed ● PMC ● Google Scholar

Erusalimsky, J. D. (2021). The use of the soluble receptor for advanced glycation-end products (sRAGE) as a potential biomarker of disease risk and adverse outcomes. *Redox Biology*, 42, 101958. doi:10.1016/j.redox.2021.101958
Crossref ● PubMed ● PMC ● Google Scholar

Gallucci, S. (2016). An overview of the innate immune response to infectious and noninfectious stressors. In M. Amadori (Ed.), *The innate immune response to noninfectious stressors* (Ch. 1, pp. 1–24). Academic Press. doi:10.1016/b978-0-12-801968-9.00001-5
Crossref ● Google Scholar

Goh, S.-Y., & Cooper, M. E. (2008). The role of advanced glycation end products in progression and complications of diabetes. *The Journal of Clinical Endocrinology & Metabolism*, 93(4), 1143–1152. doi:10.1210/jc.2007-1817
Crossref ● PubMed ● Google Scholar

Heier, M., Margeirsdottir, H. D., Gaarder, M., Stensæth, K. H., Brunborg, C., Torjesen, P. A., Seljeflot, I., Hanssen, K. F., & Dahl-Jørgensen, K. (2015). Soluble RAGE and atherosclerosis in youth with type 1 diabetes: a 5-year follow-up study. *Cardiovascular Diabetology*, 14(1), 126. doi:10.1186/s12933-015-0292-2
Crossref ● PubMed ● PMC ● Google Scholar

Holst, B., & Williamson, G. (2008). Nutrients and phytochemicals: from bioavailability to bioefficacy beyond antioxidants. *Current Opinion in Biotechnology*, 19(2), 73–82. doi:10.1016/j.copbio.2008.03.003
Crossref ● PubMed ● Google Scholar

Kato, S., Matsumura, T., Sugawa, H., & Nagai, R. (2024). Correlation between serum advanced glycation end-products and vascular complications in patient with type 2 diabetes. *Scientific Reports*, 14(1), 18722. doi:10.1038/s41598-024-69822-5
Crossref ● PubMed ● PMC ● Google Scholar

Khalid, M., Petroianu, G., & Adem, A. (2022). Advanced glycation end products and diabetes mellitus: mechanisms and perspectives. *Biomolecules*, 12(4), 542. doi:10.3390/biom12040542
Crossref ● PubMed ● PMC ● Google Scholar

Khangholi, S., Majid, F. A., Berwary, N. J., Ahmad, F., & Aziz, R. B. (2016). The mechanisms of inhibition of advanced glycation end products formation through polyphenols in hyperglycemic condition. *Planta Medica*, 82(1-2), 32–45. doi:10.1055/s-0035-1558086
Crossref ● PubMed ● Google Scholar

Lamprea-Montealegre, J. A., Arnold, A. M., McCLelland, R. L., Mukamal, K. J., Djousse, L., Biggs, M. L., Siscovick, D. S., Tracy, R. P., Beisswenger, P. J., Psaty, B. M., Ix, J. H., & Kizer, J. R. (2022). Plasma levels of advanced glycation endproducts and risk of cardiovascular events: findings from 2 prospective cohorts. *Journal of the American Heart Association*, 11(15), e024012. doi:10.1161/jaha.121.024012
Crossref ● PubMed ● PMC ● Google Scholar

Lang, F., Singh, Y., Salker, M. S., Ma, K., Pandyra, A. A., Lang, P. A., & Lang, K. S. (2020). Glucose transport in lymphocytes. *Pflügers Archiv – European Journal of Physiology*, 472(9), 1401–1406. doi:10.1007/s00424-020-02416-y
Crossref ● PubMed ● Google Scholar

Lowry, O. H., Rosebrough, N. J., Farr, A. L., & Randall, R. J. (1951). Protein measurement with the Folin phenol reagent. *The Journal of Biological Chemistry*, 193(1), 265–275. doi:10.1016/s0021-9258(19)52451-6
Crossref ● PubMed ● Google Scholar

Luo, X., Wu, J., Jing, S., & Yan, L. J. (2016). Hyperglycemic stress and carbon stress in diabetic glucotoxicity. *Aging and Disease*, 7(1), 90–110. doi:10.14336/ad.2015.0702
Crossref ● PubMed ● PMC ● Google Scholar

Maratou, E., Dimitriadis, G., Kollias, A., Boutati, E., Lambadiari, V., Mitrou, P., & Raptis, S. A. (2007). Glucose transporter expression on the plasma membrane of resting and activated white blood cells. *European Journal of Clinical Investigation,* 37(4), 282–290. doi:10.1111/j.1365-2362.2007.01786.x
Crossref ● PubMed ● Google Scholar

Nomi, Y., Kudo, H., Miyamoto, K., Okura, T., Yamamoto, K., Shimohiro, H., Kitao, S., Ito, Y., Egawa, S., Kawahara, K., Otsuka, Y., & Ueta, E. (2020). Free advanced glycation end product distribution in blood components and the effect of genetic polymorphisms. *Biochimie*, 179, 69–76. doi:10.1016/j.biochi.2020.09.010
Crossref ● PubMed ● Google Scholar

Putta, S., & Kilari, E. K. (2015). A review on methods of estimation of advanced glycation end products. *World Journal of Pharmaceutical Research*, 4, 689–699.
Google Scholar

Rhee, S. Y., & Kim, Y. S. (2018). The role of advanced glycation end products in diabetic vascular complications. *Diabetes & Metabolism Journal,* 42(3), 188–195. doi:10.4093/dmj.2017.0105
Crossref ● PubMed ● PMC ● Google Scholar

Rodrigues Oliveira, S. M., Rebocho, A., Ahmadpour, E., Nissapatorn, V., & de Lourdes Pereira, M. (2023). Type 1 diabetes mellitus: a review on advances and challenges in creating insulin producing devices. *Micromachines*, 14(1), 151. doi:10.3390/mi14010151
Crossref ● PubMed ● PMC ● Google Scholar

Ruiz, H., Ramasamy, R., & Schmidt, A. M. (2020). Advanced glycation end products: building on the concept of the “Common soil” in metabolic disease. *Endocrinology,* 161(1), bqz006. doi:10.1210/endocr/bqz006
Crossref ● PubMed ● PMC ● Google Scholar

Shen, C.-Y., Lu, C.-H., Wu, C.-H., Li, K.-J., Kuo, Y.-M., Hsieh, S.-C., & Yu, C.-L. (2020). The development of Maillard reaction, and advanced glycation end product (AGE)-receptor for age (RAGE) signaling inhibitors as novel therapeutic strategies for patients with AGE-related diseases. *Molecules,* 25(23), 5591. doi:10.3390/molecules25235591
Crossref ● PubMed ● PMC ● Google Scholar

Thomas, M. C., Söderlund, J., Lehto, M., Mäkinen, V. P., Moran, J. L., Cooper, M. E., Forsblom, C., & Groop, P. H. (2011). Soluble receptor for AGE (RAGE) is a novel independent predictor of all-cause and cardiovascular mortality in type 1 diabetes. *Diabetologia,* 54(10), 2669–2677. doi:10.1007/s00125-011-2186-5
Crossref ● PubMed ● Google Scholar

Thornalley, P. J., & Rabbani, N. (2011). Protein damage in diabetes and uremia – identifying hotspots of proteome damage where minimal modification is amplified to marked pathophysiological effect. *Free Radical Research*, 45(1), 89–100. doi:10.3109/10715762.2010.534162
Crossref ● PubMed ● Google Scholar

Twarda-Clapa, A., Olczak, A., Białkowska, A. M., & Koziołkiewicz, M. (2022). Advanced glycation end-products (AGEs): formation, chemistry, classification, receptors, and diseases related to AGEs. *Cells*, 11(8), 1312. doi:10.3390/cells11081312
Crossref ● PubMed ● PMC ● Google Scholar

Vrhovac, I., Breljak, D., & Sabolić, I. (2014). Glucose transporters in the mammalian blood cells. *Periodicum Biologorum*, 116(2), 131–138.
Google Scholar

Wang, B., Jiang, T., Qi, Y., Luo, S., Xia, Y., Lang, B., Zhang, B., & Zheng, S. (2025). AGE-RAGE axis and cardiovascular diseases: pathophysiologic mechanisms and prospects for clinical applications. *Cardiovascular Drugs and Therapy,* 39(6), 1489–1506. doi:10.1007/s10557-024-07639-0
Crossref ● PubMed ● PMC ● Google Scholar

Yeh, W.-J., Hsia, S.-M., Lee, W.-H., & Wu, C.-H. (2017). Polyphenols with antiglycation activity and mechanisms of action: a review of recent findings. *Journal of Food and Drug Analysis*, 25(1), 84–92. doi:10.1016/j.jfda.2016.10.017
Crossref ● PubMed ● PMC ● Google Scholar

ВПЛИВ БІОАКТИВНИХ РЕЧОВИН, ЕКСТРАГОВАНИХ ІЗ ПЛОДІВ ДЕРЕНУ СПРАВЖНЬОГО (*CORNUS MAS* L.), НА РІВЕНЬ КІНЦЕВИХ ПРОДУКТІВ ГЛІКАЦІЇ І РЕЦЕПТОРІВ ДО НИХ У ПЛАЗМІ КРОВІ ТА ЛЕЙКОЦИТАХ ЩУРІВ ЗА ЕКСПЕРИМЕНТАЛЬНОГО ЦУКРОВОГО ДІАБЕТУ

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Вступ. Основною причиною патофізіологічних змін за діабету є хронічний вплив гіперглікемії. За гіперглікемії посилюється глікація білків і ліпідів та, як наслідок, утворюються та накопичуються кінцеві продукти глікації (англ. Advanced Glycation End-products – AGEs). Накопичення AGEs зумовлене зниженою здатністю організму їх метаболізувати та / або екскретувати, тому ці продукти є маркерними показниками контролю як глікемії, так й інтенсивності оксидативно-карбонільного стресу в тканинах організму. Механізм дії AGEs визначається їхньою взаємодією з клітинними рецепторами – RAGEs (англ. Receptor for Advanced Glycation End-products), внаслідок якої відбувається активація сигнальних шляхів, особливо прозапальних процесів у лейкоцитах. Тому метою роботи було дослідити вплив біоактивних речовин, екстрагованих із плодів дерену справжнього (*Cornus mas* L.), на вміст AGEs і RAGEs у плазмі та лейкоцитах крові щурів за експериментального цукрового діабету.

Матеріали та методи. Експерименти проводили на групах щурів зі стрептозотоцин-індукованим цукровим діабетом, яким з 10-го дня від моменту індукції діабету *per os* упродовж 14 днів вводили екстракти плодів дерену справжнього сорту ‘Podolski’, ‘Yantarnyi‘ & ‘Flava‘ та логанову кислоту, відповідно, у дозі 20 мг/кг маси тіла. Щурі контрольної та діабетичної груп щоденно упродовж 14 днів отримували через зонд по 1 мл питної води. На 24-й день експерименту проводили забір крові. У плазмі й лейкоцитах визначали вміст флуоресцентних і нефлуоресцентних AGEs. Кількість лейкоцитів із мембранозв’язаними рецепторами до AGEs визначали імуноцитохімічним методом. Вміст розчинної форми RAGE (англ. soluble RAGEs – sRAGEs) у плазмі визначали методом імуноблот аналізу.

Результати. Досліджено один із механізмів негативного впливу високого рівня глюкози, зокрема, її здатність неензиматично реагувати з білками з утворенням AGEs. Встановлено збільшення рівня AGEs у плазмі крові щурів з діабетом та зниження рівня флуоресцентних і нефлуоресцентних AGEs у лейкоцитах. Це, ймовірно, пов'язано з порушенням транспорту глюкози у лейкоцити за гіпоінсулінемії у хворих на діабет. Виявлено достовірне збільшення кількості RAGEs+ лейкоцитів і рівня sRAGEs у плазмі крові щурів зі стрептозотоциновим діабетом. За введення екстрактів плодів дерену справжнього сортів ‘Podolski’, ‘Yantarnyi‘ & ‘Flava‘ та логанової кислоти вміст флуоресцентних і нефлуоресцентних AGEs підвищувався

в лейкоцитах щурів з діабетом до значень у контрольній групі тварин. Варто зазначити, що екстракт плодів *Cornus mas* L. сорту 'Podolski' продемонстрував найкращий ефект серед досліджуваних екстрактів, зумовивши зниження рівня AGEs у плазмі крові та рецепторів до них.

Висновки. Екстракт плодів *Cornus mas* L. сорту 'Podolski' має виражений терапевтичний потенціал для лікування порушень метаболізму глюкози за цукрового діабету. Біологічно активні речовини екстракту пригнічують глікування, утворення AGEs і нормалізують рівень RAGEs як у лейкоцитах, так і у плазмі крові.

Ключові слова: експериментальний цукровий діабет, екстракти плодів дерену справжнього, логанова кислота, лейкоцити, плазма крові, маркери оксидативно-карбонільного стресу, AGEs, RAGEs

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