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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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THERAPEUTIC USE OF RESVERATROL IN THE TREATMENT OF NEUROLOGICAL AND ENDOCRINOLOGICAL PATIENTS

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Abstract.

The article represents the data characterizing the use of resveratrol in the treatment of various diseases, including endocrinological and neurological. It was shown that resveratrol is widely used in the treatment of various diseases due to its ability to actively suppress the inflammatory process. At the same time, in autoimmune diseases resveratrol inhibits the function of the entire population of T-cells, but when it comes to the neoplastic process, it only inhibits the activity of a subpopulation of T-cells (Treg). Thus, resveratrol can be recommended in the treatment of any diseases associated with the activation of the T-cell immunity.

Key words. Resveratrol, T-lymphocytes, B-lymphocytes, immunity, apoptosis, obesity, neurodegenerative diseases, autoimmune diseases, tumors.

Molecular mechanisms of interaction between resveratrol and T-lymphocytes.

The adaptive immune response is much more permanent and depends on the responses of T- and B-lymphocytes interacting with antigen-presenting cells (APC) in peripheral lymphoid tissue over several days and weeks. But as soon as adaptive immune responses arise, Th1 and Th17, as well as subpopulations of effector T-helper cells, migrate from the lymphoid tissue into the bloodstream, infiltrate infected areas and produce their own cytokines that increase the activity of macrophages and neutrophils. Both innate and adaptive immunity control inflammation and develop an identification friend/foe system. During maturation, the immature populations of T cells acquire the ability to express antigen-specific receptors that recognize their own and foreign macromolecules. In the thymus, developing T-lymphocytes with T-cell receptors (TCR) are able to recognize high-affinity peptides, while the proteins of major histocompatibility complex (MHC) undergo apoptosis if the recognition is negative. As a protection from entry of autoreactive T cells into peripheral lymphoid tissue, regulatory T cells (Treg) are naturally secreted (nTregs). This occurs during the central development of T cells in the thymus. In the phase of active immune response, they transform into peripheral cells (iTregs). Dysfunctions of immune tolerance are rare. But when the processes of central and/or induced peripheral tolerance are severely disrupted, autoimmune diseases can occur. Abnormal T cell activation is involved in many autoimmune diseases such as insulin-dependent diabetes, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. Taking into consideration that resveratrol can suppress T-cell activation and reduce cytokine production, it is likely that it could prevent the progression of the autoimmune disease. So, in a series of experiments on mice treated with resveratrol, a significant decrease in the percentage of autoimmune diseases occurrence was registered. Histological analysis showed that the number of infiltrated cells was reduced in mice treated with resveratrol compared to control mice. This observation showed that resveratrol can prevent development of autoimmune diseases such as insulin-dependent diabetes and multiple sclerosis [1-5].

Th17 cells are subpopulation of CD4+ T cells, their development depends on signals mediated by IL-6, TGF-β, IL-21, and IL-23, as well as induction of the lineage-determining transcription factor, orphan retinoic acid-related nuclear receptor (RORγT). Unlike Th1 and Th2 cells, which become secretory cells after differentiation, Th17 cells retain their stem cell-like properties, allowing them to persist for a long time while maintaining the ability to produce functionally divergent progeny when reactivated by antigen. Moreover, Th17 cells are key initiators of proinflammatory responses by recruiting neutrophils and macrophages to damaged tissues, and through the production of IL-17 play an important role in host protection from infection by extracellular pathogens. An additional cytokine produced by Th17 is IL-23, which controls the survival and maintenance of the Th17 phenotype and is responsible for the crosstalk between innate and adaptive immunity. Furthermore, Th17 cells produce IL-22, which, just like IL-17, is beneficial in many infectious and inflammatory diseases. However, synergistically with IL-17, it may play an important role in the development of the disease due to its pro-inflammatory properties. Th17 cells are strong inducers of chronic inflammatory responses and play an important role in autoimmune diseases. Resveratrol can modulate the course of autoimmune diseases, significantly reducing the activity of the progression of the process. The protective effects of resveratrol in autoimmune diseases are also associated with a decrease in the number of Th17 cells and the production of IL-17 in the draining lymph node.

Resveratrol protection from experimental autoimmune encephalomyelitis (EAE) is not associated with a decrease in IL-17+ T cells, but with an increase in IL-17+/IL-10+ T cells and CD4-IFN-γ+, as well as suppressed expression of IL-6 and IL-12/23 p40 by macrophages. Interestingly enough, the function of resveratrol on Treg cells increases in response to T cell activation. It was found that the number of CD4+, CD25+ and Foxp3+ cells was significantly reduced in total splenocytes as well as in tumor tissues of mice injected with HS-1793, also the production of Treg inducing TGF-β showed a similar pattern. Resveratrol administration suppresses CD4+ and CD25+ populations among CD4+ cells, suppresses TGF-β

secretion, and enhances IFNγ expression in CD8+ T cells both ex vivo and in vivo, resulting in immune stimulation. Other results have shown that resveratrol reduces the expression of CD28 and CD80 and increases the production of IL-10, but does not affect the percentage of CD4+, CD25+ and Treg cells [6-8].

It should be noted that studies describing the effects of resveratrol on T cells and its specific molecular mechanisms are inconsistent in some cases. Thus, Sirt1 is involved in the tolerance of peripheral T cells, deletion of Sirt1 in T cells can induce T cell hyperactivation and lead to spontaneous autoimmune disease. In a series of experiments, resveratrol has been shown to inhibit T-cell activation and the production of antigen-specific antibodies in vivo. Inhibition of T cell activation by resveratrol is mediated by Sirt1. This is demonstrated by the observation that the inhibitory effect of resveratrol on T cell activation disappears in T cells suppressed by Sirt1. Moreover, Sirt1 expression was heightened in activated T cells and was higher in resveratrol-treated T cells than in naive T cells. Other data have demonstrated that resveratrol maintains T cell tolerance in mice by regulating the function of Sirt1, which inhibits the activation of autoreactive T cells in the thymus [1,9]. The mechanism by which resveratrol modulates T-cell activation has been partially revealed. Resveratrol increased Sirt1 acetylase activity for c-Jun, but not for activated T cell nuclear factor (NFAT) and NFκb in T cells. After T-cell activation, c-Jun moves into the nucleus. However, the effect of c-Jun was suppressed in T cells treated with resveratrol. Thus, resveratrol can inhibit T cell activation by increasing Sirt1 expression and Sirt1 deacetylase activity on c-Jun, what blocks c-Jun translocation to the nucleus. In addition, resveratrol inhibits protein kinase Cθ in T-lymphocytes of peripheral blood in a rat liver transplant model [7,10].

It has been proven that obesity adversely affects cellular immunity and increases the risk of infectious diseases. In fact, obesity dysregulates T cell generation and function as well as the ability to stimulate a peripheral T cell-mediated protective immune response and impairs wound healing. Several studies in mice have showed how resveratrol can reverse pernicious effects of T cells in diet-induced obesity. Interestingly, resveratrol as a high fat dietary supplement (HFD) reduces oxidative stress effects, supressing inflammatory genes expression and increasing Treg levels via aryl hydrocarbon receptor activation in mice with HFD induced obesity [1,2,11]. Besides, resveratrol reduces both blood glucose and plasma insulin level and increases the percentage of CD3+, CD4+/CD3+, CD8+ subsets in the C57BL/6 mice model with obesity. The received data suggest that resveratrol maintains glucose homeostasis through activation of phosphatidylinositol 3'-kinase (PI3K) and SIRT1 signaling pathways.

It is particularly remarkable that decrease in the ratio of CD3+, CD4+/CD3+, CD8+ is usually associated with malignancy or virus attack, such as HIV infection. A similar phenomenon was observed in a series of experiments with mice model with systemic lupus erythematosus. This suggested that resveratrol acts in these terms by inducing CD3+, CD4+/CD3+, CD8+. Additionally, resveratrol activates antioxidant enzyme expression mediated by the nuclear factor erythroid-2-related factor 2 (Nrf2) signaling pathway and reduces inflammation by protecting from oxidative damage and T-lymphocyte-associated chronic inflammatory response in the development of HFD-induced obesity [2,6].

Molecular effects of resveratrol and natural killer cells (NK cells) interaction.

It is known that NK cells make up about 15% of all circulating lymphocytes and are capable to lyse cancer cells in vitro without prior immune sensitization. Their main significance lies in the early defense of the host from both allogeneic and autologous cells after viral, bacterial, or parasitic infections, or against tumor cells. NK cells express various biologically active components: PRRs such as TLRs, NLRs (nucleotide oligomerization domain) and RLRs (retinoic acid gene I (RIG-I) RIG-I-like receptors). They respond to PAMPs (conservative pathogen-associated molecular structures) in a suitable environment in the presence of cytokines such as IL-2, IL-12, IL-15, or IL-18. Therefore, activated NK cells release IFN-γ, GM-CSF, TNF-α or cytotoxic granules directed to the target cell. NKs kill target cells through a variety of mechanisms. Firstly, NK cells form immune synapses. Right after they release cytoplasmic granules, organelles containing perforin (Prf1), a member of saposin-like protein family granulysin, and serine proteases such as granzyme B (GzmB) to lyse several procaspases that trigger apoptosis in the target cell. Additionally, expression of tumor necrosis factor (TNF) family members such as FAS ligand (FASL), TNF and TNF-associated apoptosis inducing ligand (TRAIL) induces tumor cell apoptosis upon formation of immune synapses. Another mechanism of killing target cells is the secretion of effector cytokines such as IFN-γ, IL-5, IL-10, IL-13, and GM-CSF after reaching certain stages of NK cell differentiation. NK cells also secrete diverse chemokines including CC motif chemokine ligand (CCL) and its varieties such as CCL2, CCL3, CCL4, CCL5, monocyte chemoattractant protein (MCP-1), macrophage inflammatory protein (MIP-1α) and (MIP- 1β), RANTES, XC chemokine motif ligand 1 (XCL1, lymphotactin), and IL-8. NK that interacts with other immune cells such as dendritic cells in areas of inflammation modulate the innate and adaptive immune response and promote T-cell response against tumors. Their ability to kill malignant cells depends on stimulation of two major structural classes of receptors on the surface of NK cells, such as C-type lectin-like family receptors and killer cell immunoglobulin-like receptors (KIRs), which inhibit and/or activate signaling. Some human activating receptors, such as various KIRs or natural cytotoxicity receptors (NCRs) such as NKp30, NKp44, NKp46, and NKp80, activate the signal transmission through protein tyrosine kinase dependent pathways. To prevent the activation of NK cells, receptors are located on the surface of the inhibitor, similar to various KIRs, which act through protein tyrosine phosphatase-dependent pathways. Resveratrol has a direct effect on the killing ability of NK cells and also affects other immune cells such as CD8+ and CD4+ T cells. Resveratrol has therapeutic potential in increasing NK activity against aggressive cellular leukemias and lymphomas by inhibiting constitutively active signaling transducers and activators of

transcriptional signaling 3 (STAT3). The ability of NK cells to kill was discovered in immortalized human myelogenous leukemia K562 cells. The cytotoxic activity of NK cells was enhanced by low concentrations of resveratrol, while high resveratrol concentrations supressed it [2,9,12].

Other results [6,13] demonstrated suppression of viability and increased apoptosis of NK cells upon incubation with high concentrations of resveratrol, while low concentrations induced upregulation of NKG2D and IFN-γ and increased killing of NK cells against K562 leukemia target cells. These data suggest that resveratrol has a dose-dependent biphasic effect, which is caused by stimulation of cell apoptosis through caspase signaling pathways in high concentration ranges. This was confirmed by a significant decrease in the number of apoptotic/necrotic cells after pretreatment with the caspase inhibitor z-VAD-FMK. In addition, this study showed a higher cytotoxic sensitivity of Jurkat cells, a human lymphoblastoid T cell line, to resveratrol. A similar dose-dependent increase in cytotoxic NK cell killing activity was also observed in tumor cell lines derived from solid tumors such as HepG2 and A549 cells after prior stimulation of immortalized NK cells (NK-92 cells) with low concentrations of resveratrol. There is also evidence that in NK-92 cells resveratrol treatment induces ERK-1/2 and JNK phosphorylation and dose-dependent activation of perforin expression. An increase in NK cell activity with a subsequent anti-cancer effect was observed in a study evaluating anti-infective properties of resveratrol in a mouse model of acute pneumonia. The resveratrol group showed increased alveolar macrophage infiltration, increased NK cell activity, decreased bacterial load in the lungs, and decreased mortality. Notably, isolated rat spleen NK cells pretreated with resveratrol showed increased killing efficiency against YAC-1 target cells. Resveratrol treatment has been shown to render promyeloblastic leukemia KG-1a cells susceptible to cytokine-induced killer-mediated cytolysis by increasing cell surface expression of natural killer group 2, member D (NKG2D) ligands, DR4 receptor and downregulation of cell surface expression of DcR1 in KG-1a cells and activation of TNF-related apoptosis-inducing ligand (TRAIL) [7,14-17].

Similar results were obtained with LNCaP human prostate adenocarcinoma cells and TRAIL-resistant PC-3 prostate cancer cells, which, after treatment with resveratrol, increased surface expression of DR4 and DR5. Also, there were observed dose-dependent activation of caspase-3 in response to treatment with resveratrol and activation of caspase-8 in response to combination of resveratrol and TRAIL [9,11,12]. Human 1205 LU metastatic melanoma cells show resveratrol-dependent hypersensitivity to TRAIL by downregulating anti-apoptotic proteins of cellular FLICE-like inhibitory protein (cFLIP) and Bcl-xL. Additionally, resveratrol sensitizes other types of cancer cells such as pancreatic, breast, colon, T-cell leukemia, neuroblastoma, melanoma, medulloblastoma and glioblastoma to TRAIL-induced apoptotic cell death. Resveratrol is also able to increase expression of CD95L on HL60 human leukemia cells and T47D breast carcinoma cells, promoting the triggering of signal-dependent apoptosis by NK cells. Due to aggregation of tumor cells and platelets, circulating tumor cells coated with aggregated platelets can escape immune response, promoting the occurrence of metastases. Cancer cells can activate platelets and their aggregation, which correlates with their metastatic potential. There is evidence of an association between platelet aggregation and cancer cell susceptibility to NK-mediated lysis. Remarkably, resveratrol inhibits platelet aggregation by reducing the gpIIb/IIIa integrin on the platelet membrane, which acts as a fibrinogen receptor involved in clot formation and creates "bridges" between platelets. Resveratrol reduces the production of TxA2, which activates platelets and thereby exacerbates aggregation by inhibiting COX1-dependent pathways [6,18-20].

Conclusion.

Thus, the represented data indicate that resveratrol can be used in the treatment of inflammation, caused by T-cell activation, and other diseases associated with T-cells. It has been proven that resveratrol regulates T-cell activation in a bidirectional way: in autoimmune disease model, it performs an inhibitory function, while in the tumor model, it reduces the inhibitory function of Treg, reducing tumor growth.

REFERENCES

1. Kataria R, Khatkar A. Resveratrol in Various Pockets: A Review. Curr Top Med Chem. 2019;19:116-122.
2. Pyo IS, Yun S, Yoon YE, et al. Mechanisms of Aging and the Preventive Effects of Resveratrol on Age-Related Diseases. Molecules. 2020;25:4649.
3. Ramírez-Garza SL, Laveriano-Santos EP, Marhuenda-Muñoz M, et al. Health Effects of Resveratrol: Results from Human Intervention Trials. Nutrients. 2018;10:1892.
4. Rintz E, Pierzynowska K, Podlacha M, et al. Has resveratrol a potential for mucopolysaccharidosis treatment? Eur J Pharmacol. 2020;888:173534.
5. Shaito A, Posadino AM, Younes N, et al. Potential Adverse Effects of Resveratrol: A Literature Review. Int J Mol Sci. 2020;21:2084.
6. Springer M, Moco S. Resveratrol and Its Human Metabolites-Effects on Metabolic Health and Obesity. Nutrients. 2019;11:143.
7. Yang X, Jiang T, Wang Y, et al. The Role and Mechanism of SIRT1 in Resveratrol-regulated Osteoblast Autophagy in Osteoporosis Rats. Sci Rep. 2019;9:18424.
8. Yan Y, Yang H, Xie Y, et al. Research Progress on Alzheimer's Disease and Resveratrol. Neurochem Res. 2020;45:989-1006.
9. Huang DD, Shi G, Jiang Y, et al. A review on the potential of Resveratrol in prevention and therapy of diabetes and diabetic complications. Biomed Pharmacother. 2020;125:109767.
10. Silva P, Sureda A, Tur JA, et al. How efficient is resveratrol as an antioxidant of the Mediterranean diet, towards alterations during the aging process? Free Radic Res. 2019;53:1101-1112.
11. Na JI, Shin JW, Choi HR, et al. Resveratrol as a Multifunctional Topical Hypopigmenting Agent. Int J Mol Sci. 2019;20:956.
12. Jardim FR, de Rossi FT, Nascimento MX, et al. Resveratrol and Brain Mitochondria: a Review. Mol Neurobiol. 2018;55:2085-2101.
13. Song YJ, Zhong CB, Wu W. Resveratrol and Diabetic Cardiomyopathy: Focusing on the Protective Signaling Mechanisms. Oxid Med Cell Longev. 2020;2020:7051845.

14. Hou CY, Tain YL, Yu HR, et al. The Effects of Resveratrol in the Treatment of Metabolic Syndrome. Int J Mol Sci. 2019;20:535.
15. Kim OY, Chung JY, Song J. Effect of resveratrol on adipokines and myokines involved in fat browning: Perspectives in healthy weight from obesity. Pharmacol Res. 2019;148:104411.
16. Li QS, Li Y, Deora GS, et al. Derivatives and Analogues of Resveratrol: Recent Advances in Structural Modification. Mini Rev Med Chem. 2019;19:809-825.
17. Moore A, Beidler J, Hong MY. Resveratrol and Depression in Animal Models: A Systematic Review of the Biological Mechanisms. Molecules. 2018;23:2197.
18. Vinokurova E.A, Ismailova D.H, Hvoshina T.N. New possibilities of personalized menopausal resveratrol phytotherapy. Doctor.Ru Gynecology. 2021;20:25-29.
19. Galiniak S, Aebisher D, Bartusik-Aebisher D. Health benefits of resveratrol administration. Acta Biochim Pol. 2019;66:13-21.
20. Farzaei MH, Rahimi R, Nikfar S, et al. Effect of resveratrol on cognitive and memory performance and mood: A meta-analysis of 225 patients. Pharmacol Res. 2018;128:338-344.