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THE EFFECT OF *GALEGA OFFICINALIS* L. EXTRACT ON THE CONTENT OF THE ADVANCED GLYCATION END PRODUCTS AND THEIR RECEPTORS IN RAT LEUKOCYTES UNDER EXPERIMENTAL DIABETES MELLITUS

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Background. Diabetes mellitus intensifies non-enzymatic glycosylation (glycation) of biomolecules under conditions of chronic hyperglycemia and facilitates accumulation of advanced glycation end products. Disorders of the cells of various tissues are caused by binding of advanced glycation end products to the corresponding receptors, the level of receptors for advanced glycation end products increases under conditions of hyperglycemia. The interaction between receptors for advanced glycation end products and advanced glycation end products leads to the formation of excessive reactive oxygen species, changes in intracellular signaling, gene expression, increased secretion of pro-inflammatory cytokines and contributes to the development of diabetic complications. The search for factors of natural origin that will slow down the development of specific complications of diabetes, determines the feasibility of studies of the corrective ability of biologically active substances isolated from medicinal plants for the process of glycation of proteins in diabetes.

Materials and methods. Experimental diabetes mellitus was induced by intraperitoneal administration of streptozotocin. Separation of blood leukocytes was performed in Ficoll density gradient. To determine the extent of advanced glycation end products and receptor for advanced glycation end products in leukocyte immunoperoxidase labeling was performed.

Results. A decrease in the content of advanced glycation end products in leukocytes under conditions of experimental diabetes mellitus was found. The obtained data indicate a possible contravention of glucose uptake by leukocytes in the studied pathology.

At the same time, an increase in exposure to the receptor for advanced glycation end products leukocyte membranes in response to chronic hyperglycemia has been demonstrated. The ability of alkaloid free fraction of *Galega officinalis* extract to reduce the content of receptors for end products of glycation on the membranes of immunocompetent cells in diabetic animals has been confirmed, which may be due to the presence of biologically active substances with hypoglycemic action in its composition.

Conclusion. Corrective effect of alkaloid free fraction of *Galega officinalis* L. extract on the content of receptor for advanced glycation end products in diabetes mellitus is mediated by its normalizing effect on carbohydrate metabolism**.**

Keywords**:** diabetes mellitus, *Galega officinalis* L., advanced glycation end products (AGEs), receptor for advanced glycation end products (RAGE), leukocytes

INTRODUCTION

Diabetes mellitus (DM) is a chronic systemic disorder characterized by hyperglycaemia. This results from lack of insulin secretion, insulin action, or both, and disturbances of carbohydrate, fat and protein metabolism. A prolonged increase in blood glucose concentration causes an increased polyol and hexosamine pathways, the hyperactivation of protein kinase C (PKC) isoforms, and the accumulation of advanced glycation end products (AGEs) (Cho, Roman, Yeboah, & Konishi, 2007; Kang & Yang, 2020).

AGEs are a compounds that are the products of nonenzymatic reactions between reducing sugars and proteins or lipids (Ahmed, 2005; Cho *et al.*, 2007; Jud & Sourij, 2019; Peng, Ma, Chen, & Wang 2011). AGEs bind to one or more of their multiple receptors found on a variety of cell types and elicit an array of biologic responses (Byun *et al.*, 2017; Ojima, Matsui, Maeda, Takeuchi, & Yamagishi, 2012; Wautier, Chappey, Corda, Stern, Schmidt, & Wautier 2001; Yamagishi, 2011; Yan *et al.*, 1994). Activation of the receptor for advanced glycation end products (RAGE) is accompanied by the generation of ROS, changes in intracellular signaling, gene expression, increased secretion of proinflammatory cytokines and contributes to the development of diabetic complications (Byun *et al.*, 2017; Hawkins & Davies, 2019; Peng *et al.*, 2011). Consequently, the most important task in combating the complications of diabetes is to reduce hyperglycemia.

At present, the issue of diabetic treatment remains unresolved and necessitates the search and development of effective and, at the same time, low toxic antidiabetic cures. The basis for the creation of antidiabetic drugs and functional foods of natural origin can be the extract of *Galega officinalis* L., which has a pronounced hypoglycemic (Hachkova *et al.*, 2021; Khokhla *et al.*, 2010) and antioxidant effects (Lupak *et al.*, 2015).

The medicinal properties of *G. officinalis* L. to reduce the level of glucose (Kleveta, 2009) in blood have been known since the Middle Ages. However, the effect was attributed to alkaloids available in the herb and seeds of the plant. Since alkaloid fraction is highly toxic, it is impossible to increase the concentration of the extract. According to our patent studies, the alkaloid free fraction of *G. officinalis* extract (AFFGE) produces sugar reducing effects as well (Kleveta *et al.*, 2009).

This study aimed at investigation of the effects of the alkaloid free fraction of *G. officinalis* extract on the content of AGEs and RAGE of the leukocyte of diabetic rats induced by streptozotocin.

MATERIALS AND METHODS

The research object. The experiments were conducted using three-month-old male Wistar rats weighing 130 g to 180 g. The rats were fed with a standard laboratory diet and water ad libitum. The protocol used in this study was carried out with the guidelines according to the "General ethical principles of experiments on animals", adopted at the I National Congress on Bioethics (Kyiv, 2001) and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, France, 1986). An approval was obtained from the Ethics Committee of Ivan Franko National University of Lviv, Ukraine (Protocol No. 5-11-2021 of 19 November, 2021).

Preparation of alkaloid-free fraction from *Galega officinalis* extract. We described the methods for obtaining and stabilizing AFFGE using surfactants of biological origin synthesized by the bacteria *Pseudomonas* sp. PS-17 (Sybirna *et al.*, 2015), as well as the analysis of its composition by components in our previous studies (Khokhla *et al.*, 2013).

Design of the experiment. Animals were randomly divided into 4 groups: 1 – control animals (Control); 2 – control animals that were treated with alkaloid-free fraction from *Galega officinalis* extract at dose 0.6 g/kg per day (Control + AFFGE); 3 – animals with experimental diabetes mellitus (EDM); 4 – animals with EDM treated with AFFGE at dose 0.6 g/kg per day. Animals from group Control + AFFGE and EDM + AFFGE were receiving stabilized water emulsion of chloroform fraction *Galega officinalis* extract (during 14 days) through a tube, animals from Control and EDM groups were receiving water in the same way and period of the day. EDM was induced by intraabdominal injection of streptozotocin (Sigma, USA) dissolved before use in 10 mM citrate buffer (pH 5.5) at a dose of 0.055 g/kg body weight.

Blood collection. After 14 days of introduction of *per os* AFFGE, blood was collected by decapitation of animals using ether chloroform anesthesia. For preventing blood clotting, samples were collected into vials with heparin (final dilution heparin: whole blood = 1:100).

Separation of blood leukocytes. Leukocytes were isolated by fractional centrifugation in ficoll-triombrastum gradient (ρ = 1.076–1.078). The collected cells were washed three times by phosphate buffer saline (PBS: (137 мМ NaCl, 2.7 мМ KCl, 10 мМ $Na_2HPO_4 \times 7H_2O$, 1.8 мМ KH_2PO_4, pH 7.4) (Lapovets & Lutsyk, 2004).

Immunocytochemical detection of glycation end products and their receptors in leukocytes. Leukocytes were applied to a glass slide (70 thousand cells in 70 μL of phosphate-buffered saline (PBS)), fixed in a solution of methanol at a temperature of -4 °C for 10 min and 2 min in chilled acetone (Tezel, Luo, & Yang 2007). To detect RAGE, fixed cells were permeabilized with 0.1% solution of Triton X-100 in PBS. Glass slides with cells were pretreated with 0.3% hydrogen peroxide (5 min) to decrease endogenous peroxidase activity. After washing with PBS, slides were incubated with 1% BSA solution in PBS (Sigma-Aldrich, USA) for 1 h at room temperature to block background staining. Slides were then incubated with the primary antibodies to AGEs (1: 300; Sigma-Aldrich, USA) for 2 h at room temperature. After that, slides were incubated with the primary antibodies to RAGE (1: 500; Proteintech, USA) for 2 h at room temperature. After a three-fold washing in PBS, the slides were incubated with the second antibody anti-rabbit IgG (1:200; Sigma-Aldrich, USA) for 1 h at room temperature. Blocking background staining and incubating with antibodies were carried out in a humid chamber. After several washes, color was developed by incubation with 3,3-diaminobensidine (DAB) with 0.015% hydrogen peroxide for 5 to 10 min. After washing, slides

were examined through a light microscopy using a × 40 Olympus IX73 inverted microscope with DP-74 digital camera. Slides that were not treated with the first and the second antibodies served as negative controls on binding specificity.

Binding of antibodies to leukocyte RAGE was assessed by peroxidase activity, which was detected by brown deposits of oxidative polymerization products of DAB in the mode of digitization of leukocyte micrographs. The intensity of immunolabeling was qualitatively graded as negative (-) and positive (+). The slides differentiated 500 cells. The content of $AGEs^-$/$AGEs^+$-cells and $RAGE^-$/$RAGE^+$-cells was calculated by proportion.

Statistical analysis of results. Statistical analysis of results was carried out using Microsoft Excel 2010 program. The calculation of the main statistical indicators was performed based on direct quantitative data (arithmetic mean value – M; standard error of the arithmetic mean – m). The difference between indices was evaluated using Student criteria. The difference was considered significant at $p \geq 0.95$ (level of significance – $P < 0.05$).

RESULTS AND DISCUSSION

Chronic hyperglycemia in diabetes causes increased non-enzymatic glycosylation processes resulting in the accumulation of AGEs (Ruiz, Ramasamy, & Schmidt, 2020).

Immunocytochemical analysis showed a decrease in the number of AGEs in the peripheral blood leukocytes of rats in experimental diabetes, as evidenced by a decrease in the number of cells with a positive ($AGEs^+$) response by 38% compared to control (**Fig. 1*A–B***). Decreased levels of AGEs in leukocytes on the background of increased

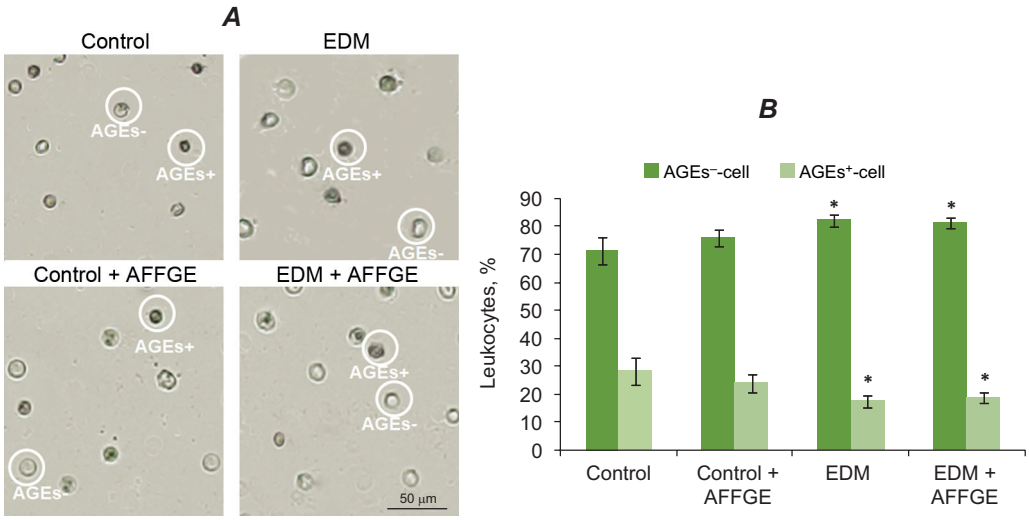

Fig. 1. Immunocytochemical analysis of peripheral blood leukocytes of rats using antibodies against RAGE AGEs: ***A*** – images of peripheral blood leukocytes of rats (× 40); ***B*** – the ratio of the number of leukocytes depending on the content in AGEs cells (EDM – experimental diabetes mellitus, AFFGE – alkaloid-free fraction from *Galega officinalis* extract). * – significant difference compared with the control, $P < 0.05$

Рис. 1. Імуноцитохімічний аналіз лейкоцитів із використанням антитіл до кінцевих продуктів глікації: ***A*** – мікрофотографії лейкоцитів периферичної крові щурів (× 40); ***B*** – співвідношення кількості лейкоцитів залежно від вмісту в клітинах кінцевих продуктів глікації (EDM – англ. experimental diabetes mellitus – експериментальний цукровий діабет, AFFGE – англ. alkaloid-free fraction from *Galega officinalis* extract – безалкалоїдна фракція екстракту козлятника лікарського). * – різниця вірогідна, порівняно з контролем, $P < 0,05$

levels of glucose and glycosylated hemoglobin in the blood of animals with EMD (Hachkova *et al.*, 2021) may indicate a contravention of glucose intake to leukocytes. Blood cells obtain glucose through insulin-independent glucose transporters GLUT1 and GLUT3. Besides, there is evidence in literature about an insulin-dependent transporter GLUT4 in granulocytes, monocytes and lymphocytes. Insulin stimulation increases the translocation of GLUT4 on the plasma membrane of mononuclear cells (Jasmin, Ali, Ferdous, Arslan, & Biswas 2019; Maratou *et al.*, 2007). We assume that a disruption of GLUT4 translocation to the leukocyte membrane under hypoinsulinemia leads to an impaired glucose uptake and a decrease in AGEs content in these cells.

When AFFGE was administered to healthy animals, the content of AGEs in rat blood leukocytes did not differ from the control. The introduction of the extract did not affect the content of AGEs in the leukocytes of diabetic animals either (**Fig. 1*A–B***).

AGEs interact with the corresponding receptors (RAGE), the expression of which increases under conditions of hyperglycemia. Hyperglycemia-induced reactive oxygen species increase the expression of RAGE (Ighodaro, 2018; Kang & Yang, 2020).

Immunocytochemical analysis showed an increase in the number of RAGE in the peripheral blood leukocytes of rats under EDM, as evidenced by an increase in the number of RAGEs$^+$-cells by 28% compared to the control (**Fig. 2*A–B***).

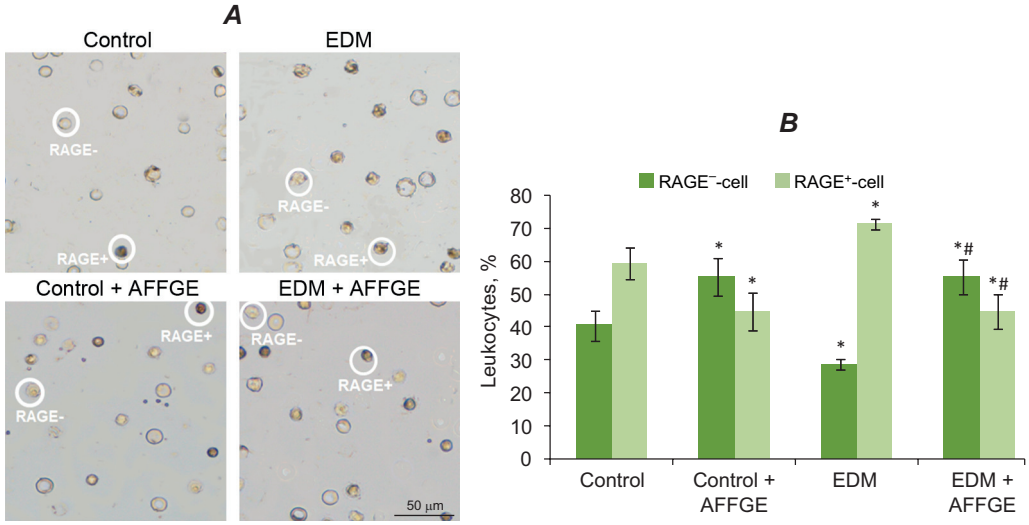

Fig. 2. Immunocytochemical analysis of peripheral blood leukocytes of rats using antibodies against RAGE: ***A*** – images of peripheral blood leukocytes of rats (× 40); ***B*** – the ratio of the number of leukocytes depending on the content in RAGE cells (EDM – experimental diabetes mellitus, AFFGE – alkaloid-free fraction from *Galega officinalis* extract). * – significant difference compared with the control, $P < 0.05$

Рис. 2. Імуноцитохімічний аналіз лейкоцитів з використанням антитіл до рецепторів кінцевих продуктів глікації: ***A*** – мікрофотографії лейкоцитів периферичної крові щурів (× 40); ***B*** – співвідношення кількості лейкоцитів залежно від вмісту в клітинах рецепторів кінцевих продуктів глікації (EDM – *англ.* experimental diabetes mellitus – експериментальний цукровий діабет, AFFGE – *англ.* alkaloid-free fraction from *Galega officinalis* extract – безалкалоїдна фракція екстракту козлятника лікарського). * – різниця вірогідна, порівняно з контролем, $P < 0,05$

Administration of AFFGE to animals with experimental diabetes mellitus resulted in a decrease in the number of cells with a RAGEs$^+$-cells response by 37 % compared with diabetes (**Fig. 2*A*–*B***). In animals of the control group, which were injected with plant extract, there was a decrease in the number of RAGEs$^+$-cells by 25 % on the background of an increase in the number of cells with a negative reaction to the test protein (**Fig. 2*A*–*B***).

We may explain the corrective effect of the AFFGE on the content of RAGE in the conditions of diabetes mellitus by reducing of reactive oxygen species generation in leukocytes (Lupak *et al.*, 2015) and its normalizing effect on carbohydrate metabolism. The administration of *Galega officinalis* extract to animals with streptozotocin-induced diabetes has a antidiabetic effect (reduces blood glucose levels, glycosylated hemoglobin concentrations, and also improvement structure of the pancreas islets and stimulates the secretion of insulin (Hachkova *et al*., 2021).

CONCLUSIONS

The obtained results prove the corrective effect of AFFGE on protein glycation processes and indicate the prospects of using the biologically active substances isolated from *Galega officinalis* L. as a basis for the creation of functional foods and antidiabetic drugs for complex therapy and prevention of complications of diabetes.

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COMPLIANCE WHITH 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, [H.H.Ya.; N.O.S.]; methodology, [F.Kh.Ye.; H.H.Ya.]; validation, [F.Kh.Ye.; H.H.Ya.]; formal analysis, [F.Kh.Ye.; H.H.Ya.].; investigation, [F.Kh.Ye.; H.H.Ya.]; resources, [F.Kh.Ye.; H.H.Ya.]; data curation, [F.Kh.Ye.; H.H.Ya.]; writing –

original draft preparation, [F.Kh.Ye.; H.H.Ya.]; writing – review and editing, [F.Kh.Ye.; H.H.Ya]; visualization, [F.Kh.Ye.]; supervision, [H.H.Ya.; N.O.S.]; project administration, [H.H.Ya.; N.O.S.]; funding acquisition, [-].

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

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ВПЛИВ ЕКСТРАКТУ КОЗЛЯТНИКА ЛІКАРСЬКОГО НА ВМІСТ КІНЦЕВИХ ПРОДУКТІВ ГЛІКАЦІЇ ТА ЇХНІХ РЕЦЕПТОРІВ У ЛЕЙКОЦИТАХ ЩУРІВ ЗА ЕКСПЕРИМЕНТАЛЬНОГО ЦУКРОВОГО ДІАБЕТУ

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Вступ. За хронічної гіперглікемії за цукрового діабету посилюються процеси неензиматичного глікозилювання (глікування) біомолекул і накопичуються кінцеві продукти глікації. Порушення функціонального стану клітин різних тканин зумовлені зв'язуванням кінцевих продуктів глікації з відповідними рецепторами, рівень яких підвищується за умов гіперглікемії. Взаємодія кінцевих продуктів глікації з їхніми рецепторами призводить до надмірного утворення активних форм оксигену, змін внутрішньоклітинного сигналювання, експресії генів, підвищення секреції прозапальних цитокінів і сприяє розвитку діабетичних ускладнень. Пошук чинників природного походження, які сповільнюватимуть розвиток специфічних ускладнень діабету, визначають доцільність досліджень коригуючої здатності біологічно активних речовин, виділених із лікарських рослин на процес глікування білків за умов цукрового діабету.

Матеріали і методи. Експериментальний цукровий діабет індукували внутрішньоочеревинним введенням стрептозотоцину. Лейкоцити периферичної крові виділяли, використовуючи градієнт густини фікол-тріомбраст. Вміст кінцевих продуктів глікації та їхніх рецепторів визначали імуноцитохімічним методом.

Результати. Встановлено зниження вмісту кінцевих продуктів глікації у лейкоцитах за умов експериментального цукрового діабету. Отримані дані свідчать про ймовірне порушення поглинання глюкози лейкоцитами за досліджуваної патології. Водночас доведено підвищення експонування на мембранах лейкоцитів рецепторів до кінцевих продуктів глікації у відповідь на хронічну гіперглікемію. Підтверджено здатність безалкалоїдної фракції екстракту козлятника лікарського знижувати вміст рецепторів до кінцевих продуктів глікації на мембранах імунокомпетентних клітин у тварин, хворих на діабет, що може бути зумовлено наявністю у його складі біологічно активних речовин із гіпоглікемічною дією.

Висновки. Коригуюча дія безалкалоїдної фракції екстракту козлятника лікарського на вміст рецепторів кінцевих продуктів глікації за умов цукрового діабету опосередкований його нормалізуючим впливом на показники вуглеводного обміну.

Ключові слова: цукровий діабет, козлятник лікарський (*Galega officinalis* L.), кінцеві продукти глікації, рецептори до кінцевих продуктів глікації, лейкоцити

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