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SCREENING RESEARCH TO ESTABLISH THE OPTIMAL COMPOSITION AND DOSE OF A NEW PLANT COMBINATION WITH ANTI-ALLERGIC ACTION

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Abstract: The article presents the results of screening studies to determine the optimal composition of a new plant composition with potential antiallergic action and the choice of the optimal therapeutic dose. The new plant combination contains standardized extracts of the herd, calendula, and hawthorn in various proportions. Based on the fact that the main promising pharmacological effects of the new plant combination are anti-allergic and anti-inflammatory action, screening studies were performed on a model of histamine edema in rats. It was found that the most promising object for further in-depth pharmacological studies is the herbal composition №2, which at a dose of 30 mg per kg is as close as possible to the effectiveness of the drug compared with the proven antihistamine effect of desloratadine and probably exceeds the effect of herbal antiallergic tesalin.

Keywords: *herbal combination agent, antiallergic action, histamine edema, screening studies*

Introduction

According to the World Health Organization, allergies affect 30% of the world's population. As a rule, these are residents of highly developed countries. One in three people has allergic rhinitis, one in ten has bronchial asthma. The main factors in the development of allergic diseases are allergists believe food allergens, excess chemical additives, and preservatives in food, environmental pollution, seasonal allergies to the pollen of flowers and plants, allergens of animals living nearly [1,2].

The problem of optimal treatment of allergic diseases has become especially acute in the last 2 years when against the background of the global pandemic COVID-19 the number of registered allergic reactions has increased significantly, and doctors around the world declare an increase in the latter diseases, during vaccination or after vaccination [3,4,5.].

Attention should also be paid to the significant increase in the use of antibiotics by the population in recent years. ExactlyAntibiotics are the most common cause of allergic reactions, due to the triggering of life-threatening immune-mediated reactions, including anaphylaxis, and severe skin side effects.

According to Blumenthal KG et al. [6] Many reactions to antibiotics documented by the doctor as allergies were unknown or not remembered by the patient, primarily skin reactions (urticaria) as well as allergic rhinitis, which many patients self-assess as a cold. This indicates that the actual number of allergic diseases is much higher than what is according to official medical statistics.

Following modern protocols and guidelines for the treatment of allergic diseases [7,8] antihistamines are recommended to be used after the onset of clinical symptoms of an allergic reaction and until their disappearance, but this group of drugs does not provide modes of prophylactic use, such as seasonal allergies to the pollen of flowers and trees. Also presented on the pharmaceutical market drugs with antihistamine action, which are exclusively artificial molecules) have several disadvantages, so the first generation of drugs hurt cognitive function, cause drowsiness, etc .; second-generation drugs and metabolites can provoke the development of cardiac arrhythmias, for some patients are hepatotoxic [9,10,11]. A promising direction for solving this complex issue of optimizing the treatment of allergic diseases may be the development and implementation of new drugs based on standardized herbal raw materials, the range of which in the modern pharmaceutical market is extremely limited. Thus, in the pharmaceutical space of Ukraine, there is only one registered drug that meets the query "anti-allergic drug from plant raw materials", which is Tesalin, manufactured by "Max Zeller Sohne AG.", Switzerland. 1 tablet of the drug contains 40 mg of native extract from the leaves of flint hybrid (Petasites hybridus). But as indicated in the instructions for medical use, the drug also has many contraindications and risks of adverse effects. Contraindications are Mr.Hypersensitivity to the active substance or any of the excipients, or to any plant in the family Asteraceae / Compositae, hepatic or renal impairment contraindicated in patients receiving anticoagulant therapy or barbiturates, pregnancy, and lactation. Side effects are often recorded from the gastrointestinal tract, a feeling of discomfort in the gastrointestinal tract (including nausea, abdominal pain / abdominal pain, diarrhea). Uncommon: Hypersensitivity reactions of the skin, including erythema, edema, pruritus, eczema, urticaria, rash. In very rare cases, severe liver damage has been observed due to the use of drugs containing an extract from the root of the hybrid flint (P. hybridus). During treatment with Tesalin should pay attention to the early signs of liver damage (pain in the upper abdomen [12]

Given the above, the search and development of new drugs based on medicinal plant raw materials is an urgent task of modern pharmacy and medicine.

To address this issue, scientists of NUPh under the leadership of prof. Gontova TM a new combined three-component herbal remedy with potential anti-allergic and anti-inflammatory action has been developed.

The purpose of this work was to conduct screening studies to establish the optimal composition and optimal dose of a new combined three-component herbal remedy (hereinafter KTHR).

Experimental part

Materials

For the experimental pharmacological study were provided 3 series of KTHR, containing in different proportions extracts of Bidens tripartita, Calendula officinalis, Grategus sanguine.

According to the range of average doses in which the plant material is clinically effective, the dose range of 10 mg/kg, 30 mg/kg, and 60 mg/kg was chosen to select the optimal dose.

How to wash comparisons were selected:

- ✓ reference blocker of histamine H1-receptors - Desloratadine, manufactured by PJSC "Technologist", Uman, (series № 20220) Ukraine.
- ✓ the only herbal drug registered in Ukraine with antiallergic action Tesalin. manufactured by Max Zeller Sohne AG., Switzerland (series № 202269)

Recalculation of doses for rats of comparison drugs was made taking into account the coefficient Yu.P. Rybolovlev [13]. It is estimated that the average daily dose of desloratadine for humans is 5 mg for rats - 0.3 mg/kg. The daily therapeutic dose of tesalin for humans is 120 mg of Petasites hybridus extract, which in terms of rats using the species sensitivity factor is 7.2 mg/kg.

Methods

Screening studies of the optimal composition and dose of KTHR with potentially anti-allergic and anti-inflammatory action should be performed under conditions of reproduction of histamine paw edema in rats. It is known that histamine is not only a mediator of allergies, but also involved in the development of inflammatory reactions.

The research was conducted on the basics in the vivarium of the Educational and Scientific Institute of Applied Pharmacy of NUPh. During the experiment, the animals were at an air temperature of 20–22 ° C, natural light regime "day and night", in standard cages, on a standard food ration. All manipulations with animals were carried out by the requirements of GLP, "General ethical principles of animal experiments (Ukraine, 2001)", the Law of Ukraine of February 21, 2006 № 3447-IV as amended "On protection of animals from cruel treatment", the decision of the National Congress on Bioethics (Kyiv, 2007) and the European Convention for the Protection of Vertebrate Animals Used for Experimental or Other Scientific Purposes [14]

Histamine paw inflammation in rats was reproduced according to the standard validated method, injected subplantarly under the aponeurosis of the hind paw 0.1% histamine solution in a volume of 0.1 ml [15]. Histamine (Sigma-Aldrich, USA) was used for the study, which is according to the standard method.

The studied herbal compositions and comparison was administered intragastrically once a day for 4 days and for 5 days 1 hour before the simulation of histamine edema. The development of edema was observed in dynamics after 30 and 60 min, for which the volume of the paws (in cm3) was measured using a digital plethysmometer Panlab (Spain) model LE 7500 version V29 / 10/2014. and compared the difference between baseline and paw volume change under edema.

The anti-exudative effect of the studied drugs and comparison drugs under conditions of histamine edema was calculated by the formula:

$$AA = (VKP - VD) / VKP \bullet 100, (\%)$$

where, AA - antiexudative activity,%; Vcp (cm3) - median foot volume in animals from the group of control pathology; Vr (cm3) is the median volume of the foot in the group of animals that received the studied drugs.

Animals (rats weighing 180-220 g) were divided into 6 heads, the following groups:

1. control pathology group (n = 6);
2. the group receiving KTHR №1 at a dose of 10 mg/kg (n = 6);
3. the group receiving KTHR №1 at a dose of 30 mg/kg (n = 6);
4. the group receiving KTHR №1 at a dose of 60 mg/kg (n = 6);
5. the group receiving KTHR №2 at a dose of 10 mg/kg (n = 6);
6. the group receiving KTHR №2 at a dose of 30 mg/kg (n = 6);
7. the group receiving KTHR №2 at a dose of 60 mg/kg (n = 6);
8. the group receiving KTHR №3 at a dose of 10 mg/kg (n = 6);
9. the group receiving KTHR №3 at a dose of 30 mg/kg (n = 6);

10. the group receiving KTHR №3 at a dose of 60 mg/kg (n = 6);
11. the group receiving the comparison drug desloratadine at a dose of 10 mg/kg (n = 6);
12. the group receiving the comparison drug Tesalin at a dose of 7.2 mg/kg (n = 6);

The obtained data set was processed by two methods of variation statistics, parametric according to Student's t-test in cases of normal distribution and nonparametric analysis (Kruskal-Wallis, Mann-Whitney test) with median, upper and lower quartiles, due to the small number of animals in the group. The accepted significance level is $p < 0.05$. Quantitative data were processed using the statistical program StatPlus 6.

Result and discussion

The results of the study are shown in tables 1 and 2.

In animals of the control pathology group, which received an injection of histamine solution under the aponeurosis of the hind paw, significant edema was registered in comparison with the initial data, which is reflected in the known mechanism of action of histamine. Histamine causes dilation of capillaries and blood stasis in them, which leads to increased permeability of their walls, the release of plasma from blood vessels, edema of the surrounding tissues.

Administration in the treatment-and-prophylactic regimen of KTHR №1 in the dose range of 10 - 60 mg/kg, had virtually no antiexudative effect and was probably inferior to the comparison drugs desloratadine and Tesalin (table.1, 2).

Therapeutic and prophylactic administration of KTHR №2 at doses of 10 mg/kg, 30 mg/kg, and 60 mg/kg had a statistically significant anti-inflammatory effect. In comparison with animals of the control pathology group, a decrease in paw edema by 65% ($p < 0.001$) and, accordingly, antiexudative activity of 58.7-66.1% were registered. It should be noted that KTHR was inferior to the classic antihistamine desloratadine (antiexudatin activity 73.5%) but statistically significantly exceeded the effectiveness of the herbal antiallergic drug tesalin (antiexudatin activity 32.2%).

The ratio of plant components (herd, calendula, hawthorn extracts) proposed for composition № 3, under the conditions of therapeutic and prophylactic administration in different doses had antiexudative activity at the level of the comparison drug tesalin and was significantly inferior to the effectiveness of KTHR №2.

Thus, the optimal ratio of plant components has KTHR № 2. The statistically significant difference between the doses of KTHR №2 30 mg/kg and KTHR №2 60 mg/kg has not been established, so for further in-depth pharmacological studies selected KTHR № 2 at a dose of 30 mg/kg.

The obtained data can be explained by the optimally selected concentration of biologically active compounds of the herd, calendula, and hawthorn extracts that are part of KRTZ № 2.

For example, in the analysis of available information sources, it was found that the compounds of the herd extract have significant anti-inflammatory and antioxidant effects.

Biologically active compounds of the standardized extract of the herd, namely polyacetylene glucoside (3E, 5E, 11E) -tridecatriene-7,9-diyne-1,2,13-triol-2-O-β-D-glucopyranoside, phenylpropanoid glucoside 2'- butoxy-ethyl coniferin and flavonoid glycoside 8,3 ', 4'-trihydroxyflavone-7-O- (6' '- Op-coumaroyl) -β-D-glucopyranoside according to Le J. et al. [16] has a potent anti-inflammatory effect on nuclear factor kappa B (NF-κB) in 293-NF-κB-luciferase report cell line induced by lipopolysaccharide (LPS).

Significant anti-inflammatory effects of compounds isolated from the herd have also been reported in Xin YJ et al [17]. Authors Shown that isookanin reduces the production of proinflammatory mediators (nitric oxide, prostaglandin E2) by inhibiting the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in LPS-stimulated macrophages. Isookanin also inhibited the expression of activator protein 1 (AP-1) and downregulated the LPS-induced phosphorylation of p38 mitogen-activated protein kinase (MAPK) and c-jun NH2-terminal kinase (JNK) in the MAPK signaling pathway.

Some scientists believe that the leading mechanism of anti-inflammatory action of the extract of the herd is a pronounced antioxidant effect [18].

Calendula extract also has antioxidant and anti-inflammatory effects [19,20,21].

As for the hawthorn extract, which is introduced in a minimal amount to KTHR № 2, its action is aimed primarily at stabilizing cell membranes and capillary-strengthening effect, as well as antioxidant activity [22,23,24,25].

The combined three-component herbal remedy under the code KTHR №2, which contains standardized extracts of the herd, calendula, and hawthorn, has a powerful anti-exudative effect under the conditions of histamine paw swelling in rats.

The obtained antiexudative activity of KTHR № 2 is as close as possible to the effectiveness of the classic antihistamine desloratadine and probably exceeds the effect of the herbal antiallergic drug tesalin.

The optimal dose for further preclinical studies aimed at establishing the antiallergic effect of KTHR № 2 is 30 mg/kg.

Conflicts of interest none

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Table 1. The effect of the combined three-component herbal remedy (KTHR) on histamine edema of the paw in rats

№	Group	V paws 30 min - V paws out	p	V paws 60 min - V paws out	p
1	Control pathology	1.21 ± 0.02 1.21 (1.12; 1.28)	-	0.68 ± 0.04 0.68 (0.49; 0.78)	-
2	KTHR № 1, 10 mg/kg	1.11 ± 0.05 1.11 (0.98; 1.26)	p2-11 <0.001 p2-12 <0.01	0.61 ± 0.04 0.61 (0.51; 0.70)	p2-11 <0.001 p2-12 <0.05
3	KTHR № 1, 30 mg/kg	1.12 ± 0.04 1.12 (0.94; 1.24)	p3-11 <0.001 p3-12 <0.01	0.60 ± 0.03 0.60 (0.50; 0.70)	p3-11 <0.001 p3-12 <0.05
4	KTHR № 1, 60 mg/kg	1.08 ± 0.05 1.08 (0.90; 1.28)	p4-11 <0.001 p4-12 <0.01	0.59 ± 0.03 0.59 (0.49; 0.69)	p4-11 <0.001 p4-12 <0.05
5	KTHR № 2, 10 mg/kg	0.50 ± 0.04 0.50 (0.43; 0.65)	p5-1 <0.001 p5-11 <0.05 p5-12 <0.01	0.46 ± 0.03 0.46 (0.38; 0.58)	p5-1 <0.01 p5-11 <0.01
6	KTHR № 2, 30 mg/kg	0.42 ± 0.01 0.42 (0.38; 0.47)	p6-1 <0.001 p6-2.3.4 <0.001 p6-8.9.10 <0.01 p6-11 <0.05 p6-12 <0.001	0.38 ± 0.01 0.38 (0.34; 0.42)	p6-1 <0.01 p6-2.3 <0.01 p6-8.9 <0.05 p6-11 <0.01 p6-12 <0.05
7	KTHR № 2, 60 mg/kg	0.41 ± 0.01 0.41 (0.38; 0.46)	p7-1 <0.001 p7-2.3.4 <0.001 p7-8.9.10 <0.01 p7-11 <0.05 p7-12 <0.001	0.38 ± 0.02 0.38 (0.32; 0.44)	p7-1 <0.01 p7-2.3 <0.01 p7-8.9 <0.05 p7-11 <0.01 p7-12 <0.05
8	KTHR № 3, 10 mg/kg	0.85 ± 0.08 0.85 (0.63; 1.10)	p8-1 <0.01 p8-11 <0.01	0.51 ± 0.03 0.51 (0.48; 0.60)	p8-1 <0.05 p8-11 <0.001
9	KTHR № 3, 30 mg/kg	0.81 ± 0.05 0.81 (0.68; 1.00)	p9-1 <0.001 p9-11 <0.001	0.48 ± 0.02 0.48 (0.41; 0.55)	p9-1 <0.01 p9-11 <0.001
10	KTHR № 3, 60 mg/kg	0.76 ± 0.06 0.76 (0.63; 0.98)	p10-1 <0.001 p10-11 <0.001	0.46 ± 0.03 0.46 (0.37; 0.53)	p10-1 <0.01 p10-11 <0.01
11	Desloratadine, 0.3 mg/kg	0.32 ± 0.03 0.32 (0.24; 0.48)	p11-1 <0.001	0.26 ± 0.02 0.26 (0.21; 0.35)	p11-1 <0.001
12	Tesalin, 7.2 mg/kg	0.82 ± 0.04 0.82 (0.65; 0.90)	p12-1 <0.001 p12-11 <0.001	0.47 ± 0.02 0.47 (0.41; 0.63)	p12-1 <0.001 p12-11 <0.001

Table 2. Antiexudative effect of the combined three-component herbal remedy (KTHR) under conditions of histamine edema of the paw in rats

№	The group	Antiexudative activity,%, for 30 minutes	Antiexudative activity,% for 60 minutes
1	Control pathology	-	-
2	KTHR № 1, 10 mg/kg	8.26	10.3
3	KTHR № 1, 30 mg/kg	7.43	11.8
4	KTHR № 1, 60 mg/kg	10.7	14.7
5	KTHR № 2, 10 mg/kg	58.7	32.2
6	KTHR № 2, 30 mg/kg	65.8	44.1
7	KTHR № 2, 60 mg/kg	66.1	44.1
8	KTHR № 3, 10 mg/kg	29.7	25.0
9	KTHR № 3, 30 mg/kg	33.0	29.4
10	KTHR № 3, 60 mg/kg	37.2	32.2
11	Desloratadine, 0.3 mg/kg	73.5	61.8
12	Tesalin, 7.2 mg/kg	32.2	30.9