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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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USAGE OF SILVER NANOPARTICLES TO RESTORE MOXIFLOXACIN EFFICACY FOR FLUOROQUINOLONE-RESISTANT M.TUBERCULOSIS CULTURES

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Abstract.

Background: Fluoroquinolones are used for the complex treatment of mono-, poly-, and multi-resistant Tuberculosis (TB) and are the most efficient among resistant TB treatment drugs. Disease caused by fluoroquinolone-resistant TB strains, especially pre-extensive TB (pre-XDR) and extensive (XDR) forms are extremely hard to manage, and treatment efficacy is quite low. With the revitalization and extension of resistant TB drugs, one of the main research domains is to study resistance inhibitors aimed at restoring the efficacy of main and priority anti-TB medications. The antibacterial properties of silver nanoparticles (AgNPs) against resistant strains responsible for various infectious diseases are supported by extensive experimental data. There are a few publications regarding the effectiveness of silver nanoparticles on resistance inhibition of TB strains, however, its action on fluoroquinolone-resistant TB strains is unexplored.

Aim: The study aimed to investigate the in vitro restoration of the anti-TB efficacy of Moxifloxacin (Mfx) using AgNPs. **Methods:** Nanocomposite- standard dose of Mfx 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 moxifloxacin-resistant mycobacterium tuberculosis isolates. The control arm consisted of 70 fluoroquinolone (Mfx)-resistant Mycobacterium tuberculosis (FQ/ R-MTB) isolates and AgNPs suspension with identical concentrations. The inhibitory effect of nanocomposites was evaluated by MTB growth rate using the BACTEC™ MGIT 960™. **Results:** The suppression process of AgNPs on FQ/R-MTB isolates started with 2,5% nanocomposite solution application and full suppression was achieved in 5% and 10% nanocomposite solutions. A standard dose of Mfx and a 2.5% solution of AgNPs increased the minimal inhibitory effect on FQ/R-MTB by 10% (total 85%) vs the isolated use of a 2.5% solution of AgNPs (75%). A similar trend was noted in both FQ/ R-MTB cohorts (rifampicin-susceptible; rifampicin-resistant). **Conclusion:** The in vitro study of the effectiveness of using AgNPs and Mfx nanocomposite on FQ/R-MTB isolates proves the potentiating effect of AgNPs at a standard dose of Mfx, overcoming the drug resistance of the pathogen, which lays the groundwork for further scientific research in this area and creating a nanocomposite that is safe for humans, which will make a significant contribution to improving the control of fluoroquinolone-resistant tuberculosis, especially, pre-XDR TB.

Key words. Tuberculosis, growth inhibition, moxifloxacin-resistance, silver nanoparticles.

Introduction.

Tuberculosis (TB) remains one of the top 10 causes of death worldwide, with 1.3 million deaths in 2022. An estimated global total of 10.6 million people fell ill with TB in 2022, equivalent to 133 incident cases per 100 000 population [1-3]. Drug-resistant Tuberculosis (DR-TB) significantly impacts the epidemiological landscape of TB. DR-TB continues to be a current global health threat, and is defined by higher morbidity and mortality, sequelae, higher cost and complexity [4]. TB treatment history reflects on the gradual development of anti-TB drug resistance throughout decades. It originated in the 20th century, in the 1940s dand has since developed increasing resistance to streptomycin (caused by monotherapy with streptomycin against TB). After 20th century, the pace of resistance development decelerated, that was related to new anti-TB drug development and complex multidrug TB therapy establishment. Since the 1980s first rifampicin resistance cases appeared. The end of 20th century marked a significant escalation in cases of multidrug resistant TB (Simultaneous resistance to two most robust anti-TB drugs; Isoniazid and Rifampicin). The challenge for 21st century is Fluoroquinolone resistant TB and its management [5]. Fluoroquinolones (FQ) have come to play an important role in the treatment of tuberculosis, particularly drug-resistant tuberculosis (DR-TB) [6]. Fluoroquinolones are used for the complex treatment of mono-, poly-, and multi resistant Tuberculosis (TB) and are the most efficient among resistant TB treatment drugs. Disease caused by fluoroquinolone resistant TB strains, especially pre-extensive TB (pre-XDR) and extensive (XDR) forms are extremely hard to manage, and treatment efficacy is quite low. With the revitalization and extension of resistant TB drugs, one of the main research domains is to study resistance inhibitors aimed at restoring the efficacy of main and priority anti-TB medications. Bactericidal properties of silver nanoparticles (AgNPs) against resistant strains responsible for various infectious diseases are supported by extensive experimental data [7-19]. There are a few publications regarding effectiveness of silver nanoparticles on resistance inhibition of TB strains, however its action on fluoroquinolone resistant TB strains is unexplored. The study aimed to investigate the in vitro restoration of the anti-TB efficacy of Moxifloxacin (Mfx) using AgNPs. The main objectives were: 1) In vitro" study of the inhibitory effect of suspensions containing different concentrations of AgNPs on FQ resistant M. tuberculosis (FQ/R -MTB) strains; 2) "In vitro" study of the effectiveness of nanocomposite with the standard dose of Mfx and different concentrations of AgNPs to investigate the presence of inhibitory effect on FQ/R-MTB strains.

Materials and Methods.

An experimental study was conducted in the National Reference Laboratory (NRL) of the National Center for Tuberculosis and Lung Diseases (NCTLD), Tbilisi, Georgia. 20 nanometer (nm) silver nanoparticles were used (AgNPs), it was purchased from "Hongwu International Group Ltd" (https://www.hwnanomaterial.com). High-speed ultrasound homogenizer, disruptor and disintegrator was used to obtain suspension of nanoparticles. (Ultrasonic Processor FS-1800N(China). In vitro experiment was performed on 140 fluoroquinolone resistant TB strains, that was obtained in clinical settings from sputum of patients with pulmonary tuberculosis. The experiment was conducted on liquid media: with usage of BACTEC™ MGIT™ 960 system. BACTEC™ MGIT™ 960 machine is used to immediately detect TB mycobacterium. Growth of mycobacterium is identified with fluorescence, which is increasing in proportion to the decrease of oxygen. The machine generates fluorescence with the usage of ultrasound waves and special computational algorithm. BACTEC™ MGIT™ 960 machine is used to detect drug susceptibility of anti-TB drugs, that gives results in 4-13days. BACTEC MGIT 960 machine applies same principle for the detection of anti-TB drug susceptibility, that means detection of mycobacterium growth with fluorescence. The test is performed with MGIT 7ml tubes and it includes control tube (without drug) and tubes with added drugs. The machine controls the increase of fluorescence in both tubes by default. If drug is active against mycobacterium (isolate is sensitive), therefore happens growth inhibition and suppression of fluorescence in tubes with drugs, while in the control tube mycobacterium grows and demonstrates increase of fluorescence. If isolate is resistance, growth of mycobacterium and increase of fluorescence is detected in both, in control tubes and in tubes with drugs. BACTEC™ MGIT™ 960 system monitors growth and therefore interprets the results, whether its sensitive or resistant. The experiment was conducted in 2 groups. In sensitivity test group, in the first experimental group, (70 culture) 100 ml silver solution was added to the tubes (different concentrations), in the second group (70 cultures) – silver solution was added with standard dose of moxifloxacin (0,25 mkg/ml). Moxifloxacin resistant isolates were selected in advance. In the beginning, moxifloxacin resistant 140 cultures were taken. To evaluate inhibitory effect of silver nanoparticles, in sensitivity test, silver nanoparticles (AgNPs) solution was added with corresponding concentrations. 6 concentrations were studied; 0,25%; 0,5%; 1%; 2,5%, 5% and 10%. Each concentration was added in 10-10 tubes, 2,5% was added in 20 tubes. Evaluation of the inhibitory activity of moxifloxacin and different concentrations of silver nanoparticles (Mfx/AgNPs) composite was carried out in a susceptibility test set with 6 different concentrations of silver solution (0,25%; 0,5%; 1%; 2,5%; 5%; 10%). In addition to the standard dose of moxifloxacin 0.25%, 0,5%; 1%; 5% and 10% solution of silver nanoparticles with moxifloxacin was added to 10 test tubes, and standard dose of moxifloxacin and 2.5% solution of AgNPs to 20 test tubes (70 test tubes in total). Effect of AgNPs and Mfx/AgNPs nanocomposite on fluoronquinolone mono and poly resistant mycobacterium tuberculosis isolates was studied and evaluated separately. The final evaluation of the results of the inhibitory activity study was carried out based on the inhibition of the growth of Mycobacterium tuberculosis as a result of the addition of the test suspension to the test tube. Statistical analysis was performed using IBM SPSS Statistics software (version 29.0.2.0). The chi-square (X2) test was used to compare the effect of two different groups: AgNPs alone and Mfx/AgNPs analysing two categorical variables for each group: growth increase vs suppression.

Results.

The study conducted on fluoroquinolone resistant mycobacterium tuberculosis isolates demonstrated, complete suppression of the growth of fluoroquinolone (moxifloxacin) resistant strains of mycobacterium tuberculosis when adding 5% and 10% silver suspensions, in case of adding 0.25%, 0.5%, 1.0% concentration solutions, the growth of FQ/R -MTB strain was observed. When adding a 2.5% suspension of AgNPs, both inhibition and growth of FQ-resistant Mycobacterium TB strains were observed in some cases. In order to increase the reliability of the obtained results, we expanded the scope of the study and added a suspension containing 2.5% concentration of silver to 10 more sensitive test tubes (20 test tubes in total), when adding 2,5 % concentration of AgNPs suspension, growth inhibition of FQ/R-MTB strains was noted in 75% of cases. (Table 1).

A similar trend was noted when adding separately for 0,25%; 0,5%; 1%; 2,5%; 5% and 10% silver suspension on Rifampicin-susceptible (susceptible to rifampicin and resistant to one or more other first-line TB medicines) and rifampicin resistant (susceptible or resistant to isoniazid [i.e. MDR-TB], or resistant to other first-line or second-line TB medicines) FQ/R-MTB strains. These on FQ-MTB isolates, when only 2.5% concentration of AgNPs suspension was added, inhibition of the growth of Rifampicin-susceptible Mycobacterium Tuberculosis (RS-MTB) strains resistant to moxifloxacin was 80% (Table 2), and 70% in the case of Rifampicin-Resistant Mycobacterium Tuberculosis (RR-MTB)-preXDR strains (Table 3).

The study found that when different concentrations of Mfx/AgNPs were added to cultures of fluoroquinolone-resistant Mycobacterium tuberculosis FQ/ R-MTB, the combination was completely ineffective at the standard dose of moxifloxacin (0,25mkg/ml) and silver suspension concentrations of 0,25%, 0,5% and 1,0%. Growth inhibition of FQ/ R-MTB strain started when using 2.5% solution of Mfx/AgNPs and complete inhibition was observed when adding 5% and 10% solution of Mfx/AgNPs. Despite statistically no significant [X_2= 0,625, degree of freedom(df:1), P-value=0,429] difference between two groups- Mfx/AgNPs and AgNPs only a bactericidal effect while applying the nanocomposite containing Mfx/AgNPs concentration of 2,5% was observed in 85% of cases, which is 10% higher than the bactericidal effect obtained by applying only. AgNPs (Tables 1,4), which confirms potentiating effect of AgNPs at a standard dose of Mfx, overcoming the drug resistance of the pathogen Mfx / AgNPs The use of Nano composite with a higher concentration (5%,10%) showed a bactericidal effect in 100% of cases (Table 4).

An identical trend (not significant at p<.05.) was noted for Rifampicin-susceptible TB (Table 5) and Rifampicin-Resistant

Table 1. *Growth inhibition of FQ-R MTB with various concentrations of AgNPs.*

Growth suppression	**The concentration of AgNPs**						
	0,25%	**0,5%**	**1.0%**	**2,5%**	**5,0%**	**10.0%**	**Total**
Suppression N (%)	0 (0%)	0 (0%)	0 (0%)	15 (75%)	10 (100%)	10 (100%)	35
Growth N (%)	10 (100%)	10 (100%)	10 (100%)	5 (25%)	0 (0%)	0 (0%)	35
Total	10	10	10	20	10	10	70

Table 2. *Growth inhibition of FQ-R, RS MTB strains with various concentrations of AgNPs.*

Growth suppression	**The concentration of AgNPs**						
	0,25%	**0,5%**	**1.0%**	**2,5%**	**5,0%**	**10.0%**	**Total**
Suppression N (%)	0 (0%)	0 (0%)	0 (0%)	8 (80%)	5 (100%)	5 (100%)	18
Growth N (%)	5 (100%)	5 (100%)	5 (100%)	2 (20%)	0 (0%)	0 (0%)	17
Total	5	5	5	10	5	5	35

Table 3. *Growth inhibition of FQ-R, RR-MTB (pre-XDR) strains with various concentrations of AgNPs.*

Growth suppression	**The concentration of AgNPs**						
	0,25%	**0,5%**	**1.0%**	**2,5%**	**5,0%**	**10.0%**	**Total**
Suppression N (%)	0 (0%)	0 (0%)	0 (0%)	7 (70%)	5 (100%)	5 (100%)	17
Growth N (%)	5 (100%)	5 (100%)	5 (100%)	3 (30%)	0 (0%)	0 (0%)	18
Total	5	5	5	10	5	5	35

Table 4. *Growth inhibition of FQ/R- MTB strains with various concentrations of AgNPs with Mfx.*

Growth suppression	The concentration of AgNPs with Mfx						
	0,25%	0,5%	1.0%	2,5%	5,0%	10.0%	Total
Suppression N (%)	0 (0%)	0 (0%)	0 (0%)	17 (85%)	10 (100%)	10 (100%)	37
Growth N (%)	10 (100%)	10 (100%)	10 (100%)	3 (15%)	0 (0%)	0 (0%)	33
Total	10	10	10	20	10	10	70

Table 5. *Growth inhibition of FQ-R, RS MTB with various concentrations of AgNPs with Mfx.*

Growth suppression	The concentration of AgNPs with Mfx						
	0,25%	0,5%	1.0%	2,5%	5,0%	10.0%	Total
Suppression N (%)	0 (0%)	0 (0%)	0 (0%)	9 (90%)	5 (100%)	5 (100%)	19
Growth N (%)	5 (100%)	5 (100%)	5 (100%)	1 (10%)	0 (0%)	0 (0%)	16
Total	5	5	5	10	5	5	35

Table 6. *Growth inhibition of FQ-R, RR-MTB (pre-XDR) with various concentrations of AgNPs with Mfx.*

Growth suppression	**The concentration of AgNPs with Mfx**						
	0,25%	**0,5%**	**1.0%**	**2,5%**	**5,0%**	**10.0%**	**Total**
Suppression N (%)	0 (0%)	0 (0%)	0 (0%)	8 (80%)	5 (100%)	5 (100%)	18
Growth N (%)	5 (100%)	5 (100%)	5 (100%)	2 (20%)	0 (0%)	0 (0%)	17
Total	10	10	10	10	5	5	35

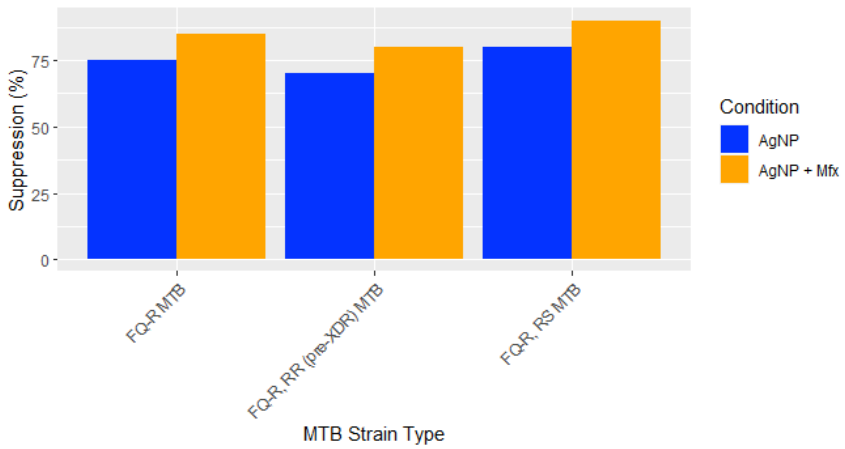

Figure 1. *Suppression rates for different conditions AgNPs vs. Mfx /AgNPs by MTB strain type (silver suspension concentration 2.5%).*

(pre-XDR) FQ-MTB isolates (Table 6) In contrast, when Mfx / AgNPs nano composite was added, 90% [X2=0,392, degree of freedom(df:1), P-value=0,531]of fluoroquinolone-resistant rifampicin-sensitive MTB isolates were exposed Mfx /AgNPs at a concentration of 2.5%, and 80% [X2=0,267, degree of freedom(df:1), P-value=0,605] when added to pre-XDR MTB cultures(Table 6). Suppression rates for different conditions AgNPs vs. Mfx/AgNPs by MTB strain type (silver suspension concentration 2.5%) are shown in Figure 1.

Discussion.

Antibiotics of the fluoroquinolone group have been used in world clinical practice for the treatment of many diseases of bacterial etiology since 1985. Their mechanism of action is related to the inhibition of chromosomal and plasma DNA-hydrase (an anzyme responsible for the stability of the spatial structure of microbial DNA). Under the influence of fluoroquinolones, the DNA of the microbial cell is despiralized and it dies, in addition, fluoroquinolones do not affect the DNA of the macroorganism. High-generation fluoroquinolones, in particular moxifloxacin, are used in the complex therapy of mono, poly and multi-resistant tuberculosis and belong to the most effective drugs from the group of drugs for the treatment of resistant tuberculosis. Therefore, the disease caused by strains of fluroquinolone resistant tuberculosis strains, especially pre-extensive tuberculosis (pre-XDR), is the most difficult to manage in terms of chemotherapy, and the treatment efficiency is quite low. The use of new anti-tuberculosis drugs (bedaquiline, delamanid) in treatment regimens for multi- and pre-XDR resistant tuberculosis has significantly improved patient outcomes, however publications related to the rise of resistant forms to bedaquiline have already appeared in the scientific medical literature. Resistance to bedaquiline and delamanid (both separately and simultaneously) has already been observed in Georgia [20]. Based on the above, it is important to constantly update and expand the arsenal of drugs for the treatment of resistant tuberculosis. One of the modern trends in the fight against resistant tuberculosis is the use of Nano technological approaches. Nanotechnology makes it possible to overcome the difficulties of anti-tuberculosis therapy, namely: introduction of antimicrobial substances directly into damaged cells through nanoparticles as carriers; also enhancing the bactericidal potential of anti-tuberculosis drugs. The mentioned properties of nanoparticles provide a basis for the implementation of interventions aimed at restoring the effectiveness of basic and priority medicines. Among the various types of nanoparticles tested for potential drug delivery systems, silver nanoparticles should be distinguished, they are characterized by bactericidal action against gram-positive and gram-negative microorganisms, including against strains resistant to antibiotics [21,22]. It should also be noted that unlike antibiotics, pathogenic bacteria rarely develop resistance to silver nanoparticles. [21] Recent studies have reported on the antibacterial and immunobiological properties of silver nanoparticles, also, the peculiarities of the action of silver nanoparticles in healthy and experimental animals infected with mycobacterium tuberculosis, taking into account the ways in which nanoparticles enter the body. In vitro studies have shown that silver nanoparticles coated with polyvinylpyrrolidone and silver nanoparticles without coating are resistant to aggregation and are homogenously distributed in the solution. Polyvinylpyrrolidone coated silver nanoparticles at a concentration of 0.05 to 50 mg/l in vitro on immunocompetent cells of mice do not cause cytotoxic effects and have a pronounced anti-tumor effect [20]. The antibacterial action of silver nanoparticles is due to the following mechanisms [21].

- Direct interaction with bacterial components (bioapki, bacterial cell membrane).
- Release of bioactive ions (e.g., Ag+).
- Disruption of multiple metabolic pathways.
- Production of reactive oxygen species.
- Genotoxicity.
- Changes in the cell wall and cytoplasm.
- Inhibition of bacterial DNA replication.
- Alteration of bacterial membrane permeability and ionic balance

It has been found that silver nanoparticles, either alone or in combination with biomolecules like peptides and chitosan, exhibit strong antimycobacterial activity. However, this effect is somewhat reduced during the intracellular replication of mycobacteria within macrophages. A promising strategic direction is the combination of silver nanoparticles with classical anti-tuberculosis drugs (that is, the creation of composite drugs), which will synergistically increase and strengthen the antimycobacterial effect on both extracellular and intracellular mycobacteria [20,21].

In our experimental study, we examined the effects of six different concentrations (0.25%, 0.5%, 1%, 2.5%, 5%, 10%) of a 20nm silver nanoparticle solution in vitro and found varying inhibitory effects on fluoroquinolone-resistant mycobacterium tuberculosis isolates. The minimal inhibitory effect of the 2.5% solution of silver nanoparticles, and the minimal bactericidal effect of the 5.0% solution was determined in vitro on mycobacterium tuberculosis strains resistant to fluoroquinolone. As e result of the study, it was determined that when adding the standard dose of moxifloxacin and the nanocomposite of a 2.5% solution of silver nanoparticles, the minimum inhibitory effect on fluoroquinolone-resistant strains of MTB increased by 10% (made up 85%) compared to the isolated use of 2,5% solution of silver nanoparticles (75%). In both cohorts of fluoroquinolone-resistant mycobacterium tuberculosis isolates (rifampicin-susceptible and rifampicin-resistant pre-XDR), the addition of the Mfx/AgNPs nanocomposite resulted in a consistent 10% increase in minimal inhibitory activity compared to the use of a 2.5% silver nanoparticle solution alone, which indicates the potentiating action of silver nanoparticles to overcome the resistance of MTB to moxifloxacin.

Our study belongs to the number of single scientific works that experimentally evaluates the effectiveness of the combined use of AgNPs and anti-tuberculosis drugs in resistant strains of MTB. A. Zakharov and co-authors [20] studied the effectiveness of the use of AgNPs and isoniazid nanocomposite in cases of proven resistance to isoniazid, and N. Kiria and co-authors [23-30] studied the effectiveness of using AgNPs and rifampicin nanocomposite in rifampicin-resistant strains of MTB. In both instances, it was confirmed that silver nanoparticles enhance the efficacy of chemotherapeutic agents (isoniazid and

rifampicin) in overcoming drug resistance in resistant strains. In the experiment, the results of our study of the action of the nanocomposite of moxifloxacin and AgNPs confirmed the synergistic effect of silver nanoparticles on moxifloxacin to overcome resistance of the pathogen.

Conclusion.

The „in vitro“ study of the effectiveness of using Mfx and AgNPs nanocomposite on FQ/R-MTB isolates proves the potentiating effect of AgNPs at a standard dose of Mfx, overcoming the drug resistance of the pathogen, which lays the groundwork for further scientific research in this area and creating a nanocomposite that is safe for humans, which will make a significant contribution to improving the control of fluoroquinolone-resistant tuberculosis, especially, pre-XDR TB.

Author contributions: TA, GP da NK conceptualizes and designed the study. NB performed bacteriological testing. LS and NK contributed to data acquisition, and TA 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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Использование наночастиц серебра для восстановления эффективности моксифлоксацина на фторхинолон-устойчивых культурах возбудителя туберкулёза

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Актуальность проблемы: Фторхинолоны используются для комплексного лечения моно-, поли- и мультирезистентного туберкулеза (ТБ) и являются наиболее эффективными среди препаратов для лечения лекарственно устойчивого туберкулеза. Заболевания, вызванные устойчивыми к фторхинолонам штаммами туберкулеза чрезвычайно трудно поддаются лечению, а эффективность лечения довольно низкая. Поэтому, необходимо постоянно расширять и обновлять лекарственную базу для лечения резистентного туберкулеза как за счет синтеза новых противотуберкулёзных препаратов, так и восстановления эффективности имеющиися приоритетных медикаментов с использованием ингибиторов стабильности. Бактерицидные свойства наночастиц серебра (AgNPs) в отношении резистентных штаммов, вызывающих различные инфекционные заболевания, подтверждаются обширными экспериментальными данными. Имеется несколько публикаций об эффективности наночастиц серебра в подавлении устойчивости штаммов туберкулеза, однако его действие на штаммы туберкулеза, устойчивым к фторхинолонам, не изучено. **Целью** исследования было изучение восстановления противотуберкулезной эффективности моксифлоксацина (Mfx) с использованием AgNPs in vitro. **Материал и методы:** нанокомпозит - стандартная доза Mfx и суспензионный раствор 20 нм наночастиц серебра (AgNPs) 6 различных концентраций: 0,25%; 0,5%; 1%; 2,5%; 5%; и 10% были добавлены к 70 моксифлоксацин-устойчивым изолятам микобактерий туберкулеза. Контрольную группу состовили 70 фторхинолон (Mfx)-устойчивых изолятов микобактерий туберкулеза (FQ/R-MTB), к которым была добавлена суспензия AgNPs с идентичными концентрациями. Ингибирующий эффект нанокомпозитов оценивали по росту MTB с использованием BACTEC™ MGIT 960™ . **Результаты**: Процесс подавления роста изолятов FQ/R-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 со стандартной дозой Mfx и 2,5% суспензии AgNPs наблюдалось увеличение минимального ингибирующего эффекта на 10% (составило 85%) по сравнению с изолированным применением 2,5% суспензии AgNPs (75%). Аналогичная тенденция отмечалвсь в обеих когортах FQ/R-MTB (рифампицин-чувствительных; рифампицин-резистентных). **Заключение:** Исследование in vitro эффективности применения нанокомпозита Mfx и AgNPs на изолятах FQ/R-MTB доказывает потенцирующее действие AgNPs к стандартной дозе Mfx, преодолевая лекарственную устойчивость возбудителя, что закладывает основу для дальнейших научных исследований в этой области. Синтезирование безопасного для человека нанокомпозита может внести значительный вклад в улучшение контроля над фторхинолон-резистентным туберкулезом.

Ключевые слова: туберкулез, резистентность к моксифлоксацину, наночастицы серебра, ингибирование роста.

ფთორქინოლონის მიმართ მდგრადი ტუბერკულოზის მიკობაქტერიის კულტურებზე ვერცხლის ნანონაწილაკების გამოყენება მოქსიფლოქსაცინის ეფექტურობის აღსადგენად

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[2]ტუბერკულოზისა და ფილტვის დაავადებათა ეროვნული ცენტრი, თბილისი, საქართველო

რეზიუმე პრობლემის აქტუალობა: ფთორქინოლონები გამოიყენება მონო-, პოლი- და მულტირეზისტენტული ტუბერკულოზის კომპლექსური მკურნალობაში და ყველაზე ეფექტურ მედიკამენტებს წარმოადგენენ რეზისტენტული ტუბერკულოზის სამკურნალო პრეპარატებს შორის. ფთორქინოლონის მიმართ მდგრადი შტამებით (FQ/R-MTB) გამოწვეული ტუბერკულოზის მართვა უკიდურესად რთულია და მკურნალობის ეფექტურობაც დაბალია. აქედან გამომდინარე, ძალზედ აქტუალურია მედიკამენტების მიმართ მდგრადი ტუბერკულოზის სამკურნალწამლო ბაზის მუდმივი გაფართოება და განახლება როგორც ახალი ტუბერკულოზის საწინააღმდეგო პრეპარატების სინთეზირების, ასევე სტაბილურობის ინჰიბიტორების გამოყენებით არსებული ტუბერკულოზის საწინააღმდეგო მედიკამენტების ეფექტურობის

აღდგენის გზით. სამეცნიერო ლიტერატურაში მწირია მონაცემები ვერცხლის ნანონაწილაკების (AgNPs) გამოყენებით ტუბსაწინააღმდეგო მედიკამენტების ეფექტურობის აღდგენის თაობაზე, ხოლო მათი ზეგავლენა ფთორქინოლონის მიმართ რეზისტენტული ტუბერკულოზის მიკობაქტერიის შტამებზე კი დღემდე პრაქტიკულად შეუსწავლელია. კვლევის მიზანს წარმოადგენდა in vitro მოქსიფლოქსაცინის ტუბსაწინააღმდეგო ეფექტურობის აღდგენის შესაძლებლობის შესწავლა AgNPs-ის გამოყენებით. მასალა და მეთოდები: ნანოკომპოზიტი-მოქსიფლოქსაცინის სტანდარტული დოზა და 20 ნმ AgNPs-ის ხსნარის 6 განსხვავებული კონცენტრაცია: 0,25%, 0.5%, 1%, 2.5%. 5% და 10% დაემატა მოქსიფლოქსაცინის მიმართ რეზისტენტული ტუბერკულოზის მიკობაქტერიის 70 იზოლატს. საკონტროლო ჯგუფი შეადგინა FQ/R-MTB-ის 70 იზოლატმა, რომელსაც დაემატა AgNPs-ის სუსპენზიის იდენტური კონცენტრაციის ხსნარები. ნანოკომპოზიტების ინჰიბიტორული ეფექტი შეფასდა ტუბერკულოზის მიკობაქტერიის ზრდის საფუძველზე BACTEC ™ MGIT 960™ ავტომატური სისტემის გამოყენებით. შედეგები: FQ/R-TB-ის იზოლატების ზრდის ინჰიბირების პროცესი დაიწყო 20ნმ AgNPs-ის სუსპენზიის დამატებისას და სრული ინჰიბირება დაფიქსირდა AgNPs-ის 5% და 10% სუსპენზიების გამოყენებისას FQ/R-TB-ის კულტურებზე. In vitro მოქსიფლოქსაცინის სტანდარტული დოზისა და AgNPs-ის 2.5% კონცენტრაციის შემცველი ნანოკომპოზიტის გამოყენებისას აღინიშნა მინიმალური ინჰიბიტორული ეფექტის ზრდა 10%-ით (85%) AgNPs-ის 2.5% სუსპენზიის იზოლირებულ გამოყენებასთან შედარებით (75%). მსგავსი ტენდენცია დაფიქსირდა FQ/R-MTB-ის ორივე (რიფამპიცინის მიმართ მგრძნობიარე; რიფამპიცინის მიმართ რეზისტენტულ)კოჰორტაში. დასკვნა: ჩვენს მიერ ჩატარებული ექსპერიმენტული კვლევის შედეგად დადგინდა ვერცხლის ნანონაწილაკების გამაძლიერებელი ეფექტის არსებობა ტუბერკულოზის მიკობაქტერიის მოქსიფლოქსაცინის მიმართ არსებული მდგრადობის დაძლევაში, რაც ქმნის შემდგომი კვლევებისსაფუძველს ადამიანისათვის უსაფრთხო ნანოკომპოზიტური პრეპარატის შესაქმნელად.

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