

## THE INFLUENCE OF ANTIDIABETIC COMBINED MEDICINAL PRODUCT GLIKVERIN BASED ON VOGLIBOSE AND QUERCETIN ON LIPID EXCHANGE INDICES UNDER CONDITIONS OF EXPERIMENTAL METABOLIC SYNDROME\*

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At present, the prevalence of diabetes mellitus (DM) has reached a pandemic scale and is one of the most pressing public health issues worldwide. According to experts from the International Diabetes Federation, 193 million people live with undiagnosed diabetes and are also at risk of developing chronic complications. It is projected that in 2045 the number of patients with diabetes will reach 629 million people [1]. In Ukraine the number of registered patients with diabetes exceeds 1.8 million people, among whom type 2 diabetes predominates (90%) [2].

In recent years, type 2 diabetes has been associated with metabolic syndrome (MetS), the prevalence of which in developed countries among people aged 40 to 75 years is 10–35%. The leading link in the pathogenesis of type 2 diabetes and MetS is insulin resistance on the background of obesity, in which there are significant disorders of carbohydrate and lipid me-

tabolism, which increase the risk of cardiovascular diseases [3]. Accelerated development of arterial hypertension, coronary heart disease under the condition of MetS, development of macro- and microangiopathies brings this pathology to 3rd place among the causes of mortality after cardiovascular and oncological pathologies. In this regard, the main strategy of modern therapy of type 2 diabetes is to prevent the development of cardiovascular complications, which involves strict control of glycemia, blood pressure, as well as lipid-lowering and antiplatelet therapy.

There is currently no clear evidence of the effectiveness of most groups of oral hypoglycemic agents in reducing the risk of diabetic macro- and microangiopathies, in addition, many of them have undesirable side effects and reduced therapeutic activity with long-term use, indicating the relevance of search and expansion of new antidiabetic drugs, which would be cha-

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racterized not only by high hypoglycemic properties, but also by prophylactic action against complications [4]. A promising direction in the development of new antidiabetic drugs is the creation of combined drugs based on existing and researched medicinal products, including ones of natural origin, which can provide potentiation of hypoglycemic action, higher compliance and reduce side effects by reducing therapeutic doses.

The combined standardized medicinal product under the conditional name «glikverin», developed at the Department of Industrial Technology of drugs of the National University of Pharmacy, contains an inhibitor of intesti-

nal  $\alpha$ -glucosidases voglibose (manufactured by «KUSUM PHARM» LLC, Sumy, Ukraine) and a powerful natural antioxidant of bioflavonoid origin quercetin (produced by PJSC SIC «Borshchahivskiy CPP», Kyiv, Ukraine). The basis for the creation and experimental study of glikverin were clinical and experimental data on the effectiveness of voglibose and quercetin in type 2 diabetes and MetS, which suggest the possibility of increasing the pharmacological action of individual components in the combination.

The aim of this work was to study the effect of glikverin on lipid metabolism in experimental metabolic syndrome.

## MATERIALS AND METHODS

The study was performed on white non-linear male rats weighing 200–220 g. The animals were kept under standard vivarium conditions. When working with animals, the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986), the «General Ethical Principles for Animal Experiments» (Kyiv, 2001) were followed. Euthanasia was performed by overdose of ether anesthesia.

MetS was simulated by keeping rats on a hypercaloric diet enriched with energy sources (containing 20% fatty food — saturated lipids (lard) and fructose ad libitum (fructose, powder, 0.1 kg, batch 20130309, LLC «Chemproduct», Ukraine) 1 g per day per 100 g of body weight) as a 10% aqueous solution) for 8 weeks [5]. The content of complex carbohydrates in the daily diet of animals was 60%.

The study drugs were administered simultaneously with the hypercaloric diet intragastrically for 8 weeks. The following groups of rats were used:

- group 1 — intact control (Control);
- group 2 — control pathology (MetS) — rats receiving a hypercaloric diet;
- group 3 — animals that were administered glikverin at a dose of 50 mg/kg on the background of hypercaloric diet (MetS + glikverin),
- groups 4–6 — animals that were administered comparison drugs on the background of hypercalorie diet: quercetin

substance at a dose of 50 mg/kg (according to the literature) — MetS + quercetin, the voglibose substance at a dose of 0.06 mg/kg (corresponds to the initial human dose of 0.3 mg/day) — MetS + voglibose and standard drug — metformin (manufactured by Metformin SANDOZ®, LEK, Poland) at a dose of 60 mg/kg (corresponds to the average daily dose for a person of 1000 mg/day) — MetS+metformin.

At the end of the experiment, the animals were weighed and body weight gain was calculated. Rats were decapitated under ether anesthesia and serum was obtained for testing. Lipid metabolism was assessed by the content of total cholesterol (TC), triacylglycerols (TAG), low and high density lipoprotein cholesterol (LDL-C, HDL-C) in serum, which were determined using standard biochemical kits of domestic production. Content of tumor necrosis factor-alpha (TNF- $\alpha$ ) in the blood of rats was determined using standard set of reagents ELISA by firm Sigma (USA) using an enzyme-linked immunosorbent analyzer Star Fax 4700.

The obtained data were processed by the methods of variation statistics. Determining the nature of the distribution of the quantitative trait in the population was carried out using the Shapiro–Wilk test. For multiple comparisons of data with normal distribution, parametric one-way analysis of variance ANOVA was performed and applied Newman–Kayles criterion. The difference was considered statistically significant at  $p < 0.05$ .

## RESULTS AND THEIR DISCUSSION

It is known that under the conditions of MetS there is a consistent development of a complex of interrelated metabolic disorders — abdominal obesity, insulin resistance, hyperinsulinemia, hypertriglyceridemia, arterial hypertension and Type 2 diabetes [6]. A key role in the development of insulin resistance, which is considered the main mechanism that triggers all the cascade of metabolically interrelated disorders in MetS, plays obesity [7, 8].

As can be seen in Fig. 1 against the background of a diet high in fats and carbohydrates, body weight gain in the MetS group significantly increased 3.1 times ( $p < 0.05$ ) compared with the intact control group, which allowed to state the development of obesity in rats (Fig.).

Administration of the combined drug glikverin significantly, by 66% ( $p < 0.05$ ) inhibi-

ted weight gain at the level of intact animals. The greatest inhibition of weight gain by 73% ( $p < 0.05$ ) was registered in animals that received a monocomponent of glikverin — a known inhibitor of  $\alpha$ -glucosidase voglibose, due to its mechanism of action, namely, the ability to reduce the absorption of carbohydrates in the intestine [9]. The use of the flavonoid quercetin has lead to a probable body weight loss of rats by 56% ( $p < 0.05$ ), although statistically inferior to voglibose.

Metformin, as a recommended first-line medicine for the treatment of type 2 diabetes that can reduce appetite [10], weakened body weight gain by 58% ( $p < 0.05$ ) and in this effect was also inferior to voglibose. Therefore, the new combination product was significantly weakening body weight gain probably to

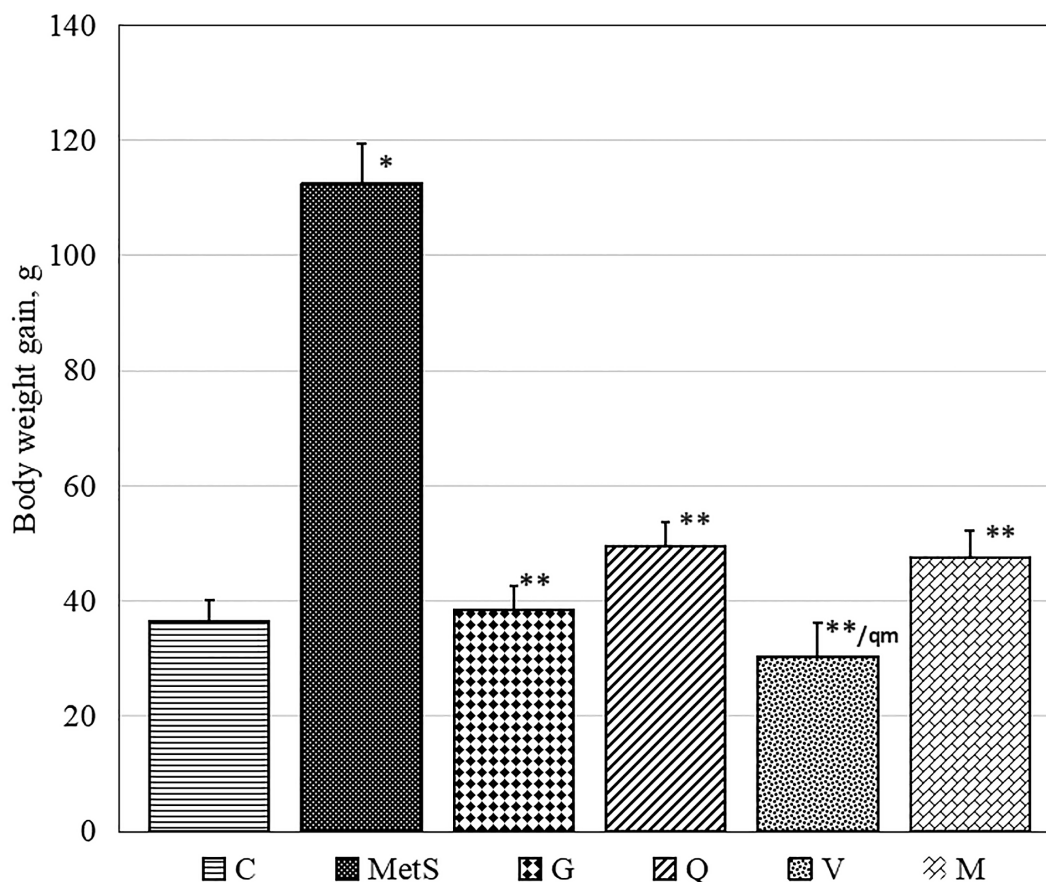


Fig. Weight gain of rats treated with glikverin and reference drugs for 8 weeks on a hypercaloric diet,  $n = 7$ .

Note.

C — control; G — MetS + glikverin, Q — MetS + quercetin, V — MetS + voglibose, M — MetS + metformin;

\* deviation is significant relative to the values of group C,  $p < 0.05$ ;

\*\* deviation is significant relative to the values of the MetS group,  $p < 0.05$ ;

q — deviation is significant relative to the values of group Q,  $p < 0.05$ ;

m — deviation is significant relative to the values of group M,  $p < 0.05$ .

Table

**Effect of glikverin and reference drugs on lipid metabolism under MetS induced by hypercaloric diet ( $X \pm S_x$ ),  $n = 7$**

Group of animals	Indicators				
	TC, mmol/l	HDL-C, mmol/l	LDL-C, mmol/l	TAG, mmol/l	TNF- $\alpha$ , pg/ml
Control	1.42 $\pm$ 0.17	0.83 $\pm$ 0.04	4.85 $\pm$ 0.31	1.52 $\pm$ 0.21	0.62 $\pm$ 0.05
MetS	2.56 $\pm$ 0.22*	0.52 $\pm$ 0.06*	8.34 $\pm$ 0.40*	3.64 $\pm$ 0.35*	1.23 $\pm$ 0.08*
MetS + glikverin	1.48 $\pm$ 0.16**/v	0.76 $\pm$ 0.06**/qvm	5.13 $\pm$ 0.45**/qvm	1.62 $\pm$ 0.39**/vm	0.76 $\pm$ 0.04**
MetS + quercetin	1.89 $\pm$ 0.12**	0.48 $\pm$ 0.05	6.47 $\pm$ 0.41**	1.90 $\pm$ 0.36**	0.54 $\pm$ 0.06**/qvm
MetS + voglibose	2.17 $\pm$ 0.23	0.42 $\pm$ 0.04	7.95 $\pm$ 0.57	2.68 $\pm$ 0.29	0.95 $\pm$ 0.05**
MetS + metformin	1.92 $\pm$ 0.21	0.39 $\pm$ 0.06	7.28 $\pm$ 0.54	2.93 $\pm$ 0.35	1.09 $\pm$ 0.04

Note.

\* deviation is significant relative to the values of group Control,  $p < 0.05$ ;

\*\* deviation is significant relative to the values of the MetS group,  $p < 0.05$ ;

q deviation is significant relative to the values of the MetS + quercetin group,  $p < 0.05$ ;

v deviation is significant relative to the values of the MetS + voglibose group,  $p < 0.05$ ;

m deviation is significant relative to the values of the MetS + metformin group,  $p < 0.05$ .

a greater extent due to the action of its constituent voglibose.

Along with obesity, one of the early manifestations of MetS is atherogenic dyslipidemia, which is a high risk factor for cardiovascular complications [11]. In the group of animals with MetS there was a marked increase 1.8 and 1.7 times ( $p < 0.05$ ) in the content of total cholesterol and LDL cholesterol, respectively, as compared with the intact control group (Table).

The evidence of lipolysis activation in adipose tissue, excessive release of free fatty acids and impaired lipid utilization in the liver was significant hypertriacylglycerolemia ( $p < 0.05$ ) (see table). At the same time, there was a significant 1.6 times ( $p < 0.05$ ) decrease in the level of HDL, which perform reverse transport of cholesterol, preventing its accumulation in the walls of blood vessels (Table).

Therefore, changes in lipid metabolism markers in the serum of rats in this model of MetS have shown the development of severe atherogenic dyslipidemia, which may later be a pathogenetic link of atherosclerosis in patients with diabetes.

In rats treated with a combination of quercetin and voglibose on the background of a hypercaloric diet, all studied parameters were normalized to the level of animals from the intact control group: total cholesterol was reduced by 1.7 times ( $p < 0.05$ ), LDL-C and TAG —

by 1.6 and 2.2 times ( $p < 0.05$ ), respectively, the level of HDL increased by 46%,  $p < 0.05$  (Table).

The content of total cholesterol in the groups of voglibose and metformin did not differ statistically from that in animals with simulated MetS, while quercetin led to its reduction by 26% ( $p < 0.05$ ). In terms of the ability to level hypercholesterolemia, glikverin was 1.5 times ( $p < 0.05$ ) superior to voglibose (Table). However, despite the relatively high values of this indicator with the use of quercetin and metformin, no statistical differences with the glikverin group have been found. The study combination significantly restored to the level of intact animals the ratio of HDL and LDL in the serum, significantly exceeding both separate components quercetin (average by 1.6 times,  $p < 0.05$ ) and voglibose (average by 1.7 times,  $p < 0.05$ ), and biguanide metformin (on average by 1.7 times,  $p < 0.05$ ) (Table). Glikverin significantly 2.2 times ( $p < 0.05$ ) suppressed hypertriacylglycerolemia. The level of TAG in the quercetin group, although acquired significant differences compared with the MetS group, but in none of the groups of reference drugs did not reach the values of intact control (Table).

Comparative analysis has shown that the pronounced antiatherogenic effect of the combined agent is due to the effect of both compo-

nents, with a predominant effect on the lipid metabolism of quercetin.

The mechanisms underlying the normalizing effect of quercetin on lipid metabolism and its antiatherogenic effects are associated primarily with antioxidant properties, as it is known that the activation of free radical processes plays a leading role in atherogenesis due to oxidative modifications of lipoproteins [12, 13]. Voglibose improves the lipid profile more likely, indirectly due to the normalization of body weight [14].

Thus, in the ability to inhibit atherogenic processes and activate the mechanisms of antiatherogenic protection glikverin statistically significantly exceeded the comparison drug metformin and some of its own monocomponents: quercetin and voglibose, which indicates a synergistic effect of the components of the studied product.

According to current data, an important role in the development of insulin resistance and MetS is played by pro-inflammatory cytokines, which are produced mainly by activated

macrophages and T-lymphocytes in particular tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [15]. In our experiment, the level of TNF- $\alpha$  in rats of the control pathology group increased by 98% ( $p < 0,05$ ) compared to intact control and correlated with the degree of obesity and impaired lipid metabolism (Fig., table).

According to the data obtained, in rats treated with glikverin the content of TNF- $\alpha$  significantly decreased by 38% ( $p < 0.05$ ). Among the comparison drugs, a statistically significant effect of reducing the TNF- $\alpha$  level was found only in the quercetin group, for which the natural antioxidant was superior to the studied combination, voglibose and metformin (Table). The result is probably related to the known anti-inflammatory properties of quercetin.

Thus, in the experimental model of MetS, glikverin significantly inhibits the gain of body weight in rats, shows a pronounced hypocholesterolemic, hypolipidemic effect and reduces the content of TNF- $\alpha$  by enhancing the effects of quercetin and voglibose in its composition.

## CONCLUSIONS

1. Keeping rats on a high-calorie diet for 8 weeks has led to obesity, atherogenic dyslipidemia and increased proinflammatory cytokine TNF- $\alpha$ .
2. The combination of voglibose and quercetin in the combined agent leads to the summation of their pharmacological effects, which is confirmed by the weakening of body weight growth, pronounced hypocholesterolemic, hypolipidemic effect and a decrease in TNF- $\alpha$ . In terms of these properties, glikverin is significantly superior to the comparison drugs quercetin, voglibose and metformin.
3. The obtained results substantiate further pharmacological study of glikverin as a promising tool for the treatment of metabolic syndrome and type 2 diabetes.

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## ВПЛИВ АНТИДІАБЕТИЧНОГО КОМБІНОВАНОГО ЗАСОБУ ГЛІКВЕРИН НА ОСНОВІ ВОГЛІБОЗУ ТА КВЕРЦЕТИНУ НА ПОКАЗНИКИ ЛІПІДНОГО ОБМІНУ ЗА УМОВ ЕКСПЕРИМЕНТАЛЬНОГО МЕТАБОЛІЧНОГО СИНДРОМУ

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**Метою** даної роботи було дослідження впливу нового комбінованого засобу глікверину на основі воглібозу та кверцетину на показники ліпідного обміну за умови експериментального метаболічного синдрому.

**Матеріали і методи.** Модель метаболічного синдрому відтворювали шляхом утримання щурів на гіперкалорійній дієті (містила 20% жирної їжі — насичені ліпіди (сало) та фруктоза ad libitum (1 г на добу на 100 г маси тіла) у вигляді 10 % водного розчину протягом 8 тижнів. При цьому вміст складних вуглеводів у добовому раціоні тварин складав 60 %. Використовували наступні групи щурів: 1 група — інтактний контроль; 2 група — щури, які отримували гіперкалорійну дієту; 3 група — тварини, яким на фоні гіперкалорійної дієти вводили глікверин у дозі 50 мг/кг, 4–6 групи — тварини, яким на тлі гіперкалорійної дієти вводили препарати порівняння: субстанцію кверцетину в дозі 50 мг/кг, субстанцію воглібозу в дозі 0,06 мг/кг та стандартний препарат — метформін у дозі 60 мг/кг. Досліджувані засоби вводили одночасно з гіперкалорійною дієтою внутрішньошлунково, протягом 8 тижнів. Ліпідний обмін оцінювали за приростом маси тіла, вмістом загального холестерину, триацилгліцеролів, холестерину ліпопротеїдів низької та високої щільності і рівнем TNF- $\alpha$  у сироватці крові.

**Результати.** Встановлено, що комбінований засіб глікверин послаблює зростання маси тіла на 66 %, що, ймовірно, обумовлено дією його складового компонента воглібозу, який уповільнює розщеплення та всмоктування вуглеводів у кишечнику. Результати дослідження ліпідного обміну в сироватці крові показали, що поєднання воглібозу та кверцетину у комбінованому засобі призводить до сумарності їх фармакологічних ефектів. Під впливом глікверину вміст загального холестерину знижувався в 1,7 рази, ХС-ЛПНЩ та ТАГ — в 1,6 і 2,2 рази відповідно, рівень ХС-ЛПВЩ підвищувався на 46 %. Порівняльний аналіз показав, що виразна антиатерогенна дія комбінованого засобу обумовлена ефектом обох складових компонентів, з переважним впливом на ліпідний обмін кверцетину. Виявлена гіпохолестеринемічна та гіполіпідемічна дія забезпечує антиатерогенний ефект, за виразністю якого глікверин значно перевершує препарати порівняння кверцетин, воглібоз та метформін. Комбінація воглібозу та кверцетину також знижувала на 38 % вміст ФНП- $\alpha$  — індуктора інсулінорезистентності за умови ожиріння. Отримані результати обґрунтовують доцільність подальшого фармакологічного вивчення антидіабетичних властивостей глікверину як перспективного засобу для лікування метаболічного синдрому та цукрового діабету 2 типу.

**Ключові слова:** глікверин, кверцетин, воглібоз, метаболічний синдром, ліпідний обмін.

## ВЛИЯНИЕ КОМБИНИРОВАННОГО ПРОТИВОДИАБЕТИЧЕСКОГО СРЕДСТВА ГЛИКВЕРИН НА ОСНОВЕ ВОГЛИБОЗА И КВЕРЦЕТИНА НА ПОКАЗАТЕЛИ ЛИПИДНОГО ОБМЕНА В УСЛОВИЯХ ЭКСПЕРИМЕНТАЛЬНОГО МЕТАБОЛИЧЕСКОГО СИНДРОМА

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**Целью** данной работы было исследование влияния нового комбинированного средства гликверина на основе воглибоза и кверцетина на показатели липидного обмена в условиях экспериментального метаболического синдрома.

**Материалы и методы.** Модель метаболического синдрома воспроизводили путем содержания крыс на гиперкалорийной диете (содержала 20% жирной пищи и фруктозу ad libitum (1 г в сутки на 100 г массы тела) в виде 10 % водного раствора в течение 8 недель. При этом содержание сложных углеводов в суточном рационе животных составляло 60 %. Использовали следующие группы крыс: 1 группа — интактный контроль; 2 группа — крысы, получавшие гиперкалорийную диету; 3 группа — животные, которым фоне гиперкалорийной диеты вводили гликверин в дозе 50 мг/кг, 4–6 группы — животные, которым фоне гиперкалорийной диеты вводили препараты сравнения: субстанцию кверцетина в дозе 50 мг/кг, субстанцию воглибоза в дозе 0,06 мг/кг и стандартный препарат — метформин в дозе 60 мг/кг. Исследуемые средства вводили одновременно с гиперкалорийной диетой внутрижелудочно в течение 8 недель. Липидный обмен оценивали по приросту массы тела, содержанию общего холестерина, триацилглицеролов, холестерина липопротеидов низкой и высокой плотности и уровню TNF- $\alpha$  в сыворотке крови.

**Результаты.** Установлено, что комбинированное средство гликверин ослабляет увеличение массы тела на 66 %, что, вероятно, обусловлено действием его составляющего компонента воглибоза, который замедляет расщепление и всасывание углеводов в кишечнике. Результаты исследования липидного обмена в сыворотке крови показали, что сочетание воглибоза и кверцетина в комбинированном

средстве приводит к суммации их фармакологических эффектов. Под влиянием гликверина содержание общего холестерина снижалось в 1,7 раза, ХС-ЛПНП и ТАГ — в 1,6 и 2,2 раза соответственно, уровень ХС-ЛПВП повышался на 46 %. Сравнительный анализ показал, что выраженное антиатерогенное действие комбинированного средства обусловлено эффектом обеих составляющих компонентов с преимущественным влиянием на липидный обмен кверцетина. Выявленное гипохолестеринемическое и гиполипидемическое действие обеспечивает антиатерогенный эффект, по выраженности которого гликверин значительно превосходит препараты сравнения кверцетин, voglibose и метформин. Комбинация voglibose и кверцетина также снижала на 38% содержание ФНО- $\alpha$  — индуктора инсулинорезистентности при ожирении. Полученные результаты обосновывают целесообразность дальнейшего фармакологического изучения антидиабетических свойств гликверина, как перспективного средства для лечения метаболического синдрома и сахарного диабета 2 типа.

Ключевые слова: гликверин, кверцетин, voglibose, метаболический синдром, липидный обмен.

## THE INFLUENCE OF ANTIDIABETIC COMBINED MEDICINAL PRODUCT GLIKVERIN BASED ON VOGLIBOSE AND QUERCETIN ON LIPID EXCHANGE INDICES UNDER CONDITIONS OF EXPERIMENTAL METABOLIC SYNDROME

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The **aim** of this work was to study the effect of glikverin based on voglibose and quercetin on lipid metabolism in experimental metabolic syndrome.

**Materials.** The metabolic syndrome model was reproduced by keeping rats on a hypercaloric diet (containing 20 % fatty food and fructose ad libitum (1 g per day per 100 g of body weight as a 10 % aqueous solution) for 8 weeks. The content of complex carbohydrates in the daily diet of animals was 60 %. The following groups of rats were used: group 1 — intact control; group 2 — rats receiving a hypercaloric diet; group 3 — animals that were administered glikverin at a dose of 50 mg/kg on the background of hypercaloric diet, groups 4–6 — animals that were administered comparison drugs on the background of hypercalorie diet: quercetin substance at a dose of 50 mg/kg, the voglibose substance at a dose of 0.06 mg/kg and standard drug — metformin at a dose of 60 mg/kg. The study drugs were administered simultaneously with the hypercaloric diet intragastrically for 8 weeks. Lipid metabolism was assessed by body weight gain, total cholesterol, triacylglycerols, low- and high-density lipoprotein cholesterol, and serum TNF- $\alpha$  levels.

**Results.** It was found that the combined product glikverin reduces body weight gain by 66%, which is probably specified by the action of its component component voglibose, which slows down the breakdown and absorption of carbohydrates in the intestine. The results of the study of lipid metabolism in blood serum showed that the combination of voglibose and quercetin in the combined agent leads to the summation of their pharmacological effects. Under the influence of glikverin, the content of total cholesterol decreased by 1.7 times, LDL-C and TAG - by 1.6 and 2.2 times, respectively, the level of HDL-C increased by 46%. Comparative analysis showed that the pronounced antiatherogenic effect of the combined agent is due to the effect of both components, with a predominant effect on the lipid metabolism of quercetin. The revealed hypocholesterolemic and hypolipidemic action provide an antiatherogenic effect. The severity of this effect, which provided glikverin, significantly exceeded the comparison agents quercetin, voglibose and metformin. The combination of voglibose and quercetin also reduced by 38% the content of TNF- $\alpha$  - an inductor of insulin resistance in obesity. The obtained results substantiate the expediency of further pharmacological study of the antidiabetic properties of glikverin as a promising tool for the treatment of metabolic syndrome and type 2 diabetes.

Key words: glikverin, quercetin, voglibose, metabolic syndrome, lipid metabolism.