Л. Мацапьяк, вед. науч. сотруд.
Национальный природный парк "Верховинский", Верхний Ясенево, Украина

АНАЛИЗ ФЛОРЫ СОСУДИСТЫХ РАСТЕНИЙ НАЦИОНАЛЬНОГО ПРИРОДНОГО ПАРКА "ВЕРХОВИНСКИЙ"

Проанализировано систематическую структуру флоры Национального природного парка "Верховинский" с последующим осуществлением критико-таксономического, биоморфологического и географического анализов, проанализирована созологическая ценность флоры. Установлено, что в составе флоры имеющиеся 675 видов высших сосудистых растений, относящихся к 5 отделам. Доминируют Magnoliophyta – 93,6%, соотношение Magnoliopsida к Liliopsida составляет 1: 3,2, что характерно для флоры Средней Европы. Это свидетельствует о примерно одинаковом возрасте флор НППВ, Украинских Карпат и Средней Европы. Итак, нами проведен систематический анализ, который подтвердил, что флора НППВ является типичной среднеевропейской с выраженными бореальными чертами. По анализу географической структуры установлена принадлежность флоры НПП "Верховинский" до среднеевропейского типа с преобладанием элементов монтанних, океанических, темперантных и субтемперантных флор. Вместе с тем в ее составе значительное участие видов, характерных для европейско-азиатских бореальных субконтинентальных флор. Проведенный анализ экологической структуры флоры указывает на преобладание в ее составе мезофитов, мезотроф, и гелиофиты, что свойственно для флор Средней Европы. Итак, нами проведен систематический анализ, который подтверждает, что флора НПП "Верховинский" свидетельствует о среднеевропейском характере и ее принадлежность к монтанно-бореальному подтипу. Установлено, что в пределах территории парка растут 71,4 % видов флоры Украинских Карпат, угражаемых в глобальном масштабе, 36,4% – в европейском масштабе, 47,8% эндемиков и 54,2% субендемиков Украинских Карпат. Самый высокий уровень созологичной значимости является для массивов Гнетеса-Фатия Банулуи (63 раритетных вида), Прелуки-Хитанка – (53 вида).

Ключевые слова: флора, сосудистые растения, эндемики, раритетные виды, НПП "Верховинский", Чивчино – Гринявские горы.

L. Matsapiak, Conduction, Sci. co-worker
National Park "Verkhovyna", Upper Ash, Ukraine

ANALYSIS OF FLORA OF WATER PLANTS OF THE NATIONAL NATURE PARK "VERKHOVINSKIY"

The systematic structure of the flora of the Verkhovyna National Nature Park was analyzed, followed by the implementation of critically-taxonomic, biomorphological, geographical analyzes, and the sosological value of the flora was analyzed.It has been established that 675 species of higher vascular plants belonging to 5 divisions are present in the flora. Dominated by Magnoliophyta – 93.6%, the ratio of Magnoliopsida to Liliopsida is 1: 3.2, which is characteristic of the flora of Central Europe.This is evidenced by the approximately equal age of the flora of NSAIDs, the Ukrainian Carpathians and Central Europe.Therefore, we conducted a systematic analysis that confirmed that the flora of the park is typical Central European with pronounced boreal features. According to the analysis of the geographical structure, the flora of NP Verkhovynskyi was found to be of the Central European type with the predominance of elements of montane, oceanic, temperant and subtemperate flora. At the same time, the composition of species typical for the Euro-Asian boreal subcontinental flora is significant in its composition. The analysis of the ecological structure of the flora indicates the predominance in its composition of mesophytes, mesotrophs, and heliophytes, which is characteristic of the flora of Central Europe. Thus, we conducted a systematic analysis, which confirmed that the flora of Verkhovyna NPP testifies to the Central European character and its belonging to the montane-boreal subtype its found that 71.4 % of the flora species of the Ukrainian Carpathians are threatened globally, 36.4% are endangered on the European scale, 47.8% are endemic and 54.2 % are subendemic within the territory of the park. The highest level of sosological significance is characteristic of the Gnetes-Fatia Banului arrays (63 rare species), Preluki-Hitanka – (53 species).

Key words: flora, vascular plants, endemics, rare species, NPP "Verhovinsky", Chivchino – Grinyavsky mountains.

UDC 577.112.8

A. Beliayeva, Intern., L. Garmanchuk, Dr. Sci, Prof.
Taras Shevchenko National University of Kyiv, Kyiv, Ukraine

CHANGING IN THE NUMBER OF CD117+ STEM CELLS, CYTOGENETIC AND CYTOKINETIC PARAMETERS UNDER THE USING OF CANDESARTAN, CANDESARTAN CILEXETIL AND RESVERATROL *IN VITRO*

Due to the increase in cardiovascular disease, it is urgent to research new effective and safe drugs and their combinations. Candesartan cilexetil, an angiotensin II receptor antagonist, is a precursor to the active form of candesartan. However, these antiischemic drugs have a cytotoxic effect, affecting the antioxidant system. Therefore, to prevent the cytotoxic effect is the need to use antioxidants. To study the effect of candesartan cilexetil, candesartan and resveratrol antioxidant in various doses and combinations on CD117+ stem cell mobilization, on the number of apoptotic and micronucleated cells and cell cycle parameters in vitro. Bone marrow cells isolated from C57Bl / 6 mice were selected for experiments. After incubation for 2 days with the means in different concentrations and combinations, the biological characteristics of the stem cells were determined. Flow cytometry was used to analyze the number of CD117 + stem cells, the ratio of apoptotic cells, cells with micronuclei and cell cycle parameters when using candesartan cilexetil, candesartan, and resveratrol in vitro. It was found that using candesartan cilexetil with resveratrol and candesartan with resveratrol promotes the formation of CD117 + stem cells from 1.2 times to almost 2 times compared with controls and 1.5 and 2.5 compared with cytostatics. Candesartan cilexetil and candesartan were cytotoxic, while resveratrol reduced the adverse effects of the substances in combination. Combination of candesartan cilexetil with resveratrol; Candesartan with resveratrol significantly increased CD117+ stem cell count and was not cytotoxic.

Keywords: Candesartan cilexetil, candesartan, resveratrol, CD117+ stem cells, apoptotic cells, micronuclei and cell cycle parameters.

Introduction. The incidence of cardiovascular diseases has increased several times in many countries all over the world. So it's necessary to study new methods of treatment of cardiovascular diseases, investigate new effective and safe drugs and combinations thereof.

Candesartan cilexetil is an angiotensin II receptor antagonist. It is a pro-drug, which converted to the active form candesartan during absorption from the gastrointestinal tract. It is used as a long-term antihypertensive agent [1]. Candesartan cilexetil increases resistance to stress and endurance during exercise in people suffering from hypertension [2]. However, it is shown that candesartan has also a number of side effects, such as dizziness, weakness, headache. High doses of candesartan cilexetil influence the formation of separate subpopulations of cells in bone marrow [3]. Resveratrol, a naturally occurring polyphenol, shows pleiotropic health beneficial effects, including antioxidant, anti-inflammatory, anti-aging, cardioprotective and neuroprotective activities [4–6]. It's found that this substance decreases the synthesis of lipids in liver and eico-

sanoids in leukocytes in animals, inhibits platelet activation/aggregation, decreases the activity of protein kinases, inhibits formation of reactive oxygen species [7].

At present stem cell technologies are widely applied for treatment of different pathologies and also cardiovascular diseases. It is shown that mobilized stem cells and endothelial progenitor cells have the capacity to migrate into the heart muscle and endothelium with the subsequent positive therapeutic effect [8–10].

In recent study we evaluate the effect of candesartan cilexetil, candesartan and safer resveratrol in different dosages and combinations on mobilization of CD117+ stem cells, on the number of apoptotic cells and micronucleated cells and parameters of cell cycle *in vitro*.

Materials and methods. Bone marrow cells, isolated from C57Bl/6 mice were sampled for further experiments. Cells were inoculated into growth medium (90 % of DMEM medium ("Sigma-Aldrich"), 10 % of fetal bovine serum ("HyClone") with addition of 0.1 % antibiotics (Antibiotic-antimycotic solution, "Sigma-Aldrich") at the cell density $10^4/cm^2$ in 6-well plates. This culture was incubated in CO_2-incubator (37 °C, 5 % CO_2) and then candesartan cilexetil, candesartan and resveratrol (we used *trans*-resveratrol) were supplied to the cell culture. The medium was changed every 3-4 days. Cells were removed by 0.25 % trypsin/EDTA solution and washed in 0.1 % PBS buffer. We studied the next doses and combinations of substances: candesartan cilexetil at 1.5 μg/ml dose and 3 μg/ml dose, candesartan at 1.5 μg/ml dose and 3 μg/ml dose, resveratrol at 1, 5, 10, 30 and 50 μg/ml doses, combination of candesartan cilexetil at 1.5 μg/ml and resveratrol at 1, 5, 10, 30 and 50 μg/ml doses, combination of candesartan at 1.5 μg/ml and resveratrol at 1, 5, 10, 30 and 50 μg/ml doses. Flow cytometry method was used for the analysis of the number of CD117+ stem cells. For this purpose, monoclonal antimouse antibodies CD117 (Beckman Coulter, США) were used. The ratio of apoptotic cells and micrinucleated cells and parameters of cell cycle were also studied by flow cytometry method.

The results of the study are presented as mean±SEM. We used Student's t-test to compare 2 samples and one-way ANOVA for multiple comparisons followed by pair-wise comparison.

Results and discussion. We investigated the effect of candesartan cilexetil, candesartan and resveratrol on changes in the number of CD117+ stem cells. Cell surface marker CD117 (or c-kit) is a marker of endothelial progenitor cells, which is a cytokine receptor and KIT gene product.

It was shown that candesartan cilexetil at 1.5 μg/ml dose didn't stimulate generation of CD117+ stem cells *in vitro* as compared to the control. Candesartan cilexetil at 3 μg/ml dose also didn't promoted production of CD117+ stem cells (Table 1). It was demonstrated that candesartan at 1.5 μg/ml and 3 μg/ml doses stimulate the formation of endothelial progenitor cells as shown in the table 1.

Table* 1. The influence of combination of candesartan cilexetil, candesartan and resveratrol on the number of CD117+ cells *in vitro

Samples	The content of CD117+ stem cells, %
1. Control	6,38±0,02
2. Cand. cilex. 3 μg/ml	**3,29**±0,01
3. Cand. cilex. 1.5 μg/ml	**7,64±0,03***
4. Cand. 3 μg/ml	**7,64±0,04***
5. Cand. 1,5 μg/ml	**6,91±0,02***
6. Resv. 1 μg/ml	6,31±0,03
7. Resv. 5 μg/ml	6,37±0,03
8. Resv. 10 μg/ml	6,40±0,02
9. Resv. 30 μg/ml	**8,56±0,02***
10. Resv. 50 μg/ml	**9,93±0,03***
11. Cand. cilex. 1,5 μg/ml and resv. 1 μg/ml	**4,27±0,03***
12. Cand. cilex. 1,5 μg/ml and resv. 5 μg/ml	**4,51±0,04***
13. Cand. cilex. 1,5 μg/ml and resv. 10 μg/ml	6,41±0,03
14. Cand. cilex. 1,5 μg/ml and resv. 30 μg/ml	**8,32±0,04***
15. Cand. cilex. 1,5 μg/ml and resv. 50 μg/ml	**9,88±0,03***
16. Cand. 1,5 μg/ml and resv. 1 μg/ml	**6,97±0,02***
17. Cand. 1,5 μg/ml and resv. 5 μg/ml	**7,43±0,03***
18. Cand. 1,5 μg/ml and resv. 10 μg/ml	**8,10±0,04***
19. Cand. 1,5 μg/ml and resv. 30 μg/ml	**8,98±0,06***
20. Cand. 1,5 μg/ml and resv. 50 μg/ml	**11,21±0,04***

* – comparising with the control ($p<0.05$);Cand. cilex. – candesartan cilexetil;Cand. – candesartan;Resv. – resveratrol.

We found that resveratrol influenced the ratio of endothelial progenitor cells in cell culture. The obtained result was dose-depended. Resveratrol at 1 μg/ml, 5 μg/ml and 10 μg/ml doses didn't increase the amount of CD117+ stem cells in comparison with the control. Application of resveratrol at 30 μg/ml and 50 μg/ml doses significantly increased the number of CD117+ stem cells *in vitro*. The largest increment of the number of endothelial progenitor cells in cell culture was observed in variant with resveratrol at 50 μg/ml dose (Table 1).

It was demonstrated that combination of candesartan cilexetil at 1.5 μg/ml dose and resveratrol at 1 μg/ml, 5 μg/ml and 10 μg/ml doses didn't stimulate the formation of CD117+ stem cells, whereas with resveratrol at 30 μg/ml and 50 μg/ml doses significantly increased the ratio of endothelial progenitor cells in cell culture as compared to the control. It was found that combination of candesartan cilexetil at 1.5 μg/ml dose and resveratrol at 30 μg/ml and 50 μg/ml doses was effective in the mobilization of CD117+ stem cells ($p < 0.05$) (Table 1).

Changing of the count of endothelial progenitor cells under using of candesartan at 1.5 μg/ml with resveratrol at 1, 5, 10, 30 and 50 μg/ml doses was studied. The effect was dose-dependent. The obtained data were also significantly higher than those recorded for individual compounds (Table 1).

The next step was investigation of the number of apoptotic cells under using candesartan, candesartan cilexetil and resveratrol *in vitro.* It was shown that candesartan cilexetil at high dose increased the amount of apoptotic cells in comparison with the control. Candesartan cilexetil at 1.5 μg/ml dose didn't change the number of apoptotic

cells as compared to the control (Table 2). Candesartan at 1.5 μg/ml and 3 μg/ml doses significantly increased the count of studied cells ($p<0.05$). It was found that the number of apoptotic cells didn't change under using resveratrol at 1, 5, 10, 30 and 50 μg/ml doses (Table 2).

Table 2. Cytogenetic parameters and parameters of cell kinetics of bone marrow cells of C57Bl/6 mice under using candesartan, candesartan cilexetil and resveratrol *in vitro*

Samples	The number of apoptotic cells, %	Distribution of cells at the stages of the cell cycle			The number of cells with micronuclei, %
		G_0/G_1, %	S, %	G_2/M, %	
1. Control	2,85±0,11	83,41±1,64	13,53±1,66	3,07±0,23	3,01±0,24
2. Cand. cilex. 3 μg/ml	**3,42±0,19***	83,78±2,05	12,06±0,95	4,16±1,31	3,13±0,25
3. Cand. cilex. 1.5 μg/ml	3,03±0,20	84,33±2,74	11,67±1,74	4,00±1,56	3,04±0,20
4. Cand. 3 μg/ml	**6,85±0,41***	83,49±2,54	13,33±2,32	3,19±0,45	**6,06±0,34***
5. Cand. 1,5 μg/ml	**5,21±0,24***	84,37±2,51	11,87±2,36	3,76±0,47	**4,96±0,12***
6. Resv. 1 μg/ml	2,88±0,13	82,92±3,01	12,74±1,85	4,34±1,25	3,09±0,14
7. Resv. 5 μg/ml	2,90±0,18	83,28±2,79	12,19±2,32	4,54±1,12	2,92±0,24
8. Resv. 10 μg/ml	2,90±0,14	80,76±3,27	14,93±2,47	4,31±0,86	3,11±017
9. Resv. 30 μg/ml	2,87±0,24	82,79±2,25	13,09±2,08	4,12±0,89	3,09±0,19
10. Resv. 50 μg/ml	2,83±0,22	83,50±2,42	13,59±2,19	2,91±0,37	2,94±0,22
11. Cand. cilex. 1,5 μg/ml and resv. 1 μg/ml	2,93±0,21	81,17±3,80	15,76±2,92	3,08±1,12	3,10±0,17
12. Cand. cilex. 1,5 μg/ml and resv. 5 μg/ml	2,91±0,25	84,51±4,17	12,01±3,74	3,49±0,62	3,01±0,25
13. Cand. cilex. 1,5 μg/ml and resv. 10 μg/ml	2,92±0,29	83,95±2,83	12,97±2,25	3,08±0,74	3,10±0,18
14. Cand. cilex. 1,5 μg/ml and resv. 30 μg/ml	2,95±0,29	80,17±5,34	15,84±5,11	3,99±0,56	3,09±0,29
15. Cand. cilex. 1,5 μg/ml and resv. 50 μg/ml	2,91±0,25	79,58±6,22	16,38±5,91	4,04±0,71	3,11±0,18
16. Cand. 1,5 μg/ml and resv. 1 μg/ml	**5,10±0,21***	81,45±3,10	13,72±2,52	4,83±1,46	**5,02±0,16***
17. Cand. 1,5 μg/ml and resv. 5 μg/ml	**5,05±0,26***	80,30±2,89	15,08±2,00	4,62±1,44	**4,85±0,38***
18. Cand. 1,5 μg/ml and resv. 10 μg/ml	**4,26±0,32***	81,14±2,76	14,16±2,59	4,71±1,03	**4,17±0,16***
19. Cand. 1,5 μg/ml and resv. 30 μg/ml	3,37±0,45	83,22±2,12	14,09±1,51	2,69±0,69	3,66±0,19
20. Cand. 1,5 μg/ml and resv. 50 μg/ml	3,12±0,34	81,35±3,81	14,22±3,11	4,43±0,96	3,52±0,36

* – comparising with the control ($p<0.05$);Cand. cilex. – candesartan cilexetil;Cand. – candesartan; Resv. – resveratrol.

It was also recorded that candesartan cilexetil didn't influence the amount of cells with micronuclei, whereas candesartan increased the contents of micronucleated cells as compared to the control result. Resveratrol didn't raise the number of test cells *in vitro* (Table 2).

Combination of candesartan cilexetil and resveratrol didn't change the amount of cells with DNA damage. It was found that resveratrol in the combination with candesartan significantly decreased cytotoxic effect of second one. Resveratrol at 50 μg/ml dose was more effective in the complex (Table 2).

We also investigated distribution of cells at stages of cell cycle. It was shown that studied substances didn't change proliferation of cells, as shown in the Table 2.

Thus, the results obtained by our combined use of antiischemic agents with resveratrol in the primary culture of MSC indicate an increase in the content of immobilized CD117 positive cells. Also in recent years, transplanted MSCs have been intensively used in regenerative medicine. [12]. The transplantation of mesenchymal stromal cells (MSCs) has emerged as an effective strategy to protect against tissue and organ injury [13].According to the ISCT criteria, MSCs must have multipotency to differentiate into somatic cells, including osteocytes, adipose cells, and chondrocytes. MSCs with multilineage potential exist prevalently in almost all tissues, and they are promising cell sources for treating multiple diseases without ethical issues [14] Also date some authors demonstrated that various dosages of resveratrol (1, 5, and 10 mg/kg) significantly decreased myocardial lesions by increasing myocardial AKT expression and decreasing caspase-3 activity during carbon monoxide-induced cardiotoxicity in rats in a dose-dependent manner [15].

Conclusions. It was found that active form candesartan stimulated formation of CD117+ stem cells *in vitro*, whereas pro-drug candesartan cilexetil decreased the number of studied cells, and both substances were cytotoxic. It was shown that resveratrol increased the number of endothelial progenitor cells and was safe for cell culture. Combination of candesartan cilexetil and resveratrol didn't change the number of apoptotic cells and cells with micronuclei. Application of resveratrol with candesartan reduced cytotoxic effect of last one. It should be noted that combinations of candesartan cilexetil with resveratrol and candesartan with resveratrol significantly increased the count of CD117+ stem cells. The obtained data was better when resveratrol was used in higher dosages. These results are important to develop new complex drug to stimulate mobilization of endothelium progenitor cells and stimulate reparative processes.

Список використаних джерел:

1. Zhao D. A Meta-analysis of antihypertensive effect of telmisartan versus candesartan in patients with essential hypertension / D. Zhao, H. Liu, P. Dong // Clin Exp Hypertens, 2019. – 41(1). – 75–79.
2. De Rosa M. Candesartan improves maximal exercise capacity in hypertensives results of a randomized placebo-controlled crossover trial / M.L. de Rosa, M. Chiariello // J. Clin Hypertens, 2009. – 11 (4). – 192–200.
3. Possible mechanism for the anemia induced by candesartan cilexetil (TCV-116), an angiotensin II receptor antagonist, in rats / I. Naeshiro, K. Sato, F. Chatani, S. Sato // Europ J. of Pharmacology, 1998. – 354 (2/3). – 179–187.
4. Adi Y. The therapeutic potential of resveratrol: a review of clinical trials / Y. Adi, L. Berman, A. Rachel et al. // NPJ Precis Oncol., 2017. – 1. – 35.
5. Brisdelli F. Resveratrol: a natural polyphenol with multiple chemopreventive properties / F. Brisdelli, G. D'Andrea, A. Bozzi // Curr. Drug. Metab., 2009 Jul. – 10(6). – 530–546.
6. Cardioprotective effect of resveratrol in a postinfarction heart failure model / A. Riba, L. Deres, B. Sumegi et al. // Oxid. Med. Cell. Longev., 2017. – 2017:6819281. doi: 10.1155/2017/6819281.
7. Resveratrol, a Natural Antioxidant, Has a Protective Effect on Liver Injury Induced by Inorganic Arsenic Exposure / Zhigang Z., Riba A., Deres L. et al. // BioMed Res. Internat. Vol. 2014, Article ID 617202, 7 pages. http://dx.doi.org/10.1155/2014/617202
8. Yan F. Protective effects of resveratrol improve cardiovascular function in rats with diabetes / F. Yan, X. Sun, C. Xu // Exp. Ther. Med., 2018. – 15:1728–1734. doi: 10.3892/etm.2017.5537.
9. Orlic D. Bone marrow cells regenerate infracted myocardium./ Orlic D., Kajstura J., Chimenti S., Jakoniuk I., Anderson S., Li B., Pickel J., McKay R., Nadal-Ginard B., Bodine D., Leri A., Anversa P. // Nature. 2001. – 410 (6829). – 701–705.

10. Orlic D. Stem cells for myocardial regeneration / Orlic D., Hill J., Arai A. // Circulation Research. 2002. – 91. – 1092–1102.

11. Mobilized bone marrow cells repair the infarcted heart, improving function and survival / D. Orlic, J. Kajstura, S. Chimenti et al. // Proc. of the Nat. Acad. of Sci. of the USA, 2001. – 98(18). – 10344–10349.

12. Chenxia Hu. The application of resveratrol to mesenchymal stromal cell-based regenerative medicine / Hu. Chenxia, Li. Lanjuan // Stem. Cell. Res. Therapy, 2019. – Vol. 10, Article number 307.

13. Minimal criteria for defining multipotent mesenchymal stromal cells. / M. Dominici, K. le Blanc, I. Mueller et al. // The internat. soc. for cell. therapy position statement. Cytotherapy, 2006. – 8(4). – 315–317. https://doi.org/10.1080/14653240600855905.

14. Salem H. Mesenchymal stromal cells: current understanding and clinical status / H. Salem, C. Thiemermann // Stem Cells (Dayton, Ohio). 2010. – 28(3). – 585–596. https://doi.org/10.1002/stem.269.

15. Resveratrol represses tumor necrosis factor α/c-Jun N-terminal kinase signaling via autophagy in human dental pulp stem cells / F. Wang, Z. Hu, X. Liu et al. // Arch. Oral. Biol. 2019. – 97. – 116–21. https://doi.org/10.1016/j.archoralbio.2018.10.020.

Reference (Scopus):

1. Zhao D., Liu H., Dong P. A Meta-analysis of antihypertensive effect of telmisartan versus candesartan in patients with essential hypertension. Clin Exp Hypertens 2019;41(1):75-79.

2. De Rosa M., Chiariello M. Candesartan improves maximal exercise capacity in hypertensives results of a randomized placebo-controlled cross-over trial. J. Clin Hypertens. 2009; 11 (4): 192–200.

3. Naeshiro I., Sato K., Chatani F., Sato S. Possible mechanism for the anemia induced by candesartan cilexetil (TCV-116), an angiotensin II receptor antagonist, in rats. Europ J of Pharmacology. 1998; 354 (2/3): 179–187.

4. Adi Y., Rachel A., Maia Y., Marina K. Holz. The therapeutic potential of resveratrol: a review of clinical trials. NPJ Precis Oncol. 2017; 1: 35.

5. Brisdelli F., D'Andrea G., Bozzi A.Resveratrol: a natural polyphenol with multiple chemopreventive properties // Curr Drug Metab. 2009 Jul;10(6):530-46.

6. Riba A., Deres L., Sumegi B., Toth K., Szabados E., Halmosi R. Cardioprotective effect of resveratrol in a postinfarction heart failure model. Oxid. Med. Cell. Longev. 2017;2017:6819281. doi: 10.1155/2017/6819281

7. Zhigang Z., Li Gao., Yanyan C., Jing Jiang., Yan Chen., Huijie Jiang., Hongxiang Yu., Anshan Shan., Baojing Cheng. Resveratrol, a Natural Antioxidant, Has a Protective Effect on Liver Injury Induced by Inorganic Arsenic Exposure. BioMed Research International. Volume 2014, Article ID 617202, 7 pages. http://dx.doi.org/10.1155/2014/617202

8. Yan F., Sun X., Xu C. Protective effects of resveratrol improve cardiovascular function in rats with diabetes. Exp. Ther. Med. 2018;15:1728–1734. doi: 10.3892/etm.2017.5537.

9. Orlic D., Kajstura J., Chimenti S., Jakoniuk I., Anderson S., Li B., Pickel J., McKay R., Nadal-Ginard B., Bodine D., Leri A., Anversa P. Bone marrow cells regenerate infracted myocardium. Nature. 2001; 410 (6829): 701–705.

10. Orlic D., Hill J., Arai A. Stem cells for myocardial regeneration. Circulation Research. 2002; 91: 1092–1102.

11. Orlic D., Kajstura J., Chimenti S., Limana F., Jakoniuk I., Quaini F., Nadal-Ginard B., Bodine D., Leri A., Anversa P. Mobilized bone marrow cells repair the infarcted heart, improving function and survival. Proc. of the Nat. Acad. of Sciences of the USA. 2001; 98 (18): 10344–10349.

12. Chenxia Hu., Lanjuan Li. The application of resveratrol to mesenchymal stromal cell-based regenerative medicine S*tem Cell Research Therapy* 2019 volume 10,Article number: 307

13. Dominici M., Le Blanc K., Mueller I., Slaper-Cortenbach I., Marini F., Krause D., Deans R., Keating A., Prockop D., Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The international society for cellular therapy position statement. Cytotherapy. 2006;8(4):315–7. https://doi.org/10.1080/14653240600855905.

14. Salem H., Thiemermann C. Mesenchymal stromal cells: current understanding and clinical status. Stem Cells (Dayton, Ohio). 2010;28(3):585–96. https://doi.org/10.1002/stem.269.

15. Wang F., Hu Z., Liu X., Feng J., Augsburger R., Gutmann J., Glickman G. Resveratrol represses tumor necrosis factor α/c-Jun N-terminal kinase signaling via autophagy in human dental pulp stem cells.

16. Arch Oral Biol. 2019;97:116–121. https://doi.org/10.1016/j.archoralbio.2018.10.020.

Надійшла до редколегії 04.10.19
Отримано виправлений варіант 04.11.19
Підписано до друку 04.11.19

Received in the editorial 04.10.19
Received revised version on 04.11.19
Signed in the press on 04.11.19

А. Бєляєва, стажер, Л. Гарманчук, д-р біол. наук, проф.
Київський національний університет імені Тараса Шевченка, Київ, Україна

ЗМІНА ВМІСТУ CD117 + СТОВБУРОВИХ КЛІТИН, ЦИТОГЕНЕТИЧНИХ ТА ЦИТОКІНЕТИЧНИХ ПАРАМЕТРІВ ПРИ ВИКОРИСТАННІ КАНДЕСАРТАНУ, КАНЦЕЗАРТАНУ, ЦИЛЕКСЕТИЛУ ТА РЕСВЕРАТРОЛА *IN VITRO*

Через наростання серцево-судинних патологій актуальним є вивчення нових ефективних і безпечних препаратів та їхні комбінації. Кандесартан цилексетил, антагоніст рецептора ангіотензину II, є попередником активної форми кандесартану. Однак ці протишемічні препарати проявляють цитотоксичну дію, впливаючи на антиоксидантну систему. Тому для запобігання цитотоксичного ефекту є необхідність використання антиоксидантів. Вивчити вплив кандесартану цилексетилу, кандесартану та ресвератролу в різних дозах та комбінаціях на мобілізацію стовбурових клітин CD117 + із стовбурових клітин кісткового мозку, на кількість апоптотичних та мікроядерних клітин та параметри клітинного циклу in vitro. Клітини кісткового мозку, виділені з мишей C57Bl/6, були відібрані для експериментів. Після інкубації протягом 2 діб із засобами в різних концентраціях та комбінаціях визначали біологічні характеристики стовбурових клітин. Протокову цитометрію використовували для аналізу кількості CD117+ стовбурових клітин, співвідношення апоптотичних клітин, клітин з мікроядрами і параметрів клітинного циклу, після інкубації первинної культури МСК з кандесартан цилексетилом кандесартаном і ресвератролом in vitro. Було встановлено, що кандесартан цилексетил і кандесартан у комбінації з ресвератролом стимулюють мобілізації CD117 + стовбурових клітин від 1,2 раза до майже в 2 рази порівняно з контролем і в 1,5–2,5 порівняно з цитостатиками в окремому застосуванні. Кандесартан цилексетил і кандесартан проявляли цитотоксичну дію, тоді як в комбінації з ресвератролом цитотоксичний ефект знижувався. Таким чином, застосування антиішемічні засоби кандесартан цилексетил і кандесартан у комбінації з ресвератролом збільшували вміст CD117+ стовбурових клітин і не був цитотоксичним.

Ключові слова: кандесартан цилексетил, кандесартан, ресвератрол, CD117 + стовбурові клітини, апоптотичні клітини, мікроядра та параметри клітинного циклу.

А. Беляева, стажер, Л. Гарманчук, д-р биол. наук, проф.
Киевский национальный университет имени Тараса Шевченка, Киев, Украина

ИЗМЕНЕНИЕ СОДЕРЖАНИЯ CD117 + СТВОЛОВЫХ КЛЕТОК, ЦИТОГЕНЕТИЧЕСКИХ И ЦИТОКИНЕТИЧНИХ ПАРАМЕТРОВ ПРИ ИСПОЛЬЗОВАНИИ КАНДЕСАРТАНА, КАНЦЕЗАРТАНУ, ЦИЛЕКСЕТИЛА И РЕСВЕРАТРОЛА *IN VITRO*

Из-за нарастания сердечно-сосудистых патологий актуальным является изучение новых эффективных и безопасных препаратов и их комбинации. Кандесартан цилексетила, антагонист рецептора ангиотензина II, является предшественником активной формы кандесартана. Однако эти противоишемические препараты проявляют цитотоксическое действие, влияя на антиоксидантную систему. Поэтому для предотвращения цитотоксического эффекта необходимо использование антиоксидантов. Цель статьи изучить влияние кандесартана цилексетила, кандесартана и ресвератрола в различных дозах и комбинациях на мобилизацию стволовых клеток CD117 + из стволовых клеток костного мозга, на количество апоптотических и микроядерных клеток и на параметры клеточного цикла in vitro. Клетки костного мозга, выделенные из мышей C57Bl / 6, были отобраны для экспериментов. После инкубации в течение 2 суток со средствами в различных концентрациях и сочетаниях определяли биологические характеристики стволовых клеток. Проточную цитометрию использовали для анализа количества CD117 + стволовых клеток, соотношение апоптотических клеток, клеток с микроядра и параметров клеточного цикла, после инкубации первичной культуры МСК с кандесартан цилексетилом кандесартаном и ресвератролом in vitro. В результате было установлено, что кандесартан цилексетил и кандесартан в сочетании с ресвератролом стимулируют мобилизации CD117 + стволовых клеток от 1,2 раза до почти в 2 раза по сравнению с контролем и в 1,5–2,5 по сравнению с цитостатиками. Кандесартан цилексетила и кандесартан проявляли цитотоксическое действие, тогда как в комбинации с ресвератролом цитотоксический эффект снижался. Таким образом, применение антиишемических средств кандесартана цилексетила и кандесартана в сочетании с ресвератролом увеличивало содержание CD117 + стволовых клеток и не было цитотоксическим.

Ключевые слова: кандесартан цилексетил, кандесартан, ресвератрол, CD117 + стволовые клетки, апоптотические клетки, микроядра и параметры клеточного цикла.