RESEARCH ARTICLE

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

CORRECTION OF MORPHOFUNCTIONAL DISORDERS IN EXPERIMENTAL PREECLAMPSY BY COMBINED USE OF TRIMETAZIDINE AND PURIFIED MICRONIZED FLAVONOID FRACTION AS WELL AS THEIR COMBINATIONS WITH METHYLAMPSY

O.E. Antsiferova[1], M.P. Teleshchenko[1], Yu.M. Tsuverkalova[1], M.V. Pokrovsky[1], V.V. Gureev[1], M.A. Zatolokina[2], A.V. Gureeva[2]

[1] Belgorod State National Research University
85, Pobeda St., Belgorod, Russia, 308015
[2] Kursk State Medical University
3, Karl Marx St., Kursk, Russia, 305041

E-mail: Gureev@bsu.edu.ru

Received 08 Oct 2020 Accepted 30 Oct 2020

The aim of the experiment was to determine the effectiveness of the combined use of trimetazidine and a purified micronized flavonoid fraction, as well as their combinations with methyldopa, in comparison with monotherapy with the same drugs in the correction of morphofunctional disorders arising in the conditions of experimental preeclampsia.

An integrated/multimethodology approach is the most effective way of treatment for preeclampsia. Therefore, an urgent task of modern pharmacology is to study the effectiveness of new drugs when used in combinations, as well as the drugs included in the standards for treatment.

Materials and methods. The study was carried out at the Research Institute of Pharmacology of Living Systems of Belgorod State National Research University. The experiment was performed on 200 female Wistar rats, weighing 250–300 g, in which an ADMA-like model of preeclampsia had been reproduced. To assess the degree of correction of emerging morphological and functional disorders, the following parameters were involved: blood pressure, a coefficient of endothelial dysfunction, microcirculation in the placenta, proteinuria, fluid contents in the greater omentum, morphometric indicators of placental tissues and fetal height and weight parameters.

Results. The combined use of trimetazidine (Preductal® MB) 6 mg/kg and a purified micronized flavonoid fraction (Detralex®) 260 mg/kg, as well as their combination with methyldopa (Dopegit®) 86 mg/kg, leads to a more pronounced decrease in the blood pressure, compared with a decrease in the coefficient of endothelial dysfunction by 2.22, 2.19 and 1.94 times, respectively, in relation to “untreated” animals. There was an increase in microcirculation indices in the placenta by 2.35, 2.21 and 2.03 times, respectively. In addition, there was an improvement in morphological parameters in the placenta and fetuses.

Conclusion. The results of the study showed a greater effectiveness of the combined use of the studied drugs in experimental preeclampsia compared to their monotherapy. This indicates the prospects for the use of trimetazidine and purified micronized flavonoid fraction in the complex therapy for preeclampsia and the need for further research in this direction.

Keywords: trimetazidine; purified micronized flavonoid fraction; preeclampsia; endothelial dysfunction; rats

Abbreviations: L-NAME – L-Nitro-Arginine Methyl Ester; VEGF – vascular endothelial growth factor; CED – coefficient of endothelial dysfunction; SBP – systolic blood pressure; DBP – diastolic blood pressure.

For citation: O.E. Antsiferova, M.P. Teleshchenko, Yu.M. Tsuverkalova, M.V. Pokrovsky, V.V. Gureev, M.A. Zatolokina, A.V. Gureeva. Correction of morphofunctional disorders in experimental preeclampsy by combined use of trimetazidine and purified micronized flavonoid fraction as well as their combinations with methylampsy. *Pharmacy & Pharmacology.* 2020;8(5):304-315. **DOI:** 10.19163/2307-9266-2020-8-5-304-315

Для цитирования: О.Е. Анциферова, М.П. Телещенко, Ю.М. Цуверкалова, М.В. Покровский, В.В. Гуреев, М.А. Затолокина, А.В. Гуреева. Коррекция морфофункциональных нарушений при экспериментальной преэклампсии сочетанным применением триметазидина и очищенной микронизированной флавоноидной фракцией, а также их комбинаций с метилдопой. *Фармация и фармакология.* 2020;8(5):304-315. **DOI:** 10.19163/2307-9266-2020-8-5-304-315

Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ

ОРИГИНАЛЬНАЯ СТАТЬЯ

DOI: 10.19163/2307-9266-2020-8-5-304-315

КОРРЕКЦИЯ МОРФОФУНКЦИОНАЛЬНЫХ НАРУШЕНИЙ ПРИ ЭКСПЕРИМЕНТАЛЬНОЙ ПРЕЭКЛАМПСИИ СОЧЕТАННЫМ ПРИМЕНЕНИЕМ ТРИМЕТАЗИДИНА И ОЧИЩЕННОЙ МИКРОНИЗИРОВАННОЙ ФЛАВОНОИДНОЙ ФРАКЦИЕЙ, А ТАКЖЕ ИХ КОМБИНАЦИЙ С МЕТИЛДОПОЙ

О.Е. Анциферова[1], М.П. Телещенко[1], Ю.М. Цуверкалова[1], М.В. Покровский[1], В.В. Гуреев[1], М.А. Затолокина[2], А.В. Гуреева[2]

[1] Федеральное государственное автономное учреждение высшего профессионального образования «Белгородский государственный национальный исследовательский университет»
308015, Россия, г. Белгород, ул. Победы, 85
[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Курский государственный университет»
305041, Россия, г. Курск, ул. Карла Маркса, 3

E-mail: Gureev@bsu.edu.ru

Получено 08.10.2020 Принята к печати 30.10.2020

Цель. Провести исследование эффективности сочетанного применения триметазидина и очищенной микронизированной флавоноидной фракцией, а также их комбинаций с метилдопой в сравнении с монотерапией этими же препаратами при коррекции морфофункциональных нарушений, возникающих в условии экспериментальной преэклампсии.

Комплексный подход является наиболее эффективным способом терапии преэклампсии. Поэтому актуальной задачей современной фармакологии остается исследование эффективности новых лекарственных препаратов при комбинированном использовании, в том числе, и с препаратами, входящими в стандарты лечения.

Материалы и методы. Исследование проводилось в НИИ фармакологии живых систем ФГАОУ ВО НИУ БелГУ. Эксперимент проводили на 200 самках крыс линии Wistar, массой 250–300 г, у которых воспроизводили ADMA-подобную модель преэклампсии. Для оценки степени коррекции возникающих морфофункциональных нарушений использовали следующие параметры: артериальное давление, коэффициент эндотелиальной дисфункции, микроциркуляцию в плаценте, протеинурию, содержание жидкости в большом сальнике, морфометрические показатели плацентарных тканей и ростовесовых показателей плодов.

Результаты. Комбинированное применение триметазидина (Предуктал® МВ) 6 мг/кг и очищенной микронизированной флавоноидной фракции (Детралекс®) 260 мг/кг, а также их сочетаное применение с метилдопой (Допегит®) 86 мг/кг, приводит к более выраженному снижению артериального давления, по сравнению со снижением коэффициента эндотелиальной дисфункции в 2,22, 2,19 и 1,94 раза соответственно по отношению к «нелеченным» животным. Происходило повышение показателей микроциркуляции в плаценте в 2,35, 2,21 и 2,03 раза соответственно. Кроме этого, наблюдалось улучшение морфологических показателей в плаценте и плодов.

Заключение. Результаты проведенного исследования показали большую эффективность комплексного применения исследуемых препаратов при экспериментальной преэклампсии по сравнению с их монотерапией. Это свидетельствует о перспективности применения триметазидина и очищенной микронизированной флавоноидной фракциии в комплексной терапии преэклампсии и необходимости проведения дальнейших исследований в этом направлении.

Ключевые слова: триметазидин; очищенная микронизированная флавоноидная фракция; преэклампсия; дисфункция эндотелия; крысы

Список сокращений: L-NAME – N-нитро-L-аргинин-метиловый эфир; ФРСЭ – фактор роста сосудистого эндотелия; КЭД – коэфициент эндотелиальной дисфункции; САД – систолическое артериальное давление; ДАД – диастолическое артериальное давление.

INTRODUCTION

For many decades, preeclampsia has remained an important medical and social problem in the countries all over the world. It occupies a leading place among the causes for maternal morbidity rate and mortality and, according to various authors, is from 9% to 25% [1, 2]. In Russia, this pathology stably occupies the 3–4th places [3]. The incidence ranges from 2% to 10% of all pregnancies and has no tendency to decrease [1, 4, 5]. In addition, preeclampsia leads to the development of pathological conditions not only in women, but also in the fetus, contributing to the disability of mothers and children [4, 6].

The problem of preventing and treating preeclampsia, as well as assessing the severity of its course and perinatal risks, is to a great extent due to the lack of con-

sensus among the medical community about its etiology and pathogenesis, although an extraordinary number of studies around the world are devoted to the investigation of this pregnancy complication [7, 8]. Herewith, preeclampsia is increasingly considered from the point of view of endothelial dysfunction [9–11], and "an oxidative stress" as a result of depletion of the antioxidant system under the conditions of placental ischemia, is one of its development mechanisms [12, 13]. The endothelial dysfunction developing against this background, leads to impaired microcirculation and tissue hypoxia and, as a result, to the development of multisystemic lesions that constitute the clinical manifestations of preeclampsia [14–16]. Therefore, the search for new drugs for the prevention and treatment of preeclampsia, is an urgent task of modern pharmacology.

In experimental studies on the model of L-NAME-induced preeclampsia in rats, the protective properties of resveratrol [17, 18], recombinant erythropoietin [19], and tadalafil [20, 21], which have endothelioprotective properties, have been demonstrated. Another promising area of prevention and correction of morphofunctional disorders that occur in preeclampsia, is the use of drugs with anti-ischemic and antioxidant properties. As a result of the previous studies, pronounced protective effects of trimetazidine and a purified micronized flavonoid fraction in the correction of morphofunctional disorders in experimental preeclampsia have been revealed, however, it should be notified that the target level has not been achieved [22–24].

Preeclampsia is a multifactorial disease. It is obvious that the increase in the effectiveness of therapy can be achieved by the complex use of drugs. Therefore, the urgent task of modern pharmacology is not only the search for new drugs for the treatment and prevention of preeclampsia, but also the study of their effectiveness in combined uses, as well as the drugs included in the standards for treatment.

THE AIM of the experiment was to determine the effectiveness of the combined use of trimetazidine and a purified micronized flavonoid fraction, as well as their combinations with methyldopa, in comparison with monotherapy with the same drugs in the correction of morphofunctional disorders arising under the conditions of experimental preeclampsia.

MATERIALS AND METHODS

Compliance with ethical principles

The study has been carried out at the Center for Preclinical and Clinical Research of the Belgorod State National Research University. The experiment was accomplished in accordance with legislative acts and guidelines regulating the conduct of experimental research in the Russian Federation: Order of the Ministry of Health of Russia dated 01.04.2016 No.199n "On the approval of the Rules of good laboratory practice" and "Guidelines for conducting preclinical studies of new drugs" ed. by A.N. Mironov. The ethical principles of handling laboratory animals were in accordance with Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. The study was approved of at the meeting of the Bioethical Commission of the Research Institute of Pharmacology of Living Systems of the Belgorod State National Research University, Protocol No.D2019/13. Keeping the animals was regulated by the norms of the Decree of the Chief State Sanitary Doctor of the Russian Federation dated 08.29.2014 No.51, GOST 33044-2014. The animals were kept in plastic cages, equipped with steel lattice lids, with a feeding recess, with a free access to food and water, on a balanced diet appropriate for the animal species. The ambient temperature was maintained at the level of 20–25°C with a relative humidity of 60–65%. The wood sawdust that had undergone preliminary UV sterilization, was used as a litter.

Modeling ADMA-like preeclampsia

The experiment was carried out on 200 white Wistar female rats weighing 250–300 g. An ADMA-like agent, a non-selective NO synthase blocker N-nitro-L-arginine methyl ether (L-NAME), was injected intraperitoneally at the dose of 25 mg/kg/per day for seven days (from the 14^{th} to the 20^{th} days of pregnancy) [25, 26]. To assess the effectiveness of the studied drug combinations, the animals had been divided into several groups (n=10).

1. Intact (Int.) (animals with oral administration of NaCl in equivalent doses from the 14^{th} to the 20^{th} days of pregnancy).
2. Modeling of ADMA-like preeclampsia (L-NAME) (N-nitro-L-arginine-methyl ester, Sigma-Aldrich), 25 mg/kg/per day.
3. L-NAME + methyldopa (Dopegit®, ZAO "Pharmaceutical Plant EGIS", Hungary), 86 (2×43) mg/kg/per day.
4. L-NAME + trimetazidine (Preductal® MB, ZAO "Servier", Russia), 6 mg/kg/per day.
5. L-NAME + purified micronized flavonoid fraction (Detralex®, ZAO "Servier", Russia), 260 mg/kg/per day.
6. L-NAME + trimetazidine 6 mg/kg/per day + purified micronized flavonoid fraction 260 mg/kg/per day.
7. L-NAME + trimetazidine 6 mg / kg + methyldopa 86 (2x43) mg/kg.
8. L-NAME + purified micronized flavonoid fraction 260 mg/kg/per day + methyldopa 86 (2×43) mg/kg/per day.

Assessment of the degree of endothelial dysfunction development in pathology modeling

The development of endothelial dysfunction in experimental animals, as well as the degree of its correction by the studied drugs and their combinations, were assessed by the calculated coefficient of endothelial dysfunction (CED) [27, 28].

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2020-8-5-304-315

$$CED = \frac{S_{NP}}{S_{ACH}}$$

The endothelial dysfunction coefficient is the ratio of the triangle area above the blood pressure recovery curve in response to 30 μg/kg nitroprusside (S_{NP}) to the triangle area above the blood pressure recovery curve in response to 40 μg/kg acetylcholine (S_{ACH}). The legs in the both triangles were indicators of the blood pressure recovery time (reaction duration) and the changes in the blood pressure in response to the intravenous administration of acetylcholine and nitroprusside, respectively.

Placental microcirculation assessment

To obtain the data on the state of microcirculation in the placenta, the equipment manufactured by Biopacsystems was used: polygraph MP100 with an LDF100C Laser Doppler Flowmetry (LDF) module and an invasive TSD144 needle probe. On the 21st day of pregnancy, under anesthesia, the level of microcirculation was measured in the projection of the placental disc at a distance of 1 mm at 4 points. The registration and processing of LDF results were carried out using the AcqKnowledge version 3.8.1. The microcirculation values were stated in perfusion units (PU) [29].

Proteinuria research

Urine collection was carried out for 12 hours using special metabolic cells. The determination of the protein amount in daily urine, was carried out by the pyrogall method. It is based on the determination of the optical density of a solution of a colored complex, formed by the interaction of protein molecules with the molecules of the complex of the pyrogallol red dye and sodium molybdate. The color intensity of the solution is proportional to the protein content. The measurements were carried out using a PE-5400 V spectrophotometer at the wavelength of 600 nm [30].

Study of the greater omentum сальник edema

On the 21st day of pregnancy, the greater omentum was removed under anesthesia, and weighed. Within 24 hours it was dried at 37°C, then weighed again. From the difference in the mass of the greater omentum before and after drying, the amount of the evaporated water was obtained in each specific piece. The water content was stated in %, relative to the total weight of the gland while the first weighing [31].

Morphological methods for assessing changes in placenta when modeling experimental gestosis

A histological study of the placenta was carried out in all the series of the experiment for a morphological confirmation of the development of modeled pathological processes and giving a comprehensive assessment of the drugs' effectiveness. The material was fixed in 10% formalin with subsequent embedding in paraffin. Histological sections of the placenta were made in a strictly vertical direction through the middle of the placental disc with the capture of all layers of the placenta and the wall of the uterine horn. The study of microslides, photorecording and morphometry, were carried out on a Leica DM4000B microscope with a video recording and an image processing system. All morphological studies were stained with hematoxylin and eosin [25].

Fetus study

The fetuses were removed from the uterine cavity, weighed, and the fetus size (craniocaudal size) was measured, followed by the calculation of the statural-weight coefficient [32].

Statistical processing of research results

Descriptive statistics was applied to all the data: the data were checked for a normal distribution. The distribution type was determined by the Shapiro-Wilk test. In case of a normal distribution, the mean (M) and a standard error of the mean (m) were calculated. The intergroup differences were analyzed by parametric (Student's *t*-test) or nonparametric (Mann-Whitney *U*-test) methods, depending on the type of the distribution. The calculations were performed using statistical programs Microsoft Excel 7.0. The groups were compared in pairs.

RESULTS

Effect of the combined trimetazidine and detralex use, as well as their combined use with methyldopa, for the correction of morphofunctional disorders in ADMA-like preeclampsia

The combined use of preductal and detralex, as well as their combined use with dopegit for the correction of morphofunctional disorders in ADMA-like preeclampsia, led to a more pronounced decrease in blood pressure. Thus, when the combined administration of preductal and detralex took place, the systolic and diastolic kinds of blood pressure decreased to 145.7±3.93 mm Hg and 100.1±3.59 mm Hg, respectively. When detralex was used individually, it decreased to 169.3±5.40 mm Hg and 125.7±4.91 mm Hg. When preductal was used individually, it decreased to and 152.5±1.99 mm Hg and 112.3±3.90 mm Hg. Herewith, the decrease of diastolic pressure was statistically significant in comparison with the reference groups (Table 1). The combined use of preductal and dopegit led to a statistically significant decrease in systolic blood pressure compared with monotherapy, and when detralex and dopegit were combined, both systolic and diastolic kinds of blood pressure decreased statistically significantly ($p<0.05$) compared with monotherapy (Table 1).

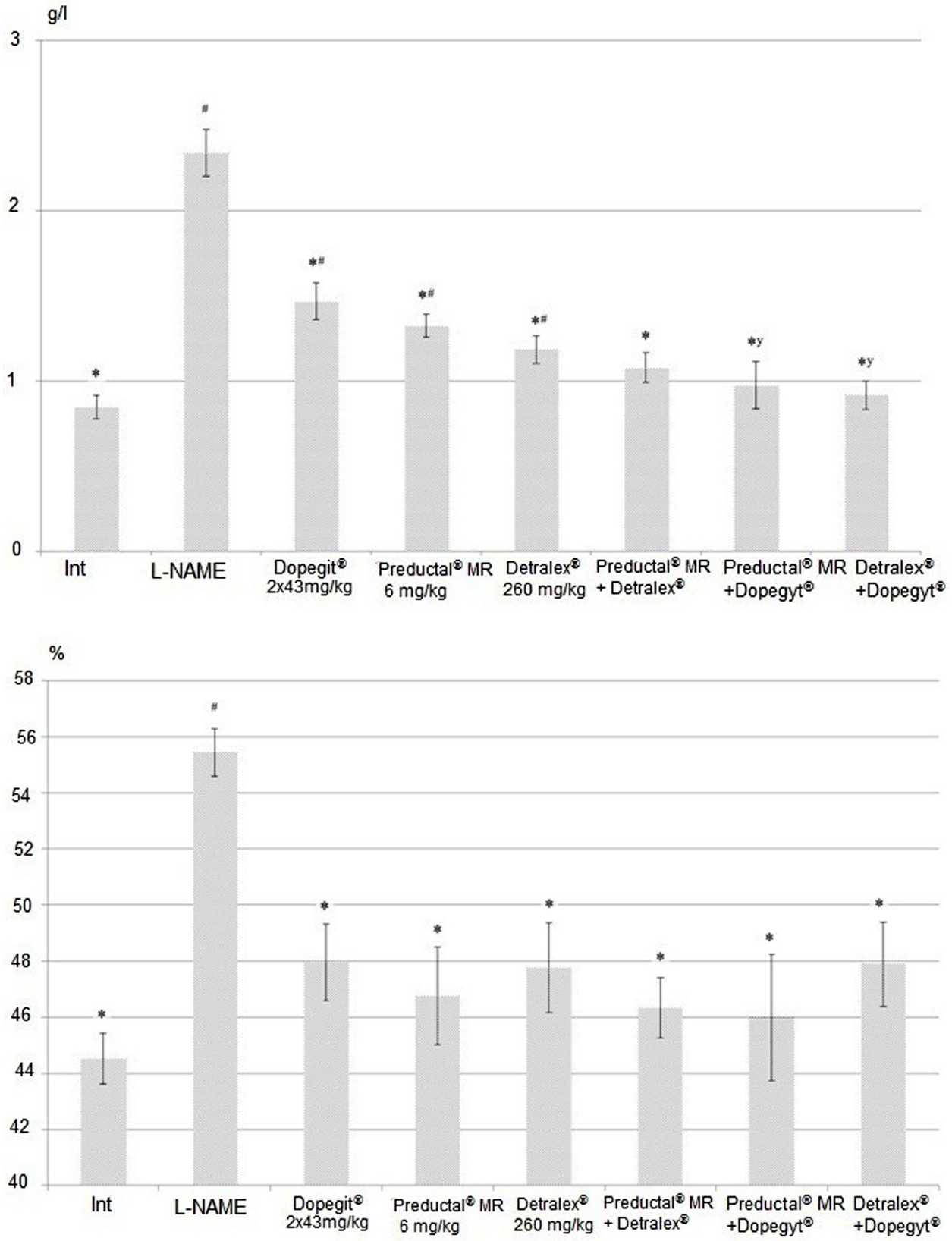

Figure 1 – The effect of the Preductal® MB and Detralex® combination, as well as their combination with Dopegit®, on proteinuria and fluid content in the tissue of the greater omentum in ADMA-like preeclampsia

Note: # – at p <0.05 in comparison with intact pregnant rats; * – at p <0.05 in comparison with the group of pregnant animals treated with L-NAME; y – at p <0.05 in comparison with both monotherapy options.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2020-8-5-304-315

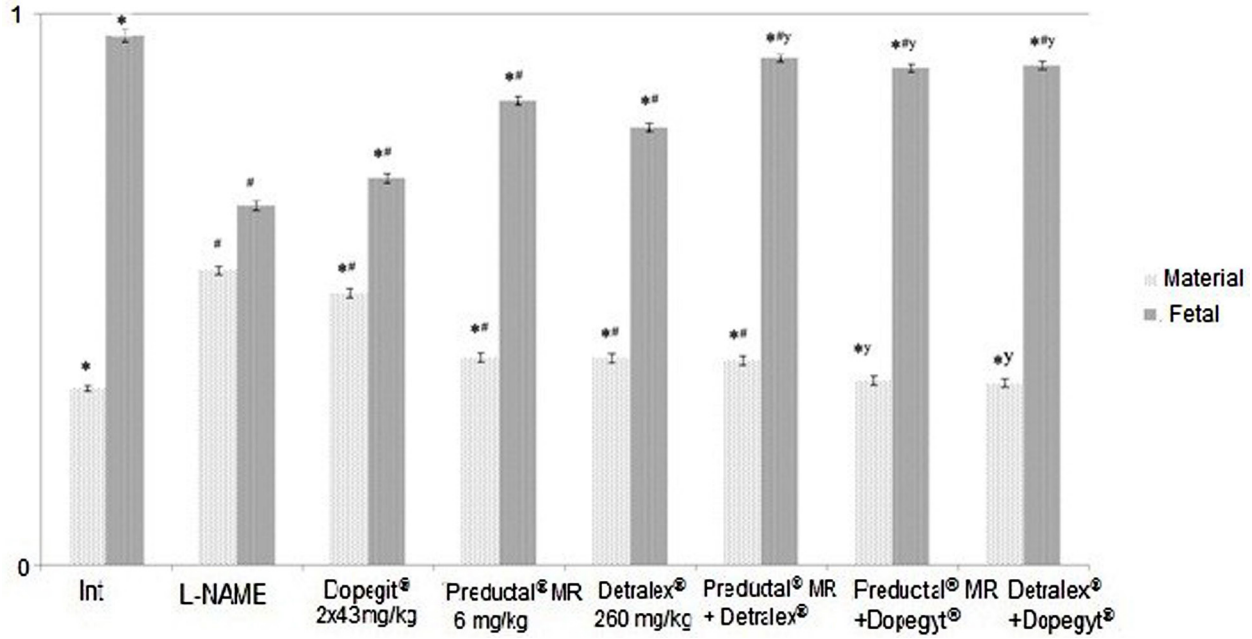

Figure 2 – The effect of the Preductal® MB and Detralex® combination, as well as their combination with Dopegit®, on the fetal and maternal size parts of the placenta, in ADMA-like preeclampsia

Note: # – at p <0.05 in comparison with intact pregnant rats; * – at p <0.05 in comparison with the group of pregnant animals treated with L-NAME; y – at p <0.05 in comparison with both monotherapy options

Table 1 – The effect of the Preductal® MB and Detralx® combination, as well as their combination with Dopegit®, on the functional parameters of the cardiovascular system in ADMA-like preeclampsia.

Indicator/Index / Group	SBP, mm Hg	DBP, mm Hg	CED, relative units.	Microcirculation, PU
Int	123.4±3.54*	83.8±5.47y*	1.21±0.13*	472.6±22.44*
L-NAME	193.6±6.28#	150.8±4.80#	2.89±0.25#	215.6±9.29#
L-NAME+ Dopegyt® 86 mg/kg	155.5±3.14*#	114.4±7.13*#	2.49±0.28#	297.8±13.41*#
L-NAME+ Preductal® MR 6 mg/kg	152.5±1.99*#	112.3±3.90*#	1.57±0.15*	402.3±15.81*#
L-NAME+Detralex® 260 mg/kg	169.3±5.4*#	125.7±4.91*#	1.79±0.11*#	394.0 ±9.87*#
L-NAME+ Preductal® MR + Detralex®	145.7±3.93*#	100.1±3.6*# y	1.30±0.05*	505.9±17.83*y
L-NAME+ Preductal® MR + Dopegyt®	138.6±3.16*#y	97.6±5.84*	1.32±0.08*	477.4±27.61*y
L-NAME+ Detralex®+ Dopegyt®	145.5±2.75*#y	97.8±2.2*#y	1.49±0.05*y	437.0±19.87*

Note: # – at p <0.05 in comparison with intact pregnant rats; * – at p <0.05 in comparison with the group of pregnant animals treated with L-NAME; y – at p <0.05 in comparison with both monotherapy options

Table 2 – The effect of the combined use of Preductal® MB and Detralex®, as well as their combined use with Dopegit®, on the density of the cell pool in the fetal and maternal parts of the placenta; the diameter of the chorionic villi and the growth-weight index of the fetuses in the correction of ADMA-like preeclampsia (M±m)

Indicator/Index / Group	Density of decidual cells, 0,008 mm²	Cell density in fetal part of placenta, 0,008 mm²	Diameter of villi, x10⁻³mkm	Growth-weight index, mm/g
Int.	118.3±2.14*	235.8±2.75*	32.40±0.41*	14.78±0.22*
L-NAME	23.1±0.33#	80.7±2.57#	17.19±0.26#	15.79±0.23#
L-NAME+ Dopegyt® 86 mg/kg	55.6±0.45*#	98.9±1.73*#	18.78±0.17*#	15.62±0.15#
L-NAME+ Preductal® MR 6 mg/kg	102.7±0.77*#	150.5±1.71*#	29.93±0.17*#	15.36±0.22*#
L-NAME+Detralex® 260 mg/kg	104.8±0.87*#	151.3±1.69*#	29.90±0.16*#	15.31±0.58
L-NAME+ Preductal® MR + Detralex®	132.7±1.92*#y	179.3±1.60*#y	34.89±0.16*#y	14.42±0.63*
L-NAME+ Preductal® MR + Dopegyt®	141.3±2.21*#y	177.6±1.59*#y	31.79±0.14*y	14.86±0.30*
L-NAME+ Detralex®+ Dopegyt®	138.8±2.29*#y	181.0±1.69*#y	26.85±0.15*#y	14.53±0.69*

Note: # – p <0.05 in comparison with the group of intact animals; * – p <0.05 in comparison with the L-NAME group; y – p <0.05 in comparison with the groups in monotherapy.

When the combinations of preductal + detralex, preductal + dopegit and detralex + dopegit were used, the coefficient of endothelial dysfunction (CED) decreased to 1.30±0.05, 1.32±0.08 and 1.49±0.05, respectively, and the microcirculation improvement was up to 505,9±17.83 PU, 477.4±27.61 PU and 437.0±19.87 PU, respectively. It should be notified that CED reached a statistically indistinguishable value from the group of intact animals when the combinations of preductal + detralex and preductal + dopegit were used. Herewith, when the combination of detralex + dopegit was used, microcirculation improved to the level of intact animals.

In the described groups, a decrease in proteinuria resulted in 1.08±0.09 g/L, 0.92±0.09 g/L, and 0.92±0.09 g/L, respectively (Fig. 1A), and the fluid content in the greater omentum decreased to 46.33±1.08%, 45.98±2.26% and 47.89±1.50%, respectively (Fig. 1B). It should be notified that in comparison with the group with monotherapy, a statistically significant ($p < 0.05$) decrease in proteinuria, was observed when using preductal + dopegit. The fluid content in the greater omentum in all the groups with a combined use of drugs, was at the level of intact animals.

A histological examination of the placenta revealed the following: a combined administration of the studied drugs to the animals with experimental preeclampsia, led to a pronounced positive dynamics of the morphological picture, which was approximate to the group of intact animals. There was a statistically significant ($p < 0.05$) increase in the density of the cellular component of the placental tissues of the maternal and fetal parts of the placenta, and the diameter of the chorionic villi, in comparison with the groups of the animals in which the studied drugs had been used in the monotherapy mode (Table 2). Only the diameter of the villi reached the level of the intact animals when the combination of Preductal® MB + Dopegit® had been used. In addition, there was a statistically significant ($p < 0.05$) increase in the fetal part of the placenta and a decrease in the maternal part of the placenta (Fig. 2). The exception was the group using Preductal® MB + Detralex®, in which there was no statistically significant change in the maternal part of the placenta compared to the groups with monotherapy with the same drugs. It should be notified that the level of the intact animals had not been reached.

The study of the height-weight ratio in fetuses in the groups with the combined administration of the investigated drugs, showed an improvement in this indicator up to the level of the intact animals (Table 2).

Thus, the combined use of Preductal® MB and Detralex®, as well as their combined use with Dopegit®, led to a significantly positive effect in the correction of ADMA-like preeclampsia compared with the use of the same drugs in monotherapy. This was reflected in a more pronounced decrease in blood pressure. The microcirculation level reached the target values. There was a pronounced positive effect on the size of the fetal and maternal parts of the placenta, the concentration of the cell pool in the maternal and fetal parts of the placenta increased, the diameter of the chorionic villi was restored. There was also a significant improvement in the morphometric parameters of the fetus.

DISCUSSION

The most pronounced positive effects in the correction of morphofunctional disorders arising under the conditions of experimental preeclampsia when using combinations of the studied drugs in comparison with the use of the same drugs in monotherapy, can be explained by the possibility of influencing various points of pathogenesis. This is ensured by the fact that each drug has its own, different from the others, mechanism for the implementation of effects.

The positive effects of trimetazidine, are explained by its capacity to improve the energy metabolism of tissues under ischemic conditions. During the oxygen starvation, under the influence of trimetazidine, the cells activate the oxidation of pyruvate for the synthesis of ATP. This leads to a decrease in oxygen deficiency by 10-12% compared to the oxidation of fatty acids, which makes it possible for the cells to use oxygen more efficiently under the conditions of the oxygen deficiency [33, 34].

In addition, trimetazidine prevents the accumulation of insufficiently oxidized fatty acid products in the mitochondria of cells, and increases the stability of cell membranes due to the inclusion of fatty acids in phospholipids [35, 36]. This leads to a decrease in the severity of the oxidative stress and, as a result of a decrease in the synthesis of reactive oxygen species by mitochondria, its negative effect [37, 38]. In addition, the endothelioprotective properties of trimetazidine due to an increase in the amount of eNOS and the synthesis of nitric oxide as one of the most important factors of vasorelaxation, also explain the effectiveness of its use [39, 40]. The capacity of trimetazidine to reduce the formation of pro-inflammatory cytokines [41, 42], can promote both a decrease in the systemic content of markers of the oxidative stress, and a decrease in the eNOS activity. In addition, the endothelioprotective properties of trimetazidine may lie in its capacity to protect the endothelium from the direct damaging action of free radicals [43] and to reduce the inactivation of nitric oxide by inactivating lipid peroxidation processes [44, 45]. The result of the realization of direct and indirect effects of trimetazidine on the endothelium, is an improvement in endothelium-dependent vascular relaxation not only in this experiment, but also in patients with chronic heart failure (CHF) [46, 47].

The effective use of Detralex is explained by the presence of its several protective properties. One of them is a pronounced anti-inflammatory and antioxidant effect [48- 51]. The anti-inflammatory effect is associated with the capacity of diosmin to reduce the production of pro-inflammatory cytokines: IL-6, IL-1β, TNF-α, etc. [52–54]. In addition, diosmin is can reduce the induced

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2020-8-5-304-315

production of NO by inhibiting eNOS [48, 53]. The antioxidant activity includes the capacity of the studied drug to increase the activity of glutathione peroxidase, superoxide dismutase, catalase [53, 55, 56], and to prevent lipid peroxidation with an increase in the activity of the antioxidant system [56, 57]. A decrease in the formation of proinflammatory cytokines and markers of the oxidative stress, leads not only to a decrease in the injury of the placental tissues, but also to the improvement in the endothelial function.

This can be confirmed by the results of the studies by other authors. Endothelioprotective effects are manifested both in the treatment for varicose veins [58, 59] and in the correction of arterial pathology [60–62]. Special attention should be paid to the data on the protective effects of diosmin in ischemia-reperfusion injuries, since this is comparable with the pathogenetic features of preeclampsia [63, 64], especially at the capillary level [65]. The molecular mechanisms by which endothelioprotective effects are realized, include: suppression of the synthesis of proinflammatory humoral factors, a decrease in the production of cell adhesion molecules, a modulating effect on the permeability of the vascular wall, a favorable effect on the ratio of prooxidant and antioxidant factors [66].

In the protective effects of flavonoids, an important role is played by their capacity to improve the drainage function of tissues [60, 67–69]. Since edema increases in ischemia or inflammatory phenomena, this disrupts tissue trophism, and an improvement in the drainage function causes the opposite effect.

Methyldopa is a prodrug by its nature, and belongs to the group of centrally acting antihypertensive drugs. Passing through the blood-brain barrier (BBB), methyldopa turns into alpha-methylnorepinephrine, which depletes the resources of norepinephrine, displacing it from the granules (which brings this drug closer to sympatholytics), excites the central α2-adrenergic receptors of the vasomotor center, causes a decrease in its rhenium, and inhibits the formation of angiotensin [70]. A decreased peripheral vascular tone is an important addition to the mechanisms of the studied drugs' action. In addition, there is evidence of the endothelioprotective properties of this drug. In an *in vitro* study, it was established that the incubation of endothelial cell culture with methyldopa, promoted the leveling of the inhibitory TNF-α effect on the endothelial NO-synthase, and also led to an increase in the content of the vascular growth factor VEGF [71]. Herewith, in the absence of TNF-α, this drug had no effect on the eNOS expression [72].

CONCLUSION

The combined use of drugs in the treatment of a lot of diseases, is the most urgent direction. The results of this study witness the fact that the use of trimetazidine and a purified micronized flavonoid fraction in the complex therapy of preeclampsia, is a promising direction necessary to continue the research in.

FUNDING

This study did not receive any financial support from outside organizations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

O.E. Antsiferova – administration of drugs to the animals, modeling of ADMA-like preeclampsia, functional tests and other studies;
M.P. Teleschenko – administration of drugs to the animals, modeling of ADMA-like preeclampsia, functional tests and other studies;
Yu.M. Tsuverkalova – administration of drugs to the animals, modeling of ADMA-like preeclampsia, carrying out functional tests and other studies;
M.V. Pokrovsky – idea, research planning, consultations on the implementation of individual stages of the experimental work;
V.V. Gureev – article writing, development of the research design;
M.A. Zatolokina – preparing samples for histological examination, morphological description of placenta sections;
A.V. Gureeva – article writing, preparing samples for histological examination, formalization of the bibliography, working with graphic materials.

REFERENCES

1. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol. 2011;25(4):391–403. DOI: 10.1016/j.bpobgyn.2011.01.006.
2. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, Gülmezoglu AM, Temmerman M, Alkema L. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323-33. DOI: 10.1016/S2214–109X(14)70227-X.
3. [Klinicheskie rekomendacii (protokol lecheniya). Gipertenzivnye rasstrojstva vo vremya beremennosti, v rodah i poslerodovom periode. Preeklampsiya. Eklampsiya]. Moskva, 2016:72. Russian
4. Ghulmiyyah L, Sibai B. Maternal mortality from pre-

eclampsia/eclampsia. Semin Perinatol. 2012;36(1):56–9. DOI: 10.1053/j.semperi.2011.09.011.
5. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010;376(9741):631–44. DOI: 10.1016/S0140-6736(10)60279-6.
6. Young B, Hacker MR, Rana S. Physicians' knowledge of future vascular disease in women with preeclampsia. Hypertens Pregnancy. 2012;31(1):50–8. DOI: 10.3109/10641955.2010.544955.
7. Medved', V.I., Duda E.M. Preeklampsiya v klinike ekstragenital'noj patologii. Pochki. 2013; 3(5):36–38. Russian.
8. Brewster JA, Orsi NM, Gopichandran N, Ekbote UV, Cadogan E, Walker JJ. Host inflammatory response profiling in preeclampsia using an in vitro whole blood stimulation model. Hypertens Pregnancy. 2008;27(1):1–16. DOI: 10.1080/10641950701826067.
9. Ray A, Ray S. Epidural therapy for the treatment of severe pre-eclampsia in non labouring women. Cochrane Database Syst Rev. 2017 Nov 28;11(11):CD009540. DOI: 10.1002/14651858.CD009540.pub2.
10. Babic I, Ferraro ZM, Garbedian K, Oulette A, Ball CG, Moretti F, Gruslin A. Intraplacental villous artery resistance indices and identification of placenta-mediated diseases. J Perinatol. 2015;35(10):793–8. DOI: 10.1038/jp.2015.85.
11. Vayssière C, Sentilhes L, Ego A, Bernard C, Cambourieu D, Flamant C, Gascoin G, Gaudineau A, Grangé G, Houfflin-Debarge V, Langer B, Malan V, Marcorelles P, Nizard J, Perrotin F, Salomon L, Senat MV, Serry A, Tessier V, Truffert P, Tsatsaris V, Arnaud C, Carbonne B. Fetal growth restriction and intra-uterine growth restriction: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians. Eur J Obstet Gynecol Reprod Biol. 2015;193:10–8. DOI: 10.1016/j.ejogrb.2015.06.021.
12. Hovhaeva PA, Tyutyunnik NV, Krasnyj A.M, Sergunina OA, Timofeeva LA, Kan NE, Tyutyunnik VL. [Oksidativnyj stress i ekspressiya genov fermentov antioksidantnoj zashchity v placente pri preeklampsii]. Farmateka. 2016; 3(316):74-76. Russian
13. Krasnyj AM, Kan NE, Tyutyunnik VL, Hovhaeva PA, Volgina NE, Sergunina OA, Tyutyunnik NV, Bednyagin LA. [Okislitel'nyj stress pri preeklampsii i pri normal'noj beremennosti]. Obstetrics and Gynecology. 2016; 5: 90-95. DOI:10.18565/aig.2016.5.90-94. Russian
14. Sidorova IS, Nikitina NA, Unanyan AL, Rzaeva AA, Kinyakin VV. [Patogeneticheskoe obosnovanie differencirovannogo podhoda k vedeniyu beremennyh s arterial'noj gipertenziej i preeklampsiej]. Obstetrics and Gynecology. 2013;2: 35-40. Russian
15. Sidorova I.S., Nikitina N.A., Unanian A.L., Rzaeva A.A., Kiniakin V.V. Evaluation of the efficiency of preeclampsia therapy in relation to the severity of gestational endothelial dysfunction. Rossijskij vestnik akushera-ginekologa. 2013; 13(3):4-8.
16. Shamshirsaz AA, Paidas M, Krikun G. Preeclampsia, hypoxia, thrombosis, and inflammation. J Pregnancy. 2012;2012:374047. DOI: 10.1155/2012/374047.
17. Zou Y, Zuo Q, Huang S, Yu X, Jiang Z, Zou S, Fan M, Sun L. Resveratrol inhibits trophoblast apoptosis through oxidative stress in preeclampsia-model rats. Molecules. 2014;19(12):20570–9. DOI: 10.3390/molecules191220570.
18. Stupakova EG, Lazareva GA, Gureev VV. Correction of morphofunctional disturbances arising when modelling Preeclampsia with resveratrol and nicorandil. Research Results in Pharmacology. 2018;4(1):59–71. doi:10.3897/rrpharmacology.4.25528
19. Gureev VV, Alekhin SA, Dolzhikov AA, Mostovoy AC. Correction of experimental adma-like pre-eclampsy. Kurskij nauchno-prakticheskij vestnik CHelovek i ego zdorov'e. 2012;1:14–19. Russian
20. Yoshikawa K, Umekawa T, Maki S, Kubo M, Nii M, Tanaka K, Tanaka H, Osato K, Kamimoto Y, Kondo E, Ikemura K, Okuda M, Katayama K, Miyoshi T, Hosoda H, Ma N, Yoshida T, Ikeda T. Tadalafil Improves L-NG-Nitroarginine Methyl Ester-Induced Preeclampsia With Fetal Growth Restriction-Like Symptoms in Pregnant Mice. Am J Hypertens. 2017;31(1):89–96. DOI: 10.1093/ajh/hpx130.
21. Pokrovskij MV, Gureev VV, Dolzhikov A, Polyanskaya OS, Mostovoj AS, Alekhin SA. Korrekciya eksperimental'nogo gestoza tadalafilom Nauchnye vedomosti Belgorodskogo gosudarstvennogo universiteta. Seriya: Medicina. Farmaciya. 2012;18(10-2 (129)):146–151. Russian
22. Antsiferova O.E., Yurakova A.V., Lokteva T.I., Severinova O.V., Gureev V.V Comprehensive assessment of the correction of morphofunctional disorders in adma preeclampsia by trimetazidine. VESTNIK OF Smolensk state medical academy. 2019;18(1). 103–108. Russian
23. Antsiferova OE, Gureev VV, Gureeva AV, et al. Comprehensive assessment of using micronised purified flavonoid fraction in the correction of disorders associated with ADMA-like preeclampsia in experiment. Research Results in Biomedicine. 2020;6(1):78–93. DOI: 10.18413/2658-6533-2020-6-1-0-7. Russian
24. Antsiferova OE, Yurakova AV, Lukyanova YS, Gureev VV, Korokin MV, Gureeva AV, Pokrovskaya TG, Gudyrev OS. Correction of asymmetric dimethylarginine-like pre-eclampsia in rats by micronized purified flavonoids fraction Drug Invention Today. 2019;12(11):2709–12.
25. Stupakova EG, Lazareva GA, Gureev VV, Dolzhikova IN, Zhilinkova LA, Gureeva AV L-NAME-induced Preeclampsia: correction of functional disorders of the hemostasis system with Resveratrol and Nicorandil. Research Results in Pharmacology. 2019;5(2):1–12. DOI:10.3897/rrpharmacology.5.35316
26. Korokin M, Gureev V, Gudyrev O, Golubev I, Korokina L, Peresypkina A, Pokrovskaia T, Lazareva G, Soldatov V, Zatolokina M, Pobeda A, Avdeeva E, Beskhmelnitsyna E, Denisyuk T, Avdeeva N, Bushueva O, Pokrovskii M. Erythropoietin Mimetic Peptide (pHBSP) Corrects Endothelial Dysfunction in a Rat Model of Preeclampsia. Int J Mol Sci. 2020 Sep 15;21(18):E6759. DOI: 10.3390/ijms21186759. PMID: 32942669.
27. Gureev VV, Pokrovskii MV, Korokin MV, Gudyrev OS, Philippova OV, Dolzhikov AA, Lazareva GA. Correction of ADMA-induced preeclampsia with use of tetrahydrobiopterin and selective inhibitor of arginase II ZB49-0010. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2015;6(5):1538–1541.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2020-8-5-304-315

28. Korokin M, Pokrovskiy M, Gudyrev O, Korokina L, Pokrovskaia T, Lazarev A, Philippenko N, Gureev V. Pharmacological correction of endothelial dysfunction in rats using e-NOS cofactors. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2015;6:1548–1552.
29. Lokteva TI, Rozhkov S, Gureev VV, Gureeva AV, Zatolokina MA, Avdeeva EV, Zhilinkova LA, Prohoda EE, Yarceva EO. Correction of morphofunctional disorders of the cardiovascular system with asialized erythropoietin and arginase II selective inhibitors KUD 974 and KUD 259 in experimental preeclampsia. Research Results in Pharmacology. 2020;6(1):29-40. DOI: 10.3897/rrpharmacology.6.50851
30. Yalamati P, Bhongir AV, Karra M, Beedu SR. Comparative Analysis of Urinary Total Proteins by Bicinchoninic Acid and Pyrogallol Red Molybdate Methods. J Clin Diagn Res. 2015;9(8):BC01–4. DOI: 10.7860/JCDR/2015/13543.6313.
31. Tyurenkov IN, Perfilova VN, Ivanova LB, Karamysheva VI. Vliyanie proizvodnyh GAMK na antitromboticheskuyu funkciyu endoteliya i sostoyanie mikrocirkulyacii u zhivotnyh s eksperimental'nym gestozom. Regionarnoe krovoobrashchenie i mikrocirkulyaciya. 2012;11(2):61–65. DOI: 10.24884/1682-6655-2012-11-2-61-65. Russian
32. Mironova AN et al. Rukovodstvo po provedeniyu doklinicheskih issledovanij lekarstvennyh sredstv. Part 1. Moscow: Grif i K; 2012. Russian.
33. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res. 2000;86(5):580–8. DOI: 10.1161/01.res.86.5.580. PMID: 10720420.
34. Dalal JJ, Mishra S. Modulation of myocardial energetics: An important category of agents in the multimodal treatment of coronary artery disease and heart failure. Indian Heart J. 2017;69(3):393–401. DOI: 10.1016/j.ihj.2017.04.001.
35. Belardinelli R, Solenghi M, Volpe L, Purcaro A. Trimetazidine improves endothelial dysfunction in chronic heart failure: an antioxidant effect. Eur Heart J. 2007;28(9):1102–8. DOI: 10.1093/eurheartj/ehm071.
36. Wei J, Xu H, Shi L, Tong J, Zhang J. Trimetazidine protects cardiomyocytes against hypoxia-induced injury through ameliorates calcium homeostasis. Chem Biol Interact. 2015;236:47–56. DOI: 10.1016/j.cbi.2015.04.022.
37. Steggall A, Mordi IR, Lang CC. Targeting Metabolic Modulation and Mitochondrial Dysfunction in the Treatment of Heart Failure. Diseases. 2017 May 10;5(2):14. DOI: 10.3390/diseases5020014.
38. Shi W, Shangguan W, Zhang Y, Li C, Li G. Effects of trimetazidine on mitochondrial respiratory function, biosynthesis, and fission/fusion in rats with acute myocardial ischemia. Anatol J Cardiol. 2017;18(3):175–181. DOI: 10.14744/AnatolJCardiol.2017.7771.
39. Mahfoudh-Boussaid A, Hadj Ayed Tka K, Zaouali MA, Roselló-Catafau J, Ben Abdennebi H. Effects of trimetazidine on the Akt/eNOS signaling pathway and oxidative stress in an in vivo rat model of renal ischemia-reperfusion. Ren Fail. 2014;36(9):1436–42. DOI: 10.3109/0886022X.2014.949765.
40. Wu Q, Qi B, Liu Y, Cheng B, Liu L, Li Y, Wang Q. Mechanisms underlying protective effects of trimetazidine on endothelial progenitor cells biological functions against H_2O_2-induced injury: involvement of antioxidation and Akt/eNOS signaling pathways. Eur J Pharmacol. 20135;707(1–3):87–94. DOI: 10.1016/j.ejphar.2013.03.027.
41. Danikiewicz A, Szkodziński J, Hudzik B, Korzonek-Szlacheta I, Gąsior M, Zubelewicz-Szkodzińska B. Effects of trimetazidine on interleukin-2 and interleukin-8 concentrations in patients with coronary artery disease. Can J Physiol Pharmacol. 2017;95(6):759–762. DOI: 10.1139/cjpp-2016-0424.
42. Szkodzinski J, Danikiewicz A, Hudzik B, Szewczyk M, Gąsior M, Zubelewicz-Szkodzinska B. Effect of trimetazidine on serum interleukin-6 and C-reactive protein concentrations in patients with stable coronary artery disease. J Biol Regul Homeost Agents. 2015;29(1):63–72.
43. Yoon JW, Cho BJ, Park HS, Kang SM, Choi SH, Jang HC, Shin H, Lee MJ, Kim YB, Park KS, Lim S. Differential effects of trimetazidine on vascular smooth muscle cell and endothelial cell in response to carotid artery balloon injury in diabetic rats. Int J Cardiol. 2013;167(1):126–33. DOI: 10.1016/j.ijcard.2011.12.061.
44. Zhang L, Ding WY, Wang ZH, Tang MX, Wang F, Li Y, Zhong M, Zhang Y, Zhang W. Early administration of trimetazidine attenuates diabetic cardiomyopathy in rats by alleviating fibrosis, reducing apoptosis and enhancing autophagy. J Transl Med. 2016;14(1):109. DOI: 10.1186/s12967-016-0849-1.
45. Statsenko ME, Fabritskaya SV, Ryndina UA. Influence of therapy with trimetazidine on the state of the main vessels and microcirculation in patients with CHF and DM type 2. The results of the original study. Meditsinskiy sovet: Medical Council. 2018;(5):65–69. DOI:10.21518/2079-701X-2018-5-65-69. Russian
46. Milinković I, Rosano G, Lopatin Y, Seferović PM. The Role of Ivabradine and Trimetazidine in the New ESC HF Guidelines. Card Fail Rev. 2016 Nov;2(2):123–129. DOI: 10.15420/cfr.2016:13:1.
47. Trukhan DI, Mazurov AL, Davydov EL. Myocardial cytoprotector trimetazidine MB-preparat, increases the effectiveness of treatment of chronic heart failure and coronary heart disease. Meditsinskiy sovet: Medical Council. 2017;(7):75–83. DOI: 10.21518/2079-701X-2017-7-75-83. Russian
48. Patel K, Gadewar M, Tahilyani V, Patel DK. A review on pharmacological and analytical aspects of diosmetin: a concise report. Chin J Integr Med. 2013;19(10):792–800. DOI: 10.1007/s11655-013-1595-3.
49. Wei D, Ci X, Chu X, Wei M, Hua S, Deng X. Hesperidin suppresses ovalbumin-induced airway inflammation in a mouse allergic asthma model. Inflammation. 2012;35(1):114–21. DOI: 10.1007/s10753-011-9295-7.
50. Maneesai P, Bunbupha S, Potue P, Berkban T, Kukongviriyapan U, Kukongviriyapan V, Prachaney P, Pakdeechote P. Hesperidin Prevents Nitric Oxide Deficiency-Induced Cardiovascular Remodeling in Rats via Suppressing TGF-β1 and MMPs Protein Expression. Nutrients. 2018;10(10):1549. DOI: 10.3390/nu10101549.
51. Shaban NZ, Ahmed Zahran AM, El-Rashidy FH, Abdo Ko-

dous AS. Protective role of hesperidin against γ-radiation-induced oxidative stress and apoptosis in rat testis. J Biol Res (Thessalon). 2017;24:5. DOI: 10.1186/s40709-017-0059-x. PMID: 28265554; PMCID: PMC5333452.

52. Ali TM, Abo-Salem OM, El Esawy BH, El Askary A. The Potential Protective Effects of Diosmin on Streptozotocin-Induced Diabetic Cardiomyopathy in Rats. Am J Med Sci. 2020 Jan;359(1):32–41. doi: 10.1016/j.amjms.2019.10.005.
53. Yarmolinsky L, Budovsky A, Yarmolinsky L, Khalfin B, Glukhman V, Ben-Shabat S. Effect of Bioactive Phytochemicals from Phlomis viscosa Poiret on Wound Healing. Plants (Basel). 2019;8(12):609. DOI: 10.3390/plants8120609.
54. Lin JT, Chang YY, Chen YC, Shen BY, Yang DJ. Molecular mechanisms of the effects of the ethanolic extract of Muntingia calabura Linn. fruit on lipopolysaccharide-induced pro-inflammatory mediators in macrophages. Food Funct. 2017;8(3):1245–1253. DOI: 10.1039/c6fo01735e.
55. Ağır MS, Eraslan G. The effect of diosmin against liver damage caused by cadmium in rats. J Food Biochem. 2019;43(9):e12966. DOI: 10.1111/jfbc.12966.
56. Elhelaly AE, AlBasher G, Alfarraj S, Almeer R, Bahbah EI, Fouda MMA, Bungău SG, Aleya L, Abdel-Daim MM. Protective effects of hesperidin and diosmin against acrylamide-induced liver, kidney, and brain oxidative damage in rats. Environ Sci Pollut Res Int. 2019;26(34):35151-35162. DOI: 10.1007/s11356-019-06660-3.
57. Berkoz M. Diosmin suppresses the proinflammatory mediators in lipopolysaccharide-induced RAW264.7 macrophages via NF-κB and MAPKs signal pathways. Gen Physiol Biophys. 2019 Jul;38(4):315–324. doi: 10.4149/gpb_2019010. Epub 2019 Jun 26. PMID: 31241043.
58. Kalinin RE, Suchkov IA, Kamaev AA, Zvyagina VI, Krylov AA. Éndoteliotropnye éffekty venotoniziruiushchikh preparatov pri lechenii bol'nykh s varikoznoĭ bolezn'iu [Endotheliotropic effects of venotonic drugs in treatment of patients with varicose veins]. Angiol Sosud Khir. 2018;24(4):72–74. Russian. PMID: 30531772.
59. Gurfinkel' II, Sasonko ML, Talov NA. Korrektsiia parametrov mikrotsirkuliatsii krovi i funktsii éndoteliia pri khronicheskoĭ venoznoĭ nedostatochnosti nizhnikh konechnosteĭ [Correction of blood microcirculation parameters and endothelial function in chronic venous insufficiency of lower limbs]. Angiol Sosud Khir. 2017;23(2):89–95. Russian.
60. Zudin AM, Gritsenko AG, Hadzhishvili IT. Vozdeĭstvie diosmina i gesperidina na kapilliarnyĭ krovotok verkhnikh konechnosteĭ u patsientov s vtorichnym sindromom Reĭno [The effects of diosmin and hesperidin on capillary blood flow of upper limbs in patients with secondary Raynaud's syndrome]. Khirurgiia (Mosk). 2017;(5):60–66. DOI: 10.17116/hirurgia2017560-66. Russian.
61. Paredes MD, Romecín P, Atucha NM, O'Valle F, Castillo J, Ortiz MC, García-Estañ J. Moderate Effect of Flavonoids on Vascular and Renal Function in Spontaneously Hypertensive Rats. Nutrients. 2018;10(8):1107. DOI: 10.3390/nu10081107.
62. Paredes MD, Romecín P, Atucha NM, O'Valle F, Castillo J, Ortiz MC, García-Estañ J. Beneficial Effects of Different Flavonoids on Vascular and Renal Function in L-NAME Hypertensive Rats. Nutrients. 2018;10(4):484. DOI: 10.3390/nu10040484.
63. Liu X, Zhang X, Zhang J, Kang N, Zhang N, Wang H, Xue J, Yu J, Yang Y, Cui H, Cui L, Wang L, Wang X. Diosmin protects against cerebral ischemia/reperfusion injury through activating JAK2/STAT3 signal pathway in mice. Neuroscience. 2014;268:318–27. DOI: 10.1016/j.neuroscience.2014.03.032.
64. Kilicoglu SS, Tanrikulu Y, Kismet K, Devrim E, Erel S, Tanrikulu CS, Aydogan A, Tasova V, Sabuncuoglu MZ, Kilicoglu B. The effect of diosmin on pancreatic injury induced by hepatic ischemia reperfusion in rats. Bratisl Lek Listy. 2013;114(3):119–24. DOI: 10.4149/bll_2013_026.
65. Mastantuono T, Battiloro L, Sabatino L, Chiurazzi M, Di Maro M, Muscariello E, Colantuoni A, Lapi D. Effects of Citrus Flavonoids Against Microvascular Damage Induced by Hypoperfusion and Reperfusion in Rat Pial Circulation. Microcirculation. 2015;22(5):378–90. DOI: 10.1111/micc.12207.
66. Mansilha A, Sousa J. Pathophysiological Mechanisms of Chronic Venous Disease and Implications for Venoactive Drug Therapy. Int J Mol Sci. 2018;19(6):1669. DOI: 10.3390/ijms19061669.
67. G, Vincenza C, De Blasis E. Effectiveness and safety of a mixture of diosmin, coumarin and arbutin (Linfadren®) in addition to conventional treatment in the management of patients with post-trauma/surgery persistent hand edema: a randomized controlled trial. Clin Rehabil. 2019;33(5):904–912. DOI: 10.1177/0269215519829797.
68. Cacchio A, Prencipe R, Bertone M, De Benedictis L, Taglieri L, D'Elia E, Centoletti C, Di Carlo G. Effectiveness and safety of a product containing diosmin, coumarin, and arbutin (Linfadren®) in addition to complex decongestive therapy on management of breast cancer-related lymphedema. Support Care Cancer. 2019 ;27(4):1471–1480. DOI: 10.1007/s00520-018-4514-5.
69. Feldo M, Wójciak-Kosior M, Sowa I, Kocki J, Bogucki J, Zubilewicz T, Kęsik J, Bogucka-Kocka A. Effect of Diosmin Administration in Patients with Chronic Venous Disorders on Selected Factors Affecting Angiogenesis. Molecules. 2019;24(18):3316. DOI: 10.3390/molecules24183316.
70. Drogovoz SM, SHtrygol' SYu, SHCHekina EG, Matveeva EV, Voloshchuk NI, Trzhecinskij SD, Zamorskij II, Oleshchuk AM, Podpletnyaya EA, SHtroblya AL, Ivancik LB, Drogovoz VV. Farmakologiya v pomoshch' vrachu, provizoru i studentu. Har'kov; 2018.
71. Xu B, Charlton F, Makris A, Hennessy A. Antihypertensive drugs methyldopa, labetalol, hydralazine, and clonidine improve trophoblast interaction with endothelial cellular networks in vitro. J Hypertens. 2014;32(5):1075–83; discussion 1083. DOI: 10.1097/HJH.0000000000000134.
72. Xu B, Bobek G, Makris A, Hennessy A. Antihypertensive methyldopa, labetalol, hydralazine, and clonidine reversed tumour necrosis factor-α inhibited endothelial nitric oxide synthase expression in endothelial-trophoblast cellular networks. Clin Exp Pharmacol Physiol. 2017;44(3):421–427. DOI: 10.1111/1440-1681.12712.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2020-8-5-304-315

AUTHORS

Oksana E. Antsiferova – postgraduate student of the Department of Pharmacology and Clinical Pharmacology, Belgorod State National Research University. ORCID ID: 0000-0002-9456-9569. E-mail: AnciferovaO@ya.ru

Maria P. Teleschenko – postgraduate student of the Department of Pharmacology and Clinical Pharmacology, Belgorod State National Research University. ORCID ID: 0000-0003-0849-4351. E-mail: marijastreltsowa@yandex.ru

Yulia M. Tsuverkalova – post-graduate student of the Department of Pharmacology and Clinical Pharmacology, Belgorod State National Research University. ORCID ID: 0000-0001-8489-247X. E-mail: cvd404@mail.ru

Mikhail V. Pokrovsky – Doctor of Sciences (Medicine), Professor, Professor of the Department of Pharmacology and Clinical Pharmacology, the Head of the Research Institute of Pharmacology of Living Systems, Belgorod State National Research University. ORCID ID: 0000-0002-2761-6249. E-mail: mpokrovsky@yandex.ru

Vladimir V. Gureev – Doctor of Sciences (Medicine), Associate Professor, Professor of the Department of Pharmacology and Clinical Pharmacology, Belgorod State National Research University. ORCID ID: 0000-0003-1433-1225. E-mail: produmen@yandex.ru

Maria A. Zatolokina – Doctor of Sciences (Medicine), Professor, Professor of the Department of Histology, Cytology, Embryology, Kursk State Medical University. ORCID ID: 0000-0002-9553-1597. E-mail: marika1212@mail.ru

Anastasia V. Gureeva – 4th year student of Medical Department of Kursk State Medical University. ORCID ID: 0000-00031719-7316. E-mail: nastasyi.207@gmail.com