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Study of the Anti-Inflammatory Activity of the Polymer Composition of Cotton Cellulose – Gossypol in Male Rats

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Abstract Gossypol is a typical representative of polyphenolic compounds and it has many pharmacological properties. The aim of this work was to study the effect of the polymer complex gossypol (PCG) - celagripp on the course of aseptic arthritis induced by various phlogogens. The experiments were carried out on sexually matured white male rats with an initial weight of 160-180 g. The anti-exudative effect of the drugs was studied on a model of acute inflammatory edema of the rat paw induced by the injection of the 0.1 ml 2% solution of formalin, 6% solution of dextran and 0.1% solution of histamine into subplantar aponeurosis. Diclofenac sodium at a dose of 10 mg/kg and PCG at doses of 10, 25 and 50 mg/kg were intragastrically administered to the experimental animals 1 hour before the reproduction of the model of inflammation, respectively. It was found that the polymer composition of gossypol from cotton cellulose has a expressed anti-inflammatory activity, which relates to the content of a polyphenolic compound in it. It is believed that its high anti-inflammatory activity in a model of histamine-induced aseptic arthritis is possibly related to antihistamine activity. It was revealed that in terms of its pharmacological activity, the polymer composition of gossypol is inferior to the activity of the reference drug diclofenac sodium in the experiments on aseptic arthritis models.

Keywords Inflammation, Exudation, Phlogogens, Gossypol polymer composition

1. Introduction

The modern concept of inflammation considers inflammation with a position of decisive participation in non-oxidative stress, since by now a lot of clinical and experimental data have been accumulated proving the important role of activated oxygen metabolites and other radicals in the pathogenesis of inflammation, in the occurrence and development of all its main stages [1]. It is accepted that the greatest role in multidirectional effect of flavanoids on the human body is played their antioxidant properties. The latter, directly or indirectly, weakens and prevents cells' damage by free radicals, which so-called reactive oxygen forms [2].

Gossypol is a typical representative of polyphenolic compounds and it has many pharmacological properties. However, its high toxicity sharply limits its widespread use. Based on this, a number of gossypol derivatives have been synthesized that exhibit a distinct immunomodulatory effect. A polymer complex of gossypol - celagrip has been synthesized, which has low toxicity and high activity to stimulate the synthesis of interferon [3,4]. The synthesis of cytokines is significantly stimulated under the influence of this compound. It is known that there are cytokines with pro- and anti-inflammatory action. Based on this, it can be assumed that celagripp can significantly change the course of aseptic inflammation. Since the use of celagripp is recommended for the treatment of acute viral infections accompanied by an inflammatory process. The study of the features of the course of the inflammatory process during the application of celagripp had important interest. However, this problem remains poorly understood.

The aim of this work was to study the effect of the polymer complex gossypol (PCG) - celagripp on the course of aseptic arthritis induced by various phlogogens.

2. Material and Methods

2.1. Experiments

The experiments were carried out on sexually matured white male rats with an initial weight of 160-180 g. Before the experiment, the animals were quarantined for 12-14 days. All animals were kept in vivarium condition (with natural lighting, at a temperature of 22-24℃, relative air humidity 55-60%) in plastic cages 55x45x15 cm in size, with sawdust bedding, 6 animals per cage. Experimental studies were carried out in accordance with the "Rules for laboratory work using experimental animals", as well as the rules given in the European Convention for the Protection of Vertebrate Animals used for Experimental Research or for Other

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The anti-exudative effect of the drugs was studied on a model of acute inflammatory edema of the rat paw induced by the injection of the 0.1 ml 2% solution of formalin, 6% solution of dextran and 0.1% solution of histamine into subplantar aponeurosis of the right hind limb of the animal [6,7,8].

Diclofenac sodium at a dose of 10 mg/kg and PCG at doses of 10, 25 and 50 mg/kg were intragastrically administered to the experimental animals 1 hour before the reproduction of the model of inflammation, respectively. The control group of rats received an equivalent volume of water. The volume of the right hind paw of the animals was measured using a plethysmometer before and 1, 2, 3 and 4 hours after the injection of dextran and histamine, and 2, 4, 6, 8 and 24 hours after the injection of formalin. The value of anti-inflammatory activity (VAA) of drugs was calculated according to the formula [6,7]:

$$VAA = Vcontrol\text{-}Vexperiment / Vcontrol \times 100 = \%$$

Where: Vcontrol - the average increased volume of the rat's paw of control group, Vexperiment - the average increased volume of the rat's paw of treated group [6].

The obtained research results were processed by the method of variation statistics using the standard StatPlus 2009 software package with an assessment of the significance of indicators (M±m) and differences in the samples under consideration by the Student's t-test. The difference was considered significant at a probability level of 95% and more ($P<0.05$).

3. Results and Discussion

Formalin edema of the rat's paw is being investigated to study both new potential anti-inflammatory drugs and the mechanism of development of the inflammatory process [9]. At the same time, after subplantar injection of formalin cardinal signs of inflammation - edema, hyperalgesia, erythema develop without damaging of the tissues of the inflamed paw. Many authors suggest using formalin edema of rodent paws as an alternative method to carrageenan edema when developing new potential anti-inflammatory drugs. [7,9,10,11].

The analysis of the results of the experimental studies showed that after the injection of formalin, there was a significant increase of the volume of paws maximum by the sixth hour of the study (more than 2.5 times), which persisted with slight fluctuations even by the end of the first day of the experiment (see Table 1). In contrast, in animals receiving PCG, the increase of the paw volume was noticeably less compared to the initial one. So, the maximum increase of the volume of the paws in control rats compared to the initial was 141.7% (by the sixth hour).

In animals, preventively receiving PCG at a dose of 10 mg/kg and 25 mg/kg, it was 113.5%, and 100.0%, respectively. At the same time, an increasing the dose of the drug to 50 mg/kg led to increase of the anti-inflammatory effect and an increase of the paw volume was 91.7% compared to the initial value. At the same time, it was 83.0% in diclofenac sodium received animals. It is noteworthy that the anti-inflammatory effect of the drug increased over time. Thus, the anti-inflammatory activity of PCG at a dose of 10 mg/kg by the end of the fourth hour was 17.0%, and by the end of the sixth hour it was 17.6%, while by the end of the first day it was 37.7%. It can be seen from the data in figure 1 that increasing of the dose of the compound by 2.5 times led to an almost twofold increasing of its anti-inflammatory activity. In the indicated periods of observation, the values of anti-inflammatory activity in 25 mg/kg were equal from 33.3 to 38.5%, and in 50 mg/kg till 50.0%. In our experiment, the anti-inflammatory activity of the classic representative of non-steroidal anti-inflammatory drugs - diclofenac sodium was 38.5-51.9%. It can be seen that the studied polymer complex of cotton cellulose - gossypol in its pharmacological activity is practically not inferior to diclofenac sodium.

Table 1. Comparative study of the effect of PCG and diclofenac sodium on the course of formalin-induced aseptic arthritis

Groups	Dose mg/кg	Volume of paw, cm^3					
		Initial	2 hour	4 hour	6 hour	8 hour	24 hour
Control	-	0,72 ± 0,03	1,11 ± 0,04* 0,39 ± 0,02	1,43 ± 0,07* 0,71 ± 0,05	1,74 ± 0,08* 1,02 ± 0,06	1,65 ± 0,06* 0,93 ± 0,04	1,24 ± 0,04* 0,52 ± 0,03
PCG	10	0,74 ± 0,02	1,07 ± 0,07* 0,34 ± 0,04	1,33 ± 0,08* 0,59 ± 0,06	1,58 ± 0,09* 0,84 ± 0,09	1,49 ± 0,09* 0,75 ± 0,07	1,10 ± 0,05 0,36 ± 0,04#
PCG	25	0,69 ± 0,02	0,96 ± 0,04* 0,27 ± 0,03#	1,18 ± 0,06* 0,49 ± 0,05#	1,38 ± 0,09* 0,69 ± 0,07#	1,29 ± 0,09* 0,60 ± 0,06#	1,02 ± 0,04* 0,33 ± 0,03#
PCG	50	0,72 ± 0,03	0,98 ± 0,06* 0,26 ± 0,03#	1,19 ± 0,09* 0,42 ± 0,05#	1,32 ± 0,10* 0,60 ± 0,06#	1,27 ± 0,09* 0,54 ± 0,05#	0,98 ± 0,06* 0,26 ± 0,04#
Diclofenac sodium	10	0,70 ± 0,04	0,94 ± 0,05* 0,24 ± 0,03#	1,13 ± 0,04* 0,43 ± 0,03#	1,28 ± 0,05* 0,58 ± 0,05#	1,20 ± 0,04* 0,50 ± 0,05#	0,93 ± 0,02* 0,25 ± 0,03#

Note: in the numerator there are absolute indicators of the volume of the paws, and in the denominator the difference in edema of the paws by the hour; * - statistically significant in comparison with the initial value of paw volume ($P<0.05$). # - statistically significant in comparison with control group's animals ($P<0.05$).

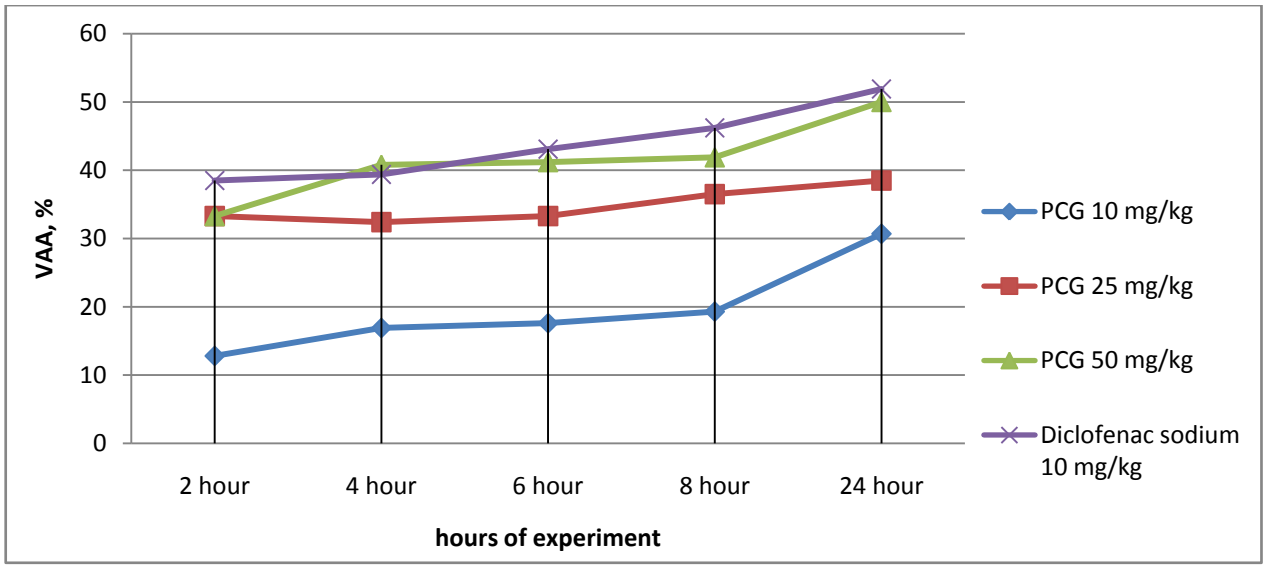

Figure 1. Anti-inflammatory activity of PCH and diclofenac sodium in formalin-induced aseptic arthritis

It is known that the mechanism of the phlogogenic action of formalin is due to its interaction with the amino groups of proteins and the release of biogenic amines and free amino acids, followed by a violation of isionium and isotony at the injection site. These data indicate significant differences of the mechanism of the phlogogenic action of formalin from other substances inducing inflammation process [1,9,12].

The anti-inflammatory activity of PCG was studied on a model of acute aseptic arthritis induced by dextran at the next stage of the experimental study.

The results of the studies showed that, a expressed edema of the rat paws developed under the influence of dextran with a maximum effect 1 hour after the injection of phlogogen, which persisted for next 4 hours of the experiment. Anti-inflammatory drugs suppressed the development of edema in rat paws. Thus, the preventive administration of a reference non-steroidal anti-inflammatory drug - diclofenac sodium reduced the volume of the paws of animals, and value of anti-inflammatory activity was 41.0% after 1 hour, 43.0% after 2 hours, after 45.0% 3 hours and 47.0% after 4 hours.

It was shown that the preventive administration of PCG also exhibits a distinct anti-inflammatory activity. As can be seen from the data of table 2, the value of anti-inflammatory activity of the PCG at a dose 10 mg/kg was 24.0-28.0% in the studied periods of the experiment, and the increasing of the dose of PCG to 25 mg/kg led to increase the antiphlogogenic effect. At the same time, the PCG at a dose of 50 mg/kg suppressed the inflammatory process at almost the same level as diclofenac sodium.

Consequently, PCG had an expressed anti-exudative effect, which was manifested in the suppression of dextran-induced aseptic arthritis.

It is believed that the development of aseptic inflammation induced by dextran is due to the release of histamine and serotonin from mast cells, which are one of the important mediators of inflammation [13].

Table 2. Comparative study of the effect of PCG and diclofenac sodium on the course of aseptic arthritis induced by dextran

Groups	Dose mg/kg	Volume of paw, cm^3				
		Initial	1 hour	2 hour	3 hour	4 hour
Control	-	0,67 ± 0,02	1,62 ± 0,08* 0,95 ± 0,09	1,55 ± 0,07* 0,88 ± 0,08	1,51 ± 0,06* 0,84 ± 0,06	1,42 ± 0,07* 0,75 ± 0,07
PCG	10	0,64 ± 0,03	1,36 ± 0,09* 0,72 ± 0,09	1,29 ± 0,09* 0,65 ± 0,09	1,25 ± 0,08* 0,61 ± 0,08	1,18 ± 0,06* 0,54 ± 0,06
PCG	25	0,71 ± 0,03	1,34 ± 0,08* 0,63 ± 0,08#	1,27 ± 0,05* 0,56 ± 0,05#	1,22 ± 0,06* 0,51 ± 0,05#	1,16 ± 0,05* 0,45 ± 0,05#
PCG	50	0,69±0,04	1,28 ± 0,11* 0,59 ± 0,07#	1,23 ± 0,10* 0,54 ± 0,08#	1,18 ± 0,10* 0,49 ± 0,07#	1,12 ± 0,07* 0,43 ± 0,05#
Diclofenac sodium	10	0,68 ± 0,04	1,24 ± 0,09* 0,56 ± 0,08#	1,18 ± 0,08* 0,50 ± 0,07#	1,14 ± 0,10* 0,46 ± 0,05#	1,08 ± 0,11* 0,40 ± 0,04#

Note: in the numerator there are absolute indicators of the volume of the paws, and in the denominator the difference in edema of the paws by the hour; * - statistically significant in comparison with the initial value of paw volume ($P<0.05$). # - statistically significant in comparison with control group's animals ($P<0.05$).

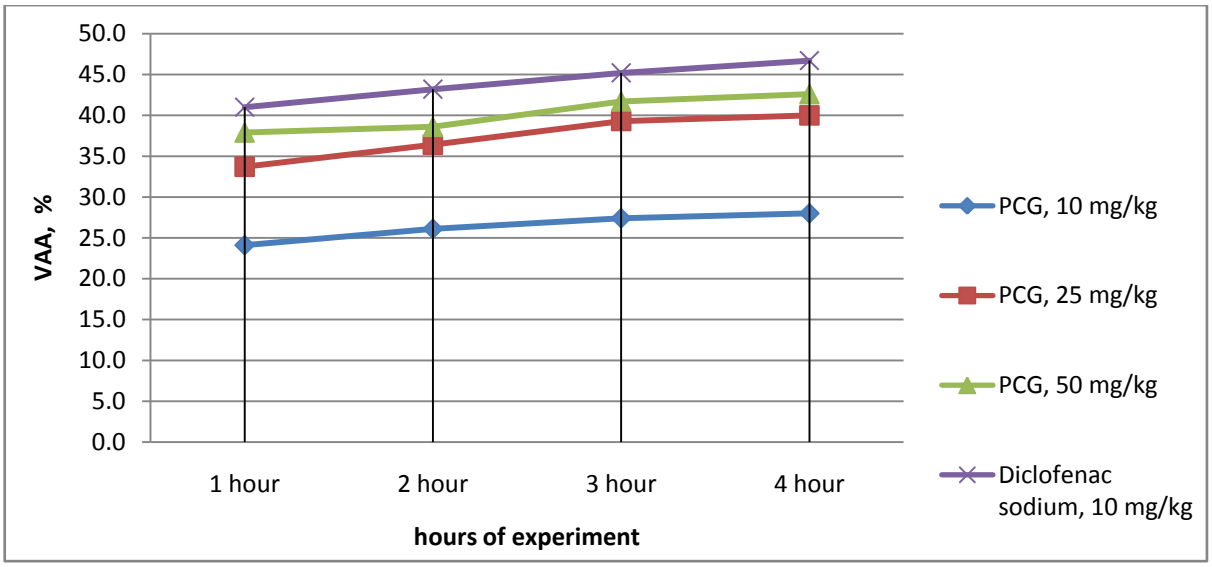

Figure 2. Anti-inflammatory activity of PCH and diclofenac sodium in dextran-induced aseptic arthritis

Table 3. Comparative study of the effect of PCG and diclofenac sodium on the course of aseptic arthritis induced by histamine

Groups	Dose mg/kg	Volume of paw, cm^3				
		Initial	1 hour	2 hour	3 hour	4 hour
Control	-	0,62 ± 0,03	1,43 ± 0,09* 0,81 ± 0,10	1,35 ± 0,10* 0,73 ± 0,11	1,27 ± 0,09* 0,65 ± 0,10	1,17 ± 0,08* 0,55 ± 0,09
PCG	10	0,63 ± 0,04	1,31 ± 0,06* 0,68 ± 0,08	1,22 ± 0,06* 0,59 ± 0,08	1,15 ± 0,05* 0,52 ± 0,08	1,05 ± 0,05* 0,42 ± 0,08
PCG	25	0,67 ± 0,02	1,26 ± 0,09* 0,59 ± 0,09	1,17± 0,09* 0,50 ± 0,08	1,09 ± 0,08* 0,42 ± 0,08	0,99 ± 0,09* 0,32 ± 0,08
PCG	50	0,57 ± 0,03	1,07 ± 0,09* 0,50 ± 0,06#	0,99 ± 0,08* 0,42 ± 0,06#	0,89 ± 0,08* 0,32 ± 0,06#	0,80 ± 0,08* 0,23 ± 0,06#
Diclofenac sodium	10	0,66 ± 0,03	1,13 ± 0,10* 0,47 ± 0,10#	1,05 ± 0,09* 0,39 ± 0,09	0,96 ± 0,08* 0,30 ± 0,08#	0,86 ± 0,07* 0,20 ± 0,08#

Note: in the numerator there are absolute indicators of the volume of the paws, and in the denominator the difference in edema of the paws by the hour; * - statistically significant in comparison with the initial value of paw volume ($P<0.05$). # - statistically significant in comparison with control group's animals ($P<0.05$).

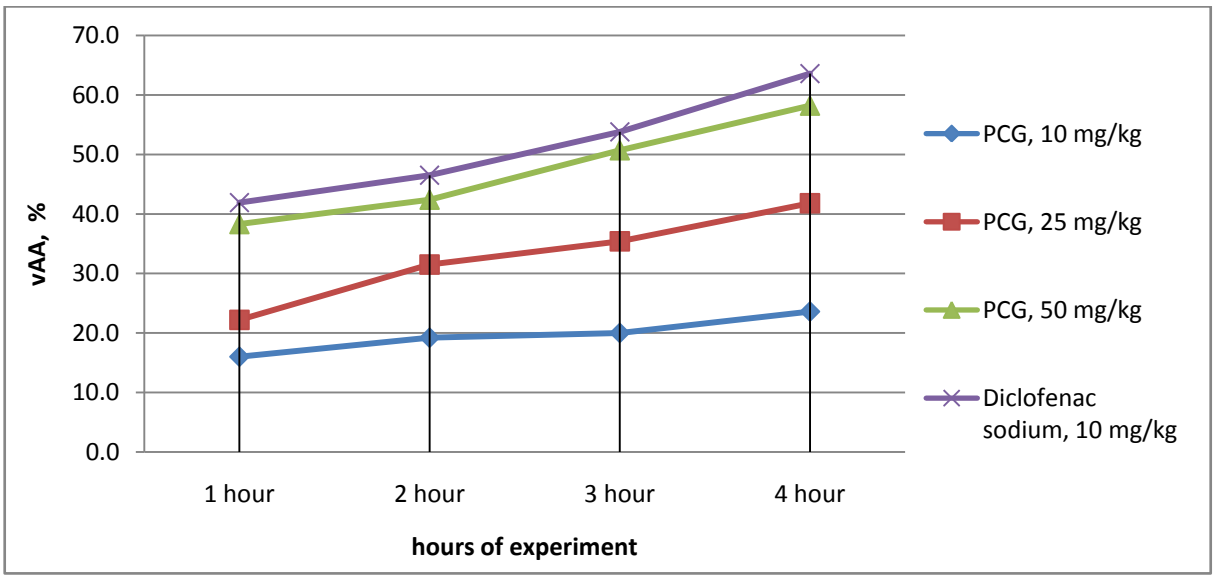

Figure 3. Anti-inflammatory activity of PCG and diclofenac sodium in histamine-induced aseptic arthritis

Based on this, in a separate series of experiments were carried out to study the antiphlogogenic activity of various doses of PCG in histamine-induced aseptic arthritis. Subplanar injection of histamine led to an increase of the paw volume of the control groups of rats compared to the initial volume by 2.3-2.5 times, which remained at a sufficiently high level by the end of the fourth hour of the experiment (see Table 3).

The increase of the paw volume of rats was significantly lower In the group of animals preventively treated with PCG at doses 10, 25, and 50 mg/kg, especially at a dose 50 mg/kg. The calculation of the value of the anti-inflammatory activity of the drug in the indicated observation periods after one hour from the beginning of the experiment was 16.0%; 27.2% and 38.3%, respectively, by the end of the second hour - 19.2%; 31.5% and 42.4% (see Fig. 3). It is noteworthy that in the following hours of observation, this indicator clearly increased. At the same time, the pharmacological activity of the drug did not significantly differ from the activity of sodium diclofenac. Therefore, it can be assumed that PCG has an antihistamine effect, which underlies its anti-inflammatory activity in dextran-induced arthritis.

Thus, the results of the conducted experimental studies allow us to conclude that PCG from cotton cellulose has a high anti-inflammatory activity, which is manifested in models of aseptic arthritis induced by formalin, dextran and histamine. It is known that they have different mechanisms of action in the development of inflammation.

It is noteworthy that the studied PCG by its pharmacological activity is not inferior to, but in some degree superior to the well-known reference non-steroidal anti-inflammatory drug diclofenac sodium. In our opinion, along with antagonistic action with histamine, the main mechanism of the anti-inflammatory activity of PCG is its high antioxidant activity, because polyphenolic compounds have the property of decreasing reactive form of oxygen.

Under these conditions, the formation of arachidonic acid during the destruction of membranes of subcellular structures is suppressed, which causes inhibition of the synthesis of cyclic endoperoxides, the main sources of the formation of prostaglandins - important mediators of inflammation. PCG with the different mechanisms of action can be used in patients in whom the use of NSAIDs cannot be used due to the development of gastro-, nephro-, cardiopathy and other complications [14,15,16].

Considering the diversity of the biological activity of polyphenols, the relatively low cost of obtaining preparations and the closeness of polyphenols to us in nature, we can assume that PCG has great perspective as anti-inflammatory agent. Along with this, the obtained results are a prerequisite for conducting experimental studies of PCG as an anti-inflammatory agent in pathologies in which the intensification of free radical oxidation processes and weakening of the antioxidant defense of the body play a leading role in their pathogenesis.

4. Conclusions

1. The polymer composition of gossypol from cotton cellulose has a expressed anti-inflammatory activity, which is due to the content of polyphenolic compounds in it.
2. Considering the high anti-inflammatory activity of the polymer composition of gossypol in the model of histamine-induced aseptic arthritis, it can be assumed that this compound has antihistaminic activity.
3. In terms of its pharmacological activity, the polymer composition of gossypol is inferior to the effect of the reference drug diclofenac sodium in various experimental models of aseptic arthritis.

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