

GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 2 (347) Февраль 2024

ТБИЛИСИ - NEW YORK



ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press.
Published since 1994. Distributed in NIS, EU and USA.

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 ВИНТИ 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 ВИНТИ 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. Корректуре авторам не высылаются, 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 computer-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 საქურაღებოლ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დაიცვათ 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 შედეგის 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 ფხიხლებში 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.

Yu-Ri Choi, Su-Bin Yu, Seoul-Hee Nam. ANTIBACTERIAL EFFECT OF CRATAEGUS PINNATIFIDA EXTRACT AGAINST ENTROCOCCUS FAECALIS A ROOT CANAL DISEASE-CAUSING BACTERIA.....	6-10
Larisa Melia, Revaz Sulukhia, Lali Pkhaladze, Nino Davidova, Archil Khomasuridze. MIFEPRISTON IN OBSTETRICS – WHY NOT?.....	11-14
Maryna Stoliarchuk. CORRELATION BETWEEN TRANSVERSE CEPHALOMETRIC PARAMETERS AND THE SEVERITY OF SKELETAL MALOCCLUSIONS.....	15-18
Deepak, Prashant Rao, Archana, Sowmya M, Sandeep. S, Suma S. A CROSS-SECTIONAL STUDY ON COVID-19 VACCINATION HESITATION AMONG UNIVERSITY STUDENTS.....	19-23
Tchernev G, Broshtilova V, Ivanov L, Alexandrov A, Smilov N, Kordeva S. DRUG RELATED NITROSOGENESIS, PHOTOCARCINOGENESIS AND ONCOPHARMACOGENESIS OF NODULAR MELANOMA: A CASE RELATED ANALYSIS CONCERNING THE POLYCONTAMINATION OF THE POLYMEDICATION WITH VALSARTAN/ HYDROCHLOROTHIAZIDE AND BISOPROLOL.....	24-27
Rawaa J. Matloob, Zeina A. Althanoon, Saad A. Algburi, Mudheher I. Salih, Marwan M. Merkhan. UPDATE ON THE USE OF METHOTREXATE IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS.....	28-33
Georgi Tchernev. (N-NITROSO) PROPAPENONE INDUCED ADVANCED NODULAR MELANOMA-FIRST REPORTED CASE IN THE WORLD LITERATURE: THE INEXTRICABLE LINKS BETWEEN THE PHOTOCARCINOGENESIS, DRUG RELATED NITROSOGENESIS AND PHARMACO-ONCOGENESIS.....	34-37
Elham M. Mahmood, Entedhar R. Sarhat, Maryam T. Tawfeq, Siham A. Wadee. HISTOLOGICAL AND BIOCHEMICAL STUDY OF THE EFFECT OF FEXOFENADINE ON SALIVARY GLAND IN RATS.....	38-40
Valerii Vovk, Igor Duda, Alla Vovk. THE EFFECT OF A MULTIMODAL APPROACH ON THE RESULTS OF TREATMENT IN SURGERY: INTEGRATION OF CHEMOTHERAPY, SURGERY, AND RADIOTHERAPY.....	41-46
Haitham Alhussain, Deepak, Bharath Chandra V, Lakshmi. R, Sumana A, Jishamol KR. EXAMINATION OF THE INCIDENCE OF POOR SLEEP QUALITY AND FACTORS ASSOCIATED FOR POOR SLEEP DURING THE VARIOUS PHASES OF PREGNANCIES.....	47-53
N. Ksajikyan, H. Aghababyan, M. Sargsyan. ASSESSMENT OF REACTIVITY TO THE BODY UNDER CONDITIONS OF PHYSICAL ACTIVITY IN STUDENTS AGED 17-20 YEARS....	54-58
Abinaya Srinivasa Rangan, Dhanush Balaji.S, Utham Chand, Raghunathan E.G, Deepthi.N, Prasanna Karthik.S. TRIGLYCERIDE – GLUCOSE INDEX, REMNANT CHOLESTEROL AND COMMON CAROTID ARTERY INTIMA-MEDIA THICKNESS AS AN ATHEROSCLEROTIC MARKER IN ISCHEMIC STROKE PATIENTS.....	59-65
Riyam AH. Al-Barwani, Entedar R. sarhat. BREAST CANCER-MODULATED OMENTIN AND VASPIN PLASMA LEVELS.....	66-69
Tchernev G, Dimova D. PERIOULAR HIGH RISK BCCS AFTER ADDITIONAL/PARALLEL INTAKE OF TORASEMIDE, MOXONIDINE AND MIRABEGRON: IMPORTANT LINKS TO SKIN CANCER RELATED (PHOTO-) NITROSOGENESIS IN THE CONTEXT OF PHARMACO-ONCOGENESIS.....	70-76
Abinaya Srinivasa Rangan, Dhanush Balaji.S, Saranya.C, Raghunathan E.G, Deepthi.N, Prasanna Karthik.S. ASSOCIATION OF MPV AND RDW WITH DISEASE ACTIVITY IN PATIENT WITH RHEUMATOID ARTHRITIS.....	77-81
Julieta Nino Gulua, Lela Sturua, Maia Khubua, Lela Shengelia. THYROID CANCER AS A PUBLIC HEALTH CHALLENGE IN GEORGIA.....	82-86
Rahma S. Almallah, Hani M. Almkhtar. MIRABEGRON INDUCED RELAXATION OF ISOLATED BOVINE CORONARY SEGMENTS: ROLE OF NO AND K+ CHANNEL.....	87-92
Gogotishvili Mariam, Gogebashvili Nino, Bakradze Mzia, Gorgiladze Tinatin, Japaridze Fridon. MANIFESTATIONS OF DISEASES OF THE ORAL MUCOSA OF PATIENTS IN THE ADJARA REGION DURING THE COVID-19 PANDEMIC.....	93-95
Nithesh Babu R, Fathima S Nilofar, Saranya Palanisamy, Gnanadeepan T, Mahendra Kumar K. EXPLORING THE INCIDENCE AND PREVALENCE OF NEW-ONSET AUTOIMMUNE DISEASE FOLLOWING COVID-19 PANDEMIC: A SYSTEMATIC REVIEW.....	96-103

E. Mosidze, A. Chikovani, M. Giorgobiani. ADVANCES IN MINIMALLY INVASIVE SURGERY FOR PECTUS EXCAVATUM: ENHANCING OUTCOMES AND PATIENT CARE.....	104-107
Nithesh Babu R, Fathima S Nilofar, Saranya Palanisamy, Gnanadeepan T, Mahendra Kumar K. SIGNIFICANCE OF NEUTROPHIL-LYMPHOCYTE RATIO AND PLATELETLYMPHOCYTE RATIO AS PROGNOSTIC MARKERS OF DISEASE SEVERITY IN SYSTEMIC LUPUS ERYTHEMATOSUS.....	108-112
Athraa E. Ahmed, Nibras H. Hameed. PREVALENCE OF FETAL CONGENITAL ANOMALIES IN PATIENTS ATTENDING TIKRIT TEACHING HOSPITAL.....	113-116
Kazantcev A.D, Kazantceva E.P, Sarkisyan I.P, Avakova A.E, Shumakova A.O, Dyachenko Y.E, Mezhenko D.V, Kustov Y.O, Makarov Daniil Andreevich, Guliev M.T, Babaeva M.M. COMPARATIVE ANALYSIS OF POSITIVE AND NEGATIVE EXPECTATIONS WITH CONTROL OF VOLITIONAL EFFORT IN YOUNG AND OLD AGES AS RISK FACTORS OF SOCIAL AGING.....	117-121
Arnab Sain, Sarah Arif, Hoosai Manyar, Nauman Manzoor, Kanishka Wattage, Michele Halasa, Arsany Metry, Jack Song Chia, Emily Prendergast, Ahmed Elkilany, Odiamehi Aisabokhale, Fahad Hussain, Zain Sohail. CURRENT CONCEPTS IN THE MANAGEMENT OF BOXER'S FRACTURE.....	122-124
Gonashvili Meri, Kilasonia Besarion, Chikhladze Ramaz, Merabishvili Gela, Beriashvili Rusudan. MEDICO-LEGAL APPLICATIONS OF FRACTURE HEMATOMA: REVIEW.....	125-130
Zynab J. Jarjees, Entedhar R. Sarhat. ASSESSMENT OF OSTEOPONTIN, SCLEROSTIN, AND OSTEOCALCIN LEVELS IN PATIENTS WITH HYPOTHYROIDISM ON MEDICAL THERAPY.....	131-135
Tchernev G, Dimova D. EDUCATION FROM DERMATOLOGISTS: THE SIMULTANEOUSLY DEVELOPMENT OF 16 KERATINOCYTIC CANCERS AFTER USE OF METFORMIN IN COMBINATION WITH LOSARTAN/ HYDROCHLOROTHIAZIDE, METOPROLOL AND NIFEDIPINE-IMPORTANT LINKS TO DRUG RELATED (PHOTO)-NITROSO-CARCINOGENESIS AND ONCOPHARMACOGENESIS.....	136-141
Ismayilov M.U, Polukhov R.Sh, Poddubny I.V, Magammedov V.A. COMPARATIVE ASSESSMENT OF SURGICAL TREATMENT OF COMPLICATIONS OF ULCERATIVE COLITIS IN CHILDREN.....	142-148
Arnab Sain, Arsany Metry, Nauman Manzoor, Kanishka Wattage, Ahmed Elkilany, Michele Halasa, Jack Song Chia, Sarah Arif, Fahad Hussain, Odiamehi Aisabokhale, Zain Sohail. THE ROLE OF DISTAL LOCKING IN INTRAMEDULLARY NAILS FOR HIP FRACTURE FIXATION: A REVIEW OF CURRENT LITERATURE.....	149-150
Buba Chachkhiani, Manana Kalandadze, Shalva Parulava, Vladimer Margvelashvili. EFFECT OF SURFACE ABRASION AND TEMPERATURE TREATMENT ON METASTABLE TETRAGONAL ZIRCONIUM DIOXIDE (EXPERIMENTAL STUDY).....	151-155
Abdulrahman A Abdulhamed, Luma W Khaleel. CARDIOPROTECTIVE EFFECT OF GLYCYRRHIZA GLABRA EXTRACT AND GLYCYRRHIZA GLABRA SILVER NANOPARTICLE AGAINST ALLOXAN AND NICOTINAMIDE INDUCED DIABETIC CARDIAC INJURY IN RATS.....	156-159
Larysa Pentiuk, Tetiana Niushko, Emiliia Osiadla. FEATURES OF BLOOD PRESSURE DAILY MONITORING INDICATORS, STRUCTURAL AND FUNCTIONAL CHANGES OF THE LEFT VENTRICLE AND VESSELS IN WOMEN WITH HYPERTENSION II STAGE OF DIFFERENT REPRODUCTIVE AGE AND THEIR RELATIONSHIP WITH SEX HORMONES LEVEL.....	160-167
Rana dawood Salman Al-kamil, Thamer F. Alkhiat, H. N. K. AL-Saman, H. H. Hussein, Dawood Chalooob Hilyail, Falah Hassan Shari. THE EFFECT OF NUTRITIONAL GENOMICS ON CARDIOVASCULAR SYSTEM.....	168-176
Sopiko Kvaratsthelia. PREVALENCE OF DENTITION, DENTAL ARCHES AND DENTAL ANOMALIES.....	177-180
Dorosh D, Liadova T, Popov M, Volobuieva O, Pavlikova K, Tsivenko O, Chernuskiy V, Hrek I, Kushnir V, Volobuiev D. THE EFFECT OF MELATONIN ON THE SERUM LEVEL OF INTERLEUKIN 31 IN HERPESVIRUS SKIN DISEASES ON THE BACKGROUND OF HIV.....	181-184

MIRABEGRON INDUCED RELAXATION OF ISOLATED BOVINE CORONARY SEGMENTS: ROLE OF NO AND K⁺ CHANNEL.

Rahma S. Almallah, Hani M. Almukhtar*.

College of Pharmacy, University of Mosul, Mosul, Iraq.

Abstract.

Background: It was already known that mirabegron, a β_3 -adrenoceptor agonist, affected cardiac muscle, data also demonstrated that mirabegron induced a relaxant effect in rat aortic vessels by a mechanism dependent on nitric oxide production. This study examined the possible effects of mirabegron on the coronary vascular tone. Results show that mirabegron induced an acute relaxant effect on coronary segments' contractility, and the relaxation is partly dependent on nitric oxide and K⁺ channel activation. These findings emphasize the need to consider these mechanisms when translating mirabegron's effects to clinical applications.

Objectives: Mirabegron, the first approved β_3 -adrenoceptor agonist, has demonstrated positive effects in heart failure. Research indicates that β_3 agonists induce prompt relaxation in rat aortic and human coronary vessels through a pathway mediated by NO. This study examined mirabegron's influence on bovine coronary segments' contractility.

Methods: Using isolated tissue baths, the impact of mirabegron on bovine coronary artery segments' contractility was assessed. The plasma level of NO was measured with a specialized kit. NO was determined by measuring plasma nitrite concentrations by spectrophotometric analysis at 540 nm.

Results: Mirabegron evoked relaxation in bovine coronary artery segments in a dose-dependent manner. However, this effect was inhibited by the presence of potassium chloride (KCl) (70mM) and methylene blue (30 μ M). Both potassium channel and NO pathways were found to play a role in the relaxations induced by mirabegron. Furthermore, mirabegron was observed to enhance in vivo nitric oxide (NO) levels, a crucial signaling molecule maintaining cardiovascular equilibrium.

Conclusions: Our findings illustrate that mirabegron induces coronary vessel relaxation through the activation of both NO and K⁺ channels. These findings emphasize the need to consider these mechanisms when translating mirabegron's effects to clinical applications.

Key words. Mirabegron, coronary, relaxation, K⁺ channels, NO.

Introduction.

Mirabegron, is a highly selective β_3 versus β_1 and β_2 adrenergic receptor agonist currently approved for the treatment of bladder overactivity. It significantly relaxes human and bladder smooth muscle via cAMP-dependent and independent pathways such as K⁺ channel activation and Rho kinase inhibition [1,2]. It also induces relaxation of the prostate [3], β_1 and β_2 adrenergic receptors are distributed in cardiac and vascular tissue, β_1 mediates the inotropic and chronotropic effect of the adrenergic system on the heart, while both β_1 and β_2 mediate the relaxant effect in the vascular tissue [4]. Moreover, results have clearly

shown that β_3 adrenergic receptors are also expressed in the heart. The latter induces a negative inotropic effect in the heart ventricle, the mechanism is not fully explained, however, results have shown that the selective β_3 agonist inhibits voltage-gated Ca²⁺ channel. In contrast, β_3 activation in atrial muscle increases Ca²⁺ current which is associated with a positive inotropic effect. In vascular smooth muscle, the involvement of β adrenergic receptors in the relaxation of the arterial smooth muscle has been proven in many studies. For example, Isoprenaline-induced relaxation of vascular smooth muscle is mediated by the activation of β_2 receptor together with β_1 receptors [5]. However, studies have demonstrated the involvement of a third β_3 -adrenergic receptor subtype in the physiological control of smooth muscle and vascular contraction. β_3 induced relaxation has been suggested with a variable mechanism in many vascular beds, the possibility was strengthened by peripheral vascular dilation induced by the injection of a selective β_3 agonist BRL 37344 in dogs [6]. The same agonist also induced in-vitro relaxation via the release of NO in rat thoracic and abdominal aorta [7], however, in the carotid artery, β_3 agonist-induced endothelium-independent relaxation [7]. Most importantly, β_3 -adrenoreceptors were identified in the endothelium of human coronary resistance microarteries, where they mediate an endothelium-dependent relaxation to both endogenous catecholamine and β_3 -adrenoreceptor-preferential agonists [8]. Mirabegron, by acting on β_3 adrenoceptor is expected to induce off-label effects on cardiac and vascular tissue [9]. Shen et al, have shown that mirabegron lowers the resistance of the peripheral resistance in dogs [6]. In humans, mirabegron slightly increases blood pressure with the recommendation of periodic examination of blood pressure in elderly hypertensive patients [10]. Thus, the aim of the present study was designed to examine the effect of mirabegron on the contractility of the isolated bovine coronary rings.

Materials and Methods.

Materials: Mirabegron was obtained from a local pharmacy. Methylene blue, DMSO and other constituents of the Krebs solution were obtained from the University of Mosul.

Tissue preparation: In this study, isolated bovine coronary arteries were used to examine the impacts of mirabegron, following established methods as previously described [11,12]. Hearts from male and female bovines were procured from local butcher shops and transported in a container filled with cold Krebs-Henseleit physiological buffer. Initial dissection procedures were carried out to isolate the anterior segment of the proximal coronary artery. Subsequently, the arterial segment was meticulously dissected and cleared of adjacent connective and adipose tissue. The artery was then divided into rings of approximately 5mm length. The segments were prepared for

connection in an isolated tissue bath setup. Each segment was suspended between two hooks in a 25ml organ bath chamber. The first hook was connected to a transducer measuring the force of contraction which was further connected to the amplifier and the Laptop, the lower hook was connected to the bottom with a special glass support. The chambers were filled with about 20 ml of Krebs-Henseleit solution containing the followings in mM: (NaCl 118, KCl 4.8, CaCl₂.H₂O 1.3, NaHCO₃ 25.0, KH₂PO₄ 1.2, MgSO₄.7H₂O, glucose 11.1). The bathes were connected to a circulating bath and thermostat to control the temperature at the physiological level of 37°C. Continuous gassing was maintained with carbogen, 95% O₂ with 5% CO₂. The experiment was recorded with iWorx LabScribe data recording and analysis software. The transducers were calibrated before each experiment using a 10-gram weight [11,12].

Tension recording: The segments were initially precontracted to about 8gm of tension. Then the segments were allowed to relax to the baseline level for about 30 to 40 minutes. Once stabilized the tissue were depolarized with 70mM KCL bath concentration. Such a concentration has been shown to depolarize the tissue and open the voltage gated Ca⁺² channel. After about 10 min at the plateau the segments were washed with normal Krebs and the process was repeated twice to improve contractility and for standardization. After washing from high K⁺ Krebs, the tissue was then precontracted with a cumulative concentration of the thromboxane analogue, U46619. The addition started at 100nM and increased to about 1µM to contract the tissue to about 70% of the KCL contraction. Subsequently, a single concentration of mirabegron, 10µM, was added to the bath for about a 2hr duration. In another set of experiments, mirabegron 10µM was added after KCl wash at the baseline for about 1hr followed by a cumulative addition of U46619. Another experiment was done to determine the effect of depolarization with 70mM KCl, and thus the role of K⁺ channel on mirabegron relaxant effect. In all experiments, the control segments were incubated with the solvent control DMSO. To investigate the influence of endothelial factors, particularly nitric oxide (NO), on the impact of mirabegron, the tissues was incubated with methylene blue at a concentration of 30µM. This specific concentration of methylene blue has been shown to effectively inhibit guanylate cyclase (GC) in bovine coronary arteries [13].

Animals: In this present investigation, a total of eighteen albino rats with weights ranging from 200 to 240 grams were utilized. The rats were kept in groups of 2 to 3 per cage, maintaining a controlled environment with a temperature range of 22 to 25°C and humidity levels between 45% and 65%. Adequate provisions of water and food were provided without restrictions. The entire experimental protocol and animal handling procedures were conducted following the ARRIVE guidelines and adopted in previous studies [14-19]. The rats were categorized into three groups, each containing six rats. These groups were defined as follows: the initial control group received solvent by oral administration; the second and third groups were orally administered mirabegron at doses of 2 mg/kg and 8 mg/kg every day for a duration of 6 days. At the end of the experiment, all rats were humanely euthanized using the decapitation method. The method of the study was approved by the Institutional Animal Care and Use Committee at the

University of Mosul, College of Veterinary Medicine (UM. VET. 2022.066).

Serum Nitric oxide: A blood sample was collected using the beheading method sacrifices. The blood was allowed to stand for approximately 30 min and then centrifuged at 2000 rpm for 15 min. Serum nitric oxide level was measured using commercial kit Elabscience® based on the Griess reaction assay [20]. The samples were measured using a spectrophotometer at a wavelength of 550 nm. The measurement of the overall concentration of nitric oxide (NO) in serum involves assessing the combined levels of nitrite (NO₂⁻) and nitrate (NO₃⁻). These substances are stable end-products of NO metabolism and serve as indirect indicators of NO presence. The total quantity of NO is typically the sum of the concentrations of nitrite and nitrate. To determine NO concentration, a method relying on the measurement of nitrite concentration in serum was employed, following Griess's reaction. In this process, nitrate was transformed into nitrite and subsequently converted into nitric acid, which reacted with Griess's reagent to produce a visible color change. The concentration of nitrite was determined through spectrophotometric analysis at 540 nm, using a standard curve as a reference. The results indicating NO content were expressed in micromoles.

Data and statistical analysis: The collected data were analyzed using a two-way ANOVA test. Results are presented as mean±standard error (SE). In cases where the ANOVA was significant, a post-hoc Bonferroni test was performed. The significance level was set at a P value less than 0.05, indicating a statistically significant mean difference. The levels of significance are denoted as follows: *** means p< 0.001, ** means p<0.01, and * means p<0.05. The results of relaxation were compared with values obtained from the DMSO solvent control. Statistical analysis for all experiments was conducted using GraphPad Prism 5 software.

Results.

Isolated tissue bath experiments: As previously demonstrated, a preliminary experiment on sheep bladder segments showed that mirabegron induced significant relaxation of bladder segments (Figure 1). More notably, 30min incubation with mirabegron significantly inhibited the contraction of isolated coronary vessels (Figure 2A), mirabegron also induced significant relaxation of the isolated bovine coronary rings precontracted with U46619 (Figure 2C) starting after approximately 30min of drug incubation. Incubation with methylene blue (30µM) abolished the inhibitory effect of mirabegron on coronary tone (Figure 2B). The rate of relaxation was determined by calculating the percentage change from the contraction induced by U46619, within a period of approximately 2 hours. Additionally, the rate of contraction was calculated as a percentage of KCl contraction. The presented values for each repetition represent the mean ± SEM, and negative values denote relaxation. The rate of relaxation induced by mirabegron was compared to a control containing DMSO (at a concentration of 0.1% v/v) over a 2-hour interval. This comparison was conducted using a two-way analysis of variance (ANOVA) followed by a Bonferroni post-hoc test. Significance was attributed to instances where the P-value was below 0.05. The symbols *** p-value < 0.001, ** p-value <0.01, and *p-value <0.05.

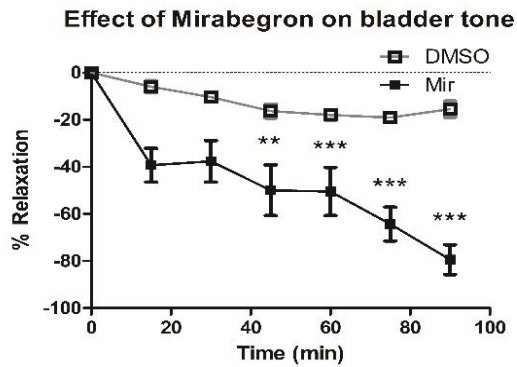


Figure 1. The effect of Mir 10 μ M on isolated bladder segments. The figure shows the significant relaxant effect of mirabegron(Mir) 10 μ M (n=5) in sheep bladder tissue precontracted with U46619.

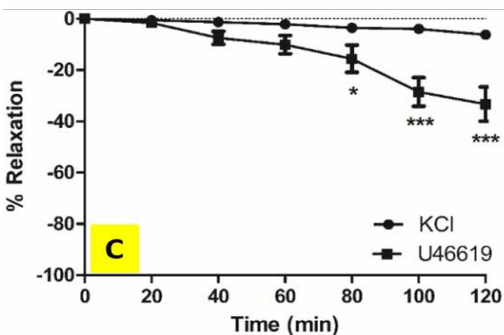
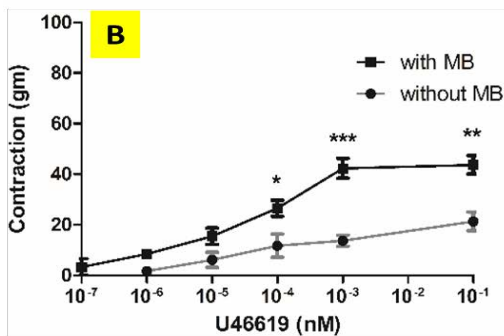
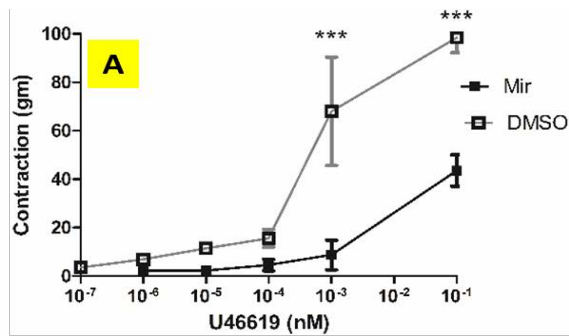


Figure 2. (A) Effect of mirabegron (Mir) incubation for 30 minutes on the contractile response of the isolated bovine coronary segments to U46619-induced contraction (n=6). (B) Effect of mirabegron (Mir) incubation for 30min on the contractile response of the isolated bovine coronary segments to U46619-induced contraction incubated with MB 30 μ M for 30min then mirabegron 10 μ M for another 30min (n=6). (C) The effect of depolarization with 70mM KCl on mirabegron relaxation in isolated bovine coronary segments (n=7). The presence of 70mM KCl significantly attenuated the relaxation caused by mirabegron when compared to precontraction induced by U46619.

NO serum level

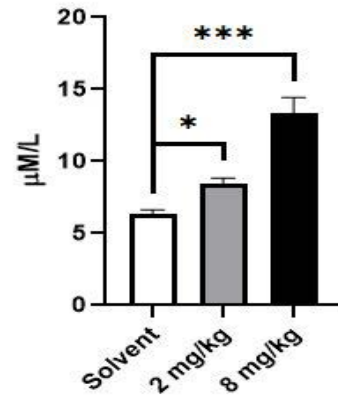


Figure 3. Shows the levels of total serum concentration of NO (NO_3^-/NO_2^-) in both the solvent-treated group as a control, and the mirabegron treated group. In the mirabegron group, the serum NO concentrations were significantly higher in comparison to the control group. Moreover, the total concentration of NO in the serum of rats treated with 8 mg/kg was higher those treated with 2 mg/kg (*= $p < 0.05$, ***= $p < 0.001$).

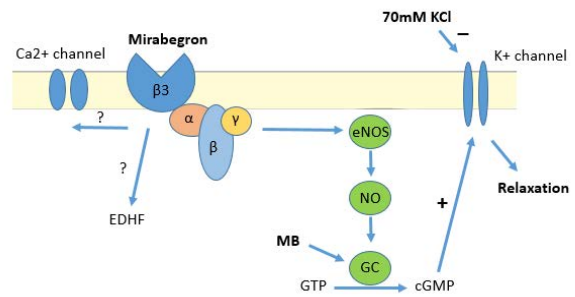


Figure 4. Suggested mechanism of mirabegron relaxation in bovine coronary vessels. Mirabegron activates eNOS in the endothelium, increases NO, and induces relaxation via K⁺ channel activation. MB inhibits GC activation and inhibits mirabegron relaxation. The addition of 70mM KCl also inhibits K⁺ channel activation and thus mirabegron relaxation. eNOS, endothelial nitric oxide synthase; GC, guanylyl cyclase; cGMP, cyclic 3',5'-guanosine monophosphate; MB, methylene blue.

Serum Nitric oxide (NO) level: The assessment of serum total NO level indicated a significant distinction between the rats subjected to mirabegron treatment and those exposed solely to the solvent (Figure 3). Results also revealed significant differences in serum NO levels between the rats treated with 2 mg/kg and those administered 8 mg/kg of mirabegron daily ($p < 0.001$). This comparison was conducted utilizing one-way ANOVA followed by a Welch and Brown-Forsythe test.

Discussion.

Mirabegron exhibited a relaxation effect on the bovine coronary artery that progressed over time. Typically, relaxation commenced within approximately 30 minutes following the addition of the drug. However, the relaxation process was gradual, reaching its peak response approximately 120 minutes after initial pre-contraction using U46619 depolarization. This

relaxation phenomenon is likely attributed to mirabegron's capability to stimulate the generation of nitric oxide (NO). methylene blue 30 μ M was able to significantly inhibit mirabegron relaxation, providing evidence for NO-dependent relaxation [13]. Experimental evidence suggests that methylene blue with such concentration was able to inhibit bovine coronary relaxation to organic nitrates by direct inhibition of endothelial nitric oxide synthase enzyme eNOs [13]. Consistent with the isometric study, the examination of NO level in the plasma of animals treated with mirabegron showed that the drug increased NO significantly and the effect was dose-dependent (Figure 3). Similarly, studies have shown that other β adrenergic agonists like epinephrine, in response to stress and exercise, terbutaline and isoproterenol-induced coronary relaxation via NO-mediated pathway. Physiologically, the coronary blood flow increases when β -adrenergic receptors are stimulated [21]. Coronary vasodilation is suggested to compensate for the increase in oxygen demand due to the increased cardiac inotropic and chronotropic effect of catecholamine, the latter can activate β 1 and β 2 adrenergic receptors with a resultant increase in cAMP and vasorelaxation, the present observations are consistent with β 1 and β 2 activation results since it suggests that the activation of β 3 would also activate additional adrenergic pathway in the coronary circulation mediated via NO production. β 3 activation also promotes circulation in the ischemic limb in the murine diabetic model and pancreatic circulation [22].

It is well accepted that mirabegron induces relaxation of the human and rat urinary bladder via activation of β 3 adrenergic receptors [23], the latter could also be related to the activation of the bladder urothelium to produce NO as a signaling molecule, mirabegron also induces smooth muscle relaxation via nitric oxide-dependent pathway in different vascular beds like thoracic and abdominal aortic vessels [24]. Similarly, in vitro studies with experimental β 3 agonists provide further evidence for β 3 induced endothelium-dependent relaxation. It was also observed that the β adrenergic blocker, nebivolol, by activation of β 3 adrenoceptor agonist, could induce endothelium-dependent vascular tissue relaxation [25], the relaxation was inhibited in genetically modified β 3 deficient rats. In vivo, studies have also shown that β 3 agonist-induced coronary vasodilation with additional cardiac inotropic effect [25]. By contrast, in rat carotid artery β 3 adrenoceptor agonist-induced endothelium-independent relaxation, the reason could be related to the difference in vascular bed and the role of NO in carotid artery relaxation [26]. It is well known that NO could have an additional relaxant effect via direct activation of Kca channels [27]. Accordingly, the study examined the role of the K^+ channel in mirabegron relaxation, Data have shown that the relaxation to mirabegron is partly dependent on the contractile agent since mirabegron-induced relaxation of vessels precontracted with U46619 significantly more than the vessels precontracted with 70mM KCl. In fact, by enhancing the K^+ level extracellularly the efflux of ions through the K^+ channel would be reduced due to a reduction in electrochemical gradient with resultant cell depolarization and the opening of the voltage-gated Ca^{+2} channel. The outcomes of these findings indicate the involvement of potassium (K^+) channels in the relaxation induced by mirabegron. Moreover, the addition of KCl to the extracellular

compartment would prevent cellular hyperpolarization and thus inhibit the role of other endothelium-derived hyperpolarizing factors, the latter need to be examined in further study [28]. Similarly, previous data also suggest a role of the K^+ channel in mirabegron-induced relaxation in lung tissue precontracted in hypoxic conditions [29]. The involvement of K^+ channels has also been suggested as a downstream signal for β 3 induced relaxation in rat aorta [30]. BRL 37344 a selective agonist for the β 3 receptor also induced endothelium-dependent relaxation of human coronary vessels. These results collectively suggest a role for β 3 receptors in smooth muscle hyperpolarization. The signalling pathway of β 3 activation in coronary vascular tissue is summarized in Figure 4.

By contrast, in the pulmonary artery CL 316 243 induced endothelium-independent relaxation via increased synthesis of cAMP while in the mammary artery, SR 58611A induced NO-dependent and independent relaxation [31]. Interestingly, in myocytes isolated from the portal vein, β 3 agonists activate voltage-gated channels through stimulation of cAMP with subsequent phosphorylation and inactivation of the channel [32]. Ca^{+2} increased intracellularly by either increased influx from voltage-gated and store-operated channels or even released from the intracellular store upon stimulation by an agonist, KCl addition to the bath would activate Ca^{+2} influx from the voltage channel, mirabegron was approved to inhibit Ca^{+2} channel in the cardiac muscle such mechanism could play a role in coronary vasodilation. Moreover, the NO released from the endothelium could also inhibit the Ca^{+2} channel. The effect of mirabegron on the Ca^{+2} channel needs further study.

Previous results suggested an inhibitory effect of β 3-adrenoceptors on human heart contractility [33], vascular β 3 adrenergic receptors like those in the heart could serve as a brake at sympathetic overstimulation, thus mirabegron-induced relaxation might contribute to a beneficial clinical hemodynamic effect via activation of β 3 receptor and increased NO especially in those with coronary artery diseases. In conclusion, the findings of the present study recommend more investigation concerning the role of β 3 in coronary pathophysiology and examination of the effects of selective β 3 agonists [31].

Conclusion.

Our findings illustrate that mirabegron induces coronary vessel relaxation through the activation of both NO and K^+ channels. These findings emphasize the need to consider these mechanisms when translating the effects of mirabegron in clinical applications.

Conflict of interest: All authors declare that there is no conflict of interest.

Acknowledgments: The authors are very grateful to the University of Mosul/College of Medicine and College of Pharmacy for their provided facilities which helped to improve the quality of this work.

REFERENCES

1. Maki T, Kajioka S, Itsumi M, et al. Mirabegron induces relaxant effects via cAMP signaling-dependent and-independent pathways in detrusor smooth muscle. LUTS: Lower Urinary Tract Symptoms. 2019;11:O209-17.

2. Alchalaby LA, Zainal AA, Mahmood MD. Stimulation of Beta-3 Adrenergic Receptors Modulated Sperm Motility and Morphology in Rat. *Tropical Journal of Natural Product Research*. 2022;6.
3. Calmasini FB, Candido TZ, Alexandre EC, et al. The beta-3 adrenoceptor agonist, mirabegron relaxes isolated prostate from human and rabbit: new therapeutic indication?. *The Prostate*. 2015;75:440-7.
4. De Stefano A, Schinzari F, Di Daniele N, et al. Mirabegron relaxes arteries from human visceral adipose tissue through antagonism of α 1-adrenergic receptors. *Vascular Pharmacology*. 2022;146:107094.
5. Gray DW, Marshall I. Novel signal transduction pathway mediating endothelium-dependent beta-adrenoceptor vasorelaxation in rat thoracic aorta. *British journal of pharmacology*. 1992;107:684.
6. Shen YT, Zhang H, Vatner SF. Peripheral vascular effects of beta-3 adrenergic receptor stimulation in conscious dogs. *Journal of Pharmacology and Experimental Therapeutics*. 1994;268:466-73.
7. Trochu JN, Leblais V, Rautureau Y, et al. Beta 3-adrenoceptor stimulation induces vasorelaxation mediated essentially by endothelium-derived nitric oxide in rat thoracic aorta. *British journal of pharmacology*. 1999;128:69-76.
8. Dessy C, Moniotte S, Ghisdal P, et al. Endothelial β 3-adrenoceptors mediate vasorelaxation of human coronary microarteries through nitric oxide and endothelium-dependent hyperpolarization. *Circulation*. 2004;110:948-54.
9. Loh RK, Formosa MF, La Gerche A, et al. Acute metabolic and cardiovascular effects of mirabegron in healthy individuals. *Diabetes, Obesity and Metabolism*. 2019;21:276-84.
10. Ito H, Matsuo T, Mitsunari K, et al. Impact of Mirabegron Administration on the Blood Pressure and Pulse Rate in Patients with Overactive Bladder. *Medicina*. 2022;58:825.
11. Almukhtar H, Garle MJ, Smith PA, et al. Effect of simvastatin on vascular tone in porcine coronary artery: Potential role of the mitochondria. *Toxicology and applied pharmacology*. 2016;305:176-85.
12. Saarti M, Almukhtar H, Smith PA, et al. Effect of mitochondrial complex III inhibitors on the regulation of vascular tone in porcine coronary artery. *European Journal of Pharmacology*. 2021;896:173917.
13. Mayer B, Brunner F, Schmidt K. Inhibition of nitric oxide synthesis by methylene blue. *Biochemical pharmacology*. 1993;45:367-74.
14. Althanoon ZA, Merkhan MM. CoQ10 dampens the deleterious impact of doxorubicin-induced liver and spleen injury in white Albino rats. *Current Topics in Pharmacology*. 2023;27.
15. Abdullah SI, Al-Bayti AA, Salih MJ, et al. Histological and Biochemical Changes Associated with Blocking of Serotonin Receptor. *Tropical Journal of Natural Product Research*. 2022;6.
16. Younis MA, Hamid OA, Dhaher R, et al. Characterization of the renal safety profiles of coumacines. *Pharmakeftiki Journal*. 2023;35.
17. Al-Shakarchi W, Saber Y, Merkhan M, et al. Acute toxicity of coumacines: an in vivo study. *Georgian Medical News*. 2023;338:126-31.
18. Saarti M, Mahmood MD, Alchalaby LA. Comparative Effect of Aripiprazole Versus Risperidone on Sperm Motility and Morphology in Rats. *Revista Electronica de Veterinaria*. 2022;304-13.
19. Mahmood MD, Younes MA, Saarti M. Pathophysiological Electrolyte Changes Connotted via Antagonism of Serotonin Receptor in Experimental Animals. *Pharmacognosy Journal*. 2022;14.
20. Sun J, Zhang X, Broderick M, et al. Measurement of nitric oxide production in biological systems by using Griess reaction assay. *Sensors*. 2003;3:276-84.
21. Graves J, Poston L. Beta-adrenoceptor agonist mediated relaxation of rat isolated resistance arteries: a role for the endothelium and nitric oxide. *British journal of pharmacology*. 1993;108:631.
22. Bubb KJ, Ravindran D, Cartland SP, et al. β 3 Adrenergic Receptor Stimulation Promotes Reperfusion in Ischemic Limbs in a Murine Diabetic Model. *Frontiers in Pharmacology*. 2021;12:666334.
23. Cernecka H, Kersten K, Maarsingh H, et al. β 3-Adrenoceptor-mediated relaxation of rat and human urinary bladder: roles of BK Ca channels and Rho kinase. *Naunyn-schmiedeberg's Archives of Pharmacology*. 2015;388:749-59.
24. Matsushita M, Horinouchi T, Tanaka Y, et al. Characterization of β 3-adrenoceptor-mediated relaxation in rat abdominal aorta smooth muscle. *European journal of pharmacology*. 2003;482:235-44.
25. Dessy C, Saliez J, Ghisdal P, et al. Endothelial β 3-adrenoreceptors mediate nitric oxide-dependent vasorelaxation of coronary microvessels in response to the third-generation β -blocker nebivolol. *Circulation*. 2005;112:1198-205.
26. Oriowo MA. Atypical beta-adrenoceptors in the rat isolated common carotid artery. *British journal of pharmacology*. 1994;113:699.
27. Bolotina VM, Najibi S, Palacino JJ, et al. Nitric oxide directly activates calcium-dependent potassium channels in vascular smooth muscle. *Nature*. 1994;368:850-3.
28. Shimokawa H, Yasutake H, Fujii K, et al. The importance of the hyperpolarizing mechanism increases as the vessel size decreases in endothelium-dependent relaxations in rat mesenteric circulation. *Journal of cardiovascular pharmacology*. 1996;28:703-11.
29. Dumas JP, Goirand F, Bardou M, et al. Role of potassium channels and nitric oxide in the relaxant effects elicited by β -adrenoceptor agonists on hypoxic vasoconstriction in the isolated perfused lung of the rat. *British journal of pharmacology*. 1999;127:421-8.
30. Rautureau Y, Toumaniantz G, Serpillon S, et al. Beta 3-adrenoceptor in rat aorta: molecular and biochemical characterization and signalling pathway. *British journal of pharmacology*. 2002;137:153-61.
31. Rozec B, Serpillon S, Toumaniantz G, et al. Characterization of beta3-adrenoceptors in human internal mammary artery and putative involvement in coronary artery bypass management. *Journal of the American College of Cardiology*. 2005;46:351-9.

32. Viard P, Macrez N, Coussin F, et al. Beta-3 adrenergic stimulation of L-Type Ca^{2+} channels in rat portal vein myocytes. *British journal of pharmacology*. 2000;129:1497-505.

33. Zhang ZS, Cheng HJ, Onishi K, et al. Enhanced inhibition of L-type Ca^{2+} current by β_3 -adrenergic stimulation in failing rat heart. *Journal of Pharmacology and Experimental Therapeutics*. 2005;315:1203-11.