ЕКСПЕРИМЕНТАЛЬНА ТА КЛІНІЧНА ФАРМАКОЛОГІЯ

Recommended by Doctor of Medicine, professor N.V.Bezditko

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PHARMACOLOGICAL RESEARCH OF INTERACTION AND THE TOTAL EFFICIENCY OF HERBAL COMPONENTS OF "POLYHERBAGASTRIN" AND "HEPATROPIN" GRANULES

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Key words: pharmacological studies; granules; medicinal plant raw material; wheat bran; gastrointestinal tract; non-allergic contact dermatitis; anti-inflammatory activity

The gastrointestinal tract (GIT) diseases are the most common diseases of internal organs. Medicinal plants exhibit a wide range of pharmacological actions, and each plant has several useful biological properties. To optimize the treatment of GIT diseases the scientists of the National University of Pharmacy have developed "Polyherbagastrin" and "Hepatropin" granules (the so-called GIT-1 and GIT-2) on the basis of native plant powders. One of the important stages of research on the optimality of the compositions selected for the treatment of GIT diseases is the study of interaction and the total efficiency of plant components. Irrespective of the cause of the GIT organs dysfunction, the inflammation of the mucosa develops the most often, and it promotes the further development of gastritis, duodenitis, hepatitis, cholecystitis, pancreatitis, colitis, etc. Thus, the aim of this work was to study the anti-inflammatory activity of individual plant components and their combined effect in "Polyherbagastrin" and "Hepatropin" granules on the model of non-allergic contact dermatitis (NCD). "Polyherbagastrin" and "Hepatropin" granules, "Polyherbagastrin" and "Hepatropin" granules without wheat bran (WB), granules of medicinal plants and WB were taken as objects for research. The experiments were carried out on white nonlinear male rats with the weight of 180-200 g. NCD was modelled by daily application of 3 drops of 5% solution of 2,4-dinitrochlorobenzene to the shorn skin area (3×3 cm) of rats for 5 days. The research carried out confirmed the anti-inflammatory activity of the granules studied on the model of NCD. The interaction of medicinal plant raw material in the ratio selected leads to a pronounced increase of the anti-inflammatory activity. The most expressive anti-inflammatory activity of "Polyherbagastrin" and "Hepatropin" granules is due to the total mutual action of WB biological active substances and individual plant components. The optimal composition of the granules obtained has been confirmed.

The gastrointestinal tract (GIT) diseases are the most common diseases of internal organs. Variety of reasons which cause them requires multifaceted actions that are inherent to phytotherapy [3]. Medicinal plants exhibit a wide range of pharmacological actions, and each plant has several useful biological properties.

To optimize the treatment of GIT diseases the scientists of the National University of Pharmacy have developed "Polyherbagastrin" and "Hepatropin" granules (the so-called GIT-1 and GIT-2) on the basis of native plant powders. One of the important stages of research on the optimality of the compositions selected for the treatment of GIT diseases is the study of interaction and the total efficiency of plant components. Irrespective of the cause of the GIT organs dysfunction, the inflammation of the mucosa develops the most often, and it promotes the further development of gastritis, duodenitis, hepatitis, cholecystitis, pancreatitis, colitis, etc. The study of the total effects of herbal medicinal products combinations and the effect of each component individually on development of inflammation has been carried out in the present research.

Among the biologically active substances (BAS) of the plant raw material (PRM), which is part of ganules (Table 1), substances of phenolic the origin are present. Due to the antioxidant properties they can weaken and eliminate the exudative component of the inflammatory response and influence on the enzymatic systems, activity of inflammatory mediators and regulate microcirculation and permeability of the vascular walls and cell membranes [2, 3, 7, 9-12].

Besides the native powders of medicinal plants the wheat bran (WB), in particular containing plant fibres (PF), is included in the composition of granules. Such approach is reasonable because of a great importance that is given today to PF in medicinal and preventive medicine [6]. The use of PF normalizes the motor function of the intestines and the intestinal microflora balance, slows the growth of putrefactive microbes, reduces the degree of fat absorption in the small intestine,

Table 1

The composition of the plant medicines

Name of plants and the raw material	Granules	
	"Polyherbagastrin"	"Hepatropin"
Corn stigmas	+	-
Chamomile, flowers	-	+
Knot-grass	+	-
Valerian, rhizomes	-	+
Wild rose, fruit	-	+
Nettle, leaves	-	+
Yellow everlasting, inflorescence	+	-
Glycyrrhiza, roots	+	+
Equisetum, grass	+	-
Calendula, flowers	-	+
Horse Chestnut, fruit	+	+
Wheat bran	+	+

the level of cholesterol in the blood, has a positive effect on vitamins and lipids exchange in the enterohepatic circulation system, etc. The risk of GIT chronic diseases is diminishes thanks to it [3].

Thus, the aim of this work was to study the anti-inflammatory activity of individual plant components and their combined effect in "Polyherbagastrin" and "Hepatropin" granules on the model of non-allergic contact dermatitis (NCD) [1, 5].

"Hepatropin" and "Polyherbagastrin" granules, "Hepatropin" and "Polyherbagastrin" granules without wheat bran (WB), granules of medicinal plants and WB were taken as objects for research. The plant composition of medicines is given in Table 1.

Materials and Methods

The experiments were carried out on white nonlinear male rats with the weight of 180-200 g. NCD was modelled by daily application of 3 drops of 5% solution of 2,4-dinitrochlorobenzene to the shorn skin area (3×3 cm) of rats for 5 days [1].

The intensity of NCD was assessed visually by the expression of the inflammatory skin response according to the point system (0 – no visible reaction; 1 – slight erythema; 2 – moderate erythema, with decorticating, point hemorrhage; 3 – clear erythema with compression and decorticating; 4 – sharp erythema with signs of hemorrhage, expressed infiltration and serous-hemorrhagic crusts with ulcers). To estimate the expressiveness of inflammation and the skin edema in animals before the beginning of the experiment; on the 6-th and 16-th day of the experiment the thickness of the skin fold measured by a trammel was determined. The anti-inflammatory activity of the objects investigated was determined on the 6th and 16th days of the study by the following formula: $A=100\% - I_{st.} x100\%/I_{cp}$, where: A – is the anti-inflammatory activity; $I_{st.}$ – is the intensity of skin lesions in the test group; I_{cp} is the intensity of skin lesions in the control pathology group. The scheme of the experiment is presented in Table 2.

The experimental data obtained were processed by the variation statistics methods (the arithmetic mean and its standard error were calculated).

To obtain the statistical conclusions when comparing the statistical sampling of relative variables after the one-way ANOVA test (or Kruskal-Wallis test for the data, which are not subject to the normal law of distri-

Table 2

The scheme of the experiment

No.	The group of animals	n	Dose, мg/kg*	Introduction	The term of introduction	Mode of introduction
1.	Pathology control (NCD)	8		Intragastrically	15 days	Prevention and treatment, the 1st to 5th day parallel with introduction of DNHB
2.	WB		800			
3.	NCD + "Polyherbagastrin" without WB		900			
4.	NCD + "Hepatropin" without WB					
5.	NCD + "Polyherbagastrin"		130			
6.	NCD + "Hepatropin"					
7.	NCD + Corn stigmas					
8.	NCD + Chamomile, flowers					
9.	NCD + Knot-grass					
10.	NCD + Valerian, rhizomes					
11.	NCD + Wild rose, fruit					
12.	NCD + Nettle, leaves					
13.	NCD + Yellow everlasting, inflorescence					
14.	NCD + Glycyrrhiza, roots					
15.	NCD + Equisetum, grass					
16.	NCD + Calendula, flowers					
17.	NCD + Horse Chestnut, fruit					

* – considering the results of the previous studies

Table 3

The effect of "Hepatropin", "Polyherbagastrin" granules and their individual plant components for the skin fold thickness under the conditions of dermatitis in rats caused by DNCB, M±m, n=8

Conditions of the experiment	Skin fold thickness, mm		
	Baseline data	5-th day	15-th day
Pathology control	1.95±0.07	3.81±0.11[1]	3.54±0.15
WB		3.55±0.12[1]	2.98±0.14[1/4/5]
Nettle, leaves		3.37±0.17[1/4/5]	2.79±0.09[1/2/3/4/5]
Corn stigmas		3.31±0.15[1/4/5]	2.78±0.14[1/2/3/4/5]
Wild rose, fruit		3.27±0.12[1/4/5]	2.67±0.12[1/2/3/4/5]
Chamomile, flowers		2.97±0.18[1/4/5]	2.60±0.13[1/2/3/4/5]
Equisetum, grass		2.95±0.13[1/2/4/5]	2.49±0.14[1/2/3/4/5]
Yellow everlasting, inflorescence		2.95±0.17[1/2]	2.56±0.20[1/2/3/4/5]
Knot-grass		2.93±0.15[1/2]	2.46±0.07[1/2/3/4/5]
Glycyrrhiza, roots		2.91±0.14[1/2]	2.49±0.11[1/2/3/4/5]
Horse Chestnut, fruit		2.89±0.13[1/2]	2.51±0.15[1/2/3/4/5]
Valerian, rhizomes		2.87±0.12[1/2]	2.50±0.11[1/2/3/4/5]
Calendula, flowers		2.85±0.14[1/2]	2.51±0.12[1/2/3/4/5]
"Polyherbagastrin" without WB		2.84±0.11[1/2]	2.37±0.08[1/2]
"Polyherbagastrin"		2.23±0.09[1/2/3]	1.96±0.10[1/2/3]
"Hepatropin" without WB		2.59±0.10[1/2]	2.32±0.07[1/2]
"Hepatropin"		2.12±0.12[1/2/3]	1.95±0.09[1/2/3]

Notes: 1 – statistically significant differences concerning the baseline data, $p < 0.05$; 2 – statistically significant differences concerning the animal pathology control group in the corresponding term of research, $p < 0.05$; 3 – statistically significant differences concerning the group of animals receiving "Polyherbagastrin" or "Hepatropin" granules without WB; 4 – statistically significant differences concerning the group of animals receiving "Polyherbagastrin" granules; 5 – statistically significant differences concerning the group of animals receiving "Hepatropin" granules.

bution) revealed differences between the experimental groups, Newman-Keuls parametric test, Student t-test for multiple comparisons or nonparametric Mann-Whitney test were used.

Differences between experimental groups were considered to be statistically significant at $p<0.05$.

For the mathematical calculations the standard statistical software package "Statistica 6,0" was used.

Results and Discussion

According to the data obtained on the 6-th day of the study after the simulation of NCD the inflammation with symptoms of hemorrhage, pronounced infiltration and formation of ulcers with hemorrhagic crusts was observed in the animals of the positive control group.

The skin fold thickness of the control animals comparing to the baseline increased by 1.9 times. By the intensity the skin lesions corresponded to 3.3-3.5 points (Table 1, Fig. 1). In 10 days after the dinitrochlorobenzene (DNCB) skin toxicity removal (the 16-th day of the experiment) manifestations of skin lesions showed a tendency to decrease in animals from the control pathology group, but remained rather pronounced: intensity up to 2-2.5 points, edema was expressed, the fold thickness was equal to 3-3.5 mm (Table 3, Fig. 1).

Analysis of the results of the first phase of the pharmacological action study of the objects investigated against the 5-day skin intoxication by DNCB has shown that individual components of medicinal plants in combination exhibit the anti-inflammatory activity of different degrees (Table 3, Fig. 1, 2). The lowest activity was shown by wheat bran – 8%, nettle leaves –19%; corn stigmas – 24%, wild rose fruit – 26%. The skin fold thickness and intensity of skin lesions under the influence these objects decreased, but had no statistically significant differences in comparison with indicators of the animal pathology control group. As was seen, the plants with more expressed anti-inflammatory and reparative actions such as [3]: chamomile flowers, equisetum grass, yellow everlasting, inflorescence, glycyrrhiza roots, horse chestnut fruit, knot-grass, calendula flowers, valerian roots and rhizomes statistically significantly reduced the skin tissue swelling and skin lesions intensity in relation to indicators of the animal pathology control group (Table 3, Fig. 1). The anti-inflammatory activity increased from 29% to 35%, respectively (Fig. 2). "Polyherbagastrin" and "Hepatropin" without WB revealed the activity of 41% and 55%, respectively, but the indicators did not have statistically significant differences with the indicators of a number of individual components (Fig.1. 2).

The most pronounced statistically significant effect concerning indicators of the animal pathology control group, as well as indicators of animals receiving the individual plant components and granules without WB (Table 3, Fig. 1, 2). was observed under the influence of the total effect of all components in the composition of "Polyherbagastrin" and "Hepatropin" – 58% and 69%. The presence of WB in their composition significantly increased the anti-inflammatory activity by 1.3 times (Fig. 1, 2).

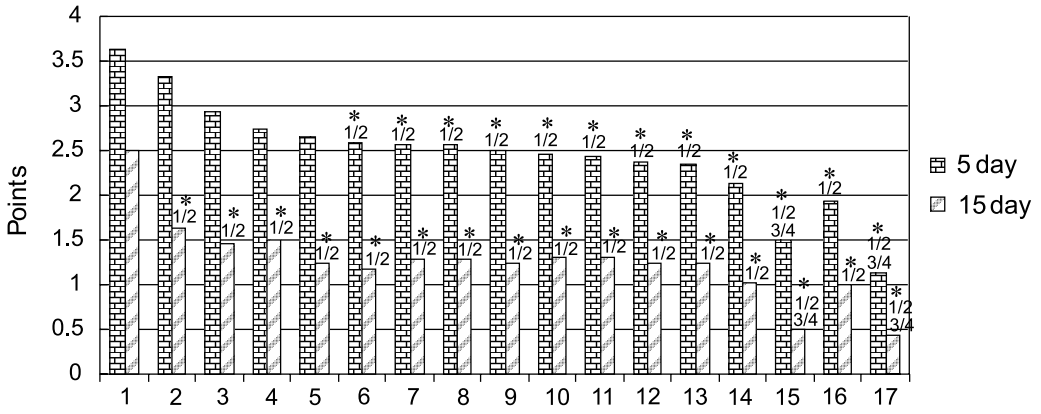

Fig. 1. The effect of "Hepatropin", "Polyherbagastrin" granules and their individual plant components on the intensity of skin lesions under conditions of dermatitis in rats caused by DNCB, M±m, n=8.

Notes: 1 – positive control; 2 – wheat bran; 3 – nettle leaves; 4 – corn stigmas; 5 – wild rose fruits; 6 – chamomile flowers; 7 – equisetum grass; 8 – yellow everlasting, inflorescence; 9 – knot-grass; 10 – glycyrrhiza roots; 11 – horse chestnut fruits; 12 – valerian rhizomes; 13 – calendula flowers; 14 – "Polyherbagastrin" w/o WB; 15 – "Polyherbagastrin"; 16 – "Hepatropin" w/o WB; 17 – "Hepatropin".

«*»: 1 – statistically significant differences concerning the animal pathology control group in the corresponding term of research, $p<0.05$; 2 – statistically significant differences concerning the group of animals receiving "Polyherbagastrin" or "Hepatropin" granules without WB; 3 – statistically significant differences concerning the group of animals receiving "Polyherbagastrin" granules; 4 – statistically significant differences concerning the group of animals receiving "Hepatropin" granules.

The comparative analysis of activity of granules at this stage of the research showed a difference in their action. The activity of "Hepatropin" without WB was higher than the activity of "Polyherbagastrin" by 11%, and with WB by 14%. The composition of "Hepatropin" granules includes such plants as chamomile flowers, calendula flowers and roots and rhizomes of valeriana. It is well known that chamomile and calendula flowers have both the anti-inflammatory and sedative activity. The rhizomes and roots of valerian reduce excitability and improve the functions of the central nervous system, regulate the cardiac function, exhibit the spasmolytic action [3]. According to the results obtained the anti-inflammatory activity of roots and rhizomes of valeriana was at the level of calendula flowers (Fig. 2). These data suggest that a more pronounced efficacy of "Hepatropin" at this stage of the investigation caused by the presence of the components with the sedative effect in its composition.

The second stage of studying the pharmacological action of "Polyherbagastrin", "Hepatropin" and their individual plant components in animals was conducted on the background of NCD by intensity of 1-3 points after DNCB application (Fig. 1). Analysis of the results in 10 days of treatment by the objects studied (the 16th day of the experiment) showed that swelling and intensity of the skin lesions significantly reduced in animals of all experimental groups in relation to the indicators of the animal pathology control group (Table 3, Fig. 1, 2). The activity of the individual components of granules after toxicity factor removal increased to 35% – 45%. The intensity of the skin lesions was reduced to 0.5-1.7 points, the skin fold thickness in the treated animals was equal to 2-3 mm (Table 3, Fig. 1, 2). The highest activity was revealed by granules of "Polyherbagastrin" and "Hepatropin" – 80% and 82%, respectively. The less activity (by 1.3 times) was shown by granules without WB (Fig. 1) – 59% and 60%, respectively (Fig. 1, 2).

Thus, after the 5-th day introduction on the background of DNCB intoxication and subsequent treatment for 10 days the expressed pharmacotherapeutic efficacy was observed in animals; it was confirmed by decrease of swelling and intensity of skin lesions.

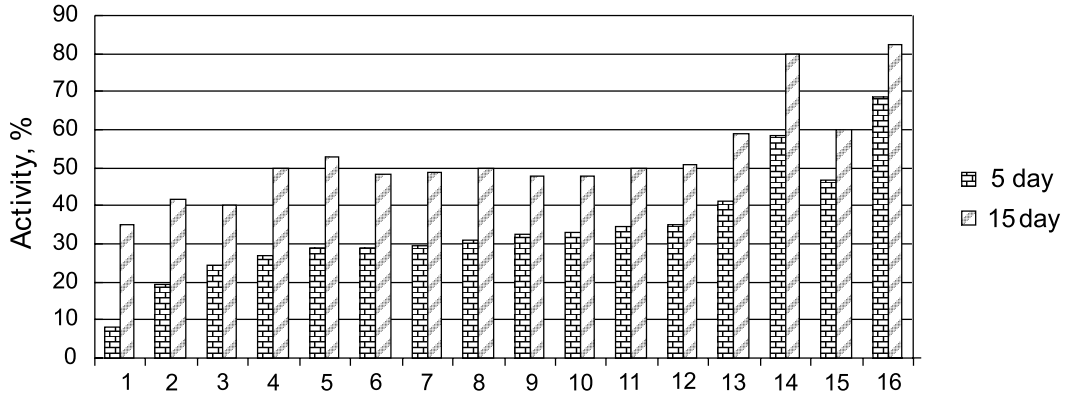

Fig. 2. The anti-inflammatory activity of "Hepatropin", "Polyherbagastrin" granules and their individual plant components under conditions of dermatitis in rats caused by DNCB, M±m, n=8.

1 – wheat bran; 2 – nettle leaves; 3 – corn stigmas; 4 – wild rose fruit; 5 – chamomile flowers; 6 – equisetum grass; 7 – yellow everlasting, inflorescence; 8 – knot-grass; 9 – glycyrrhiza roots; 10 – horse chestnut fruits; 11 – valerian rhizomes; 12 – calendula flowers; 13 – "Polyherbagastrin" w/o WB; 14 – "Polyherbagastrin"; 15 – "Hepatropin" w/o WB; 16 – "Hepatropin".

The anti-inflammatory activity of "Polyherbagastrin" and "Hepatropin" granules was 1.3-1.5 times higher in comparison with the activity of their individual components.

The presence of WB in the composition of granules significantly affected their efficiency. This is explained by display of the sorption action, metabolism normalization, potentiation of the activity of medicinal plants and increase of the organism's nonspecific resistance [5, 6].

The high anti-inflammatory activity of granules in comparison with the effect of the individual components is explained by the total effect of biologically active substances: flavonoids, saponins, coumarins, carotenoids, vitamins and microelements [3].

CONCLUSIONS

1. The study of the pharmacological action of individual plant components of "Hepatropin" and "Polyherbagastrin" granules confirmed their anti-inflammatory activity on the model of NCD.

2. The presence of plants with the sedative effect in "Hepatropin" granules increases its pharmacotherapeutic activity on the background of the animals skin inflammation.

3. The study of total effect of "Hepatropin" and "Polyherbagastrin" granules on the inflammation development demonstrates that the interaction of medicinal plant raw material in the ratio selected leads to a pronounced increase of the anti-inflammatory activity.

4. The action of "Hepatropin" and "Polyherbagastrin" granules is completed and enhanced by wheat bran.

5. The most expressive anti-inflammatory activity of "Polyherbagastrin" and "Hepatropin" granules is due to the total mutual action of WB biological active substances and individual plant components.

6. The optimal composition of "Hepatropin" and "Polyherbagastrin" granules for inflammation pharmacotherapy was confirmed by the research carried out.

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ФАРМАКОЛОГІЧНЕ ДОСЛІДЖЕННЯ ВЗАЄМОДІЇ І СУМАРНОЇ ЕФЕКТИВНОСТІ РОСЛИННИХ КОМПОНЕНТІВ ГРАНУЛ «ПОЛІГЕРБАГАСТРИН» ТА «ГЕПАТРОПІН»

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Ключові слова: *фармакологічні дослідження; гранули; лікарська рослинна сировина; висівки пшеничні; захворювання шлунково-кишкового тракту; неалергійний контактний дерматит; протизапальна активність*

Хвороби органів шлунково-кишкового тракту (ШКТ) відносяться до найбільш поширених захворювань внутрішніх органів. Лікарські рослини виявляють широкий спектр фармакологічної дії, при цьому кожна рослина має декілька корисних біологічних властивостей. З метою оптимізації лікування захворювань ШКТ вченими НФаУ на основі нативних порошків рослин розроблені гранули «Полігербагастрин» та «Гепатропін» (умовні назви «ШКТ-1» та «ШКТ-2»). Важливим етапом досліджень оптимальності обраних складів для лікування захворювань ШКТ є вивчення взаємодії і сумарної ефективності рослинних компонентів. Незалежно від причини порушення функції органів ШКТ найчастіше розвивається запалення їх слизової оболонки, що спричиняє подальший розвиток гастриту, дуоденіту, гепатиту, холециститу, панкреатиту, коліту та ін. Таким чином, метою даної роботи було вивчення протизапальної активності рослинних компонентів окремо та їх сумарної дії у гранулах «Гепатропін» та «Полігербагастрин» на моделі неалергічного контактного дерматиту (НКД). Об'єктом дослідження були гранули «Гепатропін» та «Полігербагастрин», гранули «Гепатропін» та «Полі-

гербагастрин» без висівок пшеничних (ВП), гранули лікарських рослин та ВП. Експерименти проводили на білих нелінійних щурах самцях з масою тіла 180-200 г. НКД моделювали шляхом щоденного нанесення на вистрижену ділянку шкіри (площею 3×3 см) щурів 3 крапель 5% розчину 2.4-динітрохлоробензолу протягом 5 днів. Проведені дослідження підтвердили протизапальну активність досліджуваних препаратів на моделі НКД. Взаємодія лікарської рослинної сировини в обраному співвідношенні приводить до вираженого підвищення протизапальної активності. Більш виразна протизапальна активність гранул «Полігербагастрин» та «Гепатропін» реалізується за рахунок взаємної сумарної дії біологічно активних речовин ВП та окремих рослинних компонентів. Підтверджена оптимальність складу гранул «Гепатропін» та «Полігербагастрин» для фармакотерапії запалення.

ФАРМАКОЛОГИЧЕСКОЕ ИССЛЕДОВАНИЕ ВЗАИМОДЕЙСТВИЯ И СУММАРНОЙ ЭФФЕКТИВНОСТИ РАСТИТЕЛЬНЫХ КОМПОНЕНТОВ ГРАНУЛ «ПОЛИГЕРБАГАСТРИН» И «ГЕПАТРОПИН»

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Ключевые слова: *фармакологическое исследование; гранулы; лекарственное растительное сырье; отруби пшеничные; заболевания желудочно-кишечного тракта; неаллергический контактный дерматит; противовоспалительная активность*

Болезни органов желудочно-кишечного тракта (ЖКТ) относятся к наиболее распространенным заболеваниям внутренних органов. Лекарственные растения проявляют широкий спектр фармакологического действия, при этом каждое растение имеет несколько полезных биологических свойств. С целью оптимизации лечения заболеваний ЖКТ учеными НФаУ на основе нативных порошков растений разработаны гранулы «Полигербагастрин» и «Гепатропин» (условные названия «ЖКТ-1» и «ЖКТ-2»). Важным этапом исследований оптимальности выбранных составов для лечения заболеваний ЖКТ является изучение взаимодействия и суммарной эффективности растительных компонентов. Независимо от причины нарушения функции органов ЖКТ чаще всего развивается воспаление их слизистой оболочки, что способствует в дальнейшем развитию гастрита, дуоденита, гепатита, холецистита, панкреатита, колита и т.д. Таким образом, целью данной работы было изучение противовоспалительной активности растительных компонентов в отдельности и их суммарного действия в гранулах «Гепатропин» и «Полигербагастрин» на модели неаллергического контактного дерматита (НКД). Объектом исследования были гранулы «Гепатропин» и «Полигербагастрин», гранулы «Гепатропин» и «Полигербагастрин» без отрубей пшеничных (ОП), гранулы лекарственных растений и ОП. Эксперименты проводили на белых нелинейных крысах самцах массой 180-200 г. НКД моделировали путем ежедневного нанесения на выстриженный участок кожи (площадью 3×3 см) крыс 3 капель 5% раствора 2.4-динитрохлорбензола в течение 5 дней. Проведенные исследования подтвердили противовоспалительную активность исследуемых препаратов на модели НКД. Взаимодействие лекарственного растительного сырья в выбранном соотношении приводит к выраженному повышению противовоспалительной активности. Более выразительная противовоспалительная активность гранул «Полигербагастрин» и «Гепатропин» реализуется за счет взаимного суммарного действия биологически активных веществ ОП и отдельных растительных компонентов. Подтверждена оптимальность состава гранул «Гепатропин» и «Полигербагастрин» для фармакотерапии воспаления.