

Article

PHARMACOLOGICAL ACTIVITY OF CELAGRIP IN IMMATURE RATS

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Abstract: In order to develop effective anti-inflammatory agents for use in children, the pharmacological activity of Celagrip—a polymeric derivative of gossypol—was studied. It was established that Celagrip in immature rats significantly suppresses the intensity of aseptic inflammation induced by formalin, which is manifested by a reduction in the exudation process. In this respect, Celagrip is not inferior to the well-known nonsteroidal anti-inflammatory drug (NSAID), ibuprofen. In addition to its anti-inflammatory activity, Celagrip demonstrates pronounced antipyretic and analgesic effects. In terms of analgesic action, Celagrip is somewhat inferior to ibuprofen; however, it shows comparable antipyretic activity. It is believed that the mechanism underlying these effects of Celagrip is associated with its antioxidant properties, since, similar to Kagocel, it contains a polyphenolic compound in its molecular structure. After appropriate clinical trials, Celagrip may be used in pediatrics for the treatment of diseases in which aseptic inflammation plays an important role in the pathogenesis.

Keyword: Aseptic Inflammation, Formalin, Hyperthermia, Analgesia, Adolescence, Celagrip, Ibuprofen

Introduction

The authors declare no apparent or potential conflicts of interest related to the publication of this article. Inflammation remains one of the most frequent and clinically significant pathological processes encountered in pediatric practice, serving as a fundamental mechanism in the pathogenesis and progression of a wide range of acute and chronic diseases [1]. In children, inflammatory responses are implicated not only in infectious disorders but also in immune-mediated, metabolic, and systemic conditions, making the effective management of inflammation a critical aspect of pediatric therapeutics. For this reason, nonsteroidal anti-inflammatory drugs (NSAIDs) are extensively employed in the pharmacological management of numerous pediatric diseases due to their well-established anti-inflammatory, antipyretic, and analgesic properties [2]. These agents exert their therapeutic effects primarily through inhibition of cyclooxygenase (COX) enzymes, thereby reducing the synthesis of prostaglandins and other pro-inflammatory mediators. Despite their widespread clinical utility, frequent, prolonged, or uncontrolled use of NSAIDs is often associated with the development of significant adverse effects, some of which may be severe or even life-threatening. These complications include gastrointestinal mucosal injury, nephrotoxicity, hepatotoxicity, hematological

disturbances, and hypersensitivity reactions, all of which are closely related to COX inhibition and the disruption of physiological prostaglandin synthesis [3–8]. In light of these limitations, contemporary pharmacological research increasingly emphasizes the search for alternative anti-inflammatory agents with novel mechanisms of action and improved safety profiles. According to numerous studies, one of the most promising approaches to enhancing the efficacy and safety of anti-inflammatory pharmacotherapy involves the development of drugs capable of modulating inflammatory pathways independently of classical COX inhibition [9–13]. Such agents may provide comparable therapeutic benefits while minimizing the risk of systemic adverse reactions, which is particularly important in pediatric populations. Celagrip, similarly to Kagocel, represents a polymeric derivative of gossypol and has been reported to possess pronounced antioxidant activity [14–17]. Polyphenolic compounds with antioxidant properties are known to neutralize reactive oxygen species and scavenge free radicals, thereby reducing oxidative stress, which plays a pivotal role in the initiation and amplification of inflammatory cascades. By suppressing free radical activity, these compounds inhibit the liberation and subsequent metabolism of arachidonic acid, a key precursor in the biosynthesis of cyclic endoperoxides and other inflammatory mediators. This antioxidant-mediated suppression of arachidonic acid metabolism is considered a central mechanism underlying the anti-inflammatory effect of Celagrip. Considering the critical role of inflammation in the pathogenesis of many pediatric diseases, the potential application of Celagrip in children appears highly relevant and scientifically justified. Its presumed combined anti-inflammatory, antipyretic, and analgesic effects may offer a promising therapeutic alternative, particularly in cases where conventional NSAID therapy is contraindicated or associated with substantial risk. Nevertheless, despite the theoretical and pharmacological rationale supporting its use, there is currently a lack of sufficient experimental evidence and preclinical data validating the clinical application of Celagrip in pediatric medicine. This gap in knowledge necessitates systematic investigation of its pharmacodynamic properties and therapeutic potential. Therefore, the aim of the present study was to evaluate the anti-inflammatory, antipyretic, and analgesic effects of Celagrip in prepubertal experimental animals, with the objective of establishing a scientific basis for its potential use in pediatric clinical practice [18–20].

The aim of this study was to investigate the anti-inflammatory, antipyretic, and analgesic effects of Celagrip in prepubertal animals.

Materials and Methods

Experimental studies were conducted on white rats of prepubertal age (with precisely determined birth dates), weighing 55–70 g, obtained from the vivarium of the Sanitary-Epidemiological Station of the Medical-Sanitary Association under the Ministry of Health of the Republic of Uzbekistan.

Before the start of the experiment, after a quarantine period, all animals underwent examination, including measurement of body weight, assessment of motor activity, and evaluation of skin condition. Each experimental and control group consisted of six animals.

During the study, the animals were housed in plastic cages with wood shavings as bedding, at a temperature of 20–24°C and relative humidity of at least 50%. The vivarium was equipped with proper ventilation and a regulated light–dark cycle. The diet was selected according to the age of the animals.

All experiments were conducted in accordance with the “Rules for Conducting Laboratory Work Using Experimental Animals,” as well as the standards of 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 involving laboratory animals was approved by the Ethics Committee of the Tashkent Medical Academy under the Ministry of Health of the Republic of Uzbekistan (Protocol No. 6, dated April 25, 2025).

Celagrip was the test substance in this study, while ibuprofen was used as the reference drug, as it is considered the “gold standard” among nonsteroidal anti-inflammatory drugs (NSAIDs) and is widely recognized as a benchmark comparator in evaluating the therapeutic potential and safety of drugs in this pharmacotherapeutic group.

To study the anti-exudative activity of Celagrip and ibuprofen, a classical model of experimental aseptic arthritis was used, induced by a 1% formalin solution. The phlogogenic agent (0.1 mL per animal) was administered subplantar (under the plantar aponeurosis) into the right hind paw of the rats. The paw volume prior to phlogogen administration was taken as the baseline and considered 100%.

Before induction of aseptic arthritis, rats in the control group received an equivalent volume of water intragastrically using a металлический probe, while animals in the experimental groups were administered Celagrip and ibuprofen at identical doses of 25 and 50 mg/kg. Paw volume was measured using an oncometric method with a digital plethysmometer (Ugo Basile Srl, Italy) before and at 2, 4, 6, 8, and 24 hours after formalin administration.

The criteria for evaluating the anti-phlogogenic effect of the drugs included the increase in paw volume, the degree of inhibition, and the calculation of anti-inflammatory activity.

The increase in paw volume (IPV) was calculated using the formula:

$$IPV = (O - I) / I \times 100 = \%$$

where:

IPV — increase in paw edema;

O — paw volume after phlogogen administration;

I — paw volume before phlogogen administration.

The degree of inhibition (DI) was calculated as follows:

$$DI = 100\% - [(O - I) / I (\text{treated}) : (O - I) / I (\text{control})] \times 100 = \%$$

where:

O — paw volume in treated animals;

C — paw volume in control animals (untreated).

The anti-inflammatory activity (AIA) of the drugs was also calculated using the formula:

$$AIA = (V_{\text{control}} - V_{\text{experiment}}) / V_{\text{control}} \times 100 = \%$$

where:

V_{control} — mean increase in limb volume in the control group (cm³);

V_{experiment} — mean increase in limb volume in the experimental group (cm³).

To assess the severity of the pathological process and the effectiveness of pharmacotherapy, the skin temperature of the right hind limb was measured in rats. Measurements were taken before formalin administration and 4 hours afterward. Temperature was recorded using a non-contact infrared electronic thermometer (model TF-600, Shenzhen Quik Zoom Technology Co., Ltd., China). The use of modern infrared devices allows for rapid and painless temperature measurement without inducing additional stress in animals, which is particularly important for the accuracy of physiological experiments.

Pain sensitivity of the paws was assessed similarly—before formalin administration and 4 hours afterward—using the plantar test on a Hargreaves Apparatus (Ugo Basile, Italy). The latency period of paw withdrawal in response to mechanical stimulation (needle) was recorded.

This device is designed for the quantitative assessment of pain sensitivity in animals based on the latency of paw withdrawal in response to a controlled stimulus. The method for evaluating pain sensitivity in laboratory rats was carried out using the plantar test, which is widely used in experimental physiology and pharmacology to study nociceptive responses.

Before the experiment, animals were placed in individual transparent chambers positioned on a huunnly glass or mesh platform of the device. A 10–15 minute adaptation period was allowed to minimize the effects of stress and spontaneous motor activity.

After adaptation, mechanical stimulation of the plantar surface of the rat's hind paw was performed using a thin needle or mechanical stimulator. The stimulus was carefully applied to the central part of the plantar surface through an opening or mesh platform, avoiding excessive pressure that could cause tissue injury.

The main recorded parameter was the latency period of paw withdrawal—the time (in seconds) from the onset of mechanical stimulation to the reflex withdrawal of the paw. This parameter reflects the level of pain sensitivity:

- a decrease in latency indicates increased pain sensitivity (hyperalgesia);
- an increase in latency indicates reduced pain sensitivity or the development of an analgesic effect.

To improve measurement accuracy, each paw was tested at least three times at intervals of 3–5 minutes, which prevented the development of sensitization or habituation. The final result was calculated as the average latency period. To prevent tissue damage, a maximum exposure time (cut-off time), usually 15–20 seconds, was established. If paw withdrawal did not occur within this time, the stimulus was automatically terminated.

The obtained data were subjected to statistical analysis using the Biostat 2009 software package. The results were presented as $M \pm m$, and differences between groups were evaluated using Student's t-test. Differences were considered statistically significant at a 95% confidence level ($p < 0.05$).

Results and Discussion

A classical experimental model of inflammation used to evaluate the pharmacological activity of new compounds is the model of aseptic inflammation induced by formalin [21–24]. This phlogogenic agent, by damaging tissues at the site of administration (protein coagulation), leads to the release of intracellular components and triggers immediate depolarization of protein fibers.

In addition, activation of phospholipase A₂ occurs, resulting in the release of arachidonic acid and the formation of prostaglandin E₂ (PGE₂), which causes vasodilation, increased vascular permeability, and the development of edema.

The results of experimental studies investigating the effect of Celagrip in a model of formalin-induced aseptic inflammation in prepubertal rats showed that injection of the phlogogenic agent led to a significant increase in paw volume: by 66.2% after 2 hours, 83.1% after 4 hours, and 77.9% after 6 hours from the start of the experiment. This effect subsequently decreased somewhat but remained at a high level (51.9%) even after 24 hours.

Thus, in immature animals, as in adult ones, formalin induces pronounced aseptic inflammation.

In contrast, rats treated with Celagrip exhibited a lower level of exudative response under the influence of formalin.

Specifically, at the indicated time points, the increase in paw volume at a Celagrip dose of 25 mg/kg was only 50.7%, 59.1%, and 52.1% at 2, 4, and 6 hours, respectively, and remained nearly unchanged during the later stages of the experiment. The calculated degree of edema inhibition during the observation periods ranged from 23.7% to 36.5%, while the anti-inflammatory activity (AIA) values were 29.4%, 34.4%, 38.3%, 40.4%, and 42.5% at 2, 4, 6, 8, and 24 hours, respectively. Doubling the dose of Celagrip resulted in a moderate increase in both the degree of edema inhibition and AIA values [25–28].

Therefore, Celagrip in prepubertal animals significantly suppresses the development of the exudative process, indicating its high anti-inflammatory activity.

As shown in Table 1, the well-known and widely used NSAID ibuprofen demonstrated high anti-inflammatory activity in prepubertal animals at both studied doses. At the same time, in terms of pharmacological activity (i.e., AIA), it did not differ significantly from Celagrip.

Thus, the polymeric derivative of gossypol, Celagrip, in immature animals exhibits anti-inflammatory activity comparable in magnitude to that of ibuprofen in a model of formalin-induced aseptic inflammation.

Table 1. The effect of CelAgrip and Ibuprofen on the course of formalin-induced aseptic inflammation in pre-burden rats

Groups	Dose, mg/kg	Paw volume during the studied periods (cm ³ , hours)					
		0	2	4	6	8	24
Control	-	0,77±0,0	1,28±0,08	1,41±0,08	1,37±0,07	1,29±0,06	1,17±0,06
		2	*	*	*	*	*
CegAgrip	25	0,71±0,0	1,07±0,08	1,13±0,08	1,08±0,07	1,02±0,08	0,94±0,07
		2	*	*	*	*	*
CelAgrip	50	0,74±0,0	1,08±0,07	1,14±0,08	1,09±0,07	1,04±0,08	0,95±0,09
		2	*	*	*	*	*
Ibuprofen	25	0,75±0,0	1,10±0,10	1,16±0,10	1,11±0,08	1,04±0,08	0,97±0,07
		2	*	*	*	*	*
Ibuprofen	50	0,76±0,0	1,09±0,09	1,14±0,10	1,08±0,09	1,03±0,09	0,95±0,08
		2	*	*	*	*	*

Note: * - statistically significant differences in relation to the original values of the corresponding groups

Celagrip is a synthetic polymeric antiviral drug obtained through the chemical modification of natural and semi-synthetic compounds. Its chemical structure is based on a copolymer of sodium carboxymethylcellulose (Na-CMC) and a natural polyphenolic compound—gossypol [29][30].

The Na-CMC polymer matrix acts as a carrier for biologically active functional groups and ensures high water solubility, biocompatibility, and stability of the dosage form. Gossypol, a natural polyphenol found in cotton plants, is chemically incorporated into the polymer chain. It exhibits pronounced biological activity, including antiviral, antioxidant, and immunomodulatory properties.

Within the drug composition, gossypol is covalently bound to the carboxymethylcellulose matrix, forming a stable polymer complex. The content of gossypol in the copolymer structure is approximately 3 mol%, which ensures the required pharmacological activity while maintaining low toxicity.

The macromolecular structure forms a high-molecular-weight complex with pronounced biological activity and the ability to interact with cellular structures. Due to the presence of hydrophilic carboxyl groups and phenolic fragments of gossypol, the Celagrip molecule exhibits high reactivity and can form nanostructured particles approximately 14–52 nm in size. This contributes to increased bioavailability of the active substance and prolonged drug release in biological environments.

The combination of these components creates a unique macromolecular system with antiviral, immunomodulatory, and anti-inflammatory properties.

The inflammatory process is usually accompanied by an increase in body temperature; therefore, in children, fever is often one of the first symptoms of acute respiratory infections [31-34]. Among all antipyretic agents, paracetamol and ibuprofen are recommended for use in pediatric practice, as they fully meet the criteria of high therapeutic efficacy and safety [35].

It is known that formalin-induced inflammation leads to the production of pyrogens (IL-1 β , IL-6, TNF- α), which act on the hypothalamus, increasing the set point of the thermoregulatory center and resulting in fever. The main mechanism of the antipyretic effect of NSAIDs is the inhibition of cyclooxygenase (COX), leading to a decrease in prostaglandin (PG) synthesis. Since Celagrip demonstrated a pronounced anti-exudative effect in formalin-induced aseptic inflammation, it is reasonable to investigate its potential antipyretic activity.

The study of skin temperature in formalin-affected paws of rats showed that, compared to healthy animals, formalin injection led to a 13.0% increase in local temperature after 4 hours. The selection of this observation time point was due to the fact that the most pronounced degree of exudation was observed at the 4th hour of the experiment (see table).

This finding confirms that formalin-induced inflammation is a model that adequately meets the requirements

for testing new anti-inflammatory compounds [36-40].

Table 2. Effect of CelAgrip and ibuprofen on local paw temperature in prepubertal rats with formalin-induced lesions

Groups	Dose, mg/kg	Paw temperature, °C	
		initial	in 4 hours
Healthy	-	25,13 ± 0,18	25,28 ± 0,16
Control	-	25,10 ± 0,24	28,37 ± 0,17*,#
Celagrip	25	24,58 ± 0,22	26,46 ± 0,23*,#
Celagrip	50	24,75 ± 0,32	25,66 ± 0,41
Ibuprofen	25	24,77 ± 0,31	25,38 ± 0,23
Ibuprofen	50	24,65 ± 0,34	25,15 ± 0,32

*Note: * - statistically significant differences in relation to the original corresponding groups, # - statistically significant differences in relation to healthy*

As the results of the study showed, in animals that prophylactically received Celagrip at a low dose, the increase in paw temperature was less pronounced than in control rats by 6.7%. Doubling the dose of the drug led to an enhancement of its hypothermic activity—the reduction in local temperature reached 9.5% compared to the control group.

In this series of experiments, ibuprofen demonstrated a pronounced hypothermic effect, expressed as a decrease in local temperature compared to control by 10.5% and 11.3% at doses of 25 and 50 mg/kg, respectively. The obtained data indicate that the hypothermic effect of ibuprofen at both studied doses is nearly identical and only slightly exceeds the effect of Celagrip at the higher dose.

Thus, Celagrip in immature animals, in a model of formalin-induced aseptic inflammation, exhibits a hypothermic effect comparable to that of ibuprofen, especially when administered at a higher dose.

The obtained data are consistent with the results of previous studies investigating the antipyretic effect of Celagrip in a yeast-induced fever model [41].

Chemical tissue damage induced by formalin, as noted above, leads to the release of a number of biologically active substances (histamine, bradykinin, serotonin, glutamate, substance P, and PGE₂), which activate secondary messengers, resulting in a decreased nociceptor threshold, peripheral sensitization, and усиление болевого ответа (enhancement of the pain response) [42]. Increased cytokine levels in the central nervous system contribute to the maintenance of hyperalgesia.

The experimental results presented above suggest that Celagrip, by suppressing prostaglandin formation, reduces both the exudative process and the febrile response. Based on this, it can be assumed that the drug may also possess an analgesic effect.

Studies conducted in this direction using the plantar test showed that subplantar injection of formalin led to a pronounced pain response. Specifically, at the 4th hour of the experiment, the latency period of withdrawal of the affected paw in response to the device's needle stimulus decreased by 72.5% compared to healthy animals.

In contrast, as shown in Table 3, in rats prophylactically treated with Celagrip at a dose of 25 mg/kg, the paw withdrawal time increased by 75.9% compared to control, while at a dose of 50 mg/kg the effect was more pronounced: the latency period increased by 114.7%[43].

In this series of experiments, a similar effect was observed in rats treated with ibuprofen, particularly at a dose of 50 mg/kg.

Table 3. Effect of CelAgrip and ibuprofen on pain sensitivity in formalin-induced paw lesions in prepubertal rats

Groups	Dose, mg/kg	Latent period (in seconds)	
		initial	in 4 hours
Healthy	-	14,93 ± 0,24	15,13 ± 0,26
Control	-	14,45 ± 0,27	4,15 ± 0,30*,#
Celagrip	25	15,43 ± 0,42	7,30 ± 0,44*,#
Celagrip	50	14,58 ± 0,33	8,91 ± 0,39*,#
Ibuprofen	25	15,05 ± 0,37	9,11 ± 0,46*,#
Ibuprofen	50	14,76 ± 0,47	10,43 ± 0,57*,#

Note: * - statistically significant differences in relation to the original corresponding groups, # - statistically significant differences in relation to healthy

Thus, Celagrip, like ibuprofen, exhibits a pronounced analgesic activity, although it is somewhat less potent than ibuprofen.

The analgesic activity of Celagrip was also clearly demonstrated in hyperalgesia models, particularly in the “hot plate” test and the writhing test [44].

Summarizing the results of the experimental studies in immature animals, it can be concluded that Celagrip possesses high pharmacological activity, which is manifested in the suppression of formalin-induced exudation, as well as in hypothermic and analgesic effects comparable to those of the reference NSAID, ibuprofen.

Since Celagrip has pronounced antioxidant properties, suppresses the activity of pro-inflammatory cytokines, exhibits antikinin activity, and does not adversely affect the morphofunctional state of internal organs, including the stomach, it can be assumed that it has high pharmacotherapeutic potential in the treatment of inflammatory diseases in children[45].

Conclusion

1. Celagrip in prepubertal rats suppresses the intensity of the exudative process to the same extent as ibuprofen, indicating its pronounced anti-inflammatory effect.
2. In addition to its anti-inflammatory effect, Celagrip in a model of formalin-induced aseptic inflammation exhibits an antipyretic effect, especially at higher doses, without being inferior to ibuprofen.
3. The anti-inflammatory effect of Celagrip is combined with analgesic activity, which is slightly less pronounced than that of ibuprofen.
4. It is considered possible that, after appropriate clinical trials, Celagrip may be used in the treatment of inflammatory diseases in children.

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