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AMINO ACID COMPOSITION AND PHARMACOLOGICAL ACTIVITY OF THE PLANT FRITILLARIA SEVERZOVII

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Annotation
This article presents the results of a study on the amino acid composition and biological activity of the Fritillaria severzowii plant extract. The total content of proteins and amino acids in various parts of the plant was determined during the research. Special emphasis was placed on the importance of cysteine and methionine as key components with antioxidant properties. Additionally, it was shown that the alcoholic extract of the plant exhibits hepatoprotective activity and has low toxicity.

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Introduction. The genus Fritillaria L. belongs to the Liliaceae family and includes about 100 species of perennial geophytic plants distributed in the Northern Hemisphere, mainly in temperate zones - from North America, Europe, the Mediterranean region and Central Asia to China and Japan [1]. The species was first described by E. L. Regel in 1868 under the name Sewerzowii Regel. In

1873, the author renamed it Sewerzowii (Regel) Regel. According to modern taxonomy, this species belongs to the subgenus Korolkowia Regel [2-3].

From a morphological point of view, it is a perennial herbaceous plant with a height of 25 to 50 (sometimes up to 70) cm. The stem is erect, smooth, thickened, light green, purple in the lower part and leafless. The leaves, covered with a glaucous bloom, are usually arranged alternately, sometimes opposite in the lower part, semi-stemmed, with pointed tips turning into shortened shoots. The bulb is spherical, yellow, 3-5 cm in diameter [4].

The flowers are drooping, not dense, of two types: the lower ones are bisexual, the upper ones are only staminate. The perianth consists of six free petals, green or reddish-brown, oblong-oval, 1.5-2.5 cm long. There are 6 stamens, shorter than the petals. The ovary is three-celled, with numerous ovules. The plant is found at altitudes from 1000 to 3000 meters in rocky foothills and broad-leaved forests of Kyrgyzstan, Kazakhstan, Tajikistan and Uzbekistan, on sandy-rocky soils in shrub zones [5].

In folk medicine, an infusion made from the roots of this plant is traditionally used to treat liver diseases, including hepatitis. Currently, folk healers also use an infusion of Fritillaria sewerzowii roots to treat diabetes [6].

More than 20 alkaloids were isolated from the above-ground part of the Fritillaria sewerzowii plant collected in the Saryagoch district of the Tashkent region and in the Khamza district of the Fergana region [7-9]. Previous studies examined the content of water-soluble vitamins, flavonoids, polysaccharides, macro- and microelements in the root and above-ground part of the plant collected in the Angren mountains of the Tashkent region [10-13].

The objects of this study were the organs of a plant collected in May 2023 in the vicinity of the village of Ertosh, Angren district, Tashkent region, Republic of Uzbekistan. The aim of the work was to study the amino acid composition, as well as the biological activity of the plant extract.

Experimental part.

The quantitative protein content in air-dried samples of Fritillariasewerzowii was determined by the Kjeldahl method. The protein content in various plant organs was: in bulbs - 7.78%, in shoots - 3.04%, in leaves - 8.68%, in flowers - 13.93% [14].

In order to assess the quality of the isolated protein from Fritillaria sewerzowii, an analysis of the amino acid composition was carried out. The amino acid composition was determined by hydrolyzing the protein with 20% trichloroacetic acid at a temperature of 160°C for 70 minutes under vacuum. To obtain derivatives of free amino acids, a reaction with phenyl isothiocyanate was used according to the method of Steven A.C., as a result of which FTC (phenylthiocarbamyl) derivatives were obtained. Identification of amino acids was carried out by HPLC (high-performance liquid chromatography) on an Agilent Technologies 1200 chromatograph [15-16]. The results of the studies are presented in Table 1.

Teble 1. Amino acid composition of proteins in Fritillaria sewerzowii organs, mg/g

№	Amino acids	Bulbs	Stem	Leaves	Flowers
1.	Asp acid	0,02	0,27	0,29	1,33
2.	Glu acid	0,52	0,30	0,44	0,72
3.	Ser	0,39	0,40	0,17	0,35
4.	Gly	0,08	0,08	0,10	0,30
5.	Asp	0,16	0,15	0,21	0,60
6.	Glu	0,03	0,83	0,11	0,78
7.	Cys	0	1,61	3,35	1,69
8.	Thr*	0,09	0,20	1,14	0,96
9.	Arg	0,05	0,07	0,31	2,69
10.	Ala	0,23	0,36	0,70	0,73
11.	Pro	0,17	0,40	0,75	1,06
12.	Tyr	0,09	0,24	0,86	0,78
13.	Val*	0,05	0,17	0,87	0,74

14.	Met*	0,64	0,23	1,08	1,23
15.	His	0,04	0,04	0,44	0,12
16.	Ile*	0,09	0,10	0,38	0,27
17.	Leu*	0,23	0,27	0,97	0,38
18.	Trp*	0,18	0,06	0,48	0,46
19.	Phe*	0,04	0,06	0,15	0,13
20.	Lys*	0,02	0,013	0,11	0,43
21.	Vsego	**3,16**	**5,85**	**12,91**	**15,73**

* Essential amino acids

Results and discussion

Based on the results of the study, it was found that the greatest amount of amino acids is contained in the flowers of Fritillaria sewerzowii, while their content is the lowest in the bulbs. Among the identified amino acids, the largest amount is one of the essential ones - cysteine. It is known that cysteine helps improve digestion, participates in transamination reactions, helps neutralize a number of toxic substances and protects the body from the damaging effects of radiation. It is one of the most powerful natural antioxidants[17].

Amino acids, which are part of proteins, were found in all four organs of the plant (see Table 1). Their greatest quantity was recorded in flowers, the least - in bulbs. Cysteine was found in leaves, stems and flowers, but was absent in bulbs.

Among the essential amino acids in all plant organs, methionine is quantitatively predominant. These two amino acids - methionine and cysteine - are genetically linked: methionine is a precursor of cysteine, which, in turn, is part of glutathione - an important participant in detoxification processes. Methionine has a lipotropic effect, participates in the synthesis of choline and phospholipids, promotes the production of adrenaline and creatine, activates the action of vitamins, hormones and enzymes. It is used in the treatment of toxic liver damage and in oncological studies of the brain using methionine labeled with the radioactive isotope 14C [18].

Analysis of the amino acid composition shows that the flowers contain a significant predominance of arginine, proline, methionine, cysteine and aspartic acid. Given the above, it can be concluded that moderate consumption of the plant bulbs for medicinal and especially prophylactic purposes can contribute to liver health and improve the general condition of the body. It has also been established that other organs of the plant contain significant amounts of amino acids such as cysteine, proline, methionine, threonine and leucine.

As stated earlier, Fritillaria sewerzowii bulbs are traditionally used in folk medicine to treat hepatitis. In order to study the hepatoprotective properties of the bulb extract, studies were conducted jointly with pharmacologists from the Institute of Plant Chemistry of the Academy of Sciences of the Republic of Uzbekistan.

The experiments were carried out on outbred white mice under standard vivarium conditions in accordance with the International Convention for the Protection of Vertebrate Animals used for Experimental and Scientific Purposes (Strasbourg, 1986) and the recommendations of the European Convention [19].

To study the acute toxicity and hepatoprotective activity, 2050 g of Fritillaria sewerzowii bulbs were extracted with 90% ethanol. The resulting alcohol extract was treated with chloroform to isolate the sum of neutral substances.

Acute toxicity was assessed on white male mice (weight 18–21 g). After intragastric administration (through an atraumatic metal tube) of doses of the substance from 100 to 800 mg/kg to six mice at each dose, their condition was observed for 14 days.

The fraction obtained from the roots of the plant using ethyl acetate, at a dosage of 100.0–200.0 mg/kg, did not cause significant changes in the general condition and behavior of animals during a 14-day observation.

When doses of 300.0–600.0 mg/kg were administered, slight depression of the condition and a decrease in motor activity were observed after 5–7 minutes for 60–80 minutes. At the same time, the reaction to sound and pain stimuli was maintained. No fatal cases were recorded.

Increasing the dose to 650 mg/kg resulted in an increase in the above-mentioned signs of intoxication, the reaction to external stimuli was maintained, the animals were trembling, no fatal cases were noted.

At a dose of 700.0 mg/kg, one of six animals died. At a dose of 725.0 mg/kg - in two of six. When the dose was increased to 750 mg/kg, all animals had tremors, some had convulsions, and three deaths were recorded. At a dose of 775.0 mg/kg, four of six animals died. At a dose of 800.0 mg/kg, five of six died. The administration of a dose of 825.0 mg/kg caused the death of 100% of the experimental animals within 5-10 minutes (Table 2 - will be provided if necessary).

Table 2. Acute toxicity of the sum of phenolic compounds of Fritillaria severzowii

Name of substance	**Dose, mg/kg**	**Animal death/survival**	**LD_{50}, mg/kg**
Fritillariaseverzowii	100.0	0 / 6	**736,0** (566,0 ± 833,2)
	200.0	0 / 6	
	300.0	0 / 6	
	400.0	0 / 6	
	500.0	0 / 6	
	600.0	0 / 6	
	700.0	1 / 5	
	725.0	2 / 4	
	740.0	3 / 3	
	775.0	4 / 2	
	800.0	5 / 1	
	825.0	6 / 0	

The median lethal dose (LD50) of the substances was determined using the Lichfield and Wilcoxon method [20]. When the test substance was administered orally, the median lethal dose (LD50) was 736.0 mg/kg (566.0±833.2). Based on the results obtained, it can be concluded that the ethyl acetate fraction of secondary metabolites of the Fritillaria severzowi plant, according to the GOST 12.1.007-76 standard, belongs to the group of low-toxic substances (IV class of acute toxicity).

The hepatoprotective activity of secondary metabolites of the ethyl acetate fraction isolated from the root of the Fritillaria severzowi plant was studied in male rats with an initial body weight of 150–170 g in a model of chronic toxic hepatitis using carbon tetrachloride (CCl_4).

Experiments on animals were carried out in accordance with international ethical standards (Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes).

CCl_4 was administered subcutaneously as a 50% oil solution twice a week for one month at a dose of 0.12 ml/100 g body weight [21]. Starting from the 21st day of the experiment, simultaneously with the administration of CCl_4, the rats of the first and second groups were orally administered the ethyl acetate fraction at doses of 10 and 25 mg/kg, respectively, and the rats of the third group received the reference drug phosphogliv at a dose of 50 mg/kg per day. After 7 days, under light ether anesthesia, the animals were euthanized, after which blood serum was collected for biochemical studies.

The therapeutic effect of the studied fractions was assessed based on the dynamics of the activity of alanine and aspartate aminotransferases (ALT and AST), alkaline phosphatase (ALP), the content of total protein and albumin, as well as the level of total and indirect bilirubin in the blood serum.

The analyses were carried out using standard methods using the CYANSmart device (Belgium) and CYPRESS reagent kits (Belgium). All obtained data were subjected to statistical processing using the Student t-test.

The results of the experiment showed that with prolonged administration of CCl_4, even in relatively small doses, a gradual development of pathological changes in the metabolic and functional state of the liver is observed, characteristic of the formation of chronic hepatitis.

Increased hepatocyte cytolysis was confirmed by increased activity of ALT and AST enzymes in the blood serum. The development of cholestasis was manifested by increased activity of alkaline phosphatase, and progressive hyperbilirubinemia was also observed. At the same time, the level of total protein in the blood serum decreased significantly, mainly due to a decrease in albumin.

As can be seen from the table presented, all of the indicated negative changes were so pronounced by the time the toxicant administration was completed that even a week after the CCl_4 administration was stopped, only a weak and statistically insignificant tendency toward normalization of the indicators was observed (and not in all cases).

Against this background, the introduction of the studied fraction, as well as phosphogliv, significantly prevented cytolytic-cholestatic liver damage, contributed to the preservation of protein-synthetic and glycogen-synthesizing functions of the liver, reduced the degree of fatty degeneration, and improved pigment metabolism.

Moreover, with conti+nued administration of the studied fraction and phosphogliv for two weeks after discontinuation of CCl_4, in the first case, almost complete normalization of the metabolic and functional state of the liver was observed.

Table 3. The effect of secondary metabolites of the ethyl acetate fraction of Fritillaria severzowi and the drug phosphogliv on the dynamics of changes in some biochemical blood parameters in rats with chronic hepatitis caused by carbon tetrachloride (M±m, n=6)

Experimental conditions	**Intact animals**	**CCl_4 (control) 28 days**	**CCl_4 + Fritillaria severzowi (25 mg/kg) 28+7 days**	**CCl_4 + Fritillaria severzowi (50 mg/kg) 28+7 days**	**CCl_4 + Phosphogliv 28+7 days**
ALT, µmol/l	1,06±0,04	2,72±0,15*	2,10±0,12**	2,21±0,10**	2,28±0,14**
AST, µmol/l	1,57±0,06	2,26±0,12*	1,78±0,10	1,78±0,14	1,88±0,12
Alkaline phosphatase (ALP), U/L	174±6,4	231±11,4*	190±10,8	196±9,6*	194±11,0*
Total bilirubin, µmol/l	6,35±0,20	14,32±0,36*	10,12±0,38**	10,92±0,32	10,38±0,32**
Indirect bilirubin, µmol/l	1,96±0,08	6,27±0,15*	4,22±0,20**	4,18±0,12**	4,90±0,26
Total protein, g%	7,6±0,14	6,3±0,13	7,2±0,13	6,8±0,09*	7,0±0,20
Albumin, g%	2,91±0,06	2,54±0,06	2,89±0,10**	2,66±0,12	2,74±0,08**

Note.

* — significant compared to intact animals;

** — significant compared to the control group ($p<0.05$).

As can be seen from Table 3, the hepatocyte cytolysis syndrome, assessed by the activity of the marker enzymes ALT and AST, decreased with the administration of the studied fraction at doses of 25 and 50 mg/kg for 7 days compared to the control values: ALT activity decreased by 22.8–19.0%, and AST by 23.8–21.2%. For comparison, phosphogliv reduced these values by 16.2–16.8%.

Another indicator of the effectiveness of the hepatoprotective action of the studied fraction in chronic hepatitis caused by CCl_4 was the level of alkaline phosphatase (AP). Compared with phosphogliv, the following results were obtained: when the fraction was administered for 7 days, the activity of AP decreased by 17.7–15.2% compared to the control, while phosphogliv provided a decrease of 16.1%.

Similar results were recorded when assessing hyperbilirubinemia: both total and indirect bilirubin. Thus, 28-day administration of the toxicant led to a decrease in the levels of total protein and albumin in the blood serum by 17.1% and 12.7%, respectively, compared with the values in healthy animals. The fraction (at doses of 25–50 mg/kg) and phosphogliv increased the level of total protein by 14.3–8.0% and 11.0%, respectively, compared to the control. Both substances also increased the albumin concentration, with the efficiency of their action being 13.7–4.7% for the fraction and 7.9% for phosphogliv.

Thus, the results of the study showed that in chronic hepatitis, the fraction of secondary metabolites of Fritillaria severzowi at a dose of 25 mg/kg has a more pronounced hepatoprotective effect compared to phosphogliv. This is due to its ability to optimize the metabolism of liver cells and, as a result, normalize the general condition of the hepatobiliary system.

Conclusion. Thus, based on the analysis of literary sources and the results of our own experiments with samples of the Fritillaria severzowi plant collected from a new growing site, the total protein content in the plant organs was determined. A quantitative determination of amino acids obtained by hydrolysis of proteins in four organs of the Fritillaria severzowi plant was carried out. It was established that the main components of the amino acid fraction are related sulfur-containing substances - cysteine and methionine, which have antioxidant properties either independently or due to their derivatives.

Alcohol extract of dry plant material Fritillaria severzowi, according to the results of pharmacological tests, belongs to the group of low-toxic substances and exhibits hepatoprotective activity. As a result of the conducted studies, it can be concluded that the bulbs and flowers of this plant are promising for use in the prevention and treatment of liver diseases.

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