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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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EFFICACY AND SAFETY OF SILVER NANOCOMPOSITES ON RIFAMPICIN-RESISTANT M. TUBERCULOSIS STRAINS

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Abstract.

Background: Control of rifampicin-resistant tuberculosis (RR-MTB) requires novel technologies for restoring the anti-TB efficacy of priority drugs. We sought to evaluate the ability of nanotechnology application in the recovery of the anti-tuberculosis efficacy of rifampicin.

Methods: Nanocomposite- standard dose of rifampicin and 20 nm silver nanoparticles (AgNPs) suspension solution of 6 different concentrations: 0.25%; 0.5%; 1%; 2.5%; 5%; and 10%, were supplemented to 70 rifampicin-resistant mycobacterium tuberculosis (RR-MTB) isolates. The control arm consisted of 35 RR-MTB isolates and AgNPs suspension with identical concentrations. The inhibitory effect of nanocomposites was evaluated by MTB growth rate using the BACTEC™ MGIT 960™. The safety assessment of single-use AgNPs was conducted in experimental animals.

Results: The suppression process of AgNPs on RR-MTB isolates started with 2,5% nanocomposite solution application and full suppression was achieved in 5% and 10% nanocomposite solutions. A standard dose of rifampicin and a 2.5% solution of AgNPs increased the minimal inhibitory effect on RR-MTB by 10% (total 80%) vs the isolated use of a 2.5% solution of AgNPs (70%). An experiment on animals revealed the complete safety of a single injection of ultra-high doses of AgNPs.

Conclusion: The study showed the potentiating effect of AgNPs in overcoming the resistance of MTB to rifampicin providing a scientific basis for further research.

Key words. Rifampicin-resistance, silver nanoparticles, growth inhibition, experimental animals.

Introduction.

Multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) is still a challenge for clinicians and public health authorities [1,2]. New and repurposed drugs have significantly improved treatment efficacy in patients with MDR/RR-TB, increased adherence [3], and decreased lost to follow-up rate. Also, active drug safety monitoring provided appropriate prevention, detection, and management of adverse events causing (leading to) radical improvement in treatment outcomes. Despite the encouraging data, the overall rate of favorable outcomes of MDR/RR-TB treatment is only 59% and much lower in patients with higher resistance profiles [1,4].

Several publications have appeared in the scientific medical literature regarding the developing resistance of *M. tuberculosis* (MTB) to new and repurposed drugs in recent years [5-8] and hence, we may face a drug-resistant TB crisis again [9]. To prevent the process, it is necessary to expand and update the drug base for the treatment of resistant tuberculosis constantly, which can be performed both through the synthesis of new anti-tuberculosis drugs and restoring the anti-TB efficacy of priority drugs using stability inhibitors. In the quest for more efficient anti-mycobacterial drugs that are able to overcome the "classical" issues discussed above and partially responsible for the global TB status - recently the nanoparticles gained special attention.

Nanoparticles have the ability to overcome existing mechanisms of bacterial drug resistance, such as decreasing absorption, enhancing drug efflux from microbial cells, forming bio accumulators, and fighting intracellular infection pathogens. Applying nanoparticles directly to the injury sites may allow the transportation of high concentrations of antimicrobial drugs while maintaining the optimal dose of the drug for the body; thus, overcoming the mechanisms of antibiotic resistance and reducing side effects [10].

Scientific studies have established the enhanced biocidal properties of silver, its physiological role in the normal metabolism of human substances, and the functioning of the immune system. It is possible to use small concentrations of silver in the nano-size range with multiple enhancements of biocidal properties. Only a few scientific publications are presenting the results of studies on the antibacterial and immunobiological properties of silver nanoparticles (AgNPs), the bactericidal effect of AgNPs on drug-resistant strains of various diseases [11-18], as well as the peculiarities of AgNPs action in healthy and experimental animals infected with MTB, taking into account the administration routes of nanoparticles into the body [19-23]. "In vitro" studies showed that while using a combination of AgNPs and isoniazid (in cases of proven resistance to isoniazid), there was a complete or significant inhibition of the growth of MTB [22]. There is scarce data in the scientific literature regarding the usage of AgNPs and rifampicin (RIF) on RR-TB [24,25].

The study aimed to investigate the in vitro restoration of the anti-TB efficacy of RIF using AgNPs. The main objectives were: 1) "In vitro" study of the inhibitory effect of suspensions containing different concentrations of AgNPs on RR *M. tuberculosis* (RR-MTB) strains; 2) "In vitro" study of the effectiveness of the standard dose of RIF and nanocomposite with different concentrations of AgNPs to investigate the presence of inhibitory effect on RR-MTB strains; 3) Evaluation of the safety of single administration with high and ultra-high doses of AgNPs in experimental animals.

Materials and Methods.

Study Design and Settings: We conducted an experimental study, and the bacteriological part of the research was performed in the National Reference Laboratory (NRL) of the National Center for Tuberculosis and Lung Diseases (NCTLD), Tbilisi, Georgia. The safety of AgNPs was studied on experimental animals at the Alexander Natishvili Institute

of Morphology, Ivane Javakhishvili Tbilisi State University. The study was approved by the Institutional Review Boards of the NCTLD and the Alexander Natishvili Institute of Morphology. Experiments were conducted in compliance with current international standards (The Declaration of Helsinki Convention for the Use and Care of Animals, 1964; Directive 2010-63-EU on the Protection of Animals Used for Scientific Purposes, 2010; Guide for the Care and Use of Laboratory Animals, 8th ed., 2011). Euthanasia was performed according to IACUC guidelines. (https://animal. research. uiowa.edu/ iacuc - guidelines-euthanasia).

Statistical analysis was performed using IBM SPSS Statistics software (Version 29.0.2.0). The chi-square (X^2) test was used to compare the effect of two different groups: AgNPs alone and R/AgNPs analyzing two categorical variables for each group: growth increase vs suppression.

Study Procedures.

"In Vitro" Inhibitory Study of Silver Nanoparticles (AgNPs) on RR-MTB Strains.

An "in vitro" experiment was carried out on 105 cultures of RR-MTB, which were obtained in clinical conditions from the sputum of patients with pulmonary tuberculosis. The experiment was conducted on liquid nutrient soils in a BACTEC™ MGIT 960™ system. For the experimental study AgNPs (AgNPs of 20nm) were purchased from "Hongwu International Group Ltd" (https://www.hwnanomaterial.com). High-frequency ultrasonic homogenizer, disruptor, and disintegrator (Ultrasonic Processor FS-1800N (China) was used to characterize the nanoparticle suspension size of AgNPs and was carried out on an electron microscope.

The experiment was conducted in 2 groups. In the sensitivity testing kit, in one case, only silver solution in the amount of 100 µl (with different concentrations) was applied to the samples, and in another case, the silver solution of the appropriate concentration was added along with standard dose of RIF.

To determine the growth inhibitory effect of MTB - 6 concentrations of AgNP solution on preselected RR isolates were studied: 0.25%, 0.5%, 1%, 2.5%, 5%, and 10%. Initially, 105 cultures of RR MTB were taken. Six (0.25%, 0.5%, 1.0%, 2.5%, 5%, 10%) types of suspensions were prepared from the powder of nanoparticles containing 99.9% silver: In each case 100 ml of injection water was supplemented to 0.25 g, 0.5 g, 1.0 g, 2.5 g, 5.0 g, and 10 g of silver nanoparticle powder, respectively. In all six groups, injection water was supplemented to the silver nanoparticle powder separately and centrifuged for 5 minutes. In the obtained suspension, the silver powder precipitated fast. In order to stabilize the suspension, it was placed in a homogenizer, disruptor, disintegrator and affected with 1800 W high-frequency ultrasound for 2 min three times.

For the evaluation of the inhibitory activity of AgNPs, the solution of AgNPs with an appropriate concentration was added to 35 test tubes (in the set of susceptibility test tubes). Each concentration of 0.25%, 0.5%, 1%, 5% and 10% solution were added to 5 test tubes and 2.5% solution to 10 test tubes. Evaluation of the inhibitory activity of different concentrations of AgNPs and RIF (R/AgNPs) composite was conducted on susceptibility test tubes with 6 different concentrations of silver solution (0.25%, 0.5%, 1%, 2.5%, 5%, 10%) with the supplement of a standard dose of RIF (each concentration of AgNPs solution with RIF was applied to 10 test tubes, except for the 2.5% concentration of the silver solution, applied to 20 test tubes with RIF (70 test tubes in total).

An "in vitro" experiment was carried out on cultures of RR-MTB, which were obtained in clinical conditions from the sputum of patients with pulmonary tuberculosis. The experiment was conducted on liquid nutrient soils in a BACTEC™ MGIT 960™ system. The BACTEC™ MGIT 960™ device is used for rapid detection of MTB in a test sample. MTB growth is detected by fluorescence, which increases in proportion to the decrease of oxygen in the test tube. The device emits fluorescence using ultraviolet rays and a special computer algorithm. The BACTEC™ MGIT 960™ device is also used to determine the sensitivity to anti-TB drugs, which allows interpretation of the results within 4-13 days.

Testing of susceptibility in anti-TB drugs using the BACTEC™ MGIT 960™ device is based on the same principle, which involves the detection of mycobacterial growth by fluorescence. The test is carried out with a set of MGIT 7 ml test tubes, necessarily including a control test tube (without drug) and test tubes where the drug is supplemented with an already known concentration. The device automatically and continuously monitors the increase process of fluorescence in the drug and control tubes. If the drug is active against MTB (an isolate is sensitive), growth of inhibition and suppression of fluorescence occur in the tubes including drugs, while in the control tube an increase of MTB growth and fluorescence is detected. If the isolate is resistant, growth of MTB and corresponding increase of fluorescence is observed in both control and tubes with drugs. The BACTEC™ MGIT 960™ system automatically monitors the growth process in sensitive or resistant samples and interprets results accordingly.

The final evaluation of the inhibitory activity of the study result was performed based on the inhibition of MTB growth, supplemented with the experimental suspension to the test tubes.

The Safety Study of a single-use of silver nanoparticles (AgNPs) in experimental animals.

At the first stage of the safety study with AgNPs, high and ultra-high doses of AgNPs were used in the experiment conducted on test animals (Table 1).

To evaluate the safety of 2.5% and 5% suspensions of AgNPs, white mogrel rats (of body weight 250-300 g.) were used in experimental studies. Animals were housed under standard vivarium conditions (temperature 22±2ºC, humidity 50%±5%, 12/12h light/dark cycle, free access to water and food) in polypropylene cages covered with stainless steel mesh (5 rats per cage). 8-12-week-old rats were randomly divided into four groups: five rats per group (2 female and 3 male). Female rats were non-pregnant and nulliparous. Suspensions of AgNPs (2.5% and 5%) were administered once orally using a special 2.5 ml food needle to the first and third groups; 5 ml - to the second and fourth groups, and the control group received physiological saline. Before administering the control suspension, the laboratory animals were food-restricted for 24 hours but had free access to water.

Table 1. *Study of the safety of silver nanoparticle suspension with the single administration, weight of control and experimental group rats.*

Rat	Rat weight (g)				
	Control Group	AgNPs 2,5% 1000 mg/kg	AgNPs 2,5% 5000 mg/kg	AgNPs 5% 1000 mg/kg	AgNPs 5% 5000 mg/ kg
Female	250	250	240	240	240
Female	260	250	240	250	240
Male	300	300	300	290	280
Male	270	270	260	260	250
Male	300	300	290	300	280

Abbreviations: g, gram; AgNPs - silver nanoparticles.

Group I - Rats received a single dose of 2.5% suspension of AgNPs: 2.5 ml/100 g orally for 24 hours.

Group II - Rats received a single dose of 2.5% suspension of AgNPs: 5 ml/100 g orally for 24 hours.

Group III - Rats received a single dose of 5.0% suspension of AgNPs: 2.5 ml/100 g orally for 24 hours.

Group IV - Rats received a single dose of 5.0% suspension of AgNPs: 5 ml/100 g orally for 24 hours.

The control group - received a single dose of 0.9% physiological saline.

After receiving the control suspension, the rats were monitored every 30 minutes for the first 4 hours; then every 6 hours for the first 24 hours, and twice a day for the following days. According to the recommendations of the OECD guideline for testing of chemicals, observation of the rats continued for 7 days. A week later the rats were restricted from food for 24 hours (with free access to water).

To study the histomorphological material, the rats were euthanized with CO_2 at a rate of 5 L/min in an individual chamber. For histomorphological research tissues were taken from the organs of rats of all five groups, and embedded in paraffin blocks to prepare the slides for microscope specimen; The specimens were stained with hematoxylin-eosin and observed under a light microscope

Results.

Evaluation of "In Vitro" Inhibitory Effect of Silver Nanoparticles (AgNPs) on RR-MTB Strains.

The conducted experimental study showed the complete suppression of the growth of multiresistant strains of MTB when applying 5% and 10% silver suspensions; In the case of application with 0.25%, 0.5%, and 1.0% concentration solutions, the growth of multiresistant strains of MTB was re-detected.

Applying a 2.5% solution of AgNPs showed both inhibition and growth of the RR-MTB strains.

To increase the reliability of the obtained results, we expanded the scope of the study and added the suspension containing a 2.5% concentration of silver to five more sensitive test tubes (a total of 10 test tubes). The addition of 2.5% AgNPs to the suspension showed the growth inhibition of RR-MTB strains in 70% of cases (Table 2).

The addition of RIF and different concentrations of silver nanocomposite showed the same tendency to inhibit the growth of mycobacteria as applying only AgNPs to RR-MTB cultures. The study showed complete ineffectiveness of composites including the standard dose of RIF and suspension of AgNPs 200 with the following concentrations: 0.25, 0.5%, 1.0%; Growth inhibition of RR-MTB strain started with R/AgNPs 2.5% solution, and the complete inhibition was observed in case of supplement including R/AgNPs 5% and 10% solution. Despite statistically nonsignificant ($P > 0.05$) difference between two groups - R/AgNPs and AgNPs only ($X^2 = 0.373$, degrees of freedom (df):1, P-value=0.541), a bactericidal effect while applying the nanocomposite containing R/AgNPs concentration of 2.5% was observed in 80.0% of cases, which is 10% higher than the bactericidal effect obtained by applying only AgNPs. R/AgNPs with a higher concentration of nanocomposite (5%, 10%) showed a bactericidal effect in 100% of cases (Table 2).

Table 2. *Growth inhibition of RR-MTB with various concentrations of AgNPs with RIF.*

Growth Suppression	The concentration of AgNPs in combination with RIF						
	0,25%	0,5%	1,0%	2,50%	5%	10%	Total
Suppression N (%)	0 0%	0 0%	0 0%	16 80%	10 100%	10 100%	36 93,3%
Growth N (%)	10 100%	10 100%	10 100%	4 20%	0 0%	0 0%	34 80%
Total N	10	10	10	20	10	10	70

Abbreviations: RR-MTB, rifampicin-resistant M. tuberculosis; AgNPs, silver nanoparticles, N, number.

Table 3. *Growth inhibition of RR-MTB with the various concentrations of AgNPs.*

Characteristics	The concentration of AgNPs						
	0,25%	0,5%	1,0%	2,5%	5%	10%	Total
MTB Growth Suppression N (%) of Test Tubes	0 0%	0 0%	0 0%	7 70%	5 100%	5 100%	17 90,0%
MTB Growth N (%) of Test Tubes	5 100%	5 100%	5 100%	3 30%	0 0%	0 0%	18 82,5%
Number of Test Tubes	5	5	5	10	5	5	35

Abbreviations: RR-MTB, rifampicin-resistant M. tuberculosis; AgNPs, silver nanoparticles, N, number.

The combination of 2.5% suspension of AgNPs and a standard dose of RIF has a minimal inhibitory effect on RR-MTB, and the minimum bactericidal concentration of AgNPs with the standard dose of R is equal to 5% suspension of silver.

Evaluation of a single-use of silver nanoparticles (AgNPs) in experimental animals.

In the experiment, no case of lethality was observed in rats with high and ultra-high single doses of AgNPs. At the same time, they were not restricted in food, water, defecation, diuresis, and movement.

No histomorphological changes were observed in the tissues of the first, second, and third group of rats, while the following types of changes were detected in the rats of the fourth group: 1) No pathological changes were detected in the myocardium.

In some cases, we could see extravasates, probably caused by the damage of material due to rough handling (Figure 1); 2) Hemorrhage foci were detected in the alveoli and lung interstitium (Figure 2); 3) A moderate amount of blood was observed in the liver; No pathological deviations were detected (Figure 3); 4) No pathological changes were detected in the gastrointestinal (GI) system (Figure 4); 5) Focal mineralization manifested by eosinophilia was observed in renal tubules (Figure 5).

While applying silver suspensions with the above-mentioned concentrations did not have a lethal dose - LD50 could not be determined. No histomorphological changes were noted while applying the suspension dose of 2.5 ml/100g; the use of ultra-high dose suspension of 5% AgNPs (5 ml/100g) caused some changes in lung and kidney tissue structure.

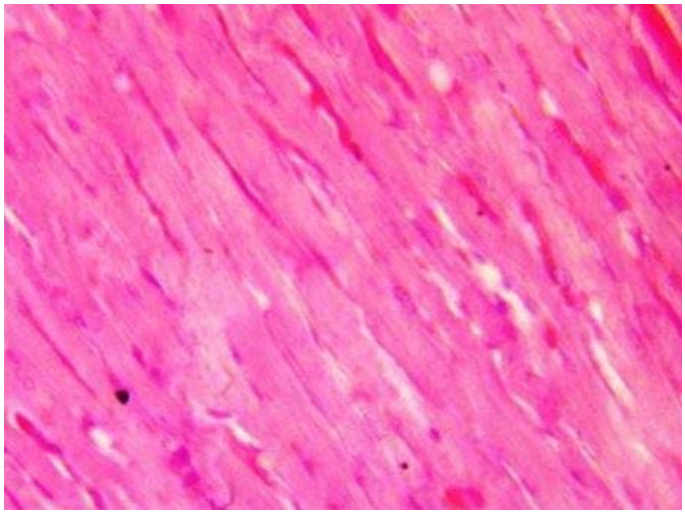

Figure 1. *Histomorphological changes in the heart tissues of rats after a single injection of high and ultra-high doses of AgNPs. Picture of normal heart muscle. Hematoxylin-eosin. x 40.*

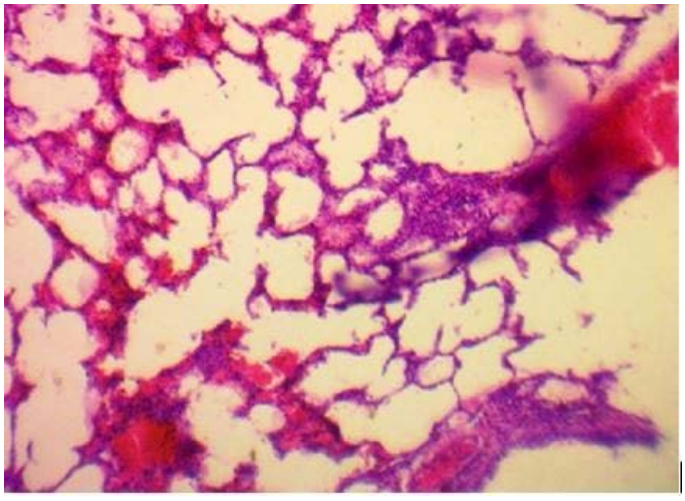

Figure 2. *Histomorphological changes in the tissues of the alveoli and lung interstitium of rats after a single injection of high and ultra-high doses of AgNPs. Hemorrhage foci were detected in the alveoli and lung interstitium. Hematoxylin-eosin. x 20.*

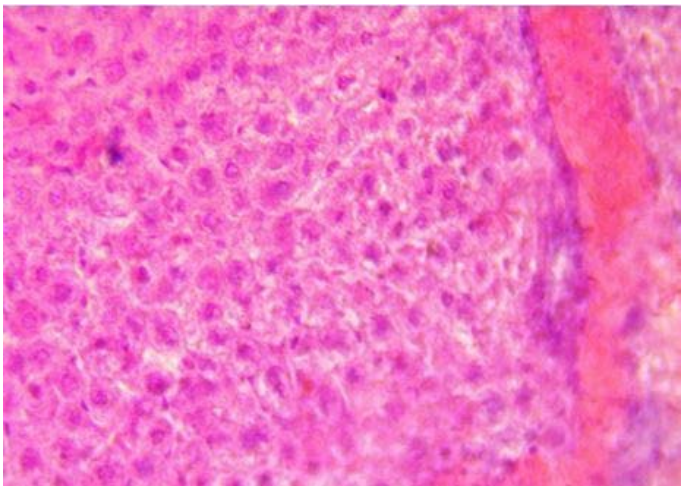

Figure 3. *Histomorphological changes in the liver tissues of rats after a single injection of high and ultra-high doses of AgNPs. Picture of normal liver, hematoxylin-eosin. x 40.*

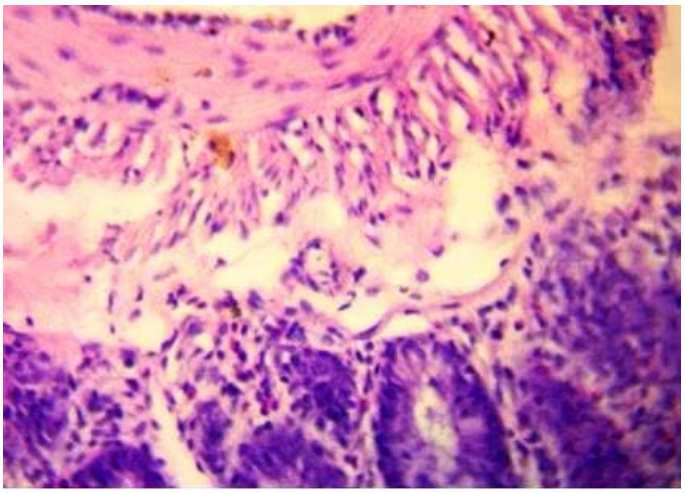

Figure 4. *Histomorphological changes in the small intestine tissues of rats after a single injection of high and ultra-high doses of AgNPs. Small intestine within normal limits. Hematoxylin-eosin. x 40.*

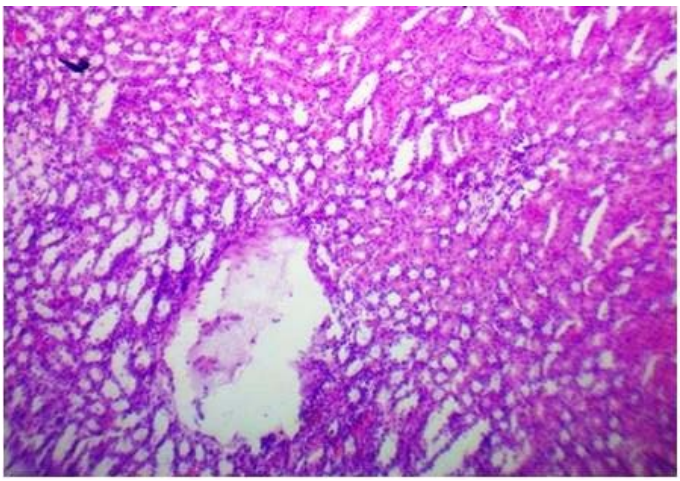

Figure 5. *Histomorphological changes in the kidney tissues of rats after a single injection of high and ultra-high doses of AgNPs. Mineralization by eosinophilia in the renal tubules of the upper part of the image. Hematoxylin-eosin. x 20.*

Discussion.

Mycobacterium tuberculosis has the extraordinary ability to adapt to the administration of antibiotics through the development of resistance mechanisms. By rapidly exporting drugs from within the cytosol, these pathogenic bacteria diminish antibiotic potency and drive the presentation of drug-resistant tuberculosis. The membrane integrity of MTB is pivotal in retaining these drug-resistant traits. Silver nanoparticles are established antimicrobial agents that effectively compromise membrane stability, giving rise to increased bacterial permeability to antibiotics. RIF is a semisynthetic, broad-spectrum antibiotic used commonly for the treatment of tuberculosis. Due to its penetrating power, it is also reported to treat various biofilm-related infections. With the emergence of RIF resistance among microbes, researchers are looking for various ways to improve its bioavailability. Umar Farooq and co-authors [24] studied Rif conjugated silver nanoparticles on methicillin resistant Staphylococcus aureus and Klebsiella pneumoniae strains and found that, nanotechnology decreasing their size of Rif to nano level, which results an increase in cell permeability. Synthesized nanoparticles showed 1.5–2-times more penetrating potential as observed by biofilm eradication and percentage viability reduction as compared to RIF alone.

The release of AgNPs within the macrophage endosomal system increase the potency of the model antibiotic RIF by as much as 76% by realised through an increase in membrane disorder of intracellular MTB [25].

Thus, the synergistic impact of the action of R/AgNPs against Mycobacterium tuberculosis is not fully studied yet, but the base of the mechanism itself is antibiofilm activity. Silver nanoparticles are established antimicrobial agents that effectively disrupt the stability of the membrane, leading to an increase in the permeability of bacteria to antibiotics (Rif).

In our experimental study, the addition of RIF standard dose and nanocomposite (with different concentrations of AgNPs) to RR-MTB strains showed complete suppression of Mycobacterium tuberculosis growth in 51,4% of cases, while in control arm supplement of 6 different concentrations of only AgNPs to RR-MTB isolates showed 48,6%. As a result of "in vitro" research, studying the effects of 20 nm AgNPs solutions at six separate concentrations, it was found that they have different inhibitory effects on RR-MTB isolates-suppression process in RR-MTB strains started with 2,5% nanocomposite solution application and full suppression was achieved in 5% and 10% nanocomposite solutions. It was established that a solution of AgNPs of 2.5% has a minimal inhibitory effect and a solution of 5.0% has a minimal bactericidal effect on RR-MTB "in vitro" strains. The study results determined that the "in vitro" application of nanocomposite including a standard dose of RIF and a 2.5% solution of AgNPs increased the minimal inhibitory effect on RR-MTB to 10% (total 80%) compared to the isolated use of a 2.5% solution of AgNPs nanoparticles (70%) indicating the potentiating effect of AgNPs to overcome the resistance of MTB to R. "In vitro" application of a nanocomposite using a standard dose of RIF, a 5% suspension of AgNPs, and a 5% solution of isolated AgNPs on RR-MTB strains showed identical results in terms of minimal bactericidal effect.

One of the main challenges of using AgNPs in humans is the safety profile of nanocomposites. Our study revealed the complete safety (absence of any type of histomorphological changes) of a single administration of AgNPs suspension (AgNPs 2.5% 1000 mg/kg; AgNPs 2.5% 5000 mg/kg; AgNPs 5.0% 1000 mg/kg) in the animal experiment. At an ultra-high dose (AgNPs 5.0% 5000 mg/kg), some non-lethal changes were detected in the tissue structures of parenchymal organs (lungs, kidneys). The study of the efficacy of an "in vitro" use of nanocomposite in RR-MTB strains (based on the results of the studied criteria), confirms the enhancing effect of nanoparticles in overcoming the resistance of the pathogen to RIF. The obtained results show that the optimal dose of nanoparticles in the composite is a concentration of 2.5%. The safety of using 20 nm AgNPs of the above-mentioned concentration was also confirmed by the experimental research.

The study highlights the urgent need to maintain the effectiveness of RIF as one of the most potent anti-TB drugs due to its unique bactericidal and sterilizing capacity. Along with developing new anti-TB drugs, it is important to prevent the acquisition of resistance to RIF and introduce new methods to restore the effectiveness of RR-MTB strains.

Our study is among few researches evaluating the efficacy and safety of AgNPs and RIF on MTB strains. Kreytsberg et al. [26] found that the efficacy of the combined application of the nanoparticles with specific anti-TB drugs significantly exceeded the isolated mode of the nanoparticle application. The bacterial growth-inhibitory activity of AgNPs with RIF was 93,3% at a concentration within the range of 2.5 – 5.0 mg/l. Ellis et al. [25] demonstrated a limited independent intramacrophagic antimycobacterial effect of multimetallic nanoparticles including AgNPs. However, the coadministration of AgNPs with subtherapeutic RIF increased the potentiating effect of RIF by reducing 69% of *M. tuberculosis* colony-forming units. Interestingly, Farooq et al. [24] showed an enhancement of antibiofilm efficiency of RIF following conjugation with silver (R/AgNPs) also in methicillin-resistant K pneumoniae and S aureus [24]. All these studies are consistent with our findings regarding the efficacy of nanocomposite of AgNP and RIF.

The main limitation of the study is that the safety assessment involved only a single administration of the AgNP suspension to experimental animals. However, we are continuing our study to evaluate the safety of AgNPs and RIF suspensions when administered multiple times following OECD GUIDELINES FOR TESTING.

Conclusion.

The in vitro study of the effectiveness of using AgNPs and RIF nanocomposite on RR-MTB isolates proves the potentiating effect of AgNPs at a standard dose of RIF, overcoming the drug resistance of the pathogen, which provides a scientific basis for an in-depth study of this actual problem.

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Author contributions: NK, GP, and NK conceptualized and designed the study. NB performed bacteriological testing, NC performed histomorphological examinations, TA and LS contributed to data acquisition, and NK wrote the first draft of the manuscript. All authors provided critical feedback and

contributed to interpreting the findings and writing of the final manuscript. All authors read and provided the final approval of the submitted version.

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Conflicts of interest: No conflicts of interest to declare.

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Ethics statement: The Institutional Review Boards of the NCTLD and the Alexander Natishvili Institute of Morphology approved the study. Experiments were conducted in compliance with current international standards (The Declaration of Helsinki Convention for the Use and Care of Animals, 1964; Directive 2010-63-EU on the Protection of Animals Used for Scientific Purposes, 2010; Guide for the Care and Use of Laboratory Animals, 8th ed., 2011). Euthanasia was performed according to IACUC guidelines. (https://animal. research. uiowa.edu/ iacuc - guidelines-euthanasia).

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Изучение эффективности и безопасности нанокомпозитов серебра в отношении рифампицин устойчивых штаммов микобактерии туберкулёза

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Резюме

Цель: Целью исследования было оценка потенциала наночастиц серебра в восстановлении противотуберкулёзной эффективности рифампицина.

Материалы и методы: К 70 рифампицин-устойчивым изолятам микобатерии туберкулёза (RR-MTB) добавляли нанокомпозит (R/AgNPs)-стандартную дозу рифампицина (R) вместе с 6 различными (0,25%; 0,5%; 1%; 2,5%; 5%; 10%) концентрациями наночастиц серебра (AgNPs). Контрольную группу составили 35 изолятов RR-MTB, к которым добавляли суспензию AgNPs в идентичных концентрациях. Ингибирующий эффект нанокомпозитов оценивали по росту микобатерии туберкулёза (MTB) с использованием BACTEC™ MGIT 960™. Оценка безопасности одноразового использования AgNPs проводилась на экспериментальных животных.

Результаты: Процесс подавления роста изолятов RR-MTB начинался при добавлении 2,5% суспензии 20 нм AgNPs, а полное подавление наблюдалось при использовании 5% и 10% суспензий AgNPs. In vitro при использовании нанокомпозита стандартной дозы рифампицина и 2,5% суспензии наночастиц серебра наблюдалось увеличение минимального ингибирующего эффекта на 10% (составило 80%) по сравнению с изолированным применением 2,5% суспензии наночастиц серебра (70%). Эксперименты на животных показали полную безопасность однократного применения сверхвысоких доз AgNPs.

Заключение. Исследование показало потенцирующий эффект AgNPs на рифампицин по преодолению резистентности к МТБ , что даёт научную основу для дальнейших исследований.

Ключевые слова: лекарственно-устойчивый туберкулёз, наночастицы серебра, подавление роста, экспериментальные животные.

vercxlis nanokompoziti efeqturobisa da usafrTxoebis Seswavla rifampicinis mimarT rezistentuli tuberkulozis mikobaqteriis Stamebze

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Sedegebi: RR-MTB izolatebis zrdis daTrgunvis procesi daiwyo rifampicinis mimarT mdgradi tub.mikobaqteriis Stamebze 20nm AgNPs-is 2,5% xsnaris damatebisas, xolo sruli daTrgunva dafiqsirda AgNPs-is 5% da 10% xsnarebis gamoyenebis SemTxvevaSi. In vitro rifampicinis standartuli dozisa da vercxlis nanonawilakebis 2,5% xsnaris nanokompozitis gamoyenebisas dafiqsirda minimaluri mainhibirebeli efeqtis zrda 10%-iT (Seadgina 80%) vercxlis nanonawilakebis 2,5% xssnaris izolirebul gamoyenebasTan (70%) SedarebiT. cxovelebze Catarebulma eqsperimentma aCvena erTjeradad AgNPs-is ultra maRali dozebis sruli usafrTxoeba.

daskvna: kvlevis Sedegad dadginda vercxlis nanonawilakebis gamaZlierebeli efeqtis arseboba rifampicinze paTogenis medikamentis mimarT winaaRmdegobis daZlevaSi, rac am mimarTulebiT gaRrmavebuli kvlevebis C□t□rebis mecnierul safuZvels qmnis.

sakvanZo sityvebi: rifampicinze rezistentuli, vercxlis nanonawilakebi, zrdis daTrgunva, eqsperimentuli cxovelebi.