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Evaluation of anti inflammatory activity of synthetic 7-flavanol derivatives

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ABSTRACT

*The inflammation is serious health problem in all industrialized countries due to carcinogens, environmental chemicals, irritant substances and microorganism. The several literatures have been reported that the limited synthetic drug information's are available from developing countries. The modern day synthetic anti inflammatory drugs possess some adverse effects such as ulcer, prevent the coagulation, nephrotoxicity and hematopoietic changes. The several herbal formulations derived from Ayurveda and its additional systems of medicine, either not yet to be scientifically validated or scientifically validated; that they have flavonoids exhibited pharmacological action against inflammation. The present study was undertaken to investigate anti-inflammatory activity of synthesized flavonoids and its derivatives compound[1]. As per the literature survey, We have synthesized flavonoids and its derivatives such as 3'4'-dinitro, 7-flavanol, 6, 4'-dinitro, 7-flavanol, 6-dinitro 7-flavanol, 6, 3'4'-trinitro, 7-flavanol, 6-acetyl, 4'-nitro, 7- flavanol, 6-acetyl, 4'-nitro, 7- flavanol and 6-acetyl, 3'4'-dinitro 7-flavanol.The carrageenan induced paw oedema methods in rats were used to comparatively evaluate the anti-inflammatory activity of selected synthesized flavonoids and its derivatives. The one dose level 300mg/kg was prepared by using synthesized flavonoids and its derivatives. The results revealed that the all synthesized flavonoids and its derivatives have shown anti inflammatory activity (*P<0.05, **P<0.01 and ***P<0.001) when compared to control and positive control group. The 3'4'-dinitro, 7-flavanol have expressed (**P<0.05) mild reduction in paw volume when compared to each other groups but positive control Indomethacin 10 mg/kg have showed (***P<0.001) more anti inflammatory activity. The 6-acetyl, 4'-nitro, 7- flavanol and 6-acetyl, 3'4'-dinitro, 7-flavanol were shown moderate reduction in paw volume when compared each other groups.*

INTRODUCTION

Inflammation is a noxious local response or protective response of living tissue against injury caused by physical trauma, noxious chemicals and microbiological agents [1]. This is type of autoimmune disorder, which is caused by foreign materials such as microorganisms and irritant substances[2].

This is type of autoimmune disorder, which is caused by foreign materials such as microorganisms and irritant substances. The inflammation has important health problem in all scientifically developed countries due to carcinogens, environmental chemicals, irritant substances and microorganism [3-5]. The prolonged inflammation leads to cancer due to activation of cell injury or continuous tissue damage. Literature survey report indicated some of the natural food materials like apple anion, green tea and other citrus fruits have different types of flavonoids, which are act against some diseases such as hyperlipidemia, cataracts, cancer, skin disorders, edema, inflammatory bowel disease, ulcer, diabetes mellitus, gout and menopause related disorder [6]. Only less number of scientific data of synthesized flavonoids and its derivatives compound are available for the treatment of inflammation [7&8]. The active phytoconstituents are isolated from natural sources and difficult to modify the isolated compound by using chemical transfusion method due to lengthy procedure, very less quantity of compounds were obtained from natural sources, unfortunately combined phytoconstituents exhibited pharmacological action and not easily identify and

characterize the isolated flavonoids and its derivatives. Based on the above mentioned reasons, a need for the search of newer antiinflammatory agent from synthetic flavonols and its derivatives using various synthetic routes and evaluation of anti inflammatory activity.

MATERIALS AND METHODS

ANIMALS

Wistar Albino rats (150-200 gm) of either sex were procured from Amrita Institute, Kerala. The experimental protocol was initially approved from the Institutional animal ethical committee under the reference no. KU/IAEC/Ph.D/065. The animals are maintained in department animal house for 7 days. They were housed in polypropylene cages and fed with standard rodent pellet diet (Baramati Agro Ltd.,) and water ad *libitum*. Maintained the room temperature 21-25 ºC and relative humidity 50-60 %. They were exposed to alternate cycle of 12 hours of darkness and 12 hours light. The animals were fasted over night for at least 12 hours. The standard oral feeding tubes and syringes were used for drug administration.

CHEMICALS AND DRUGS

Carrageenan
Saline
Carboxy methyl cellulose 0.5%
Indomethacin

PREPARATION OF DRUG SOLUTION

The synthesized flavonoids and its derivatives were formulated as suspension using 0.5% Carboxy methyl cellulose and which was used for the evaluation of anti inflammatory activity

ACUTE TOXICITY STUDIES- OECD 423 GUIDELINES5

The rats are fasted overnight, prior to dosing. The three dose levels of drugs are administered by the help of oral feeding needle over the period of 24 hours. After the drugs has been administered, food may be withheld for a further 3-4 hours in rats. The purpose of sighting study is to allow selection of the appropriate starting dose for main study. The test substance is administered to single animal in a sequential manner following from the fixed dose levels of 5, 50, 300 and 2000 mg/kg. The interval between dosing of each level is determined by the mortality, onset, duration and severity of toxic signs over the period of 24 hours, special attention given during the first 4 hours. Four hours after the drug administration, provided the food and water for 14 days and daily observed some parameters such as food intake, water intake, mortality, onset, duration and severity of toxic signs. The animal weight is recorded on weekly once. Based on the mortality result of sighting study starting dose in main study is decided and carried out with five animals per dose level (5, 50, 300 and 2000mg/kg). Based on the result on 14th day of observation, the doses for *in vivo* study are selected as 300mg/kg.

Table-1: Acute toxicity study data (OECD guidelines)

Sl. No.	Dose levels (mg/kg)	Weight of the animal (in gms)	Signs of toxicity	Weight of the animal after the study (in gms)	Onset of toxicity	Duration of study
01.	2000	230±10	Nil	232±11	Nil	14 days
02.	300	220±11	Nil	222±12	Nil	14 days
03.	50	210±15	Nil	213±10	Nil	14 days

Acute toxicity study was performed as per the OECD guide lines, used three animals for each dose levels.

CARAGEENAN INDUCED INFLAMMATION [9]

The rats were divided in to six groups and each group consists of six animals (Table –2). The drug, extract and solvents were administered by using oral feeding needle. Thirty minutes later the drug administration, 0.1ml of ml 0.1% solution Carrageenan was injected into the plantar side of the left hind paw and right paw serve as a control. The tibia - tarsal region was marked with the help of marker. The paw was immersed into the A arm region of the plethysmograph (filled with mercury) up to the fixed mark and noted the mercury changes in the B arm. Before the drug treatment, paw volume was measured by plethysmograph. After the drug treatment, paw volume was noted different time intervals at 1,2,3,4, 6, 12 and 24 hrs.

STATISTICAL ANALYSIS

The experimental raw data obtained were subjected to statistical analysis by using one way ANOVA followed by Dunnet T test (Graph pad Prism version 5.01 software).

RESULTS AND DISCUSSION

Table. No- 2: Anti-inflammatory activity of Flavanol derivatives on Carrageenan induced oedema model of inflammation

Sl. No.	Treatment	(hrs)								
		0	0.5	1	2	3	4	6	12	24
01.	Control	1.000 ±0.0	1.400 ±0.07	1.767 ±0.06	2.433 ±0.06	2.400 ±0.14	2.367 ±0.14	2.267 ±0.03	2.333 ±0.04	1.933 ±0.13
02.	Positive control	1.067 ±0.04	1.650 ±0.02	1.517 ±0.02	1.517 ±0.02***	1.533 ±0.02***	1.533 ±0.03***	1.467 ±0.02***	1.500 ±0.02***	1.500 ±0.01***
03.	Sample I (3’4’-dinitro 7-flavanol)	1.133 ±0.02	1.467 ±0.04	1.833 ±0.02	2.217 ±0.06*	2.133 ±0.03*	2.133 ±0.03**	2.017 ±0.02*	1.367 ±0.02*	1.300 ±0.01*
04.	Sample II (6,4’-dinitro 7-flavanol)	1.133 ±0.09	1.433 ±0.08	1.500 ±0.05***	1.500 ±0.06***	1.467 ±0.06***	1.367 ±0.06***	1.233 ±0.096***	1.200 ±0.076***	1.183 ±0.16***
05.	Sample III (6-dinitro 7-flavanol)	1.100 ±0.06	1.567 ±0.02	1.667 ±0.02	1.633 ±0.02***	1.600 ±0.04***	1.533 ±0.04***	1.400 ±0.046***	1.333 ±0.026***	1.333 ±0.026***
06.	Sample IV (6,3’4’-trinitro 7-flavanol)	1.033 ±0.02	1.650 ±0.02	1.733 ±0.02	1.800 ±0.03***	1.700 ±0.01***	1.600 ±0.01***	1.500 ±0.046***	1.433 ±0.026***	1.433 ±0.026***
07.	Sample V (6-acetyl, 4’-nitro, 7- flavanol)	1.150 ±0.03	1.567 ±0.02	1.703 ±0.05	2.167 ±0.05**	2.067 ±0.02**	2.067 ±0.0***	2.000 ±0.04**	1.400 ±0.06**	1.333 ±0.02**
08.	Sample VI (6-acetyl, 3’4’-dinitro 7-flavanol)	1.133 ±0.02	1.433 ±0.02	1.617 ±0.05	2.150 ±0.07**	2.100 ±0.03**	2.050 ±0.0***	2.050 ±0.02**	1.400 ±0.0**	1.267 ±0.02**

This work is used to discover a new drug from synthetic route, which may provide required pharmacological action to targeted site, which would accepted by the humans. The carrageenan induced paw oedema method in rats was used to comparatively evaluate the anti-inflammatory activity of selected traditional herbs such as synthesized flavonoids and its derivatives. The results revealed that the all synthesized flavonols and its derivatives have shown anti inflammatory activity (*P<0.05, **P<0.01 and ***P<0.001) when compared to control and positive control group. The 3’4’-dinitro, 7-flavanol have expressed (**P<0.05) mild reduction in paw volume when compared to each other groups but positive control Indomethacin 10 mg/kg have showed (***P<0.001) more anti inflammatory activity at second hour. The 6-acetyl, 4’-nitro, 7- flavanol and 6-acetyl, 3’4’-dinitro 7-flavanol were shown moderate reduction in paw volume when compared each other groups at second hour. Above specified same manner, anti-inflammatory action was prolonged between 3to 24 hours.

CONCLUSION

The present study concluded the beneficial effect of synthasized 7-flavonols and its derivatives in the control of paw oedema volume in Carrageenan induced paw oedema rats. This study confirms the rational basis for its use in synthasized 7-flavonols and its derivatives for the treatment of inflammation in patients. Further pharmacological investigations are under way to characterize active 7-flavonols and to establish exact mechanism of inflammation action, which may have fewer side effects. This work, we believe, will be useful for further inflammation research works.

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