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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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FEATURES OF THE EFFECT OF SCORPION VENOM ON THE IMMUNE DEFENSE SYSTEM OF THE MAMMALIAN LIVER (REVIEW)

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Abstract.

Introduction: Toxic liver damage due to exposure to poisons, including those of animal origin, is often associated with lymphocytic infiltration, and the nature and degree of inflammation determine the rate of progression and severity of damage. The mechanisms by which toxic compounds activate immune-mediated pathways of liver damage are still being actively studied, however, liver infiltration by effector lymphocytes is a common phenomenon, leading to the destruction of hepatocytes and cholangiocytes and a persistent shift in the structural and functional characteristics of the organ

Aim of study: To determine the features of the effect of scorpion venom on the immune defense system of the mammalian liver.

Materials and methods: A thorough literature analysis was conducted on the basis of PubMed, Google Scholar, Web of Science, and Scopus databases. When processing the search results, we chose the newest publications up to 5 years old or the most thorough publications that vividly described the essence of our topic.

Conclusion: Scorpion venom causes the development of local, cardiotoxic, neurotoxic effects and effects of autonomic nervous system. Depending on the predominance of a particular component in the venom, a wide range of clinical signs and symptoms can be observed from local reactions (hyperemia, pain, edema) to serious consequences, including respiratory, gastrointestinal, cardiac or neurological complications. The influence of toxic components on the structural and functional parameters of the mammalian liver is currently at the stage of comprehensive and thorough study. It has been established that under the conditions of administration of scorpion venom to experimental animals, hydropic degeneration and karyorrhexis of hepatocytes, fibrinoid necrosis, blood stasis in the vessels, an increase in the level of enzymes - ALT, AST, LDH were noted. At the same time, activation of the liver's immune defense mechanisms was observed. Cellular components in this case played an important role in activating inflammation and damaging the organ's structures.

Key words. Scorpion, toxins, liver, inflammation, cytokines.

Introduction.

The liver is one of the important organ that provides the body's immune defense with a high density of myeloid (such as Kupffer cells, neutrophils or macrophages) and lymphoid (such as natural killer cells, T cells or B cells) immune cells. The human liver contains about 1010 resident lymphocytes, including B cells, T cells and natural killer (NK) cells. Lymphocyte migration increases in response to the activation of inflammatory processes, and intrahepatic compartmentalization of lymphocytes determines the morphological variant of organ damage [1-4]. Toxic liver damage due to exposure to poisons, including those of animal origin, is often associated with lymphocytic infiltration, and the nature and degree of inflammation determine the rate of progression and severity of damage. The mechanisms by which toxic compounds activate immune-mediated pathways of liver damage are still being actively studied, however, liver infiltration by effector lymphocytes is a common phenomenon, leading to the destruction of hepatocytes and cholangiocytes and a persistent shift in the structural and functional characteristics of the organ [5-9].

The process of inflammatory immune response is induced by a cascade that includes the activation of organs and systems, cellular elements of defense and the release of mediators [10,11]. The impact of antigens leads to the production of antibodies as a result of a series of transformations and intercellular communication. First, antigen-presenting cells are recognized by the T-cell antigen receptor, and subsequently B-cells produce their own antibodies that are able to specifically recognize the antigen that provoked their formation. T-cells contribute to the production of immunoglobulins by B-cells by synthesizing cytokines. Two subpopulations of Th-cells, namely Th1 and Th2, have effector functions that ensure their participation in the production of cytokines secreted in response to antigenic stimulation [12-14].

Th1 cells are involved in the secretion of mainly interleukin-2 (IL-2), tumor necrosis factor (TNF-α), and interferon-γ (IFN-γ), which are responsible for the activation of macrophages and contribute to the cell-mediated immune response against pathogens or toxins [15-17]. They also induce the production of opsonizing IgG2a antibodies. Another subpopulation, Th2 cells, are required for the production of IgE and IgA and promote the expression of IL-4, IL-5, and IL-6. Th1 and Th2 cells are also involved in the production of granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-13, but to a lesser extent [18-20].

According to their mechanism of action or properties, cytokines can be classified as pro-inflammatory or anti-inflammatory. Pro-inflammatory cytokines, such as IL-1, IL-6, and TNF, are mainly responsible for triggering the immune defense in response to exogenous pathogens. However, excessive production of these mediators can contribute to negative consequences and ultimately lead to shock, multiple organ failure, or even death. Anti-inflammatory cytokines, including IL-4, IL-5, IL-6, and IL-10, are crucial for suppressing the inflammatory process and maintaining homeostasis and proper functioning of vital organs, but excessive anti-inflammatory responses can also lead to suppression of the body's immune function [21-24].

The balance between pro- and anti-inflammatory activities determines the extent of the inflammatory immune response. Anti-inflammatory cytokines counteract the effects of pro-inflammatory cytokines, and therefore the concentration of a cytokine relative to its inhibitor or antagonist will determine its ultimate effect. Cytokine imbalance mediates the development of organ damage and death following infection or trauma [25-28].

The aim of the study was to determine the features of the effect of scorpion venom on the immune defense system of the mammalian liver.

Materials and Methods.

A thorough literature analysis was conducted on the basis of PubMed, Google Scholar, Web of Science, and Scopus databases. When searching for information of the general patterns of the structure of scorpion venom and its effect of scorpion venom on the immune defense system of the mammalian liver, we used the following combinations of keywords: “scorpions”, “toxins”, “liver”, “inflammation”, “cytokines”. When processing the search results, we chose the newest publications up to 5 years old or the most thorough publications that vividly described the essence of our topic. After conducting a detailed review of the abstracts of the articles and getting acquainted with their full content, 91 sources were selected that fully corresponded to the results of the request.

Results and Discussion.

There is evidence that cytokines play a role in the development of inflammation in the cases of scorpion envenomation [29-31]. IL-1 is a pro-inflammatory cytokine that exists in two forms, IL-1α and IL-1β, both of which perform similar functions mediated through the IL-1 receptor (IL-1R). After binding to IL-1R, IL-1 induces the production of a wide range of cytokines and chemokines, as well as the expression of adhesion molecules on endothelial cells, which leads to the recruitment of inflammatory cells. In addition, IL-1 contributes to the development of vascular damage by stimulating cell proliferation and differentiation, and the release of enzymes that degrade the extracellular matrix [32]. IL-1R antagonist (IL-1Ra) is a structural homologue of IL-1 that binds to IL-1R but does not induce any cellular responses and is therefore a natural inhibitor of IL-1 activity. Both are synthesized as precursor molecules (pro-IL-1α and pro-IL-1β) by many different cell types. Pro-IL-1α is biologically active and requires cleavage by calpain to form the smaller mature protein. In contrast, pro-IL-1β is biologically inactive and requires enzymatic cleavage by caspase-1 to acquire its properties. IL-1α is predominantly membrane-bound, whereas IL-1β represents the extracellular form of IL-1. Serum IL-1 levels in humans and experimental mice injected with the venom of the Brazilian scorpion Tityus serrulatus tended to increase rapidly. High levels of these cytokines were observed in the supernatants of macrophages of mice exposed to the venom of Tityus serrulatus and its major toxins. Increased IL-1β concentrations were detected in the plasma of patients with moderate to severe Tityus serrulatus envenomation [33,34]. High levels of IL-1α and IL-1β were observed in the serum of mice exposed to the Mexican scorpion Centruroides noxius. IL-1, according to the literature, plays an important role in the pathogenesis of scorpion toxin poisoning due to its immunostimulatory and proinflammatory activities. The IL-1 system is represented by IL-1α and IL-1β, both of which are produced by various cell types through the initiation of cyclooxygenase type 2 (COX2), PLA2, and inducible nitric oxide synthase (iNOS) [35-37].

IL-6 is a multifunctional cytokine that regulates various aspects of the immune response, acute phase response, and hematopoiesis. IL-6 synthesis is driven by IL-1, and therefore serum levels are often a reflection of IL-1 activity in vivo. Unlike other cytokines, IL-6 is a pleiotropic cytokine that exerts its proinflammatory activity by being produced by a variety of cells, including B and T lymphocytes, monocytes, fibroblasts, keratinocytes, endothelial cells, mesenchymal cells, and certain tumor cell types. High levels of IL-6 have been observed in the serum of mice exposed to the venoms of the scorpions Centruroides noxius and Tityus serrulatus. IL-6 is often used in clinical practice as a marker of systemic activation of proinflammatory cytokines. It downregulates the expression of IL-1 and TNF-α, and also inhibits the production of GM-CSF, IFN-γ, and MIP-2 [38].

Systemic Effects of Venom.

Scorpion venom toxins are capable of stimulating neuroendocrine and immune responses, accompanied by the release of catecholamines, corticosteroids, prostaglandins. It has now been proven that excessive production of certain cytokines, such as IL-1 and IL-6, correlates with the severity of envenomation due to scorpion bites. In particular, an increase in the level of IL-6 in the blood serum of 8 out of 10 children who had severe envenomation by scorpions Leiurus quinquestriatus and Buthotus judaicus has been proven. The level of cytokines under these conditions was measured upon admission to the hospital and 1-3 hours after the bite. It should be noted that the concentration of IL-6 in the blood plasma returned to normal values after 12 and 24 hours, but remained higher than control levels. Similar results were obtained in related studies that described increased cytokine production after the bite of Tityus serrulatus scorpions. In experimental animals, high levels of cytokines were found in the serum of mice injected with Centruroides noxius and Tityus serrulatus venom (Figure 1) [39].

IL-8 is a mediator of cerebral reperfusion and is elevated in brain tissue, and neutralizing anti-IL-8 antibodies significantly reduced brain edema and infarct prevalence. Increased IL-8 levels were observed in the serum of patients with varying degrees of envenomation caused by the stings of the scorpions Tityus serrulatus and Leiurus quinquestriatus [40,41].

TNF-α is a pleiotropic cytokine that exerts potent pro-inflammatory effects. TNF-α is produced predominantly by monocytes and macrophages. Lymphocytes and macrophages, which are involved in the inflammatory process, mainly regulate it by activating the production of TNF-α, which in turn induces the expression of IL-1β, IL-6, adhesion molecules, proliferation of fibroblasts and procoagulant factors, as well as the initiation of cytotoxic, apoptotic and acute phase responses. TNF-α is a major inflammatory cytokine due to its ability to stimulate

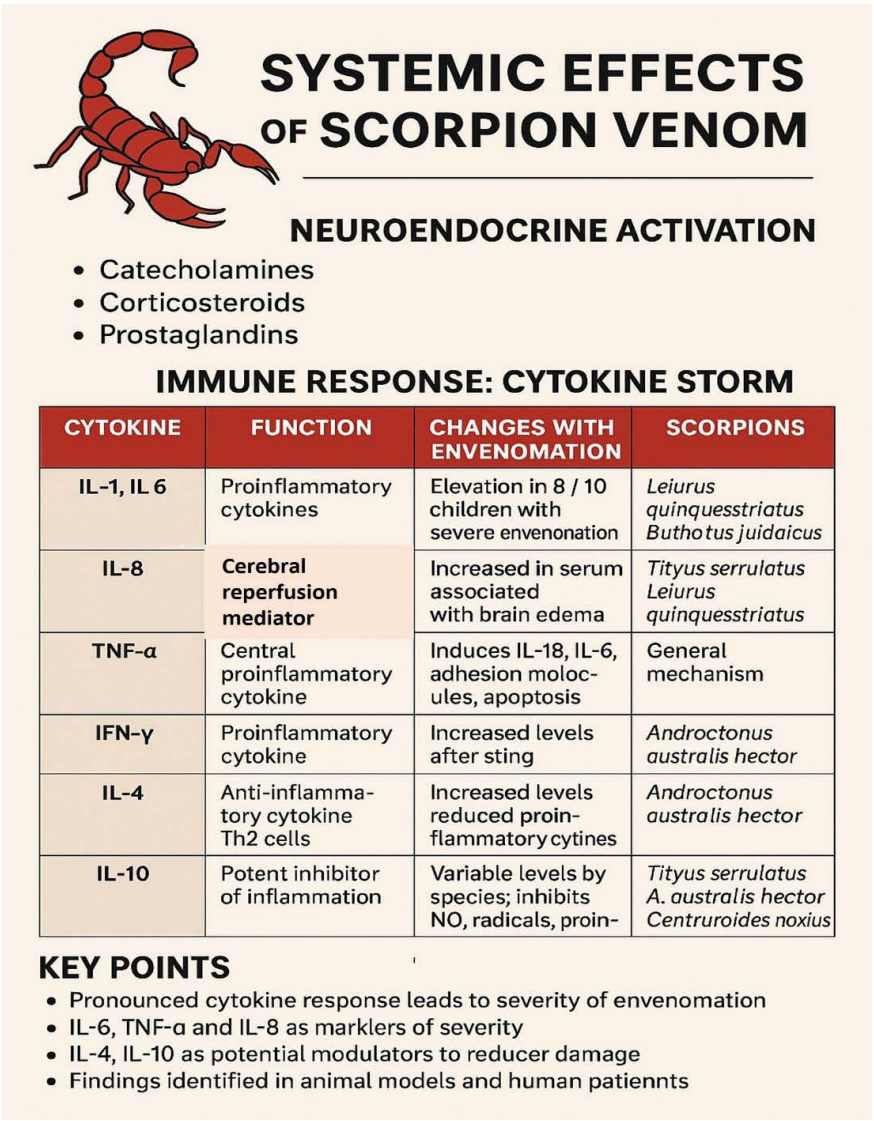

Figure 1. *Systemic effects of scorpion venom.*

the synthesis of nitric oxide (NO) and other inflammatory mediators, which cause a chronic delayed hypersensitivity reaction [42-44].

IFN-γ is expressed in high concentrations in the case of scorpion stings by various cell types, including monocytes, macrophages, Th1 cells, and natural killer (NK) cells. Increased levels of IFN-γ have been observed in humans and experimental animals following envenomation by the scorpions Centruroides noxius and Tityus serrulatus [45,46].

IL-4 is an anti-inflammatory cytokine and is able to influence on Th cell differentiation, and its early secretion leads to Th cell polarization and differentiation towards Th2-like cells. Th2 cells secrete their own IL-4, and subsequent autocrine production of IL-4 supports cell proliferation. Secretion of IL-4 and IL-10 by Th2 cells leads to suppression of the expression and release of inflammatory mediators. IL-4 is believed to be able to block or suppress monocyte-derived cytokines, including IL-1, IL-6, IL-8, TNF-α, and macrophage inflammatory protein 1 alpha. Experimental studies show that in mice deficient in the α chain of the T cell receptor (TCR-/-), which were injected with monoclonal antibodies to IL-4, a decrease in the production of mRNA for these cytokines in Th2 cells and an increase in the expression of IFN-γ were observed. Increased IL-4 production was recorded in the serum of rats exposed to the scorpion Androctonus australis hector [47].

IL-10 is produced by several cell types, including CD4+, CD8+, T lymphocytes, macrophages, monocytes, B lymphocytes, dendritic and epithelial cells. As an anti-inflammatory cytokine, it exerts potent inhibitory effects on IFN-γ, TNF-α, IL-1β, IL-2, IL-6, IL-8 and IL-12. IL-10 properties include inhibition of free radical synthesis and macrophage nitric oxide activity, as well as prostaglandin production. IL-10 levels varied significantly in the serum of patients bitten by the scorpion Tityus serrulatus and in experimental animals injected with the venom of Androctonus australis hector, Centruroides noxius and Tityus serrulatus [48,49].

Special Features of the Liver.

The liver has a unique blood supply system, which largely determines the mechanisms of the development of inflammatory processes under the influence of damaging factors. The inflammatory immune response to infectious agents and

damage is characterized by increased binding of lymphocytes to endothelial cells of sinusoidal capillaries and their enhanced migration. Vital experimental studies show that although leukocytes are capable of adhesion and migration through different parts of the liver microcirculation, the majority enter the parenchyma precisely through the hepatic sinusoids [50-52]. Sinusoidal endothelial cells of the liver demonstrate differences in the expression of adhesion molecules compared with other endothelial cells, in particular, they do not express P-selectin and have a significantly reduced expression of E-selectin. At the same time, selectins are expressed by the endothelium of portal vessels under inflammatory conditions, emphasizing the functional heterogeneity of the liver microcirculation [53,54].

Studies have confirmed that lymphocyte recruitment to the liver sinusoids occurs in a selectin-independent manner. Lymphocytes have also been shown to interact with the endothelium of the sinusoidal capillaries through adhesion receptors, including intercellular adhesion molecule-1 (ICAM-1), which is constitutively expressed by the epithelial cells of these vessels. Experimental mice deficient in ICAM-1 demonstrate a reduced degree of leukocyte adhesion to the liver sinusoids. In vitro studies using endothelial cells of the human liver sinusoidal capillaries show that lymphocyte adhesion is inhibited by blocking vascular adhesion molecule-1 (VCAM-1) and ICAM-1. In addition, VCAM-1 mediates lymphocyte capture and adhesion through α4 integrins in vivo [55-57].

Liver sinusoids also express other adhesion receptors, including vascular adhesion protein-1 (VAP-1), which mediates lymphocyte recruitment to the liver upon activation of inflammatory mechanisms. VAP-1 is a 170-kDa homodimeric glycoprotein that has semicarbazide (carbamic acid hydrazide)-sensitive monoamine oxidase activity. VAP-1 mediates lymphocyte adhesion to the endothelium of liver sinusoidal capillaries in vitro and in vivo. In addition, the enzymatic activity of VAP-1 may modulate the function of other adhesion molecules, as the presence of a substrate for VAP-1 on liver endothelial cells leads to nuclear factor κ-β-dependent activation of VCAM-1 and ICAM-1. Another adhesion molecule that plays a specific role in the liver is CD44, which has been shown to cause neutrophil sequestration in the liver by increasing the deposition of serum hyaluronan-associated protein on the epithelial lining of the sinusoids [58].

Chemokines and Cell Types.

Chemokines produced by liver cells also promote lymphocyte migration and colonization. The CC chemokine receptor (CCR)5 ligands and the CC chemokine (CCL)3–5 ligands are expressed in the endothelium of portal vessels, where they mediate lymphocyte recruitment in a number of inflammatory diseases. One of the critical events in the progression of liver damage is the infiltration of the hepatic parenchyma into the periportal tracts. Progressive liver damage is associated with high expression of the CXC chemokine receptor (CXCR)3 ligands CXCL9–11 on the endothelium of sinusoidal capillaries. These chemokines are also produced by cholangiocytes and stellate cells during inflammation. The process of transcytosis allows chemokines produced by stellate cells or subordinate hepatocytes in the local microenvironment to be transported from the basolateral surface of the endothelium to the lumen of the vessel, and chemokines secreted by cholangiocytes can be captured by retaining them in the proteoglycan-rich endothelial glycocalyx [59].

Selective recruitment at the endothelial level and subsequent compartmentalization in the liver determine the intrahepatic distribution of specific lymphocyte populations. For example, regulatory T cells (Treg) are important for controlling autoreactive T cells and resolving inflammation. They maintain stable chronic inflammation and prevent fulminant tissue destruction [60,61].

CXCL16 is an unusual chemokine that has a transmembrane domain. The CXCL16 receptor is expressed on T cells infiltrating the liver parenchyma. The unique structure of CXCL16 supports cell adhesion and also acts to promote the activation of β1 integrins, thereby enhancing binding to VCAM-1. Thus, signals mediated through chemokine receptors allow different cells to respond to a complex network of signals mediated by local interactions between the endothelium, stromal and parenchymal cells, and infiltrating leukocytes. The balance between the recruitment and survival of regulatory and effector T cells in the liver may determine the severity of organ damage [62,63].

Studies of lymphocyte migration have focused on the interaction between endothelial cells and the cells that surround them. For example, Kupffer cells surround the sinusoids and phagocytize foreign particles, and produce proinflammatory cytokines that promote leukocyte adhesion. They are also able to capture leukocytes from the sinusoidal lumen. Activated liver parenchymal fibroblasts are the main cells that form the matrix in response to injury and play a direct role in the inflammatory process. They secrete chemokines and express cell adhesion molecules such as ICAM-1 and VCAM-1. Fibroblasts and Kupffer cells can be activated by oxidative stress (OS) and innate immune signals, thereby contributing to immune-mediated liver injury. The role of resident liver macrophages in the production of pro-inflammatory cytokines and mediators, including TNF-α, IL-1β, and NO, has been proven [64-66].

The largest population of macrophages is represented in the liver as resident Kupffer cells. They constitute approximately 35% of nonparenchymal liver cells and 90% of all tissue macrophages. These intravascular cells fill the sinusoidal lumens. Kupffer cells have an incredible ability to distinguish between millions of red blood cells, platelets, and immune cells [67,68]. This property is possible in part due to opsonins that mark the pathogen as foreign; these opsonins include complement components, namely C3b and inactivated C3b. Complement receptors such as CR1, CR2, CR3, and CR4, although capable of capturing foreign agents, are completely incapable of binding to their ligands. Kupffer cell receptors that bind C3b and iC3b belong to the complement receptor immunoglobulin superfamily (CRIg), are unique and are not found in most other cells. In the liver, CRIg is critical for the capture and clearance of labeled C3b and iC3b targets [69]. In addition to expressing CRIg, Kupffer cells express a number of scavenger receptors, TLRs, complement receptors, and antibody receptors, all of which are molecules that allow Kupffer cells to detect, bind, and internalize pathogens and their associated molecules. In

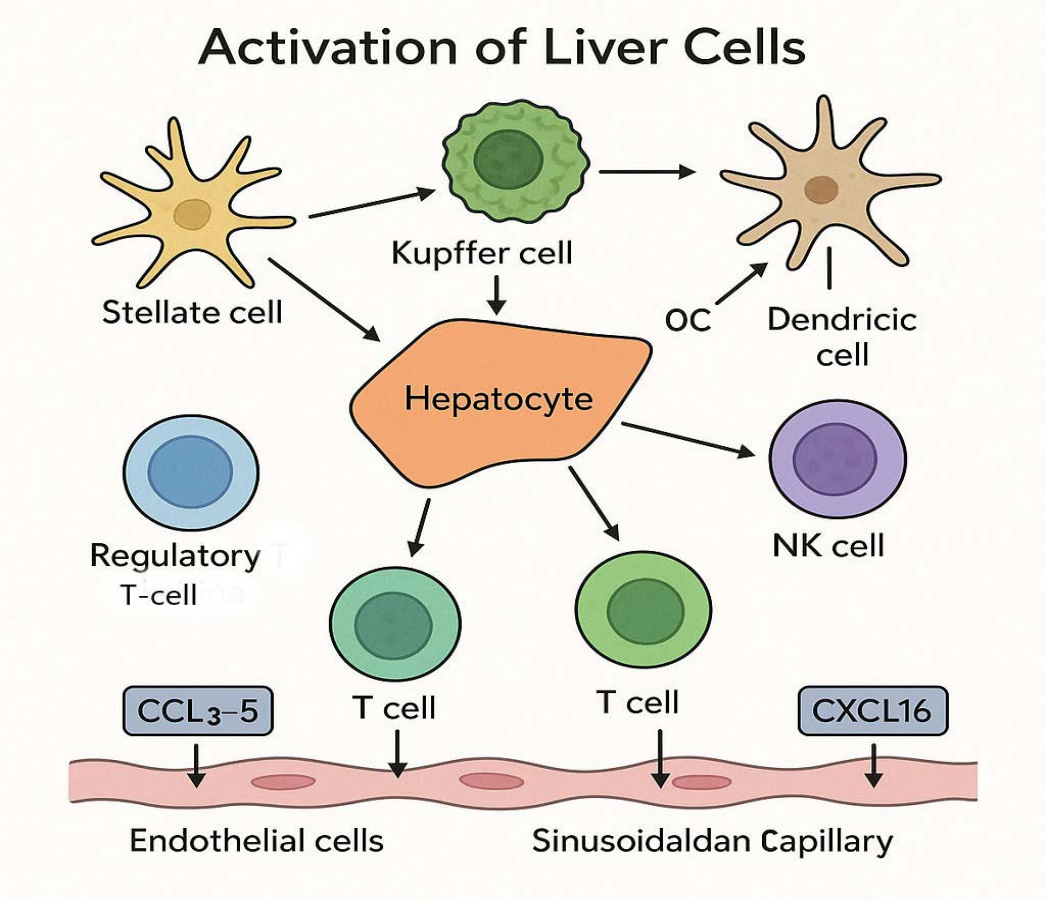

Figure 2. *Activation of liver immune cells.*

addition, these receptors, in part, drive Kupffer cell activation, which leads to the production of cytokines and chemokines, and allow this cell type to function as sentinels of the liver immune system, alerting other components of the immune system to the presence of harmful pathogens (Figure 2) [70,71].

Kupffer cells are important antigen-presenting cells (APCs) that express MHC-I, MHC-II, and costimulatory molecules required for T-cell activation. However, under normal conditions, they are weak activators of the adaptive immune response. The presence of other pathogen-associated molecules (TLR3 and TLR9 ligands) or inflammatory cytokines can modulate Kupffer cells, transforming these normally tolerant cells into potent APCs capable of activating T cells. In addition, Kupffer cells are extremely efficient in activating natural killer T cells (iNKTs) that patrol the hepatic sinusoids. Indeed, after capture, antigens can be presented to iNKT cells via CD1d, which is highly expressed on Kupffer cells [72,73].

A key role is played by natural killer cells of the liver (pit cells or NK), which have lytic activity and carry out immunological surveillance of the organ. Interacting with Kupffer cells, these cells regulate the functional activity of the latter by participating in the development of inflammation and in the regulation of cellular functions [74]. Thus, when activated, NK stimulate hematopoiesis (GM-CSF), IL-5 activity, and the inflammatory response (CXCL8). NK is the main producer of IFN-γ, which activates the fragmentation of the antigen phagocytosed by the macrophage. NK produce a large number of cytokines: chemotactic factors; tumor necrosis factors TNF-α and TNF-β; GM-CSF; serotonin; adrenaline; prostaglandins; β-endorphin and other factors [75,76]. In addition, it has been experimentally proven that, as components of innate immunity, these cells are able to adapt throughout the development of the organism. Under the influence of exogenous factors, NK cells acquire antigen-specific receptors, undergoing clonal expansion and producing “memory cells”. The functional activity of liver NKT cells is due to their high immunoregulatory potential, which is manifested in the expression of T-cell receptors (TCR), CD161c, NK1.1, NKR-P1 [77,78]. It has been proven that NKTs account for 20-30% of the total number of lymphocytes in the human liver. The functional ability of NKT cells is mainly mediated by the production of various cytokines (IFN-γ, IL-1, IL-6, IL-8, IL-9, IL-12), which play an important role in the regulation of immunological processes. It has been experimentally proven that in vivo, individual NKT cells simultaneously produce Th1-type cytokines (interferon-γ (IFNγ) and TNFα) and Th2-type cytokines (IL-4, IL-10 and IL-13). It has also been established that the marker for NKT cells is CD56, which has cytotoxic activity [79,80].

A key role in the formation of the immune response in the liver is played by liver dendritic cells (liver DCs), which stimulate the production of IFN-α, proliferation and cytotoxic activity of NK cells. Despite the fact that liver dendritic cells are less

immunogenic compared to those in the spleen or other tissues, they produce significantly higher amounts of cytokines and have a greater phagocytic ability. The low immunogenicity of liver DCs is due to differences in the subtype composition of the liver and spleen, which reflects the insufficient expression of constitutive costimulatory molecules. Thus, the liver is characterized by the presence of specific surface markers of subpopulations: lymphoid; plasmacytoid; myeloid; myeloid and plasmacytoid combination and DC-like natural killers [81,82]. Thanks to these markers, dendritic cells control disorders of innate and adaptive immunity [83,84].

Gaps and Future Challenges.

Alarmins or so-called damage-associated molecular patterns (DAMPs) are target structures that are released or induced after tissue damage. They stimulate the production of pro-inflammatory mediators in liver cells, leading to increased levels of inflammatory cytokines; for example, IL-1β, chemokines (CXCL1, CXCL9, CXCL10, CXCL11, CCL2, CCL5), growth factors (G-CSF, GM-CSF) and adhesion molecules (ICAM-1, VCAM-1) [85].

HMGB1 is an alarmin secreted by activated macrophages and monocytes. It is a nuclear nonhistone protein and is released during cell death by necrosis. HMGB1 binds to TLR2, TLR4 and AGER (advanced glycosylation end-product specific receptor). Experimental data suggest that the release of HMGB1 from necrotic hepatocytes upon exposure to toxic venom components is critical for neutrophil recruitment, increased injury and ultimately lethality [86].

IL-33 is an alarmin and IL of the IL-1 family, structurally similar to IL-18 and IL-1β. It is expressed by many cells, and its level correlates with the severity of the inflammatory process. IL-33 is synthesized as a precursor and activated by caspase-1. It induces cytokines such as IL-4, IL-13, IL-5 and IL-10. During liver injury, IL-33 plays a protective, rather than immunogenic role. By activating Th2, IL-33 enhances fibrogenesis in the liver [87].

Histological analysis of the liver parenchyma of Zahida Taibi-Djennah and Fatima Laraba-Djebari after administration of Androctonus australis hector venom to mice at a dose of 0.5 mg/kg body weight showed the presence of structural changes, and biochemical studies revealed a significant increase in AST and ALT activity. The increase in transaminase and amylase activity can be explained by the release of cholinergic and adrenergic neurotransmitters from sympathetic and parasympathetic nerve endings induced by the venom. Indeed, it has been proven that these agents cause changes in immune cells and the release of cytokines such as TNF-α and IL-6. Excessive generation of pro-inflammatory signals provokes tissue damage and multiple organ failure due to products produced by inflammatory cells (macrophages, neutrophils, NK cells, T cells and B cells). Taken together, these data indicate that Androctonus australis hector venom induces an inflammatory response, accompanied by insulin resistance, impaired carbohydrate metabolism, hyperlipidemia, and changes in liver structure and function. The results support this hypothesis, as pretreatment of animals with anti-IL-6 and anti-TNF-α prior to venom injection can prevent the biological abnormalities induced by the venom [88].

It has been demonstrated that the activation of the inflammatory process, characterized by an increase in the concentration of inflammatory cytokines after envenomation with scorpion toxins, promotes the formation of free radicals and reduces the activity of the antioxidant system. These data correlate with a significant decrease in the level of GSH and CAT activity in envenomed animals. Free radicals can react with polyunsaturated fatty acids and lead to lipid peroxidation, and also react with NO to promote the synthesis of peroxynitrites, which explains the significant increase in the levels of malondialdehyde and nitrite [89].

In addition, glucose metabolism pathways (glycolysis and the pentose phosphate pathway) are altered, leading to activation of the polyol pathway and hexosamine flux. The consequences of this activation are the accumulation of H2O2 and a decrease in the NADPH+/NADP+ ratio, which leads to a decrease in the activity of the antioxidant system and the formation of ROS. Thus, venom-induced hyperglycemia likely contributes to the OS observed in animals after scorpion stings [90,91].

Therefore, a future research requirements, such as Kupffer cell analysis in human tissue specimens, clinical cytokine monitoring, and the fractionation of toxin components along with their corresponding immunological effects, are very relevant and promising areas of development in medical science.

Conclusion.

Scorpion venom causes the development of local, cardiotoxic, neurotoxic effects and effects of autonomic nervous system. Depending on the predominance of a particular component in the venom, a wide range of clinical signs and symptoms can be observed from local reactions (hyperemia, pain, edema) to serious consequences, including respiratory, gastrointestinal, cardiac or neurological complications. The influence of toxic components on the structural and functional parameters of the mammalian liver is currently at the stage of comprehensive and thorough study. It has been established that under the conditions of administration of scorpion venom to experimental animals, hydropic degeneration and karyorrhexis of hepatocytes, fibrinoid necrosis, blood stasis in the vessels, an increase in the level of enzymes - ALT, AST, LDH were noted. At the same time, activation of the liver's immune defense mechanisms was observed. Cellular components in this case played an important role in activating inflammation and damaging the organ's structures.

Conflict of interest.

The Authors declare no conflict of interest.

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