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SEVERITY OF ENDOTHELIAL DYSFUNCTION MANIFESTATIONS IN RESPONSE TO THERAPEUTIC AND PROPHYLACTIC COMPLEX AIMED AT PREVENTING PREECLAMPSIA IN WOMEN WITH CONCOMITANT OBESITY

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Abstract. Severity of endothelial dysfunction manifestations in response to therapeutic and prophylactic complex aimed at preventing preeclampsia in women with concomitant obesity. Zelinka-Khobzey M.M., Tarasenko K.V. *Reducing the incidence of preeclampsia (PE) is one of the main tasks of modern obstetrics, since PE has been known as one of the most serious hypertensive disorders of pregnancy due to its impact on maternal and child health. This issue is especially revenant for managing pregnant women with concomitant obesity as they are at high risk for PE. Endothelial dysfunction is known as a leading pathogenetic chain in the pathogenesis of PE. Circulating endothelial microparticles (CEM) have been proved to act as markers of endothelial damage. The aim of this study is to evaluate the effectiveness of the therapeutic and prophylactic complex (TPC) developed to prevent the occurrence of preeclampsia in pregnant women with obesity of varying severity by assessing the severity of manifestations associated with the severity of endothelial dysfunction. The study included 48 pregnant women in the third trimester with physiological body weight, class I obesity and class II–III obesity without preeclampsia, similar groups with PE, and groups of pregnant women with class I obesity and class II-III obesity who had preeclampsia during the course of receiving the therapeutic and prophylactic complex. We counted circulating endothelial microparticles $CD32^+CD40^+$ in the peripheral blood by flow cytofluorometry. According to the level of expression of circulating endothelial microparticles $CD32^+CD40^+$ in the blood plasma of pregnant women with obesity of varying severity, who developed preeclampsia during the therapeutic and prophylactic course including acetylsalicylic acid, L-arginine, calcium supplements and calcium supplements in order to prevent preeclampsia, there was a decrease in the severity of endothelial dysfunction. We also observed the reduction in the incidence of obstetric and prenatal complications associated with endothelial dysfunction in pregnant women with concomitant obesity who received this course that proves its effectiveness and appropriateness in obstetric practice.*

Реферат. Вираженість проявів ендотеліальної дисфункції за умови застосування лікувально-профілактичного комплексу, спрямованого на запобігання виникнення прееклампсії у вагітних жінок із супутнім ожирінням. Зелінка-Хобзей М.М., Тарасенко К.В. *Зниження частоти виникнення прееклампсії (ПЕ) є одним з головних завдань сучасного акушерства. Особливо ця проблема є гострою у вагітних із супутнім ожирінням, оскільки ці жінки складають групу високого ризику щодо виникнення ПЕ. Ендотеліальна дисфункція є провідною патогенетичною ланкою в патогенезі ПЕ. Відомо, що циркулюючі ендотеліальні мікрочастинки (ЦЕМ) виступають маркером пошкодження ендотелію. Метою роботи було проведення оцінки вираженості проявів ендотеліальної дисфункції на фоні застосування розробленого нами лікувально-профілактичного комплексу (ЛПК), який застосовувався з метою профілактики виникнення прееклампсії у вагітних жінок при ожирінні різного ступеня тяжкості. У дослідження включено 48 вагітних жінок у III триместрі вагітності з фізіологічною масою тіла, ожирінням I ступеня й ожирінням II-III ступенів без ПЕ, аналогічні групи з ПЕ та групи вагітних з ожирінням I ступеня й ожирінням II-III ступенів, у яких все ж таки маніфестувала ПЕ на фоні*

застосування ЛПК. Досліджуваним жінкам проводився підрахунок ЦЕМ $CD32^+CD40^+$ у периферичній крові методом проточної цитофлуориметрії. Відповідно до показників рівня експресії циркулюючих ендотеліальних мікрочастинок $CD32^+CD40^+$ у плазмі крові вагітних жінок при ожирінні різного ступеня тяжкості, в яких розвинулась прееклампсія на фоні застосування запропонованого нами лікувально-профілактичного комплексу (ацетилсаліцилова кислота, L-аргінін, препарати кальцію) та напівсинтетичного діосміну з метою профілактики виникнення прееклампсії, відмічалося зниження вираженості ендотеліальної дисфункції. Зниження частоти акушерських та перинатальних ускладнень, пов'язаних з дисфункцією ендотелію у вагітних жінок із супутнім ожирінням, вагітність яких проходила на фоні застосування лікувально-профілактичного комплексу, доводить свою ефективність та доцільність для використання у цієї когорти пацієнток.

Reducing the incidence of preeclampsia (PE) is one of the main tasks of modern obstetrics, since PE has been known as one of the most serious hypertensive disorders of pregnancy due to its impact on maternal and child health. According to statistics, PE develops in a third of pregnant women with extragenital diseases [11]. Numerous epidemiological studies have shown that obesity increases the risk of preeclampsia, and current experimental data support the concept that obesity and metabolic factors such as lipids, insulin, glucose and leptin affect placental function and increase the risk of hypertension during the pregnancy [9].

Today PE is considered as a clinically manifested form of gestational endotheliopathy. Damage to the vascular endothelium and defects in the vascular wall integrity are reported as resulting from uncompensated, excess production of certain substances (endothelin, proinflammatory cytokines), as far as PE has been proven to be associated with systemic inflammatory response, endothelial dysfunction (ED), imbalance between angiogenic and anti-angiogenic factors, and metabolic disorders [4].

Among the PE clinical manifestations there are arterial hypertension, considered as a consequence of vascular spasm (hypoperfusion), and proteinuria, which results from glomerular filtration dysfunction (glomelular endotheliosis). Prolonged vascular damage leads to the damage to endothelial cells along the vascular wall that is manifested by an increase in circulating endothelial microparticles (CEM). There is evidence of increased levels of $CD31^+/42^-/CD62^+/CD105^+$ CEM in women with PE, moreover, CEMs are known as a marker of endothelial damage, and changes in their levels reflect the progression of ED under pathological conditions, or endothelial regeneration [10].

However, despite the advances in modern medicine and voluminous studies, no effective method of PE prevention has been elaborated yet. This outlines the undoubted relevance of the choice of adequate and effective tactics for managing pregnant women with concomitant obesity known as a trigger factor of endothelial dysfunction and preventing the PE occurrence.

The aim of this research is to evaluate the effectiveness of the therapeutic and prophylactic complex (TPC) developed to prevent the occurrence of preeclampsia in pregnant women with obesity of varying severity.

MATERIALS AND METHODS OF RESERCH

The study involved 48 pregnant women who gave written consent to participate in the study. Inclusion criteria for the study were as follows: physiological body weight and class I-III obesity, singleton pregnancy, III trimester of gestation, no severe extragenital diseases or conditions.

The research was conducted in accordance with the principles of bioethics set out in the WMA Declaration of Helsinki – "Ethical principles for medical research involving human subjects" and "Universal Declaration on Bioethics and Human Rights" (UNESCO).

The division of the pregnant women into groups was carried out taking into account the values of body mass index (BMI); the severity of obesity was calculated by growth and weight parameters considering the gestational age and age of women in accordance with the table proposed by N.S. Lutsenko.

The women were divided into 8 study groups (6 women in each group): the 1st group (control) involved pregnant women having physiogical body weight (i.e. BMI ranged from 18.5 to 24.9 kg/m^2), mean age was 25.2 years; the 2nd group included pregnant women with physiological body weight and PE, mean age was 25.8 years; the 3rd group included pregnant women with class I obesity, mean age was 29.2 years; the 4th group included pregnant women with class I obesity and PE, average age was 25.0 years; the 5th group included pregnant women with class I obesity and PE, which arose during the course of LPC, mean age was 32.2 years; the 6th group included pregnant women with class II-III obesity, average age was 31.1 years; the 7th group included pregnant women with class II-III obesity and PE, mean age was 26.5 years; and the 8th group – pregnant women with class II-III obesity and PE, which arose despite receiving the elaborated course of therapeutic and prophylactic measures aimed at preventing the PE occurrence of PE, mean age was 27.5 years.

We evaluated the level of $CD32^+CD40^+$ CEM in the peripheral blood. Blood sampling was performed

at maternity welfare clinics and obstetric departments of Poltava city.

The expression level of $CD32^+CD40^+$ CEM in venous blood was measured by flow cytofluorometry using murine anti-human monoclonal CD40 antibodies conjugated to FITC (BD Pharmingen, USA) and PE murine anti-human monoclonal CD32 antibodies (BD Pharmingen, USA) by the flow cytometer "EPIX XL-MCL" (Beckman Coulter, USA). Murine IgG labelled with fluorescent dyes were used as control. Data for calculating the absolute number of particles, taking into account the dilution during the measurement, were represented in the form of $A\times10^7$/l.

The pregnant women with physiological body weight were under the observation at maternity welfare clinics in accordance with the Order of the Ministry of Health of Ukraine No. 417, 15.07.2011. As pregnant women with obesity are known to be at risk for preeclampsia, they were managed according to the clinical protocol for obstetric care "Predictors, prevention, diagnosis and treatment of hypertensive disorders during pregnancy", developed by a working group of leading Ukrainian experts in obstetrics (01.11.2018). According to this protocol, pregnant women at risks including obesity are prescribed to take acetylsalicylic acid in a dose of 100 mg/day from the 12th to 36th weeks of gestation, calcium supplements in a dose of 1 g/day from the 20th week of gestation, as well as to incorporate sea food with a high content of polyunsaturated fatty acids into the daily diet. This is also in line with the clinical practice guideline prepared by the Canadian working group on hypertensive disorders of pregnancy and published by the journal "Pregnancy Hypertension" to provide a reasonable approach to the diagnosis, evaluation, and treatment of the hypertensive disorders of pregnancy [7].

The pregnant women who agreed to take the pathogenetically relevant prophylactic therapy aimed at PE preventing, received the combination of L-arginine and semi-synthetic diosmin according to the scheme from 12 to 16, 22 to 26, and from 32 to 36 weeks of gestation. Diosmin, produced in the form of tablets was prescribed in a dose of 600 mg per day orally, L-arginine produced as syrup was prescribed in a dose of 5 ml 3 times a day [3].

Quantitative data are presented in the form of standard deviation and its standard error (M±m). Statistical processing of the findings was performed by the software package "MedStat" (serial No. MS00019) using standard methods of variation statistics and Student's t-test. The difference was considered statistically significant at $p<0.05$ [1].

RESULTS AND DISCUSSION

The analysis of data obtained demonstrated the number of $CD32^+CD40^+$ CEM in the pregnant women with class I obesity and PE was by 2.9 times higher than the values of $CD32^+CD40^+$ CEM in pregnant women with class I obesity and pregnancy not complicated by PE ($9.76\pm2.66\times10^7$/l vs. $3.29\pm0.83\times10^7$/l, $p<0.05$), (Table).

Indicators of the level of $CD32^+CD40^+$ CEM expression in the peripheral blood of pregnant women with obesity after the TPC course (M±m)

Groups	Pregnant women in the III trimester	Pregnant women with preeclampsia	Pregnant women with preeclampsia during the TPC course
Pregnant women with physiological body weight	**1.33±0.54**	**7.64±1.26**	**-**
Pregnant women with class I obesity	**3.29±0.83**	**9.76±2.66** [1]	**2.92±0.48** [2, 3, 4]
Pregnant women with class II-III obesity	**8.86±1.48**	**13.13±0.55** [5]	**12.49±0.59** [6, 7, 8]

Notes: 1 – reliability when comparing the indicators of the group of pregnant women with class I obesity and the group of pregnant women with class I obesity and PE, ($p<0.05$); 2 – reliability when comparing the indicators of the group of pregnant women with class I obesity and PE and the group of pregnant women with class I obesity and PE who took the TPC course, ($p<0.05$); 3 – reliability when comparing the indicators of the group of pregnant women with class I obesity and PE who took TPC course and the group of pregnant women with physiological body weight and PE, ($p<0.05$); 4 – reliability when comparing the indicators of the group of pregnant women with class I obesity and PE who took TPC course and the control group, ($p<0.05$); 5 – reliability when comparing the indicators of the group of pregnant women with class II-III obesity and the group of pregnant women with class II-III obesity and PE, ($p<0.05$); 6 – reliability when comparing the indicators of the group of pregnant women with class II-III obesity and PE who took TPC course and the group of pregnant women with physiological body weight and PE, ($p<0.05$); 7 – reliability when comparing the indicators of the group of pregnant women with class II-III obesity and PE who took TPC course and the control group, ($p<0.001$); 8 – reliability when comparing the indicators of the group of pregnant women with obesity II-III degrees and PE who took LPK with the group of pregnant women with class I obesity and PE who also took TPC course, ($p<0.001$).

The indicators of $CD32^+CD40^+$ CEM expression in pregnant women with class I obesity who showed PE signs during the TPC were by 4.3 times lower than the expression of $CD32^+CD40^+$ CEM in pregnant women with class I obesity and PE who did not took TPC course ($2.92\pm0.48\times10^7$/l vs. $9.76\pm2.66\times10^7$/l,

respectively, $p<0.05$). The level of $CD32^+CD40^+$ CEM in the pregnant women with class I obesity and in the women with PE, which developed during the TPC course was also by 3.3 times lower than the levels of $CD32^+CD40^+$ CEM in the group of pregnant women with physiological body weight, whose pregnancy was also complicated by PE ($2.92\pm0.48\times10^7$/l vs. $7.64\pm1.26\times10^7$/l, respectively, $p<0.05$) and approached the control group ($2.92\pm0.48\times10^7$/l vs. $1.33\pm0.54\times10^7$/l, respectively, $p<0.05$) (Table).

Comparing the indicators of $CD32^+CD40^+$ CEM in the peripheral blood of the pregnant women with class II-III obesity, who developed PE during the TPC course and the indicators of $CD32^+CD40^+$ CEM in the group with similar obesity and PE who did not take the TPC course demonstrated the tendency to decrease, however, no reliability was observed ($12.49\pm0.59\times10^7$/l vs. $13.13\pm0.55\times10^7$/l, respectively, $p>0.05$). The difference between $CD32^+CD40^+$ CEM in the peripheral blood of pregnant women with class II-III obesity with diagnosed PE and pregnant women with class II-III obesity without PE was statistically significant ($13.13\pm0.55\times10^7$/l vs. $8.86\pm1.48\times10^7$/l, respectively, $p<0.05$) (Table).

The average level of $CD32^+CD40^+$ CEM in the group of pregnant women with class II-III obesity, who manifested PE when taking the TPC course was only by 1.7 times higher than the average level in the pregnant women with physiological body weight, whose pregnancy was also complicated by PE ($12.49\pm0.59\times10^7$/l vs. $7.64\pm1.26\times10^7$/l, respectively, $p<0.05$), and significantly higher compared with the control group ($12.49\pm0.59\times10^7$/l vs. $1.33\pm0.54\times10^7$/l, respectively, $p<0.001$) (Table).

Comparing the average values between the groups of pregnant women with class I and II-III obesity, which both developed PE, we observe an increase in $CD32^+CD40^+$ CEM by 21.9% in the group of pregnant women with class II-III obesity when comparing with the average values in the group of pregnant women with class I obesity ($9.76\pm2.66\times10^7$/l vs. $12.49\pm0.59\times10^7$/l, respectively, $p=0.24$) (Table).

The comparison of the indicators between the group of pregnant women with class I obesity and PE who took the TPC course and the group of pregnant women with class II-III obesity and PE who also took the TPC course, we have found out the indicators of the group of women with more severe obesity exceed those in the groups of pregnant women with less severe obesity by 5.4 times ($12.49\pm0.59\times10^7$/l vs. $2.92\pm0.48\times10^7$/l, respectively, $p<0.001$), this may indicate that the pregnant women with more severe obesity are less susceptible to the medicine correction.

The analysis of the course of pregnancy in our study groups has shown that cases of early (up to 34 weeks of gestation) and severe PE occurred only in the groups of obese pregnant women who did not took the TPC course. PE, which nevertheless manifested during the TPC course, occurred after 35 weeks of gestation and was classified as moderate and had a more positive effect on the health condition of newborns and parturients. The manifestation of early PE required the prevention of respiratory distress syndrome in the foetus, had a more severe course and led to premature birth. 16.65% of newborns born to women with PE and concomitant obesity, who did not take the TPC course we proposed, were diagnosed with neonatal encephalopathy and cerebral oedema. This pathological condition was not registered among newborns from the groups of pregnant women with PE and obesity, who took the TPC course. The clinical status of newborns assessed by the Apgar score did not require resuscitation as the scores exceeded 6.

In the majority of the pregnant women with concomitant obesity and PE who took TPC course, the intensity of PE clinical manifestations was slightly reduced compared to the pregnant women with PE and obesity who did not took the TPC course. More pronounced oedema of the lower extremities, the oedema of the upper extremities and pastosity of the anterior abdominal wall were more common in the groups which refrained from using TPC course, while in the patients of the comparison group only manifestations of leg pastosity prevailed.

Taking into account the blood pressure (BP) parameters in the group of pregnant women with PE and class I obesity who did not took TPC course, we noted that the average systolic pressure was 135.0 mm Hg, while the average systolic pressure in the group of pregnant women with PE and class I obesity who took TPC course was 130.8 mm Hg. The average diastolic pressure in the above groups ranged between 87.0 and 86.6 mm Hg. A similar pattern was observed between the groups of pregnant women with class II-III obesity and PE who did not take the TPC course and who took this course (136.6 mm Hg vs. 132.5 mm Hg for systolic pressure, respectively, and 88.9 mm Hg vs. 85.8 mm Hg for diastolic pressure, respectively). Moreover, the pregnant women with class II-III obesity and PE who took TPC did not demonstrate an increase in blood pressure more than 150/100 mm Hg.

Proteinuria in a single portion of urine was found in most pregnant women with PE and class I-III obesity who took the TPC course did not exceed 1 g/l in contrast to the pregnant women with PE and I-III obesity who did not took the TPC course, whose indices exceeded this values.

The positive effect of the TPC course we recommended was found out in the findings of hepatic

transaminases – alanine transaminase (ALT) and aspartate transaminase (AST), as in the groups of pregnant women with PE and obesity who took the TPC course, these indicators did not exceed reference indicators, but in the pregnant women with PE and obesity who did not take the TPC course, the average ALT was 44.8 IU/L, and AST was 67.4 IU/L.

Our study has demonstrated the data obtained on the increase in the CEM number in preeclampsia are identical to the results of other scientists, who prove that in the course of preeclampsia there is an increase not only in the number of microparticles derived from platelets, endothelium and various leukocytes, but in the number of microparticles derived from syncytiotrophoblasts that interact with both immune and endothelial cells as well as may contribute to systemic inflammation, which is inherent in pregnancy complicated by PE [6,5].

Increased levels of $CD31^+/CD42b^-$ CEM in the women with obesity compared to the women normal BMI are described in the works of other researchers who consider that the increase in the number of microparticles occurs due to the loss of endothelial cells resulted from inflammatory processes associated with vascular damage. It plays a direct role in atherogenesis, can activate and stimulate cells to produce inflammatory mediators such as cytokines and again evidences that obesity is a state of chronic oxidative stress and inflammation that enhances the production of free radicals, inhibits and inactivates nitric oxide (NO) reducing its availability for target cells [8]. NO is a well-known vasodilator produced by the vascular endothelium using endothelial nitric oxide synthase (eNOS). Inadequate NO production combines with an increase in blood pressure that is due to the unavailability of the substrate and confirms the feasibility of prescribing L-arginine as a NO donor [13].

The animal experiments have proven that diosmin in experimental ADMA-like PE leads to significant correction of pathological changes and results in a significant decrease in systolic and diastolic pressure, improves placental microcirculation, renewal of NO-synthesizing endothelial function, reduction of proteinuria [2]. Our study also demonstrates a decrease in blood pressure indicators during the course of L-arginine and diosmin that can be suggested as an evidence of the effectiveness of the TPC course.

Diosmin, a flavone glycoside of diosmetin, has a pronounced anti-inflammatory effect and strong antioxidant properties, which have been confirmed by improved liver transaminases indices in the experimental study with cadmium-induced liver damage [12] and is supported in our studies.

Thus, the results obtained by flow cytofluorometry have demonstrated an increase in the level of $CD32^+CD40^+$ CEM in the peripheral blood of pregnant women who developed PE that confirms the presence of endothelial dysfunction. The deterioration of these indicators progressed with increasing severity of obesity, and the maximum values were observed in obese women whose pregnancy was complicated by PE and may indicate to a more extended endothelial involvement. Lower expression rates of $CD32^+CD40^+$ CEM were registered in the groups of pregnant women with concomitant obesity who received the TPC course we elaborate, that evidences its positive effect on the state of the endothelium. General and biochemical indices also support the effectiveness of this course, which reduces the incidence of obstetric and prenatal complications associated with endothelial dysfunction.

CONCLUSIONS

1. The therapeutic and prophylactic complex including acetylsalicylic acid, L-arginine, calcium supplements and semi-synthetic diosmin have been proved to reduce the manifestations of endothelial dysfunction in pregnant women with preeclampsia and obesity, according to the results of CD32+CD40+ circulating endothelial microparticles.
2. This complex has been found out to reduce the incidence of obstetric and prenatal complications associated with endothelial dysfunction and severity of clinical manifestations of preeclampsia in pregnant women with concomitant obesity.

Contributors:

Zelinka-Khobzey M.M. – conceptualization, methodology, resources, writing – original draft, formal analysis, data curation;

Tarasenko K. V. – visualization, writing – review & editing, project administration, validation.

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REFERENCES

1. Antomonov MYu. [Mathematical processing and analysis of biomedical data]. Medinform. 2018;579. Russian.

2. Antsiferova OE, Gureev VV, Gureeva AV, Mikhaylova YuA, Kuzmin DB. [Comprehensive assessment of using micronised purified flavonoid fraction in the

correction of disorders associated with ADMA-like preeclampsia in experiment]. Scientific results of biomedical research. 2020;6(1):78-93. Russian.
doi: https://doi.org/10.18413/2658-6533-2020-6-1-0-7

3. Lakhno I. [Modern possibilities of prediction and prevention of preeclampsia]. Health of woman. 2016;7(113):44-48. Russian.
doi: https://doi.org/10.15574/HW.2016.113.44

4. Loskutova TO. [Polymorphism of genes of hemostasis system, endothelial dysfunction and regulation of blood pressure in pregnant woman with preeclampsia and fetal growth retardation]. Pathologia. 2018;15(1):29-33. Ukrainian.
doi: https://doi.org/10.14739/2310-1237. 2018.1.127709

5. Paudel KR, Panth N, Kim DW. Circulating Endothelial Microparticles: A Key Hallmark of Atherosclerosis Progression. Scientifica, 2016(2):1-9.
doi: https://doi.org/10.1155/2016/8514056

6. Redman CWG, Sargent IL. Circulating Microparticles in Normal Pregnancy and Pre-Eclampsia. Placenta. 2008;29:73-7.
doi: https://doi.org/10.1016/j.placenta.2007.11.016

7. Disorders of Pregnancy Working Group. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. J Obstet Gynaecol Can. 2014 May;36(5):416-41.
doi: https://doi.org/10.1016/s1701-2163(15)30588-0

8. Esposito K, Ciotola M, Schisano B, Gualdiero R, Sardelli L, Misso L, et al. Giugliano Endothelial Microparticles Correlate with Endothelial Dysfunction in Obese Women. The Journal of Clinical Endocrinology & Metabolism. 2006;91(9):3676-9.
doi: https://doi.org/10.1210/jc.2006-0851

9. Spradley FT, Palei AC, Granger JP. Increased risk for the development of preeclampsia in obese pregnancies: weighing in on the mechanisms. Am J Physiol Regul Integr Comp Physiol. 2015;309(11):1326-43.
doi: https://doi.org/10.1152/ajpregu.00178.2015

10. Heimrath J, Paprocka M, Czekanski A, Ledwozyw A, Kantor A, Dus D. Pregnancy-Induced Hypertension is Accompanied by Decreased Number of Circulating Endothelial Cells and Circulating Endothelial Progenitor Cells. Arch. Immunol. Ther. Exp. 2014;62:353-6.
doi: https://doi.org/10.1007/s00005-014-0278-x

11. Stevens W, Shih T, Incerti D, Ton TGN, Lee HC, Peneva D, et al. Short-term costs of preeclampsia to the United States health care system. Am. J. Obstet. Gynecol. 2017 Sep;217(3):237-48.
doi: https://doi.org/10.1016/j.ajog.2017.04.032

12. Selim M, Eraslan AG. The effect of diosmin against liver damage caused by cadmium in rats. Journal of Food Biochemistry. 2019;43(9):e12966.
doi: https://doi.org/10.1111/jfbc.12966

13. Khalaf D, Krüger M, Wehland M, Infanger M, Grimm D. The Effects of Oral l-Arginine and l-Citrulline Supplementation on Blood Pressure. Nutrients. 2019;11(7):1679.
doi: https://doi.org/10.3390/nu11071679

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