

CREATION OF TECHNOLOGY AND PHARMACOLOGICAL RESEARCH OF NEW ANTI-HYPOXIC DOSAGE FORMS BASED ON GERANIUM HOLMOVAYA GROWING IN UZBEKISTAN

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ABSTRACT

Acute toxicity, local irritant and cumulative effect of dry extract from the roots and rhizomes of the geranium were studied. The results of pharmacological experiments have shown that the dry extract of geranium hills is low-toxic, does not have local irritating and cumulative properties.

KEYWORDS: *Dry Extract of Geranium Holmovaya, Tablet, Acute Toxicity, Local Irritant Effect, Cumulative Properties, Mucous Membrane of The Gastrointestinal Tract*

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INTRODUCTION

According to the WHO forecast, it is assumed that by 2030 mortality from cardiovascular diseases will amount to 22.3 million people, or 32.7% of all deaths in the world. One of the main dangers of coronary heart disease is the suddenness of manifestation, and about 40% of the population do not even realize that their heart is exhausted from a lack of oxygen. It is 60-75% of the world's population suffer from hypoxia - a lack of oxygen in the blood and tissues, which accompanies almost all diseases of the respiratory and circulatory systems of the body.

The creation of technologies for the production of drugs obtained on the basis of domestic medicinal plants used for hypoxia reduces the share of drugs imported from foreign countries, as well as an increase in the amount of products manufactured at domestic pharmaceutical enterprises.

Hill geranium (*Geranium collinum* Steph.) of the geranium family - Geraniaceae is a perennial herb, widespread in the territory of our republic. The plant contains amino acids, mono- and polysaccharides, vitamin C, organic acids and other substances. Among the listed compounds, tannins are dominant. Their content in

underground organs is more than 20%, in grass at least 14%, i.e. Hill geranium is a polyphenol-producing plant. [1].

Pharmacological studies show that a decoction from the underground organs of geranium hill, without showing side effects on the body, has a pronounced anti-inflammatory and antihypoxic activity and exhibits a noticeable hemostatic and antistress effect [2].

MATERIALS AND METHODS

Methods have been developed for obtaining and standardizing dry extract from the underground part of the hill geranium growing in Uzbekistan.

Dry extracts were obtained by the official methods given in the literature: maceration, repercolation and percolation, the factors influencing the process of obtaining dry extracts were studied: the concentration of the extractant, the degree of grinding of the raw material, the effect of the hydromodule of the process, determination of the drying temperature, and also the results of qualitative and quantitative indicators were studied. dry extract. Each stage is scientifically analyzed, the most optimal method, extractant, hydromodule and degree of grinding of the raw material are selected.

When using the methods of maceration and repercolation, the complexity of the technological process for obtaining a dry extract of geranium was observed, the process was slow, the consumption of the extractant was high, the amount of extractives and tannins was lower than in the dry extract obtained using the percolation method, i.e. the percolation method during the extraction gave more positive results.

A technology was developed for the production of tablets of dry extract of geranium kholmova by the method of wet granulation with the use of excipients according to a scientifically based composition.

To develop a scientifically grounded composition and technology for the production of a solid dosage form - tablets for oral administration, convenient for transportation, dosed, having high productivity, resistant to the external environment, the technological indicators of dry extract of geranium are studied, taking into account the hygroscopic properties of the dry extract for the selection of the species and the amount of excipients used.

Preclinical studies of dry extract of Holmova geranium were carried out, its low toxicity and a single therapeutic dose of 0.1 g were determined.

Experiments on the study of acute toxicity were carried out on 36 white mice weighing 18-22 g, of both sexes [4]. The dry extract in the form of the sum of polyphenolic compounds (tannins) isolated from the underground organs of the geranium holmovaya was dissolved and a 15% solution was prepared, administered orally at a dose of 4000 mg / kg to 9000 mg / kg. Observation of the state of the animals was carried out for 14 days in a vivarium. Control animals were injected with physiological saline in an appropriate volume.

The local irritating effect of dry extract of knoll geranium was studied on 12 rats, weighing 160-180 g. [5]. The studied drug in the amount of 0.5-1 ml in the form of a 1-10% solution was applied to the previously trimmed areas located on the sides, one of which was scarified with a scalpel, and the other intact. The examined skin areas were covered with soft gauze. The skin reaction was recorded 30 minutes after removing the gauze and again 72 hours after that. The results were recorded by the formation of erythema, scab and edema at the site of application of the studied drug.

The study of the cumulative properties of tannins isolated from Holm geranium was carried out by the method of subchronic test in increasing doses with an intermittent mode of administration [4]. The experiments were carried out on 20 rats weighing 140-175 g of both sexes. The initial dose was 200 mg / kg. This dose was administered for 5 days, then every 5 days the dose was increased by 2 times, that is:

1-5 days - 200 mg / kg = 1000 mg / kg

6-10 days - 400 mg / kg = 2000 mg / kg

11-15 days - 800 mg / kg = 4000 mg / kg

16-20 days 1600 mg / kg = 8000 mg / kg

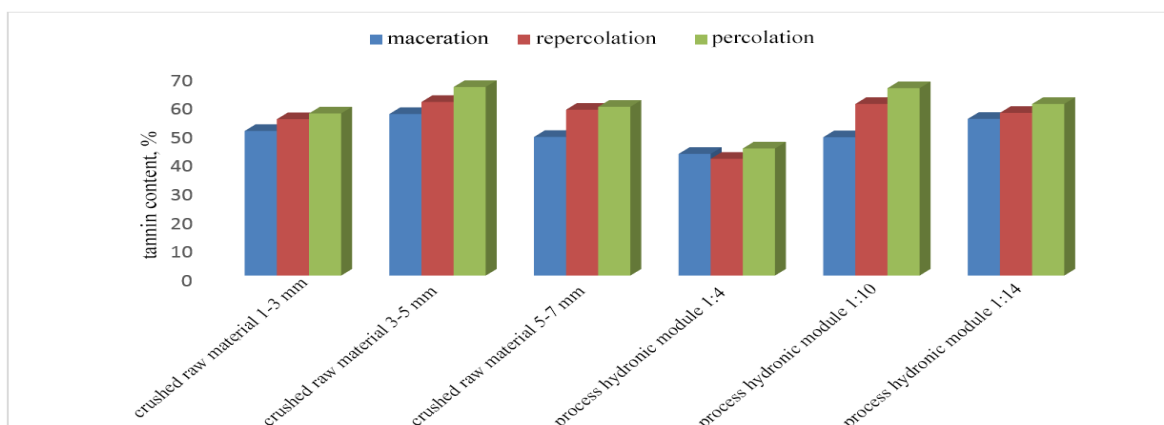
The total dose over 20 days was 15,000 mg / kg.

The animals were observed for 1 month. The condition of the animal was monitored visually, paid attention to the general condition, appetite of the animals and the reaction to external stimulation.

RESULTS AND DISCUSSIONS

When obtaining a dry extract, the completeness of the release of the active substance was greatly influenced by the degree of grinding of the raw material, the degree of grinding was chosen equal to 3-5 mm (65.7%).

The release of tannins was maximum when 40% ethanol was used as an extractant and the process hydromodule was 1:10 (65.3%), and the most optimal method was the percolation method.



Pic.1: Influence of the degree of grinding of raw materials and the hydro module of the process on the release of tannins

In terms of qualitative and quantitative indicators, the dry extract of geranium mound meets the requirements of the General Pharmacopoeia Monograph of the GF XI-edition "Extracts". The amount and standardization of tannins contained in the dry extract of Holm geranium was determined by permanganatometric titration and the content of tannins must be at least 51%. The data obtained are shown in table 1.

Table 1: Results of qualitative and quantitative indicators of dry extract of Holmovaya geranium

Defined indicators	Norm on ND	Results	Determination methods
External view	Hygroscopic powder of brown color, with a peculiar smell, astringent taste	Meets ND requirements	Organoleptic
Authenticity: tannins	1. With ammonium iron alum, the precipitate is black-green. 2. Dark brown precipitate with a solution of lead salts and potassium dichromate	Satisfactorily	Qualitative reaction to tannins
Humidity, %	Should not exceed 5%	4,9	GF XI 2-volume, C. 161.
Heavy metals, %	Should not exceed 0,01%	Less 0,01%	GF XI 2-volume C. 161.
Microbiological purity	In 1 g of the preparation, the total number of aerobic bacteria did not exceed 10 CFU, the total number of fungi was 10 CFU, Escherichia coli bacteria were not observed	Meets ND requirements	Amendment №2, GF XI 2-edition, category 4A
The amount of tannins	Not less 51%	61,65%	Permanganatometric titration

The results of a number of experiments in the preparation of tablets, carried out to select excipients that make up the Heratan tablets: loosening, binding and antifriction substances, their scientifically grounded choice was confirmed by an assessment of the quality of the tablets, as well as to study the technological parameters of the tablet masses of dry extract of Holmovaya geranium were various compositions were prepared by the method of wet granulation using 96% ethyl alcohol as a granulating substance, as well as such auxiliary substances as fillers, disintegrants and antifriction substances

The quality indicators and the results of the quantitative analysis of the Heratan tablets, obtained on the basis of the dry extract of Holmovaya geranium, met the requirements of the general pharmacopoeial monograph "Tablets" of the XI edition of the GF. The data obtained are shown in table 2.

Table 2: Results of quality assessment and quantitative analysis of "Heratan" tablets

Studied indicators	Indicators according to ND requirements	Results
Appearance	Brown, smooth edges, rounded, with a smooth surface	Corresponds
Authenticity: tannins	With ammonium iron alum, the precipitate is black-green.	Corresponds
Diameter, mm	Should be within 2,1-3,3mm	2,5mm
Height to diameter ratio, %	Should be within 30-40%	34%
Average mass and deviations from it g, %	Not less $\pm 7,5\%$	0,162+3,0 0,162-2,8
Decay, min	Up to 15 min	8-10 min
Fracture strength N	Must be at least 30,0 N	55N
Abrasion resistance	97,0-100	98,6
Dissolution, 45 min	Must be at least 75%	86,02
Microbiological purity	Change №2 k GF XI 2-volume, categories 4A	Satisfactorily
Amount of tannins	Should be between 0,051g and 0,065 g	0,0586

In the study of acute toxicity, it was found that in animals that received dry extract of geranium at a dose of 4000; 5000 mg / kg is observed short-term excitements, which after 10-15 minutes go into a state of calm. At a dose of 6000; At 9000 mg / kg, the animals were generally calmed, they gathered in a heap, became inactive, and the muscles of the limbs

relaxed.

During the observation period, 1 out of 6 animals died in the groups of animals where 5000 mg / kg of the drug was injected, and all animals died in the groups of animals where 9000 mg / kg of the drug was administered.

At the end of the experiment, some of the animals died down and the morphological state of the gastric and intestinal mucosa was examined. At the same time, it was revealed that the studied extract of geranium mothballs does not have a negative effect on the gastrointestinal mucosa.

The data obtained are shown in table 3.

Table 3: Determination of acute toxicity (LT-50) with the introduction of peros dry extract of geranium holmova (14-day observation)

Doses mg/kg	Observed effect	%, effect observation	% effect waiting	Difference between observation and expectation	Term for x2	
4000	0/6	0	2,3	5	0,115	$f=6-2=4$ (9.49) $LD_{50}=6300$ $LD_{16}=4900$ $LD_{84}=8850$ $N=5 \times 6=30$ $S=1.32$ $f_{ED50}=1.15$ $NDG=6300:1,15=5478$ $VDG=6300:1,15+7245$ $LD_{50}=6300$ $(5478 \div 7245) \text{mg/kg}$ at $p < 0,05$
5000	1/6	16,7	19	-2,3	0,0031	
6000	2/6	33,3	40	-6,7	0,017	
7000	3/6	50	60	-10	0,035	
8000	5/6	83	78	5	0,016	
9000	6/6	100	84	16	0,15 $0,3361 \times 6 = 2,0166$	

As can be seen from table No. 3, the studied dry extract of mound geranium is relatively low-toxic. The LD50 of the dry extract with a single oral administration in mice is 6300.0 (5478.0 ÷ 7245.2) mg / kg at P <0.05.

The results of the study of the local irritating effect showed that the dry extract of the hill geranium in the studied dose does not have an irritating effect on the skin. Since the ratio between the area captured by signs of inflammation (erythema, edema and redness) on the scarified area and the area on the intact area does not significantly differ (index of primary irritation-1).

The following experiments have shown that the extract of geranium knoll in the indicated concentrations does not cause any reaction from the conjunctiva either after 15 minutes or after 24-48 hours. The state of the conjunctiva of the right eye did not differ from the state of the conjunctiva of the left eye, where water was injected.

Consequently, the dry extract of geranium knoll does not have the ability to cause any local reactions from the skin and mucous membranes.

When studying the cumulative properties of the dry extract of Holmovaya geranium, it was revealed that in the experimental and control groups there were no significant differences in the weight of animals. The mucous membranes and coat of all animals were unchanged. All animals showed satisfactory appetite, all groups consumed the same amount of food and water. Respiration in all groups of animals was the same; diarrhea was not observed in any animal.

When the animals were dissected at the end of the experiment, a normal morphological picture was observed. In

all rats of the experimental and control groups, no visual changes from the gastrointestinal tract and parenchymal organs were detected.

Consequently, the studied dry extract of geranium hill does not have a cumulative effect.

Antihypoxic activity was studied in mice in comparison with the well-known drug "Mildronate". The dry extract under study has a pronounced antihypoxic effect.

CONCLUSIONS

- For the first time, a scientifically substantiated technology for obtaining a dry extract from the roots and rhizomes of hill geranium was developed. At the same time, the influence of the type of the extractant, the hydro module of the process, the degree of grinding of the raw material, the method of obtaining the extraction was studied and a percolation method
- The physicochemical and technological properties, as well as the qualitative and quantitative indicators of the obtained dry extract of the geranium are studied. The content of tannins in the dry extract of Holmovaya geranium was determined by permanganometric titration; it was found that the content of tannins should be at least 51%.
- The practical issues of composition selection, technology development and standardization of tablets based on dry extract of Holmovaya geranium under the conditional name "Heratan", which have anti-inflammatory and antihypoxic effects, have been resolved.
- Preclinical studies of the pharmacological activity of the proposed dry extract of hill geranium were carried out, as a result, they were proposed for use as an anti-inflammatory and antihypoxic agent.
- Dry extract of geranium mound belongs to the group of low-toxic substances and mound does not have a local irritating effect, and also does not accumulate in the body after repeated administration.

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