EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 12
385-390
Year: 2022

PHARMACOLOGICAL EVALUATION OF AMIDO METHYL MELOXICAM (MELOXICAM IMPURITY) FOR ANALGESIC AND ANTIINFLAMMATORY ACTIVITIES USING ANIMAL MODELS

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Article Received on 20/10/2022 **Article Revised on 10/11/2022** **Article Accepted on 30/11/2022**

ABSTRACT
Many phenolic compounds have been shown to have anti-inflammatory and analgesic effects. Flavonoids and tannins, which have been detected in phytochemical studies of natural compound ethanolic extricates, may inhibit the production of prostaglandins and bradykinins. We will use the stomach-narrowing effect of acidic corrosion to identify antinociceptive experts who function on the periphery of our nervous system. Experimenters may have discovered that extracts may reduce the number of writhes that animals experience in response to the adverse effects of the boosts. When administered to rats with carrageenan-induced paws, the chemically prepared natural substances significantly reduced inflammation.

KEYWORDS: Phenolic compounds, Inflammation, Natural substances.

INTRODUCTION

Analgesics

A drug that selectively relives pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness. A wide range of drugs are used to control pain. They range from mild over-the-counter (OTC) drugs, such as aspirin and acetaminophen, to strong general anaesthetics. Drugs that relieve pain often reduce fever and inflammation that are used to treat conditions such as

- Mild to moderate pain caused by injury or surgery
- Fever, headaches, and painful menstruation
- Rheumatoid arthritis (a chronic inflammatory disease of the peripheral joints)
- Osteoarthritis (a chronic disease that involves wear and deterioration of joints in the body, causing inflammation)
- Chronic pain associated with cancer, AIDS, multiple sclerosis, or sickle cell disease

Inflammation

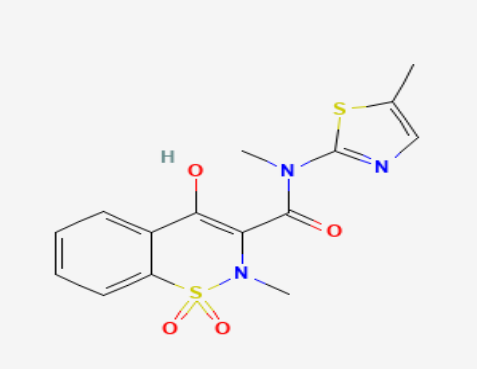
Inflammation or phlogosis is pathological response of living tissue to injuries that leads to the local accumulation of plasmatic fluid and blood cell. Although it is defense can be induced, maintain or aggravate many disease. It is a complex phenomenon, comprising of biochemical as well as immunological factors. Inflammation is recognized by following symptoms:

1. Rubor (Redness)
2. Tumor (Swelling)
3. Calor (Heat)
4. Dolor (Pain)
5. Functio laesa (LOSS of functions)

Compound

Amido methyl meloxicam (Meloxicam impurity)
Molecular formula $C_{15}H_{15}N_3O_4S_2$
Molecular weight 365.4

Chemical structure



IUPAC Name

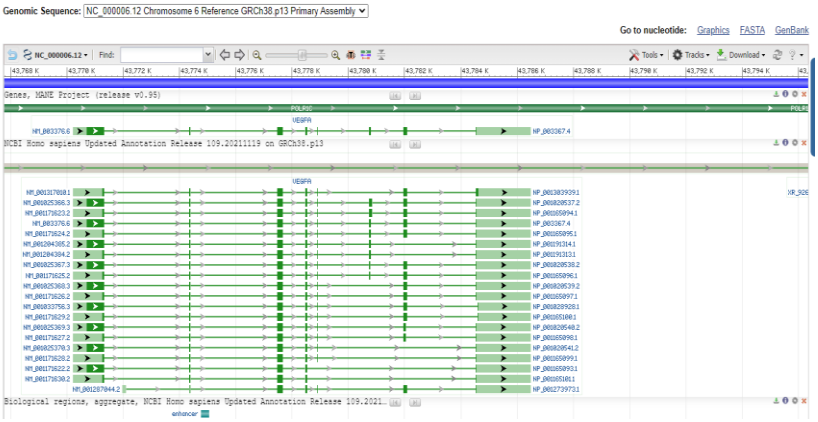
4-hydroxy-N,2-dimethyl-N-(5-methyl-1,3-thiazol-2-yl)-1,1-dioxo-1λ6,2-benzothiazine-3-carboxamide

CAS

892395-41-4

Gene

VEGFA vascular endothelial growth factor A [*Homo sapiens* (human)] Gene ID: 7422



MATERIALS AND METHODS

Animal approval

The study was conducted after obtaining from committee for the purpose of control and supervision on animals (CPCSEA) and institutional animal ethics committee (IAEC).

Animals

Swiss albino mice weighing 20-25 gm wistar rats weighing 150- 200 gm were used for this study. The animals were obtained from animal house, Nandha College pharmacy, Erode, Tamilnadu, India. On arrival, the animals were placed randomly and allocated to treatment groups in polypropylene cages with paddy husk as bedding. Animals were housed at a temperature of 24±2ºc and relative humidity of 30-70%. A12: 12 light: day cycle was followed. All animals were allowed to free access to water and bed with standard commercial pelleted chow. All the experimental procedures are protocols used in this study will be reviewed by Institutional Animal Ethics Committe of Shadan Women's college of Pharmacy, and were accordance with the guidelines of the IACE.

Pharmacological studies

Analgesic activity

Hot plate method in mice

The hot plate assay method was employed for the purpose of preferential assessment of possible centrally medicated analgesic effects of compounds. The central analgesic drug MELOXICAM was used for positive control group. In this experiment, Swiss albino mice (20-25 g) were placed on a hot plate maintained at room temperature for 15 min. Food was withdrawn on the preceding night of the experiment.

Each animal was then individually placed gently on Eddy's hot plate at 55ºC. Latency to exhibit nociceptive responses such as licking paws or jumping off the hot plate were determined at 30, 60, 90 and 120 min after administration of the drugs or vehicle.[43]

Tail immersion test

This method assessment was used to evaluate the centrally medicated analgesic effects of compounds. The animals were placed into individual restraining cages leaving the tail hanging out freely. The lower 5cm portion of the tail is marked and this part of the tail was immersed in a water bath containing water at a temperature of 55± 0.5 ºC. Withdrawing the tail from the hot water showed the analgesic effect. The reaction time was noted on a stop-watch. Each animal served as control. The average of the two values was the initial reaction time.

The reaction time of the groups were taken at 0, 30, 60, 90 and 120min. The cut off time of the immersion was 15seconds. The reaction time was measured.

Acetic acid induced writhing response in mice

This method was used to preferentially evaluate possible peripheral analgesic effects of compounds. Swiss albino male mice were fasted overnight prior to start the experiment with free access to water. The peripheral analgesic drug Diclofenac sodium (10 mg/kg) was used as a positive control.

After 30 min of treatment, the mice were injected intra peritoneally with 0.1 ml of 1% acetic acid solution to induce the characteristic writhings. The mice were then placed in an observation box and the numbers of writhing were counted in a 5min period. The response of the extract and Diclofenac sodium treated groups was compared with those of animals in the control group.[44]

Anti-inflammatory activity

Carrageenan-induced paw edema in rats

Acute inflammation was produced by injecting 0.1 ml of 1% (w/v) carrageenan suspension into the sub planter region of the right hind paw of the rats. The animals were pre treated with the drug 1hour before the administration of carrageenan.[51] The paw thickness was measured at 1, 2, 3 and 4 h after carrageenan injection by using digital vernier callipers.

Cotton pellet induced granuloma method in rats

Cotton pellets, weighing 5mg each were sterilized. Under ether anaesthesia, the pellets were introduced subcutaneously through a skin incision on the back of the animals. Starting from 30 min after the implantation of cotton pellet for all the rats.

The test drugs were administered daily for 7days. On the 8th day, the animals were sacrificed with diethyl ether. The granulomas were removed and the weighed.

Experimental design

24 Rats are divided into 4 groups of six rats each (n=06) and treated orally as follows –

Group-1: (normal): it was used as a normal saline rats seven days.

Group-2: (CMC): rats received distilled water orally daily for seven days,

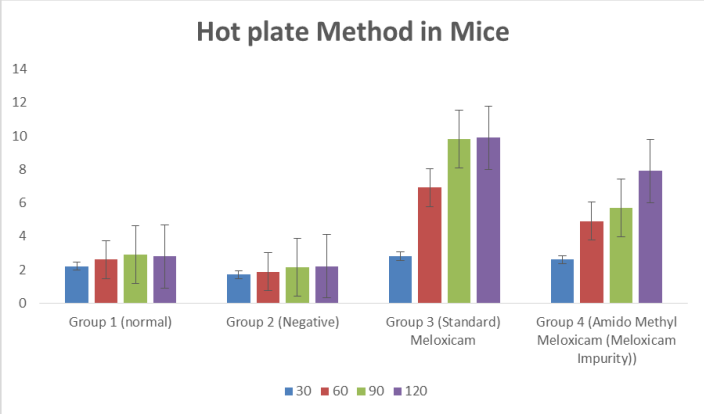
Group – 3: (CMC + MELOXICAM): rats received MELOXICAM orally daily for seven days

Group -4: (CMC + *Amido Methyl Meloxicam (Meloxicam Impurity)):* rats received extract orally for seven days

RESULTS

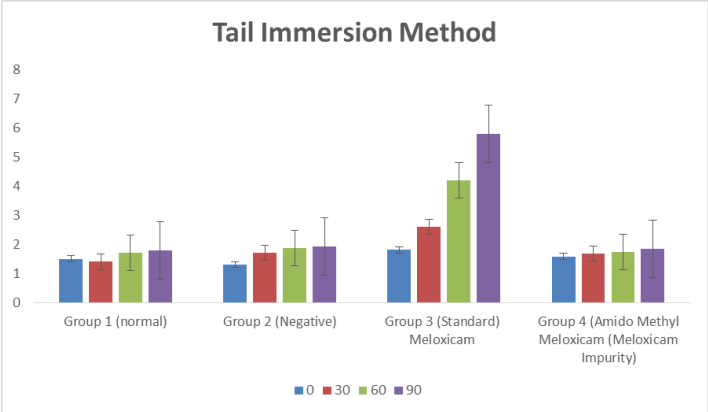
Hot plate method in mice

Treatments	30	60	90	120
Group 1 (normal)	2.2 ± 0.29	2.6 ± 0.43	2.9 ± 0.11	2.8 ± 0.09
Group 2 (Negative)	1.7 ± 0.12	1.868 ± 0.27	2.14 ± 0.10	2.21 ± 0.14
Group 3 (Standard) Meloxicam	2.8± 0.18	6.9 ± 0.16	9.8 ± 0.09	9.9 ± 0.13
Group 4 (Amido Methyl Meloxicam (Meloxicam Impurity))	2.6 ± 0.23	4.9 ± 0.18	5.7 ± 0.04	7.9 ± 0.17



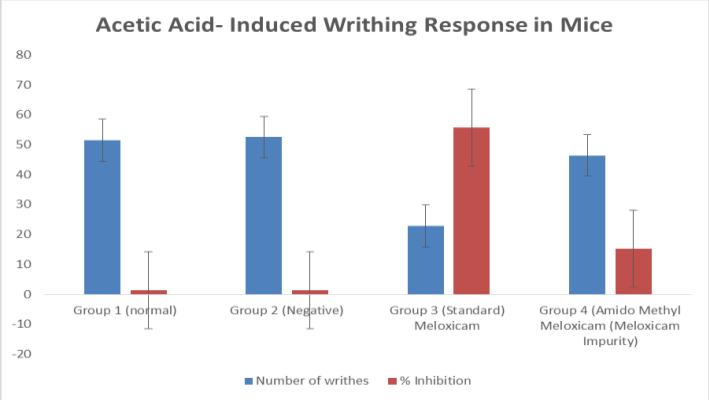
Tail Immersion Method

Treatments	0	30	60	90	120
Group 1 (normal)	1.504 ± 0.34	1.402 ± 0.26	1.701 ± 0.28	1.803 ± 0.13	1.904 ± 0.31
Group 2 (Negative)	1.304 ± 0.36	1.705 ± 0.24	1.868 ± 0.25	1.924 ± 0.15	2.156 ± 0.24
Group 3 (Standard) Meloxicam	1.806 ± 0.37	2.604 ± 0.21	4.202 ± 0.19	5.806± 0.16	5.402 ± 0.22
Group 4 (Amido Methyl Meloxicam (Meloxicam Impurity)	1.583 ± 0.46	1.684 ± 029	1.746 ± 0.26	1.835 ± 0.26	1.932 ± 0.26



Acetic Acid- Induced writhing response in mice

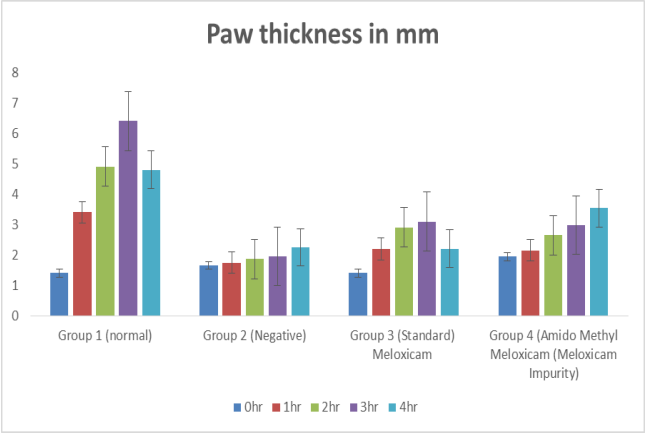
Treatments	Number of writhes	% Inhibition
Group 1 (normal)	51.464 ± 0.33	1.402 ± 0.33
Group 2 (Negative)	52.478 ± 0.26	1.412 ± 0.34
Group 3 (Standard) Meloxicam	22.819 ± 0.21	55.64 ± 0.28
Group 4 (Amido Methyl Meloxicam (Meloxicam Impurity)	46.358 ± 0.36	15.17 ± 0.22



Carrageenan-Inuced paw edema in rats

Anti inflammatory activity of ethanolic extract of organic compounds on carrageenan induced paw edema method.

	Paw thickness in mm				
Treatments	**0hr**	**1hr**	**2hr**	**3hr**	**4hr**
Group 1 (normal)	1.403 ± 0.02	3.406 ± 0.22	4.906 ± 0.04	6.405± 0.05	4.802 ± 0.08
Group 2 (Negative)	1.658 ± 0.03	1.749 ± 0.21	1.868 ± 0.07	1.957± 0.11	2.256 ± 0.09
Group 3 (Standard) Meloxicam	1.404 ± 0.05	2.203 ± 0.13	2.904 ± 0.09	3.102 ± 0.13	2.204 ± 0.05
Group 4 (Amido Methyl Meloxicam (Meloxicam Impurity)	1.946 ± 0.03	2.154 ± 0.08	2.648 ± 0.09	2.987 ± 0.11	3.543 ± 0.17

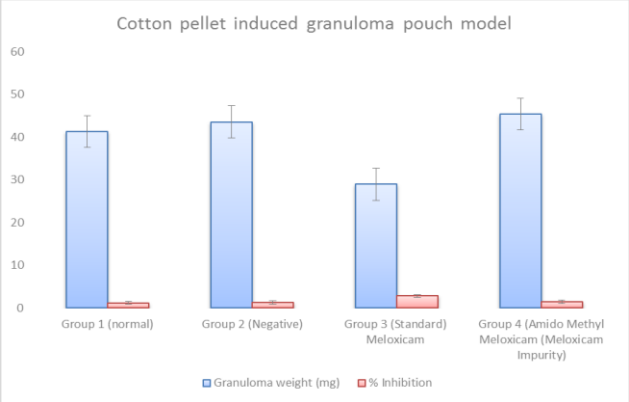


Cotton Pellet-Induced granuloma method in rats

Anti inflammatory activity of ethanolic extract of Organic compounds on Cotton pellet induced granuloma pouch model

Treatments	Granuloma weight (mg)	% Inhibition
Group 1 (normal)	41.24 ± 0.04	1.2 ± 0.09
Group 2 (Negative)	43.58 ± 0.02	1.3 ± 0.07

Group 3 (Standard) Meloxicam	28.94 ± 0.03	2.8 ± 0.02
Group 4 (Amido Methyl Meloxicam (Meloxicam Impurity)	45.42 ± 0.06	1.5 ± 0.06



DISCUSSION

Inflammation is a critical physiological response that occurs in response to many different types of harmful agents, including physical trauma, bacterial infection, chemicals, and physical phenomena, with the ultimate goal of minimising damage and facilitating tissue healing. Tissue regeneration, immune monitoring, and repair all work better when inflammation is present after damage (Vodovotz et al., 2008). We are protected by the inflammatory response, which releases cells and mediators to eliminate invaders and stop infections.

Meloxicam and its Derivatives inhibited Carrageenan-induced inflammations in rat models, indicating that it has potent anti-inflammatory effects, according to the study's findings.

CONCLUSION

In order to determine the effectiveness of natural substances in reducing inflammation, the carrageenan-induced paw edema model is often used. The current investigation demonstrated that paw edema volume was generated by Carrageenan injection, and that the amount of edema seen was greatest at the 4-hour mark. The edoema seen in the acute phase of inflammation was reduced by the Amido Methyl Meloxicam (Meloxicam Impurity).

Amido Methyl Meloxicam (Meloxicam Impurity)'s effects come from its ability to prevent the production of leukotrienes. Amido Methyl Meloxicam (Meloxicam Impurity) restrained Carrageenan-induced inflammations in rodent models, demonstrating that it has powerful anti-inflammatory impacts, concurring to the study's discoveries.

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