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RESEARCH ARTICLE

Study of certain mechanisms of anti-edema action of dry extract of medicinal plants

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ABSTRACT

Background: An actual problem of pharmacology is the search and development of new medications for treatment inflammatory diseases. **Aims and Objectives:** The mechanism of the anti-edema action of dry extract of medicinal plants (DEMPs) was established in experiments using various phlogogens. **Materials and Methods:** Experimental models of aseptic arthritis were reproduced by subplantar injection of dextran, histamine, and formalin in a volume of 0.1 ml into the hind paw of rats. The preventive effect of DEMP (50 mg/kg) was studied in comparison with diclofenac sodium (10 mg/kg) and LIV-52 (100 mg/kg). **Results:** It is believed that its mechanism is largely associated not only with the antioxidant property of the medication but also with the stimulation of the production of glucocorticoid hormones in the adrenal gland, as well as regulation of the level of pro- and anti-inflammatory interleukins, cortisol, and suppression of the formation of arachidonic acid. **Conclusions:** The multicomponent mechanism of the anti-inflammatory action of DEMPs determines its high antiexudative, antiproliferative, and antialterative properties in inflammation with different etiologies.

KEY WORDS: Inflammation; Mechanism; Anti-Inflammatory Drugs; Hormones; Interleukins

INTRODUCTION

End of the 20th century was marked by a number of major advances in molecular and cell biology that open up broad prospects for the development of effective drugs based on biomedical technologies that can solve the problem of treating a number of the most common diseases. Inflammatory diseases, including rheumatism, continue to occupy a significant place in modern medicine.[1] Nonsteroidal anti-inflammatory drugs (NSAIDs) are actively used in clinical practice in the treatment of inflammatory diseases. The number of "consumers" of NSAIDs is very large and is growing all the time. Hence, 19.2 million patients were registered systematically using NSAIDs in Russia in 2016, while 125 million packages of various NSAIDs were sold in 2017.[2] However, the use of NSAIDs is accompanied by quite significant side effects: Gastroduodenal erosion, ulcers, cardiovascular damage, progression of atherosclerosis, kidney damage, etc.[3,4] At the same time, the development of NSAID-induced enteropathy is a significant clinical problem, especially among the elderly people.[5] In this regard, an actual problem of pharmacology is the search and development of new medications for treatment inflammatory diseases. It should be noted that currently anti-inflammatory medications from medicinal plants are not widely used enough, which may have a slightly less effect, but have better tolerance and less toxicity.[6,7] A wide range of pharmacological properties such as softness and lack of side effects is considered the advantage of using herbal medications for long time. They are easily included in biochemical processes, since they are close to the human

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body in chemical nature.[6,7] We have previously shown that a mixture of extracts of medicinal plants *Glycyrrhiza glabra* L., *Hypericum scabrum* L., *Mediasia macrophylla,* and *Ziziphora pedicellata* Pazij Vved. has a distinct anti-inflammatory effect.[8,9] However, the mechanism of its anti-inflammatory action remained unexplored.

The aim of this work was to investigate the possible mechanisms of the anti-inflammatory activity of dry extract of medicinal plants (DEMPs).

MATERIALS AND METHODS

All experimental studies were carried out on sexually matured unbred white male rats, which were obtained from the vivarium of the Sanitary and Epidemiological Surveillance Department of the Main Medical Directorate under the Administration of the President of the Republic of Uzbekistan. Before the start of the experiment, all laboratory animals were carefully examined, weighed, their age, sex, and physical activity were taken into account. During the experiment, laboratory animals were kept in a vivarium in standard plastic cages by six animals in each with a standard diet and in a well-ventilated room with day/night light mode at a temperature of 20–25°C, humidity was at least 50%.

Plant Material and Preparation of Dry Extract

DEMPs were obtained from plants: *H. scabrum* L., *M. macrophylla*, *G. glabra* L., and *Z. pedicellata* Pazij Vved. Aerial parts of *Hypericum perforatum* L., *Z. pedicellata* Pazij et Vved., and *M. macrophylla* as well as root and rhizome parts of *G. glabra* L. were obtained in summer of 2017 from foothills to medium zones of mountains of Tashkent region, Fergana, Samarkand and Surkhandaryo regions of Uzbekistan. Plant material was dried under dark conditions at room temperature for 10 days. Taking into account that the soil is contained various bacterial spores, raw material of plants was treated with special methods. The dry material was milled, obtaining 4–6 mm particles and mixed in proportion 1.25:1.0:1.25:1.5 (productivity of dried extract was higher than other proportions) then extracted by water at 93–95°C temperature for 3 h. The extract was then separated from the sample residue by filtration through filter paper. The resulting extracts were concentrated in vacuum until remaining a crude solid extract, which was then dried in a thermostat at temperature of 60°C.

Experimental Models

Inflammatory edema was modeled by subplantar injection of various phlogogens, which are widely used to evaluate the anti-inflammatory activity of new potential medications, in male rats of a mixed population with an initial weight of 155–170 g.[10] Experimental models of aseptic arthritis were reproduced by subplantar injection of dextran, histamine, and formalin in a volume of 0.1 ml into the hind paw of rats. The preventive effect of DEMP (50 mg/kg) was studied in comparison with diclofenac sodium (10 mg/kg) and LIV-52 (100 mg/kg). The above medications were preventively administered intragastrically with a metal probe 1–2 h before the introduction of the phlogogen. Measurement of the paw volume of animals was carried out using a plethysmometer before and in 60, 120, 180, and 240 min after the introduction of 6% dextran solution, 0.1% histamine. After injection of 2% formalin solution, the measurement of paw edema was carried in 2, 4, 6, 24, and 48 h. The value of anti-inflammatory activity (VAA) of drugs was calculated using the formula:

$$VAA = V_{con} – V_{exp}/V_{con} \times 100 = \%.$$

where, V_{con} – the average increase in the volume of the paw in the control cm^3, V_{exp} – the average increase in the volume of the paw in the experiment cm^3.

We used samples of rat blood serum for investigation after administration of DEMP, diclofenac sodium, and LIV-52 in the studied doses.

The commercial ELISA kits were used for determining the total amount of cortisol, interleukins IL-10 and IL-1β (Human Diagnostics (Germany), Vector-Best (Russia)). The concentration of cortisol and interleukins IL-10 and IL-1β in blood serum was determined by the method of enzyme-linked immunosorbent assay.

In a separate series of experiments, adrenalectomy was performed in compliance with the rules of asepsis and antiseptics. For this, after cleaning the wool, we made a skin incision 1.5–2 cm along the spine of animals under pentobarbital sodium anesthesia (40 mg/kg). Then, we cut soft tissue 1.5–2 cm long on both sides below 12 ribs. The adrenal glands were removed together with the connective tissue cord by grasping with forceps. Soft tissues and skin were sutured in layers. After the operation, the animals received mixed food and 1% sodium chloride solution instead of water. On the 8th day after the operation, 2 h after the administration of DEMP, a dextran solution was injected subplantar and the course of the inflammatory process was investigated.

Permission from Ethic Committee of the Republic of Uzbekistan was taken for carrying out experiments on animals. All experiments were performed in compliance with the requirements of the European Convention "On Protection of vertebrate animals used for experimental and other scientific purposes" (Strasbourg 1986).

Statistics

The received results were subjected to the statistic processing with the using of standard software package BioStat 2009 on

well-known method of variation statistics with an estimation of the statistical significance of indicators (M±m) and differences between groups were analyzed using the Student's *t*-test. $P<0.05$ was considered statistically significant.

RESULTS

The observed findings of the present study are depicted in Tables 1-5.

DISCUSSION

According to many scientists, one of the important mechanisms for the development of the exudative phase of inflammation is the release of histamine, serotonin, and other biologically active substances from mast cells that increase the permeability of the vascular wall.[11-13] In this regard, as a mechanism of the antiphlogogenic effect of DEMP, there was interest to study the anti-inflammatory activity of this compound in dextran-induced inflammation, the mechanism of which is precisely related to the release of biologically active substances from mast cells. The results of experimental studies of the effect of DEMP in dextran-induced inflammation showed that the volume of the paw increased by 126.1% compared to the initial volume in intact animals under the influence of dextran. At the same time, the maximum increase in the volume of the paw was noted in 1 h after the beginning of the experiment, which was statistically significantly preserved during the past 4 h. In contrast, in

Table 1: Efficiency of DEMP, diclofenac sodium, and LIV-52 in dextran-induced paw edema

Groups	Dose, mg/kg	Volume of paw, cm^3				
		Initial	60 min	120 min	180 min	240 min
Control	-	0.45±0.01	1.41±0.06*	1.37±0.05*	1.25±0.07*	1.18±0.06*
Diclofenac	10	0.49±0.02	1.11±0.04*	1.02±0.07*	0.93±0.04*	0.84±0.05*
DEMP	50	0.51±0.02	1.11±0.06*#	1.08±0.04*#	0.99±0.03*#	0.91±0.04*#
LIV-52	100	0.52±0.02	1.39±0.04*	1.23±0.03*	1.17±0.04*	1.05±0.04*

*Statistically significant in comparison with initial index ($P<0.05$); #statistically significant in comparison with control group ($P<0.05$). DEMP: Dry extract of medicinal plant

Table 2: Efficiency of DEMP and LIV-52 in histamine-induced paw edema

Groups	Dose, mg/kg	Volume of paw, cm^3					
		Initial	30 min	60 min	120 min	180 min	240 min
Control	-	0.67±0.05	1.70±0.05*	1.63±0.05*	1.53±0.05*	1.45±0.06*	1.38±0.05*
Diclofenac	10	0.64±0.03	1.24±0.08	1.24±0.08	1.02±0.07	0.93±0.04	0.84±0.05
DEMP	50	0.68±0.03	1.36±0.06*#	1.29±0.05*#	1.19±0.05*#	1.10±0.04*#	0.97±0.04*#
LIV-52	100	0.69±0.03	1.46±0.07*#	1.38±0.08*#	1.31±0.08*	1.23±0.07*	1.13±0.07*

*Statistically significant in comparison with initial index ($P<0.05$); #statistically significant in comparison with control group ($P<0.05$). DEMP: Dry extract of medicinal plant

Table 3: Influence of DEMP, LIV-52, and sodium diclofenac to the course of inflammation dextran-induced aseptic arthritis in intact and adrenalectomized rats

Groups	Dose, mg/kg	Average volume of paw, cm^3		Average increasing of paw volume relatively to initial volume in rats		VAA, %
		Initial	After 1 h	cm^3	%	
Intact rats						
Control	-	0.92±0.04	2.08±0.10*	1.16±0.12	126.1	-
LIV-52	100	0.91±0.03	1.77±0.09*#	0.85±0.10#	94.5	26.7
DEMP	50	0.91±0.03	1.64±0.10*#	0.73±0.08#	80.2	37.1
Sodium diclofenac	10	0.87±0.03	1.55±0.06*#	0.68±0.08#	73.5	41.4
Adrenalectomized rats						
Control	-	0.87±0.03	1.99±0.09*	1.12±0.10	128.7	-
LIV-52	100	0.91±0.03	1.79±0.07*#	0.88±0.09#	96.7	21.4
DEMP	50	0.90±0.02	1.73±0.05*#	0.83±0.07#	92.2	25.9
Sodium diclofenac	10	0.92±0.05	1.59±0.05*#	0.67±0.06#	72.8	40.2

*Statistically significant in comparison with initial index ($P<0.05$); #statistically significant in comparison with control group ($P<0.05$). DEMP: Dry extract of medicinal plant

Table 4: Content of cortisol in periphery blood of rats after inflammation induced by dextran and formalin

Groups	Content of cortisol in periphery blood of rats, ng/ml					
	Dextran-induced inflammation			Formalin-induced inflammation		
	After 1 h	After 2 h	After 3 h	After 1 h	After 2 h	After 3 h
Intact	32.5±1.9	-	-	32.5±1.9	-	-
Control	75.0±5.8#	42.5±2.2#	30.0±2.1	72.3±5.9#	43.3±3.1#	33.3±1.2
DEMP, 50 mg/kg	385.0±25.0*#	75.3±3.5*#	47.4±2.2*#	440.0±22.4*#	83.3±3.1*#	43.3±1.2*#
Diclofenac sodium, 10 mg/kg	370.0±22.4*#	39.70±2.1*#	35.0±4.2*	440.0±25.4*#	36.7±1.2	30.0±3.7
LIV-52, 100 mg/kg	165.0±25.0*#	34.4±1.2	30.0±2.0	350.0±24.1*#	38.3±1.6	30.0±2.0

#Statistically significant comparing to intact group; *statistically significant comparing to control group. DEMP: Dry extract of medicinal plant

Table 5: Content of interleukins 10 and 1β in rat's blood after the induction inflammation by dextran and formalin

Groups	Dextran-induced inflammation		Formalin-induced inflammation	
	IL-10, pg/ml	IL- 1β, pg/ml	IL-10, pg/ml	IL- 1β, pg/ml
Intact	30.11±1.76	20.06±1.11	30.11±1.76	20.06±1.11
Control	10.05±0.65#	30.22±1.27#	20.24±1.09#	30.11±1.27#
DEMP, 50 mg/kg	52.07±1.22*#	4.42±0.37*#	50.04±1.21*#	5.07±0.69*#
Diclofenac sodium, 10 mg/kg	50.02±1.27*#	4.05±0.22*#	59.10±1.45*#	4.16±0.28*#
LIV-52, 100 mg/kg	40.07±1.15*#	3.11±0.45*#	39.08±1.32*#	4.10±0.21*#

#Statistically significant comparing to intact group; *statistically significant comparing to control group. DEMP: Dry extract of medicinal plant

animals previously treated with DEMP, it led to a significant suppression of the exudation process, in which the VAA was 37.1% [Table 1].

Consequently, the mixture of dry extracts from local medicinal plants has a distinct anti-exudative effect indicating its VAA. In terms of practical application, it is important to establish the effective dose of new compounds. From the above data, it can be seen that the effective dose of the studied medication is 50 mg/kg in experimental aseptic arthritis induced by dextran. Since the investigated medication is extracts of several medicinal plants, we have chosen LIV-52 for comparison its activity. LIV-52 is a complex medication from a number of medicinal plants. It should be noted that there is no information about special studies to establish the anti-exudative activity of this medication in the available literature. We used LIV-52 at a dose of 100 mg/kg, which, according to the literature, is effective as a hepatoprotector.[14,15] The results of a separate series of experiments to study the anti-exudative effect of LIV-52 on the model of dextran inflammation showed that this phytopreparation clearly exhibits an anti-exudative effect, which amounted to 26.7%.

NSAIDs from various groups of chemical compounds that do not selectively block cyclooxygenase are widely used in the treatment of human diseases, in the pathogenesis of which inflammation plays an important role. Among these NSAIDs, diclofenac sodium is considered the reference drug.[16,17] Proceeding from this, we studied the anti-inflammatory activity of sodium diclofenac using its effective anti-inflammatory dose in a separate group of animals.[18] The experimental results showed that diclofenac sodium suppresses the development of exudation quite pronounced with a maximum expression of activity after 1 h from the beginning of the experiment. At the same time, the calculation of the anti-inflammatory activity showed that it was 41.4%.

Thus, DEMP has a distinct anti-exudative effect in dextran-induced model of aseptic inflammation in experiment, which in its anti-inflammatory activity significantly exceeds LIV-52, and it is not inferior to the reference NSAID diclofenac sodium. Therefore, it can be stated that the suppression of the releasing of biologically active substances such as histamine and serotonin by mast cells is played an important role in the mechanism of the anti-inflammatory action of DEMP.

Histamine has a multilateral effect on the human body, in particular, it causes an increase of vascular permeability, bronchospasm, and a decrease of blood pressure as well as an increase of secretion of gastric juice by stimulating H_1 receptors located in the vessels, bronchi, and stomach.[13,19] Histamine is essentially found simultaneously in the site of inflammation at the onset of damage. It causes the expansion of the vessels, increases their permeability, and stimulates the endings of pain nerves. Thus, histamine triggers an acute inflammatory response. The appearance of histamine in the inflammation focus is closely related to the degranulation of mast cells, in which the synthesis of new mediators such as proteases, proteoglycans, eosinophil chemotaxis factors, kinins, complements, eicosanoids, leukotrienes (platelet activation factor), and others from the lipids of the membranes of activated mast cells and basophils is stimulated.[13]

As noted, the development of aseptic inflammation induced by dextran is related to the release of histamine and serotonin from mast cells, which are one of the important mediators of inflammation.[13] Based on this, in a separate series of experiments, we investigated the effect of DEMP on the course of histamine inflammation.

The results of the studies have shown that there is an expressed increase in exudation processes under the influence of histamine. Thus, histamine led to an increase of the paw volume by more than 2.5 times 30 min after its injection in intact rats. Subsequently, the effect gradually weakened, however, even by the end of 4 h of the experiment, the volume of the paws exceeded the initial volume by 2.1 times. In contrast, in rats that were previously administered DEMP and diclofenac sodium, the paw volume increased only 2 times. At the same time, the value of the anti-inflammatory activity of the drug (VAA) was 34.0% and 35.9%. It is noteworthy that the anti-exudative activity DEMP at a dose of 50 mg/kg was at the level of sodium diclofenac and exceeded the well-known drug LIV-52, in which VAA was only 25.2% in the present experiment [Table 2].

Therefore, the antihistamine effect is possibly one of the important links in the mechanism of the anti-exudative action of DEMP. Most likely, DEMP prevents the release of biologically active substances from mast cells in induction of inflammation.

Glucocorticoids (GCs) produced by the adrenal glands have a pronounced anti-inflammatory effect as a result of the suppression of the activity of phospholipase A2, which are necessary for the synthesis of arachidonic acid. In this case, GCs have indirect effects, they promote the synthesis and release of a group of endogenous proteins – lipocortins (annexins), which inhibit A2 phospholipases. Therefore, it is important to carry out experiments on adrenalectomized (AE) animals for investigation the mechanism of anti-inflammatory action of new medications in experiment.

The results of the study showed that the administration of dextran leads to increase the volume of paws by 126.1% in relation to the initial volume of paw in intact animals, it was 128.7% in AE animals. It can be seen that there was almost the same effect – the development of exudation in both groups of animals in dextran-induced inflammation. We observed a similar effect in animals that were preventively administered sodium diclofenac and LIV-52 [Table 3]. In contrast, in rats previously treated with DEMP, dextran led to an increase of the paw volume by 80.2%, where the VAA was 37.1%, and it led to an increase of the paw volume by 92.2% (VAA was 25.9%) in AE animals. It is seen that the AE leads to a certain decrease of VAA of the DEMP. This is probably related to that DEMP contains licorice root, which has the property of stimulating the production of GC, which has an anti-exudative effect [Table 3].

Consequently, one of the mechanisms of anti-inflammatory activity of DEMP is also the stimulation of adrenal function leading to the release of GC. This assumption is approved by the results of the next series of experiments to study the effect of DEMP on the level of the adrenal hormone cortisol. The obtained results showed that the level of cortisol in the blood increased by more than 2 times under the influence of dextran [Table 4]. Such effect was also observed in experiments with formalin. It is logical to assume that the reaction of the mammalian organism to the effects of the phlogogen, as a rule, manifests with an increase of the level of cortisol, which has an anti-inflammatory effect. It is noteworthy that many substances with anti-inflammatory action, in many ways, manifest their pharmacological activity precisely with an increase of the level of cortisol in the blood. It is known that the reference NSAIDs – diclofenac sodium increased the level of cortisol almost 4 times, and DEMP had almost the same effect. Liv-52 in this aspect had a distinctly low degree of stimulation.

Therefore, it can be stated that anti-inflammatory medications create the background for the realization of their anti-inflammatory effect by increasing the content of cortisol in the blood. In this regard, DEMP was more effective than other investigated medications.

The anti-inflammatory effect of corticosteroids is largely associated with their influence on the formation of cell-mediated cytotoxicity and apoptosis. It is known that GCs reduce the excretion of the adhesion molecules, thereby reduce a chemotaxis and, in general, the clearance function of cells of the mononuclear phagocyte system, since they suppress the formation of superoxide in neutrophils.[20] At the same time, GC reduces the number of monocytes, both in the bloodstream and in the focus of inflammation. Therefore, cortisol prevents the accumulation of macrophages in the focus of inflammation in animals. If we take into account that macrophages contain a large amount of biologically active substances that digest the object of phagocytosis, it becomes clear that decreasing their number in the focus of inflammation has an inhibitory effect on the alteration process, since corticosteroids regulate the release of enzymes from lysosomes.[21] It is believed that the effect of cortisol on macrophages is associated with inhibition of metabolism in macrophages and the accumulation of neutrophilic lipids and carbohydrates. It is noteworthy that cortisol prevents the release of cathepsin-D from macrophages.[22] The above data explain the mechanism of the anti-inflammatory action of the investigated medications, which causes a high concentration of cortisol in the blood of experimental animals in the initial periods of aseptic inflammation induced by dextran and formalin.

It is known that cytokines play an important role in the regulation of the body's response to external stimuli. They also have a great influence on the course of the inflammatory

process and also have antiproliferative, antimicrobial, and antitumor effects.[23] It is believed that in the mechanism of anti-inflammatory drugs of the steroid structure – GC, their inhibitory effect on the production of cytokines (IL-1 and tumor necrosis factor-α) occupies an important place.[23] GCs inhibiting the activity of phospholipase A_2 suppress the formation of arachidonic acid, which is necessary for the synthesis of prostaglandins. Considering the above, it seems important to study the content of not only cortisol but also interleukins in inflammation process.

The results of experimental studies in this regard showed that the content of IL-10 decreased 3 times compared with the level of healthy rats in dextran-induced inflammation. At the same time, the level of IL-1β increased by 46.0%. We found similar changes of results in animals in which aseptic inflammation was reproduced with formalin. Thus, compared to healthy rats, the content of IL-10 decreased by 33.0%, while IL-1β, on the contrary, increased by 45.4%. It can be seen from the above data that aseptic inflammation was characterized by a decrease the level of IL-10 and an increase the content of IL-1β. The degree of changes in the concentration of the last one did not depend on the phlogogenic agent, at the same time, a decrease of the level of IL-10 was 2 times more in dextran-induced inflammation than formalin-induced one. Considering that IL-10 has anti-inflammatory and IL-1β pro-inflammatory properties,[24] it becomes clear that the development of aseptic inflammation aggravates by an increase of IL-1β at the background of a decrease of IL-10.

There was great interest to determine the effect of anti-inflammatory medications on the level of the studied cytokines. As can be seen from the data in Table 5, the reference NSAID – diclofenac sodium significantly increased the level of IL-10 by almost 4 times in animals with dextran-induced inflammation on the background of significant decreasing of IL-1 (85.6%) compared to untreated animals.

We found a similar effect in animals that had previously received DEMP. From the data in Table 4, it can be seen that the preventive use of LIV-52, although it had a unidirectional effect on the level of the studied cytokines, the degree of effect was noticeably lower. It should be noted that the changes in the level of interleukins under the influence of the studied medications differed markedly from the values of healthy animals.

Thus, the level of IL-10 under the influence of sodium diclofenac, DEMP, and LIV-52 increased by 65.6, 72.4, and 32.7%, respectively. At the same time, in the animals previously treated with the above medications, the level of IL-1β was low by 80.4, 78.6, and 85.0%, respectively, compared to the values of healthy rats. It should be noted that the effect of the studied medications on the level of the studied cytokines practically did not differ in dextran- and formalin-induced inflammation.

Consequently, the mechanism of the anti-inflammatory action of NSAIDs and medication obtained from plant raw-materials is unidirectional and manifests itself in a decrease of the level of pro-inflammatory and an increase of anti-inflammatory interleukins. This was especially manifested a rather sharp decrease of IL-1β (4–5 times) in the blood compared to healthy rats. It is believed that IL-1β, a peptide synthesized primarily by monocytes, macrophages, and vascular endothelium, has an effect on the vascular wall, promoting leukocyte adhesion, increasing the synthesis of platelet aggregation factor, enhancing the progulatory activity of the endothelium, and increasing the synthesis of plasminogen activator. All this not only supports the process of inflammation but also aggravates it. Therefore, a decrease of its concentration in the early period of inflammation has a beneficial effect on the outcome of pathology.[25]

Thus, the analysis of the obtained results allows us to conclude that the mechanism of the anti-inflammatory action of the mixture of medicinal plants is multicomponent and is largely associated not only with the antioxidant property of the medication but also with the stimulation of the production of GC hormones of the adrenal gland, regulation of the level of pro- and anti-inflammatory interleukins, cortisol, and suppression of the formation of arachidonic acid, which is a precursor to the formation of prostaglandins. The multicomponent mechanism of the anti-inflammatory action of DEMP determines its high antiexudative, antiproliferative, and antialterative properties in cases of inflammation of various etiologies.

CONCLUSIONS

The mechanism of the antiphlogogenic action of DEMP is associated with to a certain extent by the suppression of the release of biologically active substances from mast cells, like histamine. Taking into account the lower anti-inflammatory activity of DEMP in AE animals, it can be assumed that stimulation of the adrenal glands is an important link in the mechanism of the antiphlogogenic action of this medication, which is confirmed by the stimulation of cortisol by the medication in various types of inflammation. In the mechanism of the anti-inflammatory action of sodium diclofenac, DEMP, and LIV-52, an important place is occupied by the elimination of the disturbances of the content of pro- and anti-inflammatory cytokines.

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