

## ANNOTATION

on the thesis with the theme «**Development of new drugs, techniques and technologies of their manufacture from domestic raw materials**

**(*Cistanche Salsa*)»**

for the Doctor of Philosophy Degree (PhD) on the 6D110600 – Pharmacy specialty  
**of Elmira Kartbayeva Bekbolovna**

**Relevance.** The flora of the Republic of Kazakhstan is a renewable source of biologically active substances and has 6000 species of vascular plants, which belong to 1300 genera and 159 families. The uniqueness of Kazakhstan's flora is that it is rich for taxa with specific geographical confinement - endemics, the number of which is up to 515 species. However, no systematic pharmacognostic analysis and, as a consequence, standardization approaches limit their use in medicine. Only 230 species of the flora of Kazakhstan variety are used in officinal medicine and only 92 species are included in the State Register of Medicinal Products of the Republic of Kazakhstan. Only 26% of medicinal plants (about 1,500) have proved biological activity and used in drug therapy of various diseases as a part of complex herbal remedies, as well as monodrugs. For insufficient study of the local flora representatives, in terms of pharmacognosy, also says the fact that only for 20 out of nearly 515 endemics of Kazakhstan were conducted studies, and only 0.02% of the species is related to medicines with a particular geographic region of growth.

One of these little known and not used in official Kazakh medicine species is a wild medicinal plant-parasite cistanche saline *Cistanche salsa* (C.A. Mey.) G. Beck) from broom rape *Orobanchaceae* Vent. family which differs by complex chemical composition and is used in China, Korea, Japan and the United States as a biologically active agent. The plant is positioned as a source of herbal remedies with broad-spectrum tonic, antioxidant activity, as well as means for the prevention of erectile dysfunction. To this day an increase in exports of raw materials to the Republic of China is observed, where stocks are depleted and from the year 2000 cistanche saline is included in the Red Data Book of China.

Despite the rapid pace of development of Kazakhstan's pharmaceutical industry, raw cistanche does not find adequate attention from the manufacturers: bulks are produced mainly for export purposes, there is no domestic production of drugs in the pharmaceutical market. This is due to the lack of a systematic approach to the standardization of raw materials and, as a consequence of regulatory documents on quality control, making it impossible to develop medicines.

In this regard, research in the field of standardization of raw materials *Cistanche salsa* (C.A. Mey.) G. Beck), in accordance with international and Kazakh requirements for export purposes, as well as the establishment of national anti-inflammatory, wound healing and tonic effect on the basis of biologically active substances (BAS ) of cistanche saline stolons is relevant and practically important area of modern pharmaceutical research as to solve complex tasks aimed

at import substitution of drugs by domestic resources utilizing the flora of Kazakhstan.

**Dissertation subject relation to research projects and programs.** The thesis is done within the framework of scientific and technical program of MES of RK "Focused development of university science oriented to innovative result" in the framework of the state order for the budget program 055 "Fundamental and applied scientific research" on the subject: "Development of new drugs, techniques and technologies of their manufacture from domestic raw materials» (№ of state registration 0112RK02043, 2012-2015 years).

**Purpose of the study.** Pharmaco-technological research of cistanche saline stolons *Cistanche salsa* (C.A. Mey.) G. Beck), development of new drugs on their basis and their standardization.

**Objectives:**

- carry out phytochemical studies of individual groups of BAS of *Cistanche salsa* stolons for "Quantitative content" standardization criterion selection;
- optimize the technology to produce dry extract of cistanche stolons in experimental-industrial conditions and develop the manufacturing instruction;
- develop an optimal technology for the production of cistanche stolons extracts: liquid and dense carbon dioxide in terms of industrial development;
- develop rational dosage form (capsules) for creating a drug based on dry extract;
- select the parameters of standardization, to validate methods and develop projects of AND for *Cistanche salsa* stolons and finished herbal medicines;
- conduct a study of the stability for *Cistanche salsa* stolons and developed medicines;
- confirm the prospect of the creation of new drugs based on cistanche saline stolons by studying its pharmacological activity and biopharmaceutical aspects.

**Subject of the study.** The raw material for the study were *Cistanche salsa* (C.A. Mey.) G. Beck) from broom rape *Orobanchaceae* Vent. family, gathered in the flowering phase (April-May) in the vicinity of the village Bakanas, Almaty region. The dried length of 1-2 cm, 2-3 cm thick, with a scaly surface. Color from the surface and at the turn brownish-brown, has a core with the tar content of dark brown color. The smell is weak. The taste is sweet, astringent.

**Methods of the study.** Standard pharmacopoeia SP RK methods were used and some traditional and innovative technological methods of obtaining extracts. The treatment results of experimental studies conducted by statistical methods using a personal computer with Microcal Origin, Statistica 6 and Excell programs.

**Scientific novelty of the results.**

For the first time a technology for producing cistanche stolons by special technology is developed, novelty confirmed by innovative patents: № 26875 "Method of obtaining raw materials of physiologically active cistanche saline for use in the pharmacy"; Number 29370 "A method for producing physiologically active materials of cistanche saline for use in the pharmacy".

For the first time an optimal technology of liquid, dry and dense carbon dioxide extracts *Cistanche salsa* stolons is developed and their standardization conducted in compliance with the SP RK. The novelty of the research is confirmed by innovative patents: № 29371 № 29371 «*Cistanche salsa*» сұйық сығындысын алудың әдісі», № 31031 "A method for producing carbon dioxide extract of «*Cistanche salsa*»; № 31408 «Method of producing a dry extract of «*Cistanche salsa*»».

For the first time encapsulated dosage form based on the dry extract of *Cistanche salsa* is obtained, codenamed "Cistanphyt" and standardization conducted. The stability of the developed medicines and vegetable raw materials were conducted, the results of which showed the safety of biologically active substances during storage under proper conditions (storage temperature  $(25 \pm 2) ^\circ \text{C}$ , relative humidity  $(60 \pm 5)\%$ ).

The research of pharmacological activity for *Cistanche salsa* stolons and developed medicines were held that allowed to establish an anti-inflammatory and immune corrective activity. Toxic metric test allowed to carry developed medicines to Class V toxicity.

#### **The practical significance of the results.**

Development of new drugs, "cistanche saline, fragmented stolons", "cistanche saline stolons extract liquid", "cistanche saline stolons dry extract", "cistanche saline stolons dense carbon dioxide extract", "Capsules "Cistanphyt".

Developed drug from *Cistanche salsa* offered as potential drugs for the experimental series on production in "FitOleum" and "Fitoaromat."

Designed rational technological scheme of production of new drugs and technological regulations, according to which the production site LLP "FitOleum" (Issyk) reproduced the technology getting in the industrial environment and established a series of pilot-scale preparations.

Methods of quality assessment, as set out in AND projects, tested and validated at pilot scale batches of study drugs.

Based on the results of a project developed monographs and dossiers submitted to RSE "National Center for Expertise of medicines, medical devices and medical equipment" MHSD RK to include the monograph "Cistanche stolons" in the State Pharmacopoeia of the Republic of Kazakhstan. Prepared a series of industrial products for commercialization in accordance with ST RK 712-1907-12-TOO (DUT) -02-2013 "BAA cistanche liquid extract «SALAMAT» and ST RK hep-1509-1910-02 01-2012 "BAA Cistanche".

The results have been implemented in the production of pharmaceutical enterprise LLP "FitOleum".

**Approbation.** Scientific-practical conference on the results of scientific and technical program "Development of new drugs, excipients, methods and technologies of their production from domestic raw materials" and "Development of technology and formulations, anti-inflammatory and antimicrobial action on the basis of pine oil" ( Almaty, 2012), Proceedings of the work approved at the XVII International Scientific Conference "Oncology - XXI Century" (Spain, 2013), the Republican scientific-practical conference with international participation "Topical

issues of evidence-based medicine and drug supply" (Karagandy 2013 ), scientific - practical conference "Actual problems of education, science and industry in Pharmacy" (Tashkent, 2013), I Russian scientific-practical conference with international participation "Innovations in the health of the nation" (St. Petersburg, 2013), the International Scientific-practical conference "Modern trends in medical education and health care in the world. Opportunities for international cooperation "(Almaty, 2013), II Russian scientific-practical conference with international participation "Innovations in the health of the nation"(St. Petersburg, 2014).

**Publications:**

The results of research published in 24 scientific papers, including:

- articles in international journals included in the Scopus (Elsevier) and Web of Science (Clarivate analytics) database - 2;
- articles in journals recommended by the Committee on the Control of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan - 7;
- abstracts and articles at international scientific conferences - 6;
- articles in the international journals - 1;
- patent for invention of utility model – 8.

The scope and structure of the thesis

The thesis is presented on 148 pages of typewritten text in a computer set, contains 37 tables, 25 figures, a list of references, including 149 sources, as well as applications from the letter A to IO. The work consists of an introduction, a literature review, a section devoted to materials and research methods, three sections of own research, and conclusions.