ANNOTATION

of the dissertation work Zholdasbayev's Mussa Erkinuly on the topic

«Development of technology for obtaining a new drug of anti–inflammatory and antioxidant action based on *Prunella vulgaris* L. », submitted for the degree Doctor of Philosophy (PhD) in the specialty 8D07201 - «Technology of pharmaceutical production»

Relevance of the research topic

The relevance of the problem under study in the dissertation work is to provide the population of the Republic of Kazakhstan with high-quality, effective and affordable domestic medicines, which is an important priority in the pharmaceutical industry. To achieve this goal in the field of drug technology, it is necessary to conduct research on the optimal use of Kazakhstani plant raw materials. According to the Concept of Healthcare Development of the Republic of Kazakhstan until 2026, approved by the decree of the Government of the Republic of Kazakhstan dated November 24, 2022, it is presented that the main principles of the development of the pharmaceutical industry are state support for domestic developments, the development of a competitive pharmaceutical industry and medical science; ensuring the availability of safe, high-quality and effective medicines, medical devices and their rational use. In this regard, the search for approaches for a more complete use of our own resources of wild and cultivated plant raw materials and the creation on its basis of original phytopreparations that are affordable, at the same time not inferior in quality to their competitive counterparts is relevant.

Medicinal products based on herbal ingredients can be used in all fields of medicine without exception. The effective use of domestic plant raw materials for the development of medicines with a high content of biologically active substances, including dry extracts, is a promising direction in pharmaceutical science.

Great scientific interest plants of the family *Lamiaceae*, which, due to biologically active compounds in their composition, have a wide range of pharmacological activity. Such plants include *Prunella vulgaris* L. *Prunella vulgaris* L. contains many classes of compounds, such as mono- and sesquiterpenoids, di- and triterpenoids, steroids, phenylpropanoids, coumarins, flavonoids, higher fatty acids, vitamins, nitrogen-containing compounds, tannins and so on. The plant, due to its high vitamin C content, is used in folk medicine to stop bleeding and treat colds. The presence of sufficient amounts of phenylpropanoid ursolic acid and sesquiterpenoid caryophyllene has an overwhelming effect on the growth and spread of various types of cancer. It has been proven that the phenolpropanoid rosemary acid, contained in alcohol extracts of *Prunella vulgaris* L., has pronounced anti-inflammatory and antioxidant properties. In humans, reactive oxygen species cause inflammation due to oxidative stress. Constant inflammation generates a large amount of free radicals, which eventually cause additional inflammation. This endless vicious circle can harm the human body.

In this regard, the development of a gel dosage form technology based on a dry extract of *Prunella vulgaris* L., growing on the territory of Kazakhstan, is promising and scientifically sound for the pharmaceutical industry of the Republic of Kazakhstan.

The purpose of the dissertation research: Development of technology for obtaining the substance and finished dosage form of a new anti-inflammatory and antioxidant agent based on *Prunella vulgaris* L. and their standardization.

Objects of research: Raw materials of *Prunella vulgaris* L., dry extract, gel.

Subject of research: Optimal conditions for the extraction of *Prunella vulgaris* L. for the quantitative determination of rosemary acid, quality indicators of the dry extract and its biological activity, method and technology for obtaining anti-inflammatory and antioxidant agents, regulatory documentation for the gel and for the substance.

Research objectives:

1. To conduct a pharmacognostic study of the herb *Prunella vulgaris* L. and determine the indicators, quality standards, shelf life, stocks and prevalence of *Prunella vulgaris* L.

2. To develop methods for obtaining biologically active substances from *Prunella vulgaris* L. under conditions of ultrasonic activation, to screen for anti-inflammatory and antioxidant activity and to select samples promising for the development of a new drug, to determine the acute toxicity of dry extract of *Prunella vulgaris* L.

3. To develop the composition and technology of a ready-made dosage form of an anti-inflammatory and antioxidant agent based on a dry extract of *Prunella vulgaris* L.

4. To develop methods of quality control of the developed medicinal product based on *Prunella vulgaris* L., to determine the shelf life and storage conditions of the gel. To develop a RD project for the production of a gel based on the substance of a dry extract of *Prunella vulgaris* L.

5. To develop a feasibility study for the production of an anti-inflammatory and antioxidant agent with a dry extract of *Prunella vulgaris* L.

Scientific novelty

- For the first time, the anti-inflammatory and antioxidant effects of experimental samples of dry extracts of *Prunella vulgaris* L. obtained as a result of ultrasonic cavitation were studied, where it was revealed that the dry extract obtained by ultrasonic cavitation with 70% ethyl alcohol has anti-inflammatory and antioxidant activity;

- The composition of a new anti-inflammatory and antioxidant drug based on a dry extract of *Prunella vulgaris* L. has been developed for the first time in the form of a gel;

− For the first time, a technology has been developed for the production of a dry extract of *Prunella vulgaris* L. with anti-inflammatory and antioxidant effects;

− For the first time, methods of quality control of the developed medicinal product based on *Prunella vulgaris* L. have been developed, the term and conditions of its storage have been determined.

The scientific novelty of the dissertation research is confirmed by patents of the Republic of Kazakhstan for utility model №8611 dated 11.10.2023 «Application of dry extract of *Prunella vulgaris* L. as a cytotoxic agent» and №8813 dated 02.02.2024 «Application of dry extract of *Prunella vulgaris* L. as an antimicrobial agent».

Provisions submitted for protection

- obtaining ultrasonic extracts of *Prunella vulgaris* L. Search for a promising sample of extracts with anti-inflammatory and antioxidant effects;
- experimental studies of the preparation of a substance (ultrasonic aqueous-ethanol and aqueous extracts) from *Prunella vulgaris* L.;
- development of the composition of an anti-inflammatory and antioxidant drug based on a dry extract of *Prunella vulgaris* L. in the form of a gel;
- regulatory documents for the gel in the form of a draft RD and laboratory regulations for obtaining.

Practical significance of the results obtained

Based on the pharmaceutical substance of the dry extract of *Prunella vulgaris* L., a gel dosage form of anti-inflammatory and antioxidant action has been developed.

According to the results of an acute toxicity study, the dry extract does not have toxic properties and is recommended as an anti-inflammatory and antioxidant agent.

Laboratory regulations for the preparation of pharmaceutical substances and gels have been developed.

The technological process of obtaining extracts of *Prunella vulgaris* L. by ultrasound method has been introduced at the School of Pharmacy of the NCJSC «Karaganda Medical University».

Personal contribution of a doctoral student

All the above experimental results of the dissertation research were obtained by the author himself, which indicates the personal contribution of the applicant to the technology of

medicines. The author carried out studies on the anatomical and morphological features of *Prunella vulgaris* L., isolated and developed samples of extracts obtained by ultrasonic cavitation with ethyl alcohol and water, identified their compositions using HPLC-MS analysis, and developed methods for obtaining ultrasonic extracts. Samples were screened for anti-inflammatory, antioxidant, antimicrobial activity and cytotoxicity. Laboratory regulations for the substance and the mild dosage form have been developed. Statistical processing of the obtained results has been carried out and they are designed in accordance with the requirements for the design of the dissertation work.

Approbation of the results of the dissertation

The results and main provisions of the scientific work are presented at: VI International Scientific and Practical Conference «Science and Education in the modern world: challenges of the XXI century» (Astana, 2020); XI International Scientific and Practical Conference «Priorities of pharmacy and dentistry: from theory to practice» (Almaty, 2022); XI International Scientific and Practical Conference of young Scientists «Modern trends in the development of health saving technologies» (Moscow, 2023).

Publications

The main provisions of the dissertation are reflected in 9 published works, including 2 patents of the Republic of Kazakhstan for a utility model, 1 article in journals recommended by the Committee for Quality Assurance in Science and Higher Education; 3 articles in an international scientific publication included in the Scopus database.

Scope and structure of the dissertation

The dissertation is presented on 165 pages of typewritten text, includes 22 figures and 47 tables; it consists of an introduction, 7 chapters, a conclusion, a list of used sources and appendices. The list of references includes 135 literary sources.

CONCLUSIONS:

The dissertation work is devoted to the development of technology for a new drug of anti-inflammatory and antioxidant action based on *Prunella vulgaris* L.

As a result of the conducted research, the following conclusions can be drawn:

1. When studying the distribution, raw materials and prospects, it was revealed that the herb *Prunella vulgaris* L. is a renewable source of plant raw materials for the production of medicines. Significant reserves of raw materials have been identified in the East Kazakhstan region: the area of thickets with the participation of *Prunella vulgaris* L. herb amounted to 41.2 hectares with an operational reserve of 5.7 tons and the volume of possible collection of raw materials -3.4 tons. Due to the polymorphism of the species, a pharmacognostic study of the herb *Prunella vulgaris* L. collected in the territory of the Ulutau region was carried out, diagnostic anatomical and morphological signs were established that allow identification. Diagnostic signs of the raw material of the *Prunella vulgaris* L. are the shape and location of the leaves on the stem, the absence of devastation. The stems of the plant are brown, tetrahedral, erect or ascending, simple or branched, smooth from below, with sparse and rather long, upward-lying hairs along the ribs at the top. Flowers on short pedicels in false whorls, collected in head-shaped and spike-shaped, ovate or oblong inflorescences. The parameters and quality standards of *Prunella vulgaris* L. plant raw materials have been established. According to the results of the research conducted to determine the quality parameters of *Prunella vulgaris* L. plant raw materials, the data obtained are included in the draft regulatory documentation on raw materials.

2. For the first time, the technology for obtaining dry extract of *Prunella vulgaris* L. was developed and quality parameters were studied: the comparatively maximum extract yield is provided by double extraction by ultrasound of air-dry raw materials, 70% ethanol at an ultrasonic frequency of 40 kHz, for 30 minutes; the main component of the extract is phenylpropanoid rosemary acid up to 7.6%, laboratory regulations for the production of dry extract have been developed raw materials of *Prunella vulgaris* L. and the indicators and quality standards of the dry extract of the herb *Prunella vulgaris* L. have been established. The shelf life of the dry extract of the common blackhead is 24 months. A draft regulatory document has been

developed for the substance *Prunella vulgaris* L. dry extract. Screening for the biological activity of *Prunella vulgaris* L. extracts obtained by various methods revealed that the dry extract obtained by extraction with 70% ethyl alcohol under ultrasonic cavitation of *Prunella vulgaris* L. raw materials has pronounced anti-inflammatory and antioxidant activities and belongs to low-toxic compounds, namely Hazard class IV.

3. For the first time, a composition of a mild dosage form containing a dry extract of *Prunella vulgaris* L., carbopol 940 as a gel base and glycerin as a plasticizer, with the following component ratio by weight (%): dry extract of *Prunella vulgaris* L. obtained under ultrasonic cavitation – 1.0 g; carbopol – 2.0 g; glycerin – 2.0 ml; NaOH hydroxide 2.0 ml; twin-80 – 1.0 ml; mint essential oil – 0.5 ml; purified water – up to 100 ml. A technology for obtaining a mild dosage form based on a dry extract of *Prunella vulgaris* L. has been developed.

4. Reproducible results of physico-chemical, biopharmaceutical, pharmacological parameters of a gel based on a dry extract from the grass of the *Prunella vulgaris* L. have been obtained. The methods of qualitative and quantitative determination of the active substance of rosemary acid in a mild dosage form (gel) based on an extract from the grass of the *Prunella vulgaris* L. by the HPLC-MS method have been developed. For the first time, quality specifications and RD projects, laboratory regulations for a soft dosage form based on dry extract of *Prunella vulgaris* L. have been developed.

5. A feasibility study of the product has been developed, which shows the feasibility of producing an anti-inflammatory and antioxidant agent with an extract of *Prunella vulgaris* L. on an industrial scale.