POSSIBILITIES OF GOUTWEED USE IN THE COMPOSITION OF THE FUNCTIONAL FOODS FOR THE PROPHYLAXIS OF URIC ACID METABOLISM DISORDERS

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Innovative processes in the development of the food industry in Ukraine, related to the introduction of the world's achievements in science, technique and technology, determine the need of the appropriate training of engineering specialists. In the market conditions of the development of food enterprises, the activity of the manufacturing engineer is related to the development and introduction of new types of food products into the production and the expansion of their assortment, the search for innovative food technologies, the development and introduction of equipment that meets the current conditions of resource, energy saving, safety and quality.

The collective monograph scholars of the four universities of Kharkov is intended for specialists in the field of food engineering.The monograph outlines the conceptual framework for preparing future engineers-technologists in the food industry for creative professional activities.

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PART 4. THE POSSIBILITIES OF GOUTWEED (Aegopodium podagraria L.) USE IN THE COMPOSITION OF THE FUNCTIONAL FOODS FOR THE PROPHYLAXIS OF URIC ACID METABOLISM DISORDERS

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Abstract: The data concerning the chemical composition of the promising herbal raw material – goutweed (*Aegopodium podagraria L., Apiaceae)* aerial part are summarized. Biological activity of the preparations obtained from this raw material is elucidated with the special emphasis on the possibilities of uric acid metabolism regulation. The disorders of the latter, mostly hyperuricemia, are not limited to the risk of gout and are involved into the development of hypertension, insulin resistance, metabolic syndrome and other states. The ways for hyperuricemia correction need further improvement and the use of the substances of herbal origin including the functional products seems to be promising. In this context the possibilities of the development of snack bars containing goutweed aerial part powder are discussed.

Keywords: goutweed (Aegopodium podagraria L.), herbal raw material, uric acid metabolism, functional foods, snack bars.

Herbal products attract much attention nowadays, both in the field of drug development and in the region of functional foods and dietary supplements production. Substances of herbal origin are able to exert favourable pharmacological activity (their complex composition may stipulate synergistic effects that explain the efficacy of such drugs despite the moderate activity and/or concentration of the individual components). On the other hand, toxicity is inherent in all of the substances independently of their origin, and a significant credit of trust, which the herbal products have gained, does not always correspond to reality. Disadvantageous interactions of the herbal substanses with the drugs or food simultaneously taken are also possible. Thus, the verification of the efficacy and safety of the herbal products is crucial [1–3].

4.1. Aegopodium podagraria L. (goutweed) and its chemical composition

Among the plants promising for the development both of the drugs and functional foods or dietary supplements, *Aegopodium podagraria L.* (goutweed) attracts much attention. It is a perennial plant of the Apiaceae family indigenous to Europe, Siberia, the Caucasus, Kazakhstan and Central Asia mountainous regions and has been naturalized in North America and Australia. Goutweed is widely used in traditional medicine and consumed as vegetable and as fodder plant [4–9].

The plant is ubiquitous and this herbal raw material is available for drugs and dietary supplements manufacturing [3,8].

The technology of water extract and the tincture obtaining from goutweed aerial part in accordance with the requirements of State Pharmacopoeia of Ukraine was described previously [10,11].

Studies of the nutrient content of goutweed aerial part confirmed its high nutritional value. In the field of the functional foods development, the technology of the combined meat products containing goutweed was developed, which allows increasing the content of vitamins, minerals, flavonioids, and fiber. The feasibility of the processes of the raw material harvesting, drying, preserving was also estimated and the corresponding guidelines and standarts were proposed [12].

Phytochemical and pharmacological studies of goutweed have intensified recently. Hydroxycinnamic acids, flavonoids, coumarins, polyacetylene compounds, essential oil components, micro- and macroelements are present in goutweed aerial part. The capillary electrophoresis method was applied to establishing electrophoretic fingerprints of leaves and stems of *Aegopodium podagraria L.* [13]. The procedures of hydroxycinnamic acids quantitative assay in goutweed aerial part (or leaves and flowers) were described [14,15], and various chromatographic methods were proposed for the analysis of this raw material as well as preparations obtained from it [13, 15].

The data concerning the chemical composition of *Aegopodium podagraria L.* aerial part are summarized in Table 4.1.

Hydroxycinnamic acids and flavonoids, together with the components of the protein polysaccharide complex, are believed to mediate biological activity of goutweed aerial part to a great extent [5, 15, 30, 31].

4.2. The data available on goutweed aerial part preparations and their components influence on the uric acid metabolism

Gout is the disease known from the ancient times. It is one of the most common manifestations of the purine metabolism disturbances, with the increase in uric acid blood concentration (hyperuricemia) as the main pathological mechanism. Nowadays there is a significant increases in gout prevalence (up to 3–6% of the general population, and, in some countries, up to 10%). Asymptomatic hyperuricemia is especially widespread in the modern world, its prevalence is estimated to be 10–20% of adults in industrial countries. The negative impact of hyperuricemia is not limited to the risk of gout development, as it is associated with hypertension, insulin resistance, metabolic syndrome and other states. Hyperuricemia is interelated with the pathological changes in the vascular wall and kidneys with the numerous vicious circles being formed. Besides, hyperuricemia may develop as a side effect of diuretics and other drugs [32–34]. The ways for its correction need further improvement and there are possibilities for the succesful use of the substances of herbal origin.

Table 4.1

The chemical composition of *Aegopodium podagraria L.* aerial part

Leaves/aerial part	Flowers/inflorescence	References
1	2	3
Phenolic compounds		
Hydroxycinnamic acids and their derivatives		
Caffeic acid, ferulic acid, trans-cinnamic acid, chlorogenic acids	Caffeic acid, chlorogenic acids	[14–18]
Coumarins		
Umbelliferone, aesculin, aesculetin, scopoletin, coumarin, angelicin, bergapten, xanthotoxin	–	[17–19]
Flavonoids		
Quercetin, kaempferol, rutin, quercetin ramnozide, hyperoside, isoquersitin, buplerin	Quercetin, kaempferol, trifolin, kaempferol biglucoside	[16–18,20], own data
Vitamins		
Ascorbic acid, carotenoids	–	[17,18,21]
Free amino acids		
Aspartic acid, threonine, serine, glutamine, proline, glycine, alanine, valine, methionine, isoleucine, leucine, tyrosine, arginine phenylalanine, histidine	–	own data
Organic acids		
Malic acid, citric acid	–	[17,18]
Fatty acids		
Palmitic, oleic, linoleic, linolenic	Lauric, palmitic, hexadecadienic, hexadecatrienic, stearic, oleic, linoleic, linolenic, arachidic	[22]
Carbohydrates		
Glucose, galactose, xylose, rhamnose, fructose, arabinose, umbelliferose	Glucose, fructose, umbelliferose	[16,17,20]
Components of essential oil		
α-caryophyllene, limonene, β- phellandrene etc.	β-farnesene, trans-α-bergamotene, α-farnesene etc.	[13,23,24], own data
Cyclitols		
Scylite, glucinol	–	[17,20,25]
Other compounds		
Choline, polyacetylene compounds		[26,27]
Chlorophylls, β-sitosterol	–	[17,20,25]
Macro- and microelements		
K, Ca, Mg, Na, Si, P, Fe, Cu, Mn, Mo etc.		[13,28,29]

The Latin species name was given to goutweed by Linnaeus in accordance with its use in gout and the diseases with similar symptomatology, that was traditional in European folk and monastic medicine [6,35]. The expediency of this approach has been confirmed by pharmacological research. Hypouricemic and uricosuric action was established for preparations obtained from *Aegopodium podagraria L.* aerial part, the data are summarized in Table 4.2. In addition to the influence on uric acid metabolism that is principal in gout and hyperuricemia, goutweed extract and the tincture suppress inflammation (on the model of carrageenin-induced rat paw oedema) [36].

Table 4.2

Summarised data of the experimental studies elucidating goutweed aerial part preparations influence on uric acid metabolism

Model	Preparation, dose	Effects	Reference
1	2	3	4
Intact rats	Aerial part water extract, 100 mg/kg and 1 g/kg	Unchanged renal excretion under the conditions of the water-loading test (after course administration of the extract for 3–4 days) and under the conditions of spontaneous diuresis (afteradministration of the extract for 3–4 days or 10 days)	[36,37]
	Aerial part tincture, 1 ml/kg and 5 ml/kg	Dose-dependent diuretic and uricosuric action under the conditions of spontaneous diuresis (after course administration of the tincture at a dose of 5 ml/kg for 3–4 days, if the course lasts 10 days, uric acid excretion decreases that may be associated with the possible enhancement of the inhibitory influence on xanthine oxidase, as well as with transitory changes in the renal transport	
Rats with oxonate-induced hyperuricemia	Aerial part water extract, 1 g/kg; aerial part tincture, 1 ml/kg and 5 ml/kg	Hypouricemic action (all preparations), the extract increases uric acid excretion, the tincture at a high dose tends to such an effect, while the tincture at a low dose reduces it, similar to allopurinol	[36]
Intact mice	Leaves water extract, 1 g/kg; leaves tincture, 1 ml/kg and 5 ml/kg; flavonoid trifolin, 50 mg/kg	Dose-dependent hypouricemic action associated with xanthine oxidase inhibition (after course administration for 6-7 days)	[31]

continuation of table 4.2

1	2	3	4
Mice with oxonate-induced hyperuricemia	Leaves water extract, 1 g/kg; leaves tincture, 1 ml/kg and 5 ml/kg; flowers water extract, 1 g/kg; flowers tincture, 1 ml/kg and 5 ml/kg; flowers essential oil, 1 mg/kg; flavonoid trifolin, 50 mg/kg, course administration for 6-7 days	Hypouricemic action (all preparations). Hypouricemic action of trifolin, leaves tincture (5 ml/kg) is mainly due to xanthine oxidase inhibition, under the influence of flowers tincture (1 ml/kg) it's realized by uric acid excretion increasing. The effect of leaves tincture (1 ml/kg), flowers tincture (5 ml/kg), leaves extract, flowers extract, leaves protein-polysaccharide complex and flowers essential oil combines these mechanisms	[31]
Alloxan-induced diabetic mice	Aerial part tincture, 1 ml/kg, course administration for 3 weeks	Partial restoration of uricemia, significantly decreased in diabetic mice (3 weeks after diabetes induction)	[38]
Rats receiving excess fructose combined with hydrochloro-thiazide	Aerial part water extract, 1 g/kg, course administration for 10 weeks	Hypouricemic effect (10 weeks after model induction), uric acid excretion tends to the increase under the conditions of spontaneous diuresis and remains unchanged in water-loading test	[39,40]
Rats receiving a single dose of ethanol (9 g/kg intragastri-cally)	Aerial part water extract, 100 mg/kg; 1 g/kg, and tincture, 1 and 5 ml/kg, prophylacti-cally for 7 days	The absence of unfavourable shifts in uricemia	[41]
Rats receiving dexamethasone (5 mg/kg subcutaneously for 5 days)	Tincture, 1 ml/kg for 5 days (per se or combined with metfor-min, 50 mg/kg)	Uricemia remains unchanged in all groups, the tincture, in contrast to metformin, decreases uric acid excretion in water-loading test	[42]

Antiinflammatory effect is also verified in vitro and partially attributed to polyacetylene falcarindiol possessing marked COX-1 inhibitory activity [27]. Goutweed tincture at the effective antiinflammatory dose also increases erythrocyte osmotic fragility [36] and positive membranotropic action as well as counteraction to the oxidative stress may partially facilitate inflammation suppression.

4.3. Possibilities of the development of the functional product containing goutweed aerial part powder

Among the functional products snack bars attract much attention, not only as an energy and protein source needed in intensive physical work [43], but as a possibility for metabolism normalization through the different mechanisms [44–47].

As discussed above, uric acid metabolism disorders – gout and asymptomatic hyperuricemia – are wide-spread among the modern people, while the numbers of functional foods for such subjects are limited. There was a need to combine goutweed raw material (dry powder of aerial part) with other acceptable components. It is well known that cherries (*Cerasus vulgaris Mill.*) exert beneficial effects on purine metabolism [48,49]. Common bilberry (*Vaccinium myrtillus L.*) and pumpkin (*Cucurbita pepo L.*) are also generally appreciated for numerous health benefits [50,51]. Valuable functional properties together with the nutritional values are inherent in sunflower (*Helianthus annuus L.*) seeds texturized defatted flour, which is abundant as a by-product of oil making. This substance attracts much attention now as a component of functional foods with numerous benefits [52, 53].

Three compositions for snack bars manufacturing were developed, as shown in Tables 4.3.–4.5.

At the next stage of the study the influence of the compositions for snack bar on uric acid metabolism was determined in the intact rats after course administration.

Noninbred albino rats breeded in the Central Scientific-Research Laboratory of National University of Pharmacy (Ukraine) were used. Male rats were housed in a well-ventilated animal room at a controlled temperature and relative humidity, on a natural light-dark cycle. Food and water were supplied ad libitum. All the experimental protocols were in accordance with "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."

The doses of the compositions for snack bar were estimated proceeding from the assumption that 2 bars per day (60 g) are used by a person with 70 kg weight. The dose for rats was calculated using the interspecies ratios for dose conversion according to [54] and it equaled 5 g/kg. In the study of the effects of composition for snack bar №1 ("cherry") the dose increased twofold was also used.

Table 4.3

The composition for snack bar №1 ("cherry")

Component	Content, g	Relative contents
Oat flakes	1,74	0,109
Dried cherries	9,75	0,613
Heat-treated defatted sunflower seeds (grains)	2,1	0,132
Dried apples	2,1	0,132
Dried plums	2	0,126
Dry powder of goutweed aerial part	0,885	0,05
In total	15900	1000

Table 4.4

The composition for snack bar №2 ("bilberry")

Component	Content, g	Relative contents
Oat flakes	1,74	0,109
Dried bilberries	1,75	0,110
Dried pumpkins	6,75	0,503
Heat-treated sunflower seeds (grains)	2,1	0,132
Dried apples	2,1	0,132
Dried plums	2	0,126
Dry powder of goutweed aerial part	0,885	0,05
In total	15900	1000

Table 4.5

The composition for snack bar №3 ("pumpkin")

Component	Content, g	Relative contents
Oat flakes	1,74	0,109
Dried cherries	1,75	0,110
Dried pumpkins	6,75	0,503
Heat-treated sunflower seeds (grains)	2,1	0,132
Dried apples	2,1	0,132
Dried plums	2	0,126
Dry powder of goutweed aerial part	0,885	0,05
In total	15900	1000

Snack bars compositions were given to the rats one hour before the feeding. In the preliminary observations it was established that the animals willingly consumed them and this was observed during the whole period of the studies.

In the first series of the experiment the rats were randomly assigned to 3 groups: intact control (n=9) and the animals receiving the composition for snack bar №2 ("bilberry," n=7) and the composition for the snack bar №3 ("pumpkin," n=6) at doses of 5 g/kg.

In the second series of the experiment the rats were randomly assigned to 3 groups: intact control (n=9) and the animals receiving the composition for snack bar №1 ("cherry") at doses of 5 g/kg (n=9) and 10 g/kg (n=6).

On day 16, the water loading was given to the animals (after an overnight fast) at a rate of 3% of the body weight (the rats were previously adapted to the conditions of the experiment). After that the urine was collected in the metabolic cages for 2 h. Blood samples were obtained from a cut at the tip tail, plasma was obtained by the immediate centrifugation (the anticoagulant heparin in vitro), and uric acid level was measured by uricase method. The uric acid concentration was measured in urine using the reaction with phosphotungstic reagent. Excretion for 2 h was calculated.

On days 18–19, the excretory renal function was analyzed under the conditions of the spontaneous diuresis. The animals were previously adapted to the conditions of the experiment. Then the urine was collected in the individual metabolic cages for 24 hours with free access to tap water (the last portion of the bars was given 1 hour before the placing of the animals into the metabolic cages). The uric acid concentration was measured as stated above and excretion for 24 h was calculated.

Concentrations of metabolites in urine are devoided of homeostatic significance, still uric acid concentration in urine are also presented considering their importance for uro/nephrolithiasis development.

Commercially-available kits from Filisit-Diagnostika (Ukraine) were used for biochemical assays.

Medians, 25% and 75% percentiles (upper and lower quartiles) were calculated as recommended for biomedical research. The traditionally used arithmetic means and their standard errors (M±m) are also given. The comparison of the central tendencies of independent samples was performed by the criterion of Mann-Whitney U.

Results. As can be seen in Figure 4.1, the compositions №2 and №3 at a dose of 5 g/kg did not change the uric acid level in blood, while composition 1 at a similar dose exerted a significant hypouricemic effect (Figure 4.2). The increment in the dose led to the elimination of the effect. Proceeding from the content of the herbal components, it can be supposed that a hypouricemic effect can be attributed to the components of cherry [49, 55] intensified by the other components (especailly those containing chlorogenic acid as it inhibits xanthine oxidase, the same effect is also inherent in its metabolites caffeic and ferulic acids [56,57]).

The further studies have confirmed the absence of the involment of the renal mechanisms into the hypouricemic effect of the investigated composition №1 in terms of the experiment (Figures 4.3–4.4). The renal excretion remained unchanged under both conditions of the kidney functioning. Despite somewhat decreased diuresis in rats receiving the studied composition at a low dose, uric acid concentration in urine was only slightly elevated. In spontaneous diuresis all the values did not undergo changes.

As can be seen in Figurei 14.5–4.6, the compositions №2 and №3 at a dose of 5 g/kg did not change all the studied parameters of renal uric acid excretion. They also did not influence on diuresis. Other favourable metabolic effect are possible for these compositions and further studies are expedient.

Conclusions

Thus, the investigated composition №1 after 16 days of administration at a dose of 5 g/kg (corresponding to the 60 g dose for a person with 70 kg body weight) causes statistically significant hypouricemic effect in rats. This effect is dose-dependent and is not evident against the background of the dose of 10 g/kg. The mechanism of action is not connected with the changes in renal excretion of uric acid and worth further investigation. The investigated compositions №2 and №3 demonstrate neutrality in regard to the purine metabolism.

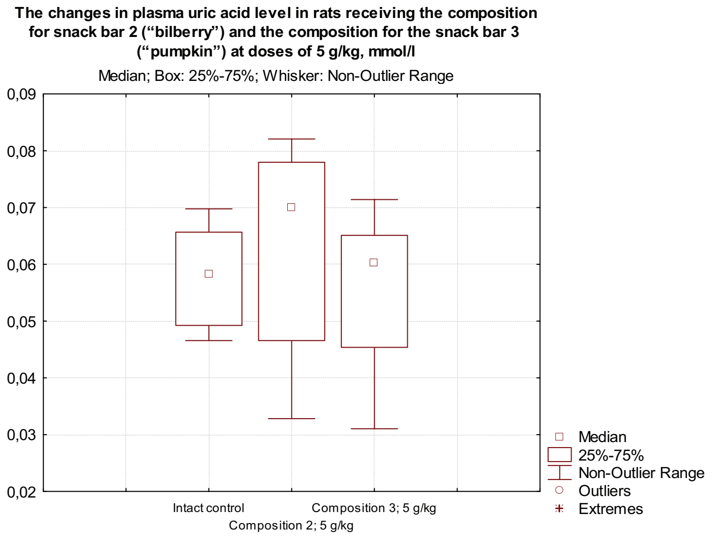

Figure 4.1 – Plasma uric acid levels in rats receiving the composition for snack bar 2 (“bilberry”) and the composition for the snack bar 3 (“pumpkin”) at doses of 5 g/kg, mmol/l

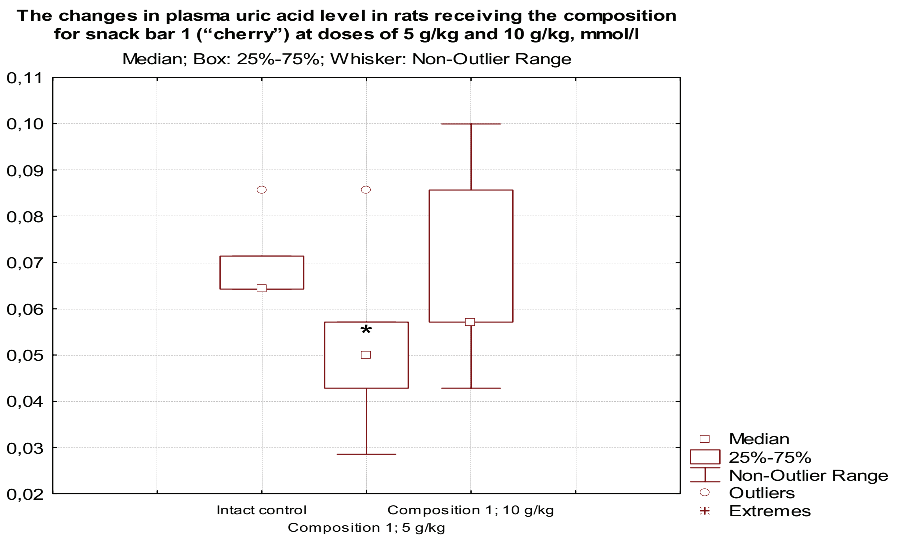

Figure 4.2 – Plasma uric acid levels in rats receiving the composition for snack bar 1 (“cherry”) at doses of 5 g/kg and 10 g/kg, mmol/l

Note. * – $p<0.05$ compared to intact control

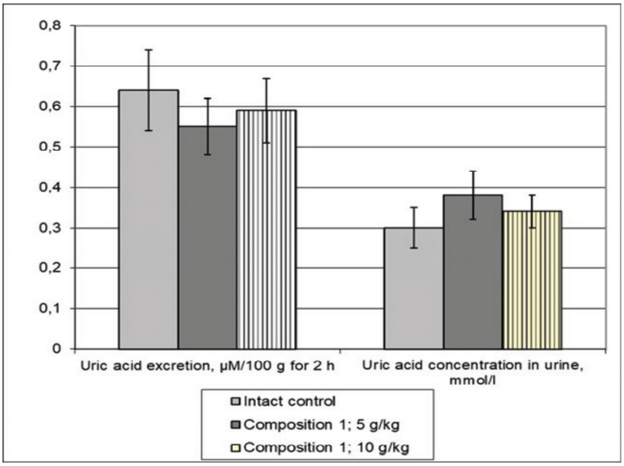

Figure 4.3 – Renal uric acid excretion under the conditions of water loading in rats receiving the composition for snack bar 1 (“cherry”) at doses of 5 g/kg and 10 g/kg

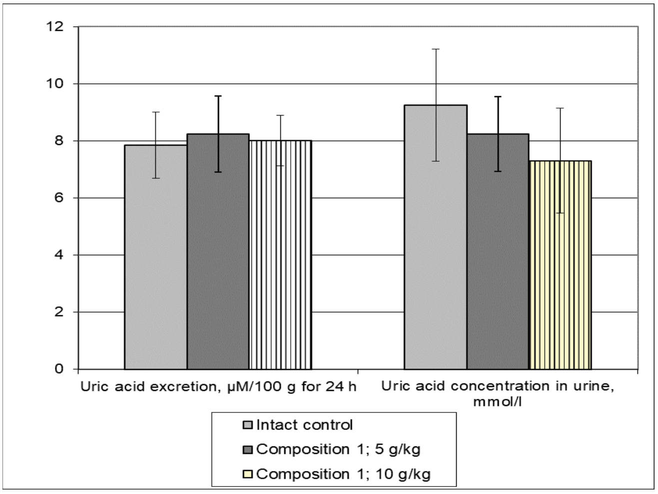

Figure 4.4 – Renal uric acid excretion under the conditions of spontaneous diuresis in rats receiving the composition for snack bar 1 (“cherry”) at doses of 5 g/kg and 10 g/kg

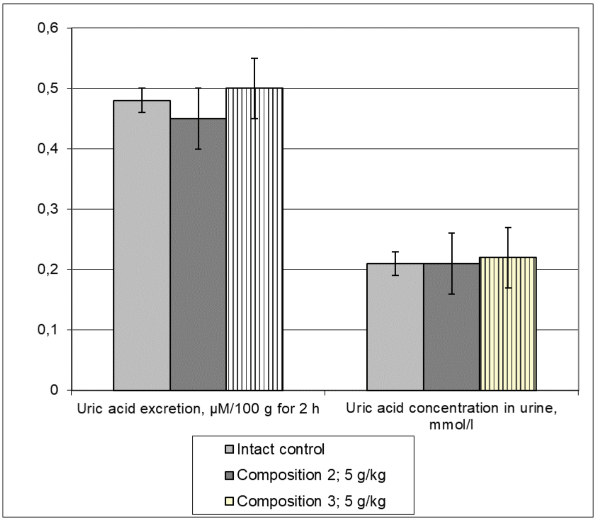

Figure 4.5 – Renal uric acid excretion under the conditions of water loading in rats receiving the composition for snack bar 2 ("bilberry") and the composition for the snack bar 3 ("pumpkin") at doses of 5 g/kg

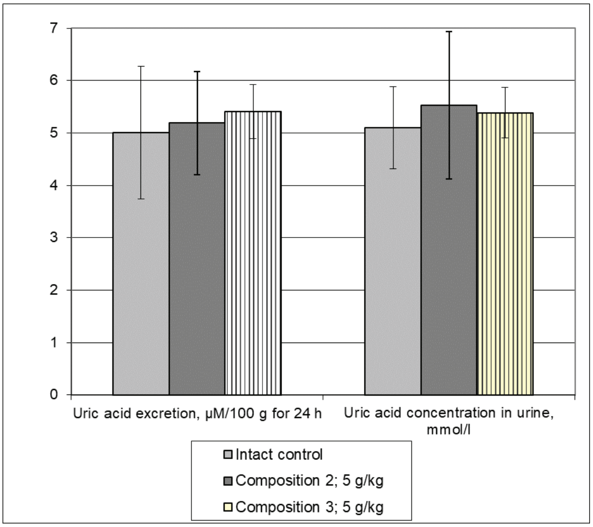

Figure 4.6 – Renal uric acid excretion under the conditions of spontaneous diuresis in rats receiving the composition for snack bar 2 ("bilberry") and the composition for the snack bar 3 ("pumpkin") at doses of 5 g/kg