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Original Article

Peels of Citrus Fruits: A Potential Source of Anti-inflammatory and Anti-nociceptive Agents

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ABSTRACT

Introduction: The present study was contemplated to evaluate the anti-inflammatory and analgesic potentials in peels of some commercially grown Citrus fruits of South India *viz,* Lime (*Citrus aurantifolia*), Orange (*Citrus reticulata*), Sour Orange (*Citrus aurantium*), Pomello (*Citrus grandis*) and Citron (*Citrus medica*). **Methods:** The peel of the fruits were separated and subjected to cold extraction using 70% alcohol. The extracts obtained were screened for the presence of phytoconstituents by qualitative phytochemical analysis; the anti-inflammatory activity of extracts at 250 and 500mg/Kg body weight concentrations were assessed by *in vivo* Carrageenan induced rat paw edema model and *in vitro* HRBC membrane stabilization assay whereas Tail immersion and Hot plate methods have been used to evaluate their analgesic property. **Results:** The results revealed that, all extracts treated animals have shown significant decrease in paw edema volume at 3rd and 4th hour of treatment and increase in reaction time in tail immersion and hot plate readings at 120 and 150 min and are comparable to the standards. From the results it was evident that Citron peel extract exhibited significant anti-inflammatory and analgesic property in all models. Preliminary phytochemical investigation revealed that extracts were bestowed with presence of flavonoids, terpenoids, steroids, glycosides, alkaloids, carotenoids and phenolic compounds which might be responsible for the antinociceptive and anti-inflammatory activities. **Conclusion:** From the results it was evident that all citrus fruits have prominent activity in terms of parameters assessed in a dose dependent manner and are more effective in the later phase. The study thus documents that Citrus peels are good sources of anti-inflammatory and anti-nociceptive agents.

Key words: Citrus peel, Phytochemicals, Carrageenan, HRBC, Tail immersion, Hot Plate.

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INTRODUCTION

Inflammation is a local response of living mammalian tissues to injury. It is a body defense reaction in order to eliminate or limit the spread of injurious agents typically characterized by an increase in tissue permeability and endothelial leukocyte influx of blood into the interstitium, causing edema.[1-2] Though inflammation is a normal response to tissue injury, often it is uncontrolled in chronic autoimmune diseases such as rheumatoid arthritis and Crohn's disease, or when related to allergic response such as asthma and anaphylactic shock.[2] Analgesia is an "unpleasant sensory and emotional experience that is caused by actual or potential tissue damage", usually evoked by an external and internal noxious stimulus.[3-4] Inflammation and pain are common non-specific manifestations of many diseases. Various endogenous mediators such as histamine, serotonin, bradykinin, prostaglandins, etc are most abundant in inflammatory cells and among them prostaglandins are ubiquitous substances that indicate and modulate cell and tissue responses involved in pain and inflammation.[5-6]

The inflammatory agents exhibit therapeutic properties by blocking the action or synthesis of these mediators. The most widely used medicines in modern practice are cyclooxygenase (COX) inhibitors *i.e.* NSAIDs and opioids which are effective for the treatment of inflammation and pain.[7-8] These drugs block COX-1 and COX-2 enzymes involved in prostaglandin production. However, their chronic use particularly in patients with arthritis or other chronic inflammatory diseases is associated with adverse effects such as gastrointestinal perforation, ulceration, bleeding and renal toxicity mainly due to the blockade of COX-1. Therefore the need arises for the development of newer anti-inflammatory and analgesic agents from natural sources with more powerful activity and with lesser side effects as substitutes for chemical therapeutics.[7-10] In this context the present study was executed to explore for more naturally available alternatives, so that their therapeutic values can be assessed and expanded.

Several epidemiological studies have suggested that the consumption of fruit and vegetables is associated with a reduced risk of cardiovascular disorders and cancers,[10-11] and neurodegenerative diseases such as Parkinson's and Alzheimer's diseases,[12] as well as

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positive effects on inflammation and aging.[13] The genus Citrus, which belong to the family of Rutaceae, is a rich bounty of edible fruits of different species and they are one of the main fruit tree crops grown throughout the world and have long been valued as part of a nutritious and tasty diet. The contribution of Citrus species in deterrence of life threatening diseases have been assessed and it has been reported that citrus fruits exhibit a wide range of promising biological properties due to their phenolic profile and antioxidant properties. In addition to this, it provides an ample supply of vitamins, minerals, dietary fibers, essential oils and carotenoids content which makes citrus a health-benefit promoting fruit.[14-17] Although Citrus fruits are one of the most popular world fruit crops that are highly consumed worldwide as fresh produce, juice, most often the peel is discarded as waste which contains a wide variety of secondary components with substantial antioxidant activity in comparison with other parts of the fruit.[17-18]

Several studies have shown that citrus fruits exhibit pharmacological properties such as anti-cancer,[19] antioxidant, anti-diabetic[20] antipyritique, antitoxic,[21] hypolipidemic,[22] regulation of metabolic syndrome,[23] delayed onset of Alzheimer's disease[24] and many more. Recent literature also reviewed anti-inflammatory and analgesic activity in various citrus fruits.[25] However the comparative study on peel of Citrus fruits localized to South India has not been evaluated. Therefore the present study aims to evaluate the pharmacological potential of ethanolic peel extracts of some selected commercially grown Citrus fruits of South India against pain and inflammation by both *in vivo* and *in vitro* methods in view of their use in the local treatment of some painful inflammatory conditions.

MATERIALS AND METHODS

Collection of Plant material

The Citrus fruits were procured from a local market of Shimoga, Karnataka. Which were authenticated by the Taxonomist, Department of Botany, Sahyadri Science College, Shimoga. The fruits selected include Lime (*Citrus aurantifolia*), Orange (*Citrus reticulata*), Sour Orange (*Citrus aurantium*), Pomello (*Citrus grandis*) and Citron (*Citrus medica*).

Preparation of extracts

The fruits selected were washed under running tap water followed by washing with distilled water to remove the surface debris. Then the peel of the fruits was separated and exactly 1000g of the separated peel was subjected to extraction procedure using 70% ethanol.[17]

Qualitative phytochemical analysis

The phytochemical screening was performed for testing the different chemical groups present in peel extracts of all Citrus fruits.[26-27]

Experimental animals

Healthy adult Wistar strain of albino rats of both sexes, weighing 150-200 g were used for the *in vivo* evaluation. Animals were maintained under standard condition of 12:12 hours light/ dark cycle and at an ambient temperature of 23 ± 2°C, with 65 ± 5% humidity. Animals were fed with standard rat chow pellet obtained from Champaka Foods and Feeds, Bangalore, India and water *ad libitum*. All the studies were conducted according to the ethical guidelines of CPCSEA after obtaining necessary clearance from the committee (NCP/IAEC/CL/244/2013-14 dated 24-03-2014).

Acute Toxicity Studies

Acute toxicity study was performed to ascertain any lethal effects of the extracts as per stair case method[28] and mice were closely observed during the first 4 h after the administration of the treatments, and then once daily during the following 14 days. Even though, the animals were safe for maximum dose (5000-mg/kg-body weight) there were few changes in the behavioural response like alertness, touch response and restlessness. Therefore 1/20th and 1/10th of maximum tolerated dose *i.e.* 250 and 500 mg /kg body weight were chosen for the study.

Anti-inflammatory activity

Carrageenan-induced paw oedema

The method used was similar to that described by Winter *et al*.[29] The albino rats of either sex were divided into twelve groups of six animals each. Group I served as control and received the suspension of 0.1% carrageenan in physiological saline and Group II received Indomethacin at 20 mg/Kg body weight intraperitoneally as a standard drug. Group III-XII received ethanolic extracts of Lime, Orange, Sour Orange, Pomello and Citron respectively at doses of 250 and 500 mg/ Kg body weight. Acute edema in left hind paw of the rats was induced by the sub plantar injection of 0.1 ml of freshly prepared (1% w/v) carrageenan suspension in normal saline 30 min after the drug administration. The paw volume was measured at 0, 60, 120, 180, 240 and 300 min after the carrageenan injection using plethysmometer. Mean decrease in the paw volume was measured. The percentage inhibition of paw oedema was calculated by,

$$\text{Percentage inhibition of paw oedema} = (1 - Vt/Vc) \times 100$$

Where,

Vc = increase in paw volume (average inflammation) of the control group of rats at a given time; and

Vt = inflammation of the peel extracts treated rats at the same time.

Human erythrocyte membrane stabilization assay

The HRBC membrane stabilization method was used to estimate *in vitro* anti-inflammatory activity of Citrus peel extracts.[30] Blood was collected from healthy volunteers and was mixed with equal volume of sterilized Alsever's solution. This blood solution was centrifuged at 3000 rpm and the packed cells were collected. The packed cells were washed with isosaline solution thrice and a 10% v/v suspension was made with isosaline. This HRBC suspension was used for the estimation of anti-inflammatory property. Different concentrations of extract and standard were separately mixed with 1ml of phosphate buffer, 2 ml of hyposaline and 0.5 ml of HRBC suspension. All the assay mixtures were incubated at 37°C for 30 min and centrifuged at 3000 rpm for 20 min. The hemoglobin content in supernatant solution was estimated by a spectrophotometer at 560 nm.

The hemolysis percentage was calculated by assuming the hemolysis produced by the control group as 100%. The percentage of HRBC membrane stabilization or protection was calculated using the formula,

$$\text{Percent protection} = 100 - (\text{OD of extract treated sample} / \text{OD of control}) \times 100.$$

Antinociceptive activity

Tail immersion test

The analgesic activity was determined by measuring drug-induced changes in the sensitivity of the mice to heat stress applied to their tails.[31] Swiss albino mice weighing between 20-35 g were used for evaluation of analgesic activity. The selected mice were then divided in to twelve groups of six mice each. Group I served as control and received vehicle only intraperitoneally. Group II received diclofenac at a dose of 20 mg/Kg which served as standard. Group III-XII intraperitoneally received doses of 250 and 500 mg/Kg ethanolic extracts of Lime, Orange, Sour Orange, Pomello and Citron respectively. The initial reading was taken immediately before administration of drugs and then at 30, 60, 90, 120,150, and 180 min after the administration. Tail flick latency difference or mean increase in latency after drug administration was used to indicate the analgesia produced by test and standard drugs.

Hot Plate method

The paws of mice and rats are very sensitive to heat at temperatures which are not damaging the skin.[32] The responses are jumping, withdrawal of the paws and licking of the paws. The animals are placed on the hot plate and the time until either licking or jumping occurs is recorded by a stopwatch. Swiss albino mice weighing between 20-35g were used for evaluation of analgesic activity. Animals were divided into twelve groups, each group containing six animals each. Group I served as the control with no protection. Group II animals received the standard drug of Diclofenac 20 mg/kg body weight, whereas group III to XII animals were administered intraperitoneally with of ethanolic extracts Lime, Orange, Sour Orange, Pomello and Citron at a concentration of 250 mg and 500 mg/Kg body weight respectively. The temperature of the hot plate was maintained 55±1°C, mice were placed on the hot plate and the time in seconds (latency period) taken for mouse to react to the thermal pain by licking its paw or jumping was recorded. Observations were made before and after administration of respective drugs at an interval of 30 min for three hours.

Statistical Analysis

Data analyzed using one way analysis of variance (ANOVA) followed by Turkey's pair wise comparison test. Values are expressed as mean ± SEM (n = 6 in each group). The results obtained were compared with the control group. P value < 0.01 was considered statistically significant.

RESULTS

Qualitative phytochemical analysis

The preliminary qualitative phytochemical investigation documented that the peel extracts of all five citrus fruits showed the presence of many bioactive compounds *viz.* polyphenols, flavonoids, terpenoids, steroids, glycosides, alkaloids and carotenoids. However saponins were present in peel extracts of Orange, Citron and Sour Orange while absent in peel extracts of Lime and Pomello.

Anti-inflammatory activity

Carrageenan-induced paw edema

The effects of citrus peel extracts and standard indomethacin on paw edema induced by carrageenan are summarized in Table 1. Administration of carrageenan to the rats showed a steady rise in paw volume at different time intervals in control group and the standard drug Indomethacin treated group showed a constant decrease in paw edema volume. However administration of citrus peel extracts at different doses exhibited reduction in inflammation in a dose dependent manner. From the results it was evident that at 250 mg the Lime, Orange, Sour Orange and Citron peel extracts exhibited significant (P<0.01) reduction in paw edema at 3rd, 4th and 5th hour which was found to be 1.98±0.02, 1.94±0.11, 1.95±0.04; 1.8±0.03, 1.27±0.06, 1.19±0.04; 1.94± 0.04, 1.86±0.08, 1.83±0.05 and 1.76±0.06, 1.18±0.02, 1.10±0.02 manifesting a percent reduction of 10.15, 25.45, 17.56; 18.26, 45.54, 54.48; 12.17, 20.61, 30.14 and 20.17, 49.62, 58.08 respectively. While Pomello peel extract showed significant reduction only at 5th hour. The reduction in paw volume in Lime, Sour Orange and Pomello peels was prominent at 500 mg dose recording mean values and percent inhibition of [1.5±0.04 (31.9%), 1.02±0.04 (56.2%), 1.19±0.04 (54.7%)], [1.4±0.05 (36.62%), 0.96±0.06 (58.66%), 1.06±0.03 (59.62%)] and [1.74±0.05 (21.32%), 1.34±0.07 (42.46%), 1.36±0.12 (48.37%)] respectively at 3rd, 4th and 5th h respectively. But Citron and Orange peel extract elicited significant (P<0.01) reduction of 1.52±0.04 (10.87%), 1.61±0.08 (23.71), 1.23±0.06 (44.12), 0.71±0.03 (69.32), 0.45±0.03 (82.77) and 1.54±0.03 (9.84%), 1.67±0.09 (20.78%), 1.3±0.07 (40.88%), 0.86±0.04 (63.29%), 0.59±0.04 (77.47%) at different time intervals. It is also evident from the data that the anti-inflammatory activity was positively correlated to time intervals exhibiting highest inhibition of paw volume at 3rd and 4th hour at all the treatment under study.

Human erythrocyte membrane stabilization assay

The protection of human blood erythrocyte membrane by five different peel extracts and the standard against lysis evoked by hypotonic solution was presented in the Table 2. From the results it was found that all the citrus peel extracts exhibited notable protection of the human RBC against the damaging effect of hypotonic solution in a dose dependent manner which was found to be highest at 25 mg/ml concentration where in the Citron peel extract showed maximum protection of 85.26±0.37% followed by Orange (80.32±0.81), Sour Orange (54.43±0.9), Lime (53.08±0.4) and Pomello (45.77±0.87). The standard indomethacin showed a maximum protection of 92.48±0.83% at 10 mg/ml concentration.

Antinociceptive activity

Analgesic effects of ethanolic extracts of five citrus peels by tail immersion and hot plate methods are presented in Table 3 and Table 4 respectively. The onset of reaction to thermal induced pain in both the models was significantly shorter in the control group than in those administered with extract or Diclofenac for any period of evaluation of pain. In tail immersion method a significant (P<0.01) rise in reaction time was noticed at both 250 mg and 500 mg concentration by all the peel extracts at 120 and 150 min which were found to be 7.83±0.6, 10.17±0.6; 9.83±0.6, 12.67±0.84; 8.33±0.49, 10±0.68; 6.83±0.6, 8.83±0.65; 10.17±0.79, 13.5±0.85 and 10.33±0.49, 12.33±0.95; 12.83±0.83, 15.67±1.05; 10.83±0.7, 13.17±0.79; 7.83±0.7, 10.17±0.48; 13.17±0.7, 17.33±0.88 respectively for Lime, Orange, Sour Orange, Pomello and Citron. On the other hand in Hot plate method also a significant (P<0.01) elevation in reaction time was recorded at 120 and 150 min for both the concentrations of the extracts with latency time of 10.17±0.75, 11.17±0.95; 11.17±0.6, 13.33±0.67; 10.33±0.49, 11.5±1.18; 8.17±0.7, 9.83±0.6; 12.83±0.6, 15.5±0.89 and 11.33±0.56, 13.17±0.79; 14.83±1.05, 17.17±0.6; 11.5±0.43, 14.17±0.48; 9.5±0.56, 11.5±0.76; 15.67±0.71, 18.83±0.7 at 250 and 500 mg for Lime, Orange, Sour Orange, Pomello and Citron respectively. Standard drug Diclofenac recorded the reaction time of 5.17±0.75, 6.83±0.48, 10.5±0.62, 14.67±1.2, 18.17±1.11, 15.67±0.71 and 9.17±0.79, 12.83±0.6, 15.17±0.79, 17.33±0.8, 21.17±0.6, 19.67±0.49 in tail immersion and hot plate methods at different time intervals. Hence from the results, it was evident that the extracts showed dose dependent increase at different interval of time and the prominent increase was noted at 120 and 150 min. It is also apparent from the data that, among the extracts the Citron peel extract was found to be highly effective for analgesic activity versus the other peel extracts irrespective of time intervals and dosage.

DISCUSSION

Recently, interests in potent pharmacological properties and clinical applications of natural products for replacing synthetic drugs are mounting.[33] In spite of major scientific and technological progress in combinatorial chemistry, drugs derived from natural products still make an enormous contribution to drug discovery today.[34] In this milieu, use of animal models in drug discovery and inflammation research is mainstay. As the inflammatory basis of disease becomes clear, anti-inflammatory food and food products become of greater interest.[33-34] The research opportunities in nutrition to explore the relationship between a food and food components for an improved state of health and well-being or reduction of disease present the greatest challenge to scientists now and in the future.[35] A lot of researches have documented that extracts from medicinal plants, fruits and vegetables contain such type of phytoconstit-

Table 1: Anti–inflammatory effects of ethanolic extracts of five Citrus fruit peels on carrageenan induced paw edema.

Treatment group	Dose	60 min	120 min	180 min	240 min	300 min
Control		1.7±0.03	2.11±0.08	2.2±0.03	2.34±0.07	2.63±0.04
Standard	20 mg	1.26±0.02**	1.3±0.02**	0.95±0.04**	0.62±0.06**	0.3±0.03**
	%	25.65±1.94	38.12±2.05	56.8±2.12	73.84±1.95	88.62±1.16
Lime	250 mg	1.65±0.05	1.99±0.08	1.98±0.02**	1.94±0.11**	1.95±0.04**
	%	3.09±1.11	5.57±0.52	10.15±0.81	17.56±2.45	25.45±1.78
	500 mg	1.58±0.04	1.73±0.05**	1.5±0.04**	1.02±0.04**	1.19±0.04**
	%	7.19±0.88	17.64±2.09	31.9±2.35	56.2±2.13	54.7±1.57
Orange	250 mg	1.64±0.03	1.96±0.08	1.8±0.03**	1.27±0.06**	1.19±0.04**
	%	3.52±0.41	7.23±0.92	18.26±1.04	45.54±2.37	54.48±2.16
	500 mg	1.54±0.03**	1.67±0.09**	1.3±0.07**	0.86±0.04**	0.59±0.04**
	%	9.84±0.88	20.78±1.89	40.88±2.57	63.29±1.71	77.47±1.1
Sour Orange	250 mg	1.64±0.05	1.97±0.08	1.94±0.04**	1.86±0.08**	1.83±0.05**
	%	3.71±1.74	6.67±0.57	12.17±1.54	20.61±2.19	30.14±2.02
	500 mg	1.56±0.04*	1.72±0.06**	1.4±0.05**	0.96±0.06**	1.06±0.03**
	%	8.82±1.09	18.13±2.3	36.62±2.58	58.66±3.05	59.62±1.38
Pomello	250 mg	1.66±0.06	2.01±0.08	2.07±0.04*	2.08±0.04*	2.17±0.05**
	%	2.76±1.73	4.46±0.36	6.16±0.91	10.95±1.48	17.28±1.46
	500 mg	1.61±0.05	1.87±0.04*	1.74±0.05**	1.34±0.07**	1.36±0.12**
	%	5.88±1.16	10.9±2.32	21.32±1.69	42.46±3.51	48.37±3.79
Citron	250 mg	1.64±0.03	1.94±0.07	1.76±0.06**	1.18±0.02**	1.10±0.02**
	%	4.01±0.39	7.87±0.49	20.17±2.01	49.62±1.78	58.08±1.45
	500 mg	1.52±0.04**	1.61±0.08**	1.23±0.06**	0.71±0.03**	0.45±0.03**
	%	10.87±1.22	23.71±2.37	44.12±2.86	69.32±1.91	82.77±0.88

P values: ** P< 0.01, *P< 0.05, Values are expressed in mean ±SEM, n=6 animals in each group. One way ANOVA followed by Turkey's, Pairwise comparison tests

Table 2: Anti –inflammatory effects of ethanolic extracts of five Citrus fruit peels and standard indomethacin on HRBC membrane stabilization assay.

Concentration (mg/ml)	Lime	Orange	Sour Orange	Pomello	Citron	Concentration (mg/ml)	Standard
5	11.86±0.41	17.4±0.56	17.33±0.46	2.42±0.42	22.22±0.32	2	17.65±0.85
10	23.39±0.29	34.97±0.56	31.11±0.56	12.56±0.84	39.16±0.37	4	37.4±0.53
15	34.55±0.41	55.3±0.96	40.22±0.49	19.44±0.7	55.34±0.37	6	59.7±1.09
20	45.7±0.2	67.78±1.04	51.25±0.68	30.43±0.89	76.18±0.32	8	76.38±0.96
25	53.08±0.4	80.32±0.81	54.43±0.91	45.77±0.87	85.26±0.37	10	92.48±0.83

Table 3: Effect of ethanolic extracts of five Citrus fruit peels in tail immersion model of analgesia in mice.

Treatment Group	Dose (mg)	0 min	30 min	60 min	90 min	120 min	150 min	180 min
Control		2.67±0.21	2.67±0.33	2.5±0.22	2.67±0.33	2.67±0.33	2.5±0.22	2±0.26
Standard	20	2.83±0.17	5.17±0.75 *	6.83±0.48**	10.5±0.62**	14.67±1.2 **	18.17±1.11 **	15.67±0.71 **
Lime	500	2.67±0.33	4.0±0.37 *	5.33±0.42**	7.83±0.79**	10.17±0.6 **	12.33±0.95 **	11.5±0.85 **
	250		2.83±0.4	3.33±0.33*	5.67±0.42**	7.83±0.6 **	10.33±0.49 **	8.83±0.48 **
Orange	500	2.83±0.4	4.67±0.61*	6.00±0.37**	9.67±1.05**	12.67±0.84**	15.67±1.05 **	13.67±0.76 **
	250		3±0.52	4.00±0.52*	7.17±0.6 **	9.83±0.6 **	12.83±0.83 **	10.67±0.71 **
Sour Orange	500	2.67±0.33	4.17±0.31*	5.33±0.42**	8.0±1.18 **	10±0.68 **	13.17±0.79 **	11.17±0.54 **
	250		2.83±0.31	3.17±0.31	6.17±0.48**	8.33±0.49 **	10.83±0.7 **	9.17±0.6**
Pomello	500	2.67±0.33	3.17±0.31	4.0±0.52 **	6.67±0.76**	8.83±0.65 **	10.17±0.48 **	9.17±0.48 **
	250		2.67±0.33	2.83±0.31	4.17±0.48*	6.83±0.6 **	7.83±0.7 **	7.00±0.45 **
Citron	500	2.67±0.21	4.83±0.87 *	6.67±0.33**	9.83±0.6 **	13.5±0.85 **	17.33±0.88 **	14.83±1.05 **
	250		3.17±0.31	4.17±0.48*	8.5±1.12 **	10.17±0.8 **	13.17±0.7 **	11.83±0.79 **

P values: * * P< 0.01 Values are expressed in mean ±SEM, n=6 animals in each group. One way ANOVA followed by Turkey's, Pairwise comparison tests

Table 4: Effect of ethanolic extracts of five Citrus fruit peels in Hot plate model of analgesia in mice.

Treatment Group	Dose(mg)	0 min	30 min	60 min	90 min	120 min	150 min	180 min
Control		5.33±0.61	5.5±0.43	5.67±0.42	5.33±0.42	5.5±0.43	5.33±0.49	4.33±0.33
Standard Diclofenac Sodium	20	5.67±0.67	9.17±0.79**	12.83±0.6**	15.17±0.79**	17.33±0.8 **	21.17±0.6 **	19.67±0.49**
Lime	500	5.00±0.37	5.83±0.6	8±0.58**	10.5±0.76 **	11.17±0.95 **	13.17±0.79 **	11.5±0.56 **
	250		5.17±0.31	7.33±0.56*	9.17±0.48 **	10.17±0.75 **	11.33±0.56 **	10.17±0.7 **
Orange	500	5.17±0.54	7.33±0.49	9.67±0.67**	11.17±0.6 **	13.33±0.67 **	17.17±0.6 **	15.33±0.88**
	250		6.5±0.56	8.83±0.54**	9.83±0.48 **	11.17±0.6 **	14.83±1.05 **	12.67±0.33**
Sour Orange	500	5.5±0.34	6.17±0.31	8.33±0.71**	10.83±0.91**	11.5±1.18 **	14.17±0.48 **	12.33±0.42**
	250		5.33±0.42	7.17±0.48*	9.17±0.48 **	10.33±0.49 **	11.5±0.43 **	10.17±0.79**
Pomello	500	5.00±0.52	5.33±0.42	7.33±0.76	8.17±0.48 **	9.83±0.6 **	11.5±0.76 **	9.67±0.67 **
	250		5.17±0.31	6.17±0.6	7.33±0.61 *	8.17±0.7 **	9.5±0.56 **	8.33±0.33 **
Citron	500	5.17±0.48	8.67±0.33**	10.83±0.4**	12.67±0.67 **	15.5±0.89 **	18.83±0.7 **	17±0.68 **
	250		7.5±0.5 *	9.67±0.33**	11.00±0.52 **	12.83±0.6 **	15.67±0.71 **	14±0.58 **

P values: * * P< 0.01 Values are expressed in mean ±SEM, n=6 animals in each group. One way ANOVA followed by Turkey's, Pairwise comparison tests

uents that might be responsible for treating diseases.[13,36] The peel of citrus fruits is reported to have several beneficial activities.[37] In traditional Chinese medicine, the dried peel of *Citrus reticulate* has been widely used for centuries as a remedy for treating indigestion and fighting respiratory tract inflammatory syndromes such as asthma and bronchitis.[38] In the present study, peels of five different citrus fruits namely Lime, Orange, Sour Orange, Pomello and Citron commonly grown in South India were used for the evaluation of anti-inflammatory and analgesic activities by using reliable *in vivo* and *in vitro* models to provide scientific support to rationalize the folklore or traditional claims for treating inflammation.

Carrageenan-induced inflammation is a sensitive and most feasible experimental model of acute inflammation for detecting active non-steroidal anti-inflammatory agents.[39] The development of carrageenan-induced edema is bi-phasic; the first phase is attributed to the release of histamine, serotonin and kinins and the second phase is associated to the release of prostaglandins and bradykinins.[40-44] The suppression of the first phase may be due to inhibition of the release of early mediators, such as histamine and serotonin, and the action in the second phase may be explained by an inhibition of cyclo-oxygenase. It has been reported that second phase of oedema is sensitive to most clinically effective anti-inflammatory drugs, which has been frequently used to access the anti-oedematous effect of natural products.[45-46] The results of the present research revealed that peels of all the citrus fruits studied possessed a significant anti-oedematogenic effect on paw oedema induced by carrageenan. From the results it was observed that Citron peel extract showed maximum reduction in paw volume at 3rd 4th and 5th hour time interval in a dose dependent manner which is almost equal to standard drug indomethacin followed by peel extracts of Orange, Sour Orange, Lime and Pomello respectively. In general, the anti-inflammatory activity is more evident at the later phases of time interval. Therefore, it can be inferred that the inhibitory effect of different extracts on carrageenan-induced inflammation could be due to inhibition of the enzyme cyclooxygenase leading to inhibition of prostaglandin synthesis.[47]

Further HRBC method was selected for the *in vitro* evaluation of anti-inflammatory property because the erythrocyte membrane is analogous to the lysosomal membrane[48] and its stabilization implies that the extract may as well stabilize lysosomal membranes. Stabilization of lysosomal membrane is important in limiting the inflammatory response by preventing the release of lysosomal constituents of activated neutrophil, such as bactericidal enzymes and proteases, which cause further tissue inflammation and damage upon extra cellular release. There is increasing evidence that lysosomal enzymes play an important role in the development of acute and chronic inflammation.[49] Most of the anti-inflammatory drugs exert their beneficial effect by inhibiting either release of lysosomal enzymes or by stabilizing lysosomal membrane which is one of the major events responsible for the inflammatory process.[50] Extracts of all the Citrus fruits showed significant stabilization towards hypotonicity induced HRBC membrane lysis at different concentrations in a dose dependent manner. However Citron peel revealed a higher percentage protection followed by Orange, Sour Orange, Lime and Pomello. These results provide evidence for membrane stabilization as an additional mechanism of their anti-inflammatory effect. Thus the stabilization of RBCs membrane further establishes the anti-inflammatory potentials of Citrus peel extracts.

Pain is a complex event, centrally modulated *via* a number of complex processes including opiate, dopaminergic, descending noradrenergic and serotonergic systems.[47] In the present study thermal nociception hot plate and tail immersion tests have been used to assess the analgesic property of the extracts. The tests are very useful for discriminating between centrally acting morphine like analgesics and non-opiate analgesics, giving positive response to the former only.[51-52] It was evident from the results that all the peel extracts possess potent analgesic property in a dose dependent manner however; Citron peel extract at 500 mg/Kg body weight was found to be more effective than the others irrespective of time intervals. The analgesic effect produced by the tests may be *via* central mechanisms involving mentioned receptor systems.

The preliminary qualitative phytochemical analysis documented that, all the extracts of citrus fruits are bestowed with the presence of therapeutically effective bioactive compounds *viz.* polyphenols, flavonoids, terpenoids, steroids, tannins, glycosides, alkaloids and carotenoids. The core chemical classes of anti-inflammatory and analgesic agents have been reported from natural sources containing polyphenols, flavonoids, alkaloids, terpenoids, saponins, steroids and tannins.[53] These phytochemicals act by the inhibition of mediators which probably play a key role in preventing inflammation, as because inflammatory cytokines induces cyclooxygenase-2 (COX-2) and prostaglandin E2 synthesis, which have a critical role in the pathogenesis of inflammatory diseases.[54] The phenolic compounds present in plants are found to possess potent anti-inflammatory activity which was reported by Roy *et al.*[55] Garg *et al.*[56] Among the various, flavonoids have beneficial effects in a number of

inflammatory conditions. Some of them act as phospholipase inhibitors and some have been reported as TNF-α inhibitors in different inflammatory situations.[53] Flavonoids are known to inhibit the enzyme prostaglandin synthetase, more specifically the endoperoxidase and reported to produce anti-inflammatory effects.[57] Since, prostaglandins are also involved in the pain perception inhibition of their synthesis and distraction of synthesis of eicosanoids by flavonoids might be the possible reason for the analgesic activity of the extract.[58-59] Indeed, many essential oils showed inhibitory activity against the production of cytokines have shown that flavonoids and limonoid present in the plant Citrus are responsible for the anti - tumor and anti-inflammatory activity.[60] The possible activity of citrus flavonoids in anti-inflammatory and anti-allergic responses was well documented.[61] Lee *et al*. reported that Citrus flavonoids are able to inhibit the kinases and phosphodiesterases essential for cellular signal transduction and activation and inhibit cells involved in inflammation and the immune response.[62] There are also reports on the role of tannins in anti-nociceptive activity.[63] Apart from this, phytosterols have been reported to lower some of the pro-inflammatory cytokines including C-reactive protein[64] and alkaloids have been found to have pain-killing activity[65] suggesting their role against inflammation. The anti-inflammatory effects of triterpenes have been attributed to various mechanisms including inhibition of lipoxygenase and cycloxygenase activities.[66] Hence the analgesic and anti-inflammatory effects produced by the citrus peel extracts may be attributed individually or collectively to the flavonoids, limonoids, steroids, alkaloids, terpenes and tannins. Of all the mechanisms for the anti-inflammatory effects of the plants, their actions on endogenous pro-inflammatory mediators are remarkable.

From the above verdicts it can be concluded that the ethanolic extract of all citrus peels possessed promising anti-inflammatory and analgesic activities. The study also revealed that the peel extracts of Citron possessed a significant anti-oedematogenic, anti-haemolytic and analgesic effect followed by Orange, Sour Orange, Lime and Pomello peel extracts. This significant action of the peel extracts may be due to the inhibition of any inflammatory mediators coupled with lysosomal membrane stability by the phytoconstituents present in the extracts.

CONCLUSION

Citrus fruits are considered as an exemplary source of nutrients and bioactive compounds. The results of present study authentify the folk lore information on the anti-inflammatory and analgesic property of citrus fruits. It can be concluded that the peels of all the citrus fruits studied possess potent anti-inflammatory and anti-nociceptive activity. The broad range of activity of the extracts suggests that, multiple mechanisms mediated by the phytoconstituents are responsible for the potent activity. Hence the study demonstrates the efficacy of peels of Lime, Orange, Sour Orange, Pomello and Citron as effective therapeutic agents in the treatment of acute inflammations. The research will be useful in optimization of composition of fruits and would be a very cost-effective approach of disease prevention, since diet-induced health improvements would not carry any added costs for the health sector and will be of immense help in functional food industry.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

HRBC: Human Red Blood Cell; **NSAID's:** Non Steroidal Antiinflammatory Drugs; **COX:** Cyclooxygenase; **TNF-α:** Tumor Necrosis Factor alpha.

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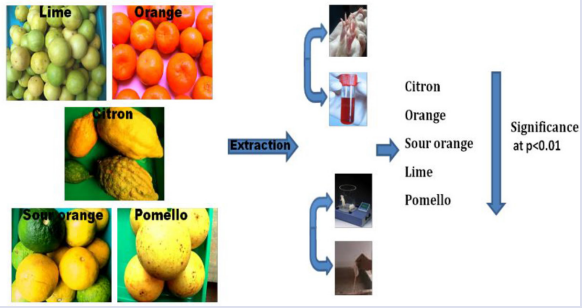
GRAPHICAL ABSTRACT



SUMMARY

- The present study was aimed to evaluate the anti-inflammatory and analgesic potentials in peels of some commercially grown Citrus fruits of South India *viz*, Lime. Orange, Sour Orange, Pomello and Citron.
- The anti-inflammatory activity of extracts at 250 and 500 mg/Kg body weight concentrations were assessed by *in vivo* Carrageenan induced rat paw edema model and *in vitro* HRBC membrane stabilization assay whereas Tail immersion and Hot plate methods have been used to evaluate their analgesic property.
- From the results it was evident that all Citrus fruits have prominent activity in terms of parameters assessed in a dose dependent manner and are more effective in the later phase. The study thus documents that Citrus peels are good sources of anti-inflammatory and anti-nociceptive agents.

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