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COMPARATIVE STUDY OF THE EFFECTS OF IBUPROFEN AND CELAGRIP ON THE COURSE OF ASEPTIC INFLAMMATION INDUCED BY VARIOUS PHLOGOGENS IN THE PREPUBERTAL PERIOD

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Abstract:
The anti-inflammatory activity of Ibuprofen and CelAgrip was studied in a comparative aspect in prepubertal experimental animals. Inflammation in two-month-old rats was induced by subplantar injection of carrageenan, dextran, and histamine. In a separate series, the effects of the drugs on the proliferative phase of inflammation were studied using the "cotton pellet" model. It was found that both studied drugs significantly suppressed the inflammatory process in all models of aseptic inflammation induced by various phlogogens. Alongside exudation, the drugs also clearly suppressed the process of proliferation. No significant differences in the pharmacological activity of Ibuprofen and CelAgrip were identified, although the mechanisms of anti-inflammatory action of these drugs are presumed to differ. It is considered that CelAgrip can be used instead of Ibuprofen as an effective anti-inflammatory agent in pediatric practice.

Keywords: Ibuprofen, CelAgrip, phlogogens, prepubertal age, exudation, proliferation, free radical oxidation.

CONFLICT OF INTEREST:
The authors declare no obvious or potential conflicts of interest related to the publication of this article.

INTRODUCTION

Inflammation is an important component of the complex biological response of the body to harmful stimuli. One of the key risk factors for its development is age. The interplay of diseases during childhood increases the number and severity of complications, worsens the quality of life, leads to excessive use of medications, and limits the potential for rational pharmacotherapy [1]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are most frequently used to suppress aseptic inflammation, hyperthermia, and pain syndrome [2,3]. Consequently, NSAIDs are among the most commonly used medications in daily medical practice, with many available over-the-counter and easily accessible to the population [4,5].

However, despite the wide range of modern NSAIDs, the problem of effective pharmacotherapy for diseases primarily driven by inflammation remains unsolved, especially in terms of recurrence [6,7]. Moreover, NSAID use is typically associated with significant side effects, not only from the gastrointestinal tract (gastropathy, enteropathy, ulcers, bleeding, hepatitis) but also from the cardiovascular system (edema, increased blood pressure, heart failure), kidneys, and liver (elevated liver enzymes, impaired kidney function) [8–14]. Vision disorders, hematologic abnormalities, and allergic reactions are also possible [15–17]. The development of selective cyclooxygenase (COX) inhibitors did not resolve these issues; instead, it introduced new adverse effects [18].

This underscores the urgent need to use NSAIDs with consideration of not only comorbid conditions but also the functional state of internal organs, particularly in pediatric practice.

It is known that the polymer composition of gossypol—CelAgrip and Kagocel—has pronounced anti-inflammatory properties [19–24]. A review of recent literature highlights a lack of studies on the pharmacodynamics of NSAIDs in children. This provided the rationale for the current study.

OBJECTIVE:

To investigate the features of the anti-inflammatory activity of CelAgrip during the prepubertal period in experimental animals.

MATERIALS AND METHODS

Experimental studies were conducted on white male rats, two months of age, weighing 65–80 grams, obtained from the vivarium of the Sanitary-Epidemiological Station of the Medical-Sanitary

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Association under the Ministry of Health of the Republic of Uzbekistan. Prior to the experiments, all animals underwent a two-week quarantine, after which they were examined, weighed, and evaluated for age, sex, motor activity, and skin condition. Each experimental and control group consisted of six animals.

During the experiments, the laboratory animals were kept in the vivarium in plastic cages with wood shavings as bedding, at a temperature of 20–24°C, humidity not less than 50%, in well-ventilated rooms with a light/dark cycle. Feeding was adjusted according to age. All experimental procedures complied with the "Guidelines for laboratory work using experimental animals" and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (ETS No. 123, Strasbourg, 18.03.1986). The study protocol was approved by the Ethics Committee of the Tashkent Medical Academy, Ministry of Health of the Republic of Uzbekistan (Protocol No. 6 dated April 25, 2025).

The tested drug was **CelAgrip** in tablet form (manufacturer: Radiks, Uzbekistan). **Ibuprofen** tablets were used as the comparator drug, regarded as the "gold standard" of nonsteroidal anti-inflammatory drugs (NSAIDs) and recognized as a benchmark for assessing the therapeutic potential and safety of drugs in this pharmacotherapeutic group [25] (manufacturer: Borisov Pharmaceutical Plant, Belarus).

To evaluate the **anti-exudative activity** of CelAgrip and Ibuprofen, classical models of experimental aseptic arthritis were used, induced by solutions of various phlogogenic agents in the following concentrations: dextran (6%), histamine (0.1%), carrageenan (1%) [26,27]. Solutions were injected (0.1 ml per animal) subplantarly (under the plantar aponeurosis) into the dorsal surface of the right hind paw of rats. The volume of the paw before phlogogen administration was considered the baseline and taken as 100%.

Using a metal gastric probe, animals in the control group received an equivalent volume of water orally 1 day and 1 hour before the induction of aseptic arthritis, while the experimental groups received CelAgrip and Ibuprofen at doses of 10, 25, and 50 mg/kg. Paw volume was measured using an oncometric method with a digital plethysmometer (Ugo Basile Srl, Italy) at the following intervals:

- **For histamine-induced inflammation:** before and 30, 60, 90, and 120 minutes after injection
- **For dextran and carrageenan-induced inflammation:** before and 1, 2, 3, and 4 hours after injection

Assessment criteria for anti-phlogogenic effects included paw volume increase, inhibition index, and calculation of anti-inflammatory activity.

- **Paw Edema Increase (PEI)** was calculated by the formula [27,28]:
PEI=O−BB×100PEI = \frac{O - B}{B} \times 100PEI=BO−B×100
Where:
  - **PEI** – paw edema increase (%),
  - **O** – paw volume after phlogogen injection,
  - **B** – baseline paw volume before phlogogen injection.
- **Inhibition Degree (ID)** was calculated as:
ID=(1−O−B(O−B)control)×100ID = \left(1 - \frac{O - B}{(O - B)_{\text{control}}} \right) \times 100ID=(1−(O−B)controlO−B)×100
Where:
  - **O** – treated group,
  - **(O - B)control** – control group (untreated)
- **Anti-Inflammatory Activity (AIA)** was calculated using the formula [24,37]:
AIA=Vcontrol−VexperimentalVcontrol×100AIA = \frac{V_{\text{control}} - V_{\text{experimental}}}{V_{\text{control}}} \times 100AIA=VcontrolVcontrol−Vexperimental×100
Where:
  - **Vcontrol** – mean volume increase in control group (cm³),
  - **Vexperimental** – mean volume increase in the experimental group (cm³)

To study the **anti-proliferative phase** of inflammation, the **"cotton pellet" model** was used [26,27]. The model involved subcutaneous implantation of sterile cotton pellets (10 mg each) under the interscapular skin of rats under general anesthesia and aseptic conditions.

CelAgrip and Ibuprofen were freshly prepared and administered once daily orally at doses of 10, 25, and 50 mg/kg on the day of the operation and for the following seven days. Control animals received drinking water in the same volume. On the eighth day, 24 hours after the last dose, the animals were euthanized under general anesthesia, and the cotton pellets surrounded by granulation tissue were removed. The **wet weight** of each pellet was measured using electronic scales (SINKO, Japan, 2014), and the pellets were then dried at 60°C to constant weight.

The degree of **proliferative phase** was evaluated by comparing the granulation tissue mass between the control and experimental animals relative to the initial pellet weight. The **exudative reaction** was assessed by the difference between the wet and dry weights of the granuloma [26,27].

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Statistical Analysis:
Experimental results were processed using standard methods of variational statistics via the StatPlus 2009 software. Data are presented as **Mean ± standard error (M ± m)**. The **Student's t-test** was used to assess the significance of differences. A **p-value < 0.05** was considered statistically significant.

Results of the Study

In experimental pharmacology, **models of aseptic inflammation induced by various phlogogens** are commonly used to study the pharmacological characteristics of new anti-inflammatory agents [26,29–31]. Based on this approach, the first series of our experiments used a **carrageenan-induced inflammation model** to evaluate the **anti-exudative activity of CelAgrip** compared to **Ibuprofen** at various doses, administered preventively via the enteral route.

The results of this experimental series demonstrated that **carrageenan injection in intact animals significantly increased paw volume** by 30.7%, 38.7%, 49.3%, and 58.7% at 1, 2, 3, and 4 hours post-injection, respectively. Notably, the **exudative response was more pronounced at later time points** compared to the earlier stages of observation.

In contrast, in the group of rats **preventively administered Ibuprofen at 10 mg/kg**, paw volume increased by **26.3%, 31.1%, 35.1%, and 37.1%** at the same respective time points. Increasing the dose 2.5- and 5-fold led to a **slightly enhanced effect**, although similar to the control group, the **degree of inflammation was still more intense at later time points**.

The calculated **inhibition of inflammation** with Ibuprofen at a dose of 10 mg/kg ranged from **15–37%**, and at 25 mg/kg it was **26.7–41.7%**, with no significant additional benefit observed at 50 mg/kg (see Table 1). The **anti-inflammatory activity (AIA)** of Ibuprofen in prepubescent rats at the mentioned doses was as follows in the **first hour** of observation: **15.2%, 23.9%, and 26.1%**, respectively.

In the **second hour**, AIA values were **20.7%, 29.3%, and 31.0%**,

In the **third hour** – **29.7%, 37.8%, and 39.2%**,

In the **fourth hour** – **37.5%, 39.8%, and 42.0%**, respectively.

These results clearly show that **with increasing time and dose of Ibuprofen, its AIA increases** accordingly.

Thus, **Ibuprofen effectively reduces the degree of exudation** in prepubescent rats, as evidenced by the increasing **inhibition index**.

From the data presented, it is evident that **almost identical results were obtained in the group of animals preventively treated with CelAgrip.**

Table 1
Effect of CelAgrip and Ibuprofen on the Course of Aseptic Arthritis Induced by Carrageenan (M±m, n=6)

Groups	Dose, mg/kg	Paw volume, cm³ (hours of study)				
		Original	1	2	3	4
Control	-	0,75±0,03	0,98±0,06*	1,04±0,05*	1,12±0,05*	1,19±0,06*
CelAgrip ST/PVA	10	0,73±0,02	0,93±0,09 11,6/13,0	0,97±0,08* 15,8/17,2	1,00±0,09* 24,5/27,0	1,04±0,07* 28,0/29,5
CelAgrip ST/PVA	25	0,71±0,03	0,89±0,06 18,2/21,7	0,92±0,06* 24,2/27,6	0,95±0,07* 31,0/35,1	0,98±0,06* 35,5/38,6
CelAgrip ST/PVA	50	0,72±0,02	0,91±0,08 25,7/17,4	0,94±0,08* 27,6/24,1	0,985±0,08* 30,8/28,4	1,00±0,07* 34,1/36,4
Ibuprofen ST/PVA	10	0,74±0,04	0,94±0,10 15,0/15,2	0,97±0,09* 20,3/20,7	1,00±0,09* 24,9/29,7	1,02±0,09* 37,0/37,5
Ibuprofen ST/PVA	25	0,77±0,03	0,94±0,09 26,7/23,9	0,98±0,08 31,7/29,3	1,00±0,07* 39,0/37,8	1,04±0,07* 41,7/39,8
Ibuprofen ST/PVA	50	0,76±0,04	0,93±0,08 27,8/26,1	0,96±0,08 32,7/31,0	0,97±0,10 41,9/39,2	1,02±0,09* 43,1/42,0

Note: * – statistically significant differences compared to baseline values,
IR – inhibition rate of edema over time (%),
AA – anti-inflammatory activity (%).

Thus, **CelAgrip**, an interferon inducer, **suppresses the development of carrageenan-induced aseptic inflammation**, similarly to the **non-selective COX inhibitor**. It is known that the phlogogenic action of carrageenan involves **two distinct phases**: the **initial phase (1–2 hours)**, which is mediated by the **kinin system**, and the **late phase (3–4 hours)**, primarily

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driven by **prostaglandins** [7,36,37]. Based on this, it is logical to assume that **both tested drugs predominantly inhibit the prostaglandin-dependent phase of inflammation**.

In the **next series of experiments**, we examined the **effects of CelAgrip compared to Ibuprofen** on the course of **dextran-induced aseptic inflammation**. Dextran is widely used in experimental pharmacology because **inflammation induced by it develops rapidly** and **objectively reflects the anti-exudative efficacy** of the test drugs [26,30,35].

Analysis of the results from this series of experiments showed that **one hour after dextran injection**, paw volume increased **by 2.4 times**. In the subsequent hours of the experiment, this effect gradually weakened, but even by the end of the fourth hour, the paw volume remained approximately **doubled**.

As shown in **Table 2**, **CelAgrip and Ibuprofen clearly suppress the development of dextran-induced aseptic arthritis**.

Table 2
Effect of CelAgrip and Ibuprofen on the Course of Aseptic Arthritis Induced by Dextran (M±m, n=6)

Groups	Dose, mg/kg	Paw volume, cm3 (hours of study)				
		Original	1	2	3	4
Control	-	0,54±0,02	1,28±0,08*	1,19±0,07*	1,12±0,07*	1,06±0,08*
CelAgrip ST	10	0,55±0,02	1,04±0,10* 35,0	0,96±0,09* 38,3	0,90±0,08* 41,1	0,84±0,08* 44,8
CelAgrip ST	25	0,58±0,03	1,05±0,08* 40,9	0,97±0,07* 44,2	0,91±0,08* 46,7	0,85±0,09* 51,0
CelAgrip ST	50	0,56±0,02	1,01±0,06* 41,6	0,92±0,07* 46,7	0,86±0,08* 50,5	0,80±0,07* 55,2
Ibuprofen ST	10	0,53±0,02	1,04±0,07* 29,9	0,96±0,08* 32,5	0,91±0,09* 33,6	0,85±0,08* 37,5
Ibuprofen ST	25	0,57±0,03	1,05±0,09* 38,7	0,97±0,08* 41,7	0,91±0,09* 43,9	0,85±0,08* 48,9
Ibuprofen ST	50	0,59±0,03	1,05±0,10* 43,1	0,97±0,09* 46,5	0,91±0,10* 49,5	0,84±0,09* 56,2

Note:

- – statistically significant differences compared to baseline values,
- ST – degree of edema inhibition by hours (%),
- AIA – anti-inflammatory activity (%).

Thus, the **anti-inflammatory activity (AIA)** of **CelAgrip** and **Ibuprofen** at a dose of **10 mg/kg** during the **first hour** of observation was **33.8% and 31.1%**, respectively. At subsequent time points (2, 3, and 4 hours), **an increase in AIA** was observed, reaching **40.0%, 43.1%, and 48.1%** in the **CelAgrip** group and **33.8%, 34.5%, and 38.4%** in the **Ibuprofen** group. Increasing the dose of both drugs led to a moderate enhancement of this effect.

As shown in **Table 2**, the **degree of inflammation inhibition** by CelAgrip showed a **dose-dependent trend**, with the highest effect observed at **50 mg/kg**, particularly at the fourth hour of observation (**55.2%**). **Similar changes in the degree and direction of the anti-inflammatory response** were observed in the group of animals pre-treated with Ibuprofen.

Thus, **CelAgrip and Ibuprofen demonstrate high anti-inflammatory activity** in the **dextran-induced model of aseptic inflammation**.

It is believed that the **phlogogenic effect of dextran** is associated with the **release of histamine from mast cells** [26,36], which increases **vascular permeability** and leads to **edema formation**. Considering this mechanism, we conducted a separate series of experiments to **comparatively assess the effects of CelAgrip and Ibuprofen on histamine-induced aseptic arthritis**.

The results of this experimental series showed that **within 30 minutes after histamine injection**, paw volume increased **2.1 times**, and although the effect diminished slightly over time, it **remained elevated 1.8 times** by the end of the second hour. As presented in **Table 3**, both **test drugs dose-dependently inhibited paw edema**. However, at **lower doses**, **CelAgrip** and **Ibuprofen** demonstrated **weak anti-inflammatory activity**, while increasing the dose to **50 mg/kg** resulted in a **notable anti-inflammatory effect**. Nevertheless, the degree of this effect **did not**

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reach the levels observed in the carrageenan or dextran models, suggesting that **additional components may be involved** in the AIA of the tested agents.

Despite this, **both drugs statistically significantly suppressed the severity of edema**.

Table 3
Effect of CelAgrip and Ibuprofen on the Course of Aseptic Arthritis Induced by Histamine (M±m, n=6)

Groups	Dose, mg/kg	Paw volume, cm3 (minutes of study)				
		Original	30	60	90	120
Control	-	0,72±0,03	1,51±0,11*	1,42±0,10*	1,36±0,11*	1,30±0,10*
CelAgrip ST	10	0,66±0,02	1,34±0,09* 5,5	1,28±0,08* 8,1	1,19±0,08* 9,8	1,13±0,08* 11,0
CelAgrip ST	25	0,76±0,04	1,40±0,11* 22,9	1,32±0,08* 24,0	1,26±0,08* 26,1	1,21±0,08* 26,0
CelAgrip ST	50	0,73±0,03	1,35±0,07* 22,1	1,27±0,06* 23,7	1,22±0,07* 24,6	1,17±0,06* 24,7
Ibuprofen ST	10	0,77±0,03	1,43±0,10* 21,4	1,35±0,09* 22,3	1,29±0,08* 24,1	1,23±0,07* 25,3
Ibuprofen ST	25	0,70±0,02	1,33±0,09* 17,4	1,25±0,08* 19,0	1,20±0,07* 19,4	1,15±0,07* 19,6
Ibuprofen ST	50	0,73±0,03	1,34±0,10* 23,3	1,26±0,09* 25,1	1,24±0,08* 21,5	1,19±0,07* 21,2

Note:

- – statistically significant differences compared to baseline values,

ST – edema inhibition rate by hour (%),
AIA – anti-inflammatory activity (%).

To test this assumption, a series of experiments was conducted to investigate not only the **exudative** but also the **proliferative phase** of inflammation. The results of experiments performed using the **cotton pellet-induced granuloma model** showed that **seven-day administration** of the test drugs led to a reduction in the **wet weight of the implanted granuloma** by **18.6%, 31.8%, and 34.9%** in animals treated with **CelAgrip**, and by **21.2%, 30.1%, and 33.6%** in animals treated with **Ibuprofen**, respectively, at doses of **10, 25, and 50 mg/kg**.

It is evident that **both drugs distinctly suppress the exudative phase of inflammation** in the **cotton pellet implantation model**. This finding further confirms the **anti-exudative properties** of the studied agents.

The **proliferation process** is one of the key components of inflammation [37,38]. In our experiment, the effect of the drugs on proliferation was assessed by calculating the **dry weight of the granuloma** from the weight of the implanted cotton pellet [26,36]. The results showed that **both drugs suppressed the proliferative process** at all tested doses. As presented in **Table 4**, the **dry granuloma weight** in animals treated with **CelAgrip** was reduced by **24.4%, 46.6%, and 49.1%**, and in those treated with **Ibuprofen** by **27.9%, 41.7%, and 45.3%**, respectively, at doses of **10, 25, and 50 mg/kg**.

Considering the literature and the obtained data, it can be concluded that the **anti-inflammatory activity (AIA)** of **Ibuprofen** is associated with **inhibition of COX-1 and COX-2**, leading to the suppression of cyclic endoperoxide formation from **arachidonic acid**, a precursor of **prostaglandin PGE_2**, a key inflammatory mediator [25].

Since **CelAgrip** contains **polyphenolic compounds**, including **gossypol**, which possess strong **antioxidant properties** [39], its AIA is likely related to **inhibition of free radical formation**, which otherwise leads to **biological membrane damage** and **release of arachidonic acid**.

Table 4
Antiproliferative Activity of CelAgrip and Ibuprofen in Rat Pups Using the "Cotton Pellet" Granuloma Model (M±m, n=6)

Groups	Doses, mg/kg	Wet granuloma mass, mg	Dry granuloma mass, mg

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Control	-	237,83 ± 11,54	76,17 ± 3,28
CelAgrip	10	193,50 ± 12,60*	57,61 ± 4,70*
CelAgrip	25	162,15 ± 7,11*	40,67 ± 1,86*
CelAgrip	50	154,81 ± 6,87*	38,75 ± 3,75*
Ibuprofen	10	187,31 ± 11,34*	54,88 ± 6,31*
Ibuprofen	25	166,11 ± 6,67*	44,36 ± 3,35*
Ibuprofen	50	157,80 ± 7,39*	41,67 ± 2,42*

Note: * – values that differ significantly from the control group (P<0.05).

CONCLUSIONS

1. In models of acute inflammation induced by various phlogogens, *CelAgrip* significantly suppresses paw edema and, in terms of its activity, is not inferior to *Ibuprofen*.
2. *Ibuprofen* and *CelAgrip* demonstrated a pronounced dose-dependent antiproliferative effect in the *cotton pellet* model.
3. The mechanism of anti-inflammatory action (AIA) of *Ibuprofen* is associated with the inhibition of *COX-1* and *COX-2*, while *CelAgrip* exerts its effect by suppressing free radical processes.
4. The use of *CelAgrip* instead of *Ibuprofen* as an anti-inflammatory agent is considered feasible in animals of prepubertal age.

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