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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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NEUROPROTECTIVE FITNESS OF LOSARTAN AGAINST DOXORUBICIN INDUCED NEUROTOXICITY IN WHITE ALBINO RATS

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Abstract.

Background: Doxorubicin (Dox) is clinically effective anticancer agent with cytotoxic downside features of neurotoxicity. Losartan (LST), an angiotensin II type 1 receptor blocker (ARB), is antihypertensive with reported pleiotropic effects, hence, the current study was sought to identify the protective effects of losartan in mitigating Dox-induced neurotoxicity in a white Albino rat model.

Methods: Fifty-six adult rats were sub-classified into males and females for each intervention. The groups include control, Dox alone, LST alone, combined Dox and SLT. After sacrificing, the brain was harvested for preparation of slides. Slides were stained and images captured.

Results: Sections from control groups and LST alone were intact in both sexes. Sections from Dox groups in either sex demonstrated moderate to severe tissue changes represented as vascular congestion, glial activation, and focal gliosis. The combination groups of Dox and LST demonstrated restored architecture represented by reduced congestion and gliosis in dose dependent manner with female showing better positive response compared to male.

Conclusion: LST provided histological notable protective effects against Dox insults neurotoxicity in white Albino rats.

Key words. Losartan, doxorubicin, neuroprotection, renin-angiotensin system.

Introduction.

Doxorubicin (Dox) is an anthracycline anticancer agent commonly used for different type of hematological and solid malignancies [1]. Their applications were counteracted by downside side effects of cytotoxicity, including cardiotoxicity, hepatotoxicity, nephrotoxicity, and neurotoxicity [2]. The cognitive impairment associated with Dox characterized by memory deficits, attention difficulties, and impaired executive function [3].

The pathophysiology of Dox-induced neurotoxicity is complex, encompassing oxidative damage, mitochondrial upset, neuroinflammation, and neuronal apoptosis [4]. The pathogenesis at molecular levels involved various biomolecules with renin-angiotensin system (RAS) being a part in overall pathways [5]. Angiotensin II binding to AT1R activates the membrane-bound NADPH oxidase complexes, generating reactive oxygen species (ROS), including superoxide anions, leading to mitochondrial disruption, lipid peroxidation of neuronal cell membrane, stimulation of proinflammatory nuclear factor-kappa B (NF-κB) pathways, resulting in neuronal apoptosis, brain neuroinflammation, and perturbing blood-brain barrier, ultimately leading to neurodegeneration [6-8].

Binding of angiotensin II and activation of AT1R on cerebral immune cells (microglia and astrocytes), and cerebral endothelial cells provoke subcellular events that activates the NF-κB signalling pathway of inflammation, eventually generating proinflammatory biomolecules, including tumor necrosis factor-α, interleukin-1β, interleukin-6, cyclooxygenase-2, and inducible nitric oxide synthase [9,10]. These changes create a proinflammatory milieu leading to activation of microglial cells and astrocytes, resulting neuronal dysfunction alongside disruption of blood-brain barrier, enhancing immune cells infiltration [11]. These pathways participate in chemotherapy-associated cognitive impairment, including Dox [12].

Losartan is antihypertensive that induce vasodilation by binding to AT1R in peripheral tissue. In central nervous system, losartan blocks AT1R resulting in reducing oxidative stress and hence down regulating NADPH oxidase activity, reducing lipid peroxidation, improving mitochondrial functions in neuronal tissues [6]. Moreover, losartan block the master NF-κB neuroinflammatory pathway mitigating microglial activation and dampening the pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) generation [6]. The dualistic effects on oxidative stress and inflammation eventually ends with blood-brain barrier protection, reduction of neuron apoptosis, encourage neuronal fitness, and brain resilience against xenogenic insults. The present study sought to identify the cytoprotection capacity of losartan against neurotoxic insult of Dox.

Materials and Methods.

Animals and housing: The present study started with 56 adult Albino Wistar rats, kindly provided by College of Veterinary Medicine, University of Mosul. The animals were housed in standard polypropylene cages under standard condition outlined in table 1.

Experimental design: Rats were allocated into eight experimental groups (n = 7 per group), as detailed in Table 2. To check sex-dependent effects of LST, rats were subclassified into males and females for each intervention. All oral medications were performed using a gavage needle, and drugs were instantly prepared before each administration.

Histological processing and analysis: After sacrificing, the brain were harvested for preparation of slides based on standard steps outlined in Table 3.

The semiquantitative scoring was conducted by histopathologist as outlined in Table 4.

Results.

Control female group: The section from the female rat brain in the control group visualized by normal neurons morphology

with clear pyramidal shapes, and clearly visible nuclei (Figure 1 and Table 5).

Control male group: The section from the male rat brain in the control group visualized by normal intact neurons with clear pyramidal shapes, and clearly visible nuclei (Figure 2 and Table 5).

Losartan female group: The section from the female rat brain in the LST treatment group demonstrated by mild congestion, mild neuronal degeneration, and mild gliosis (Figure 3 and Table 5).

Losartan male group: The section from the male rat brain in the LST treatment group demonstrated by mild neuronal degeneration and mild gliosis (Figure 4 and Table 5).

Dox female group: The section from the female rat brain in the doxorubicin treatment group demonstrated sever hyperemic vascular meningeal congestion, large areas of sub-meningeal bleeding in the meningeal area, multiple foci of reactive gliosis (Figure 5 and Table 5).

Dox male group: The section from the male rat brain in the doxorubicin treatment group demonstrated large congestion within the cerebral ventricular plexus, large area of reactive gliosis (Figure 6 and Table 5).

LST10+Dox female group: The section from the female rat brain in the losartan (10 mg) plus doxorubicin treatment group demonstrated moderate congestion of the cerebral ventricular plexus, great areas of reactive gliosis (Figure 7 and Table 5).

LST10+Dox male group: The section from the male rat brain in the losartan (10 mg) plus doxorubicin treatment group demonstrated moderate congestion within the cerebral ventricular plexus, and reactive areas of gliosis due to neural insult (Figure 8 and Table 5).

Table 1. *Standard acclimatization condition for animal accommodation conditions.*

Features/condition	
Age	**2 months**
mean body weight	250 g
light/dark cycle	12-hour
Relative humidity	50–60%.
Temperature	22–24°C
Food	standard rodent chow
Water	water ad libitum

Table 2. *Drugs and doses used in the exposed groups.*

Studied groups	**No. rats**	**DW, PO, 13 days**	**NS, single IP dose, day 14**	**LST, PO, 10mg/kg/day for 13**	**LST, PO, 25mg/kg/day for 13**	**Dox, Single IP dose, 15mg/kg at day 14**
Control-Female	7	*	*	#	#	#
Control-Male	7	*	*	#	#	#
Dox-Female	7	*	#	#	#	*
Dox-Male	7	*	#	#	#	*
LST-Female	7	#	*	*	#	#
LST-Male	7	#	*	*	#	#
LST+Dox-Female	7	#	#	*	*	*
LST+Dox-Male	7	#	#	*	*	*

Day 16, brain tissue collected after the rats were sacrificed by cervical spine dislocation.
Drugs and distilled water were given by gavage needle
Dox vial (Doxo-cell 50 mg, STADAPHARM Gmbh (Germany)) was diluted for administration using normal saline
Losartan tablets (Losart 10mg, Pioneer (Iraq)) were dissolved in distilled water
*Indicates the used drugs at indicated timepoint, #indicate this agent or dug not used for the specified group
NS=normal saline, DW=distilled water, PO=per oral, IP=intraperitoneal

Table 3. *Summarized histological steps for brain slides preparation.*

Step	**Histological Step**	**Procedure Description**
1	Tissue harvesting	Brain tissue harvested after euthanization the rats.
2	Fixation	Tissue 10% neutral buffered formalin for 48 hours.
3	Washing	Fixed tissues washed under tap water.
4	Dehydration	Tissue passed on graded alcohol solutions (80% alcohol up to absolute alcohol).
5	Clearing	Alcohol replaced by xylene.
6	Impregnation	Tissue placed in warm paraffin wax.
7	Embedding	Tissue embeded in a mold full with warm liquid paraffin and left to solidify into paraffin block.
8	Trimming	The paraffin block trimmed
9	Sectioning	Thin sections were cut using a microtome.
10	Mounting	Sections mounted on glass slides and dried.
11	Deparaffinization and Rehydration	Paraffin removed and tissues rehydrated
12	Staining	Hematoxylin and Eosin (H&E).

Table 4. *The description of pathological finding based on scoring system.*

Histological Parameter	–	+	++	+++
Vascular congestion	No congestion	few vessels congestion	Several vessels congestion	Severe dilation of multiple vessels
Focal gliosis	No gliosis	Limited areas gliosis	Multiple areas gliosis	Extensive areas gliosis
Glial activation	No activation	Slight activation of glial cells	Clear activation of glial cells	Severe activationof glial cells

Table 5. *Summarized histological scores.*

Slide	**Vascular congestion**	**focal gliosis**	**glial activation**	**Overall neuropathy score**
Control group in Female rat	-	-	-	-
Control group in male rat	-	-	-	-
Losartan (10mg) group in Female rat	-	-	+	-
Losartan (10mg) group in male rat	-	-	+	-
Doxorubicin group in Female rat	+++	++	++	++
Doxorubicin group in male rat	+++	++	++	++
Losartan 10mg+Doxorubicin female group	++	+	+	+
Losartan 10mg+Doxorubicin male group	++	+	+	+
Losartan 25mg+Doxorubicin female group	-	+	+	-
Losartan 25mg+Doxorubicin male group	-	+	+	-

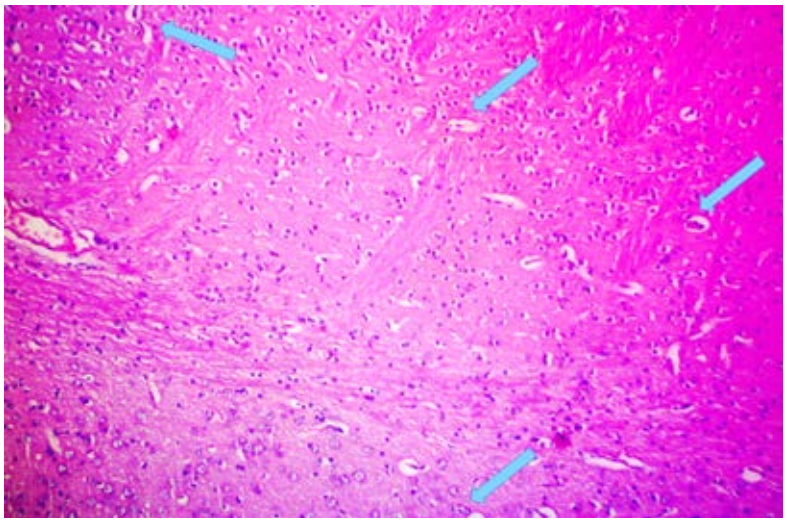

Figure 1. *Brain section for female rats in the control group stained by hematoxylin and eosin, representing cerebral cortex (Blue arrows) and axons with normal periaxonal myelin spaces at the cerebral medulla. Magnification at 100X.*

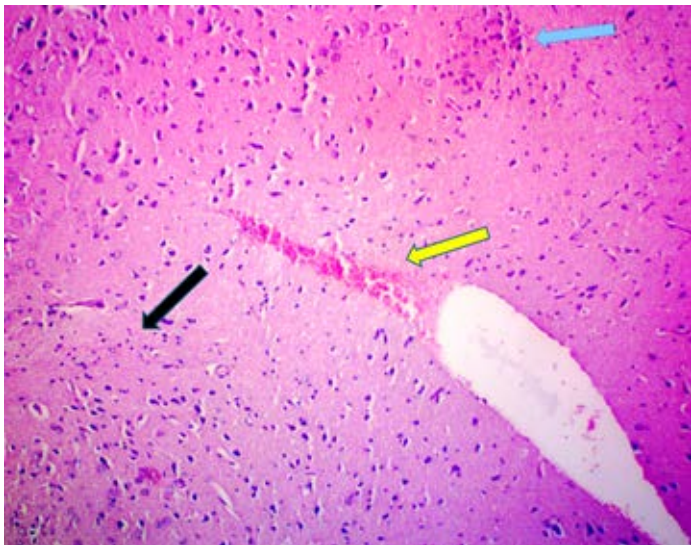

Figure 2. *Brain section for male rats in the control group stained by hematoxylin and eosin, representing the blue arrow is cerebral cortex, and axons with normal periaxonal myelin spaces at the cerebral medulla at the black arrow, and the yellow arrow are localized vessels, Magnification at 100X.*

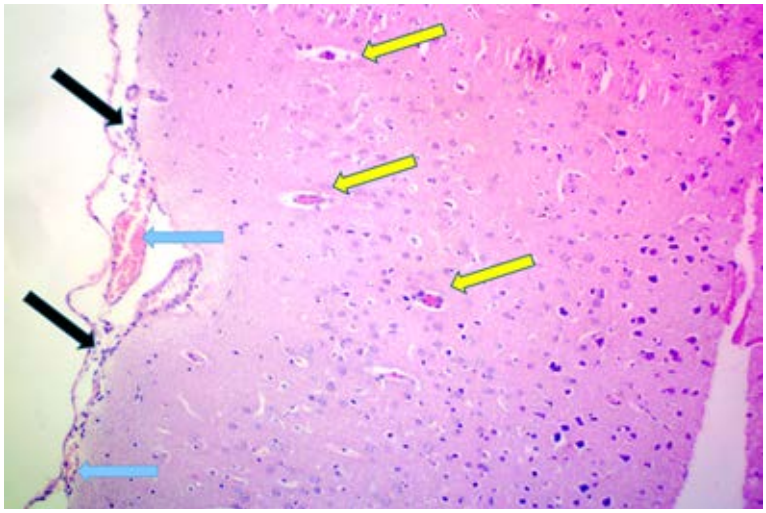

Figure 3. *Brain section for female rats in the losartan group stained by hematoxylin and eosin, representing meningeal arteries (Blue arrows), Inflammatory cells infiltrations (Black arrows) and peri axonal mild edema (Yellow arrows), Magnification at 100X.*

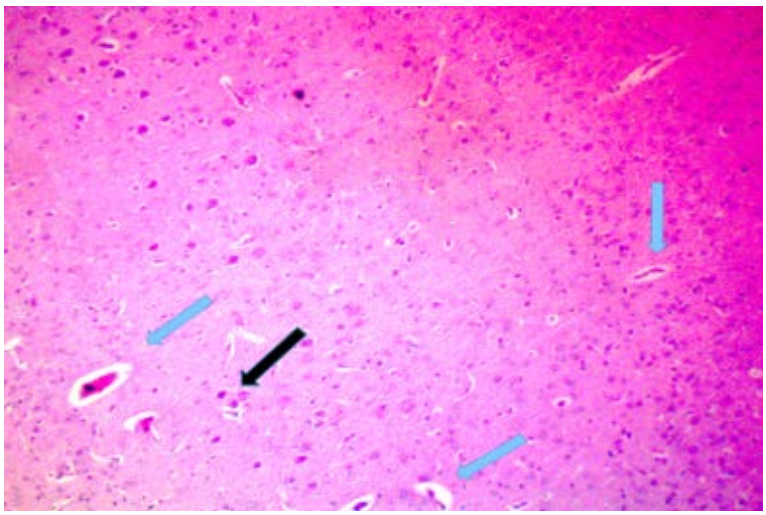

Figure 4. *Brain section for male rats in the losartan group stained by hematoxylin and eosin, representing mild degeneration (Blue arrows), with mild gliosis (Black arrows), 100X.*

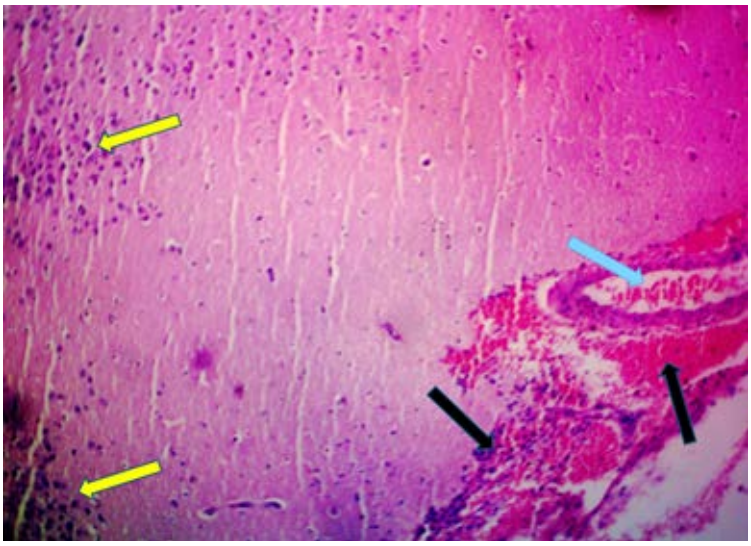

Figure 5. *Brain section for female rats in the doxorubicin group stained by hematoxylin and eosin, representing by the blue arrow is hyperemic meningeal arteriole, black arrow is submeningeal hemorrhage, and yellow arrow as multiple foci of gliosis, Magnification at 100X.*

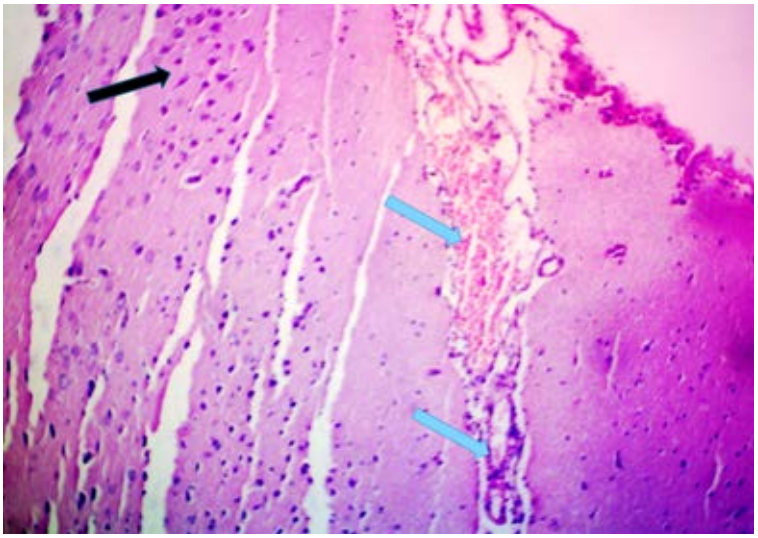

Figure 6. *Brain section for male rats in the doxorubicin group stained by hematoxylin and eosin, representing congested cerebral ventricular plexus (Blue arrow) with gliosis (Black arrow), Magnification at 100X.*

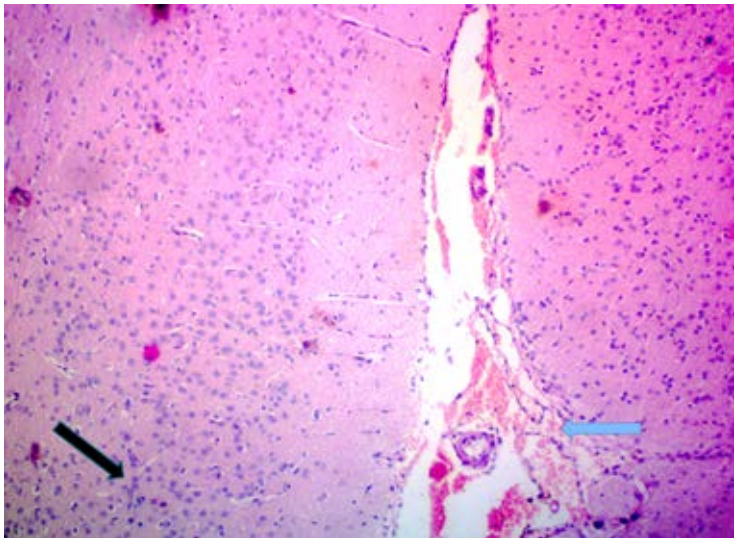

Figure 7. *Brain section for female rats in the losartan10mg+doxorubicin group stained by hematoxylin and eosin, representing congested cerebral ventricular plexus (Blue arrows) with gliosis (Black arrows), Magnification 100 X.*

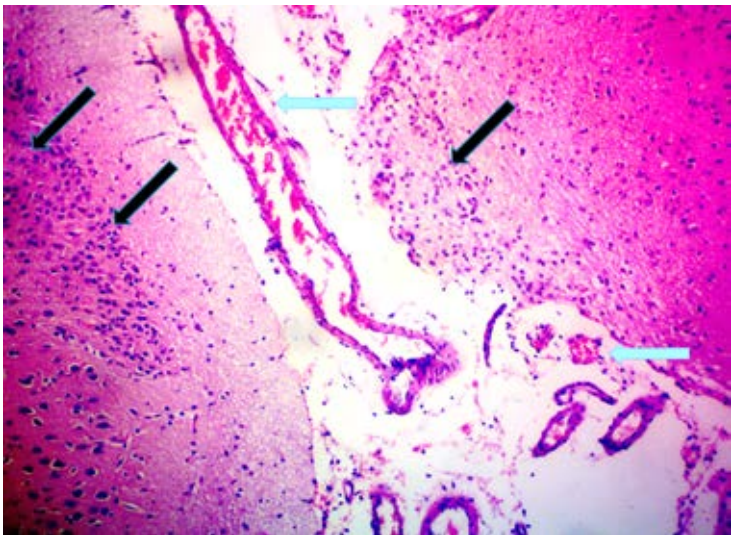

Figure 8. *Brain section for male rats from losartan10mg+doxorubicin group stained by hematoxylin and eosin, representing congested cerebral ventricular plexus (Blue arrows) with gliosis (Black arrows), Magnification 100 X.*

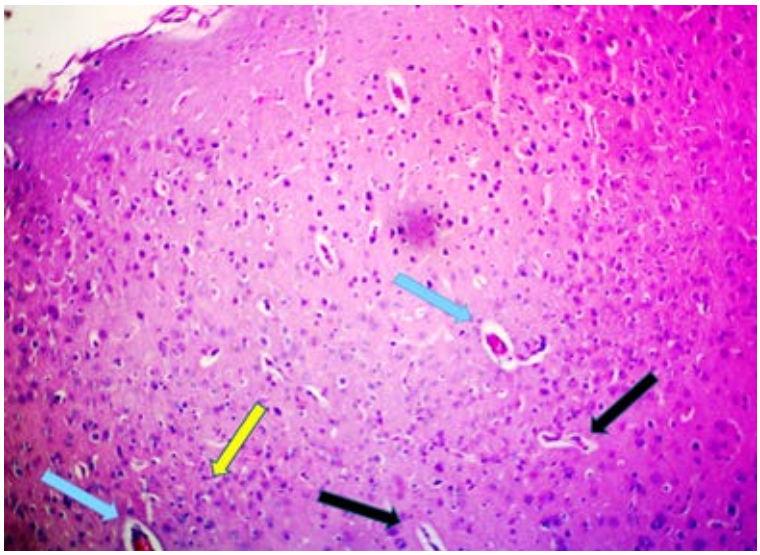

Figure 9. *Brain section for female rats in the losartan 25mg+doxorubicin group stained by hematoxylin and eosin, representing by blue arrow as congested cerebral capillary, black arrow is degeneration of neuronal axons, and the yellow arrow is foci of gliosis, Magnification at 100X.*

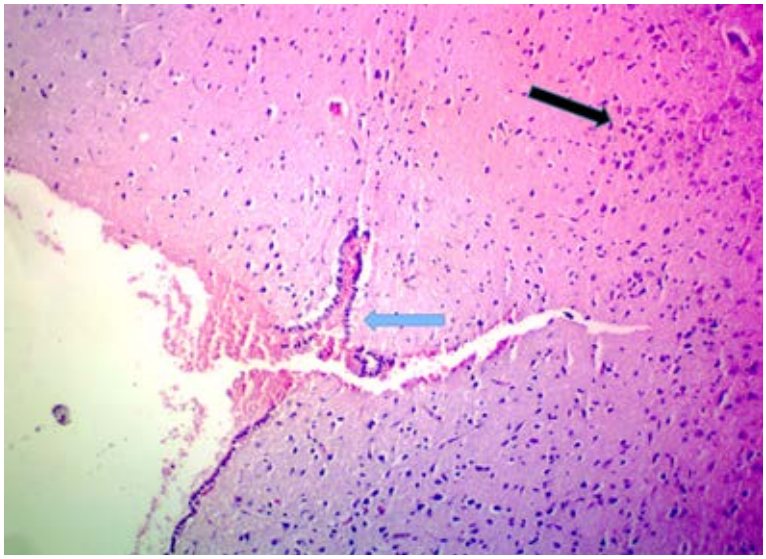

Figure 10. *Brain section for male rats in the losartan25mg+doxorubicin group stained by hematoxylin and eosin, representing congested cerebral ventricular plexus (Blue arrows) and gliosis (Black arrows), Magnification at 100X.*

LST25+Dox female group: The section from the female rat brain in the losartan (25 mg) plus doxorubicin treatment group demonstrated mild histological changes, represented by mild congested cerebral capillaries, mild degeneration of neuronal axons, and mild foci of gliosis (Figure 9 and Table 5).

LST25+Dox male group: The section from the male rat brain in the losartan (25 mg) plus doxorubicin treatment group demonstrated mild histological changes, represented by mild vascular congestion resulting in engorgement of the ventricular plexus. The section also demonstrated mild gliosis, reflecting a low proliferation of glial cells in response to neural damage by Dox (Figure 10 and Table 5).

Discussion.

The present study offered histological findings for the LST-neuroprotective effects of against Dox neurotoxicity in a rat model, with results demonstrating that dose- and sex play a role in the treatment response. These outcomes reflecting protective effects against acute neurological injury and toxicity.

The histological findings of Dox-group demonstrated neuropathological alterations, which do harmonized with the mode of action of Dox brain damage. After Dox exposure, vascular congestion and glial activation were visualized in female group versus bleeding in focal epidural region and focal gliosis in male group, reflecting that Dox-induced neurotoxicity via multiple pathological pathways [13,14]. The bleeding and congestion reported could be explained in the context of Dox-induced impairment of blood-brain barrier (BBB) integrity leading to direct damage of cerebral vascular endothelial cells [2], resulting in release of proinflammatory cytokines and activation of MAPK inflammatory signaling pathway. The glial activation after Dox-exposure linked to the neuroinflammatory effects of Dox resulting in modulation of microglial cell density [15]. The changes further aggravated by Dox-induced oxidative

stress and mitochondrial upset [4]. Sex variation in response to Dox focused on ventricular vascular changes and focal gliosis in male rats versus diffuse vascular changes in females, these differences potentially related to genetic variations of the mutation of BRCA1 and BRCA2 proteins roles in modulating oxidative stress in neural cells [3].

Co-administration of LST and Dox provided protective effects against Dox-induced neurotoxicity in dose dependent manner and gender-based response. At low LST dose, female and male groups demonstrated moderate vascular congestion and reactive gliosis, however, at higher dose of LST, congestion was minimal and glial activation was low, especially in female group. Earlier study conducted on lipopolysaccharide (LPS)-inflammation in mouse model by Salmani et al., (2020) demonstrated that LST suppressed brain neuroinflammatory response and hence improved cognitive function, mitigated oxidative stress, reduced anxiety behaviors [6]. In alternative study, blocking angiotensin receptor resulted in inhibition of apoptosis through angiotensin mediated pathways, reflecting that losartan has anti-apoptotic and tissue protective effects [16]. In aged mouse model for Alzheimer's disease research conducted by Ongali et al., (2014), blocking angiotensin receptors have resulted in neutralization of oxidative stress, attenuated astrogliosis, and reduced vascular congestion [17].

The better positive response achieved with high dose LST could potentially explained in the context of the higher concentration required for full occupancy of all receptors and hence modulate intracellular signaling pathways, alongside sufficient penetration into brain. Moreover, the better positive response associated with female sex than male, perhaps reflecting that hormonal contribution in the response to angiotensin blockade in female, confirmative future study required.

The limitations of the present study include that histological section represent one site of the brain at one time point necessitating future section of the whole organ and incorporation of different time point of exposure. Moreover, histological findings required additional incorporation of biochemical measurement of oxidative stress products, inflammatory biomolecule, and apoptotic markers.

Conclusion.

Losartan mitigated Dox induced neurotoxicity in a rat model, including vascular congestion, glial activation, and axonal degeneration, particularly in female rats and at high dose. These results revealed that AT1 receptor antagonism might be promising option for providing protection for acute neurological toxicity by drugs or xenobiotics, nevertheless, further cognitive and behavioural study required to confirm these improved outcomes.

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