

ABSTRACT

dissertation for the degree of Doctor of Philosophy (PhD) in the specialty
"8D05101 - Biology"

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General characteristics of the work. The dissertation is devoted to the study of toxico-pharmacological properties of a biologically active complex based on *Rumex tianschanicus* Losinsk.

Relevance of the research work.

Currently, a large number of antiulcer agents of different pharmacological groups are presented in clinical practice, the action of which is aimed at stimulating protective mechanisms or limiting damaging factors. The most frequently used agents prescribed for almost any pathology of the stomach are antisecretory agents that reduce the production of hydrochloric acid by the parietal cells of the gastric glands, and antacids that neutralize acid. These agents are undoubtedly highly effective both in therapeutic and prophylactic use. However, their mechanism of action implies the suppression of the digestive function of the stomach as a whole, since an acidic environment is necessary for the activation and functioning of gastric enzymes, as well as for the denaturation of food proteins and increasing the availability of chyme for enzymes. Consequently, the main side effect of these drugs is dyspeptic disorders. In addition, it was noted that due to the suppression of the antiseptic activity of gastric juice with long-term use of these drugs, patients have an increased risk of developing infectious diseases of the gastrointestinal tract, as well as aspiration pneumonia, which occurs when pathogenic bacteria are introduced from the stomach into the respiratory tract. Medicines that provide protection of the gastric mucosa and / or stimulate the regeneration of erosive and ulcerative defects without inhibiting gastric secretion are poorly represented in the pharmacy network. At the same time, the results of medical statistical studies indicate the need to develop such drugs for the prevention of ulceration when using gastrototoxic drugs (NSAIDs) and to restore the gastric mucosa in atrophic gastritis, exacerbations of peptic ulcer disease. The prescription and use of gastroprotective agents (misoprostol, carbenoxol, etc.), which have pronounced protective and regenerative properties, is largely limited by frequently occurring side effects such as abdominal pain, diarrhea, disruption of water-salt metabolism, and menstrual cycle.

Thus, the current research task is to search for and develop antiulcer agents of a new structural type that have gastroprotective properties, are safe and do not weaken the digestive function of the stomach. A promising direction is to study the activity of plant compounds, which usually have a wide range of pharmacological action, low toxicity and high availability in natural raw materials. The use of natural compounds allows us to obtain substances with more pronounced activity and direction of action compared to the original molecules. One of the potential sources of natural substances with a wide range of therapeutic action are Kazakh plants of the genus *Rumex* L., eleven of which have industrial reserves in the

territory of the Republic of Kazakhstan, being promising plant raw materials for domestic pharmaceutical enterprises. This work is devoted to the study of the toxicopharmacological properties of the biologically active complex based on *Rumex tianschanicus* Losinsk.

Purpose of the work: To study the toxico-pharmacological properties of the biologically active complex based on *Rumex tianschanicus* Losinsk.

Research objectives:

1. To study the chemical composition and content of the main groups of biologically active substances (BAS) of the roots of *R. tianschanicus* L.;
2. Conduct an analysis of the acute and chronic toxicity of the biologically active complex (complex) obtained from the roots of the plant *R. tianschanicus* L.;
3. To study the antiulcer activity of the complex on a model of gastric ulcer induced by indomethacin;
4. To study the anti-inflammatory activity of the complex, *R. tianschanicus* L. on models of inflammation induced by histamine and formalin;
5. To study the antioxidant activity of the complex based on *Rumex tianschanicus* L., using the methods of β -carotene-linoleic acid, DPPH, ABTS, CUPRAC, and the method of metal chelation;

Object of study– a complex obtained from the roots of *Rumex tianschanicus* Losinsk.

Research methods. During the research work on the topic of the dissertation, the following methods were used: hematological, biochemical, cytological, histological, physiological, phytochemical, pharmacological.

Scientific novelty and significance of the dissertation work.

The novelty of the research is the fact that no one has previously studied the effect of the biologically active complex from the roots of the Kazakh plant species *R. tianschanicus* on the treatment of inflammatory diseases of the digestive system.

For the first time, the safety and effect of a complex of *R. tianschanicus* roots on indomethacin-induced gastric ulcers in rats and histamine-induced paw inflammation have been demonstrated

For the first time, new experimental data have been obtained on the biological effect of a complex of *R. tianschanicus* roots on the experimental treatment of acute, chronic, erosive gastritis and gastric ulcers.

For the first time, new experimental data on the biological action of a root complex based on the plant under study has been obtained *R. Tianschanicus* for the treatment of stomach ulcers.

Theoretical significance of research work is that the results of preclinical trials obtained in this work serve as a basis for the development of a drug from the roots of *R. tianschanicus* L. for the purpose of effective treatment of inflammatory diseases of the gastrointestinal tract (GIT).

In addition, experimental substantiation and evidence of the safety and effectiveness of the biologically active complex of the roots of *R. tianschanicus* L. will allow us to recommend the development of new methods for the selective extraction of industrially important classes of plant biologically active substances

and, thereby, increase the competitiveness of domestic pharmaceutical enterprises of the Republic of Kazakhstan in foreign markets.

Practical significance of the results obtained.

The research results presented in the dissertation, allow in prospects to expand the range of pharmacologically active natural flavonoids and anthraquinones produced in the Republic of Kazakhstan. This will create the opportunity to introduce to the domestic pharmaceutical market a new export-oriented and import-substituting drug with a wide spectrum of action, intended for the treatment of inflammatory processes and lesions of the mucous membrane of the gastrointestinal tract.

The main provisions submitted for defense:

1. Comparative phytochemical analysis demonstrates the highest content of biologically active substances in the roots of *R. tianschanicus* Losinsk in the dormant phase;

2. The complex obtained from the roots of *R. tianschanicus* is safe according to the assessment of acute and chronic pharmacotoxicity in vivo and has hepato-, nephro- and hemotoxic properties;

3. Oral administration of a complex based on *R. tianschanicus* to laboratory rats for 10 days causes regeneration of gastric mucosal ulcers in an experimental model;

4. According to the data of an experimental study on laboratory rats, a complex of *R. tianschanicus* roots is a prophylactic agent for stomach ulcers;

5. The complex based on *R. tianschanicus* has anti-inflammatory properties in experimental modeling of histamine-induced edema of the mouse paw;

6. The complex based on *R. tianschanicus* has antioxidant activity according to the results of DPPH, ABTS, CUPRAC tests.

Personal contribution of the doctoral student in the preparation of each publication consisted of collecting data on the subject of research, collecting plants, performing laboratory research on plants and animals, including analysis, interpretation and presentation of the results obtained, and preparing publications.

Connection with the plan of the main scientific works. The dissertation work was completed within the framework of two PTF №11465435 "Development and use of new genomic technologies to protect organisms from mutagenic effects, increase the productivity of natural resources and improve the quality of life of the population" 2021-2022. Scientific Director of the MSHE RK for 2020-2022. Project Supervisor c.b.s., Professor L.B. Dzhanisugurova.

Review and approval of work results. The main results of the dissertation were annually presented at the scientific and technical council of the faculty of "Biology and biotechnology", at meetings of the department of "Biodiversity and bioresources" of the Kazakh National University named after Al-Farabi and the Academic Council of the RSE on the REM "Institute of Genetics and Physiology". The results of the dissertation are included in the Report on scientific research work on project No. OP11465435.

Research results.

1. Phytochemical studies revealed that the root extract of *R. tianschanicus* L., growing in Kazakhstan, contains a high content of flavonoids, anthraquinones, and phenolic compounds.

2. Toxicopharmacological studies showed that a complex based on the roots of *R. tianschanicus* L. causes a statistically significant ($p \leq 0.05$) decrease in the total body weight and organ mass coefficients of laboratory animals.

3. Statistically significant ($p < 0.05$) changes in the number of peripheral blood cellular elements were observed, while hematopoiesis remained unchanged during the oral administration of the root-based complex of *R. tianschanicus* L.

4. For the first time, it was shown that a root-based complex of *R. tianschanicus* L. exhibits pronounced anti-ulcer activity, significantly reducing the number of ulcerative lesions in the gastric mucosa. The anti-ulcer activity index of the complex was 2.1 with prolonged use and 2.3 with prophylactic use.

5. It was shown that the root-based complex of *R. tianschanicus* L. exhibits anti-inflammatory activity on a mouse histamine paw edema model, comparable to the reference drug diclofenac. This is confirmed by a statistically significant ($p \leq 0.05$) reduction in paw mass to $17.94 \pm 1.75\%$, compared to the reference drug at $16.03 \pm 1.56\%$.

6. It was established that the root-based complex of *R. tianschanicus* L. possesses antioxidant properties based on DPPH, ABTS, CUPRAC tests, and the metal chelation method. This is confirmed by a statistically significant ($p \leq 0.05$) reduction in the test indicators: DPPH ($IC_{50} = 8.45 \pm 0.33 \mu\text{g/mL}$), ABTS ($IC_{50} = 5.68 \pm 0.21 \mu\text{g/mL}$), and CUPRAC ($IC_{50} = 7.01 \pm 0.40 \mu\text{g/mL}$).

Approbation of work.

The main provisions of the dissertation are presented in 10 printed works, of which:

1 article in an international scientific publication included in the Scopus database:

4 articles in journals from the list recommended by the Committee for Control in the Sphere of Education and Science of the Committee on Education and Science of the Republic of Kazakhstan:

Publication of research results. The main content of the dissertation was published in 10 printed works, including 1 article in international peer-reviewed journals with impact factor, included in the Scopus (Q1) and Web of Science databases; 4 articles in journals from the list of publications recommended by the Committee for Quality Assurance in Education and Science (CQAES) of the Ministry of Education and Science of the Republic of Kazakhstan for the publication of the main results of scientific activity, 5 theses in the materials of international and republican conferences, of which 1 is foreign.

Structure and scope of work. The dissertation consists of 90 pages of text and introduction, literature reviews, materials and methods, results and discussion, conclusion, 215 bibliographies, 3 appendices, 21 tables, 23 figures.