# To the pharmacology of "St. John's herb" (St. John's wort - Hypericum perforatum) O.D. Barnaulov

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Pharmacological properties of St. John's wort (Hypericum perforatum).

The third report: The comparative estimation of gastroprotective properties Hypericum perforatum and Hypericum quandrangulum

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### **SUMMARY**

The antidestructive, gastroprotective activity of the extracts of St. John's wort and St. John's wort tetrahedral was compared with the activity of dealcoholized tincture of ginseng. The drugs were administered enterally preventively for 7 days. Methods of ligation of the pylorus in rats, immobilization or reserpinization of mice were used. In all 3 models, St. John's wort infusions showed distinct antidestructive activity, comparable to the more active ginseng. These results indicate the ability of St. John's wort preparations to cause a state of nonspecifically increased resistance (SNPS) of the body, to exhibit antidestructive activity. For SNPS, limitation of the volume and severity of lesions is characteristic. The legitimacy of the widespread use of St. John's wort in folk and traditional medicine as a preventive measure has been experimentally confirmed.

Key words: phytopharmacology, types of St. John's wort, antidestructive, gastroprotective activity.

#### **RESUME**

The antidestructive, gastroprotective activity of Hypericum perforatum and H. quandrangulum herbal infusions was compared with such activity of Panax ginseng root's dealcoholizated tincture. All plant drugs were introducted enteraly preventively during 7 days. Methods of pylorus ligated rats (Shay rats) and mise immobilization or injection of reserpine were used. Both Hypericum infusions demonstrated distinct antidestructive activity, which may be compared with strong activity of Panax ginseng. These results illustrated the ability of Hypericum infusions to cause the state nonspecific high resistance (SNHR) of organism and their antidestractive action. The one of the main characteristic SNHR is limitation size and heaviness destructions.

Keywords: phytopharmacology, Hypericum species, antidestructive, gastroprotective activity.

# INTRODUCTION

Armenian doctor, encyclopedic scientist, Amirdovlat Amasiatsi, referring to Dioscorides, Paten, Ipna, other authors and his own experience, briefly noted wound healing, monthly, uterostimulating, diuretic, anti-inflammatory, analgesic, anthelmintic, detoxifying properties of seeds [1]. Attention is focused on the ability of St. John's wort "to dissolve black and yellow bile" (ie melancholy). I. D. Karomatov [2], summarizing the experience of using St. John's wort in traditional Iranian-Tajik medicine and a number of modern sources, among the impressive list of previously listed medicinal properties identified antiulcer, choleretic, sedative, antidepressant, antibacterial, antispasmodic, tonic, effectiveness for nocturnal enuresis, infertility, malaria.

The multivolume reference book "Plant Resources of the USSR" [3] gives a brief description of 29 of 52 species of St. John's wort, with the most fully characterized Z. perforatum. I will briefly list the main directions of use of St. John's wort preparations, highlighted in this source: "stimulates the activity of the heart and tissue regeneration", has a general tonic effect, vasoprotector, stomatitis, purulent wounds, phlegmon, etc. (topically), gallstone disease, depressive conditions with anxiety and fear, pulmonary tuberculosis, tuberculous laryngitis, pneumonia, bronchial asthma, other bronchopulmonary diseases, hypertension, circulatory failure, cancer of the liver, stomach, ovaries and other localizations, arthritis, rheumatism, other inflammatory diseases, nervous, female diseases (without specification), finally, stomach ulcer, 12 duodenal ulcer, gastritis, dyspeptic disorders. The seeds have a strong laxative effect, the aerial part to a lesser extent. St. John's wort contains anthraquinones. Even this incomplete list allows us to understand the popularity of the plant, the rationality of using St. John's wort in almost all areas of medicine, since, according to the terminology of traditional medicine, it is a universal medicine.

Earlier I covered my own experimental data on cerebroprotective [4] and wound-healing properties [5] of the infusion of the aerial part of the perforatum. The screening characteristic of the gastroprotective properties of phytopreparations makes it possible to assess not so much the effectiveness of phytopreparations for peptic ulcer disease, but rather their ability to cause a state of nonspecifically increased resistance

(SNPS) of the organism [6, 7] on models of the formation of mucosal erosion [6] with preventive course administration of the studied agents. In the event that the generally accepted models of immobilization, painful irritation and the like are used, the results of the experiment allow us to evaluate the plus to all the stress-limiting activity, which is very important in the work of a phytotherapist [7, 8, 9]. When using aspirin, butadione, atophan, indomethacin for the formation of gastric erosions, in addition to assessing the plant's ability to cause SNPS, it is possible to draw practical conclusions about its effectiveness in removing the side effects of non-steroidal anti-inflammatory drugs (NSAIDs).

The purpose of this work is a comparative assessment of antidestructive, in particular, gastroprotective properties of St. John's wort preparations, as a particular manifestation of its ability to cause SNPS.

### MATERIAL AND RESEARCH METHODS

Infusions of 1:10 of the aerial part of Z. perforatum and Z. tetrahedral H. quandran-gulum (or according to the new classification of Z. spotted H. maculatum) were prepared according to the State Pharmacopoeia on the day of their introduction by a probe into the stomach of animals in an amount of 0.5 ml / 10 g (5 g / kg in terms of air dry raw materials). Ginseng was used as a control reference drug, a classical phytoadaptogen. Completely dealcoholized pharmacy tincture of ginseng 1:10, supplemented to the original volume with water with drops of Tween-80 (emulsifier in case of precipitation) was also administered orally at the same dose. In the control, the animals were injected with water. The preventive course of drug administration to achieve SNPS lasted 7 days.

We used the classical method of pylorus ligation in nonlinear male rats (180-200 g) according to H. Shay [10] with our updates. At night, animals were deprived of food with free access to water. As a sokogonny after the operation, 1 ml / 100 g of a solution (1: 200) of a bouillon cube was injected into the stomach. Lesions of the cicatricial part of the stomach were graded on erosion, usually slightly stained with hydrochloric acid hematin, small, medium, large and giant ulcers with a diameter of up to 1.5 - 2.5 - 5.0 and more than 5.0 mm, respectively. The following indicators were statistically compared:

- 1) The number of animals without destruction in general and of each of their species. A significant increase in these indicators in comparison with control indicates a strong antidestructive effect.
- 2) The average number of all and each type of destruction per 1 animal in the group. Reliable decline of all or most of these indicators, especially the sum of all ulcers, indicates a distinct protective effect.
- 3) Registration of the drug's ability to shift the percentage of destruction towards the lungs lesions, for example, a decrease in the number of all, large, medium ulcers with a corresponding increase in the proportion of erosions, small ulcers. This result was indicative of weak activity.

When using the widely used method, the extensive literature on the role of neurogenic, reflex, peptic, vascular components in the formation of destruction of the proventriculus was taken into account.

We used the method developed by us [6] for immobilization of male SHR mice for 18-20 hours (deprivation of food for 5-6 hours), with 2-hour cooling at the beginning of the experiment. Cooling, as we have confirmed experimentally, is necessary for the reason that simply immobilization of mice, burrowing animals, does not lead to the formation of erosions in the control in all mice, or they are formed in small quantities (there is nothing to compare with). Erosion was graded under a binocular loupe into small (dust-like), medium (point-like, up to 2 mm in diameter) and large, more often strip-like. In these experiments, the weight ("melting") of the spleen was recorded, correlated to the weight of the mouse in mg / kg, which allows one to judge the stress-limiting effect of the drug. All erosions in rats and mice are brightly stained with hydrochloric acid hematin, which facilitates their counting. A method for reserpinization of mice has also been developed. The conditions of the previous method were observed: deprivation of food for 5-6 hours, cooling for 2 hours, counting destruction after 18–20 hours, a similar gradation of lesions. A special sensor was used to record the rectal temperature of mice with an electrothermometer at the end of the experiment. The advantage of performing experiments on mice lies in the seriality, the possibility of using a large number of animals, spending a smaller amount of scarce drugs in course, multi-day training of animals. For statistical processing, we used the generally accepted Fisher-Student test t, as well as  $\chi^2$ . The advantage of performing experiments on mice lies in the seriality, the possibility of using a large number of animals, spending a smaller amount of scarce drugs in course, multi-day training of animals. For statistical processing, we used the generally accepted Fisher-Student test t, as well as  $\chi^2$ . The advantage of performing experiments on mice lies in the seriality, the possibility of using a large number of animals, spending a smaller amount of sc

## **RESULTS AND ITS DISCUSSION**

The generally accepted model of pyloric ligation in rats (Shay rats) has been standardly used for 70 years in the search for remedies for the treatment of patients with peptic ulcer disease. The specificity of the study of phytopreparations is the need for precisely course preventive administration to assess their ability to induce a state of nonspecifically increased body resistance (SNPS), similar to classical phytoadaptogens. The theory of SNPS, the doctrine of adaptogens, known to the whole world today, were developed by our most talented domestic pharmacologist N.V. Lazarev and his school [8]. It takes some time to reach this state. With a single injection, phytopreparations do not mobilize endogenous defense mechanisms, they do not have a significant antidestructive effect on models of erosive and ulcerative lesions of the scar and secretory part of the stomach

After 7 days of administration, a dealcoholized tincture of ginseng had a strong antidestructive effect, significantly reducing the number of animals with ulcerative lesions and, in general, with destruction (Table 1). Ginseng reduced the average number of all sizes and overall ulcers per animal per group. Against its background, not ulcerative, but light erosive destruction prevailed, which fully corresponds to the SNPS postulates about the possibility of reducing the volume and severity of damage against the background of classical phytoadaptogens. Using this most effective classical phytoadaptogen as a control, we evaluated the legitimacy of the frequent use of St. John's wort for peptic ulcer disease in traditional and folk medicine. Infusion of Z. perforatum reduced the number of animals with ulcers of small, medium and large sizes, but, unlike ginseng, not in general with ulcers in total. The average number of small, large and all ulcers was significantly less than in the control, but, as in the case of ginseng, the average index of all destruction did not change. Unlike ginseng, Z. perforatum did not reduce the number of medium-sized ulcers. All phytopreparations increased the percentage of light erosive lesions and decreased the percentage of ulcerative lesions. The absence of a decrease in the number of animals with different types of destruction allows us to attribute the activity of the infusion of Z. tetrahedral not to strong, but to distinct. Despite the obvious differences in the activity of phytopreparations in relation to control, the formal rules of statistical processing oblige to compare them in relation to each other. In no way are the types of St. John's wort inferior to ginseng and do not differ from each other. However, their inequality is obvious, and therefore, in contrast to the control, phytopreparations can be arranged in the following row in decreasing activity: dealcoholized tincture of ginseng ≥ infusion of Z. perforatum ≥ infusion of Z. tetrahedral. The results are shown in table. 1, obtained on a rigid model of injury to the gatekeeper, allow us to consider the use of St. John's wort species in severe destructive diseases of the stomach justified.

Comparative assessment of the antidestructive activity of phytopreparations on the rat doorkeeper dressing model

Plant Erosion small Ulcers are medium large Total ulcers Grade destruction (number activity animals) one 5.2 ± 2.1 25.1 8.1 ± 2.2 38.8 3.9 ± 1.1 18.8 3.6 ± 0.7 17.2 15.6 ± 5.1 20.8 ± 5.1 Control (24)3.0 ± 0.9 19.0 9.1 ± 3.1 \* 16.1 ± 7.5 H. perforated one  $7.0 \pm 1.8$ 4.6 ± 1.1 \* 1.5 ± 0.6 <sup>3</sup> strong 43.3 \* 9 28.7 \* 10\* 9.0 7 56.7 \* 100 H. tetrahedral one  $8.2 \pm 2.4$  $5.3 \pm 1.7$ 2.8 ± 0.6 \* 15.5 1.7 ± 1.1 \*  $9.8 \pm 4.5 \ 18.0 \pm 6.8$ distinct 45.6 \* 29.5 \* 9.4 \* 54.4 \* 100 (25)7.2 ± 3.1 2.3 ± 0.7 15.2 10\* 7.9 ± 3.0 \* 15.1 ± 5.8 one 2  $4.4 \pm 2.0^{3}$ strong Ginseng  $1.2 \pm 0.6$ 52.3 \* 100

Notes: 1 - the average number of destruction per animal in the group  $\pm$  confidence interval; 2 - the percentage of these lesions from the total number of destruction; 3 - the number of animals without destruction; \* - differences with the control are statistically significant at p  $\leq$  0.05 according to the criteria: Fischer-Student t or  $\chi^2$ .

The model of immobilization stress (Table 2), like the previous one, is a generally accepted test for detecting not so much gastroprotective, but rather stress-limiting properties of drugs. In mice in serial experiments, it is difficult and hardly possible to cleanly isolate the adrenal glands and the thymus gland and reliably establish changes in their mass.

Let me remind you that Selye's triad is considered to be "melting" of the thymus, an increase in the mass of the adrenal glands and the formation of erosive (not ulcerative!) Lesions of the mucous membrane of the secretory part of the stomach. A classic example is gastric stress erosion in parachutists, as well as those arising in other extreme conditions. On the model of immobilization stress developed by us in mice, it is possible, however, to trace the obstacle of phytopreparations to the "melting" (essentially destruction) of the immunocompetent organ of the spleen. In our experiments, only ginseng tincture reliably prevented a decrease in its mass (Table 2). Against the background of infusions of St. John's wort species, it did not differ significantly from the activity of ginseng, but also from the control. This indicator indicates the stress-limiting activity of drugs, their ability to prolong the stage of stress resistance, postponing the stage of exhaustion, which has long been established for classical phytoadaptogens [6, 11, 12] and confirmed in these experiments for ginseng. By preventing the spleen from melting, the stress-limiting activity of St. John's wort species cannot be considered obvious. But the following indicators of the Selye triad - erosive lesions of the stomach [8], made it possible to make sure that the judgment about the activity of the drug was inappropriate only for one indicator - the "melting" of the spleen.

table 2

Table 1

Comparative assessment of the antidestructive activity of drugs when immobilizing and cooling mice

Plant (quantity			Erosion		Total erosion	Weight spleen, in	Grade activity
animals)		small	average	large			
Control (23)	one 2 3	5.7 ± 2.1 8.8 one	2.4 ± 0.9 24.7 5	1.6 ± 0.7 16.5 7	9.7 ± 2.4	3.6 ± 0.6	
H. perforated (20)	one 2 3	3.7 ± 0.9 * 67.3 4	1.1 ± 0.7 * 20.0 10	0.7 ± 0.5 * 12.7 12	5.5 ± 1.4 *	4.1 ± 0.7	Distinct
Z. tetrahedral (20)	one 2 3	4.2 ± 2.1 70.0 3	1.2 ± 0.7 * 20.0	0.6 ± 0.3 * 10.0	6.0 ± 2.1 *	4.0 ± 0.4	Distinct
Ginseng (18)	one 2 3	2.5 ± 1.0 * 56.8 6 *	1.3 ± 0.6 * 29.6	0.6 ± 0.4 * 13.6 10	4.4 ± 1.1 *  one hundred 6 *	6.3 ± 1.3 *	Strong

Note: the weight of the spleen in intact mice is  $5.4 \pm 1.3$  mg / kg, from which the corresponding indicators do not significantly differ in the groups that received infusions of St. John's wort and the ginseng preparation. For other notes, see table. one.

Ginseng increased the number of animals without small and all in the amount of erosive lesions, which, when registered, plus a decrease in the average number of each size of erosions and all of them in total, makes it possible to consider its activity to be strong. Without examining in detail the indicators of destruction of the gastric mucosa against the background of preventive preparation of mice with infusions of St. John's wort (Table 2), I note that there are no significant differences from ginseng and from each other in any of them. However, the location of phytopreparations in relation to the control in decreasing activity is obvious: ginseng  $\geq$  Z. perforated  $\geq$  Z. tetrahedral. When evaluating the results obtained, it is important to take into account that extreme and persistent stresses are the cause of the onset, exacerbation, and progress of not only peptic ulcer, but also hypertensive, cerebrovascular disease, ischemic heart disease, brain (with subsequent heart attacks,

Direct extrapolation of the results of methodically simple, rather screening experiments into practice is hardly possible. So, the vulgar interpretation of the studied phytopreparations only as antiulcer, gastroprotective agents, which takes place today, is sinful of limitation and is only partially correct. Data on the presence of stress-limiting properties in infusions of St. agitation. This is confirmed by our own long-term experience of clinical observations when St. John's wort is included in the block of synergists that effectively reduce the symptoms of neuroticism [13].

It is relevant to use a battery of methods to confirm the ability of St. John's wort preparations to induce SNPS with its inherent increase in stress resistance, to exert an adaptogenic effect. The experimental results expand the arsenal of plants with adaptogenic properties and our understanding of the widespread occurrence of these properties in plants, of the presence in them of a biologically determined interest in the health of mammals, which, in turn, participate in their reproduction. So, the seeds of St. John's wort, like many other plants, in the gastrointestinal tract of animals undergo acid-enzymatic stratification, increase germination and, in addition, weaken, which contributes to the spread of the species, population.

Experimental work of O.N. Zabrodin [14] proved that one of the essential pathogenetic mechanisms of the formation of neurogenic, stress-induced erosions of the gastric mucosa in acute painful stress (electric current) is the depletion of the depot of catecholamines in the sympathetic terminals. It was proposed to introduce the precursor of catecholamines L-dopa into the complex therapy of patients with peptic ulcer disease, which, unfortunately, was not reflected in clinical practice, in particular, due to the high cost of its drugs. O.N. Zabrodin is one of the brilliant confirmations of the theory of the adaptive-trophic function of the sympathetic nervous system, created by our great compatriot, physiologist L.A. Orbeli [15], recognized all over the world. For the rapid artificial depletion of the depot of catecholamines in the sympathetic terminals, you can use the rauwolfia alkaloid snake reserpine, which at first served as an antipsychotic in a psychiatric clinic, and then as an antihypertensive agent, which is almost never used today, since among the numerous complications are erosion, stomach ulcers, and bleeding. However, as a pharmacological analyzer with a clearly established mechanism of action (destruction of organs and tissues due to impaired trophic function of the sympathetic nervous system), reserpine is popular. It was of interest to find out whether it is possible to prevent the destructive effect of reserpine on the gastric mucosa with the preventive administration of phytopreparations, which is of great theoretical and practical importance, for example, when accompanied by phytotherapy,

Dealcoholized ginseng tincture showed a strong protective effect on the model of reserpine and cooling-induced gastric destruction, increasing the number of animals without erosions (Table 3), decreasing the average number of animals per animal in the group. Displacement towards lighter lesions (weak

action) did not happen. But antagonism with reserpine manifested itself even in relation to limiting the decrease in rectal temperature, which indicates the initiation of protection by ginseng through sympathetic mechanisms. Infusions of Z. perforatum and Z. tetrahedral had a distinct anti-destructive effect, formally not differing from each other and from ginseng in any way. Nevertheless, in comparison with the control, we register everything the same as in the previous models, the distribution by activity: ginseng  $\geq Z$ . perforatum  $\geq Z$ . tetrahedral. In folk, household herbal medicine, the studied types of St. John's wort were not distinguished. Screening experiments make it possible to classify both of them as active. In previous experiments, complete protection from the destructive action of reserpine was recorded by tricyclic antidepressants and MAO-inhibitors when administered once [6], which, in addition, prevented a drop in rectal temperature and adynamia caused by reserpine. But these results, with a known mechanism of action of drugs, are a kind of laboratory games and have nothing to do with practice. People will not consume aggressive mediator poisons in order to improve their health, increase the body's resistance to stress, chemical influences. However, in addition to the laxative effect of anthraquinone hyperecin, MAO-inhibiting activity was also established [16], which is hardly of practical importance, since the total herbal preparations of St. John's wort were not compared by the authors. It is essential that the consumption of, for example, St. John's wort tea, according to a widespread custom, prevents a decrease in the adaptive-trophic function of the sympathetic nervous system, which can be not only a pathogenetic mechanism, but also the end of many diseases. Experimental confirmation of the mechanisms of the fortifying, anti-destructive, stress-limiting action of St. John's wort and many other popular tea surrogates could serve to revive the tradition of their more frequent or even constant use, which can play a positive role in improving the nation's health and reducing morbidity. which can be not only a pathogenetic mechanism, but also the end of many diseases. Experimental confirmation of the mechanisms of the fortifying, antidestructive, stress-limiting action of St. John's wort and many other popular tea surrogates could serve to revive the tradition of their more frequent or even constant use, which can play a positive role in improving the nation's health and reducing morbidity. which can be not only a pathogenetic mechanism, but also the end of many diseases. Experimental confirmation of the mechanisms of the fortifying, anti-destructive, stress-limiting action of St. John's wort and many other popular tea surrogates could serve to revive the tradition of their more frequent or even constant use, which can play a positive role in improving the nation's health and reducing morbidity.

Table 3
Comparative assessment of the antidestructive activity of phytopreparations on the model of gastric erosion in mice caused by reserpine

Plant (quantity animals)		Erosion			Total erosion	Rectal	Grade activity
		small	average	large		temperature	activity
Control (31)	one	7.0 ± 2.1	1.5 ± 0.6	1.1 ± 0.2	9.6 ± 2.1	32.5 ± 0.6 °C	
	2	72.9	15.6	11.5	one hundred		
	3	one	7	9	one		
H. perforated (30)	one	5.1 ± 1.5	0.7 ± 0.3 *	0.6 ± 0.3 *	6.4 ± 1.7 *	33.2 ± 0.8 °C	Distinct
	2	79.6	11.0	9.4	one hundred		
	3	4	10	12	3		
Z. tetrahedral (30)	one	5.5 ± 2.2	0.6 ± 0.4 *	0.6 ± 0.3 *	6.7 ± 2.7	33.0 ± 0.7 °C	Distinct
	2	82.1	8.95	8.95	one hundred		
	3	5	12	thirteen	5		
Ginseng (20)	one	4.2 ± 1.4 *	0.6 ± 0.4 *	0.3 ± 0.25 *	5.1 ± 2.7 *	33.8 ± 0.5 * °C	Strong
	2	82.4	11.8	5.8	one hundred		
	3	7 *	12*	15*	7 *		

Note: rectal temperature in intact mice is  $37.4 \pm 0.4$  °C; the rest of the notes see table. one.

Discussing the experimental results, it should be noted the presence of antidestructive, stress-limiting activity in infusions of St. John's wort species, somewhat less pronounced, but comparable to that of ginseng. It is obvious that infusions of St. John's wort species are capable of causing SNPS with its inherent mobilization of the mechanisms of self-defense, limiting the volume and severity of lesions. To assess the antidestructive activity of St. John's wort infusions, 3 classical methods of the formation of experimental destruction of the stomach and proventriculus were used. On all models, on 2 species of animals, similar results were obtained, which largely guarantees their reliability. Erosions and ulcers of the cicatricial part of the stomach, complex in pathogenesis, provide mainly a reflex, neurogenic mechanism of their formation, but also peptic, judging by the interpretations of foreign researchers (peptic ulcer). Since the studied drugs are not antacids, cholinolics and antihistamines, the most probable (and complex in terms of multicomponent) mechanism of their action is to increase the resistance of target cells to alteration. In the Shay rats model, the stress-induced component of the formation of destruction is by no means excluded, but it is presented in a purer form under immobilization stress.

One of the characteristics of SNPS is the prolongation of the stage of resistance and the delay of the stage of depletion of stress, which is observed in varying degrees of severity with the course of administration of St. John's wort and especially ginseng. When using the model of destruction caused by reserpine, the presence of indirect adrenomimetic activity in drugs is essential. From the substrate point of view, it is easy to explain, since for

ubiquitous flavonoids, including those contained in St. John's wort, and phenol carboxylic acids, I have previously proven the ability to prolong the action, slow down the oxidation of adrenaline [6, 13]. In addition, the antioxidant activity manifested by almost all herbal preparations of plants and, to a lesser extent, plant polyphenolic compounds, the ability of the former to mobilize the activity of superoxide dismutase (another evidence of the achievement of SNPS) is also one of the mechanisms of antidestructive action [13]. This mechanism is essential when using any method of damage to the secretory and cicatricial parts of the stomach. In the formation of a methodological approach and interpretation of the results obtained, three cornerstone theories of medicine are involved: the teachings of G. Selye about the general adaptation syndrome [8], the theory of SNPS and the theory of classical adaptogens by N.V. Lazareva [7], the theory of adaptive-trophic function of the sympathetic nervous system by L.A. Orbeli [15].

#### CONCLUSIONS

- 1. On all three models of experimental gastric destruction during pyloric ligation in rats, Immobilization or reserpinization of mice, data were obtained on the distinct antidestructive activity of extracts of St. John's wort and Z. tetrahedral, similar to that of dealcoholized tincture of ginseng.
- 2. The results of experiments suggest that preparations of two types of St. John's wort, like classical adaptogen ginseng, cause a state of nonspecific resistance of the body.
- 3. Comparison of the antidestructive activity of the studied species of St. John's wort indicates their interchangeability.

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