GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 10 (355) Октябрь 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 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.

GEORGIAN MEDICAL NEWS
No 10 (355) 2024

Содержание:

GEORGIAN MEDICAL NEWS
No 10 (355) 2024

THE EFFECT OF VITAMIN D ON THE HISTOLOGICAL STRUCTURE OF LIVER AND LUNG IN MICE TREATED WITH AMPHOTERICIN B

Noori Taha Alkhafaji[1], Mareb H. Ahmed[2], Bashar Rasim Karem[3].

[1]*Department of Basic Nursing Sciences, Faculty of Nursing, University of Telafer, Nineveh, Iraq.*

[2]*Department of Dentistry, University of Al-Noor, Nineveh, Iraq.*

[3]*Department of Biology, College of Education for Pure Science, University of Mosul, Ninevah, Iraq.*

Abstract.

The aim of this work is to investigate the effects of L-AMB (Amphociene) on liver and lung tissues in adult mice, and the role of vitamin D3 in reducing its side effects.

Amphotericin B (AMB), a polyene macrolide antibiotic, is used to treat serious fungal infections and leishmaniasis. It may cause increased serum aminotransferase and hyperbilirubinemia due to interference with hepatic cytochrome P450. This study aimed to determine whether vitamin D could improve liver and lung structural changes. We divided the twenty-four adult male mice into the following groups: The first group (G1) received normal saline orally for 28 days. In the second group (GII), Liposomal amphotericin B (L-AMB) (5 mg/kg body weight) was given for 28 days intravenously. In the group (GIII), vitamin D3 was given daily at a dose of 10000 IU. The fourth group received intravenously L-AMB at a dosage of 5 mg/kg body weight and vitamin D orally for 28 days. Liver sections of group II showed coagulative necrosis and vacuolar degeneration of hepatocytes, as well as Kupffer cell hyperplasia and inflammatory cell infiltration. Group IV showed a normal architecture of liver tissue with mild vacuolation and cloudy swelling of the hepatocytes. The lung sections of the treated group showed interstitial hemorrhages, hemosiderin pigmentation, inflammatory cell infiltration, and accumulation of serous exudate in alveoli. Group IV showed clear alveoli with a few red blood infiltrates. The study found that L-AMB causes structural changes in liver and lung tissue, and treatment with vitamin D3 reduced its deteriorating effects. Monitoring liver and lung function tests in patients with fungal infections who are taking L-AMB for a prolonged period is essential for preventing and treating liver and lung dysfunction.

Key words. Liposomal amphotericin B (L-AMB), Vitamin D3, antifungal agents, liver, lung, mice.

Introduction.

It was initially isolated from soil Actinomycete sp in the late 1950s. AMB discovery and its use in medicine are regarded as significant scientific breakthroughs of the 20th century [1]. In vitro, AMB has demonstrated effectiveness against a wide range of clinical fungal isolates, including the majority of Candida species, the Mucorales, Aspergillus spp, endemic mycoses, and brown-black and hyaline molds. It has proven to be successful in combating Leishmania species as well [2]. There are several types of AMB available, such as lipid-based formulations like liposomal amphotericin B (L-AMB), conventional deoxycholate, and amphotericin B lipid complex (ABLC). These formulations vary in terms of toxicity, efficacy, and distribution within the body [3]. L-AMB is a form of amphotericin B is encapsulated in liposomes, which are made up of phospholipids and cholesterol. This formulation reduces amphotericin B's toxicity, protects it from degradation, and increases its efficiency. When compared to conventional AMB deoxycholate, L-AMB is more effective, has a reduced resistance rate, and has fungicidal activity [4]. The guidelines from the European Consensus on Molecular Medicine and Mycoses Study Group Education and Research Consortium suggest L-AMB as the primary treatment for both invasive mucormycosis and cryptococcal meningitis, with a recommended initial dose of 5 mg/kg per day. The dosage can be increased to 10 mg/kg per day in cases of progressive illness, brain involvement, or solid organ transplantation. L-AMB is generally administered slowly and intravenously [5-6]. Due to its broad spectrum of activity, low risk of resistance, low risk of medication interactions, and lack of therapeutic drug monitoring, L-AMB is commonly prescribed to children from one month to eighteen years old [7]. Its main disadvantages are a low risk of moderate-to-severe renal impairment and absence of an oral preparation [8].

L-AMB has a prolonged half-life in plasma, with a half-life of around 152 hours according to one study [9]. It also remains in various tissues for extended periods, with differences observed in different tissues. A study in rats showed that a significant amount of the drug was still present in the organs of uninfected animals 72 hours after administration. The spleen and liver retain most of L-AMB after intravenous administration, followed by the kidneys, and then the lungs in numerous studies [10]. L-AMB penetrates various regions of the rabbit lung model, with detectable concentrations found in lung tissue, and macrophages in the lungs' alveoli. It is difficult to determine the extent and speed of penetration in these regions, but estimates suggest that it reaches around 10% of different sub-compartments within the lung [11].

Liver injury caused by AMB therapy is typically mild and reversible, with an incidence rate of up to 32% for L-AMB [12]. Severe liver damage is rare but has been reported in some cases. The injury usually occurs within 4 to 14 days of starting treatment and is characterized by elevated liver enzymes. Clinically evident liver injury and treatment discontinuation due to AmB preparations are uncommon [12-13]. In a case-control study conducted on 587 recipients of bone marrow transplants, 1/3 of those who received L-AMB therapy had increased blood bilirubin and transaminases. [14]. A study on 141 therapy courses in pediatric patients, the transaminases in the liver increased in 59% of instances, leading to treatment cessation in only one patient [15]. AMB disrupts the synthesis of fungal cell walls by selectively binding to ergosterol, an essential membrane lipid found in the cell membranes of protozoa and fungi. Ergosterol is similar to cholesterol in mammals, and helps maintain membrane integrity, fluidity, and the proper positioning of fungal proteins

within the membrane. This process ultimately leads to pore formation, leakage of cellular components, depolarization, and cell death [16]. Due to similarity of mammalian membranes and fungal membranes, AMB is also highly toxic to patients [17]. AMB not only disrupts the cell membrane but also causes the accumulation of reactive oxygen species (ROS) inside the cell, leading to oxidative damage which contributes to the ability of antifungal compounds to inhibit fungal growth and is a major mechanism of cell toxicity. Fat-soluble vitamins can effectively stop lipid peroxidation and maintain the integrity of the cell membrane because they can pass through the membrane [18].

Vitamin D (VD) is a fat-soluble steroid hormone that plays a crucial in preventing and treating various diseases, including COVID-19 and asthma [19]. Oral vitamin D supplementation has been found to have a protective effect by balancing oxidative stress, reducing oxidative components, and increasing the antioxidant capacity of serum and lung tissue in a mouse model of induced acute asthmatic inflammation [20]. VD can be produced by the skin when exposed to sunlight or obtained through food [21]. It includes various forms such as Vitamin D3, 1,25-dihydroxycholecalciferol, 7-dehydrocholesterol, and Vitamin D2 [22]. VD functions as an antioxidant and a prooxidant [23]. regulates the immune system by controlling suppressor T lymphocytes, cytokine synthesis, and modulating cellular apoptosis processes [24]. It has also been shown to support mitochondrial respiratory function, inhibit oxidative stress, and decrease chronic inflammation [25].

Studies on vitamin D/hormone have received a lot of attention in recent years. The purpose of the current study was to look at VD's preventive qualities against liver and lung tissue damage induced by L-AMB in mice.

Materials and Methods.

Drugs used: Liposomal Amphotericin B (AMPHONEX vial) was purchased from (Bharat Serum) pharmacy. Each vial contains 50 mg of amphotericin B, manufactured in Bharat, India. Vitamin D3 (cholecalciferol) was obtained from Sigma Chemical Co., United States.

The study's design: This research was designed as an intervention, non-randomized, Open-ended experimental study.

Experimental design:

At the start of the study, the animals were randomly divided into 4 groups, with six animals in each group.

Group I (the negative control): was left without intervention to measure the baseline parameters, and they had free access to food and distilled water throughout the study period.

Group II (treated group): mice were received a diluted L-AMB (5 mg/kg B. wt. given intravenously in the lateral tail vein slowly over 20 minutes) repeated for 4 weeks.

Group III (Vitamin D3): mice of this group received Vitamin D3 10000 IU/kg and dissolved in sterile corn oil before use (for 4 weeks).

Group IV (L-AMB + Vitamin D3): the mice in this group received a daily intravenous dose of L-AMB (5 mg/kg body weight) via the lateral tail vein slowly over 20 minutes and a daily dose of Vitamin D3 (10000 IU) for 4 weeks.

A spontaneous and unexpected death occurred in one mouse from Group II three days after the experiment began, which appeared to be incidental. No deaths were reported in Group I, III, or IV throughout the daily follow-up of the animals.

After 28 days, the mice were sacrificed by cervical dislocation under light anesthesia. 12 hours following the last administration of L-AMB, the abdominal cavity was opened. The liver and lungs were quickly dissected and cleaned with normal saline. Tissue samples were then fixed in 10% neutral buffered formalin. After embedding the tissue samples in paraffin, they were cut to a thickness of 5 µm, deparaffinized, then hydrated, stained by H&E, and examined using light microscopy (Leica, Germany) for histopathological evaluation.

Ethical clearance:

The experimental protocols for this work were authorized by Alnoor University College, and the research was approved by the local ethical committee. It also complies with the guidelines for safeguarding animals used in experiments provided by the European Council Directive (2010/63/EU) of September 22, 2010.

Results.

Group G1 (control group): Every animal in this group stayed alive and continued to be active throughout the experiment. They were well fed and responded quickly to stimulants. The liver is a large organ found in the right upper quadrant of the abdomen. It is brown in colour, congested, has a smooth surface, and is firm in consistency. The liver slices from this group appeared normal, with visible bile ducts, sinusoids, healthy hepatocytes, and a typical liver lobular architecture (Figure 1).

The lungs are two organs that are located on either side of the heart, they are lobulated; the right lung has five lobes, while the left lung is single, surrounded by a thin pleura with fewer respiratory bronchioles, normal alveoli, and a relatively large airway lumen (Figure 2).

Group II:

The liver of the L-AMB drug-treated group showed coagulative necrosis in the hepatocytes, hyperplasia of the Kupffer cells, and inflammatory cell infiltration (Figure 3). Focal infiltration of lymphocytes was demonstrated in (Figure 4). The focal infiltration of lymphocytes was also concentrated around the portal area in association with hyperplasia of the bile cuniculi (Figure 5). In addition to the cogaulative necrosis, vacuolar degeneration in hepatocytes was also found (Figure 6). Examined lung sections showed alteration in the shape of alveoli, massive interstitial hemorrhages, deposition of hemosiderin pigmentation, and mononuclear inflammatory cells were infiltrated (Figure 7). The alveoli show the deposition of serous exudate in the alveoli (Figure 8).

Group III:

In the vitamin D3 treated group, the liver was lobulated and brownish in appearance. It had a typical porta hepatic and hepatocyte cord arrangement around the central vein with blood sinusoids between (Figure 9). The lung also displays a typical normal structure. The lining epithelium of alveoli is simple squamous epithelium with flattened nuclei (Figure 10).

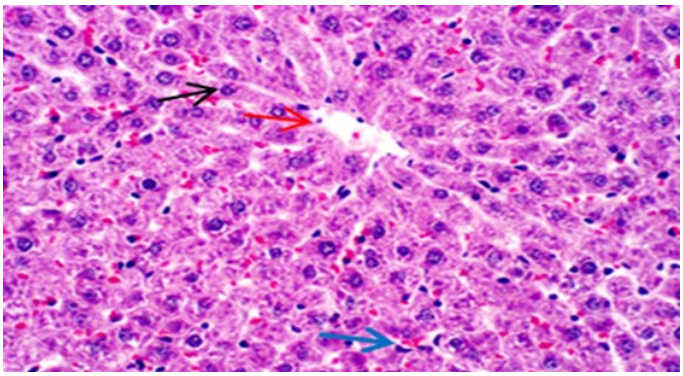

Figure 1. *The first group's liver photomicrograph shows the typical structural arrangement of the liver: normal hepatic cords (Black arrow), Kupffer cells (Blue arrow), and central vein (Red arrow). H&E.*

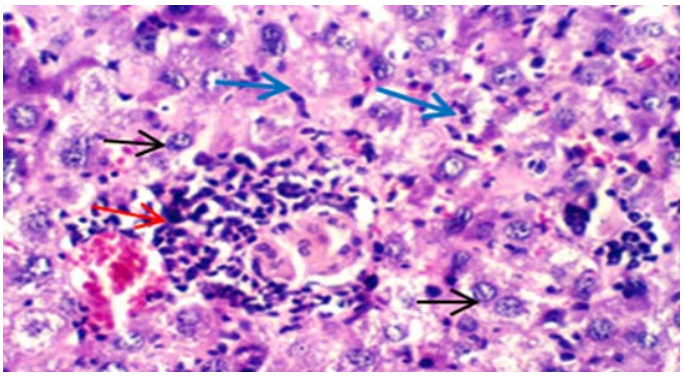

Figure 4. *Liver photomicrographs of the amphotericin-treated group. Showed cogaulative necrosis in the hepatocytes (Black arrow), hyperplasia of Kupffer cells (Blue arrow), and focal infiltration of lymphocytes (Red arrow). H&E. 400x.*

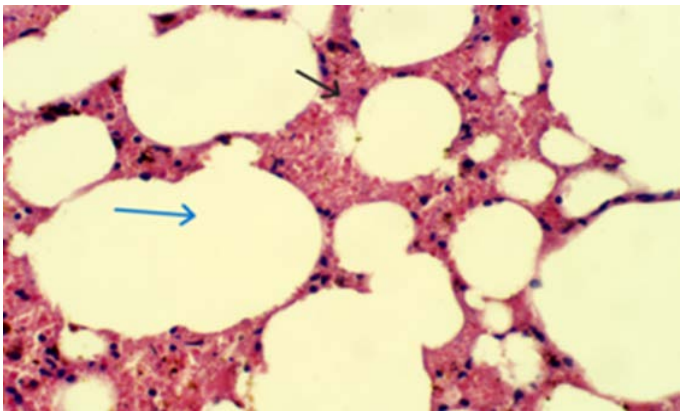

Figure 2. *The first group's lung photomicrograph shows its normal structural organization. normal alveolar wall (Black arrow) and alveolar space (Blue arrow). H&E. 400x.*

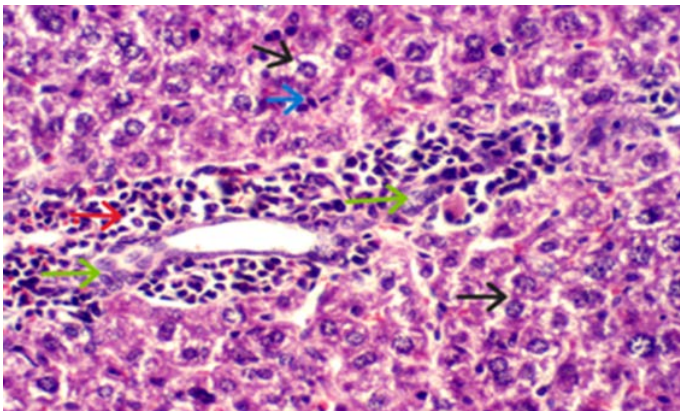

Figure 5. *Liver photomicrographs of the amphotericin group. showed cogaulative necrosis in the hepatocytes (Black arrow), hyperplasia of Kupffer cells (Blue arrow), focal lymphocyte infiltration around the portal area (Red arrow), as well as hyperplasia of bile cuniculi (Green arrow). H&E. 400x.*

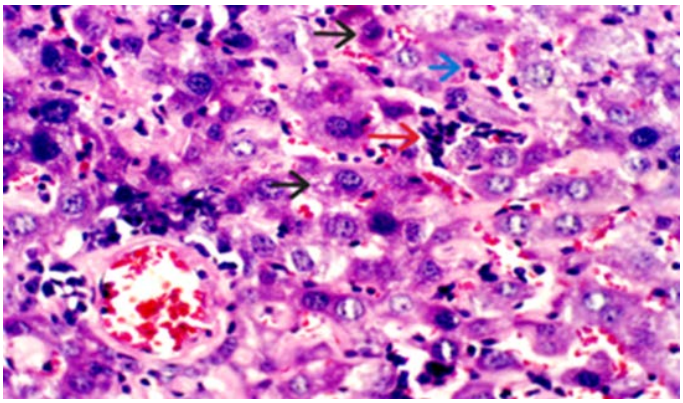

Figure 3. *Liver photomicrographs of the amphotericin-treated group. Showed cogaulative necrosis in the hepatocytes (Black arrow), hyperplasia of Kupffer cells (Blue arrow), and infiltration of inflammatory cells (Red arrow). H&E. 400x.*

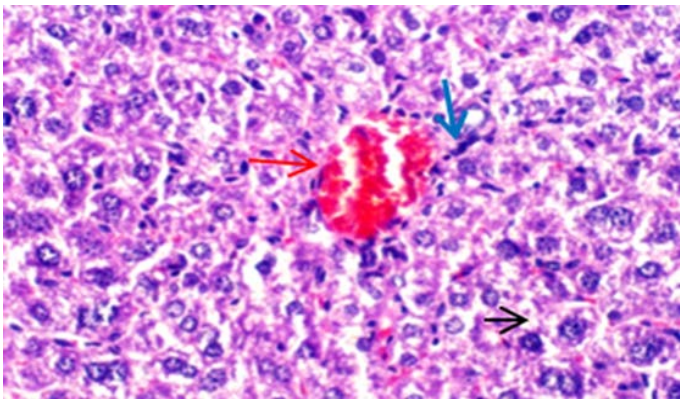

Figure 6. *Liver photomicrographs of the amphotericin group. A vacuolar degeneration is shown in the hepatocytes (Black arrow), as well as hyperplasia in the Kupffer cells surrounding the central vein (Blue arrow) and congestion in the central veins (Red arrow) (H&E. 400x).*

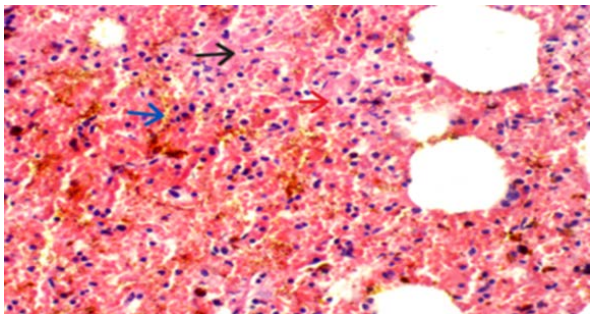

Figure 7. *Lung, amphotericin group. Showed massive interstitial hemorrhages (Black arrow), deposition of hemosiderin pigmentation (Blue arrow), and infiltration of mononuclear inflammatory cells (Red arrow). H&E. 400x.*

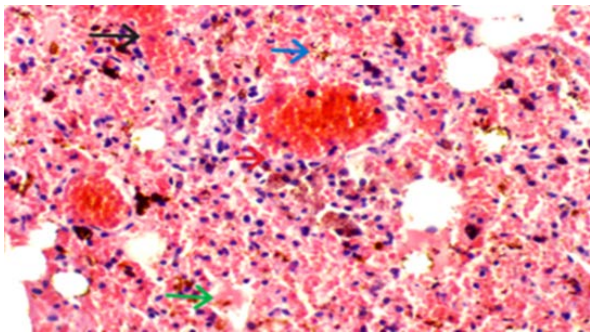

Figure 8. *Lung, amphotericin group. Shown interstitial hemorrhages (Black arrow), deposition of hemosiderin pigmentation (Blue arrow), infiltration of mononuclear inflammatory cells (Red arrow), and deposition of serous exudate in alveoli (Green arrow). H&E. 400x.*

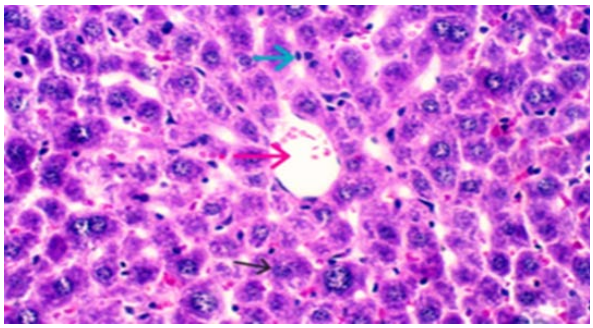

Figure 9. *Liver photomicrographs of Liver, photomicrograph of the vitamin D group. Showed normal hepatic cords (Black arrow), Kupffer cells (Blue arrow), central vein (Red arrow). H&E. 400x.*

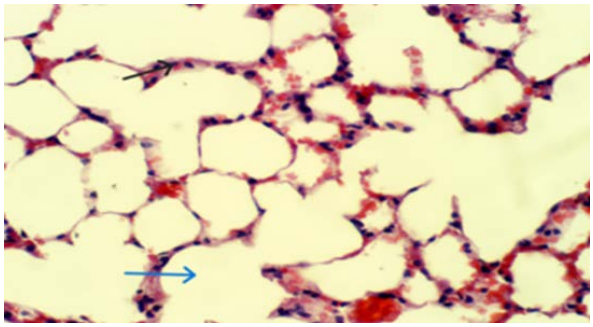

Figure 10. *Lung photomicrograph of the vitamin D treated group. Showed normal alveolar wall (Black arrow), alveolar space (Blue arrow). H&E. 400x.*

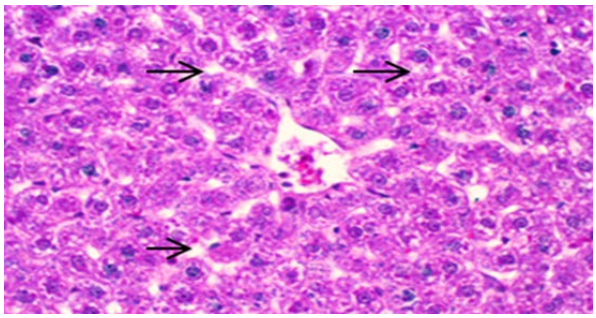

Figure 11. *Liver photomicrograph of group IV Amphotericin with vitamin D. Showed vacuolar degeneration in hepatocytes (Black arrow). H&E. 400x.*

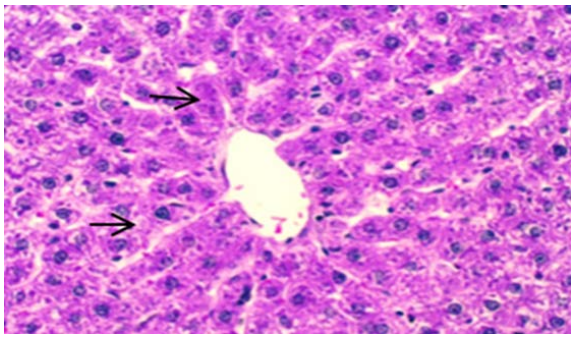

Figure 12. *Liver photomicrograph, Amphotericin with vitamin D group. Showed cloudy cell swelling in hepatocytes (Black arrow). H&E. 400x.*

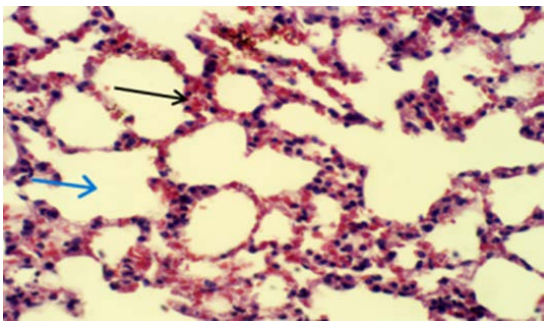

Figure 13. *Lung photomicrograph, Amphotericin with vitamin D group. Showed few infiltrations of red blood cells in the alveolar walls (Black arrow), with normal alveolar space (Blue arrow). H&E. 400x.*

Group IV:

Liver: characteristic of normal liver lobules architecture has normal central vein and normal hepatocytes, some with mild vacuolar degeneration seen, and cloudy cell swelling in a few hepatocytes (Figures 11 and 12).

Lung: shows apparently normal alveoli with few infiltrations of red blood cells in the alveolar walls. The spaces of alveoli are normal (Figure 13).

Discussion.

AMB is a class of antifungal medications used to treat life-threatening fungal infections. It is typically used when other antifungal medications have not been effective, however, it

appears that toxic drug effects have the potential to develop, and clinicians have to be conscious of the potential for lung and liver toxicity when using L-AMB therapy This study suggested that L-AMB may affects the liver and lungs. AMB induces the development of ion channels in the fungal cell membrane by binding to ergosterol, leading to depolarization and cell death. It also produces oxidative injury and increases membrane permeability [16]. Additionally, it stimulates phagocytic cells to assist in clearing fungal infections. AMB is poorly absorbed orally and is given parenterally. Its pharmacokinetics are non-linear, with high concentrations in tissues such as the liver, lungs, bone marrow, spleen, and kidneys [26]. The increase in severely weakened immune system patients due to AIDS, CORONA, and immunosuppressive techniques has led to a rise in fungal infections. This has raised concerns about the safety of antifungal drugs like AMB despite their widespread use.

This study revealed that administering L-AMB at a therapeutic dosage of 5 mg/kg b.wt intravenously for 28 consecutive days caused hepatocyte cogaulative necrosis, Kupffer cell hyperplasia, and inflammatory cell infiltration. These findings suggest hepatocyte damage is likely caused by toxic injury. Lymphocyte infiltration was observed around the portal area along with hyperplasia of bile canaliculi (Fig.5). Vacuolar degeneration in hepatocytes was also identified (Fig.6). The hepatic changes observed in this study support the findings of Messa et al. [27]. who examined the effects of AMB in dogs and rats. Their study concluded that the liver is the primary organ affected by AMB toxicity. Dogs showed hepatic inflammation (periportal and centrilobular), while rats exhibited acute hepatic necrosis. Contrary to prior experimental studies, which showed that AMB significantly reduced Kupffer cell phagocytic activity in isolated perfused rat livers [28]. our research demonstrated Kupffer cell hyperplasia, indicating that L-AMB stimulates phagocytic cells. We attribute this discrepancy to the higher dosage of the medication in our experiment than in those previous investigations, and we use experimental mice instead of isolated perfused rat livers. The hyperplasia of bile canaliculi could be secondary to drug-induced liver injury; Gaeta et al. reported that AMB has been shown in experiments to decrease both bile acid secretion and bile flow in isolated, perfused livers [29]. The exact mechanism by which AMB leads to liver damage is not fully understood. However, it is believed that the lipid component of L-AMB has a strong tendency to bind with lipoproteins and cellular membranes, causing the accumulation of AMB in the liver resulting in impaired hepatic function [30]. AMB drug can reduce liver metabolic capacity and cytochrome P450. Research by Inselmann G. observed reduced liver weight and reduced propafenone metabolism in rats given AMB-deoxycholate (3 mg/kg/day, intraperitoneal) for 4 days. AMB may affect the hepatic microsomal mixed-function oxidase system, which metabolizes various substances. The cytochrome P450 facilitates this process by eliminating different compounds. Cytochrome P-450 concentration may be decreasing due to decreased production or increased catabolism [31]. AMB affects the metabolic function of the liver in rats. Patel and colleagues [32]. previously reported a 21% rate of hepatotoxicity due to L-AMB. Although severe hepatotoxicity is an uncommon side effect of AMB treatment in humans, careful drug monitoring is advised, particularly for patients taking other drugs that are metabolized in the liver. The lung microanatomy in group 2 that received L-AMB showed massive interstitial haemorrhages, hemosiderin pigmentation, infiltration of mononuclear inflammatory cells, and alveolar serous exudate. As far as we know, no studies have been published on the histological changes in the lung caused by AMB treatment in mice. Reports of severe acute respiratory events, such as dyspnea, chills, and tremors, have been recorded after receiving an infusion of AMB, including fatal reactions [36]. Julio et al. (2001) examined 21 cases and provided guidelines for the safe continuation of therapy for patients who had these reactions. The chest X-rays showed widespread lung infiltrates, leading to irreversible cardiac and respiratory arrest, and the autopsy showed fluid exudate in the lungs on both sides. However, the exact mechanisms causing these reactions are not clear, leading to confusion in their management. Our findings of interstitial hemorrhages and the presence of serous exudate in the alveoli align with the results of McDonnell et al. (1985). Their study also found alveolar oedema (leakage of water and albumin) and the accumulation of red blood cells outside the blood vessels in the lungs of rats treated with AMB 1 mg/kg Iv. AMB increases pulmonary blood vessel permeability and vasoconstriction. The deposition of hemosiderin pigmentation could be a result of excessive breakdown of the iron-containing cells following hemorrhage, probably due to the rupture of endothelial cells leading to lung damage. Studies in the animal model have shown that AMB causes morphologic alterations to the endothelial cells and directly damages them [35].

In group 3, Vitamin D3 (10000 IU/kg and dissolved in sterile corn oil before use) given for four weeks orally showed a nearly normal liver and lung histology and no indication of microanatomy alterations in comparison to the control.

Mice In group 4, who got L-AMB medication therapy together with prior to administration of V-D showed fewer liver and lung cytoarchitecture changes compared to group 2 mice. This may be related to vitamin D's antioxidant properties. As far as the author is aware, no research has been done on the protective effects of vitamin D complex in mice after LAMB therapy, aside from a previous investigation into the protective impact of vitamins A and E in protecting liver cells from damage caused by free radicals generated by AMB [37]. Vitamin D is important for liver health, and a deficiency can increase the risk of liver diseases like cirrhosis. Vitamin D supplements may help manage liver conditions. Patients with liver disease often have low levels of vitamin D [38]. A study by Hassani in 2021 found that vitamin D protects the liver of rats from necrosis, fibrosis, and damage caused by toxins such as thioacetamide by acting as an antioxidant and anti-fibrotic agent. Vitamin D acts as a direct and indirect antioxidant. It works directly as a membrane antioxidant [39]. Indirectly, it increases the activity of natural antioxidant enzymes such as glutathione peroxidase, catalase, superoxide dismutase, and glutathione, which are all part of the body's antioxidant defense system [40]. The biological effects of vitamin D are mediated by the vitamin D receptor (VDR), which is a member of the nuclear

hormone receptor superfamily. Previous studies have indicated that the vitamin D receptor (VDR), participates in regulating macrophage activity [41]. VDR is an extremely expressive in nonparenchymal cells, particularly in hepatic macrophages, but not in hepatocytes. VDR activation suppresses inflammation and shifts hepatic macrophages from proinflammatory to anti-inflammatory, resulting in improvements in hepatic steatosis, insulin resistance, and tissue repair [42].

VDR is also found in hepatic stellate cells (HSCs) and cholangiocytes. VDR ligands, such as vitamin D3 or calcitriol, target HSCs, and may help to improve chronic liver diseases, like fibrosis. Following excessive liver injury, cholangiocytes, are activated, leading to the release of proinflammatory cytokines. Activation of VDR in cholangiocytes exerts beneficial anti-inflammatory effects and might reduce liver damage [43]. Deficiency of Vitamin D has been related to increased risk of chronic cholestatic disorders, including primary sclerosing cholangitis and biliary cirrhosis, indicating a potential hepatoprotective effect [44].

Research has shown vitamin D effectiveness in treating various health issues, including respiratory tract infections, metabolic disorders, cardiovascular conditions, cancer, autoimmune diseases, and viral infections. Supplementation is often recommended, especially for children and adolescents, to prevent nutritional rickets and reduce the risk of respiratory infections [45]. The anti-inflammatory and antioxidant properties of vitamin D are well known [25]. It is essential for lung health, as well as its well-known functions in calcium and phosphate regulation. The presence of vitamin D receptors (VDR) in many lung cells, along with the ability of pulmonary cells to respond to it, suggests that the lung is a target for its effects [46]. Studies have shown that vitamin D supplementation is effective in protecting against pulmonary injury, promoting tissue healing, and reducing oxidative stress. It is believed to protect against acute lung injury (ALI), a severe lung condition often caused by infections, through various mechanisms such as directly suppressing angiotensin II production, reducing the synthesis of pro-inflammatory cytokines, and having antioxidant properties to counteract oxidative stress, which is a major contributor to ALI pathogenesis [47]. Studies both in vivo and in vitro have shown how vitamin D affects oxidative stress in the lungs. It was observed that human airway epithelial cells, when stimulated with LPS or hydrogen peroxide, produce less reactive oxygen species when 25(OH)D3 is present [48]. In 2020, Yalçın et al. discovered that VD can protect rats from doxorubicin-induced lung injury by reducing the level of total oxidant status (TOS) and the expression of transient receptor potential melastatin 2 (TRPM2), a Ca2+ permeable cation channel [49]. Additionally, the total antioxidant status (TAS) in serum was significantly increased. Recent studies suggest that vitamin D can decrease oxidative stress, support mitochondrial functions, reduce the risk of infections, autoimmune diseases, and impairments to DNA repair, aiding healthy aging [25]. Accordingly, vitamin D3 supplementation has begun to take place in the treatment protocol for respiratory diseases such as influenza and COVID-19.

In this study, group 4 showed a beneficial effect from the administration of VD3, as it reversed tissue structure to become similar to the control group. This suggests that VD3 reduces liver damage and tissue lung injury induced by L-AMB.

Conclusion.

The current study found that vitamin D3 has a protective effect against the harmful effects of L-AMB on the liver and lungs. The results of the present study demonstrated that following the use of vitamin D3 orally, there is an improvement in the structure of the liver and lung in histopathologic examinations and recovery from the harmful effects of giving L-AMB to mice. Further studies are essential to ascertain its applicability in human subjects receiving L-AMB. Consequently, for patients frequently using this drug, co-administration of vitamin D3 at prophylactic doses is recommended.

Acknowledgments.

Thank Dr. Saevan Saad Al-Mahmood (Department of Veterinary Pathology. University of Mosul) for your support of group.

Funding:

Nil

Authors' contributions:

N.T & M.H: Conceptualized, design of this study, animal experiments, Visualization, wrote the original manuscript, wrote- reviewed & edited the manuscript. B.R.: Methodology, software. All authors read and approved the final manuscript.

Conflicts of interest:

There are no conflicts of interest.

Data availability:

All references are open access, allowing data to be accessed online.

REFERENCES

1. Cavassin F.B, Baú-Carneiro J. L, Vilas-Boas R.R, et al. Sixty years of amphotericin B: an overview of the main antifungal agent used to treat invasive fungal infections. Infectious Diseases and Therapy. 2021;10:115-147.
2. Escribano P, Mesquida A, López-Montesinos S, et al. Amphotericin B, itraconazole, posaconazole, and isavuconazole MICs against clinical Mucorales isolates obtained by visual inspection and spectrophotometric reading according to the EUCAST 9.4 procedure. Med Mycol. 2023;61:myad045.
3. Hamill RJ. Amphotericin B formulations: a comparative review of efficacy and toxicity. Drugs. 2013;73:919-934.
4. Cavassin F.B, Baú-Carneiro J.L, Vilas-Boas R.R, et al. Sixty years of amphotericin B: an overview of the main antifungal agent used to treat invasive fungal infections. Infectious Diseases and Therapy. 2021;10:115-147.
5. Cornely O.A, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019;19:e405-21.

6. Lanternier F, Poiree S, Elie C, et al. Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis. J Antimicrob Chemother. 2015;70:3116-23.
7. Mendoza-Palomar N, Garcia-Palop B, Melendo S, et al. Antifungal stewardship in a tertiary care paediatric hospital: the PROAFUNGI study. BMC Infect Dis. 2021;21:100.
8. Maertens J, Pagano L, Azoulay E, et al. Liposomal amphotericin B-the present. J Antimicrob Chemother. 2022;77:ii11-ii20.
9. Bekersky I, Fielding R.M, Dressler D.E, et al. Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate in humans. Antimicrobial agents and chemotherapy. 2002;46:828-833.
10. Gershkovich P, Wasan E.K, Lin M, et al. Pharmacokinetics and biodistribution of amphotericin B in rats following oral administration in a novel lipid-based formulation. J Antimicrob Chemother. 2009;64:101-108.
11. Groll A.H, Lyman C.A, Petraitis V, et al. Compartmentalized intrapulmonary pharmacokinetics of amphotericin B and its lipid formulations. Antimicrobial agents and chemotherapy. 2006;50:3418-3423.
12. Tverdek F.P, Kofteridis D, Kontoyiannis D.P. Antifungal agents and liver toxicity: A complex interaction. Expert Rev. Anti Infect. Ther. 2016;14:765-776.
13. Loo A.S, Muhsin S.A, Walsh T.J. Toxicokinetic and mechanistic basis for the safety and tolerability of liposomal amphotericin B. Expert Opin. Drug Saf. 2013;12:881-895.
14. Fischer MA, Winkelmayer WC, Rubin RH, et al. The hepatotoxicity of antifungal medications in bone marrow transplant recipients. Clin Infect Dis. 2005;41:301-7.
15. Kolve H, Ahlke E, Fegeler W, et al. Safety, tolerance and outcome of treatment with liposomal amphotericin B in paediatric patients with cancer or undergoing haematopoietic stem cell transplantation. Journal of antimicrobial chemotherapy. 2009;64:383-387.
16. Rybak JM, Fortwendel JR, Rogers PD. Emerging threat of triazole-resistant Aspergillus fumigatus. The Journal of Antimicrobial Chemotherapy. 2019;74:835-842.
17. Wu A, Grela E, Wójtowicz K, et al. ABCA1 transporter reduces amphotericin B cytotoxicity in mammalian cells. Cellular and Molecular Life Sciences. 2019;76:4979-4994.
18. Moradi A, Ziamajidi N, Ghafourikhosroshahi A, et al. Effects of vitamin A and vitamin E on attenuation of titanium dioxide nanoparticles-induced toxicity in the liver of male Wistar rats. Molecular biology reports. 2019;46:2919-2932.
19. Albergamo A, Apprato G, Silvagno F. The Role of Vitamin D in Supporting Health in the COVID-19 Era. Int. J. Mol. Sci. 2022;23:3621.
20. Adam-Bonci T.I, Bonci E.A, Pârvu A.E, et al. Vitamin D supplementation: oxidative stress modulation in a mouse model of ovalbumin-induced acute asthmatic airway inflammation. International Journal of Molecular Sciences. 2021;22:7089.
21. Ellison DL, Moran HR. Vitamin D: Vitamin or Hormone? Nurs Clin North Am. 2021;56:47-57.
22. Wiseman H. Vitamin D is a membrane antioxidant. Ability to inhibit iron-dependent lipid peroxidation in liposomes compared to cholesterol, ergosterol and tamoxifen and relevance to anticancer action. FEBS letters. 1993;326:285-8.
23. Timar A, Saberi-Karimian M, Ghazizadeh H, et al. Evaluation of the serum prooxidant-antioxidant balance before and after vitamin D supplementation in adolescent Iranian girls. Adv Med Sci. 2019;64:174-80.
24. Dattola A, Silvestri M, Bennardo L, et al. Role of Vitamins in Skin Health: A Systematic Review. Curr. Nutr. Rep. 2020;9:226-235.
25. Wimalawansa SJ. Vitamin D deficiency: Effects on oxidative stress, epigenetics, gene regulation, and aging. Biology. 2019;8:30.
26. Groll AH, Rijnders BJA, Walsh TJ, et al. Clinical Pharmacokinetics, Pharmacodynamics, Safety and Efficacy of Liposomal Amphotericin B. Clin Infect Dis. 2019;68:S260-S274.
27. Massa T, Sinha D.P, Frantz J.D, et al. Subchronic Toxicity Studies of N-D-Ornithyl Amphotericin B Methyl Ester in Dogs and Rats. Toxicological Sciences. 1985;5:737-753.
28. Gaeta GB, Ames PR, Mansi L, et al. Amphotericin B-induced depression in the phagocytic function of the isolated rat liver and its prevention by nifedipine. J Hepatol. 1990;10:168-173.
29. Gaeta G.B, Utili R, Adinolfi L.E, et al. Effects of amphotericin B on the excretory function and the colloid clearance capacity of the perfused rat liver. Journal of hepatology. 1989;8:344-350.
30. Lemke A, Kiderlen A.F, Kayser O. Amphotericin B. Appl Microbiol Biotechnol. 2005;68:151-162.
31. Inselmann G, Volkmann A, Heidemann H.T. Comparison of the effects of liposomal amphotericin B and conventional amphotericin B on propafenone metabolism and hepatic cytochrome P-450 in rats. Antimicrobial agents and chemotherapy. 2000;44:131-133.
32. Patel G.P, Crank C.W, Leikin J.B. An evaluation of hepatotoxicity and nephrotoxicity of liposomal amphotericin B (L-AMB). Journal of Medical Toxicology. 2011;7:12-15.
33. Collazos J, Martínez E, Mayo J, et al. Pulmonary reactions during treatment with amphotericin B: review of published cases and guidelines for management. Clinical Infectious Diseases. 2001;33:e75-e82.
34. McDonnell T.J, Chang S.W, Westcott J.Y, et al. Role of oxidants, eicosanoids, and neutrophils in amphotericin B lung injury in rats. Journal of Applied Physiology. 1988;65:2195-2206.
35. Cutaia M, Bullard S.R, Rudio K, et al. Characteristics of amphotericin B-induced endothelial cell injury. The Journal of laboratory and clinical medicine. 1993;121:244-256.
36. Johnson M.D, Drew R.H, Perfect J.R. Chest discomfort associated with liposomal amphotericin B: report of three cases and review of the literature. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 1998;18:1053-1061.
37. Salehzadeh A, Salehzadeh A, Maghsood A.H, et al. Effects of vitamin A and vitamin E on attenuation of amphotericin B-induced side effects on kidney and liver of male Wistar rats. Environmental Science and Pollution Research. 2020;27:32594-32602.
38. Ravaioli F, Pivetti A, Di Marco L, et al. Role of vitamin D in liver disease and complications of advanced chronic liver disease. International Journal of Molecular Sciences. 2022;23:9016.

39. Hassani M.K. Role of vitamin D as protective agent against induced liver damage in male rats. Archives of Razi Institute. 2021;76:1815-1822.
40. Preedy V.R. (Ed.). Diabetes: Oxidative stress and dietary antioxidants. Academic Press. 2020.
41. Zhou Y, Dong B, Kim K.H, et al. Vitamin D receptor activation in liver macrophages protects against hepatic endoplasmic reticulum stress in mice. Hepatology. 2020;71:1453-1466.
42. Dong B, Zhou Y, Wang W, et al. Vitamin D receptor activation in liver macrophages ameliorates hepatic inflammation, steatosis, and insulin resistance in mice. Hepatology. 2020;71:1559-1574.
43. Ding N, Ruth T.Y, Subramaniam N, et al. A vitamin D receptor/SMAD genomic circuit gates hepatic fibrotic response. Cell. 2013;153:601-613.
44. Wang R, Hu W. Asprosin Promotes β-cell Apoptosis by Inhibiting the Autophagy of β-cell via AMPK-mTOR Pathway. Journal of cellular physiology. 2021;236:215-221.
45. Demay M.B, Pittas A.G, Bikle D.D, et al. Vitamin D for the prevention of disease: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2024;109:1907-1947.
46. Gayan Ramirez G, Janssens W. Vitamin D actions: the lung is a major target for vitamin D, FGF23, and Klotho. Journal of Bone and Mineral Research Plus. 2021;5:e10569.
47. Tao S, Zhang H, Xue L, et al. Vitamin D protects against particles-caused lung injury through induction of autophagy in an Nrf2-dependent manner. Environmental toxicology. 2019;34:594-609.
48. Lan N, Luo G, Yang X, et al. 25-Hydroxyvitamin D3-deficiency enhances oxidative stress and corticosteroid resistance in severe asthma exacerbation. PloS one. 2014;9:e111599.
49. Yalçın A, Türk A, Aydın H, et al. Effects of Vitamin D on doxorubucin-induced lung injury and TRPM2 immunoreactivity in rats. Journal of Surgery and Medicine. 2020;4:1236-1239.