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ASSESSMENT OF PHARMACOLOGICAL PROPERTIES OF A NEW PHYTOCOMPOSITION

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ANNOTATION

In an experiment, the antiexudative, analgesic and antipyritic activity of a phytocomposition consisting of extracts of medicinal plants *Herba alhagi, Folium Uvae ursi, Fructus Rosae, Glycyrrhiza glabra* and *Flores chamomillae* was studied on adult male rats and mice. It has been established that the studied phytocomposition has distinct pharmacological properties, so it suppresses exudation processes, reduces the threshold of pain sensitivity and elevated body temperature. In terms of its pharmacological activity, the phytocomposition is superior to canephron and not noticeably inferior to diclofenac sodium. It is believed that the new phytocomposition may be a potential anti-inflammatory medicine for the pharmacotherapy of diseases in the pathogenesis of which inflammation plays a significant role.

Key words

exudation, analgesia, hyperthermia, medicinal plants, phytocomposition.

The presence of a number of pharmacological properties such as antiexudative, antipyretic and analgesic properties of non-steroidal anti-inflammatory drugs (NSAIDs) allows widespread use them in many pathologies. The arsenal of modern NSAIDs is quite wide, but the development of a number of side effects are factors limiting their regular use [1, 2, 3,4, 5]. This is largely due to their ability to easily penetrate various tissue barriers, which determines their systemic action [6, 7]. Recently developed medicines with a different mechanism of action - genetically engineered biological medicines have not led to a fundamental solution of the treatment of chronic inflammatory diseases due to the high cost of them [8, 9]. Considering the above, it seems relevant to search and study new anti-inflammatory medicines. In this regard, preparations developed on the basis of medicinal plants have significant advantages over synthetic ones since they contain natural complexes of biological active substances, macro- and microelements in the most accessible and digestible form. This is the reason why approximately 80% of the world population currently uses herbal medicines [10]. We have previously

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established the anti-inflammatory activity of a new phytocomposition (PC) consisting of dry medicinal plant extracts: *Herba alhagi, Folium Uvae ursi, Fructus Rosae, Glycyrrhiza glabra* and *Flores chamomillae* [11, 12, 13]. However, a number of pharmacological properties of this PC remained insufficiently studied.

The purpose of this work was to study the antipyretic, analgesic and antiexudative activity of the new PC.

Материалы и методы исследования

The antiexudative, analgesic and antipyritic activity of a new FC consisting of extracts of medicinal plants *Herba alhagi, Folium Uvae ursi, Fructus Rosae, Glycyrrhiza glabra* and *Flores chamomillae* were studied during the study. Experimental studies were carried out on adult white male mice weighing 18-22 g and adult white male rats weighing 165 -180 g, obtained from the vivarium of the Department of Sanitary and Epidemiological Surveillance of the Main Medical Department under the Administration of the President of the Republic of Uzbekistan. The animals were kept in a vivarium under standard conditions in cages at a room temperature of 22±3°C, relative humidity 60-70%, under natural light conditions (day/night). Feeding was carried out using a standard laboratory diet with an unlimited amount of drinking water. Before the start of the experiment, the animals were divided into groups of 6 rats and mice. Animals were moved in cages from the vivarium to the laboratory. The studies were carried out in accordance with the rules of good laboratory practice (GLP) for preclinical studies, as well as the rules and International recommendations of the European Convention for the Protection of Vertebrate Animals Used for Experimental Research or for Other Scientific Purposes (Strasbourg, 1986) [14].

Experiments in control and experimental groups were carried out in parallel. The test medicines were administered intragastrically with a special metal probe in doses of FC 50 mg/kg, Canephron 100 mg/kg and diclofenac sodium 10 mg/kg, 1 day and 1 hour before the reproduction of the models. Diclofenac sodium (Belmedpreparaty, Belarus) and Canephron (Bionorica SE., Germany) were chosen as reference drugs.

Carrageenan (λ-Carrageenan plant mucopolysaccharide, Sigma-Aldrich) was used to study anti-inflammatory activity. 30 minutes after the administration of compounds and comparison drugs, 0.1 ml of a 1% aqueous solution of carrageenan was injected under the aponeurosis of the rear left paw of rats. The paw volume was measured using oncometric method using a plethysmometer (Ugo Basile Srl, Italy), the initial volume of the paw was assessed (before the administration of carrageenan), as well as the volume of the paw after 2 hours (early phase of development of exudation), 4-6 hours (piccarrageenan edema) and 24 hours after the induction of inflammation (late phase of development of exudation) [15].

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An acute exudative reaction (peritonitis) was induced by intraperitoneal injection of 1% acetic acid [16]. After 3 hours, the animals were sacrificed, the abdominal cavity was opened, and the exudate was collected. The anti-exudative effect was judged by the reduction in the volume of exudate as a percentage of the control. Anti-inflammatory activity was expressed as a percentage of edema suppression:

Inflammation Suppression Percentage = (Vc-Ve) : Vc x 100

Where, Vc and Ve are the average increase in the volume of ascitic fluid in control and experimental animals, respectively.

To measure rectal temperature (T), a TPEM-1 thermometer (Russia) was used; temperature readings were recorded with an accuracy of 0.1°C. Before the administration of baker's yeast, the basal level of rectal temperature was measured in the animals, after which a 20% suspension of baker's yeast, preheated in a water bath to 37°C, was injected subcutaneously into the area between the shoulder blades at a dose of 10 ml/kg [17]. In order to determine the dynamics of fever, the rectal temperature was measured six hours later and every hour thereafter after injection of the yeast suspension. After 8 hours, a peak fever (T_{max}) was noted; animals whose temperature increased by more than 0.5°C were included in the further experiment. At the maximum of the fever (i.e., 8 hours after the introduction of yeast), the above medicines were administered intragastrically, after which, the temperature measurements were taken after 1 hour (T_{1h}), 2 hours (T_{2h}), 3 hours (T_{3h}) to assess the dynamics of the action of the compound.

Analgesic activity was determined on adult white male mice in the “hot plate” test, based on behavioral reactions controlled by supraspinal structures in response to painful stimulation [18]. The animals were placed on a metal plate heated to an average of 55 °C, surrounded by a cylinder. The time from the moment of placement on the hot surface until the appearance of a behavioral response to nociceptive stimulation in the form of jumping, withdrawing and licking the hind paws was recorded [19]. Peripheral analgesic activity was studied by changes in the nociceptive reactions of animals in the “writhing test” model. Writhing was induced in mice by a single intraperitoneal injection of a 0.6% acetic acid solution (1 ml per 100 g of animal weight) [20]. The studied medicines were administered 1 day and 1 hour before the administration of acetic acid, and the number of writhings was counted for 10 minutes.

The obtained data were processed by the method of variation statistics using the paired Student's test and one-way analysis of variance using the standard software package BIOSTAT 2009 with an assessment of the significance of indicators (Mean±Std error). Differences in the compared groups were considered significant at a significance level of 95% $p < 0.05$.

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Research results

Non-steroidal anti-inflammatory drugs have anti-inflammatory activity, a distinct manifestation of which is the suppression of the exudation process. One of the most commonly used tests to determine anti-inflammatory activity is the carrageenan test, unlike formalin-induced paw edema, in which injury of the paw is not observed. The development of edema after carrageenan injection develops in several phases, in each of which the release of various mediators is observed. In the initial (early) phase and at the peak of exudation (the first 2 hours after the induction of inflammation), the release of histamine, serotonin and bradykinin predominates; at a later stage, the release of prostaglandins is observed [18].

The results of studies on a model of aseptic arthritis induced by carrageenan showed that preventive administration of the studied FC clearly suppresses the exudation process. Thus, in control animals (placebo), the injection of carrageenan led to an increase in the volume of the paws by 76.4; 123.6 and 109.1% compared to the initial volume, respectively, after 2, 4 and 6 hours from the moment of injection of flogogen. At the same time, the volume of the paws remained statistically significantly increased even after 24 hours from the beginning of the experiment.

Consequently, the development of inflammation under the influence of carrageenan develops to a greater extent in the fourth hour of the experiment and persists for quite a long time.

In contrast, preventive administration of canephron - a herbal medicine had a moderate reduction in the intensity of aseptic inflammation. Thus, its anti-inflammatory activity in the above observation periods was 4.8; 8.8 and 16.7% respectively. We found a higher antiflogogenic effect in groups of animals receiving sodium diclofenac and FC. From the data in Table 1, it can be seen that after 2, 4 and 6 hours from the start of the experiment, the anti-inflammatory activity of diclofenac sodium was 33.3; 42.6 and 45.0%, and the studied FC - 28.6; 38.2 and 41.7% respectively.

Table 1

Study of the effect of phytocomposition, canephron and diclofenac sodium on the course of aseptic inflammation induced by carrageenan (M±m, n=6)

Groups	Paw volume, cm^3(hours of study)				
	initial	2 hours	4 hours	6 hours	24 hours
Control	0,55±0,02	0,97±0,06*	1,23±0,06*	1,15±0,05*	0,80±0,07*
Canephron	0,53±0,03	0,93±0,06*	1,15±0,05*	1,03±0,08*	0,69±0,07
Diclofenac	0,55±0,02	0,83±0,04*	0,94±0,06*	0,88±0,06*	0,62±0,05
FC	0,57±0,02	0,87±0,07*	0,99±0,07*	0,92±0,07*	0,66±0,04

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Note: * - significant difference with the initial indicators of the corresponding groups of animals.

Consequently, the new phytocomposition is clearly superior to canephron by its antiflogogenic activity and it is not significantly inferior to diclofenac sodium.

It is known that the antiexudative activity of drugs is also assesed by the method of inducing aseptic peritonitis by intraperitoneal injection of acetic acid [21, 22]. Therefore, in the next series of experiments, we studied the antiexudative activity of FC in a model of aseptic peritonitis. It was established that intraperitoneal injection of acetic acid leads to the formation of exudative fluid in control group's animals in a volume of 3.18 ± 0.23 ml during the first 3 hours from the start of the experiment. At the same time, in animals preventively receiving canephron, diclofenac sodium and FC, volume of fluid was 2.43 ± 0.26; 1.78 ± 0.14 and 1.95 ± 0.16 ml., so, the suppression of the intensity of the exudation process under the influence of medicines was 23.6; 44.0 and 38.7% respectively.

In modern clinical practice, the prevalence of pain syndrome is extremely high due to the numerous and diverse ethiological causes [23]. Anti-inflammatory drugs, as noted, are characterized by suppression of pain sensitivity due to a decrease in excitation of nociceptors by inflammatory mediators, a change in the reaction of the inflammatory focus, and the influence of a number of biologically active substances secreted into the focus of inflammation by leukocytes [24, 25]. It can be seen in table 2 that the number of writhings after intraperitoneal administration of acetic acid for 10 minutes was 37.33 ± 1.5 times in healthy animals. At the same time, in animals preventively receiving canephron it decreased by only 7.0%, and in animals receiving diclofenac sodium and FC - by 41.9 and 38.8%, respectively. It can be seen that FC has a distinct analgesic activity. This conclusion is confirmed by the results of the experiment conducted on the "hot plate" model [24]. Thus, if in healthy mice, the onset of twitching and licking due to the sensation of pain in the paws began 28.84 ± 2.61 seconds from the start of placing them on the hot plate, then in animals receiving preventive canephron it lengthened by only 4.5%, then under the influence of diclofenc sodium and FC it was 76.2 and 68.3% more than control group.

Table 2

Analgesic activity of phytocomposition, canephron and diclofenac sodium on the "writhing" and "hot plate" model (M±m, n=6)

Medicine	Absolute number of "writhings" in 10 minutes	Pharmacological activity,%	Beginning of time for twitching and licking paws, seconds	Pharmacological activity,%
Control	37,33 ± 1,51	-	28,84±2,61	-
Canephron	34,71±3,03*	15,6	30,15±2,91	4,5

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diclofenac	21,66±2,16*	41,9	50,83±4,41*	68,3
PC	22,83±1,84*	38,8	48,53±4,29*	78,4

Note: * - statistically significant differences compared to control.

Consequently, canephron in this model and in the previous one did not exhibit analgesic activity, while diclofenac sodium and FC exhibited a clear analgesic effect.

In experimental pharmacology, the classic model for inducing of hyperthermia is pyrogenal-induced fever, in which, Pyrogenal is used for inducing the fever. Pyrogenal is a lipopolysaccharide isolated from bacteria *Salmonella typhi*. This model has proven itself well in testing various compounds as antipyretics in laboratory animals. However, the increase in body temperature in response to the injection of lipopolysaccharide is extremely unstable in small individuals. In this regard, the model of yeast-induced fever, in which brewer's or baker's yeast can be used to induce the hyperthermia of the body in laboratory animals, has become widespread for studying the antipyretic properties of medicines in small rodents [17,26,27].

At the next stage of the study, we conducted experiments to study the antipyretic activity of PC. From the data in Table 3 it is clear that the initial rectal temperature of animals of different groups practically did not differ from each other. The injection of a suspension of nutritional yeast led to an increase in temperature during the eight hours of the experiment by 3.1 - 3.3%, which remained with slight fluctuations in the next three hours of the experiment. Administration of the studying medicines led to a decrease in rectal temperature. Thus, 1 hour after the administration of Canephron, the body temperature decreased by 13.0%, and after two and three hours by 22.6 and 33.0%, respectively, compared to before administration of the medicine. We found a more distinct effect in animals receiving diclofenac sodium and PC. Under the influence of which the decrease in temperature respectively was 29.7 and 17.7; 39.8% and 29.2; 46.9 and 42.5% in the specified periods of the study. These data allow us to conclude that in terms of its hypothermic activity, canephron is somewhat inferior to PC, which is not statistically significantly different from the results, especially in the fourth hour of the experiment.

Table 3

Changes the body temperature of rats on a model of yeast-induced fever after administration of a phytocomposition, canephron and sodium diclofenac

(M±m, n=6)

Groups	$T_{initial}$	$T_{max.}$	$T_{after\ 1\ hour}$	$T_{after\ 2\ hour}$	$T_{after\ 3\ hour}$

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Control	38,26±0,08	39,46±0,07* 1,20±0,08	39,33±0,06* 1,07±0,07	39,25±0,06* 0,99±0,07	39,13±0,08* 0,87±0,07#
Canephron	38,48±0,07	39,63±0,13* 1,15±0,10	39,48±0,15* 1,00±0,08	39,37±0,16* 0,89±0,07	39,25±0,16* 0,77±0,06#
Diclofenac	38,65±0,07	39,93±0,07* 1,28±0,11	39,55±0,09* 0,90±0,08#	38,42±0,10* 0,77±0,07#	39,33±0,16* 0,68±0,06#
PC	38,43±0,07	39,56±0,08 1,13±0,10	39,36±0,11 0,93±0,08	39,23±0,10 0,80±0,07#	39,08±0,08 0,65±0,06#

Note: the numerator is the absolute body temperature, and the denominator is the difference in initial and current body temperature. * - significant difference in relation to the initial index, # - significant difference in relation to the corresponding periods of the study comparing control group.

Consequently, the new PC has distinct antiexudative, analgesic and antipyretic activity. In this regard, PC is superior to canephron, a well-known herbal medicine, and is not noticeably inferior to diclofenac sodium. In our opinion, the mechanism of the pharmacological activity of PC probably lies in its antioxidant properties due to the content of flavonoids in it [15, 18, 28, 29, 30]. Thus, the PC clearly suppress the intensity of free radical oxidation of lipids, leading to the formation of arachidonic acid, the main source of prostaglandin synthesis [25]. Considering the absence of a toxic effect of PC, as with acute and chronic administration [31], as well as its high anti-inflammatory activity in various models of aseptic inflammation, the presence of a clear antiproliferative and anti-alterative activity [11, 12, 13] and the data of this study, we can conclude that PC might be a potential anti-inflammatory medicine for the pharmacotherapy of diseases in the pathogenesis of which inflammation plays a significant role.

Conclusions

1. A phytocomposition consisting of extracts of medicinal plants *Herba alhagi, Folium Uvae ursi, Fructus Rosae, Glycyrrhiza glabra* and *Flores chamomillae* has a distinct anti-exudative activity.

2. In experimental animals on the “hot plate” and “writhing” model, the studied phytocomposition exhibits clear analgesic activity.

3. On the model of yeast-induced fever, the studied phytocomposition, like sodium diclofenac, exhibits an antipyritic effect.

4. In terms of its pharmacological activity and spectrum of action, the phytocomposition is not significantly inferior to diclofenac sodium.

5. The developed phytocomposition can be a potential medicine in the treatment of diseases in the pathogenesis of which inflammation plays a significant role.

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