UDC 615.316:533.072.61
DOI: 10.15587/2519-4852.2024.299230

DEVELOPMENT OF ANTIFUNGAL GEL, COMPOSITION AND TECHNOLOGY BASED ON POMIFERIN METABOLITE ISOLATED FROM FRUITS OF MACLURA AURANTIACA GROWING IN KAZAKHSTAN

Serzhan Mombekov, Yerkebulan Orazbekov, Nurila Sadykova, Assel Kozhamzharova, Sarzhan Sharipova, Zhaksylyk Makhatov, Nazym Pushkarskaya

The aim. *The purpose of this study is to develop the optimal composition and rational gel technology under the conventional name "Kaz-P7" based on the antifungal pomiferin.*
Materials and methods. *The object of the study is the substance pomiferin.*
Based on the physicochemical properties of the gel (poorly soluble in water) and technological properties structurant – Carbopol Ultrez 20 (swelling) chosen optimal solvent system: DMSO-PG-water (1:4:1) corresponding to the maximum solubility of drug and polymer provides swelling.
Following the requirements of GF RK I, vol. 1, 2.2.8, 2.2.10 was determined by rotational viscometric method. Rheological properties of the sample are determined using rotational viscometer "Rheolab QC" (firm "Anton Paar", Austria) with coaxial cylinders CC27/S-SN29766 determined. The rheological parameters were studied at a temperature of 20–35 °C using the MLM U15c thermostat included in the rheostat.
Results. *Gel dosage forms provide better bioavailability of the drug substance. In addition, gels are a more modern dosage form, pleasant in terms of organoleptic characteristics.*
The technology of gel manufacturing consists of two parallel processes: preparation of the drug substance solution and its introduction into the base. From the point of view of biopharmacy, which studies the biological effect of drugs depending on their physical properties, dosage form and preparation technology, the greatest release of the drug substance occurs when it is introduced into the dosage form in dissolved form.
Pomiferin administered in the dissolved state has the most therapeutic effect on the gel base. At the same time, active pharmaceutical ingredients (APIs) were dissolved in different solvents with gradual heating. The ratio of solvents DMSO-PG-water (1:4:1) at which the developed dosage form will be more structured, stable, and thixotropic gel is established.
Conclusions. *Fungal skin diseases are among the most frequently discussed problems in the literature. The relevance of this topic is determined by the high prevalence of pathogens, which account for 37–42 % of all skin diseases. It was experimentally established that for the complete neutralization of one gm of carbopol Ultraz 20 in the DMSO-PG-water solvent system (1:4:1), one gm of triethanolamine (pH 7.0) is consumed. The optimal diluent consisting of DMSO-PG- water in the ratio (1:4:1) was selected by physico-chemical analysis methods, and one gm of triethanolamine (pH 7.0) was selected as the neutralizing agent. The following composition was chosen as the optimal gel model: API-3.0, DMSO-3.0, PG-50.0, Carbopol Ultrez 20–1.0, and Triethanolamine-1.0. The optimal composition and technology of the gel codenamed "Kaz-P7" based on the substance obtained by pomiferin was developed*
Keywords: *optimal formulation, efficient technology, antifungal activity, gel, pomiferin, Kaz-P7*

How to cite:
Mombekov, S., Orazbekov, Y., Sadykova, N., Kozhanova, K., Kozhamzharova, A., 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. doi: http://doi.org/10.15587/2519-4852.2024.299230

1. Introduction

This work was conducted in the framework of quality by design project involving the production of antifungal pharmaceutical gel. The work included identifying the quality target product profiles from historical values for previous laboratory batches, which were used to construct a D-optimal experimental design. Fungal diseases have long been known; our gel has potent antifungal activity compared with drugs "Flucytosine" and "Fucis".

Bioassay-guided fractionation of ethanolic extract of Maclura aurantiaca fruits growing in Kazakhstan led to the isolation and identification of nine known compounds: Osajin (**1**), Auriculatin (**2**), 3' hydroxyeuchrenone b9 (**3**), Euchrenone b9 (4), Dihydrokaempferol 3-O-β-D-glucopyranoside (**5**), Kaempferol-3-O-β-D-glucopyranoside (**6**), pomiferin (**7**), auriculasin (**8**), and warangalone (**9**).

Fungal infections of the skin and nails make up a large part of human infectious diseases. It is a more social problem than of a medical nature and can adversely affect the patient's quality of life. Fungal resistance to medical treatment could happen from incorrect or inef-

fective treatment. More than 69,000 species of fungi are described and studied, and human pathogens have found about 400 species of fungal infections, a quarter of which are the most common. To prevent this, very unpleasant diseases will only thoroughly be personal hygiene and public prevention [1–4]. The fungal cells are distinguished by the type of action between fungicidal and fungistatic agents. According to a source producing distinguish two groups antimycotics: Antibiotics and natural substance pomiferin agents. The most promising is synthetic antimycotics, the specificity of which is caused by their direct effects on the fungal cell, structure, and metabolism. Efficacy of fruit Maclura aurantiaca isolation new compounds pomiferin antifungal, used in the treatment of superficial dermatomycosis, largely depends on the degree of lipophilicity of the compound as well as the properties of the ointment base, promoting a better release of the substance and its penetration into the deeper layers of the skin and its appendages to the site of localization of the pathogen [5–8].

Maclura aurantiaca, pomiferin derivatives are basic antifungal agents. They are characterized by high activity against dermatophytes, moulds, and yeast-like organisms; fungistatic and antimicrobial action type; fairly good penetration into the stratum corneum of the epidermis; negligible toxicity; and lack mushrooms' natural resistance to these drugs [9, 10]. For outdoor, antifungals are characterized by seasonality of demand. The warm season is the most favourable for the development of fungal infections. Pretty high temperatures and, as a consequence, the increased humidity, visits to places, and significant crowds - all factors that contribute to and further spread of skin and nail fungal infections [11–13]. During this period, an increased demand for antifungal drugs was regularly observed. Pharmaceutical institutions should be on time to respond to consumer demands to prevent the emergence, ensure the availability of a wide range within the group, and provide the necessary advice to interested buyers. The range of exterior antifungals is still dominated by imported products. Currently registered in Kazakhstan, about 20 trade names of antifungal drugs for external use. At the same time, regarding preparations, local production accounts for only 7 % of sales in value terms. In the past three years, the tendency to increase sales of Russian products is clearly provoking, however, dynamic and rather modest in terms of value growth of about 2 % [14–16]. Considering the above, we have developed a mild formulation based on the substance pomiferin with antifungal activity.

The purpose of this study is to develop the optimum composition of the antifungal gel and rational technologies under the code name "Kaz-P7".

2. Planning (method logy) of research

In Table 1, a representation of the research planning process is shown.

Table 1

Planning of the research

Step 1	Critical evaluation of literature data on the chemical composition, distribution, therapeutic properties, and antimicrobial activity of *Maclura aurantiaca,* as well as the name in different countries
Step 2	The optimal composition of the gel based on the substance pomiferin isolated from the fruits *Maclura aurantiaca* was selected
Step 3	A technological and apparatus scheme for gel production has been developed

3. Materials and methods

The results of the study were conducted between 2018 and 2022 years.

We studied the segment of antifungal drugs in Kazakhstan's modern pharmaceutical market. For the study, drugs were chosen from the following groups according to ATC classification: D01A1 "Antifungal preparations for external use", D01A2 "antifungal dermatological preparations systemic", and D01A3 "Antifungal drugs for the treatment of scalp". In total, on the market in Kazakhstan are 13 antifungal preparations with active ingredients. Eight enterprises of Kazakhstan produce antifungal medicinal preparations of five active substances: Itraconazole, ketoconazole, terbinafine, fluconazole, and clotrimazole. The Kazakhstan market of antifungal drugs depends on imports. The share of imported antifungal products reaches 88 %. Based on the physicochemical properties of the gel (poorly soluble in water) and technological properties structurant – Carbopol Ultrez 20 (swelling) chosen optimal solvent system: DMSO-PG-water (1:4:1) corresponding to the maximum solubility of drug and polymer provides swelling. The rotational viscometer method identified the factors influencing the process of structure formation Carbopol Ultrez 20: Polymer concentration, degree of neutralization, and temperature. It was found that the developed drug has thixotropic properties and a structured and stable system [17, 18]. Selection of the concentration of active pharmaceutical ingredient (API) selected by the results of studies of antifungal activity in various embodiments of the gel in vitro experiments agar diffusion method. It was found that the gels containing Pomiferin in 3.0 % and 5.0 % are promising for creating formulations with antimicrobial properties.

4. Results

The invention relates to developing antifungal gel for external use, based on the compound Pomiferin. The object of the present invention is to expand the range of antifungal agents obtained from natural sources.

The following studies were carried out for optimal composition and rational gel technology (Fig. 1).

When developing gels with an antifungal effect, it is necessary to consider that they should have the appropriate melting point. The gels are liquified at high temperatures and can flow out of the containers, not sticking when applied to the surface. To achieve this aim, a study was carried out to find out the influence of temperature on the process of gel formation. To determine the temperature of the gels, based on RAP, the amount of 25.0 g

was placed in a measuring container of a rotational viscometer "Rheotest-2" and thermostat for 20 min. At each test, the temperature ranges from 20 °C to 90 °C in steps of 10 °C. After that, the gels' viscosity and the plots of viscosity versus temperature were measured. It has been experimentally established that 1 g of triethanolamine (pH 7.0) is consumed to completely neutralize 1 g Carbopol Ultrez 20 in a DMSO-PG-water (1:4:1) solvent system. For organic amines, a sharp increase in the values of the effective viscosity of the system is characteristic of an increase in the system's pH to 5. In the range of pH values from 5 to 11, the effective viscosity of the bases remains practically unchanged, which can be explained by the complexation of the polyacid with the amines to be studied. Physicalchemical methods of analysis selected the optimal diluent, consisting of PEG, DMSO, and water in the ratio (1:4:1), and 1 g of triethanolamine (pH 7.0) was chosen as the neutralizing agent.

Based on the rheological studies of the gel under the conventional name "Kaz-P7" and their analysis, it was found that samples No. 3 and No. 5, with an active substance content of 3 % and 5 %, have a positive effect on the structural and mechanical properties of the soft dosage form. They have optimal structural and mechanical characteristics and are a thixotropic system, sufficiently stable and plastic, capable of spreading onto the skin and providing the necessary stability of the system in the process of technological operations. Samples with 3 % and 5 % pomiferin content are promising for further work.

The choice of API concentration was made based on the results of the study of the antifungal activity of various gel variants in vitro experiments by diffusion into agar (well method). Based on the antifungal activity results, physicochemical properties (solubility) of API, and technological properties of carbopol Ultrez 20, we selected the composition of the gel "Kaz-P7" (Table 2).

Table 2

Selection of models of gel under the conventional name "Kaz-P7"

Gel composition	Gel model (No)							
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8
API (Pomiferin)	1.0	1.5	2.0	2.5	3.0	3.5	4.0	5.0
DMSO	2.0	2.25	2.50	2.75	3.0	3.25	3.75	4.0
PG	45.5	45.75	50.0	50.25	50.50	50.75	60.00	60.25
Carbopol Ultrez 20	0.125	0.25	0.50	0.75	1.0	1.125	1.225	1.5
Triethanolamine	0.125	0.25	0.50	0.75	1.0	1.125	1.225	1.5
Purified water	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0	Up to 100.0
Visual assessment of the formulations								
Appearance	1	2	3	4	5	6	7	8
	Homogeneous yellow-coloured gel	Homogeneous yellow-coloured gel	Homogeneous yellow-coloured gel	Homogeneous yellow-coloured gel	Homogeneous yellow-coloured gel	Homogeneous yellow-coloured gel	Homogeneous yellow-coloured gel	Homogeneous yellow-coloured gel
Stability assessment of formulations								
Stability after 24 h	1	2	3	4	5	6	7	8
	Turbidity, stratification. Not stable	Seal. Not stable	Stratified. Not stable	Stratified. Not stable	Stable, approved	Liquefaction. Not stable	Liquefaction. Not stable	Stable, approved

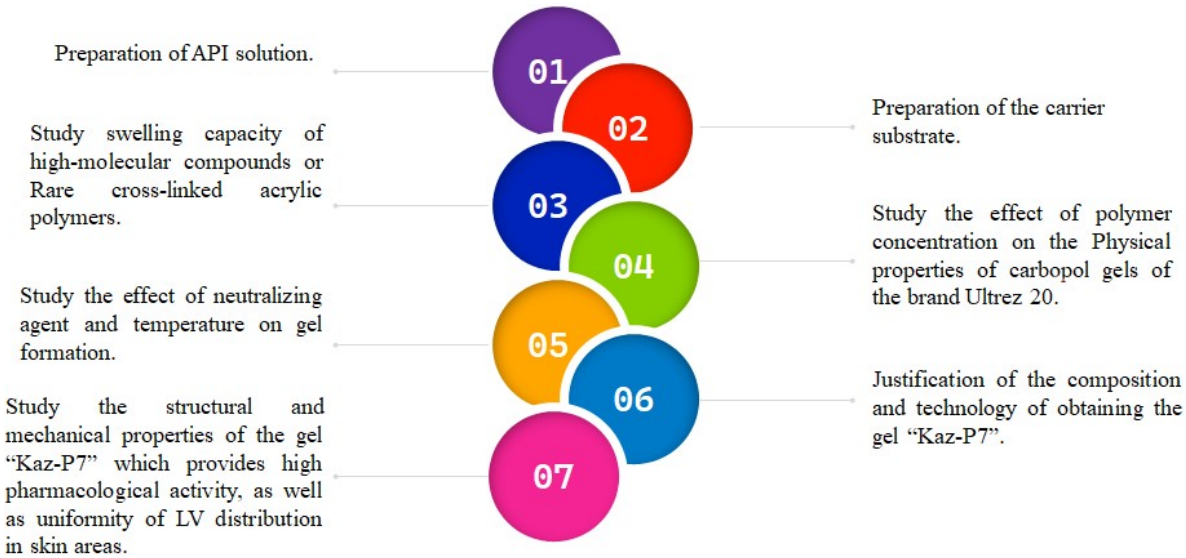

Fig. 1. Research carried out to determine the optimal composition and rational technology

The gel composition was based on antifungal activity, physical-chemical properties (solubility) of API, and technological properties of Carbopol Ultrez 20. (Table 3).

Table 3

The gel "Kaz-P7" based on substances derived pomiferin

Active substance	
The API	3.0 %
Excipients	
DMSO	3.0 %
PG	50.50 %
Carbopol Ultrez 20	1.0 %
Triethanolamine	1.0 %
Purified water	41.50 %

Note: API – pomiferin; DMSO – dimethylsulfoxide; PG – propylene glycol

The content of DMSO and PG is set in the research of the solubility of APIs and supported by experimental studies on the swelling and the rheological properties of the gel Carbopol Ultrez 20. The mixture of solvents DMSO-PG-water (1:4:1) in the selected ratio, which, on the one hand, provides the complete dissolution of the API and, on the other hand, compensates for the fall of Padania viscosity characteristics of the system. The selected amount of water is sufficient for a selected amount of swelling Carbopol Ultrez 20. Included in the composition of triethanolamine is a neutralizing agent that plays a role and enables gel bases to have constant rheological performance in a wide pH range. Based on the studies, the defined technology for the production of the gel composition is as follows: by weighing the required amounts of API, DMSO, PG, Carbopol Ultrez 20, triethanolamine, and purified water. API is dissolved in a mixture of DMSO and PG with constant stirring. Carbopol Ultrez 20 was dispersed in water. After swelling, Carbopol Ultrez 20 is introduced into a dispersion of triethanolamine and stirred to obtain a homogeneous gel.

Technological scheme of gel production.

Based on the conducted research, the optimal technology of gel production was developed, consisting of the following stages: Sanitisation of the room and equipment, process clothing, preparation of purified water, and preparation of pharmaceutical substance.

According to the requirements of Good Manufacturing Practice (GMP), the production process begins with sanitisation of the room, equipment, and processed clothing to prevent microbial contamination of production.

The finished product was a gel of light yellow colour, packed into tubes and placed in a labelled cardboard pack.

The technological scheme of obtaining gel on the basis of Pomiferin is presented in Fig. 2.

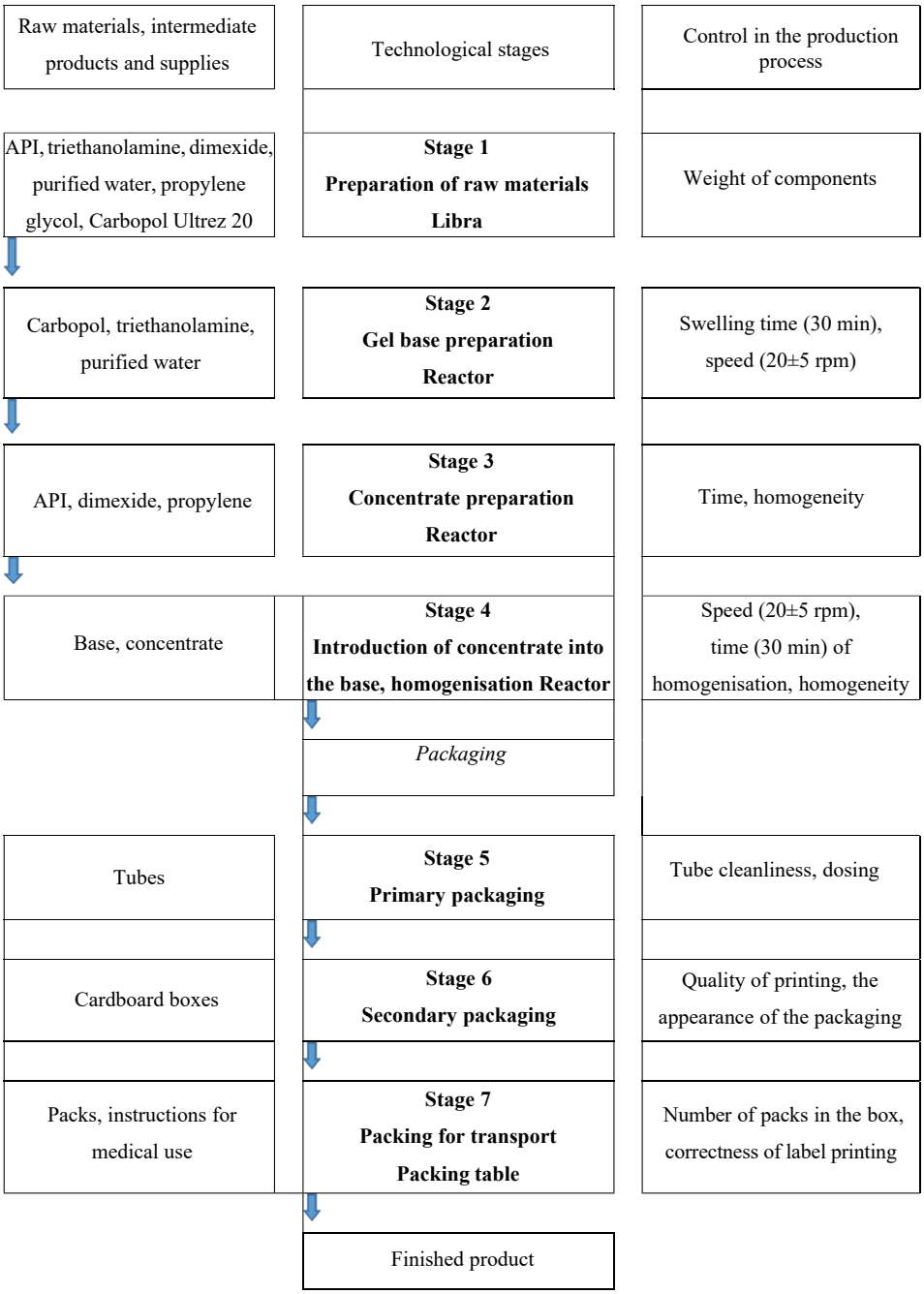

Fig. 2. Block diagram of the manufacturing process of gel «Kaz-P7» 3 %

5. Discussion

Most of the medicines used in official medicine were previously used in folk medicine herbal medicines. It should be noted that one of them, which has found application in folk medicine for the treatment of malignant tumours, nosology of skin diseases and joint diseases with its antimicrobial effect, and also not previously investigated in our country, is the substance of the plant type, the genus – Maclura aurantiaca.

Maclura aurantiaca – medicinal raw materials of plant origin, in folk medicine, was used to treat malignant tumours, joint and skin diseases, tumours of the intestinal tract and pancreas, fibroids, and prostate.

According to the study's authors, extracts of fruits of the orange Maclura are an effective tool for treating experimental tumours in animals.

The chemical composition of the orange Maclur, according to the literature, is described by the plant growing in the territories of the United States of America and Ukraine, Turkmenistan, and Uzbekistan. However, it can not be said that this information coincides with data on this plant growing on the territories of Kazakhstan. The reason for this was the composition of various biological substances in the research material, which varies depending not only on the species of the plant itself but also on the geographical condition of growth and soil.

It has become known that some compounds of flavone have activity in the treatment of a malignant tumour. As a result of interest in the study of individual compounds of the isoflavone group, the activity of isoflavone has been proven to be effective in the treatment of the aetiology of a malignant tumour, which accounts for a large percentage of the fruits of the Maclura aurantiaca.

Thus, the production of medicines based on Maclura aurantiaca for the treatment of malignant tumours and joint and skin diseases using modern technological methods is the main solution for reducing dependence on the import of the pharmaceutical market of the Republic of Kazakhstan.

At the present stage of development, the Kazakh pharmaceutical market is a highly profitable and rapidly developing sector of the country's national economy, which is extremely dependent on imported products, such as medicines from specific substances or mixtures of substances, human blood and medicines consisting of antibiotics. But at the same time, the Kazakh pharmaceutical industry has all the prerequisites, especially a large plant material reserve of medicinal plants, for the production of domestic medicines. At the same time, to support the domestic pharmaceutical industry, the state annually increases the volume of domestic products in public procurement within the guaranteed volume of free medical care, investments in the fixed capital of pharmaceutical production, and also enters into long-term contracts with domestic producers and contract production customers for 10 years.

The pharmaceutical industry is more dominant, and the threat characterises the lack of capacities for the production of medicines to expand the range of medicines due to domestic production. In Iran's pharmaceutical industry, one of the main weaknesses is the lack of international standards in the production of drugs [19]. The weaknesses of India's pharmaceutical industry are the weak comprehensive infrastructure in several districts and the presence of more unorganised players in the field of food and nutraceuticals, which compromises quality, leads to an increasingly competitive environment, and creates fierce price competition [20]. The main problems of the countries of the Eurasian Economic Union are still considered to be low export potential and dependence on imports of raw materials and packaging materials [21].

Particularly, omega fat acid groups, which the body can only acquire externally, are crucial for the functioning of the cardiovascular system [22].

Research in the field of determining such activities as anti-inflammatory, analgesic, antipyretic, wound healing and anti-cancer has not been carried out at this moment. This situation opens up new opportunities for the study of this plant species in so many different directions [23].

Practical Relevance. From the fruit of Maclura orange, the extracted substance Pomiferin. Developed a pharmaceutical investigation of the gel on the basis of the substance Pomiferin. Technological regulations, design and analytical regulatory documents, production and experimental samples of the gel and the substance of Pomiferin have been developed. A technical and economic rationale has been developed for the gel, made on the basis of the substance Pomiferine.

New pure compounds with high activity were extracted from Maclura Orange, and the structure was identified.

The activity of pomiferin, other individual compounds and biological extracts was determined, on the basis of which the composition of the phytopreparation was developed;

The scientific novelty of the study is confirmed by the patent of the Ministry of justice of the Republic of Kazakhstan No. 3001, 09.07.2018 issued to the utility model «Gel antifungal action on the basis of a pomiferin received from fruits of Maclura aurantiaca»

Research limitations. The solubility of the main active substance in DMSO solvent was limited by the possibility of altering its nature. We experimentally determined the optimal ratios for dissolution. Additionally, substantial changes in technological parameters during drug development typically demand more resources in terms of personnel, materials, and time.

Prospects for further research. Thus, the production of medicines based on the Maclura aurantiaca for the treatment of malignant tumors, joint and skin diseases using modern technological methods is the main solution for reducing dependence on the import of the pharmaceutical market of the Republic of Kazakhstan.

Our next study is the introduction of a medicinal product into the state register of the Republic of Kazakhstan.

6. Conclusions

In view of the study of microbiological studies (antifungal activity), physical-chemical properties (solubility) API, and technological properties Carbopol Ultrez 20 designed optimal composition and gel technology, code-named "Kaz-P7" based on substances derived Pomiferin.

Fungal skin diseases are one of the most frequently discussed problems in various dermatological forums and scientific journals. The relevance of this topic is determined by the high prevalence of this pathology, which, according to the literature, accounts for 37–42 % of all skin diseases. In view of the study of microbiological studies (antifungal activity), physical-chemical properties (solubility) API, and technological properties Carbopol Ultrez 20 designed optimal composition and gel technology, code-named "Kaz-P7" based on substances derived pomiferin.

A critical parameter for the evaluation of soft dosage forms is stability during storage. The final choice of formulation will be established on the basis of the results of the study of the stability of the obtained samples during storage.

Conflicts of snterest

The authors declare that they have no conflict 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.

Funding

The research was supported by an internal university scholarship of the Asfendiyarov Kazakh National Medical University, «Standardization of medicinal plant raw materials (*Sorbus aucuparia* L.). and the development of an optimal technology for obtaining the extract.», approved by the Rector's Order No. 312 dated 06/18/2021 «On the allocation of an internal university scholarship for scientific research in the field of medicine and healthcare», and was funded by the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan (Grant No.AP15473446). The cost of publication will be covered as part of this project.

Data Availability

The data will be made available on reasonable request.

Use of artificial intelligence

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

Acknowledgment

The authors would like to thank the faculty, as well as the PhD doctoral students of the Faculty of Pharmacy and Pharmaceutical Technology, for their support in this work. Also thanks to NCNPR for support.

References

1. Orazbekov, Y., Ibrahim, M. A., Mombekov, S., Srivedavyasasri, R., Datkhayev, U., Makhatov, B., Chaurasiya, N. D., Tekwani, B. L., Ross, S. A. (2018). Isolation and Biological Evaluation of Prenylated Flavonoids from Maclura pomifera. Evidence-Based Complementary and Alternative Medicine, 2018, 1–8. https://doi.org/10.1155/2018/1370368

2. Eatedal, H., El-All, A., Osman, N. A., El-Mahmoudy, A. M., Hassan, A. N. (2016). Synthesis of new pyrimidine derivatives and evaluation of their anticancer and antimicrobial activities. Asian Journal of Pharmaceutical and Clinical Research, 9 (2), 306–313.

3. Aljelawi, R. O., Kadhem, M. F. (2016). Production, purification, and characterization of bioactive metabolites produced from rare actinobacteria pseudonocardia alni. Asian Journal of Pharmaceutical and Clinical Research, 9 (9), 264–272. https://doi.org/10.22159/ajpcr.2016.v9s3.14961

4. Karges, J., Xiong, K., Blacque, O., Chao, H., Gasser, G. (2021). Highly cytotoxic copper(II) terpyridine complexes as anticancer drug candidates. Inorganica Chimica Acta, 516, 120137. https://doi.org/10.1016/j.ica.2020.120137

5. Rodrigues, J. A. O., Oliveira Neto, J. G. de, da Silva de Barros, A. O., Ayala, A. P., Santos-Oliveira, R., de Menezes, A. S., de Sousa, F. F. (2020). Copper(II):phenanthroline complexes with l-asparagine and l-methionine: Synthesis, crystal structure and in-vitro cytotoxic effects on prostate, breast and melanoma cancer cells. Polyhedron, 191, 114807. https://doi.org/10.1016/j.poly.2020.114807

6. Hošek, J., Šmejkal, K.; Parnham, M. J. (Ed.). Flavonoids as Anti-inflammatory Agents. ICompendium of Inflammatory Diseases. Basel: Springer, 482–497. https://doi.org/10.1007/978-3-7643-8550-7_19

7. Bozkurt, İ., Dilek, E., Erol, H. S., Çakir, A., Hamzaoğlu, E., Koç, M., Keleş, O. N., Halici, M. B. (2017). Investigation on the effects of pomiferin from Maclura pomifera on indomethacin-induced gastric ulcer: An experimental study in rats. Medicinal Chemistry Research, 26 (9), 2048–2056. https://doi.org/10.1007/s00044-017-1913-y

8. Ribaudo, G., Coghi, P., Zanforlin, E., Law, B. Y. K., Wu, Y. Y. J., Han, Y., (2019). Semi-synthetic isoflavones as BACE-1 inhibitors against Alzheimer's disease. Bioorganic Chemistry, 87, 474–483. https://doi.org/10.1016/j.bioorg.2019.03.034

9. Trávní˘cek, Z., Van˘co, J., Dvo˘rák, Z. (2020). Heteroleptic complexes of copper with osajin or pomiferin and their utilization for the preparation of drugs for the treatment of tumour diseases. WO2021018324A1.

10. Leláková, V., Šmejkal, K., Jakubczyk, K., Veselý, O., Landa, P., Václavík, J. et al. (2019). Parallel in vitro and in silico investigations into anti-inflammatory effects of non-prenylated stilbenoids. Food Chemistry, 285, 431–440. https://doi.org/10.1016/j.foodchem.2019.01.128

11. Jomová, K., Hudecova, L., Lauro, P., Simunkova, M., Alwasel, S. H., Alhazza, I. M., Valko, M. (2019). A Switch between Antioxidant and Prooxidant Properties of the Phenolic Compounds Myricetin, Morin, 3′,4′-Dihydroxyflavone, Taxifolin and 4-Hydroxy-Coumarin in the Presence of Copper(II) Ions: A Spectroscopic, Absorption Titration and DNA Damage Study. Molecules, 24 (23), 4335. https://doi.org/10.3390/molecules24234335

12. Brezáni, V., Leláková, V., Hassan, S., Berchová-Bímová, K., Nový, P., Klouček, P. et al. (2018). Anti-Infectivity against Herpes Simplex Virus and Selected Microbes and Anti-Inflammatory Activities of Compounds Isolated from Eucalyptus globulus Labill. Viruses, 10 (7), 360. https://doi.org/10.3390/v10070360

13. Bertucci, J. I., Liggieri, C. S., Colombo, M. L., Vairo Cavalli, S. E., Bruno, M. A. (2015). Application of peptidases from Maclura pomifera fruit for the production of active biopeptides from whey protein. LWT - Food Science and Technology, 64 (1), 157–163. https://doi.org/10.1016/j.lwt.2015.05.041

14. Corrons, M. A., Liggieri, C. S., Trejo, S. A., Bruno, M. A. (2017). ACE-inhibitory peptides from bovine caseins released with peptidases from Maclura pomifera latex. Food Research International, 93, 8–15. https://doi.org/10.1016/j.foodres.2017.01.003

15. Reyes Jara, A. M., Liggieri, C. S., Bruno, M. A. (2018). Preparation of soy protein hydrolysates with antioxidant activity by using peptidases from latex of Maclura pomifera fruits. Food Chemistry, 264, 326–333. https://doi.org/10.1016/j.foodchem.2018.05.013

16. Petrovic, S., Todorovic, B., Stojiljković, M., Petrovic, S., Savic, S., & Stojiljkovic, S. (2018). Macro- and micro-element composition of Osage orange Maclura pomifera L. (Moraceae). Journal of Elementology, 23 (4), 1399–1411. https://doi.org/10.5601/jelem.2018.23.1.1484

17. Prakash, S., Somiya, G., Elavarasan, N., Subashini, K., Kanaga, S., Dhandapani, R., Sivanandam, M., Kumaradhas, P., Thirunavukkarasu, C., Sujatha, V. (2021). Synthesis and characterization of novel bioactive azo compounds fused with benzothiazole and their versatile biological applications. Journal of Molecular Structure, 1224, 129016. https://doi.org/10.1016/j.molstruc.2020.129016

18. Nepovimova, E., Svobodova, L., Dolezal, R., Hepnarova, V., Junova, L., Jun, D. et al. (2021). Tacrine – Benzothiazoles: Novel class of potential multitarget anti-Alzheimeŕs drugs dealing with cholinergic, amyloid and mitochondrial systems. Bioorganic Chemistry, 107, 104596. https://doi.org/10.1016/j.bioorg.2020.104596

19. Mamedyarov, Z. (2018). Pharmaceutical sector in iran: current status and prospecs. World Economy and International Relations, 62 (7), 57–62. https://doi.org/10.20542/0131-2227-2018-62-7-57-62

20. Tare, S., Bageria, S. (2019). SWOT analysis of indian pharmaceutical industry: in referance to indian sme pharma industry approchestowards competitive advantage. International Journal of Innovation in Engineering Research & Management, 6 (1).

21. Tashenov, A., Cherednichenko, N. (2023). Development Prospects for the Pharmaceutical Market of the Single Economic Space. Eurasian Development Bank. Sector Report No.18. Available at: https://ssrn.com/abstract=4109101

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

23. 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

Received date 02.11.2023
Accepted date 22.02.2024
Published date 29.02.2024

Serzhan Mombekov*, PhD, Associate Professor, School of Pharmacy, S. D. Asfendiyarov Kazakh National Medical University, Tolebi str., 94, Almaty, Kazakhstan, 050000

Yerkebulan Orazbekov, PhD, Faculty of Pharmacy, South Kazakhstan Medical Academy, Al-Farabi sq., 1, Shymkent, Kazakhstan, 160019

Nurila Sadykova, Doctor Residency, School of General Medicine, S. D. Asfendiyarov Kazakh National Medical University, Tolebi str., 94, Almaty, Kazakhstan, 050000

Assel Kozhamzharova, Associate Professor, School of Pharmacy, S. D. Asfendiyarov Kazakh National Medical University, Tolebi str., 94, Almaty, Kazakhstan, 050000

Sarzhan Sharipova, Associate Professor, School of Pharmacy, S. D. Asfendiyarov Kazakh National Medical University, Tolebi str., 94, Almaty, Kazakhstan, 050000

Zhaksylyk Makhatov, Faculty of Pharmacy, South Kazakhstan Medical Academy, Al-Farabi sq., 1, Shymkent, Kazakhstan, 160019

Nazym Pushkarskaya, Master, School of Pharmacy, S. D. Asfendiyarov Kazakh National Medical University, Tolebi str., 94, Almaty, Kazakhstan, 050000

***Corresponding author:** *Serzhan Mombekov, e-mail:* mombekov.s@kaznmu.kz