UDC 616.379-008.64: 541.49
DOI https://doi.org/10.32782/2226-2008-2024-3-2

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CORRECTIVE EFFICACY OF NIACIN-OXY-ETHYLIDENE-DIPHOSPHONATE GERMANATE (MIGU-4) ON THE MODEL OF STREPTOZOTOCIN-INDUCED DIABETES

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Background. Using organic germanium compounds is promising for developing pharmacological agents to prevent diabetes mellitus complications.

The study aimed to investigate the effectiveness of niacin-oxyethylene diphosphonate germanate (MIGU-4) on hyperglycemia, insulin level, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP) activities, content of proteins, bilirubin, cholesterol, triglycerides, low and high-density lipoproteins (LDL and HDL, respectively) in the blood serum of rats with STZ-induced diabetes. A separate task was to compare the effectiveness of MIGU-4 with the use of vitamin E.

Materials and methods. Diabetes was induced in male Wistar rats by intraperitoneal administration of streptozotocin (65.0 mg/kg). MIGU-4 was administered intraperitoneally at 25.0 mg/kg for four weeks.

Results. MIGU-4 caused a decrease in glucose levels by 50.9% and increased insulin content by 25.1% ($p < 0.05$) in diabetic rats. Besides, MIGU-4 restored albumin content ($p < 0.05$), reduced total bilirubin by 42.2%, cholesterol – by 30.6%, triglycerides – by 35.4%, LDL – by 58.6% and increased HDL by 48.4% ($p < 0.05$). The use of MIGU-4 reduced the activity of AST and ALT by 70,1% and 42.3% ($p < 0.05$). The activity of ALP and LDH was also reduced by 76.6% and 53.3% ($p < 0.05$). With vitamin E (100.0 mg/kg), AST and ALT activity decreased by 64.0% and 36.4% ($p < 0.05$) and remained higher than in control by 33.3% and 37.0%, respectively ($p < 0.05$). The activity of ALP and LDH decreased by 79.7% and 52.1% ($p < 0.05$).

Conclusions. MIGU-4 restores lipid metabolism, corrects serum liver function indices, and positively affects blood glucose and protein levels in streptozotocin-induced diabetes. Its effects (25.0 mg/kg) were comparable with those caused by vitamin E (100.0 mg/kg).

Key words: streptozotocin, diabetes mellitus, niacin-oxy-ethylidene-diphosphonate germinate, lipids, aminotransferases, vitamin E.

УДК 616.379-008.64: 541.49

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КОРИГУЮЧА ЕФЕКТИВНІСТЬ НІАЦИН-ОКСІЕТИЛЕНДИФОСФОНАТОГЕРМАНАТУ (МІГУ-4) НА МОДЕЛІ СТРЕПТОЗОТОЦИН-ІНДУКОВАНОГО ДІАБЕТУ

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Метою дослідження є вивчення впливу ніацин-оксіетилендифосфонатогерманату (МІГУ-4) на метаболічні показники в сироватці крові щурів із стрептозотоцин (СТЗ)-індукованим діабетом. Діабет викликали у щурів-самців лінії Вістар застосуванням СТЗ (65,0 мг/кг). МІГУ-4 вводили протягом 28 діб дозою 25,0 мг/кг. МІГУ-4 знижував вміст глюкози на 50,9 %, а також збільшував вміст інсуліна на 25,1 % ($p < 0,05$), зменшував рівень загального білірубіну на 42,2 %, холестерину – на 30,6 %, тригліцеридів – на 35,4 %, ліпопротеїнів низької щільності – на 58,6 %, активність аспартат- та аланін амінотрансфераз – на 70,1 % та на 42,3 %, лужної фосфатази та лактатдегідрогенази – на 76,6 % та 53,3 % відповідно ($p < 0,05$), збільшував вміст ліпопротеїнів високої щільності на 48,4 % ($p < 0,05$). Виразність ефектів МІГУ-4 відповідала таким, які викликав вітамін Е дозою 100,0 мг/кг.

Ключові слова: стрептозотоцин, цукровий діабет, ніацин-оксіетилендифосфонато германат, ліпіди, амінотрансферази, вітамін Е.

Introduction

Taking into account high prevalence, constant increase in the incidence of diabetes mellitus and the severity of complications, the search for effective pharmacological agents and pathogenetic substantiation of their efficacy is an urgent scientific and practical problem [1].

The most widely used diabetes model is the administration of streptozotocin (STZ), which is characterised by selective toxicity to pancreatic β-cells [2, 3]. Under the influence of STZ, insulin secretion by β-cells is disrupted by DNA methylation, which leads to an increase in poly ADP-ribose polymerase (PARP) activity, followed by a critical decrease in nicotinamide adenine dinucleotide and ATP production. At the final stage, intracellular nitric stress occurs with excessive production of nitric oxide, which causes DNA fragmentation, making insulin production impossible [2]. Thus, the key events in the onset and further development of diabetes are associated with the production of free radicals [2–4].

It has been established that the use of organic germanium compounds is effective in the treatment of diseases or pathological conditions, the pathogenesis of which includes mechanisms of inflammation, oxidative stress, decreased immunological reactivity, including manifestations of diabetes mellitus [5]. Accordingly, the antioxidant effectiveness of niacin-oxyethylene

diphosphonate germanate [Ge(OH2(Oedph)]*H2O – (MIGU-4) provides a corrective effect on the manifestations of experimental diabetes mellitus [3, 4]. It is worth noting that niacin, as a component of MIGU-4, also has an ability to block the manifestations of alloxan-induced diabetes in rats when administered at doses of 10.0 and 15.0 mg/kg [6]. These properties of the components of MIGU-4 indicate significant prospects for its use in diabetes mellitus.

However, a great number of complications, in particular, on the side of the functional state of the liver and metabolic disorders associated with hepatocyte activity, indicate the need to study the hepatotropic pharmacodynamic effects of drugs that are tested for antidiabetic activity [3, 4, 6].

The aim of the study is to investigate the antidiabetic efficacy of the course of MIGU-4 administration in relation to hyperglycemia, insulin content, activity of aspartate aminotransferase (CP 2.6.1.1; AST), alanine aminotransferase (CP 2.6.1.2; ALT), lactate dehydrogenase (CP 1.1.1.27; LDH), alkaline phosphatase (CP 3.1.3.1; ALP), as well as the content of proteins, bilirubin, cholesterol, triglycerides, low and high density lipoproteins (LDL and HDL, respectively) in the blood serum of rats with STZ-induced diabetes. A separate task was to compare the effectiveness of MIGU-4 and vitamin E.

Material and methods

The study was conducted within a long-term experiment on 47 male Wistar rats weighing 180–270 g from the vivarium of the Odesa National Medical University (ONMedU). The animals were kept under standard conditions of temperature (23±2°C), humidity (60%) and a 12-hour light/dark cycle with free access to water and food. All procedures were carried out in accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals adopted by the National Institutes of Health (Bethesda, USA) and the Declaration of Strasbourg, as well as with the permission of the ONMedU Bioethics Committee (Protocol No. 3 of 14.03.2018).

Male rats (47 experimental animals) were divided into the following groups:

– Control group 1 – rats with 0.9% NaCl solution injection (8 animals);

– STZ-diabetes with 0.9% NaCl solution injection (8 animals);

– Control group 2 – rats with MIGU-4 injection at a dose of 25.0 mg/kg, i.p. (7 animals);

– STZ-diabetes with MIGU-4 injection at a dose of 5.0 mg/kg, i.p. (7 animals);

– STZ-diabetes with MIGU-4 injection at a dose of 25.0 mg/kg, i.p. (9 animals);

– STZ-diabetes with vitamin E administration at a dose of 100.0 mg/kg, i.p. (8 animals).

Diabetes mellitus was modeled by intraperitoneal (i.p.) administration of STZ (Sigma Aldrich, USA) at a dose of 65.0 mg/kg, which was previously dissolved in buffered sodium citrate solution (pH 4.5) [3, 4]. The rats with a blood glucose level of at least 16.7 mmol/L were used in the study. After the use of STZ, experimental animals were observed for four weeks. Then during the next 4 weeks the rats were treated, and 24 h after the last administration of drugs, the studied parameters were examined.

Food intake was determined by subtracting food residues from the diet of rats – the procedure of weighing food residues was carried out at intervals of 2 days. The daily body weight gain of rats was also calculated and daily water consumption was taken into account [6].

Niacin-oxy-ethylene-diphosphonate-germanate (MIGU-4, synthesised under the supervision of Professor I. Y. Seifullina, Doctor of Science in Medicine at the I. I. Mechnikov Odesa National Medical University) was administered at doses of 5.0 mg/kg and 25.0 mg/kg, i.p. MIGU-4 was administered for four weeks, starting from the 30th day from the inclusion of rats to observation. In a separate group, vitamin E – (±)-α-tocopherol, DL-rac-α-tocopherol (Sigma Aldrich) was administered at a dose of 100.0 mg/kg, i.p. The rats of the control group were injected 0.5 ml of 0.9% sodium chloride saline under similar conditions.

Total cholesterol, triglycerides, HDL and LDL were measured colorimetrically at a wavelength of 520 nm. In particular, the content of HDL and LDL was determined by the method of preliminary precipitation of the blood serum LDL using polyethylene glycol and expressed in mg/dL [7]. The blood serum insulin content was determined by the enzyme-linked immunosorbent assay (ELISA) using reagents of Diaclone (France) [8]. Content of proteins was determined by Lowry's method [9]. Albumin was determined by the bromocresol method and expressed in g/dL [10].

The activity of aspartate and alanine aminotransferases (AST and ALT), lactate dehydrogenase (LDH) were determined in the blood serum by the method [11] and expressed in μM pyruvate/min per mg of protein. The activity of alkaline phosphatase (ALP) was expressed in μM of released phenol/min per mg of protein [11].

Statistical processing of data was performed using the statistical software SPSS 17.0 (USA). The ANOVA method and Newman Keuls statistical test were used to determine differences. The mean value (M), standard deviation (SD) and error of the mean (m) were calculated. The results were considered significant differences from the control at $p<0.05$.

Results of the study

The obtained results showed that in rats with diabetes mellitus, blood glucose level was 4.76 times higher than in rats of Control group 1, and insulin level was by 39.4% lower ($p < 0.05$) (Table 1). In addition, an increase in water and food consumption was observed – by 75.2% and 30.7%, respectively, as well as a decrease in body weight growth by 41.7% ($p < 0.05$).

The use of MIGU-4 at a dose of 25.0 mg/kg was accompanied by a significant decrease in glucose level – by 50.9% ($p < 0.05$), which at the same time remained by 57.2% higher than in rats of Control group 1. Insulin content significantly increased by 25.1% and remained by 18.0% lower than in Control group 1 ($p < 0.05$). Daily water intake decreased by 55.1% ($p < 0.05$), food intake – by 13.9% ($p > 0.05$), while daily body weight gain increased by 22.4% ($p < 0.05$) (see Table 1).

At the background of vitamin E (100.0 mg/kg) administration, the glucose content decreased by 75.0% and was simultaneously higher than in Control group 1 by 40.0% ($p < 0.05$). It should be noted that the glucose level also decreased significantly compared to rats treated with

MIGU-4 (by 28.7%) ($p < 0.05$). The insulin level remained lower than in Control group 1 by 14.2% ($p < 0.05$) and exceeded the corresponding value in diabetic rats by 29.0% ($p < 0.05$). There was also a decrease in water and food consumption by 46.7% and 17.6%, respectively ($p < 0.05$). The daily body weight gain exceeded the same indicator in diabetic rats by 9.7% ($p > 0.05$) and was significantly lower compared to rats treated with MIGU-4 at the highest of investigated doses (by 13.9%) ($p < 0.05$) (see Table 1).

The development of STZ-induced diabetes was accompanied by a decrease in blood proteins (by 14.8%, $p < 0.05$), in particular, a decrease in albumin content was 21.1% ($p < 0.05$) (Table 2). In addition, there was an increase in total bilirubin by 44.8% ($p < 0.05$), cholesterol – by 33.2%, triglycerides – by 55.9%, low-density lipoprotein (LDL) – by 69.8% and a decrease in high-density lipoprotein (HDL) by 43.4% ($p < 0.05$).

The use of MIGU-4 at a dose of 5.0 mg/kg reduced triglyceride and LDL cholesterol levels by 21.0% and 21.1%, respectively ($p < 0.05$). At the same time, both indicators exceeded those recorded in rats of Control group 1 by 15.5% and 71.5% ($p < 0.05$).

The use of MIGU-4 at the highest dose (25.0 mg/kg) caused an increase in the total protein and albumin content by 7.2% ($p > 0.05$) and 23.1% ($p < 0.05$). The content of total bilirubin decreased by 42.2%, cholesterol – by 30.6%, triglycerides – by 35.4%, LDL – by 58.6% and HDL increased by 48.4% ($p < 0.05$). Moreover, only the level of triglycerides significantly exceeded the corresponding indicator in the Control group 1 under similar treatment conditions – by 31.7% ($p < 0.05$). On the background of vitamin E administration, the content of total proteins and albumin increased by 5.8% ($p > 0.05$) and 24.4% ($p < 0.05$), respectively, and the decrease in total bilirubin was 49.0% ($p < 0.05$). The content of cholesterol, triglycerides and LDL decreased by 25.0%, 42.3% and 46.0% ($p < 0.05$). All these indicators significantly exceeded those in the Control group 1 ($p < 0.05$). LDL level increased by 53.7% ($p < 0.05$) (see Table 2).

The activity of AST and ALT in the blood of rats with diabetes exceeded 4.16 and 2.5 times, respectively ($p < 0.05$) the corresponding values in Control group 1 (Table 3). The activity of ALP and LDH was also 2.56 and 2.52 times higher than in Control group 1 ($p < 0.05$). The use of MIGU-4 in

Table 1

General characteristics of STZ-induced diabetes under experimental treatment (M±SD)

	Investigated parameters				
	Glucosa (mg/dL)	**Insulin (μg/ml)**	**Water consumption (ml/day)**	**Food intake (g/day)**	**Increase in body weight (g/day)**
Control group 1 (0.9% NaCl i.p.) (n = 8)	94.21±3.34	51.43±1.92	27.0±2.0	18.5±1.13	4.5±0.24
STZ-diabetes (0.9% NaCl i.p.) (n = 8)	448.6±10.36*	31.62±0.84*	107.0±5.0*	26.7±1.54*	2.8±0.15*
Control group 2 MIGU-4 (25.0 mg/kg) (n = 7)	92.37±4.23#	49.66±1.52#	25.6±2.7#	19.0±0.95#	4.3±0.21#
STZ-diabetes+ MIGU-4 (5.0 mg/kg) (n = 7)	398.55±11.26 *	35.71±1.14*	82.0±4.2*#	25.0±1.76*	2.9±0.10*
STZ-diabetes+ MIGU-4 (25.0 mg/kg) (n = 9)	220.34±9.76 *#	42.21±1.70*#	48.0±3.0*#	23.0±1.35	3.6±0.18*#
STZ-diabetes+ vitamin E (100.0 mg/kg) (n = 8)	157.0±7.12 *#&	44.12±1.83*#	57.0±4.0*#	22.0±1.24*	3.1±0.14*&

Note: * – $p < 0.05$ compared to control group 1; # – $p < 0.05$ compared to rats with STZ-diabetes; & – $p < 0.05$ compared to rats with STZ-diabetes and MIGU-4 (25.0 mg/kg) administration.

Table 2

Effect of MIGU-4 on the level of proteins and lipids in the blood serum of rats with STZ-diabetes (M±SD)

	Proteins (g/dL)	**Albumin (g/dL)**	**Total bilirubin (mg/dL)**	**Cholesterol (mg/dL)**	**Triglyceride (mg/dL)**	**LDL (mg/dL)**	**HDL (mg/dL)**
Control group 1 (0.9% NaCl i.p.) (n = 8)	8.04±0.22	4.55±0.12	1.95±0.15	63.82±1.79	36.51±1.52	10.79±1.17	41.76±3.87
STZ-diabetes (0.9% NaCl i.p.) (n = 8)	6.85±0.19*	3.59±0.09*	3.53±0.17*	95.6±2.21*	82.7±1.95*	35.64±2.73*	23.62±1.81*
Control group 2 MIGU-4 (25.0 mg/kg) (n = 7)	7.92±0.14#	4.60±0.16#	1.88±0.19#	61.09±2.20#	37.46±1.67#	12.23±1.40#	38.21±3.30#
STZ-diabetes+ MIGU-4 (5.0 mg/kg) (n = 7)	7.00±0.22*	4.19±0.18	3.07±0.22*	75.5±1.25*#	69.32±2.26*	28.01±2.07*#	26.52±1.95*
STZ-diabetes+ MIGU-4 (25.0 mg/kg) (n = 9)	7.38±0.21	4.67±0.18#	2.04±0.11#	66.30±2.08#	53.42±2.12*#	14.74±1.38#	45.78±3.89#
STZ-diabetes+ vitamin E (100.0 mg/kg) (n = 8)	7.27±0.23	4.75±0.23#	1.80±0.20#	71.75±2.14*#	47.80±1.19*#	19.22±2.13*#	51.03±3.05#

Note: * – $p < 0.05$ compared to Control group 1; # – $p < 0.05$ compared to STZ-diabetic rats.

Table 3

Activity of aminotransferases, alkaline phosphatase and lactate dehydrogenase in the blood serum under MIGU-4 administration (M±SD)

	AST (μM pyruvate/min per mg of protein)	ALT (μM pyruvate/min per mg of protein)	ALP (μM released phenol/ min per mg of protein)	LDH (μM pyruvate/min per mg of protein)
Control group 1 (0.9% NaCl i.p.) (n = 8)	42.45±2.23	27.63±1.12	0.23±0.03	4.27±0.16
STZ-diabetes (0.9% NaCl i.p.) (n = 8)	176.83±7.53*	68.82±3.63*	1.28±0.09*	10.75±0.47*
Control group 2 MIGU-4 (25.0 mg/kg) (n = 7)	44.67±2.52#	31.13±1.68#	0.29±0.04#	4.53±0.17#
STZ-diabetes+ MIGU-4 (5.0 mg/kg) (n = 7)	160.23±8.03*	57.21±2.52*	1.17±0.05*	9.64±0.41*
STZ-diabetes+ MIGU-4 (25.0 mg/kg) (n = 9)	54.72± 2.61#	39.72± 1.14*#	0.30±0.04#	5.02±0.19#
STZ-diabetes+ vitamin E (100.0 mg/kg) (n = 8)	63.6±3.33*#	43.8±1.45*#	0.26±0.03#	5.15±0.21#

Note: * – $p < 0.05$ compared to Control group 1; # – $p < 0.05$ compared to STZ-diabetic rats.

the lowest dose (5.0 mg/kg) was not effective in terms of significant changes in the studied parameters in diabetic rats ($p > 0.05$). Against the background of MIGU-4 administration at a dose of 25.0 mg/kg, AST and ALT activity decreased by 70.1% and 42.3%, respectively ($p < 0.05$). Moreover, ALT activity remained higher as compared with Control group 1 by 30.4% ($p < 0.05$). The activity of ALP and LDH also decreased by 76.6% and 53.3% ($p < 0.05$). With vitamin E (100.0 mg/kg), AST and ALT activity decreased by 64.0% and 36.4% ($p < 0.05$) and simultaneously exceeded that in Control group 1 by 33.3% and 37.0%, respectively ($p < 0.05$). The activity of ALP and LDH decreased by 79.7% and 52.1% ($p < 0.05$) (see Table 3).

Discussion

Consequently, the obtained results showed that the development of experimental STZ-induced diabetes is accompanied by a decrease in body weight, increase in food and water intake with a simultaneous decrease in daily body weight gain in rats against the background of decrease in insulin level and hyperglycemia. In addition, a decrease in blood proteins and albumin level, lipid metabolism disorders with a typical increase in cholesterol, triglycerides, and LDL with a decrease in HDL content were detected. Besides, high levels of nonspecific tissue damage markers such as ALP and LDH with an increase in blood aminotransferase activity indicate hepatocyte destruction [7, 8].

These disorders are typical for experimental models of diabetes mellitus [12]. In particular, diabetes induced by a high-fat diet in rats is accompanied by severe dyslipidemia with hypertriglyceridemia, a decrease in high-density lipoproteins and an increase in high-density lipoproteins [7, 12]. Such changes are associated with morphological signs of hepatosteatosis, increased serum bilirubin and glucuronic acid levels. The results obtained in our study indicate that lipid metabolism disorders are inherent in STZ-induced diabetes.

The use of MIGU-4 at the highest dose (25.0 mg/kg) caused a moderate hypoglycemic effect, increased blood insulin level, reduced water and food consumption in rats with STZ-induced diabetes, and increased daily body weight gain. At the same time, these indicators remained significantly different from those in Control group 1. The severity of the effects of MIGU-4 was similar to the use of vitamin E (100.0 mg/kg), which, however, caused greater hypoglycemia, while MIGU-4 significantly increased the daily body weight gain of rats with STZ-induced diabetes.

As for the hypoglycemic effect of MIGU-4, it is important to note that the antioxidant effects of organic germanium compounds are associated with an increase in the content of α-tocopherol in the blood plasma of mice [13]. In its turn, the use of α-tocopherol (vitamin E) provides the hypoglycemic effect by stimulating receptors that activate peroxisome proliferators -alpha and -gamma (PPAR-α PPAR-γ) [14, 15]. Taking into account that similar α-tocopherol-mediated effects of MIGU-4 are observed against the background of simultaneous implementation of its antioxidant, anti-inflammatory and antidyslipidemic effects, it is possible to enhance the effect of the drug's hypoglycemic effect by combining the mechanisms of these effects. It is also possible that niacin may contribute to the corrective effects of MIGU-4, as its use at a dose of 1–2 grams per day causes an increase in HDL content by 20% against the background of a reduction in triglycerides and LDL content [16], and increases the activity of antioxidant enzymes in experimental diabetes [17].

Administration of MIGU-4 provided positive dynamics of protein and lipid content in the blood of rats with STZ-induced diabetes. The intensity of the effects of MIGU-4 (25.0 mg/kg) on the total protein and albumin content was similar to the effect of vitamin E (100.0 mg/kg), while the effectiveness of MIGU-4-induced restoration of lipid metabolism was somewhat higher, taking into account that most (three of four) of the studied parameters did not differ from the control, while during vitamin E administration, the most (three of four) parameters exceeded those in the control group.

The enzymatic activity of the blood, which is determined by hepatic metabolism (aminotransferases AST and ALT), as well as enzymes-markers of inflammatory tissue damage (ALP and LDH), the level of which significantly increases in rats with STZ-induced diabetes [7, 11], showed a clear trend towards a decrease against a background of MIGU-4 administration. The intensity of the corrective effect was

similar to the effectiveness of vitamin E (100.0 mg/kg), except for AST activity, the normalisation of which was more pronounced under MIGU-4 treatment.

Thus, the results obtained indicate the systemic nature of the protective effect of MIGU-4 in the development of STZ-induced diabetes mellitus, which provides the restoration of lipid metabolism, provides correction of aminotransferase activity and has a positive effect on blood glucose and protein levels. The use of MIGU-4 as a drug in combination with thiazolidinedione antidiabetic drugs, which are activators of PPAR-γ receptors, is promising.

Conclusions

1. The course administration of MIGU-4 has a moderate hypoglycemic effect and leads to a moderate increase in insulin level. The intensity of the corrective effect of MIGU-4 (25.0 mg/kg, i.p.) corresponded to that of vitamin E (100.0 mg/kg, i.p.), except for the degree of hypoglycemia, although the effectiveness of MIGU-4 was higher in terms of daily body weight gain.

2. The use of MIGU-4 (25.0 mg/kg, i.p.) prevents diabetes-induced lipid metabolism disorders, namely, an increase in the content of cholesterol, triglycerides, low-density lipoproteins, with a simultaneous decrease in the content of high-density lipoproteins in the blood serum.

3. The course administration of the germanium-containing compound MIGU-4 at a dose of 25.0 mg/kg, i.p., causes a decrease in the activity of aminotransferases (AST and ALT), nonspecific markers of tissue alteration – ALP and LDH, as well as bilirubinemia, hypoprotein- and hypoalbuminemia, which occur during STZ-induced diabetes.

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Надійшла до редакції 22.03.2024.
Прийнята до друку 30.08.2024.
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