

## ANNOTATION

to dissertation work on the topic «**Pharmacognostic and technological aspects of obtaining a dosage form based on the extract of *Ferula asafoetida* L.**» for the degree of Doctor of Philosophy (PhD) on specialty 6D074800 – «Technology of pharmaceutical production»  
**of Rakhymbayev Nurgali Amanbayuly**

### **Relevance of the research topic.**

The national project of the Ministry of Health of the Republic of Kazakhstan, «High-quality and affordable health care for every citizen Healthy Nation» is aimed at increasing the share of domestic pharmaceutical products to 50% in 2025.

The main objectives of the project are to increase the human and scientific potential of the pharmaceutical and medical industries, the development of domestic production of medicines and medical products.

There are more than 6,000 plant species in the flora of Kazakhstan, but they are insufficiently studied as a source of medicinal raw materials, and only a few plant species are used in the field of domestic production. In this regard, one of the main tasks of pharmaceutical science and practice is the search for plants as potential sources of pharmacologically active compounds, the study of chemical compositions, and the development of optimal technology for the production of pharmaceutical substances and medicines based on them.

One of the plants that has not yet been fully studied and is not used in medicine is *Ferula asafoetida* L.

In the eastern folk medicine of India, Iran, China, and Central Asian countries, the *Ferula asafoetida* L. was widely used in the treatment of measles, ulcers, various tumors, syphilis (D. Dadabaeva, 1972), tuberculosis, seizures, gastrointestinal diseases, etc. (A. Amirdovlat, 1989).

This plant raw material, the chemical composition of which is very rich in biologically active substances, is widespread in the flora of Iran, Afghanistan, Tajikistan, Uzbekistan, and Kazakhstan.

More than 180 species of the genus *Ferula* L. are known, and they are one of the most polymorphic generations of the genus *Umbelliferae* (*Apiacea* Lindl). The main habitat of representatives of the genus is Central Asia and Kazakhstan. The *Ferula asafoetida* L. is widespread in Kazakhstan - on the Embin plateau, on the western small hills, the Aral Sea, Moyinkum, Balkhash-Alakol, Kyzylkum, Turkestan, in the mountains of Chu-Ile, Karatau, in the Mangystau peninsula, on the Northern and Southern plateaus.

The root of *Ferula asafoetida* L. contains terpenoid coumarins, furocoumarins, flavonoids, sesquiterpene lactone, esters of terpene alcohols and aromatic acids, essential oils with an unpleasant garlic odor, and the odor comes from polysulfide inclusions.

The *Ferula asafoetida* L. is traditionally used in the treatment of various diseases such as whooping cough, asthma, ulcers, epilepsy, abdominal pain, bronchitis, intestinal parasites, cramps, poor digestion, and influenza. The *Ferula asafoetida* plays an important role in the digestion of food lipids, improving the

outflow of bile and increasing the secretion of bile acids, as well as increasing the activity of digestive enzymes of the pancreas and small intestine. Recent pharmacological and biological studies have shown that the *Ferula asafoetida* L. has several pharmacological effects, such as antioxidant, antimicrobial, antiviral, antifungal, anticancer chemotherapeutic, antidiabetic, carcinogenic, antispasmodic and hypotensive, relaxing and neuroprotective effects.

However, scientific research on the medicinal plant «*Ferula asafoetida* L.» in Kazakhstan has not been carried out at the proper level. Therefore, chemical, pharmacological, and pharmaceutical research on the *Ferula asafoetida* L. as a medicinal plant material and the development of drugs based on it is an important scientific and practical problem for pharmacy and medicine.

**Purpose of the dissertation research:**

Pharmacognostic study of plants of *Ferula asafoetida* L. as a source of plant raw material and manufacture of a dosage form based on extracts obtained from underground parts of plants.

**Objectives of the research:**

- pharmacognostic and phytochemical analysis of the underground part of *Ferula asafoetida* L.;
- development of an effective technology for obtaining an extract from the plant raw material of the underground part of *Ferula asafoetida* L. and its standardization;
- determination of the component composition, acute toxicity and antimicrobial activity of the carbon dioxide extract of the underground part of *Ferula asafoetida* L.;
- development of technology for obtaining a dosage form (gel) based on carbon dioxide extract of *Ferula asafoetida* L. and standardization;
- development of a feasibility study for gel production.

**Objects of research:** Medicinal plant raw material *Ferula asafoetida* L. from the genus of umbrella plants, its carbon dioxide extract, and gel prepared based on the extract.

**Methods of research:** pharmaceuticals-technological, pharmacognostic, physical, physico-chemical, pharmacological, statistical.

**Subject of study:** distribution area of medicinal plant raw material *Ferula asafoetida* L., determination of pharmacognostic features; development of rational technology for obtaining extracts and standardization; determination of pharmacological activity and safety of carbon dioxide extract of the underground part of *Ferula asafoetida*; development of technology for gel production based on carbon dioxide extract *Ferula asafoetida* L. and standardization;

**The main provisions of the thesis research put to the defense:**

Results of pharmacognostic studies and standardization of the underground part of the medicinal plant *Ferula asafoetida* L.;

Technology for obtaining extract from the plant raw material of the underground part of *Ferula asafoetida* L. and the results of safety and antimicrobial activity studies;

Results of the technology for preparing an antimicrobial gel based on the

carbon dioxide extract of *Ferula asafoetida* L. and standardization.

**Scientific novelty:**

For the first time in Kazakhstan:

- the indicators of the quality and stability of the underground part of the *Ferula asafoetida* L., growing in the Turkestan region have been determined and standardized;

- A technology for obtaining carbon dioxide extract from the underground part of the *Ferula asafoetida* L. has been developed and acute toxicity has been assessed, pronounced antimicrobial activity has been proven;

- The technology of obtaining an antimicrobial gel based on the carbon dioxide extract of the *Ferula asafoetida* L. has been developed and standardized.

The scientific novelty of the research is confirmed by the patent for the invention in the RSE «National Institute of Intellectual Property» dated 08/20/2021, registration number No. 35010 «Method for obtaining carbon dioxide extract from the roots of the plant *Ferula asafoetida* L.»

**Practical significance of the research:**

- the technology of collecting and harvesting medicinal plant raw materials *Ferula asafoetida* L. is proposed. Identified by reference No.01-08/2 of the RSE at the Institute of Botany and Phytointroduction of the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan (Appendix A);

- the technology of collecting and harvesting medicinal plant raw materials *Ferula asafoetida* L. has been introduced. «Zerde-Phyto» LLP (Appendix B);

- a ND project has been developed for the carbon dioxide extract of *Ferula asafoetida* L., obtained before critical conditions from the underground part (Appendix G);

- a method for obtaining carbon dioxide extract from the underground part of *Ferula asafoetida* L. (Appendix D) and the standard of the organization «Zhanafarm PLP» LLP (Appendix ZH) have been introduced;

- the draft of technological instructions on the method of obtaining carbon dioxide extract from the underground part of *Ferula asafoetida* L. is presented by «Zhanafarm PLP» LLP (Appendix E);

- method for obtaining carbon dioxide extract from the underground part of *Ferula asafoetida* L. implemented at the Department of Pharmaceutical Technology of NAO «KazNMU named after S. Zh. Asfendiyarov» (Appendix I);

- a method for obtaining carbon dioxide extract from the underground part of *Ferula asafoetida* L. implemented at the Department of Pharmaceutical Disciplines of the NAO «Astana Medical University» (Appendix N);

- The project of ND gel obtained on the basis of carbon dioxide extract of the underground part of *Ferula asafoetida* L. (appendix K) has been developed;

- the technology of gel production based on carbon dioxide extract from the underground part of *Ferula asafoetida* L. has been introduced at «DOSFARM» LLP (Appendix L);

- a draft of technological instructions for the production of gel based on

carbon dioxide extract of the underground part of *Ferula asafoetida* L. has been developed and approved by «DOSFARM» LLP (Appendix M);

#### **Author's personal contribution.**

On the topic of the dissertation work, the dissertation conducted an independent review and analysis of domestic and foreign literature, carried out practical work on all the tasks set. This is confirmed by the results of studies obtained in laboratory and production conditions using modern equipment and literature.

The reliability and validity of the research results is confirmed by the focus on solving the actual problem of the work performed, the implementation of regulatory documents in a modern research center and projects.

#### **Conclusions:**

1. Pharmacognostic analysis of the underground part of *Ferula asafoetida* L. was carried out and identified on the basis of anatomo-morphological features.

The qualitative and quantitative analysis determined polysaccharides ( $0.421\pm 0.075\%$ ), tannins ( $3.490\pm 0.012\%$ ), flavonoids ( $0.18\pm 0.002\%$ ), phenolic compounds ( $0.27\pm 0.008\%$ ), alkaloids ( $0.045\pm 0.003\%$ ), coumarin ( $1.860\pm 0.005\%$ ), saponins ( $2.279\pm 0.041\%$ ), organic sulfur compounds (disulfide, bis(1-methylpropyl) at least 9%), 4 macronutrients (Ca, Mg, Na, K), 5 micronutrients (Mn, Cu, Zn, Fe, Ni), amino acids and fatty acids (oleic acid-46.1%, linoleic acid-43%).

In accordance with the requirements of SPh RK and GACP rules the technology of collection and quality specification of underground part of *Ferula asafoetida* L. was developed. At temperature  $25\pm 2^\circ\text{C}$  and relative humidity  $60\pm 5\%$  storage period was 24 months.

2. An effective method and technology for obtaining extract from the underground part of *Ferula asafoetida* L. has been developed.

- The extract was obtained by percolation and carbon dioxide extraction under subcritical conditions;

- carbon dioxide extraction under subcritical conditions was selected as an effective extraction method and the technological scheme was drawn up;

- The quality specification of carbon dioxide extract of *Ferula asafoetida* L. was developed. The shelf life of the extract was 24 months. A draft regulatory document for carbon dioxide extraction of *Ferula asafoetida* L. substance was developed.

Validation on the method of quantitative determination of sulfur-containing compound disulfide, bis(1-methylpropyl) in the carbon dioxide extract of the underground part of *Ferula asafoetida* L. was carried out.

3. The carbon dioxide extract of *Ferula asafoetida* L. revealed 33 chemical compounds. The highest amount of di-n-butylidithiophosphinic acid(11.91%), disulfide, bis (1-methylpropyl) (9.63%), 1,2-dithiolane (4.26%), thioxolone (3.46%), 6-(methylthio)hexa-1,5-dien-3-Ola (2.51%), 1,4-dithian-2,5-dione, 3,6-dimethyl - (2.49%), ethyl oleate (14.13%) and oleic acid (10.87%) were identified. The total content of sulfur compounds among the identified components in carbon dioxide extract was 46.3%.

The safety study of carbon dioxide extract of *Ferula asafoetida* L. showed that according to the classifications of Hodge and Sterner and K. K. Sidorov tables it

belongs to class IV - the group of «practically non-toxic substances».

The carbon dioxide extract of *Ferula asafoetida* L. showed significant antimicrobial activity on gram-positive bacteria (*S. aureus*, *B. subtilis*), gram-negative bacteria (*E. coli*, *K. pneumoniae*, *S. enterica*) and to fungi (*C. albicans*, *A. niger*).

4. Rational composition of gel with carbon dioxide extract of *Ferula asafoetida* L.: plant pharmaceutical substance (carbon dioxide extract) - 3 g, auxiliary substances: carbopol Ultrez 10 (gel-forming substance) - 1 g, 10% NaOH solution (neutralizer) - pH 6.5-7.5, glycerin (plasticizer) - 10 g, tween-80 (emulsifier) - 3 g, benzyl alcohol (preservative) - 0.5 g, purified water.

The technology of gel production with addition of carbon dioxide extract of *Ferula asafoetida* and quality specification was developed, stability was determined.

5. Feasibility study of carbon dioxide extract of *Ferula asafoetida* L. and gel obtained on its basis was developed. As a result, the cost of one copy of the gel with the addition of carbon dioxide acid extract of *Ferula asafoetida* L. amounted to 776.78 tenge, and the wholesale price –1009.82 tenge. The proposed feasibility study of the product showed the feasibility of producing medicines on an industrial scale.

#### **Approbation of the results of the dissertation:**

The main results of the research carried out on the topic of the dissertation are presented at the VI International Scientific Conference of Young Scientists and Students «Prospects for the development of biology, medicine and Pharmacy» (Shymkent, 2018), an international scientific and practical conference dedicated to the memory of Professor R. Dilbarkhanov «Formation and prospects of development of the scientific school of Pharmacy: continuity of generations» (Almaty, 2019, 2020), X International Scientific and Practical Conference «Modern achievements of pharmaceutical technology» dedicated to the 60th anniversary of the birth of Doctor of Pharmaceutical Sciences, Professor E. V. Gladukh (Kharkov, Ukraine, 2023), presented and published in the materials of the I International Forum «Asfen.forum, new generation – 2023» (Almaty, 2023).

#### **Publications:**

The results of the dissertation research have been published in 13 scientific papers, including:

- article in Scopus journal, included in the international database - 1;
- in publications recommended by the Ministry of Education and Science of the Republic of Kazakhstan, the Committee for Control in the Field of Education and Science - 4;
- abstracts in the materials of the international scientific and practical conference -7;
- patent for invention -1.

#### **Connection of work with the plan of government and scientific programs:**

The dissertation work was carried out within the framework of the state program of the Republic of Kazakhstan «Comprehensive Plan for the Development of the Pharmaceutical and medical industry for 2020-2025» and the intra-university scientific and technical project of the Kazakh National Medical University named

after Asfendiyarov «Standardization of medicinal plant raw materials *Ferula asafoetida* L. and the development of an effective technology for its extraction». Registration number No. 0119RKI0305).

**Scope and structure of the dissertation:**

The dissertation work consists of 146 text-typed pages on a computer, including 50 tables, 41 figures, 178 domestic and foreign literature, and appendices A-P. The work consists of an introduction, a literary review, materials and methods, three sections on individual practical studies, and conclusions.