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PLASMA-RICH PLATELETS ANTI-INFLAMMATORY EFFECT IN CONDITIONS OF CARRAGEENAN-INDUCED PAW EDEMA IN RATS

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The purpose of the study was to determine the expression of platelet-rich plasma anti-inflammatory effect in conditions of its complex use in a model of carrageenan-induced paw edema in rats. Experimental studies were performed in conditions of carrageenan-induced exudative aseptic inflammation. Rats were undergone to separate and combined platelet-rich plasma and ellagic acid injections. Diclofenac sodium was used as a reference drug. The inflammatory response indexes, pro-inflammatory cytokine content, and inducible NO-synthase activity in the paw tissue of animals were determined 30 min, 1, 2, 4, and 6 hours after carrageenan administration. The data obtained revealed rats' hind paw edema reduction, an inflammatory index decrease, and TNFα and IL-1β release block after platelet-rich plasma and ellagic acid combined administration in conditions of carrageenan-induced aseptic inflammation. The investigated compound's anti-inflammatory effect was maximal at the delayed stages of inflammatory reaction, starting from 4 hours until the end of the trial. The authors proved the principal possibility of anti-inflammatory efficacy increasing as a result of platelet-rich plasma and ellagic acid combined administration in the form of additivity. The possibility of anti-inflammatory efficacy increasing by platelet-rich plasma added to a complex pharmacological regimen was demonstrated. The revealed platelet-rich plasma and ellagic acid combined administration anti-inflammatory efficacy and a pathogenetic background of this protective effect implementation in carrageenan-induced rat paw inflammation prove the reasonability of this pharmacological scheme anti-inflammatory efficacy clinical testing.

Key words: aseptic inflammation, carrageenan, rats, paw edema, ellagic acid, platelet-rich plasma, pathophysiological mechanisms, pathogenetically oriented pharmacocorrection.

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ПРОТИЗАПАЛЬНИЙ ЕФЕКТ ЗБАГАЧЕНОЇ ТРОМБОЦИТАМИ ПЛАЗМИ ПРИ КАРАГІНАН-ІНДУКОВАНОМУ НАБРЯКУ ЛАПИ У ЩУРІВ

Метою дослідження було визначення вираженості протизапального ефекту збагаченої тромбоцитами плазми за умов комплексного застосування на моделі карагенан-спричиненого набряку лапи щурів. Експериментальні дослідження проводили за умов карагенан-індукованого ексудативного асептичного запалення. Щурам роздільно та сумісно уводили збагачену тромбоцитами плазму та елагову кислоту. Диклофенак натрію застосовували в якості референт-препарату. Через 30 хв, 1, 2, 4 та 6 год після введення карагенану визначали показники запальної реакції, а також вміст прозапальних цитокінів та активність індуцибельної NO-синтази в тканині лапи тварин. Отримані дані свідчать про редукцію вираженості запального набряку лапи щурів, зниження запального індексу та блокаду вивільнення фактору некрозу пухлини та інтерлейкіну-1 в разі сумісного введення збагаченої тромбоцитами плазми та елагової кислоти. Виявлена протизапальна дія досліджуваних субстанцій виявилася максимальною на відтермінованих стадіях запальної реакції, а саме, починаючи з 4 год досліду, і тривала до кінця досліду. Автори доводять принципову можливість підвищення ефективності протизапального ефекту в результаті сумісного введення збагаченої тромбоцитами плазми та елагової кислоти у вигляді ефекту адитивності. Авторами продемонстровано можливість підвищення ефективності протизапального лікування шляхом додавання до комплексної схеми збагаченої тромбоцитами плазми. Висвітлена протизапальна ефективність сумісного введення збагаченої тромбоцитами плазми та елагової кислоти та патогенетична обумовленість даного захисного ефекту при карагенан-ініційованому запаленні лапи щурів доводить доцільність клінічного тестування протизапальної ефективності даної фармакологічної схеми.

Ключові слова: асептичне запалення, карагенан, щури, набряк лапи, елагова кислота, збагачена тромбоцитами плазма, патофізіологічні механізми, патогенетична фармакокорекція.

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The body's inflammatory reaction is its defense in response to altering agents' influence of allergic, toxic infectious genesis, etc., which initiate redness and edema manifestation together with local circulatory confusions, pain, and other functional disorders in the site of the lesion [1]. According to fundamental ideas, inflammation can manifest in the body through acute and chronic pathological reactions. As a rule, an organism itself can cope with an acute inflammatory reaction by its own immune defense activation, another clinical manifestation characterizes conditions with chronic inflammation that require more expressed, sometimes pharmacologically induced immune defense activation and are characterized by comorbid pathological reactions with cardiovascular, digestive, muscle-skeletal and other systems involvement [4, 13].

Inflammatory reaction treatment, as a rule, requires the prescription of anti-inflammatory drugs of both steroidal and non-steroidal nature, antibiotics, and local symptomatic therapy. One could see the risk of severe adverse reactions and complications from the cardiovascular, digestive, excretory, blood, and other systems with prolonged use of these anti-inflammatory pharmacological compounds, which requires anti-inflammatory treatment change and discontinuation every so often [12].

That's why the mechanisms of the oldest and most well-known pathological reaction – the inflammatory reaction – still require further explanation, i.e., their pathophysiological mechanisms and anti-inflammatory therapy modification.

Lipoperoxidation acceleration, overexpression of pro-inflammatory cytokines and growth factors that function as pro-inflammatory mediators, both nitric oxide synthase and arachidonic acid synthesis activation, and other pathobiochemical mechanisms were shown to be involved in acute inflammation pathogenesis [1, 4]. Basophilic leukocyte degranulation with histamine, serotonin, and bradykinin release, cyclooxygenase activation with prostaglandins level increase were proved to be involved in the mechanisms of the early stage of inflammatory reaction while the processes of neutrophil infiltration and vascular reactions occurring as a result of pathobiochemical reactions are more attributed to the delayed stage of inflammation [1].

The carrageenan-induced paw edema model is frequently used to investigate the acute inflammatory response pathophysiological mechanisms and determine the anti-inflammatory treatment efficacy [2, 10]. The pharmacological compounds that effectively counteract lipoperoxidation acceleration, prevent active free radicals' formation, pro-inflammatory cytokines release and protein mediators of inflammation formation, and inhibit both the cyclooxygenase and the hyperactive inducible form of nitric oxide activity are believed to have marked anti-inflammatory properties pertaining with modern anti-inflammatory pharmacological drugs [9].

Investigation of the anti-inflammatory activity of plant-derived compounds characterized by various biological and pharmacological effects, including anti-inflammatory [9], is promising among all other possible ways for new substances with anti-inflammatory activity screening. We are interested in the plant polyphenol profile of anti-inflammatory activity, and we chose ellagic acid (EA), which provides antioxidant, analgesic, anticancer, and anti-inflammatory effects [5, 8, 14].

Otherwise, the anti-inflammatory properties of autologous platelet-rich plasma (PRP) were shown [11, 15], which we consider as a possibility to check the likelihood of anti-inflammatory effect enhancement in the case of PRP and EA combined administration.

The purpose of the study was to determine the expression of platelet-rich plasma anti-inflammatory effect in conditions of its complex use in a model of carrageenan-induced paw edema in rats, we also investigated the mechanisms of platelet-rich plasma complex administration anti-inflammatory efficacy.

Materials and methods. Experimental studies were performed on 250 white matured male Wistar rats. The animals were kept in individual boxes with 12 hours of light and dark, humidity of 60 %, and constant temperature of 22±1 C, with free access to water and food. Animal preparation, all interventions, anesthetics, and withdrawal from the experiment were carried out in full compliance with the requirements of the Guidelines of the State Pharmacological Center of the Ministry of Health of Ukraine (Kyiv, 2001), as well as the GLP rules provided by the European Commission for the supervision of laboratory and other studies, by Code of Scientist of Ukraine.

Animal euthanasia was carried out by the provisions regulated by Annex 8 of the "Rules for the humane treatment of laboratory animals" and "Sanitary rules for equipment, equipment, and maintenance of experimental biological clinics (vivarium)" No. 1045-73.

The following experimental groups were used: 1 – control (intact rats, n=6); 2 – rats with intraplantar carrageenan injection (n=8); 3 – rats with intraplantar carrageenan injection which received the reference drug diclofenac sodium (DFS; per os; 2.5 % solution; 8.0 mg/kg; "Lubnypharm", Ukraine, n=6); 4 – rats with intraplantar carrageenan injection which received PRP (n=8); 5 – rats with intraplantar carrageenan injection which received EA (2,3,7,8 tetrahydroxy(1)benzopyranol (5,4,3-cde)(1])benzopyran-5,10-dione; i.p.; 30 mg/kg; OOO "Khimlaboreaktiv", Ukraine; n=8); 6 – rats with intraplantar carrageenan injection which received EA and PRP (n=8).

The inflammatory reaction was induced by subplantar carrageenan (1.0 %; 0.1 ml) injection into the foot of the right hind paw. The reference drug and studied pharmacological compounds were administered to animals 40 min before carrageenan administration. The rats were observed after for 6 hours. The expression of paw aseptic exudative inflammation manifestations was monitored 30 min, 1, 2, 4, and 6 hours after the carrageenan intraplantar administration – the volume and thickness of inflammatory edema were measured. The volume of edema was measured using a digital plethysmometer 37140 ("Ugo Basile", China), and the thickness of the edema – with the help of an electronic caliper YT-7201 ("YATO", Poland) [2]. Rat paw edema was calculated by the formula (a-b) in which "a" and "b" meant rats' right paw volume before and

after the carrageenan injection and certain pharmacological compounds administration. Anti-inflammatory activity (inflammatory response suppression index) was calculated in percentage according to the level of edema reduction in the animals' hind paws after the studied pharmacological compounds administration compared to similar indexes in rats with carrageenan-induced paw edema, which were taken as 100 %.

Rats were euthanized at the indicated time intervals after carrageenan intraplantar administration. Their right paw was cut off, and its homogenate was prepared in 500 μl of buffer containing protease inhibitors. Tumor necrosis factor-alpha (TNFα) and interleukin-1-beta (IL-1β) contents were determined in rats' paw homogenates using a commercial ELISA kit ("eBioscience", USA) according to the manufacturer's instructions. The inducible NO-synthase (iNOS) activity in the homogenate was determined using the nitratereductase enzyme with the simultaneous calculation of nitrites and nitrates content according to the manufacturer's instructions ("Cayman", USA).

Platelet-rich plasma prepared according to the standard method was immediately injected into the rats' right hind paws (0.2 ml, linearly, retrogradely, from two points) [15].

Table 1

The influence of PRP on pharmacological correction of carrageenan-induced inflammatory reaction in the rat paw

Experimental groups	Indexes of the paw edema, M±m		
	Edema thickness, mm	Edema volume, ml	Inflammatory response suppression index, %
30 min			
Control, n=6	0	0	-
Paw edema, n=8	3.2±0.3*	0.22±0.02*	100
Paw edema+DFS, n=6	1.3±0.1	0.12±0.01	54.5
Paw edema+PRP, n=8	2.6±0.3*	0.17±0.02*	77.2
Paw edema+EA, n=8	2.4±0.3*	0.18±0.02*	81.1
Paw edema+PRP+EA, n=8	2.7±0.3*	0.17±0.02*	77.2
1 hour			
Control, n=6	0	0	-
Paw edema, n=8	4.7±0.5*	0.31±0.02*	100
Paw edema+DFS, n=6	1.5±0.2#	0.18±0.01	58.1
Paw edema+PRP, n=8	4.1±0.4*	0.27±0.03*	87.1
Paw edema+EA, n=8	3.6±0.4*	0.23±0.02*	74.2
Paw edema+PRP+EA, n=8	4.2±0.4*	0.24±0.02*	77.4
2 hours			
Control, n=6	0	0	-
Paw edema, n=8	6.8±0.6*	0.57±0.04*	100
Paw edema+DFS, n=6	0.9±0.1#	0.11±0.01#	19.3
Paw edema+PRP, n=8	5.2±0.5*	0.44±0.04*	77.2
Paw edema+EA, n=8	4.3±0.4*	0.33±0.03*	57.9
Paw edema+PRP+EA, n=8	4.6±0.4*	0.34±0.03*	59.6
4 hours			
Control, n=6	0	0	-
Paw edema, n=8	9.1±0.9**	0.84±0.08**	100
Paw edema+DFS, n=6	1.1±0.2##	0.11±0.02##	13.1
Paw edema+PRP, n=8	4.1±0.4*#	0.32±0.03*#	38.1
Paw edema+EA, n=8	3.4±0.3*#	0.24±0.02*#	28.6
Paw edema+PRP+EA, n=8	3.0±0.3*#	0.22±0.02*#	26.2
6 hours			
Control, n=6	0	0	-
Paw edema, n=8	8.7±0.8**	0.91±0.08**	100
Paw edema+DFS, n=6	0.3±0.1##	0.04±0.01##	4.4
Paw edema+PRP, n=8	3.6±0.4*#	0.27±0.03*#	29.7
Paw edema+EA, n=8	3.1±0.3*#	0.22±0.02*#	24.8
Paw edema+PRP+EA, n=8	1.6±0.2##@	0.13±0.01##@	14.3

Notes: * – $p<0.05$ and ** – $p<0.01$ – significant differences of the studied indexes compared to analogous control indexes; # – $p<0.05$ and ## – $p<0.01$ – significant differences of the studied indexes compared to analogous indexes in rats with paw edema; @ – $p<0.05$ – significant differences of the studied indexes compared to analogous indexes in rats with paw edema with PRP administration (Kruskal-Wallis criteria statistic criteria were used in all calculations).

The data obtained were statistically analyzed with the help of the nonparametric Kruskal-Wallis test. The minimal statistical probability was determined at $p<0.05$.

Results of the study and their discussion. The manifestation of carrageenan-induced acute exudative aseptic inflammation in rats characterized by inflammatory reaction exudative component significant increase which maximal expression was recorded at 4 hours of the pathological process, which was manifested by both the thickness and volume of edema significant increase vs the control values (9.1±0.9 mm and 8.84±0.08 ml, respectively; $p<0.01$; Table 1).

Separate and combined PRP and EA administration could not affect the expression of carrageenan-induced paw edema during the first 2 hours ($p>0.05$). The values of investigated indexes 4 hours after carrageenan administration in the case of PRP and EA separate and combined administration were considerably less compared with similar indexes in rats with paw edema (in all cases $p<0.05$) but continued to remain higher than in intact rats (in all cases $p<0.05$). The index of inflammatory reaction inhibition in rats of these three groups was comparable and varied from 26.2 % to 38.1 % relative to the same data in rats with hindpaw edema without pharmacological drug administration (in all cases, $p<0.05$).

Both PRP and EA administration at the 6 hours of trial initiated an identical reduction of paw inflammation indexes, which were 58.6 % and 70.3 % (paw thickness and volume after PRP administration) and 64.4 % and 75.8 % (paw thickness and volume after EA administration) less pertaining the similar indexes in rats with carrageenan-induced paw edema without pharmacological compounds administration. The values of investigated carrageenan-initiated paw inflammation indexes in case of PRP and EA combined administration were equal, correspondently, to 1.6±0.2 mm and 0.13±0.01 ml which, being less than the same indexes in rats with paw edema without treatment (in all cases $p<0.01$), turned out to be by 2.25 and by 2.08 times less vs the analogous indexes in rats with paw edema with PRP injection (in all cases $p<0.05$). The significant changes in the edema of the rats' hind paws in thickness and volume at the 6th hour of the trial were confirmed by a decrease in the inflammatory reaction severity index.

PRP administration failed to affect the studied cytokines – TNFα and IL-1β – overexpression at the early stage of the acute inflammatory carrageenan-induced reaction (Table 2).

Table 2

The influence of PRP on the main indices of carrageenan-induced inflammatory reaction in the rat paw

Experimental groups	The investigated indices rate in rats paw, M±m		
	TNFα, pg/ml	IL-1β, pg/ml	iNOS, μM
30 min			
Control, n=6	98.4±8.7	76.7±6.7	38.9±3.6
Paw edema, n=8	1258.3±11.7**	1746.5±14.3**	64.1±5.7*
Paw edema+DFS, n=6	455.5±39.3*#	568.4±51.1*#	56.1±4.8*
Paw edema+PRP, n=8	1062.7±10.3**	1488.3±13.6**	65.3±5.7*
Paw edema+EA, n=8	762.7±64.7*#	698.6±62.4*#	61.7±5.8*
Paw edema+PRP+EA, n=8	1126.3±10.9**	1394.3±12.9**	62.6±5.6*
1 hour			
Control, n=6	86.3±8.8	79.2±6.1	36.4±3.3
Paw edema, n=8	1816.3±14.2	2427.5±22.1	82.3±7.6*
Paw edema+DFS, n=6	267.2±24.8*##	327.6±31.3*##	44.6±4.3#
Paw edema+PRP, n=8	1154.3±10.7**	1627.4±14.8**	58.4±5.3*
Paw edema+EA, n=8	846.2±76.3**#	783.4±71.2**#	62.8±6.2*
Paw edema+PRP+EA, n=8	963.3±87.4**#	821.7±76.3**#	54.1±4.8*
6 hours			
Control, n=6	98.4±8.7	76.7±6.7	37.6±3.7
Paw edema, n=8	1525.3±13.6	2175.5±19.4	72.1±6.8*
Paw edema+DFS, n=6	198.3±17.4*##	236.2±21.6*##	31.2±2.9#
Paw edema+PRP, n=8	658.6±54.3*#	811.7±72.1*#	53.6±4.9*
Paw edema+EA, n=8	537.6±48.4*#	619.3±56.8*#	48.6±4.1#
Paw edema+PRP+EA, n=8	344.7±32.1*##@	502.3±43.6*##@	40.3±3.7#

Notes: * – $p<0.05$ and ** – $p<0.01$ – significant differences of the studied indexes compared to analogous control indices; # – $p<0.05$ and ## – $p<0.01$ – significant differences of the studied indices compared to analogous indexes in rats with paw edema; @ – $p<0.05$ – significant differences of the studied indices compared to analogous indexes in rats with paw edema with PRP administration (Kruskal-Wallis criteria statistic criteria were used in all calculations).

TNFα and IL-1β content in rats' paws 1 hour after EA administration was 53.4 % and 67.7 % less compared with such indexes in animals with paw edema without pharmacological compounds administration (in all cases $p<0.05$). It's worth noting that the studied indexes, about those in intact rats (in all cases, $p<0.01$), remained significantly changed. Similar changes in the investigated pro-inflammatory cytokines content in the paw tissue of rats 1 hour after carrageenan administration were registered after PRP and EA combined administration.

We recorded the comparable changes in TNFα and IL-1β content in paw tissue of rats after PRP and EA combined administration, which still remained higher when compared with similar data in rats with edema without treatment and, however, were significantly less about control values (in all cases $p<0.05$).

Pro-inflammatory cytokines levels after PRP and EA co-administration decreased by 4.43 and 4.33 times, respectively, when compared with such indexes in paw tissue of rats with edema without treatment (in all cases $p<0.01$) and was on 47.7 % and 38.1 %, respectively, less pertaining the corresponding indexes in rats with carrageenan paw edema with PRP administration (in all cases $p<0.05$).

The iNOS activity remained stable until the end of the trials. One could see significant changes in its activity during the 6-hour trial interval. The iNOS activity after EA injection decreased by 32.6 % 6 hours after carrageenan administration and by 44.1 % – after PRP and EA combined administration vs the same index in rat paw tissue with carrageenan administration without treatment (in all cases $p<0.05$).

Thus, all the data obtained indicate the achieved and statistically confirmed possibility of anti-inflammatory efficacy increasing by PRP adding to the complex pharmacological regimen.

This conclusion is characterized by the reduction of inflammatory edema expression in rats' paws after PRP and EA combined administration in conditions of carrageenan-induced aseptic inflammation. Involved in the inflammatory reaction, pro-inflammatory cytokines release block was also achieved.

The revealed studied substances' pro-inflammatory effect was maximal at the postponed stages of carrageenan-induced inflammatory reaction, starting from 4 hours of the trial, and preserved till the end of the experiment. PRP and EA combined administration failed to affect the iNOS activity dynamics. It should be stressed that the anti-inflammatory efficacy of PRP and EA, both separate and combined administration, was less than the same effect of the reference drug DFS.

While discussing the data obtained, we would like to stress firstly the supposedly utopian nature of the idea of a completely solved problem of inflammation pharmacological correction. On the contrary, the data indicate its diversity and clinical manifestations polymorphism, the increase in cases of acute inflammatory reaction transition to a chronic manifestation [1, 4]. According to fundamental ideas, inflammation is a local reaction in response to damage, and the contemporary picture of prevailing clinical cases shows an organism's systemic reaction in response to phlogogenic altering factors impact [3, 10]. Such a brief declaration allows us to declare the importance of both experimental and clinical observations devoted to inflammation pathogenesis, new leading links clarifying, and new schemes for this typical pathological process of complex pathogenetically oriented therapy development.

Secondly, we consider it essential to study the perspective of the development of anti-inflammatory therapy schemes with an impact on inflammatory syndrome leading to pathobiochemical links. Hence, we consider essential not so much the proven EA anti-inflammatory effects in conditions of carrageenan-induced rats' paw inflammatory edema but the highlighted principal possibility of anti-inflammatory efficacy increasing due to PRP and EA co-administration. We are confident of achieving an additive effect as a result of the combined administration of plant polyphenol and a liquid with a mixture of authentic biologically active components, which, in our opinion, is an interesting and promising fact that requires intensive experimental verification and clinical testing.

Thirdly, the results received correspond to clinical data which show the possibility of TNFα, IL-1β, and high-sensitivity C-reactive protein blood concentrations decline in patients with knee joint osteoarthritis after PRP use [11]. It's interesting that these pro-inflammatory cytokines mediate and enhance the inflammatory reaction by initiating a self-sustaining cyclic mechanism that negatively affects the intracellular structures and cellular membrane stability as well as the body's organs and systems' functional activity. It turns out that the revealed effect of pro-inflammatory cytokines release block in conditions of carrageenan-induced inflammation has an applied importance since it allows us to break the "vicious circle" of the pathogenesis of this self-reinforcing and self-sustaining phlogogenic pathological reaction.

Fourthly, we can't ignore the reasons for our PRP choice in these studies. Initial data concerning PRP protective effects for cellular regeneration, cartilage, and bone repair for sports medicine, traumatology, and dentistry were subsequently added, significantly expanding the range of this source of biologically active substances applications. Currently, it is considered possible to use PRP with an anti-inflammatory purpose due to its growth factors [6, 7]. The ability of PRP to enhance local perfusion with tissue supply improvement and its reparative effect in the stage of proliferation was also proved [7], which also increases the range of indications for PRP anti-inflammatory efficacy testing. An advantage of PRP therapy is the physiological repair process simulation by autologous growth factors release, which is also essential because of the activation of endogenous sanogenetic mechanisms.

Finally, we consider it fundamentally important that PRP and EA combined administration not only reduces the carrageenan-initiated aseptic inflammation expression but also realizes the possibility of

inflammatory reaction main pathogenetic links affecting through a proven decrease of TNFα and IL-1β content and a slight inhibition of iNOS activity.

Therefore, the revealed PRP and EA combined administration anti-inflammatory efficacy and a pathogenetic background of this protective effect implementation in carrageenan-induced rat paw inflammation prove the reasonability of this pharmacological scheme anti-inflammatory efficacy clinical testing.

Conclusions

1. The expression of rats' hind paw edema reduction, an inflammatory index decrease, and TNFα and IL-1β release block were achieved after PRP and EA combined administration in conditions of carrageenan-induced aseptic inflammation.

2. The investigated compounds' anti-inflammatory effect was maximal at the delayed stages of the inflammatory reaction, starting from 4 hours and continuing till the end of the trial. The combined administration of PRP and EA in these conditions did not affect the iNOS activity.

3. PRP and RE separate and combined administration anti-inflammatory efficacy was less compared with the same of DFS.

4. The principal possibility of anti-inflammatory efficacy increasing due to PRP and EA combined administration in the form of additivity was proved to require intensive experimental verification and clinical testing.

5. The data obtained indicate the possibility of anti-inflammatory efficacy increasing by PRP adding to a complex pharmacological regimen.

6. The revealed PRP and EA combined administration anti-inflammatory efficacy together with a pathogenetic background of this protective effect implementation in carrageenan-induced rat paw inflammation prove the reasonability of this pharmacological scheme anti-inflammatory efficacy clinical testing.

Prospects for further research aimed at prospective experimental verification of plasma-rich platelets and ellagic acid combined administration anti-inflammatory efficacy mechanisms of implementation of this anti-inflammatory scheme clinical testing.

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