BIOCHEMICAL EVALUATION OF ANTI-INFLAMMATORY ACTION OF CELECOXIB AND CAFFEINE IN A FORMALIN PAIN MODEL IN RATS

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ABSTRACT

Background. Inflammation is a reaction of living tissue on injury. Nowadays there is a wide spectrum of anti-inflammatory medications that are used for the treatment of many problems. But because their application is associated with a wide range of side effects, there is a need for the development of new pharmaceutical compositions to maximise patient safety.

Aim. To carry out biochemical evaluation of anti-inflammatory action of celecoxib in combination with caffeine on the biochemical markers of inflammation (sialic acids and ceruloplasmin) and to determine its anti-exudative action on formalin-induced paw edema in rats.

Materials and Methods. The study involved male Wistar Albino Glaxo (WAG) line rats, divided into six treatment groups: control, formalin-induced, celecoxib (5 mg/kg), caffeine (0.6 mg/kg), a combination of celecoxib and caffeine (5 mg and 0.6 mg/kg), and diclofenac sodium (8 mg/kg). Biochemical studies were carried out by using the blood serum samples of white laboratory rats (WAG line). Anti-inflammatory activity of celecoxib and its pharmaceutical composition with caffeine was studied using the formalin-induced paw edema model. The animals were divided into the same groups as in the Anti-Exudative Activity (AEA) study.

Results. It was shown, that composition of celecoxib and caffeine exerted higher anti-inflammatory activity versus celecoxib and it is efficient in relation to the exudation processes. Biochemical studies of celecoxib, caffeine and their composition on the level of sialic acid level and ceruloplasmin level in the blood serum as well as study of anti-exudative activity of the proposed composition have shown, that caffeine potentiates pharmacological activity of celecoxib in formalin-induced paw edema model.

Conclusion. The findings indicate that the combination of celecoxib and caffeine is a promising therapeutic option for inflammatory conditions.

Keywords: *anti-inflammatory drugs, anti-exudative action, biomarkers of inflammation.*

Introduction

Inflammation is a fundamental pathological process linked to various diseases. Anti-inflammatory drugs, both long- and short-acting, including non-steroidal and steroidal types, are employed for treating inflammatory conditions. These drugs vary in chemical structure and mechanism, primarily functioning through the inhibition of CycloOXygenase (COX) enzymes responsible for prostaglandin synthesis [1–4]. COX exists in three isoforms: COX-1 (protects gastrointestinal mucosa), COX-2 (inducible and associated with inflammation), and COX-3 (involved in fever regulation). Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) predominantly inhibit COX-2 to mitigate inflammation while minimizing COX-1-related side effects. The anti-inflammatory effects of NSAIDs are largely attributed to their inhibition of COX-2 activity, while the side effects, particularly gastrointestinal complications, are primarily due to COX-1 inhibition. Furthermore, NSAIDs can also influence the synthesis of leukotrienes and superoxide radicals, affecting cellular membrane activity, neutrophil aggregation, and lymphocyte function [5–8].

Celecoxib, a well-known COX-2 inhibitor, is widely used for pain management due to its efficacy and lower gastrointestinal side effects. It is effective for treating various conditions, including rheumatoid arthritis, dysmenorrhea, and migraine. Importantly, at therapeutic concentrations, celeco-

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xib does not inhibit COX-1, which contributes to its favorable safety profile. However, its efficacy can be enhanced through combinations with adjuvants, such as caffeine [9–12]. Recent research indicates that caffeine can act as an adjuvant to NSAIDs, enhancing their anti-inflammatory and analgesic effects. Caffeine has been studied in conjunction with various NSAIDs, including coxibs, to improve therapeutic outcomes [12–19]. This study investigates the Anti-Exudative Activity (AEA) of a combination of celecoxib and caffeine, comparing it to individual components and the reference drug sodium diclofenac, as well as its effects on biomarkers of inflammation: Sialic Acids (SA) and Ceruloplasmin (Cp).

The **aim** of study was to carry out biochemical evaluation of anti-inflammatory action of celecoxib in com-bination with caffeine on the biochemical markers of inflammation (sialic acids and cerulo-plasmin) and to determine its anti-exudative action on formalin-induced paw edema in rats.

Materials and Methods

The anti-exudative activity was assessed using a formalin-induced paw edema model in male Wistar Albino Glaxo (WAG) rats weighing (300–350) g. The animals were acclimatized for 14 days under controlled vivarium conditions (at an air temperature of [23–25]°C with lighting set at 100 lx in the room and 20–40 lx in the cages). All studies were conducted according to the "General Principles of Ethical Conduct for Experiments on Animals" (Ukraine, 2001), which comply with the provisions of the European Convention "On Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986).

Rats were divided into six treatment groups:

1. Control group (received a single intragastric dose of 3% starch mucus)

2. Formalin-induced group (a 2% formalin solution was injected subplantarly into the rat's hind paw, and a 3% starch mucus was given intragastrically);

3. Subplantar 2% formalin injection and a single intragastric dose of 5 mg/kg celecoxib as suspensions in 3% starch mucus;

4. Subplantar 2% formalin injection and a single intragastric dose of 0.6 mg/kg caffeine celecoxib as suspensions in 3% starch mucus;

5. Subplantar 2% formalin injection and a single intragastric dose of combination containing celecoxib (5 mg/kg) and caffeine (0.6 mg/kg) as suspensions in 3% starch mucus;

6. Subplantar 2% formalin injection and a single intragastric dose of 8 mg/kg sodium diclofenac) as suspensions in 3% starch mucus.

The treatments were administered intragastrically, and paw volume was measured before and after treatment using a digital plethysmometer (IITC Life Science, USA). Changes in rat paw volume at different time points were expressed in milliliters (mL). The AEA was calculated as a percentage inhibition of inflammation (PII) according to the following formula:

$$PII = \frac{V_c - V_0}{V_c} \times 100\% \qquad (1)$$

where:

V_c – paw volume in the control group minus initial paw volume before edema, mL;

V_o – paw volume after edema minus initial paw volume before edema, mL.

Biochemical studies were conducted using blood serum samples from white laboratory rats (WAG line). The anti-inflammatory activity of celecoxib and its pharmaceutical composition with caffeine was investigated using the formalin-induced paw edema model. The animals were divided into the same groups as in the AEA study.

The level of serum SA was measured using the "SialoTest" from the Research and Production Centre "Eco-Service". The procedure involved adding 1 mL of hydrolyzing agent to test tubes containing 2 mL of distilled water and 0.6 mL of blood serum samples. The solutions were mixed thoroughly and then placed in a boiling water bath for 5 minutes. Following this, the samples were centrifuged at 3000 rpm for 5 minutes to collect the supernatant.

0.4 mL of a color-producing reagent was added to 2 mL of the supernatant. This reactive mixture was incubated in a boiling water bath for 15 minutes, then cooled with tap water. After cooling, 2 mL of distilled water was added to each test tube, and the contents were mixed again. The absorbance was measured at 540 nm using a photocolorimeter. Sialic acid concentrations (CSA, mmol/L) were calculated based on absorbance values, using the following formula:

$$C_{SA} = \frac{A_{sam} \times C_{cal}}{A_{cal}} \qquad (2),$$

where:

A_{sam} – absorbance of the investigated serum sample;

C_{cal} – concentration of the calibrator (mmol/L);
A_{cal} – absorbance of the calibrator.

The conversion factor (K) was determined prior to each measurement using the formula:

$$K=2/A_{cal} \quad (3)$$

where:
A_{cal} – absorbance of the calibrator.
2 represents the concentration of sialic acids in the calibrator (mmol/L) [20].

Ceruloplasmin levels were measured using the Ravin method, where ceruloplasmin catalyzes the oxidation of p-phenylenediamine, yielding a purple product [34].

The reaction mixture comprised 1.58 mL of a 0.5M sodium acetate buffer solution (pH 5.5), 0.2 mL of freshly prepared 0.5% p-phenylenediamine dihydrochloride solution, and 0.02 mL of the serum sample. The mixture was incubated at 37°C in a water bath for one hour. To terminate the reaction, 0.2 mL of a 0.5% sodium azide solution was added. For control purposes, a control sample was prepared by adding 0.2 mL of sodium azide before the incubation.

Absorbance was measured at 530 nm, and ceruloplasmin concentration was calculated using a standard optical density coefficient:

$$C(Cp) = A_0 \times 5.83 \quad (4),$$

where:
C(Cp) – molar concentration of ceruloplasmin in the sample;
A_0 – optical density of ceruloplasmin in the sample.
5.83 – optical density coefficient according to Ravin's method, expressed in micromoles of active protein per liter (μmol/L) [21].

All procedures performed in this study complied with the regulations established by the State Pharmacological Center of the Ministry of Health of Ukraine [22]. Ethical guidelines, cost-effectiveness, and statistical considerations were taken into account when determining the number of animals and their allocation to the study groups [23]. All experiments were conducted in the afternoon, correlating with the circadian rhythms that influence the pharmacological parameters of the investigated drugs and their activities.

The findings were statistically analyzed using Statistica 6.0 (Statsoft, USA), employing the Student t-test to determine the significance of differences between groups.

Results

Our experimental studies on formalin-induced paw edema demonstrated that celecoxib (Group 3) achieved an Anti-Exudative Activity (AEA) of 50%, which was 6% higher than that of the reference drug, sodium diclofenac (Group 6). In comparison, the AEA of caffeine alone (Group 4) was markedly lower, at just [18.3–2.7]% times less than that of celecoxib. Interestingly, the addition of caffeine to celecoxib (Group 5) enhanced its AEA by 5% compared to celecoxib alone.

Based on these findings, the investigated drugs and proposed pharmaceutical composition can be ranked in terms of their AEA against formalin-induced paw edema in rats as follows. The composition containing celecoxib and caffeine (55.5%) is more effective than celecoxib (50%), which is more effective than sodium diclofenac (44%), which in turn is more effective than caffeine (18.3%).

To further substantiate our findings regarding the anti-exudative activity of the pharmaceutical composition and its individual components, we performed biochemical analyses of inflammatory markers. Specifically, we measured the levels of SA and Cp in rat blood serum after treatment for formalin-induced paw edema with the proposed pharmaceutical compositions and their components. These results were compared to those obtained with the reference drug, sodium diclofenac.

To further substantiate our findings regarding the anti-exudative activity of the pharmaceutical composition and its individual components, we performed biochemical analyses of inflammatory markers. Specifically, we measured the levels of SA and Cp in rat blood serum after treatment for formalin-induced paw edema with the proposed pharmaceutical compositions and their components. These results were compared to those obtained with the reference drug, sodium diclofenac.

The subsequent phase of the study focused on evaluating the effects of celecoxib, caffeine (as an adjuvant), their combination, and the reference drug sodium diclofenac on Cp activity in the blood serum of rats. A statistically significant increase in Cp levels was observed in Group 2, showing a 2.8-fold increase compared to the control group (Group 1). Following celecoxib administration (Group 3), Cp levels in the blood serum of rats decreased by 1.2 times compared to the formalin edema group (Group 2). This difference was statistically significant when compared to both the control

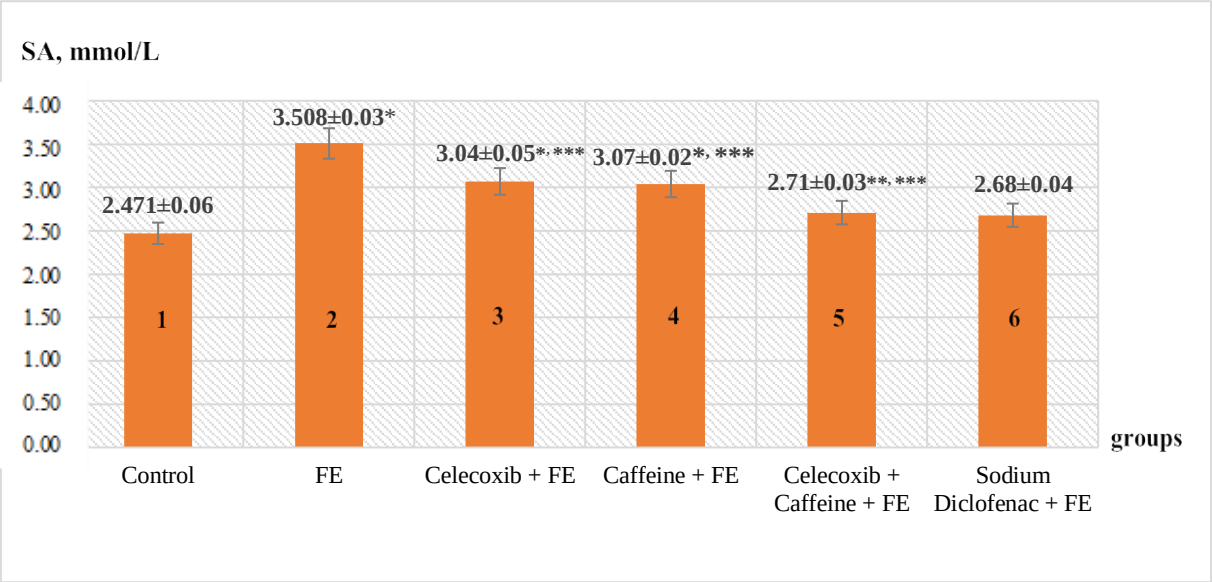

Fig. 1. Effect of celecoxib, caffeine, and their pharmaceutical composition on the SA level in rat blood serum in the formalin-induced paw edema model.

Note: difference between groups is shown as (mean ± standard error), all results are significant ($p<0.05$);
* – difference compared to the control group;
** – difference compared to the formalin edema group;
*** – difference compared to the formalin edema group;
**** – difference compared to the celecoxib and formalin edema group.

group (Group 1) and the sodium diclofenac group, although no significant difference was found between Groups 3 and 2.

In Group 4, the administration of caffeine resulted in a reduction of Cp levels in the rat blood serum by 1.6 times compared to the formalin edema group (Group 2), indicating a statistically significant difference from the results in Group 2. Moreover, caffeine effectively lowered the level of the inflammation marker ceruloplasmin in the formalin-induced inflammatory model. A statistically significant difference was observed in comparison with the control group but not in comparison with the sodium diclofenac group (Figure 2).

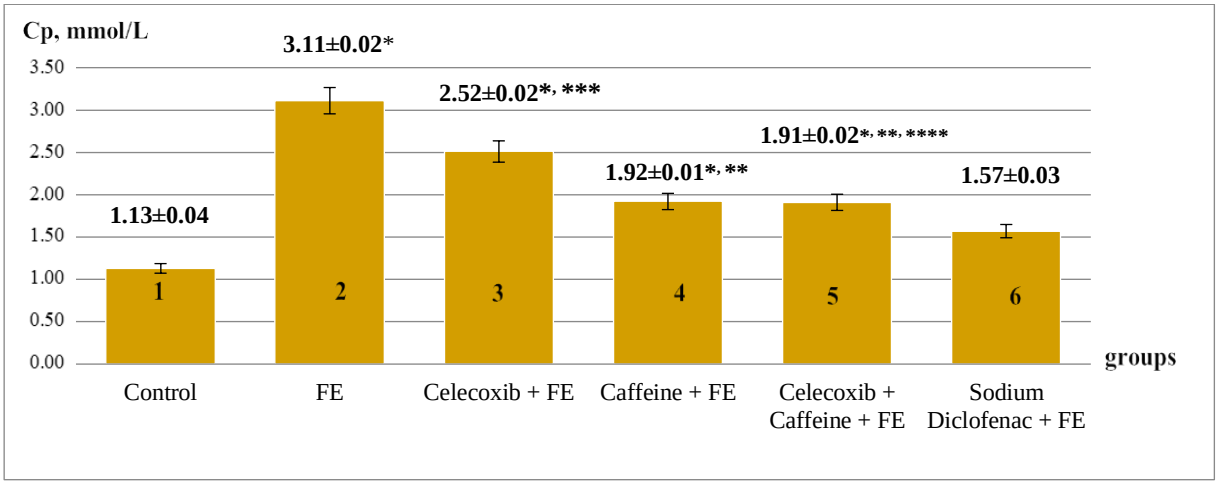

Fig. 2. Effect of celecoxib, caffeine, and their pharmaceutical compositions on the ceruloplasmin level in rat blood serum in the formalin-induced paw edema model.

Note: difference between groups is shown as (mean ± standard error), all results are significant ($p<0.05$);
* – difference compared to the control group;
** – difference compared to the formalin edema group;
*** – difference compared to the formalin edema group;
**** – difference compared to the celecoxib and formalin edema group.

Overall, the research demonstrated that caffeine (with an AEA of 18.3%) enhances the AEA of celecoxib (with an AEA of 50 %), and the proposed pharmaceutical composition of celecoxib and caffeine (with an AEA of 55.5%) is effective in mitigating exudative processes.

Acute-phase proteins, such as Cp, which belongs to the α-globulin group, are valuable biomarkers for diagnosing inflammatory diseases, as their levels increase during acute inflammation. This motivated our previous studies, which investigated the influence of coxibs on blood serum ceruloplasmin activity in rats using the formalin-induced edema model. Our findings established a positive effect of coxibs on Cp levels, with rofecoxib demonstrating greater efficacy than celecoxib.

It is well-known that one of the mechanisms by which NSAIDs exert their anti-inflammatory effects is through the inhibition of inflammatory responses, partly due to their ability to modulate oxidation and phosphorylation processes. Disruptions in the barrier properties of lipid membranes play a significant role in the development of inflammatory processes and pain syndromes. One major trigger for such disruptions is the activation of Lipid PerOxidation (LPO), which is regulated by the body's physiological antioxidant systems. A compromise in any of these protective mechanisms can lead to the activation of LPO.

During inflammation, ProstaGlandins (PGs) and leukotrienes are formed as a result of the enzymatic oxidation of arachidonic acid, leading to increased formation of free radicals that enhance LPO. Consequently, we studied the inhibitory effects of coxibs, particularly their pharmaceutical compositions with caffeine, on LPO processes. This was evidenced by a decrease in Conjugated Diene (CD) levels in the blood serum of rats subjected to formalin-induced edema.

Sialic acid is another important biomarker of inflammation. Sialic acids are normal components of all tissues and biological fluids in the human body and constitute a major part of glycoproteins and glycolipids. When freed from glycoproteins, sialic acids can inactivate certain bacterial and viral agents, which is why elevated sialic acid levels are observed in various pathological states characterized by inflammation.

In our earlier studies, we found that proposed pharmaceutical compositions of oxicams with caffeine affected serum sialic acid levels in rats. Additionally, we demonstrated that adjuvant caffeine positively impacts the anti-inflammatory activity of piroxicam and meloxicam, as evidenced by changes in sialic acid levels.

Biochemical investigations into the anti-inflammatory actions of celecoxib and caffeine revealed that both celecoxib (group 3) and caffeine (group 4) decreased sialic acid levels in the blood serum of laboratory animals relative to the model group (group 2). Statistically significant differences were observed between the treatment and control groups, confirming that the combination of celecoxib and caffeine significantly reduced sialic acid levels in relation to formalin-induced paw edema (group 2). In contrast, celecoxib alone (group 3) showed statistically significant similarities to both the reference drug and the intact control group.

The combination of celecoxib and caffeine (group 5) exhibited enhanced anti-inflammatory activity compared to celecoxib alone in formalin-induced rats. The pharmaceutical composition of celecoxib and caffeine (group 5) significantly reduced ceruloplasmin levels in both the model group (group 2) and the group treated solely with celecoxib (group 3). No statistically significant difference was noted between the results of the group treated with the reference drug and the control group.

Conclusion

The experimental studies of celecoxib, caffeine, and the proposed pharmaceutical compositions containing both agents in a formalin-induced paw edema model have demonstrated that caffeine enhances the anti-exudative activity (AEA) of celecoxib. The effectiveness of the investigated drugs and their composition, based on AEA, follows this order: the combination of celecoxib and caffeine is the most effective, followed by celecoxib alone, then sodium diclofenac, with caffeine being the least effective.

Therefore, we consider the pharmaceutical composition of celecoxib and caffeine to be effective in addressing exudation processes in this model.

Biochemical studies have shown that caffeine enhances the pharmacological activity of celecoxib by reducing sialic acid levels in blood serum. Based on their ability to reduce SA levels in blood plasma, the investigated drugs and their composition can be ranked as follows: the combination of celecoxib and caffeine is equally effective as sodium diclofenac, while celecoxib alone is as effective as caffeine.

Consequently, the proposed pharmaceutical composition containing celecoxib and caffeine is deemed effective in lowering sialic acid levels in rat blood serum in the formalin-induced edema model.

Furthermore, the results of biochemical studies indicate that caffeine acts as an adjuvant in reducing ceruloplasmin levels. In terms of reducing ceruloplasmin levels, sodium diclofenac is the most effective, followed by the combination of celecoxib and caffeine, which has the same effect as caffeine, while celecoxib alone is the least effective.

Overall, our findings demonstrate that the proposed pharmaceutical composition of celecoxib and caffeine possesses anti-inflammatory activity. We also see potential for further experimental and biochemical studies of this composition in zymosan- and carrageenan-induced edema models.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the authors.

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Consent for publication

All authors give their consent to publication.

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