American Journal of Medicine and Medical Sciences 2020, 10(7): 503-508
DOI: 10.5923/j.ajmms.20201007.13

The Effect of Dry Extract Obtained from Rhus Cariaria in Experimental Models of Edema and Inflammation

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Abstract The effect of dry extract obtained from Sumakha [Rhus cariaria L.] leaves (DES) on various phases of inflammation was studied using white sexually mature male rats in this study. It was found that the DES has a distinct antiexudative and antiproliferative activity comparing to the standard non-steroidal anti-inflammatory drug – diclofenac sodium (voltaren). Studies in rats have shown that the dry extract of Rhus cariaria has a distinct antiexudative effect in aseptic arthritis induced by dextran, histamine and formalin. The mechanism of the antiexudative effect was found to be because of both astringent and its antioxidant properties. The effect of the DES was obtained after enteral administration with the the dose of 25 mg/kg. The results of this experimental study indicate the possibility of using this dry extract for anti-inflammatory effect. The combination of antiviral and anti-inflammatory activity of Rhus cariaria will make it possible to increase the effectiveness of the treatment against to virus-induced pathologies in some conditions.

Keywords Dry extract, Anti-inflammatory activity, Inflammation, Medicinal plants

1. Introduction

Nowadays in the pathogenesis in which inflammation plays a leading role, a large number of drugs have been using (selective and non-selective non-steroidal anti-inflammatory drugs, glucocorticoid, basic anti-inflammatory drugs, biological drugs) [3,16,19]. The use of optimal regimens of these drugs does not provide a sufficient therapeutic effect [14]. Long-term use is generally associated with the risk of developing severe adverse reactions, which requires the search for new, more effective anti-inflammatory drugs, despite the abudance of traditional non-steroidal anti-inflammatory drugs on the market [5,14,28].

The medical practice in pharmacotherapy of many common pathologies is dominated by the use of drugs from natural origins. Herbal preparations are often used without any prescriptions, and patients are at the risk of exceeding the established therapeutic doses up to undesired level and facing some side effects [12]. Therefore, conducting experimental studies on the specific activity of herbal preparations is one of the important tasks of pharmacology. In this aspect, our attention was focused on dry extract isolated from the plant Rhus cariaria, which had a distinct anti-inflammatory activity on aseptic arthritis induced by various flagogens [6,7]. Considering that inflammation because of various etiologies occurs during the simultaneous course of exudation, alteration, and proliferation, it was of interest to study on the antiproliferative activity of the dry extract isolated from Sumakha leaves (DES) [Rhus cariaria L.]. Literature data show that the Tannin obtained from Sumach leaves have not effective only in inflammatory processes of the oral cavity, but they also used to treat skin diseases, which are probably associated with its anti-inflammatory formations [1]. These data have not been specifically investigated yet.

The aim of this study was to study the anti-inflammatory activity of the dry extract isolated from Sumakha leaves (DES) [Rhus cariaria L.] and to compare results with the standard non-steroidal anti-inflammatory drug diclofenac sodium.

In order to study the content of polyphenols in individual parts of the plant, the Institute of Bioorganic Chemistry, Academy of Sciences of the Republic of Uzbekistan named after Academician A. Sadykov used dried leaves collected during its flowering. The raw material was first extracted with chloroform to remove lipophilic compounds, then the raw material was dried and extracted three times with 70% acetone. The resulting extracts were condensed using a rotary evaporator and the aqueous concentrate was treated with ethyl acetate. The ethyl acetate fraction was concentrated in a rotor evaporator and precipitated with hexane. According to the results of studies on individual

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Published online at http://journal.sapub.org/ajmms

organs of plants, it is observed that the leaves of Sumakha make up 1.88-6.67%. As a result of qualitative reactions, it was observed that the sum of polyphenols contains about 70 compounds belonging to the class of flavonols, phenolic acids and tannins.

2. Material and Methods

In the experiments, the preparation of the dry extract isolated from Sumach leaves (DES) (Rh. Coriaria) [23] was used. To assess the anti-inflammatory activity of this dry extract, its effect was determined on three models (two exudative arthritis models and "cotton pellet" model). The experiments were performed on outbred rats weighing 140 - 185 g. Before the experiment, all laboratory animals were examined considering their body weight, age, gender, and motor activities. After an external examinations, the experiment was started. The entire period of preparations, experiment, during the implementations, laboratory animals were kept in the vivarium at a temperature of 20-25℃, humidity of at least 50%, in a well-ventilated room and in day/night light mode, in standard plastic cages, 6 animals in each cages, with a standard diet, the daily requirement was in accordance with the age of the animals. All laboratory animals participating in the experiment before the start of the experiment had a healthy appearance and were observed active.

2.1. The Antiexudative Effect of DES

The antiexudative effect was studied on a model of acute inflammatory edema of the paw of the rat, induced by introducing injection of 0.1 ml of solutions of 6% dextran, 0.1% histamine and 2% formalin solution to under the plantar aponeurosis of the right hind limb of an animal [4,8,22]. Previos to the experiment, animals received was administered intragastrically DES at a dose of 25 mg/kg and the other group recevied diclofenac sodium 10 mg/kg. Animals of the control group (comparison group) received an equivolume amount of drinking water. The measurement of the volume of the right hind paw of animals was carried out using a plethysmometer before and after 60, 120, 180 and 240 minutes after the introduction of the flagogen (dextran, histamine) and after 2, 4, 6, 24 and 48 hours after the introduction of the formalin. The values of anti-inflammatory activity (AIA) were calculated.

2.2. The Antiproliferative Activity of DES

To determine the antiproliferative activity of the DES, experimental studies were carried out on sexually mature white rats - males with an initial weight of 165-185 g, kept under standard vivarium conditions, quarantined for at least 12-14 days. Each group consisted of 6-7 animals. On the model of "cotton pellet (granuloma)" studied the effects of drugs on the antiproliferative phase of inflammation [9,15]. This model was created by implanting a sterile cotton swab (weighing 10 mg) in rats under the back skin. The operation was performed under aseptic conditions under general anesthesia. On the day of the operation and at the next seven days, the animals were daily administered the drug intragastrically, with the dose10 mg/kg (diclofenac sodium), 10 and 25 mg/kg (DES). Control animals received drinking water in an appropriate volume. 24 hours after the last injection of the preparations (on the eighth day), animals were sacrificed under the general anesthesia and cotton balls were removed, weighed on an electronic balance (SINKO, Japan, 2014) and dried at a temperature of 60℃ to until reaching to constant weight. The degree of the proliferative phase was judged by the difference between the mass of the dried granuloma and the initial mass of the cotton ball. The exudative reaction was evaluated by the difference between the masses of raw and dried materials [24,27].

The experiments were carried out in accordance with the "Rules for the use of experimental animals", as well as the rules adopted in the European Convention for the Protection of Vertebrate Animals used for experimental research or for other scientific purposes (ETS No. 123, Strasbourg, 03/18/1986).

2.3. Statistical Analysis

The results of experimental studies were investigated statistically using the standard StatPlus 2009 software package. Significance of indicators (M±m) and differences between the samples were determined using the Student t-test. The difference was accepted significant at a probability level of 95% or more ($p<0.05$).

3. Results and Discussion

The results of experimental studies showed that on the model of aseptic arthritis induced by dextran, DES has a pronounced anti-inflammatory effect. Therefore comparing with the control that were administred the amount of polyphenols paw volume increased by 121.0% one hour after the introduction of the flagogen agent. At the same time, in control animals the degree of increase in the volume of the legs was 185.2% (Table 1). It is seen that under the influence of the tested compound, the exudative process is clearly suppressed. Moreover, the anti-inflammatory activity of the drug was 28.3%, 31.1%, 33.3% and 43.7% after 1,2,3 and 4 hours rewspectively after the introduction of the flagogen. In similar periods, the anti-inflammatory activity of the reference NSAIDs - diclofenac sodium was 38.0%, 40.5%, 47.9% and 55.2%, respectively. It can be seen that DES is slightly better than the classic reference non-steroidal anti-inflammatory drug - diclofenac sodium.

The development of the exudation process under the influence of dextran is known to be associated with damage to mast cells and the release of histamine and serotonin from them [9]. Given this circumstance, we subsequently conducted separate studies to study the effect of DES on the course of exudation on a model of histamine inflammation.

Histamine is known to be a mediator of inflammation. Studies showed that after 30 minutes from the onset of flagogen action, the paw volume in control rats increased by 130.8%, and in rats treated with diclofenac sodium, the degree of increase in paw volume was less (89.0%). A similar effect can be seen from the data in Table 2. Moreover, the anti-inflammatory activity of diclofenac sodium was 3 < found to be 3.3%, and extract represented 30.1% activity. It is noteworthy that the anti-inflammatory activity of the studied compounds are very high comparing with diclofenac sodium.

Table 1. Antiexudative activity of the DES isolated from Sumach and diclofenac sodium on a model of dextran edema on animals

Groups	Dose mg/ kg	Volume of the foot, см^3				
		Source (zero point)	1 hour	2 hour	3 hour	4 hour
The control	-	0,61±0.02	1,74±0,04* 1,13±0,04	1,67±0,02* 1,05±0,04	1,57±0,02* 0,95±0,03	1,48±0,02* 0,86±0,04
Diclofenac sodium	10	0.62±0.02	1,32±0,02* 0,70±0,03#	1,25±0,02* 0,63±0,02#	1,12±0,03* 0,50±0,04#	1,01±0,03* 0,38±0,04#
DES	25	0,67±0.04	1,48±0,03* 0,82±0,03#	1,40±0,04* 0,73±0,03#	1,31±0,06* 0,64±0,04#	1,16±0,04* 0,50±0,03#

Note: *****-in comparison with initial index (P<0,05);
#- in comparison with control group respectively to the same hours (P<0,05).

Table 2. Antiexudative activity of the DES isolated from Sumach and diclofenac sodium on a model of histamine edema on animals

Groups	Dose mg/kg	Volume of the foot, см^3,				
		source (zero point)	30 min	60 min	90 min	120 min
The control	-	0,67±0,02	1,60±0,06* 0,93±0,05	1,54±0,05* 0,87±0,05	1,47±0,05* 0,81±0,04	1,43±0,05* 0,77±0,03
Diclofenac sodium	10	0,70±0,03	1,32±0,04* 0,62±0,02#	1,26±0,05* 0,56±0,02#	1,18±0,04* 0,48±0,02#	1,11±0,04* 0,41±0,03#
DES	25	0,69±0,02	1,34±0,04* 0,65±0,05#	1,26±0,03* 0,57±0,04#	1,19±0,03* 0,50±0,03#	1,10±0,05* 0,41±0,03#

Note: In Table1 and 2 in the numerator are absolute indicators of the volume of the legs, and in the denominator the difference is the swelling of the legs by the clock; the sign * - reliability to the source, # - reliability with the control of the corresponding clock (P<0.05).

Table 3. Antiexudative activity of "DES" and "diclofenac sodium" on the model of formalin edema on animals

Groups	Dose mg/ kg	Volume of the foot, см^3					
		source (zero point)	2 hour	4 hours	6 hours	24 hours	48 hours
The control	-	0,67±0,02	1,22±0,05* 0,54±0,03	1,38±0,05* 0,71±0,07	1,47±0,08* 0,80±0,07	1,37±0,09* 0,70 ± 0,07	1,27±0,08* 0,60 ± 0,07
Diclofenac sodium	10	0,65±0,04	1,07±0,02* 0,44±0,03#	1,15±0,03* 0,52±0,03#	1,16±0,03* 0,53±0,02#	1,07±0,04* 0,44±0,03#	0,97±0,04* 0,34±0,03#
DES	25	0,67±0,02	1,11±0,07* 0,43±0,07#	1,19±0,06* 0,52±0,06#	1,21±0,08* 0,54±0,07#	1,11±0,06* 0,43±0,06#	1,02±0,05* 0,35±0,04#

Note: - absolute indicators of the volume of the legs, and in the denominator the difference in swelling of the legs by the clock; the sign * - reliability to the source, # - reliability with the control of the corresponding clock (P<0.05).

Table 4. Antiexudative and antiproliferative activity of the sum of the DES from Rhus cariaria (n=6, M±m)

Group	Dose mg/ kg	Wet weight mg	Dry weight mg	Difference, Mg
Control	-	372,8±23,6	102,7±5,6	270,2±20,7
Diclofenac sodium	10	272,2±11,1*	70,2±5,3*	202,0±6,6*
DES	10	281,16±15,87*	61,8±3,9*	219,3±11,8*
DES	25	258,3±11,9*	65,8±5,2*	192,5±8,3*

Note: * Indicates values significantly different from control (P<0.05)

All results indicate that DES has a distinct anti-inflammatory activity similar to the classic reference drug - diclofenac sodium. Since DES has been using as a tanning agent, it can be assumed that it tightens the walls of blood vessels to inhibit production of liquids leading to a decrease the degree of edema. From these results, substances that have tanning (astringent) effects are used in the treatment of pathology of the skin, mucous membranes [13]. Under the influence of the latter, gelification (partial reversible coagulation of proteins) of the surface layer of the cytoplasm of cells is observed, forming a film that protects the ends of sensitive nerves. Along with this, it must be bare in mind that the studied DES compound contains polyphenols, which are known to have antioxidant, antiradical properties. The suppression of free radicals under the influence of the latter leads to inhibition of the destruction of phospholipids of cell membranes which serves production of arachidonic acid. Since arachidonic acid with the participation of cyclooxygenase is converted into cyclic endoperoxides and, accordingly, prostaglandins, the main mediators of inflammations can be occured [10]. In our opinion, the combination of these two properties in one drug (DES) can effectively suppress the inflammatory process.

The results s-showed the effects of anti-inflammatory drugs with provation of formalin which subplanetary administered leads to a more than twofold increase in the volume of the legs of rats compared to the control, which remains practically unchanged over the next 48 hours. This fact indicates the development of aseptic arthritis in rats.

The phlogogenic effect of formalin, as is known, is due to its interactions with the amino groups of proteins and the release of biogenic amines and free amino acids with subsequent violation of isoion and isotonia at the injection site [18]. Formalin-induced damage to the tissues of the animal's paws leads to the development of chronic and localized inflammation and pain. In this case, a two-phase nociceptive effect of formalin is noted - a neurogenic component in the first hour of the pathological process followed by an inflammatory response of tissues in a later period [11]. These data indicate significant differences in the mechanism of the phlogogenic action of formalin from other substances that induce inflammation [18,21]. Therefore, this model of aseptic inflammation is widely used to determine the anti-inflammatory activity of new compounds in experimental pharmacology [11].

Under the influence of the reference drug, from the group of non-steroidal anti-inflammatory drugs - diclofenac sodium [3], the severity of the exudation process was less and the increase in the volume of the legs compared to the initial parameters was 64.6%, 76.9%, 78.5%, 64.6% and 49, 2% after 2, 4, 6, 24 and 48 hours, respectively. We found an almost identical effect in animals that preventively received with DES. At the same time, the anti-inflammatory activity of diclofenac sodium in the studied periods of observation was 18.5 - 43.3%, and in animals receiving DES these were 20.4 - 41.7% (Table 3).

As is known, the anti-inflammatory effect of diclofenac sodium is associated with the inhibition of cyclooxygenase activity, which produces cyclic endoperoxides and a precursor of prostaglandins. The latter is a mediator of inflammations cause the development of pain, fever and inflammation [10]. However, the long-term use of non-steroidal anti-inflammatory drug - diclofenac sodium is well known in patients, the experience with it more than 60 years. It also causes gastro- nephropathy, and also has hepatotoxicity [26]. Therefore, the search for new and less toxic agents, compared with existing non-steroidal anti-inflammatory drugs, still is a general need. In practice it shows a great success and it can be achieved for other compound if a search is made for non-steroidal anti-inflammatory drugs among the components of other plant materials. It can be assumed that the DES containing flavonoids with a distinct antioxidant effect and they suppres the intensity of lipid peroxidation in biological membranes and inhibits the formation of arachidonic acid, which is a main substrate for the formation of cyclic endoperoxides. At the same time, it is believed that the greatest role in the effect of flavonoids on the human body is played because of their antioxidant properties. Flavonoids can be classified as non-enzymatic antioxidants that can directly or indirectly weaken or prevent damage of cell membranes occurred by free radicals [17,29].

Research conducted by employees of the Institute of Bioorganic Chemistry, Academy of Sciences of the Republic of Uzbekistan named after Academician A. Sadykov was shown that polyphenolic compound with pronounced antioxidant activity, which has been shown on both natural and artificial membranes [1]. Proceeding from this, it can be considered that DES prevents damage of biological membranes by flagogens due to the quenching of free radicals.

In this experimental study, the effects of anti-inflammatory drugs are most often studied using the Cotton pellet model. Moreover, the technique allows us to simultaneously evaluate the effect of the studied substances on the exudative and proliferative phases of the inflammations at the same time. The results showed that the sum of the polyphenols isolated by Rhus cariaria have a distinct antiproliferative activity. As it is given in table 4, in the control group, subcutaneous implantation of sterilized cotton balls weight 10 mg after eight days increased by 37 times. Moreover, its dry weight was found to be increased more than 10 times. Therefore, subcutaneous implantation of cotton balls significantly induces not only the exudative, but also the proliferative phases of inflammation.

A classic representative of non-steroidal anti-inflammatory drugs - diclofenac sodium in the same conditions exhibited anti-proliferative and anti-exudative activity. In comparison with the control, the weight of wet granulomas in rats receiving diclofenac sodium during seven days decreased by 27.0%, and dry weight by 31.0%. This shows that, this drug can clearly suppressed both the exudative and proliferative phases of inflammation. It was also observed similar changes in rats treated with DES. The

decrease in wet weight of granulomas was 25.6% at a dose of 10 mg/kg, 31.0% at a dose of 25 mg/kg.

Typically, a decrease in the dry weight of granulomas by 30.0 and 36.0%, respectively, is related with the dose of the drug. The results obtained also supports the conclusions mentioned from experiments with aseptic arthritis, and it can be said that Rhus cariaria has a distinct antiproliferative effect that is not very different from the standard non-steroidal anti-inflammatory drug - diclofenac sodium.

Tissue proliferations during the inflammation can be seen as a result of the multiplication of local cellular elements in the inflammated tissues. Moreover, as noted above, it develops from the very beginning of exposure to a flagogenic agent, along with alteration and exudation, and it becomes predominant in a later period, as the exudative and infiltrative process subsided [9,27]. The most important condition for the progression of proliferation is the effectiveness of cleaning of dead white blood cells from the tissue. The leading role is played by macrophages-hematogenous (monocytes) and tissue (histiocytes) origins [20]. Based on this, it can be assumed that the studied compounds enhance the process of phagocytosis. Eliminating the remaing leukocytes and destroyed tissues, macrophages are important. Proliferation is replaced by regeneration, which consists in the proliferation of connective tissue, neoplasm of blood vessels, and to a lesser extent in the multiplication of specific tissue elements. Subsequently, the granulation tissue fills the defects and is replaced by connective tissue to form a scar. Therefore, suppression of proliferations is an important factor in preventing a gross structural and functional changes in the inflamed areas of a tissues or organs. It is believed that there is a good correlation between the activity of non-steroidal anti-inflammatory drugs in the experiment on models of granulomas and the clinical efficacy of drugs for collagen production [24,27].

Since it is commonly believed that if the anti-inflammatory activity of a new compound exceeds 30%, the drug has a pronounced an anti-inflammatory effect [25].

Thus, the studied DES from Rhus cariaria - have an anti-inflammatory effect, helping to reduce the exudative and proliferative phases of inflammation.. Given the safety of DES even with prolonged use [30] and its distinct anti-inflammatory properties, this compound can be recommended being a good an effective agent for the treatment of acute and chronic inflammatory diseases.

4. Conclusions

1. The sum of the DES from Rhus cariaria has a distinct antiexudative and antiproliferative activity, being slightly better thane standard non-steroidal anti-inflammatory drug, diclofenac sodium.
2. The mechanism of the antiexudative effect of the sum of the polyphenols of the leaves of Rhus cariaria consists in both its astringent and antioxidant properties.
3. The effective antiproliferative activity of the DES fromf Rhus cariaria can be achived with enteral a dose of 25 mg/kg.
4. The results of this experimental study indicate that the use DES from Rhus cariaria as an effective anti-inflammatory agent is possible.

Abbreviations

DES- dry extract obtained from Sumakha [Rhus cariaria L.] leaves

AIA- anti-inflammatory activity

NSAID- non-steroidal anti-inflammatory drug

REFERENCES

[1] Abdullazhanova N.G. et al., 2011, New polyphenolic compound of this family Euphorbiaceae. Reports of the Academy of Sciences of the Republic of Uzbekistan.; 3, p.60-62.

[2] Akopov I.E., The most important domestic medicinal plants and their applications. “Medicine”. Tashkent, (1986), p.567.

[3] Badokin V.V., 2007, Voltaren as a standard of non-steroidal anti-inflammatory drugs in modern rheumatology. Clinical Pharmacology and Therapy.,; 16(2), p.78-82.

[4] Fedosov P.A. et al., 2016, The study of anti-inflammatory and capillaroprotective activity of chitosan gel with taurine and allantoin. VGU Bulletin, chemistry series. biology. pharmacy., 4, p.147-151.

[5] Kazaishvili Yu.G., Popov N.S., 2013, Study of the anti-inflammatory activity of new derivatives of thiadiazole in formalin paw edema in rats. Modern problems of science and education., 3. Availabe at: http://www.science-education.ru/109-9598.

[6] Khakimov Z.Z., Abzalov Sh.R., Rakhmanov A.Kh., Rashidov S.Z., 2018, The intensity of the exudative phase of inflammation with the prophylactic administration of the sum of polyphenols from the leaves of Sumach. Infection, immunity and pharmacology., 1, p.73-77.

[7] Khakimov Z.Z., Rakhmanov A.Kh., Abzalov Sh.R., Rashidov S.Z., 2019, The influence of rutan and voltaren on the process of exudation induced by formalin. Pharmaceutical Bulletin of Uzbekistan., 1, p.44-47.

[8] Khakimov Z.Z., Rakhmanov A.Kh., Mavlanov Sh.R., 2017, The study of antiflagenic activity of collection from local medicinal plants. Infection, immunity and pharmacology., 3, p.226-230.

[9] Khakimov Z.Z., Rakhmanov A.Kh., Ulmasov M.A., 2016, The study of anti-inflammatory and antipyretic activity of voltaren in experimental acute hepatodystrophy. Reports of the Academy of Sciences of the Republic of Uzbekistan., 5, p.97.

[10] Kharkevich D.A., Pharmacology. "GEOTAR-MEDIA.".

Moscow, (2017), p.908.

[11] . Kong H.Kh., Khaziakhmedova V.N., Ziganshina L.E., 2015, Modeling of inflammatory edema: are interchangeable models?. Experiment. and wedge. pharmacol., 78(7), p.24-31.

[12] Krishen K.L. et al., 2009, Evaluation of the anti-inflammatory effect of drugs based on sage. Cytokines and inflammation., 8(4), p.67-72.

[13] Mashkovsky M.D. Medicines. RIA "Новая волна". Moscow, (2008), p.1206.

[14] Mavlyanov I.R., Rizamuhamedova M.Z., Bikenova G.T., Pharmacoepidemiological and pharmacoeconomic aspects of rheumatoid arthritis. "Noshirlik yog'dusi". Tashkent, (2017), p.148.

[15] Mironov A.N., Guidelines for preclinical studies of drugs. Part one. M: Grif and K, (2012), p.944.

[16] Nasonov E.L., 2008, New opportunities for the pharmacotherapy of rheumatic diseases - inhibition of interleukin-6. Clinical Pharmacology and Therapy., 17(1), p.60-67.

[17] Novikov V.E., Klimkina E.I., 2005, Possibilities of pharmacological protection of liver function. Bulletin of the Smolensk State Medical Academy., 1, p.107-117.

[18] Novikov V.E., Pozhilova E.V., Ilyukhin S.A., 2015, The effect of antihypoxants on the development of acute formalin edema. Clinical Pharmacology and Drug Therapy Reviews., 13(1), p.41-44.

[19] Novikov V.E., Ilyukhin S.A., 2013, The effect of hypoxene on the effectiveness of acetylsalicylic acid in acute inflammation. Experimental and Clinical Pharmacology., 76(4), p.32-35.

[20] Novitsky V.V., Pathophysiology. HIGH SCHOOL: IATE MEPhI., (2018), p.896.

[21] Polukonova N.V. et al., 2015, Anti-inflammatory, fever-reducing and antimicrobial activity of flavanoid containing Avrana officinalis extract (Gratiola officianilis L.). Experiment. and wedge. Pharmacol., 78(1), p.34-38.

[22] Rakhmanov A. Kh. et al., 2016, Features of the anti-inflammatory activity of voltaren in experimental acute hepatitis. Monthly Scientific Journal. Novosibirsk., 1(19), p.68-72.

[23] Salikhov Sh.I., Kim R.Yu., Mavlyanov S.M. et al., 2007, Determination of anti-influenza activity of drugs based on polyphenols of plant materials. Medical Journal of Uzbekistan., 5, p.64-67.

[24] Shiretorova V.G., 2014, Anti-inflammatory activity of Pinus Sibirica Du Tour seed shell extract. Basic research., 12, p.354-352.

[25] Talalaeva O.S., Mishenko N.P., Bruchanov V.M. et al., 2012, The effect of histochrome on the exudative and proliferative phases of experimental inflammation. Bulletin SB RAMN., 32(4), p.28-31.

[26] Usmanova Sh.E., Yakubov A.V., Hamraev A.A., 2014, The synthesis of nitric oxide in the gastric mucosa and kidney tissue with indomethacin-induced gastro- and nephropathy and ways of its correction. Experimental and clinical gastroenterology. Moscow., 6, p.73-77.

[27] Vengerovsky A.I., Burkova V.N., Yudina N.V., Yatsenkova A.I., 2012, Anti-inflammatory and analgesic effect of polar lipids of antlers of maral and peat during experimental inflammation. Bull. Siberia Honey., 6, p.31-35.

[28] Zhuravleva M.V. et al., 2016, The rational use of NSAIDs is a balance of efficiency and safety. International Journal of Applied and Fundamental Research., 6(4), p.687-696.

[29] Zverev Y. F., 2017, Flavonoids through the eyes of a pharmacologist. Antioxidant and anti-inflammatory activity. Reviews on clinical pharmacology and drug therapy., 15(4), p.5-13.

[30] Pirnyazov A.Zh., Mavlyanov S.M., Abdullazhanova N.G. et al., 2002, Rutan is an effective antiviral agent of plant origin. Bulletin of the GulSU., 1, p.26-31.