UDC 616.31:612.313

Serzhan MOMBEKOV
PhD Deputy Director of Science JSC "Scientific Center for Anti-infectious Drugs", Al-Farabi str., 75a, Almaty, Kazakhstan, 050000 (mombekov.s@kaznmu.kz)
ORCID: *0000-0001-8805-9880*
SCOPUS: *6503851956*

To cite this article: Mombekov S. (2025). Vyvchennia rechovyn hostroi ta pidhostroi toksychnosti protyhrybkovoi dii na osnovi pomiferynu z plodiv *Maclura aurantiaca* [Study of acute and subacute toxicity substances with antifungal action based on pomyferin from fruits *Maclura Aurantiaca]*. *Fitoterapiia. Chasopys – Phytotherapy. Journal*, *1*, 184–190, doi: https://doi.org/10.32782/2522-9680-2025-1-184

STUDY OF ACUTE AND SUBACUTE TOXICITY SUBSTANCES WITH ANTIFUNGAL ACTION BASED ON POMYFERIN FROM FRUITS *MACLURA AURANTIACA*

Actuality. *The study of the toxicity and biological activity of pomyferin, a compound derived from the fruits of Maclura aurantiaca, is crucial for the further development of effective and safe pharmaceuticals. This research also contributes to expanding our knowledge of potential applications of plant-based compounds in medicine.*

Aim. *The primary objective of this study was to investigate the pharmacological properties of pomyferin from the fruits of Maclura aurantiaca, with a focus on evaluating its acute and subacute toxicity.*

Materials and methods. *The acute toxicity of the pomyferin extract was studied following the guidelines approved by the Pharmacological Committee of the Republic of Kazakhstan. The experiments involved male and female white mice, each weighing between 18.0 and 22.0 grams. The mice were kept on a standard diet and housed in a vivarium under controlled conditions. Each experimental group consisted of six animals.*

Results. *The results demonstrated no pathological changes in the general health indicators of the mice during the entire study period. The animals in all groups remained active, and no signs of intoxication or alterations in respiratory, cardiovascular, or central nervous system functions were observed.*

Conclusions. *Based on the findings, it was concluded that the animals treated with the pomyferin substance showed no differences from the control group. The treated animals were active, displayed normal reflexes, and had regular water and food intake, with no impairment in their natural functions. Therefore, pomyferin is considered a low-toxicity substance (hazard class IV) and holds promise for further clinical studies.*

Key words: *substance, fluconazole, pomyferin, maclura aurantiaca.*

Сержан МОМБЕКОВ
заступник директора з науки, АТ «Науковий центр протиінфекційних препаратів», вул. Аль-Фарабі, 75а, м. Алмати, Казахстан, 050000 (mombekov.s@kaznmu.kz)
ORCID: *0000-0001-8805-9880*
SCOPUS: *6503851956*

Бібліографічний опис статті: Момбеков С. (2025). Вивчення речовин гострої та підгострої токсичності протигрибкової дії на основі поміферину з плодів *Maclura aurantiaca*. *Фітотерапія. Часопис, 1*, 184–190, doi: https://doi.org/10.32782/2522-9680-2025-1-184

ВИВЧЕННЯ РЕЧОВИН ГОСТРОЇ ТА ПІДГОСТРОЇ ТОКСИЧНОСТІ ПРОТИГРИБКОВОЇ ДІЇ НА ОСНОВІ ПОМІФЕРИНУ З ПЛОДІВ *MACLURA AURANTIACA*

Актуальність. *Вивчення токсичності та біологічної активності поміферину з плодів Maclura aurantiaca має велике значення для подальшої розробки ефективних і безпечних препаратів, а також для розширення знань про потенційне застосування рослинних сполук у медицині.*

Мета роботи. *Дослідження фармакологічної дії субстанції на основі поміферину з плодів Maclura aurantiaca, виявлення такої дії, як гостра та підгостра токсичність.*

Матеріали та методи. *Дослідження гострої токсичності досліджуваного екстракту проводили згідно з методичними рекомендаціями, затвердженими Фармакологічним комітетом Республіки Казахстан. У дослідах використовували лінійних білих мишей масою 18,0–22,0 однієї статі та віку, розділених на групи по 6 тварин, які утримувалися на стандартній дієті в умовах віварію.*

Результати роботи. *Дослідження показали відсутність патологічного характеру, змін загальних показників протягом усього періоду досліджень. Тварини в усіх групах залишалися активними, ознак інтоксикації та змін з боку дихальної, серцево-судинної, центральної нервової систем не зафіксовано.*

Висновки. *За результатами дослідження встановлено, що тварини, які отримували досліджувану речовину, не відрізнялися від контрольних. Тварини були активними, їх рефлекси – жвавими, споживання води та їжі було нормальним, природні функції не були порушені. Таким чином, речовина поміферин є малотоксичною речовиною (IV клас небезпеки) і може бути рекомендована для клінічних досліджень.*

Ключові слова: *речовина, флуконазол, поміферин, Maclura aurantiaca.*

Introduction

The World Health Organization (WHO) estimates that over 80% of the global population, particularly in developing countries such as Ethiopia, India, and Rwanda, rely on herbal medicines for primary healthcare. In areas with limited access to modern medical services, herbal and plant-based remedies play a critical role in both maintaining health and treating various diseases (De Smet, 2002; WHO, 2004; Onaga, 2001; Oberlies, 2004).

People consume natural products they think they are safe and not have harmful effects (Ha, et al., 2018).

Herbal preparations are also widely utilized in Western medicine. Approximately 30% of all pharmaceuticals approved for use are derived from plants. These include both active medicinal compounds and components such as extracts and oils, which form the basis of numerous drugs used to treat a range of diseases, including cardiovascular, neurological, and inflammatory disorders (Sidorov, 2004; Kuzdenbaeva et al., 2000).

For a long time, plants have been used as a promising source of therapeutic agents. Currently, many developed drags, even against cancer, could be derived from natural products of their chemically modifield derivatives (Prasad et al., 2014).

Medicinal plants can contain many secondary metabolites, some of which are very complecs. Nevertheless, herbs used to treat certain diseases are generally used without any scientific knowledge or evidence of toxicological effects (Brondani at al., 2017; Koriem et al., 2019).

The exact number of medicinal plant species in Kazakhstan remains uncertain, with the list continually expanding as new species are discovered and identified each year (Mombekov et al., 2024).

In recent years, the incidence of fungal diseases has steadily increased. Contributing factors include an aging population, with the prevalence of mycosis reaching 50% among the elderly. This group serves as a constant reservoir for infection, particularly with intrafamilial transmission, which epidemiological studies indicate affects 28% of younger and middle-aged individuals. The rise of dermatophytosis is also linked to an increase in immunocompromised individuals, whether due to congenital or acquired conditions. Additionally, the worsening environmental and socio-economic conditions in Kazakhstan have contributed to a higher incidence of underlying somatic conditions that predispose individuals to fungal infections (Rode et al., 2000; Gottfredsson et al., 2001).

Various medicinal plants, including Maclura aurantiaca, have been used in traditional medicine to treat fungal diseases. The biological composition of Maclura aurantiaca makes it a unique natural antifungal agent with a broad spectrum of activity. The medicinal properties of Maclura aurantiaca are attributed to its mature fruit, which contains a variety of flavonoids that help restore the body's immune defenses, promoting the healing of fungal infections. Despite its potential, the plant has not yet been widely utilized by pharmaceutical companies due to limited research (Tsao et al., 2003).

Currently, clinical practice includes a range of antifungal drugs, both systemic and topical. However, the toxic and side effects associated with many of these medications often limit their use. For example, the antibiotic griseofulvin is known for its high toxicity and teratogenic effects. Similarly, imidazole and triazole derivatives such as fluconazole and clotrimazole can cause hepatotoxicity and adverse effects on endocrine organs when used systemically. When used topically, these substances may provoke allergic reactions. Prolonged local use can further increase the risk of these reactions (Kumarasinghe et al., 2000).

Recent studies have shown that certain formulations, such as gels, exhibit potent antifungal activity, outperforming drugs like “Flucytosine” and “Fucis” (Mombekov et al., 2024).

The bioassay-guided fractionation method, commonly used to isolate compounds with significant biological activity, plays a vital role in discovering new natural products with therapeutic potential. Through this method, active fractions are tested for various biological effects, such as antimicrobial, anticancer, or anti-inflammatory properties, guiding the identification of substances suitable for further medicinal exploration (Orazbekov et al., 2018).

In light of these challenges, the search for, development of, and implementation of highly active, low-toxic

drugs capable of specifically targeting pathogenic fungi without adversely affecting the human body is an ongoing and relevant area of research. The acute and subacute toxicity test is a method based on an evaluation of the harmlessness and safety of chemicals, as well as an analysis of their mode of action. Acute and subacute systemic toxicity studies are used for hazard disclosure and risk management in the context of the production, handing and use of chemicals (Li et al., 2020).

Aim.The aim of this study is to investigate the pharmacological action of a substance based on pomyferin from the fruits of Maclura aurantiaca, focusing on its acute and subacute toxicity.

Materials and methods. The study of the acute toxicity of the extract was conducted following the methodological guidelines approved by the Pharmacological Committee of the Republic of Kazakhstan (Kuzdenbaeva et al., 2000). The experiments were carried out using linear white mice, each weighing between 18.0 and 22.0 grams, of the same age and sex, divided into groups of six animals. The mice were maintained on a standard diet and housed under vivarium conditions.

The source of the animals and the location of the study was the vivarium of Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan.

To assess acute toxicity, the suspension of the studied substance was administered orally to the animals in doses ranging from 5 to 15 mg. In parallel, the acute toxicity of the pomyferin extract was compared to that of fluconazole, a substance known for its antifungal properties. The animals were observed for a period of 7 days.

Subacute toxicity was studied on white mongrel mice, each weighing between 18.0 and 22.0 grams. The animals were divided into three groups: a control group and two experimental groups, each with 10 mice. The experimental groups received the studied substance or a comparator substance with their food at a dose of 20 mg daily for 14 days (Huang et al., 2020).

Throughout the experiment, various parameters were monitored, including the general condition of the animals, behavioral characteristics, motor activity, coordination of movements, response to tactile, pain, light, and sound stimuli, respiratory rate, heart rate, skin condition, food and water consumption, body weight changes, and pupil size. Additionally, pathomorphological manifestations of toxicity were evaluated macroscopically and microscopically at the end of the study, after the animals were euthanized (via decapitation under light ether anesthesia).

This study also aimed to evaluate the organoleptic properties of the plant material, a critical step in preclinical assessment to confirm its suitability for further pharmacological, toxicological, and analytical investigations (State Pharmacopoeia of the Republic of Kazakhstan, 2008; Kantureyeva et al., 2024; Bazaraliyeva et al., 2024; Turgumbayeva et al., 2023).

Research results and discussion. The experiments revealed no pathological changes in the general health indicators of the animals throughout the entire study period. The animals in all groups remained active, with no signs of intoxication or alterations in the respiratory, cardiovascular, or central nervous systems. The condition of the fur and mucous membranes remained unchanged. Food and water consumption was consistent with baseline levels, and the body weight of the animals remained stable throughout the experiment. Histological examinations showed that the internal organs (liver, kidneys, and lungs) appeared normal, with no significant changes detected. Importantly, no deaths were observed among the animals, so the determination of the LD_{50} could not be performed.

Macroscopic examination. Upon autopsy of the experimental group animals, the internal organs in the thoracic and abdominal cavities appeared normal in color, consistency, and anatomical structure. The organs were positioned correctly, and their sizes and shapes were consistent with the control group. The heart presented no abnormal changes; its muscle was dense and brownish in color. The surface of the lungs was pale pink, and the lungs collapsed upon opening the chest. The tissue inside also had a uniform pale pink color, and the mucous membrane of the extrapulmonary bronchi was smooth, shiny, and pale pink with no signs of hemorrhaging.

The mucous membrane of the stomach was also pale pink, shiny, and folded, without any hemorrhages or ulcerations. The mucous membranes of the small and large intestines were smooth, velvety, and free from hemorrhages or ulcers. The liver was of normal size and shape, with a thin, transparent capsule. Its tissue had a brownish color and a moderately dense consistency. The kidneys appeared normal in size and shape, with a smooth, uniform surface and a brownish-gray color. The cortex and medulla were clearly distinguishable upon sectioning. The spleen had a dark cherry color, smooth surface, and dense consistency.

Histological examination. Histological analysis of the lungs from mice in the experimental group that received the extract, in all dilutions, showed that the alveolar cavities were clear, and the epithelium of the bronchial tree was intensely stained. Only a few areas of fresh hemorrhages, likely resulting from decapitation, were observed. No signs of circulatory disturbances were found.

Overall, these findings suggest that the studied extract did not cause any significant toxic effects or alterations in the general health or internal organs of the animals,

further supporting the conclusion that the substance is of low toxicity.

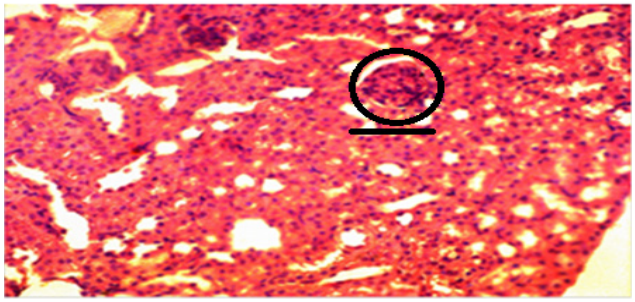

Fig. 1. Lungs of mice from the experimental group

In the Fig. 1, the inflamed lungs of the mice in the experimental group can be seen within the marked circular shape. Additionally, the effect of the given substance on the inflamed lungs can be observed, leading to the conclusion that the inflammation is resolving.

When examining the kidneys of mice in the experimental group that received the pomyferin substance at all dilutions (Fig. 2), the tubular epithelium appeared uniformly stained, with the nuclei clearly absorbing the dye. The normal histological structure of the kidneys was preserved, showing no signs of hemorrhages or edema. These findings further indicate the lack of toxic effects on renal tissue following administration of the pomyferin substance.

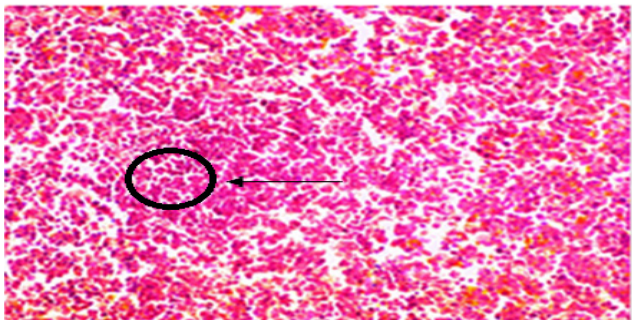

Fig. 2. Mouse kidneys from experimental groups

The kidneys of the mice in the experimental group show changes in the marked areas, with the direction indicated from left to right, and the level of resolution in the central part of the circle can be observed.

When examining the liver of mice in the experimental group (Fig. 3), hepatocytes exhibited intense dye absorption, with no signs of hemorrhage. The histological structure remained intact, and the arrangement of the hepatic lobules was normal. No circulatory disturbances were observed, indicating that the pomyferin substance did not cause any adverse effects on liver tissue.

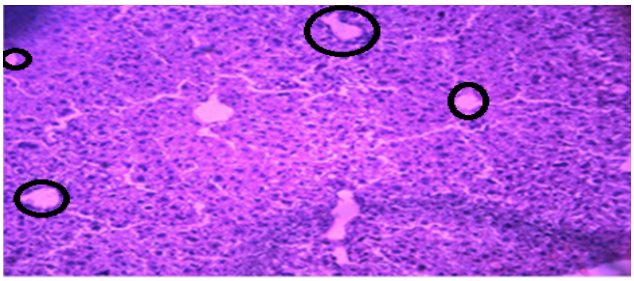

Fig. 3. Liver of mice from experimental groups

The image shows diffuse changes in the livers of the mice. The study revealed circularly marked changes in the liver during inflammation.

Thus, both macroscopic and microscopic examinations of the internal organs revealed that the oral administration of the studied substance in all dilutions, both in single and repeated doses over a 4-week period, did not induce any general pathological or specific destructive changes in the internal organs of the animals. These findings suggest the absence of a toxic effect, allowing the substance to be classified as a practically non-toxic preparation, belonging to the IV toxicity class.

The acute toxicity studies conducted showed no significant differences in the effects between the test substance and the compared samples (Table 1).

No animal deaths were observed within the studied dose range, both in the assessment of the test substance and in the experimental and reference samples. In terms of acute toxicity, the studied substance showed no significant differences from the pomyferin sample. Body weight fluctuations in the mice across all groups did not exceed 10% and were not statistically significant; likewise, the relative weight of internal organs remained unchanged. The general condition and behavior of the animals receiving the test substance were similar to the control group. The animals were active, exhibited lively reflexes, and maintained normal food and water intake. Natural bodily functions were not impaired.

Table 1

Study of acute toxicity of the test substance based on pomyferin from fruits *Maclura aurantiaca*

No.	Groups	Experiment	Animal species, rat mice grams	Range	Collation
1	Control	Purified water	18–22 grams	5–10 to 15 mg	1 : 10, 1 : 20, 1 : 30
2	Research	Pomiferin	18–22 grams	5–10 to 15 mg	1 : 10, 1 : 20, 1 : 30
3	Comparison	Fluconazole	18–22 grams	5–10 to 15 mg	1 : 10, 1 : 20, 1 : 30

During the subacute toxicity study, no lethal outcomes were observed in any of the animal groups throughout the observation period. All animals remained active, with no changes recorded in the respiratory, cardiovascular, or central nervous systems. The condition of the fur and mucous membranes remained unchanged. The determination of LD_{50} is presented in Table 2.

Table 2

Determination of LD50 of a substance based on pomyferin from fruits *Maclura aurantiaca*

No		Samples under study	
		No. 1 Substance under study	**No. 2 Flucytosine substance**
1	Survived	25	28
2	Died	1	0
3	Z	0	0
4	D	1	1
5	Zd	0	0

Z is the average number of mice killed between groups closest to the doses studied; D is the interval between doses; Zd is the product of the average number of mice killed between groups and the interval between doses.

LD_{50} was calculated using formula (1):

LD_{50} = LD_{100} – (1), where

n – is the number of animals in the experimental group;

ΣDz is the sum of all products of the average number of mice killed between groups and the interval between doses;

LD_{50} > No. 1 and No. 2 samples, since no death of animals was observed when administered in the dose range from 10 to 50 mg.

Conclusions

Acute and subacute toxicity studies of the substance based on pomyferin extracted from the fruits of Maclura aurantiaca **(Maclura orange) included a thorough analysis of changes in the organs and tissues of animals following administration of the test substance. The results demonstrated that no significant toxic effects were observed during the experiment, such as acute reactions involving the central nervous system, respiratory or cardiovascular systems, or damage to internal organs, indicating the safety of the test substance.**

The absence of clinically evident signs of intoxication, normal biochemical blood test parameters, and the lack of morphological changes in the organs and tissues of the animals allowed the classification of this substance as low-toxic, belonging to hazard class IV on the toxicity scale (low-hazard substances). These findings support the potential for further use of pomyferin from Maclura aurantiaca **in pharmaceutical and biomedical applications, provided that the recommended doses and administration regimens are followed.**

In conclusion, based on the toxicological studies conducted, it can be affirmed that the substance has low toxicity, which opens up promising opportunities for its use as an active ingredient in the development of medical products with antimicrobial, antioxidant, and anti-inflammatory activities.

BIBLIOGRAPHY

Bazaraliyeva A., Turgumbayeva A., Kartbayeva E., et al. GC-MS based characterization, antimicrobial activity of garlic CO_2 subcritical extract (*Allium sativum*). *Farmacia* 2024. No. 71 (1). P. 123–130. https://doi.org/10.3897/pharmacia.71.e12456.

Brondani J.C., Reginato F.Z., Brum E.D.S, Vencato M.D.S, Lhamas C.L., Viana C., da Rocha, M.I.U.M, Bauermann L.D.F., Manfon M.P., et al. Evalution of acute and subacute toxicity of hydroethanolic extract of Dolichandra unguis-cati L. leaves in rats. J Ethnopharmacol. 2017. No. 202. P. 147–153. https://doi.org/10.1016/j.jep.2017.03.011.

De Smet PA Herbal remedies. *N. Engl. J. Med*. 2002. Dec 19. 347 (25). P. 2046–2056. DOI: 10.1056/NEJMra020398.

Gottfredsson M., Jessup C.J., Cox G.M., Perfect J.R., Ghannoum M.A. Fungal phospholipase activity and susceptibility to lipid preparations of amphotericin B. ASM Journals Antimicrobial Agents and Chemotherapy. 2001. Vol. 45, No. 11 P. 3231–3233. DOI: 10.1128/aac.45.11.3231-3233.2001.

Huang W., Percie du Sert, N., Vollert, J., Rice, A.S.C. General principles of preclinical study design / *Handb. Exp. Pharmacol.* 2020. Vol. 257. P. 55–69. DOI: 10.1007/164_2019_277.

Ha A.W., Kang H.J. Kim S.L., Kim M.H. Kim W.K., et al. Acute and subacute toxicity evaluation of corm silk extract. Prev. Nutr. Food Sci. 2018. No. 23. P. 70–76. DOI: 10.346/pnf.2018.23.1.70.

Kantureyeva A., Ustenova G., Zvonar Pobirk A., Mombekov S., Koilybayeva M., Amirkhanova A., et al. Ceratosaurus arenarius: Botanical Characteristics, Proximity, Mineral Composition and Cytotoxic Activity. *Molecules*, 2024. Vol. 29 (2), 384 p. https://doi.org/10.3390/molecules29020384.

Kuzdenbaeva R.S., Rakhimov K.D., Shin S.N., Chukanova G.N. Preclinical study of local anesthetic activity of new biologically active substances. Methodical manual. Almaty, 3 p. 2000.

Kumarasinghe S.P., Kumarasinghe M.P. Itraconasol puis therapy in chromoblastomycosis. *Eur. J. Dermatol.* 2000. No. 3. P. 220–222.

Koriem K.M.M., Arbid M.S., El-Attar M.A., et al. Acute and subacute toxicity of Ammi visnaga on rats. Interdisip. Toxicol. 2019. No. 12. P. 26–35. https://doi.org/10.2478/intox-2019-0004.

Li Y., Zhuang Y., Tain W., Sun L., et al. In vito acute and subacute toxicities of phenolic extract from rambutan (Nephelium lappaceum) peels by oral administration. Food Chem. 2020. No. 320. P. 126618. https://doi.org/10.1016/j.foodchem-2020-126618.

Mombekov S., Datkhayev U., Kalamkul D., Kozhamzharova A., Baidullayeva A., Assel M., Kantureyeva A., Yessimsiitova Z., Yussayeva D., Beken Z., Kydyrkhanova A., Karbozova A., Zhuravel I. Study of the chemical components of CO2 extracts from the fruits of Sorbus aucuparia L. *ScienceRise: Pharmaceutical Science*. 2024. No. 2 (48). P. 83–89. https://doi.org/10.15587/2519-4852.2024.303000.

Mombekov S., Orazbekov Y., Sadykova N., Kozhamzharova A., Sharipova S., Makhatov Z., Pushkarskaya N. Development of antifungal gel, composition and technology based on pomiferin metabolite isolated from fruits of Maclura aurantiaca growing in Kazakhstan / ScienceRise: Pharmaceutical Science. 2024. No. 1 (47). P. 79–85. https://doi.org/10.15587/2519-4852.2024.299230.

Prasad R., Koch B., et al. Antitumor activity of ethanolic extract Dendrobium fromosum in T-cell lymphoma: An in vitro and in vivo study. Biomed Res. Int. 2014. Issue 1. P. 753451. https://doi.org/10.1155/-2014-753451.

Onaga L. Cashing in nature's pharmacy: bioprospecting and protection of biodiversity could go hand in hand. *EMBO Rep*. 2001. No. 2. P. 263–265. DOI: 10.1093/embo-reports/kve077.

Oberlies N.H., Kroll D.J. Camptothecin and taxol: historic achievements in natural products research. *J. Nat. Prod.* 2004. Vol. 67. P. 129–135. DOI: 10.1021/np030498t.

Orazbekov Yerkebulan, Mohamed A. Ibrahim, Serjan Mombekov, Radhakrishnan Srivedavyasasri, Ubaidilla Datkhayev, Bauyrzhan Makhatov, Narayan D. Chaurasiya, Babu L. Tekwani, and Samir A. Ross. Isolation and Biological Evaluation of Prenylated Flavonoids from *Maclura pomifera.* Evidence-based Complementary and Alternative Medicine. Volume Article ID 1370368. 2018. https://doi.org/10.1155/2018/13 70368.

Rode M.E., Morgan M.A., Ruchelli E., Forouzan I. Candida chorioamnionitis after serial therapeutic amniocenteses: a possible association. *J Perinatol*. 2000. Vol. 20. P. 335–337.

State Pharmacopoeia of the Republic of Kazakhstan; Zhibek-Zholy: Almaty, Kazakhstan, 2008. Volume 1, 592 p.

Sidorov K.K. On the hormonization of domestic and international classifications of acute toxicity of chemical compounds Sidorov K.K. *Toksikol. vest.* 2004. No. 6. P. 2–5.

Tsao R., Yang R., Young J.C. Antioxidant isoflavones in Osage orange, Maclura pomifera (Raf.) Schneid. *J. Agric. Food Chem*. 2003. Vol. 51, No. 22, pp. 6445–6451. DOI: http://dx.doi.org/10.1021/jf0342369.

Turgumbayeva A., Zhanat T., Zhakipbekov K., Kalykova A., Kartbayeva E., Mombekov S., et al. A Review on The Medicinal Plant Echinops Ritro Species: Phytochemistry and Biological Activity. *Farmacia*, 2023. No. 71 (3). P. 455–462. https://doi.org/10.31925/farmacia.2023.3.2.

WHO. Issues guidelines for herbal medicines. *Bull. World Health Organ.* 2004. Vol. 82. 238 p. PMC2585928 (Review date: 20.10.2024).

REFERENCES

Bazaraliyeva, A, Turgumbayeva, A, Kartbayeva, E, et al. (2024). GC-MS based characterization, antimicrobial activity of garlic CO_2 subcritical extract (*Allium sativum*). *Farmacia,* 71 (1): 123–130. https://doi.org/10.3897/pharmacia.71.e12456.

Brondani, J.C., Reginato, F.Z., Brum, E.D.S, Vencato, M.D.S, Lhamas, C.L., Viana, C., da Rocha, M.I.U.M, Bauermann, L.D.F., Manfon, M.P., et al. (2017). Evalution of acute and subacute toxicity of hydroethanolic extract of Dolichandra unguis-cati L. leaves in rats/J.Ethnopharmacol., 202, 147–153. https://doi.org 10.1016/j.jep.2017.03.011

De Smet PA (2002). Herbal remedies. *N. Engl. J. Med*. Dec 19, 347 (25), 2046–2056. DOI: 10.1056/NEJMra020398.

Gottfredsson, M., Jessup, C.J., Cox, G.M., Perfect, J.R., & Ghannoum, M.A. (2001). Fungal phospholipase activity and susceptibility to lipid preparations of amphotericin B. ASM Journals Antimicrobial Agents and Chemotherapy, 45 (11), 3231–3233. DOI: 10.1128/aac.45.11.3231-3233.2001.

Huang, W., Percie, du Sert, N., Vollert, J., & Rice, A.S.C. (2020). General principles of preclinical study design. *Handb. Exp. Pharmacol.* 257, 55–69. DOI: 10.1007/164_2019_277.

Ha, A.W., Kang, H.J. Kim, S.L., Kim, M.H. Kim, W.K., et al. (2018). Acute and subacute toxicity evaluation of corm silk extract. Prev. Nutr. Food Sci., 23, 70–76. DOI: 10.346/pnf.2018.23.1.70.

Kantureyeva, A., Ustenova, G., Zvonar Pobirk, A., Mombekov, S., Koilybayeva, M., Amirkhanova, A. et al. (2024). Ceratosaurus arenarius: Botanical Characteristics, Proximity, Mineral Composition and Cytotoxic Activity. Molecules, 29 (2), 384. https://doi.org/10.3390/molecules29020384.

Kuzdenbaeva, R.S., Rakhimov, K.D., Shin, S.N., & Chukanova, G.N. (2000). Preclinical study of local anesthetic activity of new biologically active substances. Methodical manual. Almaty, 3 p.

Kumarasinghe, S.P., & Kumarasinghe, M.P. (2000). Itraconasol puis therapy in chromoblastomycosis. *Eur. J. Dermatol.* 3, 220–222.

Koriem K.M.M., Arbid M.S., El-Attar M.A., et al. (2019). Acute and subacute toxicity of Ammi visnaga on rats. Interdisip. Toxicol. 12, 26–35. https://doi.org/10.2478/intox-2019-0004

Li, Y., Zhuang, Y., Tain, W., Sun, L., et al. (2020). In vito acute and subacute toxicities of phenolic extract from rambutan (Nephelium lappaceum) peels by oral administration. Food Chem., 320, 126618. https://doi.org/10.1016/j.foodchem-2020-126618.

Mombekov, S., Datkhayev, U., Kalamkul, D., Kozhamzharova, A., Baidullayeva, A., Assel, M., Kantureyeva, A., Yessimsiitova, Z., Yussayeva, D., Beken, Z., Kydyrkhanova, A., Karbozova, A., & Zhuravel, I. (2024). Study of the chemical components of CO2 extracts from the fruits of Sorbus aucuparia L. *ScienceRise: Pharmaceutical Science*, 2 (48), 83–89. https://doi.org/10.15587/2519-4852.2024.303000.

Mombekov, S., Orazbekov, Y., Sadykova, N., Kozhamzharova, A., Sharipova, S., Makhatov, Z., & Pushkarskaya, N. (2024). Development of antifungal gel, composition and technology based on pomiferin metabolite isolated from fruits of Maclura aurantiaca growing in Kazakhstan. ScienceRise: Pharmaceutical Science, 1 (47), 79–85. https://doi.org/10.15587/2519-4852.2024.299230.

Prasad, R., Koch, B. et al. (2014). Antitumor activity of ethanolic extract Dendrobium fromosum in T-cell lymphoma: An in vitro and in vivo study /Biomed Res. Int., 1, 753451. https://doi.org/10.1155/-2014-753451.

Onaga, L. (2001). Cashing in nature's pharmacy: bioprospecting and protection of biodiversity could go hand in hand. *EMBO Rep*. 2, 263–265. DOI: 10.1093/embo-reports/kve077.

Oberlies, N.H., & Kroll, D.J. (2004). Camptothecin and taxol: historic achievements in natural products research. *J. Nat. Prod.* 67, 129–135. DOI: 10.1021/np030498t.

Orazbekov Yerkebulan, Mohamed A. Ibrahim, Serjan Mombekov, Radhakrishnan Srivedavyasasri, Ubaidilla Datkhayev, Bauyrzhan Makhatov, Narayan D. Chaurasiya, Babu L. Tekwani, and Samir A. Ross. (2018). Isolation and Biological Evaluation of Prenylated Flavonoids from *Maclura pomifera.* Evidence-based Complementary and Alternative Medicine. Volume Article ID 1370368. https://doi.org/10.1155/2018/1370368.

Rode, M.E., Morgan, M.A., Ruchelli, E., & Forouzan, I. (2000). Candida chorioamnionitis after serial therapeutic amniocenteses: a possible association. *J Perinatol*. 20, 335–337.

State Pharmacopoeia of the Republic of Kazakhstan (2008). Zhibek-Zholy: Almaty, Kazakhstan, 1, 592.

Sidorov, K.K. (2004). On the hormonization of domestic and international classifications of acute toxicity of chemical compounds. *Toksikol. vest.* 6, 2–5.

Tsao, R., Yang, R., & Young, J.C. (2003). Antioxidant isoflavones in Osage orange, Maclura pomifera (Raf.) Schneid. *J. Agric. Food Chem*. 51 (22), 6445–6451. DOI: http://dx.doi.org/10.1021/jf0342369.

Turgumbayeva, A., Zhanat, T., Zhakipbekov, K., Kalykova, A., Kartbayeva, E., Mombekov, S. et al. (2023). A Review on The Medicinal Plant Echinops Ritro Species: Phytochemistry and Biological Activity. *Farmacia*, 71 (3), 455–462. https://doi.org/10.31925/farmacia.2023.3.2.

WHO (2004). Issues guidelines for herbal medicines. *Bull. World Health Organ.* 82, 238. PMC2585928 (Review date: 20.10.2024).

Стаття надійшла до редакції 02.12.2024
Стаття прийнята до друку 06.02.2025

Conflict of interest

The authors declare that they have no conf lict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

Financing

The study was performed without financial support.

Data Availability

The data will be made available at a reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

Contribution of the authors:

Mombekov S.E. – data collection and analysis, article writing; critical review; final approval of the article, conclusions.

Email address for correspondence with the authors: **mombekov.s@kaznmu.kz**