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STANDARDIZATION OF "FLUCAM" OINTMENT

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Abstract: In recent years, the interest of specialists in the problem of immunocorrective therapy has increased significantly, primarily due to the significant increase in immunodeficiency conditions and the understanding that the development of most pathological processes is caused by a disruption in the functions of the immune system. Immunotropic drugs of plant origin have a gentle effect on the body, restore immunity, mobilize the reserve defense mechanism, and increase the effectiveness of therapy due to the content of various biologically active substances. The inclusion of plant immunomodulators that affect both humoral and cellular immune responses, as well as factors of non-specific resistance of the body, in the treatment of various immunodeficiency conditions makes it possible to increase the effectiveness of the therapy. Taking into account the above circumstances, the authors obtained a dry extract from a multi-component plant composition, which served as the basis for creating an ointment with immunomodulatory action "Flucam". The latter, being practically non-toxic and having no side effects on the body, exhibits a pronounced immunomodulatory effect, surpassing in its activity known foreign analogues. In order to promote the said ointment in medical practice, studies have been conducted on its standardization. The characteristics of authenticity and quality indicators of the ointment have been determined, and methodological techniques for the qualitative and quantitative determination of the main active substances - glycyrrhizic acid and tannins - have been developed. At the same time, an important place is given to the so-called "end-to-end standardization", which is based on the assessment of the quality of the original plant composition, dry extract and the ointment obtained from it by the content of the same biologically active compounds. This, to a certain extent, allows for a sufficient guarantee of the quality and constant composition of the finished product.

Keywords: "Flucam" ointment, herbal composition, dry extract, standardization, authenticity, microbiological purity, glycyrrhizic acid, tannins.

СТАНДАРТИЗАЦИЯ МАЗИ «ФЛЮКАМ»

Аннотация: В последние годы интерес специалистов к проблеме иммунокорригирующей терапии значительно возрос, что связано, прежде всего, с существенным увеличением числа иммунодефицитных состояний и пониманием того, что развитие большинства патологических процессов обусловлено нарушением функций иммунной системы. Иммунотропные препараты растительного происхождения оказывают мягкое действие на организм, восстанавливают иммунитет, мобилизуют резервные защитные механизмы и повышают эффективность терапии за счет содержания различных биологически активных веществ. Включение растительных иммуномодуляторов, влияющих как на гуморальные, так и на клеточные иммунные реакции, а также на факторы неспецифической резистентности организма, в лечение различных иммунодефицитных состояний позволяет повысить результативность терапии. С учетом вышеизложенных

обстоятельств авторами был получен сухой экстракт из многокомпонентной растительной композиции, который послужил основой для создания мази с иммуномодулирующим действием «Флюкам». Последняя, будучи практически нетоксичной и не оказывая побочных эффектов на организм, проявляет выраженное иммуномодулирующее действие, превосходя по своей активности известные зарубежные аналоги. С целью внедрения указанной мази в медицинскую практику проведены исследования по её стандартизации. Определены показатели подлинности и качества мази, разработаны методические приёмы для качественного и количественного определения основных действующих веществ — глицирризиновой кислоты и дубильных веществ. При этом важное место занимает так называемая «сквозная стандартизация», которая основана на оценке качества исходной растительной композиции, сухого экстракта и полученной из него мази по содержанию одних и тех же биологически активных соединений. Это в определённой мере обеспечивает достаточную гарантию качества и постоянства состава готового продукта.

Ключевые слова: мазь «Флюкам», растительная композиция, сухой экстракт, стандартизация, подлинность, микробиологическая чистота, глицирризиновая кислота, дубильные вещества.

“FLUCAM” MALHAMINI STANDARTLASHTIRISH

Annotatsiya: So‘nggi yillarda immunokorrektiv terapiya muammosiga mutaxassislarning qiziqishi sezilarli darajada ortdi. Buning asosiy sabablari immunodefitsit holatlarining keskin ko‘payishi hamda ko‘pgina patologik jarayonlarning rivojlanishi immun tizimi funksiyalarining buzilishi bilan chambarchas bog‘liq ekanligining anglanishidir. O‘simlik kelib chiqishli immunotrop preparatlar organizmga yumshoq ta’sir ko‘rsatib, immunitetni tiklaydi, zaxira himoya mexanizmlarini safarbar etadi va tarkibidagi turli biologik faol moddalar hisobiga terapiya samaradorligini oshiradi. Turli immunodefitsit holatlarini davolashda gumoral va hujayraviy immun javoblarni, shuningdek, organizmning nospesifik rezistentlik omillarini faollashtiruvchi o‘simlik immunomodulyatorlaridan foydalanish davolash samaradorligini sezilarli darajada oshirish imkonini beradi. Shu omillarni hisobga olgan holda, mualliflar ko‘p komponentli o‘simlik kompozitsiyasidan quruq ekstrakt tayyorlab, uning asosida immunomodulyator xususiyatga ega “Flucam” malhamini yaratdilar. Ushbu malham deyarli toksik bo‘lmaganligi va organizmga nojo‘ya ta’sir ko‘rsatmasligi bilan ajralib turadi hamda o‘zining yaqqol ifodalangan immunomodulyator ta’siri bo‘yicha mavjud xorijiy analoglardan ustunlik qiladi. Mazkur malhamni tibbiy amaliyotga joriy etish maqsadida uning standartlashtirish bo‘yicha tadqiqotlar olib borildi. Malhamning haqiqiyligi va sifat ko‘rsatkichlari aniqlanib, asosiy faol moddalar — glitsirrizin kislotasi va tanninlarni sifat va miqdoriy aniqlashning metodik yondashuvlari ishlab chiqildi. Shu bilan birga, muhim o‘rin “skvoznoy standartlashtirish” tamoyiliga berildi, ya’ni boshlang‘ich o‘simlik kompozitsiyasi, quruq ekstrakt va undan tayyorlangan malham sifatini bir xil biologik faol birikmalar miqdori asosida baholashdan iboratdir. Bu esa, o‘z navbatida, yakuniy mahsulotning sifatini va tarkibining barqarorligini yetarli darajada kafolatlash imkonini beradi.

Kalit so‘zlar: “Flucam” malhami, o‘simlik kompozitsiyasi, quruq ekstrakt, standartlashtirish, haqiqiylik, mikrobiologik tozaligi, glitsirrizin kislotasi, tanninlar.

INTRODUCTION

According to the World Health Organization, in recent years, due to ever-increasing environmental and social pressure, a significant decrease in the body's resistance has been

observed, leading to a weakening of the immune defense. Against the background of a decrease in the functional activity of the immune system, the severity of the treatment of many infectious diseases is noted, their prognosis worsens, and multiple resistance to antimicrobial drugs is formed. Under these conditions, the patient needs to use all the adaptive mechanisms necessary to combat diseases [1], primarily immune correction aimed at strengthening weakened immune defenses, correcting the imbalance of immune responses, weakening pathologically active immune processes and suppressing autoaggressive immune responses [2].

Medical indications for activating immunity include opportunistic infections (herpes viruses, Candida fungi and other opportunistic pathogens), contagious infections (viruses, bacteria, protozoa, fungi), chronic infectious and inflammatory processes, as well as chronic ulcers and non-healing wounds [2]. It should be noted that both opportunistic and contagious infections are more severe against the background of weakened immunity, as well as chronic diseases. In principle, assistance to the immune system is necessary in the severe course of any infectious diseases. This largely determines the increased interest of specialists in the problem of immunocorrective therapy [3-6].

Despite the significant expansion of the arsenal of drugs used to correct immunity, clinical medicine needs new, effective and safe immunomodulators, including those of plant origin.

Medicinal plants, due to their biological affinity for body tissues, low toxicity and availability, are valuable raw materials for obtaining immunotropic drugs [7, 8].

Immunotropic drugs of plant origin have a gentle effect on the body, restore immunity, mobilize reserve defense mechanisms, and increase the effectiveness of therapy due to the presence of various biologically active substances [9, 10].

It is necessary to take into account that medicinal plants used in the complex treatment of immune system disorders contain various biologically active substances, affect various systems and by various mechanisms. Therefore, to ensure a more complete and rapid therapeutic effect, it is advisable to use several plant components simultaneously. This problem is successfully solved with the help of multicomponent plant compositions [11].

It is believed that from the variety of biologically active substances of plants included in such compositions, the body can, through self-regulation, select the components that are missing for it and include them in metabolic processes. The therapeutic effectiveness of the mixtures is due to the manifestation of general patterns of synergism of active and accompanying substances, the summation and potentiation of their pharmacological effects, allowing several problems to be solved simultaneously with minimal risk of toxic and allergic complications [12].

Taking into account the above circumstances, we have developed a new multi-component composition (collection) based on local medicinal plants for the correction of immunodeficiency states. It includes the herb of St. John's wort, lemon balm, chamomile flowers, stinging nettle leaves, walnut, sage, oak bark, licorice roots, felt burdock and dandelion.

The selection of the specified components and their ratios was carried out based on literature data on the pharmacological properties, chemical composition and experience of using plant raw materials in folk and scientific medicine, taking into account the results of pharmacological screening and the availability of a sufficient raw material base for all components to organize its industrial production.

When compiling the composition, it was also kept in mind that, along with providing the main therapeutic effect, the composition should have a complex effect on the body as a whole, normalizing the functioning of many systems.

It is also attractive because it includes medicinal plants, provided with a sufficient raw material base in our country. Preclinical pharmacological studies have shown that the “Flucam” collection, being practically non-toxic and having no side effects on the body, has a pronounced immunomodulatory activity.

In the future, taking into account the trend of converting medicinal plant raw materials into water-soluble dry extracts, characterized by precise dosing, ease of use, stability during storage, high content and complex action of biologically active substances, a dry extract of the same name was obtained on the basis of the developed multi-component plant composition “Flucam”.

Preclinical pharmacological studies have shown that the dry extract “Flucam”, being practically non-toxic and having no side effects on the body, exhibits a pronounced immunomodulatory effect. In particular, on the model of prednisolone immunosuppression it was found that in its immunomodulatory activity it is not inferior to foreign analogues - the drugs “Immunal” (“Lekd.d.” Slovenia) and “Viusid” (Catalysis S.L., Spain), and in some cases even surpasses them. At the same time, it was shown that the test drug improves weakened areas of the immune system without affecting its healthy areas, which allows the drug to be used for a long time without a negative effect on the entire immune system as a whole [13-17].

Since immunotropic drugs are indicated, among other things, as indicated above, for activating immunity in opportunistic (herpes viruses, Candida fungi) and contagious (viruses, bacteria, protozoa, fungi) infections, as well as chronic infectious and inflammatory processes, chronic ulcers and non-healing wounds, we used the dry extract “Flucam” to develop a soft dosage form on its basis – “Flucam” ointment. As is known, an essential condition for the promotion of new herbal medicines in medical practice is their standardization, unification of indicators, norms and methods of quality assessment [18-23].

The aim of our study was to develop methods for standardizing a new ointment with immunomodulatory action based on a dry extract of the multicomponent herbal composition “Flucam”.

MATERIALS AND METHODS OF THE RESEARCH.

The object of the study was experimental samples of the ointment “Flucam” based on a dry extract of a multicomponent herbal collection.

Standardization of the ointment was carried out in accordance with the guidelines of the European Pharmacopoeia (PhEur), the State Pharmacopoeia of the Republic of Uzbekistan and the International Conference on Harmonization of Technical Requirements for Registration of Medicinal Products (ICH) [24-26] for the following indicators: description; authenticity; weight of package contents; acidity; particle size; homogeneity; foreign impurities; microbiological purity; quantitative determination; storage stability and shelf life.

Taking into account that the plant composition, which served as the basis for obtaining the dry extract "Flucam", as well as the extract itself, were previously standardized for tannins and glycyrrhizic acid, these biologically active compounds were used by us as the main quality criteria for the ointment “Flucam” during its chemical standardization, i.e. the principle of "end-to-end" standardization was in demand, ensuring the unification of standards and methods for assessing quality in the series raw materials - dry extract (substance) - finished medicinal product (ointment) [27-29].

To determine the authenticity of “Flucam” ointment, the following qualitative reactions are offered.

1. Determination of tannins

3.0 g of ointment are placed in a 100 ml beaker, 20 ml of water are added, heated in a water bath until completely dissolved and filtered. 3 drops of iron chloride (III) solution are added to 2 ml of the filtrate.

2. Determination of glycyrrhizic acid

The retention time of the peak of the substance under study should correspond to the retention time of the peak of the standard of the corresponding name (see the section "Quantitative determination").

Mass of package contents. Four tubes together with their contents are weighed (each separately). Each tube is emptied of its contents by rinsing it with hot water P, the remaining moisture is carefully removed with filter paper and weighed again. The mass of the package contents is calculated based on the difference in the obtained masses (tubes with and without contents).

About 10.00 g of the test ointment (m-g) is dissolved in 50 ml of a mixture of equal volumes of ethyl alcohol (96%) and petroleum ether, previously neutralized with a 0.1 M potassium hydroxide solution or 0.1 M sodium hydroxide solution, using 0.5 ml of phenolphthalein solution as an indicator. If necessary, heat at a temperature of about 90 °C until the test ointment is completely dissolved. Then the dissolved test ointment is titrated with a 0.1 M potassium hydroxide solution or 0.1 M sodium hydroxide solution until a pink color appears that does not disappear within 15 seconds (n-ml titrant). In the case where heating was used to improve dissolution, the temperature is maintained at about 90 °C during the titration.

Particle size 0.01 g of ointment was placed on a glass slide, covered with a cover slip, fixed by gentle pressure and viewed using a microscope.

Homogeneity 0.01 g of ointment was placed on a glass slide, covered with a cover slip, fixed by gentle pressure and viewed in transmitted light.

Microbiological purity The study of “Flucam” ointment for microbiological purity was carried out under aseptic conditions in accordance with the instructions of the article of the State Pharmacopoeia of the Republic of Uzbekistan “Methods of microbiological control of drugs” [25].

The quantitative content of tannins in “Flucam” ointment was determined using the official method of permanganometric titration.

2 g (accurately weighed) of the ointment are weighed, placed in a 500 ml conical flask, poured in 250 ml of purified water heated to boiling and boiled with a reflux condenser on an electric hotplate with a closed spiral for 30 minutes with occasional stirring. The liquid is cooled to room temperature and filtered about 100 ml into a 200-250 ml conical flask. Then 25 ml of the obtained extract are pipetted into another 750 ml conical flask, added 500 ml of purified water, 25 ml of indigosulfonic acid solution and titrate with constant stirring with a potassium permanganate solution (0.02 mol/l) until a golden yellow color. A control experiment in parallel is conducted.

1 ml of potassium permanganate solution (0.02 mol/l) corresponds to 0.004157 g of tannins in terms of tannin.

The content of tannins in the ointment (X) in percentage is calculated using the formula:

$$x = \frac{(V - V_1) \cdot 0{,}004157 \cdot 250 \cdot 100}{m \cdot 25},$$

where: V is the volume of potassium permanganate solution (0.02 mol/l) used for titration of the extract, in milliliters;

V_1 - the volume of potassium permanganate solution (0.02 mol/l) used for titration in the control experiment, in milliliters;

0.004157 is the amount of tannins corresponding to 1 ml of potassium permanganate solution (0.02 mol/l) (in terms of tannin), in grams;

m - ointment mass in grams; 250 - total volume of extract in milliliters; 25 - volume of extract taken for titration, in milliliters.

The quantitative content of glycyrrhizic acid was determined by high-performance liquid chromatography (HPLC) [25] on an "LC – 20 prominence" chromatograph ("Shimadzu Corporation, USA") according to the method [30, 31].

Chromatography conditions:

– column: 3.0x150 mm, 4.6 mm, ZORBAXSBC18 or similar;

– mobile phase: 3.85 g ammonium acetate is dissolved in 720 ml water, 5 ml concentrated acetic acid and 280 ml acetonitrile are added;

– flow rate: 1.0 ml/min;

– detection: spectrophotometer at 254 nm;

– injection: 20 µl.

– solvent: 50% ethanol

Preparation of the test solution. 10 g (accurately weighed) of the ointment are weighed and placed it in a 250 ml conical flask with a ground joint. 100.0 ml of the solvent are added. The flask is attached to a reflux condenser and heated in a boiling water bath for 30 min, shaking periodically to wash away particles from the flask walls. The hot extract is filtered through cotton wool into a 250 ml measuring flask so that particles do not fall on the filter. The cotton wool is placed in the extraction flask, added 50 ml of 50% ethyl alcohol and perform the extraction. The extract is filtered into the same measuring flask. After cooling, the volume of the extract is brought to the mark with 50% ethyl alcohol and mixed. Then it is filtered through a membrane filter (nominal pore size 0.45 µm).

Preparation of standard solution. 25 mg of monoammonium glycyrrhizate SSS are dissolved in a 100 ml measuring flask in the solvent and brought the volume of the solution to the mark with solvent.

20 µl of the test solution and the solution of glycyrrhizic acid SS are alternately chromatographed on a chromatograph, obtaining at least 5 chromatograms (Fig. 1, 2).

The analysis under the above conditions was carried out 5 times. The relative standard deviation of the peak area of glycyrrhizic acid did not exceed 2.0%. The content of 18β-glycyrrhizic acid is calculated using the following formula:

$$x = \frac{A_1 \cdot m_2 \cdot p \cdot 250 \cdot 1000 \cdot 823}{A_2 \cdot m_1 \cdot 100 \cdot 100 \cdot 840},$$

where A_1 - the area of the 18β-glycyrrhizic acid peak on the chromatogram obtained with the test solution;

A_2 - the peak area of 18β-glycyrrhizic acid on the chromatogram obtained with a standard solution;

m_1 - the mass of the ointment under study used to prepare the test solution, in grams;

m_2 - mass of SSS monoammonium glycyrrhizinate used to prepare the standard solution, in grams;

p - percentage of 18β-glycyrrhizic acid in monoammonium glycyrrhizate SSS;

823 – molecular weight of 18β- glycyrrhizic acid;

840 - molecular weight of monoammonium glycyrrhizate.

Other indicators that standardize the quality of “Flucam” ointment are determined using well-known pharmacopoeial methods [24, 25].

The stability of the drug under natural storage conditions and its compliance with regulatory requirements over time were also studied [31,32].

RESULTS AND DISCUSSIONS.

Figures 1, 2 and Table 2 present the results of determining the main active ingredients.

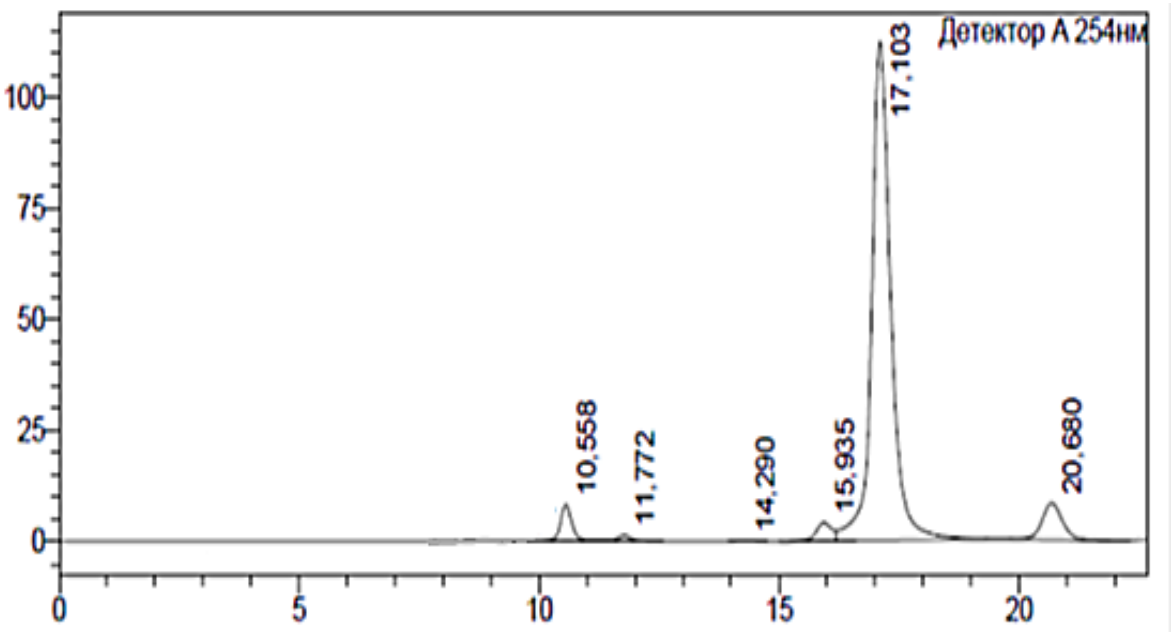

Fig. 1. Chromatogram of a standard solution

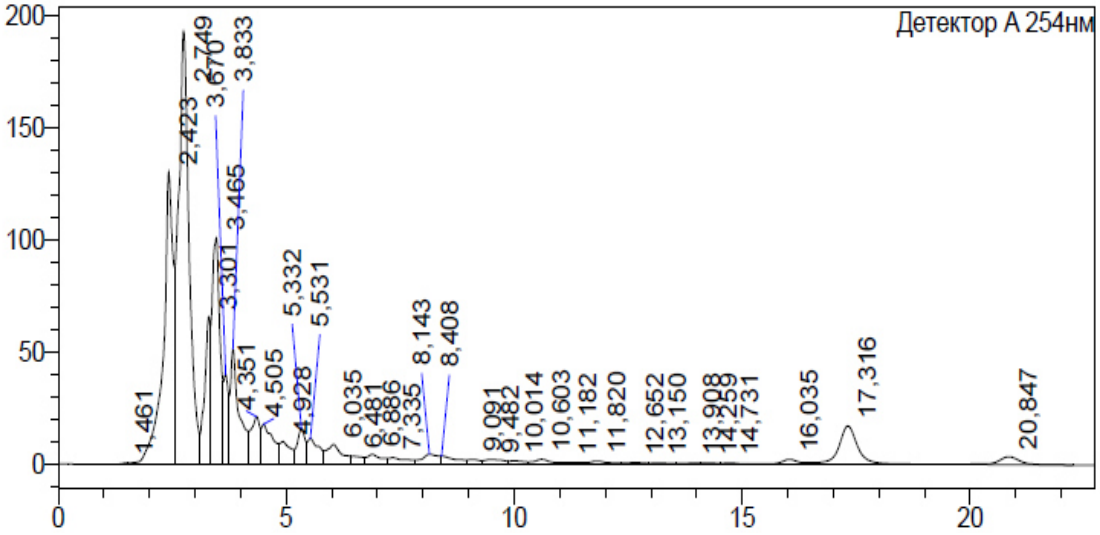

Fig. 2. Chromatogram of the test solution

The presented chromatograms show a corresponding response in the detection ranges characteristic of glycyrrhizic acid, which confirms the presence of the studied component in the ointment. The retention time for the solution of the substance under study (Fig. 2) was determined in the ranges characteristic of glycyrrhizic acid SS (Fig. 1), and the peak area corresponded to the calculated concentrations of the active substance.

The data obtained during the study of the stability of “Flucam” ointment under natural storage conditions are presented in Table 1.

Table 1. Results of determining the stability of "Flucam" ointment under natural storage conditions

Indicator	1 year	2 years	2.5 years
Tannin content, %	5.07	4.93	4.25
Glycyrrhizic acid content, %	0.982	0.956	0.895
pH раствора	6.23	6.08	6.23
Homogeneity	Corresponds	Corresponds	Corresponds
Particle size	< 100 µm	< 100 µm	< 100 µm
Microbiological purity	Corresponds	Corresponds	Corresponds

Table 1 shows that the tested ointment maintains high stability in key parameters. Only a slight decrease in the concentration of active substances is observed after 2.5 years of storage. Therefore, the shelf life of the ointment is set at 2 years.

The authenticity indicators and quality characteristics of "Flucam" ointment ascertained as a result of this study are summarized in Table 2.

Table 2. Specification of "Flucam" ointment for external use 5%, 20 g.

Indicators	Methods	Norms
Description	Visually, organoleptically	Light brown ointment with a faint odor
Authenticity A. Glycyrrhizic acid	HPLC	The retention time of the peak of the test substance should correspond to the retention time of the peak of the standard of the corresponding name (see section "Quantitative determination").
B. Tannins	Qualitative reaction with iron chloride solution	A black-green coloration is formed
Weight of package contents	Gravimetry PhEur, p 2.9.17	20.0 g ± 3.0 %
pH	Potentiometrics, PhEur p 2.2.3	From 5.0 to 6.5
Acidity	Titration, PhEur p 2.2.3	Not more than 0.5 mg
Particle size	Microscopically, PhEur p 2.9.38	Not more than 100 microns
Homogeneity	Visually, PhEur p 2.2.5	It should be homogeneous.
Quantitative determination of glycyrrhizic acid Tannins	PhEur, p 2.2.29, HPLC Permanganometric titration	Not less than 0.90 mg/g Not less than 4.5%

Microbiological purity	PhEur, p 2.6.12, 2.6.13, SP RUz	The total number of aerobic bacteria (in 1 g of sample) is no more than 10^5 CFU. The total number of yeast and mold fungi (in 1 g of sample) is no more than 10^4 CFU. Escherichia coli, in 1g should be absent. Salmonella, at 25g should be absent. Enterobacteria resistant to bile in 1 g should be absent.
Package	20.0 g in tubes with appropriate markings, 1 tube together with instructions for use in a cardboard package.	
Marking	In accordance with regulatory documents	
Storage conditions	Store in a dark place at a temperature not exceeding 30^0C. Do not freeze.	
Shelf life	2 years.	
Pharmacological action	Immunomodulator, interferon inducer.	

CONCLUSIONS

The present study comprehensively determined the authenticity criteria and quality parameters for the novel immunomodulatory ointment “Flucam”, developed on the basis of a standardized multicomponent herbal dry extract. Validated analytical methods for the qualitative and quantitative determination of the main bioactive constituents-tannins and glycyrrhizic acid-were established, enabling reliable quality control across all manufacturing stages in accordance with the principle of end-to-end standardization. Stability testing under natural storage conditions confirmed that the ointment retains its physicochemical properties, microbiological purity, and active compound content for a period of at least two years. The findings serve as the scientific foundation for drafting regulatory documentation and provide justification for the introduction of “Flucam” ointment into clinical practice as a safe, effective, and plant-derived immunomodulatory medicinal product.

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