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SCREENING STUDY OF THE ANTIHYPERGLYCEMIC ACTION OF NEW SOLID QUERCETIN DISPERSIONS

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The aim *– to screen new solid dispersions of quercetin for the presence of antihyperglycemic action and to identify the most active substances that are promising for the creation of antidiabetic drugs.*
Materials and methods. *The object of the study was 4 new solid dispersions of quercetin, developed at the National University of Pharmacy. Solid dispersions of quercetin were prepared by the liquid-phase method; hydroxypropyl methylcellulose (HPMC) or polyvinylpyrrolidone (PVP) in ratios of 1:1 and 1:2 were used as a carrier. The antihyperglycemic effect of the studied substances at a dose of 50 mg/kg was assessed in rats by the ability to lower blood glucose levels after carbohydrate loading in a model of impaired glucose tolerance induced by dexamethasone and in experimental type 2 diabetes mellitus induced by dexamethasone.*
Results. *It was found that with impaired glucose tolerance, a solid dispersion of quercetin with HPMC (1:1) showed a pronounced antihyperglycemic effect – the glucose level 30 minutes after glucose load significantly decreased by 28 % and did not differ from the action of metformin, which was confirmed by the value of the area under glycemic crooked. When solid dispersions with PVP (1:1 and 1:2) were used, the antihyperglycemic effect was less pronounced. In a model of type 2 diabetes mellitus, a significant antihyperglycemic effect was found only in a solid dispersion of quercetin with HPMC (1:1) at the metformin level, which indicates an increase in the solubility and absorption of quercetin.*
Conclusions. *A pronounced antihyperglycemic effect at the metformin level was found in a solid dispersion of quercetin with HPMC in a 1:1 ratio with impaired glucose tolerance and type 2 diabetes mellitus. It has been proven that a solid dispersion of quercetin with HPMC is a promising substance for creating a monocomponent drug or for inclusion in a new antidiabetic combined drug*
Keywords: *quercetin, solid dispersion, hydroxypropyl methylcellulose, polyvinylpyrrolidone, diabetes mellitus, screening, antihyperglycemic action*

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1. Introduction

Diabetes mellitus, as defined by the World Health Organization, is a state of prolonged increase in blood sugar levels, which can be caused by a number of external and internal factors with the development of absolute or relative insulin deficiency, which leads to a violation of carbohydrate, fat and protein metabolism. Over the past decades, the rate of spread of diabetes mellitus has accelerated significantly. According to the International Diabetes Federation (IDF), the number of patients with diagnosed diabetes mellitus among the adult population (20–79 years) in the world in 2045 will amount to 629 million [1].

Despite the constant improvement of directions in the treatment of type 2 diabetes, which prevails in the population of patients with diabetes, the achievement of normoglycemia and the prevention of chronic complications (such as retinopathy, angiopathy, neuropathy) remains a challenge, which indicates the need for the use of multicomponent method, which corresponds to the combination therapy using various groups of pharmacological agents [2].

The most used are combinations of oral antihyperglycemic drugs of various groups (for example, metformin in combination with sulfonylurea, sulfonylurea in combination with exenatide, etc.), which reduce the side effects of the components by reducing the doses of substances included in composition of the combination. However, drug combinations with antihyperglycemic action do not always provide prevention of complications of type 2 diabetes mellitus, which indicates the relevance of the development of new combined drugs.

Potential components of combined antidiabetic drugs can be herbal substances that are effective due to a wide range of pharmacological action and are quite safe with prolonged use. It should be noted that today in different countries of the world a large number of herbal substances are being studied in order to create effective antidiabetic drugs and available literature data on the experience of experimental and clinical use of phytopreparations in the complex therapy of type 2 diabetes mellitus [3, 4]. Possible mechanisms of the therapeutic action of plant components include inhibition of the activity of α-glucosidase and α-amylase, the effect on glucose uptake by peripheral tissues and

glucose transporters GLUT4, increased insulin secretion and proliferation of β-cells of the pancreas, inhibition of protein tyrosine phosphatase [3]. It has now been proven that most of these mechanisms, due to the pronounced antioxidant properties of phytopreparations, which are able to weaken the oxidative stress developing in patients with type 2 diabetes mellitus, combine the main links of glucose toxicity and cause severe chronic complications of the disease [5, 6]. One of the phytopreparations of interest as a potential antidiabetic drug is the well-known and sufficiently studied flavonol quercetin – 2(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromene-4-OH, which exhibits anti-inflammatory, antispasmodic, antihistamine, diuretic effect, has powerful antioxidant, radioprotective and antitumor properties [7, 8].

Due to the insufficient solubility of quercetin and poor absorption in the gastrointestinal tract, scientists are constantly trying to improve the solubility and bioavailability, which will significantly expand the list of medical indications for the use of this natural bioflavonoid [9, 10].

The aim of this study was to conduct pharmacological screening of new solid dispersions of quercetin for antihyperglycemic action and to identify substances that are promising for the creation of antidiabetic drugs.

2. Planning (methodology) of research

At present, a standardized solid dispersion of quercetin with polyethylene oxide and neusilin has already been obtained at the National University of Pharmacy, which, together with voglibose, is included in the composition of a new combined antidiabetic agent under the code name "Glikverin". The pronounced antihyperglycemic and antidiabetic effect of "Glikverin" has been experimentally proven in models of insulin resistance, type 2 diabetes mellitus and metabolic syndrome [11].

Considering previous experience in creating a solid dispersion with quercetin [12] at the Department of Industrial Technology of Drugs of the National University of Pharmacy (NUPh). Using a new technological approach, new samples of hard quercetin dispersions based on various carriers were obtained. It is planned to conduct their pharmacological screening for antihyperglycemic action, which will justify the creation of a drug for the treatment of type 2 diabetes mellitus.

Considering previous experience in creating a solid dispersion with quercetin [12] at the Department of Industrial Technology of Drugs of the NUPh by Doctor of Pharmacy Kovalevska Inna under the guidance of Doctor of Pharmacy, professor Ruban Olena, using a new technological approach, new samples of hard quercetin dispersions based on various carriers were obtained.

Since the main criterion for compensating for diabetes mellitus is a decrease in the level of hyperglycemia, two experimental models with high reproducibility and a short course were selected for screening: a model of impaired glucose tolerance induced by dexamethasone and a model of type 2 diabetes induced by dexamethasone [13].

Stages:

1. Study of the antihyperglycemic effect of solid dispersion samples on the model of impaired glucose tolerance.

2. Study of the antihyperglycemic effect in type 2 diabetes mellitus.

3. Determination of the most promising solid dispersion of quercetin for the development of new antidiabetic drugs.

4. Identification of promising directions for further research.

3. Materials and methods

Studies of drugs were carried out at the Central research laboratory of the National University of Pharmacy in 2021.

3. 1. Study subjects

The objects of the research were 4 samples of solid dispersion of quercetin. Hydroxypropyl methylcellulose (HPMC) or polyvinylpyrrolidone (PVP) was used as a carrier in a ratio of 1:1 and 1:2 (Table 1).

Table 1

Composition of the investigated samples of solid dispersions of quercetin

Sample number	Composition of samples
No. 1	HPMC : quercetin, 1:1
No. 2	HPMC : quercetin, 1:2
No. 3	PVP : quercetin, 1:1
No. 4	PVP : quercetin, 1:2

Solid dispersions were obtained by the liquid-phase method [14]. The technology for obtaining a solid dispersion of quercetin with carrier consists of several stages: obtaining a solution of API in ethanol 96 % (a portion of quercetin is dissolved in ethanol 96 % in a ratio of 1 to 3 with constant stirring), the resulting solution is mixed with a portion of the carrier (HPMC or PVP) with constant stirring at least 200 vol/min for 20 minutes until a homogeneous mass of a slightly yellow color is obtained. Microcrystalline cellulose is added to the mass of quercetin with carrier (HPMC or PVP) with constant stirring at 50 rpm until a fluffy homogeneous mass is obtained, dried in a dryer with air circulation at a temperature of 60 °C±5 until the final mass is not more than 3 %. Calibration takes place through a 1 mm sieve.

3. 2. Research methods

The study of the hypoglycemic properties of the solid dispersion of quercetin was carried out in accordance with the guidelines for the experimental study of new antidiabetic agents [13].

Experiments were performed on white nonlinear male rats weighing 130–410 g raised in the National University of Pharmacy vivarium nursery. The animals were kept in standard vivarium conditions: at a temperature of 20–22 °C, humidity no more than 60–70 %, air exchange volume (extract-inflow) 8/10, day/night light mode in standard aluminium cages, no more than 5 animals in each.

The work with animals was carried out in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 1986), «Procedure for

conducting experiments, experiments on animals by scientific institutions» [15].

Directive 2010/63/EU of European Parlament and Council on the protection of animals used for scientific purposes and the law of Ukraine «On the protection of animals from cruelty» No. 3477-IV dated 21.02.2006. The NUPh Bioethics Commission did not find any violations of moral and ethical norms in the planning and conduct of research work (No. 4 of 02.10.2020).

The studies were carried out in comparison with antidiabetic means from a group of biguanides – metformin tablets, 500 mg (produced by Lek S. A., Poland, an enterprise of the Sandoz company). Metformin was used at a dose of 60 mg/kg of body weight in rats, which was calculated using the coefficient of species sensitivity [16, 17].

The experimental dose of the investigated solid dispersions of quercetin was selected on the basis of previously obtained results in the study of solid dispersions of quercetin with polyethylene oxide and neusilin and amounted to 50 mg/kg [11].

Solid dispersions of quercetin and the reference drug metformin were administered to animals in the form of solutions intragastrically in the morning on an empty stomach using a metal probe.

Reproduction of the experimental model of impaired glucose tolerance was carried out on 3-month-old male rats weighing 130–160 g using dexamethasone [13]. Dexamethasone (dexamethasone-KRKA, solution for injection 4 mg/ml amp., 1 ml (KRKA, Slovenia)) was injected subcutaneously at a dose of 0.125 mg/kg for 13 days.

Animals were divided into the following groups: intact control; control pathology, 4 groups of rats receiving samples of solid dispersion of quercetin No. 1–4 at a dose of 50 mg/kg; a group of rats receiving metformin at a dose of 60 mg/kg.

At 14 on day, the animals were measured basal blood glucose and an oral glucose tolerance test (OGTT) was performed.

The blood glucose levels of the animals were determined on an empty stomach and at time points using the glucose oxidase method using a OneTouch Select glucometer (LifeScan Scotland Limited, UK). For this purpose, the animals were punctured along the tail vein, brought the device with a test strip inserted, and the device automatically took 1.5 μl of blood. The glucose in the blood reacts electrochemically with the reagents in the test strip, producing a weak electrical current. The strength of the current changes in proportion to the blood glucose content. Linear measurement ranges 1.1–33.3 mmol/L.

An oral glucose tolerance test was performed as follows. In rats after an overnight fast (16-18 hours) on an empty stomach, the initial blood glucose levels were determined, and a glucose solution was injected intragastrically at a rate of 3 g/kg. Further, the concentration of glucose in the blood was measured 30, 60, 120 minutes after the carbohydrate load [13].

Antihyperglycemic activity was evidenced by the ability of solid dispersions of quercetin to reduce the level of glycemia at the 30th minute of OGTT (the time of maximum rise in blood glucose in experimental rats in response to intragastric carbohydrate load). Additionally, according to the results of OGTT, the value of the integral indicator of the plane under the glycemic curves (glicemic area under curve, AUCglu (mmol/L min) was calculated.

Type 2 diabetes mellitus was modelled on 18-month-old male rats weighing 320-410 g by subcutaneous administration of dexamethasone (Dexamethasone-KRKA, solution for injection 4 mg/ml amp., 1 ml (KRKA, Slovenia)) at a dose of 0.125 mg/kg for 13 days [13]. Rats were divided into experimental groups as in the previous experiment.

The antihyperglycemic activity of solid dispersions of quercetin was assessed by the dynamics of basal blood glucose: baseline data, on days 7 and 14.

3. 3. Statistical analysis

Statistical processing of the obtained results was carried out according to the generally accepted methods of variation statistics with the determination of the arithmetic mean and average error (M±m) by Student's t-test using the standard computer program "Statistica 6.0". The planes under the glycemic curves were calculated using the statistical software package "MedCalk, v. 9.3.7.0".

4. Results

The results of studying the antihyperglycemic effect of samples of solid dispersions of quercetin with impaired glucose tolerance are shown in Table 2.

Conducting an oral glucose tolerance test allows to reproduce in intact animals the state of postprandial hyperglycemia with an increase in blood glucose at the 30th minute of the experiment (Table 2).

On the 14th day in animals with control pathology, at the 30th minute of the glucose tolerance test, glycemia significantly exceeded the initial values by 2,2 times (p<0.001), after 60 minutes it gradually decreased, but after 120 minutes of the experiment it did not normalize to physiological parameters (Table 2). At the same time, the area under the glycemic curves was the highest among all experimental groups and significantly differed from the value of the intact control, which indicated impaired glucose tolerance in rats of control pathology.

The use of solid dispersions of quercetin showed that samples No. 1, 3 and 4 reliably prevent the development of hyperglycemia caused by carbohydrate load (Table 2). At the same time, samples No. 3 and 4 (PVP : quercetin, ratio 1:1 and 1:2) reduced blood glucose levels by 19 and 21 %, respectively, while sample No. 1 (HPMC: quercetin, 1:1) showed distinctly antihyperglycemic effect – the glucose level 30 minutes after glucose load significantly decreased by 28 % (p<0.05) compared with the indicator of the control pathology group and did not differ from the effect of metformin (Table 2).

The use of sample No. 2 (HPMC : quercetin, 1:2) in this model turned out to be ineffective, the dynamics of changes in the concentration of glucose in the blood of rats at all-time intervals and AUCglu did not differ significantly from the control pathology.

Table 2

Antihyperglycemic effect of solid dispersions of quercetin in the model of impaired carbohydrate tolerance induced by dexamethasone under the condition of OGTT, (M±*m*), *n*=7

Experimental conditions	Glycemic level, mmol/l				
	Initial data	30 minutes	60 minutes	120 minutes	AUCglu, mmol/l · min
Intact control	4.40±0.26	7.52±0.31*	5.94±0.46	4.19±0.45	287.41±22.58
Control pathology (glucose 3 g/kg)	4.15±0.43	8.92±0.46*	7.84±0.43*	6.96±0.41*	413.26±24.45*
Sample No. 1, 50 mg/kg+glucose	4.13±0.46	6.41±0.36*/**	5.42±0.37**	4.47±0.29**	304.31±18.76**
Sample No. 2, 50 mg/kg+glucose	4.23±0.19	7.97±0.38	6.73±0.39	5.84±0.33	343.52±35.42
Sample No. 3, 50 mg/kg+glucose	4.27±0.28	7.25±0.34*/**	6.28±0.35**	5.12±0.38**	316.17±15.42**
Sample No. 4, 50 mg/kg+glucose	4.18±0.30	7.09±0.31*/**	6.04±0.36**	5.43±0.35**	311.59±25.04**
Metformin, 60 mg/kg+glucose	4.22±0.29	6.28±0.36*/**	5.17±0.32**	4.31±0.39**	293.53±32.16**

*Note: * – p<0.05 relative to the intact control; ** – p<0.05 relative to the control pathology; n – the number of rats in the group*

Comparative analysis of the planes under the AUCglu glycemic curves, which is an integral parameter for assessing glucose load, confirmed the OGTT data.

Thus, the results obtained showed the antihyperglycemic properties of samples No. 1, 3, 4, which suggests an increase in the degree of release and absorption of quercetin due to the constituent components of these solid dispersions.

At the next stage, the antihyperglycemic properties of solid dispersions of quercetin were investigated in a model of type 2 diabetes mellitus caused by dexamethasone.

In our experiment, subcutaneous administration of dexamethasone to rats of the control group on the 7th day led to statistically significant moderate basal hyperglycemia, which persisted and significantly increased by 26 % compared to the initial values on the 14th day of the experiment (Table 3). Thus, the results obtained showed the development of experimental type 2 diabetes mellitus in animals.

Table 3

Antihyperglycemic effect of solid dispersions of quercetin in a model of type 2 diabetes mellitus induced by dexamethasone (M±*m*), *n*=7

Experimental conditions	Glycemic level, mmol/l		
	Initial data	7 days	14 days
Intact control	6.18±0.34	6.24±0.62	6.04±0.31
Control pathology (diabetes)	6.26±0.38	7.47±0.33*	7.89±0.48*
Sample No. 1, 50 mg/kg (diabetes)	5.90±0.25	7.04±0.41	6.51±0.21**
Sample No. 2, 50 mg/kg (diabetes)	5.81±0.40	7.23±0.39	7.42±0.56
Sample No. 3, 50 mg/kg (diabetes)	6.29±0.53	7.58±0.66	6.99±0.62
Sample No. 4, 50 mg/kg (diabetes)	5.47±0.20	7.51±0.68	6.71±0.45
Metformin, 60 mg/kg (diabetes)	5.83±0.45	6.36±0.47	6.28±0.42**

*Note: * – p<0.05 relative to the initial data; ** – p<0.05 relative to the control pathology; n – the number of rats in the group*

At the first observation period, the administration of all samples of solid dispersions of quercetin practically did not restrain the growth of hyperglycemia, in contrast to metformin, which, although not significantly, reduced the glucose level by 15 % compared to the control group (Table 3).

On the 14th day of the experiment, in the group of rats receiving sample No. 1 (HPMC:quercetin, 1:1), a significant antihyperglycemic effect was established (decrease in glycemia by 17 %, $p<0.05$), which is comparable to the effect the reference drug metformin (Table 3).

Test samples No. 3 and No. 4 showed only a positive trend towards lowering blood glucose levels. Perhaps, with a longer period of use, these investigated substances will exhibit an antihyperglycemic effect.

Sample No. 2, as in the model of impaired glucose tolerance, did not affect the glucose level at the end of the experiment, which allows us to conclude that it is inexpedient to use this solid dispersion of quercetin as a component of a combined antidiabetic drug.

5. Discussion

The experimental model of impaired glucose tolerance induced by dexamethasone was characterized by an excessive increase in the level of glycemia after carbohydrate loading and indicated the development of prediabetes due to the formation of insulin resistance and secondary or primary dysfunction of β-cells [18, 19].

Testing of rats treated with solid dispersions of quercetin with HPMC and PVP made it possible to establish the ability of samples 1, 3, 4 to provide a sufficient balance between the flow of exogenous glucose into the blood and the processes of its utilization by peripheral tissues and to state the presence of antihyperglycemic action with almost complete normalization glycemia to the level of intact animals after 120 minutes.

Further, it was important to confirm the results of the previous experiment and to evaluate the antihyperglycemic properties of solid dispersion samples of quercetin in a model of type 2 diabetes mellitus induced by dexamethasone. It is known that excessive doses of glucocorticoids can lead to impairment of the secretory function of β-cells of the pancreas and the development of insulin resistance as a result of a direct effect on the expression of glucose transporters GLUT1 and GLUT4 [20].

During the experiment, a significant antihyperglycemic effect was revealed only in sample No. 1 (solid dispersion of quercetin with HPMC, 1:1) at the level of metformin, which indicates the maximum transition of

quercetin to the amorphous state and its higher solubility in this solid dispersion.

Taking into account the wide range of pharmacological properties of quercetin, including stimulation of insulin secretion, increased glucose uptake by peripheral tissues, pronounced anti-inflammatory and antioxidant properties [21, 22], The results obtained indicate the prospects for further research for in-depth pharmacological study of the solid dispersion of quercetin with HPMC in a ratio of 1: 1.

Study limitation. To expand the understanding of the antihyperglycemic properties of a solid dispersion of quercetin with HPMC, it would be advisable to study the level of insulin in the blood and calculate the HOMA index.

Prospects for further research. In the future, it is planned to study the antidiabetic properties and mechanisms of the therapeutic action of a solid dispersion of quercetin with HPMC on experimental models of diabetes mellitus and metabolic syndrome.

6. Conclusions

The solid dispersion of quercetin with HPMC in a 1:1 ratio was found to have a significant antihyperglycemic effect. The new substance of quercetin is effective at the metformin level in experimental insulin resistance and type 2 diabetes mellitus.

Solid dispersion of quercetin with HPMC in a 1:1 ratio is a promising substance for further in-depth pharmacological study for the purpose of to create a new antidiabetic agent.

Conflict of interests

The authors declare that they have no conflicts of interest.

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References

1. International diabetes federation Diabetes Atlas. Available at: http://www.diabetesatlas.org

2. Dedov, I. I., Shestakova, M. V., Mayorov, A. Y., Vikulova, O. K., Galstyan, G. R., Kuraeva, T. L. et. al. (2017). Standards of specialized diabetes care. Edited by Dedov II, Shestakova MV, Mayorov AY. 8th edition. Diabetes Mellitus, 20 (1S), 1–121. doi: http://doi.org/10.14341/dm20171s8

3. Unuofin, J. O., Lebelo, S. L. (2020). Antioxidant Effects and Mechanisms of Medicinal Plants and Their Bioactive Compounds for the Prevention and Treatment of Type 2 Diabetes: An Updated Review. Oxidative Medicine and Cellular Longevity, 2020, 1–36. doi: http://doi.org/10.1155/2020/1356893

4. Pang, G.-M., Li, F.-X., Yan, Y., Zhang, Y., Kong, L.-L., Zhu, P. et. al. (2019). Herbal medicine in the treatment of patients with type 2 diabetes mellitus. Chinese Medical Journal, 132 (1), 78–85. doi: http://doi.org/10.1097/cm9.0000000000000006

5. Savka, I. I., Savka, T. B. (2020). Mechanisms of Macro-, Micro- and Ultramicroscopic Transformation of Bodies in Type 2 Diabetes. Ukrainian Journal of Medicine, Biology and Sport, 5 (2), 36–42. doi: http://doi.org/10.26693/jmbs05.02.036

6. Sharafetdinov, K. K., Plotnikova, O. A., Pilipenko, V. V., Nikitjuk, D. B. (2020). Oxidative stress and increasing antioxidant defence in type 2 diabetes. Clinical Nutrition and Metabolism, 1 (3), 127–136. doi: http://doi.org/10.17816/clinutr50340

7. Tarakhovskii, Iu. S., Kim, Iu. A., Abdrasilov, B. S., Muzafarov, E. N. (2013). Flavonoidy: biokhimiia, biofizika, meditsina. Puschino: Sunchrobook, 310.

8. Shi, G.-J., Li, Y., Cao, Q.-H., Wu, H.-X., Tang, X.-Y., Gao, X.-H. et. al. (2019). In vitro and in vivo evidence that quercetin protects against diabetes and its complications: A systematic review of the literature. Biomedicine & Pharmacotherapy, 109, 1085–1099. doi: http://doi.org/10.1016/j.biopha.2018.10.130

9. Riva, A., Ronchi, M., Petrangolini, G., Bosisio, S., Allegrini, P. (2018). Improved Oral Absorption of Quercetin from Quercetin Phytosome®, a New Delivery System Based on Food Grade Lecithin. European Journal of Drug Metabolism and Pharmacokinetics, 44 (2), 169–177. doi: http://doi.org/10.1007/s13318-018-0517-3

10. Chen, X., McClements, D. J., Zhu, Y., Chen, Y., Zou, L., Liu, W. et. al. (2018). Enhancement of the solubility, stability and bioaccessibility of quercetin using protein-based excipient emulsions. Food Research International, 114, 30–37. doi: http://doi.org/10.1016/j.foodres.2018.07.062

11. Kononenko, N. M., Ruban, O. A., Chikitkina, V. V., Kovalevska, I. V. (2020). The influence of antidiabetic combined medicinal product glik verin based on voglibose and quercetin on lipid e xchange indices under conditions of experimental metabolic syndrome. Problems of Endocrine Pathology, 74 (4), 124–130. doi: http://doi.org/10.21856/j-pep.2020.4.16

12. Kovalevska, I. V., Ruban, E. A., Kutsenko, S. A., Kutova, O. V., Kovalenko, Sv. M. (2017). Study of physical and chemical properties of solid dispersions of quercetin. Asian Journal of Pharmaceutics, 11 (4), 805–809.

13. Stefanova, O. V. (Ed.) (2001). Doklinichni doslidzhennia likarskykh zasobiv. Kyiv: Avitsenna, 528.

14. Kovalevska, I., Ruban, O. (2018). Development of the methodological approach of obtaining preparations based on solid dispersions. ScienceRise: Pharmaceutical Science, 4 (14), 4–8. doi: http://doi.org/10.15587/2519-4852.2018.140756

15. Poriadok provedennia naukovymy ustanovamy doslidiv, eksperymentiv na tvarynakh (2012). Nakaz Ministerstva osvity, nauky, molodi ta sportu Ukrainy. Nakaz No. 249. 01.03.2012. Ofitsiinyi visnyk Ukrainy, 24, 82.

16. Rybolovlev, Iu. R., Sidliarov, D. P., Afonin, N. I. (1981). Prognosticheskaia otsenka bezopasnosti veschestv dlia cheloveka po konstantam ikh biologicheskoi aktivnosti. Toksikologicheskie aspekty bezopasnosti gotovykh lekarstvennykh form. Moscow, 9–10.

17. Nasri, H., Rafieian-Kopaei, M. (2014). Metformin: Current knowledge. International Journal of Research in Medical Sciences, 19 (7), 658–664.

18. Mauvais-Jarvis, F. (2018). Gender differences in glucose homeostasis and diabetes. Physiology & Behavior, 187, 20–23. doi: http://doi.org/10.1016/j.physbeh.2017.08.016

19. Zand, A., Ibrahim, K., Patham, B. (2018). Prediabetes: Why Should We Care? Methodist DeBakey Cardiovascular Journal, 14 (4), 289–297. doi: http://doi.org/10.14797/mdcj-14-4-289

20. Sakoda, H., Ogihara, T., Anai, M., Funaki, M., Inukai, K., Katagiri, H. et. al. (2000). Dexamethasone-induced insulin resistance in 3T3-L1 adipocytes is due to inhibition of glucose transport rather than insulin signal transduction. Diabetes, 49 (10), 1700–1708. doi: http://doi.org/10.2337/diabetes.49.10.1700

21. Bardy, G., Virsolvy, A., Quignard, J. F., Ravier, M. A., Bertrand, G., Dalle, S. et. al. (2013). Quercetin induces insulin secretion by direct activation of L-type calcium channels in pancreatic beta cells. British Journal of Pharmacology, 169 (5), 1102–1113. doi: http://doi.org/10.1111/bph.12194

22. Eitah, H. E., Maklad, Y. A., Abdelkader, N. F., Gamal el Din, A. A., Badawi, M. A., Kenawy, S. A. (2019). Modulating impacts of quercetin/sitagliptin combination on streptozotocin-induced diabetes mellitus in rats. Toxicology and Applied Pharmacology, 365, 30–40. doi: http://doi.org/10.1016/j.taap.2018.12.011

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