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Assessment of Anti-Inflammatory Effects of Divalent Metal Complex of Coumarin in Rat Models

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ABSTRACT

Coumarin derivatives are effective in the treatment of a variety of ailments, including cancer, HIV, bacterial infections, nervous system weakness, and inflammation. The current work aims to evaluate the anti-inflammatory effects of coumarin divalent metal complexes in experimentally induced inflammation in rat models. The anti-inflammatory properties of synthetic divalent metal complex of coumarin derivatives were studied using acute and subacute animal models. In acute anti-inflammatory models, histamine, carrageenan, and formalin were injected into the paws of experimental animals to cause inflammation seen in the form of paw edema. A sterile cotton pellet was implanted in the subacute inflammatory model or cotton pellet-induced granuloma paradigm. Coumarin derivatives and the standard drug diclofenac were used to treat the edematous animals. Anti-inflammatory activity was determined by measuring the amount of paw edema and the weight of the cotton pellet. Normal group animals' paw volume did not alter. The paw volume of untreated inflammation-induced rats was substantially higher. The paw edema in the group animals treated with synthetic coumarin derivatives was close to normal animals. Its action was proportionate to that of the standard drug diclofenac sodium. In experimental rats, synthetic coumarin compounds show promised anti-inflammatory properties.

Keywords: Anti-inflammatory, Coumarin derivatives, Diclofenac sodium, Inflammatory mediators, Rats.

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INTRODUCTION

Inflammation is the primary reaction of vascularized tissues to infections and other types of injury or damage, resulting in diapedesis of blood cells as well as host defense chemicals from the systemic circulation to the sites of distress in an effort to remove the offending agents.[1] The process of inflammation, which entails a series of cellular and microvascular responses to both eliminate injured tissue and regenerates new tissue allows the body to repair damaged tissue.[2] Inflammation is defined by five pre-eminent signs; rubor (redness), calor (heat), tumour (swelling), dolor (pain) and function laesa (loss of function).[1] Nowadays, inflammation is regarded as a nonspecific defences that neutralises and eliminates the pathogen or causative regardless of the kinds.[3] Coumarins (2H-chromen-2-ones), commonly referred to as benzopyran-2-ones, are a class of naturally occurring polyphenolic compounds possessing a lactone core. Coumarins exhibit a wide range of meticulously researched pharmacological characteristics. They have garnered comprehensive investigation from a range of chemical and pharmacological chemists due to advancements in their physicochemical parameters, varied biochemical properties, and many directed synthetic routes.[4] Coumarin is produced from the shikimate pathway and is synthesised as the parent molecule of a broad category of secondary bioactive molecules known as coumarins by a variety of medicinal and fragrant plants.[5] 1-benzopyran-2-one is the common name of coumarins and International Union of Pure and Applied Chemistry identification as 2H-chromen-2-one, and basic core of coumarins are picturised as below. (Figure 1) Coumarin's conformational flexibility is an important structural motif that attracts attention to various drug discovery and drug development.[6] Its impending pharmacological efficacies aided in the creation of an early synthetic method for producing coumarin-like compounds. These chemicals are utilised as a preliminary step for creating important heterocyclic compounds. When 3-acetyl coumarin and an aromatic aldehyde

are combined, 3-cinnamoyl coumarin is produced, with acetyl coumarin serving as a by-product.[7] Pyridine, isooxazolines, 1, 5-benzodiazepines, and heterocyclic nitrogen-containing chemicals are all synthesised using 3-cinnamoyl coumarins.[8] Coumarins demonstrates various activities such as anti-thrombotic, anti-inflammatory, antianxiety, anticonvulsant, antioxidant, vasorelaxant, cytotoxic, anti-HIV, anti-tubercular and antimicrobial properties.[9-14] Nonsteroidal anti-inflammatory medicines (NSAIDs), which are presently accessible anti-inflammatory agents, have a variety of undesirable consequences such as bleeding, ulcer formation, gastrointestinal abnormalities, and may even induce cardiac concerns.[15] As a result, a safer anti-inflammatory agent is required. In light of the foregoing, we proposed to explore the anti-inflammatory action of synthesised divalent metal complexes of coumarins in carrageenan, formalin, histamine-induced inflammation, and cotton pellet-induced granuloma in experimental rat models.

MATERIAL AND METHODS

Ethical permission for undertaking this study was garnered by the Institutional Animal Ethics Committee of KLE College of Pharmacy (MPH03/KLECOPH/19). The entire experimental procedure was scrutinized and authorised by the same IAEC.

Animals:

Pathogen-free Female adult albino mice weighing roughly 18-25g body weight and albino Wister rats of both sexes weighing 150-250g were acquired from the animal laboratory and housed in cages with unfettered access to water and food, and perpetuated in typical day light (6:00 in the morning to 6:00 in the evening) and dark environments from 6:00 in the evening to 6:00 in the early). The rats and mice were acclimated to laboratory settings before beginning the experiment. Following a few days of acclimatization to the prescribed laboratory setting, these animals were randomly selected and separated into corresponding experimental groups. The segregated animals were housed in the animal laboratory's clean and ventilated environment. For LD50 value quantification, mice were employed, and rats were used for acute-subacute anti-inflammatory activities.

Chemicals and Instruments:

We procured Histamine, Carrageenan, and Formalin from Himedia Ltd. in Mumbai. Marketed drug of diclofenac sodium, sterile cotton and all the other lab grade chemicals utilized in this study were gleaned from KLE College of Pharmacy, Hubballi, Karnataka, India. The acute anti-inflammatory effects of coumarin derivatives were studied using plethysmometer.

Study Design:

Group I: Control
Group II: Standard diclofenac drug (10mg/Kg)
Group III: Coumarin derivative (Compound I)
Group IV: Coumarin derivative (Compound II)
Group V: Coumarin derivative (Compound III)

Acute Toxicity Study:

Acute toxicity study was bolstered on albino mice weighing between 18 and 25g. The step-by-step Up-Down technique was chosen for these toxicity tests. The overnight fasting female mice were divided at random ensuring 3 animals in each group. Using a stomach tube, mice were given coumarin derivatives suspension in doses of 100, 500, 1000 and 2000 mg/Kg body weight. Each mouse was observed individually every 30 minutes to check if the test substance induced poisoning or death, then every four hours for the first 24 hours, with close attention.[16]

Acute Anti-Inflammatory Model: Induction of Paw Edema

Histamine Induced Hind Paw Edema:

Six Albino rats weighing 150 to 200 g were placed into five groups. These rats were administered with distilled water, the standard drug diclofenac, and coumarin derivative compounds I, II, and III orally. Following half an hour of the treatment, inflammation was instigated by injecting 0.1mL of 1mg/mL of lately devised histamine in saline in to the sub-plantar area of right hind paw in every rat. For the tenacity of the anti-inflammation activity investigation, a histamine-incited paw edema model was employed. The anti-inflammatory pursuit of test substances was evaluated by measuring the rats' paws' volume. Using a digital plethysmometer, paw volume was measured at different time intervals i.e. 0, 0.5, 1, 2 and 3 hours following inflammation induction using volume displacement technique.[17]

Carrageenan-induced rat paw edema model

Five groups contained Six Albino rats weighing around 150-200g. To cause inflammation, 0.05 ml of 1% carrageenan was administered into the sub-plantar area of the right hind paw. These five groups of mice were given distilled water, standard drug diclofenac and compounds I, II, and III of the coumarin derivatives

before 30 minutes of induction. Paw edema was measured using the plethysmographic quantification approach throughout time periods of 0, 0.5, 1, 2, and 3 hours to identify the inflammation. [18,19]

Rat model of formalin-induced hind paw edema

Six albino rats, each weighing between 150 and 200g apiece were segregated into five groups. Diclofenac standard drug, distilled water and compounds I, II, and III of the coumarin derivatives were apportioned to these five clusters of animals, respectively. To cause inflammation, 0.1 ml of 1% v/v formalin was shot into the right hind paw's sub-plantar region after 30 minutes. By measuring the volume of the paw i.e., paw edema using the plethysmographic quantification technique at intervals i.e. 0, 0.5, 1, 2 and 3 hours, test drugs' potency to reduce inflammation was evaluated.[20,21]

Sub-Acute Anti-Inflammatory Activity: Cotton pellet-effectuated granuloma model

The cotton wool used for weaving the subacute inflammation model. Five groups of albino rat were made containing six animals in each. Distilled water, standard drug diclofenac, and compounds I, II, and III of the coumarin derivatives were administered to these five groups of animals, respectively. After 30 minutes, sterile cotton wool measuring 10 $\pm$ 1.0mg were grafted into rats' backs aseptically. For seven days, the treatment was given once per day. On the eighth day, rats were put under anaesthesia while surgically dissecting cotton pellets and drying them at 60^0 C. The average weight of cotton pellets was determined.[22,23]

Statistical Analysis

Results are represented by mean $\pm$ Standard Error of Mean (SEM). The obtained results were perused using One-way ANOVA followed by Dunnett's multiple comparison tests were employed to evaluate the results. Graphpad Prism software was employed to analyse the result. *p* value of 0.05 or less is deemed statistically significant.

RESULTS

Acute toxicity study:

From preliminary tests, it was clearly shown that animals could tolerate a highest dosage of 2000 mg/kg body weight with just a few behavioural alterations, such as vigilantism, touch replication, and restlessness. Thus, 200 mg/kg weight was employed as the treatment dosage for the further experiments at the 10% maximum abode dose. Considering $1/10^{th}$ of maximum dose, the acute toxicity was not observed in albino mice with respect to food intake, behaviour and gait either in first 4 hours of observation or after 24 hours. No animals died because of the test compounds. These data imply that the test compounds are safe for use in animals.

Acute Anti-Inflammatory Activity:

Outcomes of coumarin derivatives on histamine-induced rats' hind paw edema:

Animals in the histamine control group had constant increase in the size of their paw (paw edema) due to inflammation. When compared to the histamine control group, the conventional diclofenac sodium therapy considerably delays development of paw edema ($p < 0.05$). Moreover, it lessens the slight inflammation that develops every 1^{st}, 2^{nd}, and 3^{rd} hourly. Following treatment with coumarin derivatives paw edema was greatly reduced compared to the control group. Compounds II and III of coumarin derivatives significantly reduced the paw inflammation after two and three hours (p 0.05). Paw edema volumes of all groups of experimental animals are summarised in table 02. (table 02)

Effect of coumarin derivatives on carrageenan-induced rats' hind paw edema:

Continuous increase in paw volume seen in carrageenan control group rats. The accustomed drug diclofenac sodium treatment suppresses significantly ($p<0.05$) the development of paw edema as compare to carrageenan control group. Standard drug continuously decreases edema volume (inflammation) at time interval of 1, 2 and 3 hours. Test compounds coumarin derivatives administration exhibit reduction of paw volume when compare to carrageenan control group. Among three coumarin derivatives compound II and III exhibit significant ($p<0.05$) reduction of inflammation in paw at 2 and 3 hours, these results were comparable to standard drug effect. For the result of edema in negative control, standard and test drugs treatment groups (Table 3).

Rats in the carrageenan control group consistently had enlarged paws (paw edema) due to inflammation. As compared to the carrageenan control group, the conventional drug diclofenac sodium treatments substantially inhibit the development of paw edema ($p < 0.05$). The inflammation was subsided by standard diclofenac at every 1, 2 and 3 hours. Coumarin derivatives treated group animals shown more substantial decrease in paw volume as compared to the carrageenan control group. Specifically compounds II and III, two of the three coumarin derivatives, considerably lowered the paw inflammation at 2 and 3 hours ($p < 0.05$) and these outcomes were comparable to a standard diclofenac drug's impact. The results of paw edema of negative control, standard drug, and test drug treatment groups are summarised in Table No. 03.

Effect of coumarin derivatives on formalin induced hind paw edema:

At 0 minutes, there was no discernible difference in the average paw volume among all the group of animals. The inflammation in the formalin-induced animals increased gradually over the course of 30 minutes to 3 hours. The conventional treatment of animals with diclofenac sodium showed a conspicuous reduction in paw inflammation in analogy to the formalin control group ($p < 0.05$) at every 1st, 2nd and 3rd hourly. Interventional compounds exhibited anti-inflammatory effects. When three test compounds were taken into account, coumarin derivative compounds II and III showed a significant decrease in inflammation in the paw at 2 and 3 hours ($p < 0.05$), and their anti-inflammatory effects were equivalent to those of standard drug treatment. The summary of results is given in Table No. 04.

Sub-Acute Anti-Inflammatory Action: Effect of coumarin derivatives on Cotton pellet granuloma in experimental rats

Animals' subacute inflammation was assessed using a cotton pellet granuloma model. The animals in the control group that were in the usual condition had a considerable rise in wet weight granuloma due to inflammation and no therapeutic intervention. The animals given the normal dose of diclofenac sodium saw a substantial decrease in transudate weight as matched to the comparison group ($p < 0.05$). When juxtaposed with the healthy control group, the test drug-treated rats displayed a decrease in both the transudate weight and the wet weight granuloma. Out of three, two coumarin derivative compounds i.e., II and III showed a substantial decrease in wet weight granuloma and transudate weight ($p < 0.05$). Our findings demonstrate that the coumarin derivative compounds II and III have potent anti-inflammatory effects, and that they are markedly different from diclofenac. The outcomes are displayed in Table No. 05

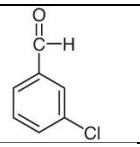
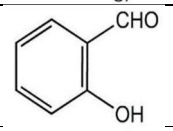
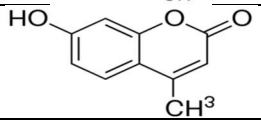
DISCUSSION

This study evaluates anti-inflammatory potential of synthetic coumarin derivative drugs in experimentally induced animal models using acute and sub-acute anti-inflammatory models. Till date, they are frequently employed to evaluate a drug's anti-edematous effects. As previously noted, coumarins contribute to prominent classes of naturally occurring molecules. Because of the growing interest in its chemistry, it continues to be valuable and beneficial as a biologically active agent. The process of inflammation involves a series of events that may be triggered by different stressors. The three stages of inflammatory mechanisms are as follows: Acute phase, which is characterized by increased capillary permeability and local vessel dilatation and is moderated by discharge of serotonin and histamine. Subacute episode is defined by the presence of white blood cells and phagocytic cells which is mediated by Prostaglandins, lysosomes, and proteases. Lastly, chronic Phase which is marked by tissue fibrosis and degeneration.[1]

In the present investigation, acute toxicity studies—which correlate to acute inflammation—were the primary emphasis. Acute inflammation is characterized by three primary traits. First, dilatation of tiny blood vessels resulting in increased blood flow; Second, increased microvasculature susceptibility that enables leukocytes and plasma proteins to migrate out of the systemic circulation; The third stage involves leukocyte expulsion from the microcirculation, aggregation in the location of injury, plus stimulation to remove the poison.[24] As previously known, histamine, a fundamental amine, increases the vascular permeability by acting as a potent vasodilator and is also an important mediator of inflammation. The animals (control group) administered with histamine showed an increase in the volume of paw edema indicating its maximum value at 120 minutes. The edema in the diclofenac (10 mg/kg) and test drug (200 mg/kg)-received groups decreased significantly as juxtaposed to the control group. This change in their proliferation indicates, these substances, although successfully limiting the release of histamine with other mediators, may not be effective in decreasing the release of prostaglandins. So, in light of the findings and prior information, coumarins may significantly block the histamine.[25] Biphasic carrageenan-induced inflammation resulting in paw edema in rats is used to assess the acute inflammatory action of the test drugs. Phase I is mediated by mediators such as serotonin, histamine, and kinins, while phase II is explained by increased generation of PGs, oxygen-free radicals, and inducible cyclooxygenase (COX-2).[26,27] When compared to control group, diclofenac dramatically reduced the paw volume from the start of the study to when it is over at 120 minutes. Contrarily, compound I shown negligible results while compounds II and III of coumarin derivatives displayed audible anti-inflammatory action. A formalin edema model closely approximates actual arthritis in humans.[28] Between the control and treatment animal groups, the formalin paw inflammatory method's activity for the changes in the quality of paw edema volumes was statistically significant. Inflammatory granulomas are a hallmark of sub-acute process. The weight of the cotton pellet granuloma's dry component and the proportion of granulomatous tissue are related.[29] The volume of granulomas caused by cotton pellets was significantly decreased by compounds II and III as well as the reference drug diclofenac sodium. In this investigation, compound II and compound III decreased the cotton pellet's dry weight and wet weight in comparison to group controls for all three compounds.

This happens as a result of their capacity to lower fibroblast counts and make less collagen and mucopolysaccharide, both of whose constitute essential phases of the inflammatory process crucial for tissue remodelling.[30]

Table 01: Name and Structure of Coumarin-derivates used in the analysis.

ID No[a]	Name of Compounds	Dose	Structure	Preparation
I	**3-chloro benzaldehyde**	200 mg/Kg		Raw derivative was involuted with copper metal to form coumarin Schiff base
II	**2-hydroxy benzaldehyde**	200 mg/Kg		
III	**4-methyl coumarin**	200 mg/Kg		

[a]The use of the same roman numerals suggests the identification of the coumarin compounds as follows

Table 02: Effect of coumarin derivatives on Histamine induced hind paw edema in experimental rats

Groups (n=6/group)	Dose	Volume of paw (ml) Represented as Mean ± SEM				
		0 min	**30 min**	**60 min**	**120 min**	**180 min**
Histamine control	0.1 ml	1.02 ± 0.08	1.53 ± 0.21	1.92 ± 0.34	2.36 ± 0.24	2.14 ± 0.37
Diclofenac sodium	10 mg/kg	1.03 ± 0.06	1.49 ± 0.34*	1.73 ± 0.33*	1.57 ± 0.48*	1.51 ± 0.32*
Compound I	200 mg/kg	0.96 ± 0.13	1.60 ± 0.47	1.89 ± 0.58	1.91 ± 0.56	1.88 ± 0.36*
Compound II	200 mg/kg	1.06 ± 0.15	1.37 ± 0.36	1.52 ± 0.46*	1.65 ± 0.59*	1.62 ± 0.48*
Compound III	200 mg/kg	0.99 ± 0.25	1.32 ± 0.35	1.55 ± 0.46*	1.58 ± 0.307*	1.57 ± 0.37*
*Statistically significant in analogy with histamine control group ($p < 0.05$)						

Table 03: Results of coumarin derivatives on hind paws edema in carrageenan induced experimental rat

Groups (n=6/group)	Dose	Volume of paw (ml) Results are represented as Mean ± SEM				
		0 min	**30 min**	**60 min**	**120 min**	**180 min**
Distilled water	0.1 ml	0.98 ± 0.06	1.58 ± 0.12	1.89 ± 0.26	2.24 ± 0.18	2.06 ± 0.21
Diclofenac sodium	20 mg/kg	1.04 ± 0.18	1.46 ± 0.24*	1.67 ± 0.24*	1.53 ± 0.25*	1.42 ± 0.24*
Compound I	200 mg/kg	1.06 ± 0.15	1.52 ± 0.34	1.71 ± 0.62	1.89 ± 0.82	1.86 ± 0.49*
Compound II	200 mg/kg	1.03 ± 0.20	1.33 ± 0.44	1.41 ± 0.57*	1.53 ± 0.48*	1.45 ± 1.04*
Compound III	200 mg/kg	0.96 ± 0.32	1.36 ± 0.24	1.45 ± 0.32*	1.57 ± 0.31*	1.49 ± 0.45*
*Statistically significant in analogy with carrageenan control group ($p < 0.05$)						

Table 04: Results of coumarin derivatives on hind paws edema in formalin induced experimental rat

Groups (n = 6/groups)	Dose	Volume of paw (ml) Results are represented as Mean ± SEM				
		0 min	**30 min**	**60 min**	**120 min**	**180 min**
Formalin control	0.1 ml	0.95 ± 0.24	1.54 ± 0.29	1.92 ± 0.25	2.32 ± 0.24	2.14 ± 0.29
Diclofenac sodium	10 mg/kg	0.96 ± 0.19	1.51 ± 0.35*	1.73 ± 0.24*	1.61 ± 0.27*	1.39 ± 0.23*
Compound I	200 mg/kg	1.03 ± 0.18	1.57 ± 0.37	1.86 ± 0.33	1.92 ± 0.38	1.89 ± 0.39*
Compound II	200 mg/kg	0.98 ± 0.25	1.41 ± 0.36	1.63 ± 0.45*	1.73 ± 0.37*	1.68 ± 0.46*
Compound III	200 mg/kg	1.13 ± 0.46	1.39 ± 0.27	1.51 ± 0.34*	1.53 ± 0.45*	1.51 ± 0.31*
*Statistically significant in contrast to carrageenan control group ($p < 0.05$)						

Table 5: Results of coumarin derivatives on Cotton pellet granuloma in experimental rats

Groups (n = 6/group)	Dose	Wet weight (g) Mean ± SEM	Dry weight (g) Mean ± SEM	Transudative weight (g) Mean ± SEM
Normal control	0.1 ml	201.8 ± 0.05	56.17 ± 0.15	154.33 ± 1.71
Diclofenac sodium	10 mg/kg	120.53 ± 2.55*	50.53 ± 0.06*	75.9 ± 2.48*
Compound I	200 mg/kg	156.4 ± 1.70*	48.94 ± 1.05*	104.72 ± 0.05*
Compound II	200 mg/kg	138.67 ± 3.03*	53.01 ± 2.04*	84.78 ± 0.03*
Compound III	200 mg/kg	131.77 ± 2.10*	51.89 ± 1.92*	81.34 ± 0.63*
*Statistically significant compared to normal control group ($p < 0.05$).				

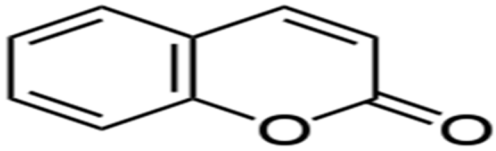


Figure 1: IUPAC Identification of 2H-chromen-2-one

CONCLUSION

Of the three synthesised divalent metal complex coumarins, it is evident from the results that compounds II (2-hydroxy benzaldehyde) and III (4-methyl coumarin) have anti-inflammatory properties in carrageenan, formalin, histamine-induced inflammation, and cotton pellet-induced granuloma in experimental rat models. In conclusion of this research work, coumarin derivative compound II and III exhibits anti-inflammatory property, and their usage is safe in animals. To fully understand these compounds' specific mechanism of action, further thorough research is required.

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DATA AVAILABILITY

All the authors declare that data pertaining to this manuscript/research work will be provided on request.

CONFLICT OF INTEREST

The potential conflicts of interest were discussed and resolved between the authors and hence reports to have no conflict of interest.

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AUTHORS' CONTRIBUTION

All the authors have genuinely contributed equally contributed in this research and preparation of this manuscript.

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