ISSN 0975 - 6299 Vol 2 / Issue 3 / Jul - Sept 2011

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE PHARMACOLOGY

ANTI-INFLAMMATORY ACTIVITY OF *BENINCASA HISPIDA* FRUIT

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ABSTRACT

The present study was designed to investigate anti-inflammatory activity of Petroleum ether and Methanolic extract of *Benincasa hispida* fruit. Both the extracts at the dose of 300 mg/kg body weight, produced dose dependent and significant inhibition of carrageenan- induced paw edema, histamine induced paw edema and cotton pellet-induced granuloma in rat model. In carrageenan- induced paw edema model, petroleum ether and methanolic extracts showed maximum inhibition in inflammation (0.270 ± 0.063, 0.307 ± 0.043 respectively) as compared to control group (1.27 ± 0.059) which were comparable with standard valdecoxib (0.247 ± 0.033). In histamine-induced paw edema, both the extract showed maximum inhibition (62.86% and 54.84% respectively) as compared to control group, which were comparable with that of standard drug cetrizine (95.24%). Petroleum ether and methanolic extracts showed slight reduction in granuloma tissue formation in cotton pellet implanted rats, which were not significant with that of standard drug diclofenac sodium.

KEY WORDS

Benincasa hispida, carrageenan- induced paw edema, histamine-induced paw edema, cotton pellet-induced granuloma

INTRODUCTION

The attention of pharmacologists throughout the world has been focused on finding out safer and potent anti-inflammatory drug. This is not surprising since inflammatory disorders like rheumatoid arthritis have worldwide prevalence, occur in all races and ethnic groups and have onset early adulthood, sometimes crippling the afflicted person to render him economically nonproductive[1].

Anti-inflammatory drugs offer symptomatic relief in the inflammatory diseases when the underlying cause of inflammation is unidentified. Anti-inflammatory drugs, presently available for the treatment of joint inflammation of various kinds, have undesirable side effects such as causing peptic ulcers, GI complications, including bleeding and perforation due to inhibition of prostaglandin synthesis[2,3,4]. Therefore search for safer and effective drug is up surged. Therefore, plant remedies have become increasingly popular and are often preferred to synthetically derived pharmaceuticals.

The natural products today symbolize safety in contrast to the synthetic drugs that are regarded as unsafe to humans and environment. So, people are returning to the natural products with the hope of safety and security. Numerous evidences have shown that increased consumption of fruit and vegetables reduces the risk of various pathological events such as cancer, cardiovascular, cerebrovascular diseases[5, 6].

Benincasa hispida (Thunb) Cogn. (Family*:* Cucurbitaceae) is commonly known as *Bhuru Kolu* or *Safed Kolu* (Gujarati), *Petha* (Hindi), white pumpkin or wax gourd or ash gourd (English), and *Kushmanda* (Sanskrit). It is a large climbing or trailing herb with stout, angular and hispid stem widely cultivated in tropical asia. Fruits of this plant are traditionally used as a laxative, diuretic, tonic, aphrodisiac, cardiotonic, urinary calculi, blood disease, insanity, epilepsy, and also in cases of jaundice, dyspepsia, fever, and menstrual disorders[7].

The methanolic extract of the fruit is reported to possess antiulcer[8], antihistaminic, and antidepressant activities[9]. Phytochemical review indicates the presence of triterpenes: alnusenol, multiflorenol, iso-multiflorenol; flavone: iso-vitexin; and sterols: lupeol, lupeol acetate, and beta-sitosterol[10].

A number of cucurbitaceae plants have been shown to possess anti inflammatory activity, viz. *Cucurbita moschata*[11] (Fruit)*, Momordica charantia*[12] (Immature fruits), *Cucumis melo*[13](Mature fruit), etc. Hence, the objective of the present study was to evaluate anti inflammatory activity of methanolic and petroleum ether extracts of *Benincasa hispida* fruit using different experimental models.

MATERIAL AND METHODS

Collection of plant*:* The fresh fruit of *Benincasa hispida* was collected from the local vegetable market of Ahmedabad, Gujarat. The authentification of the plant was done in the department of Pharmacognosy, L.M. College of Pharmacy, Ahmedabad, and Gujarat, India.

Method of extraction: The fruit were air dried, seeds were separated and then dried mass was powdered using mixture. 100 gm of dried powder was defatted with petroleum ether (% yield of 0.5%w/w) and extracted with methanol (500ml × 5time) using soxhlet apparatus. Then methanolic extract was separate out using vacuum evaporator. Total yield of methanolic extract was 20% w/w. Methanolic extract was further fractionated with ethyl acetate in

separating funnel and ethyl acetate fraction was evaporated to dryness (% yield was 1.2 %w/w). The remaining powder was dried and extracted with distilled water to give aqueous extract (500 ml x 6; yield was 5% w/w). All the extracts were stored in a glass bottle in refrigerated condition throughout the period of experiment.

Drugs and Chemicals: Carrageenan (Sigma Chemical Company, St. Louis, MO, USA), Valdecoxib (Zydus cadila Ltd, Ahmedabad.), Cetrizine (Zydus cadila Ltd, Ahmedabad), Diclofenac sodium (Zydus cadila Ltd, Ahmedabad) and all other chemicals used were of analytical grade.

Animals: Wistar albino rats (200-250gm) and swiss albino mice (25-30gm) of either sex were used for the present study. The animals had free access to standard pellet diet and water ad libitum. The animals were divided into groups of six animals each and fasted for 12 hours before the experiment. This experiment complied with the guidelines for animal experimentation of our laboratory and approved by Institutional Animal Ethics Committee (IAEC).

Carrageenan –induced paw edema in rats[14]

Table 1
Experimental design for anti-inflammatory studies in rats

	Group	Treatment	Dose
I-	Control	Aqueous suspension of 1% w/v sodium CMC	10 ml/kg; p.o.
II-	Treatment	Petroleum ether extract of *Benincasa hispida*	300 mg/kg, p.o.
III-	Treatment	Methanolic extract of *Benincasa hispida*	300 mg/kg, p.o.
IV-	Treatment	Ethyl acetate extract of *Benincasa hispida*	300 mg/kg, p.o.
V-	Treatment	Aqueous extracts of *Benincasa hispida*	300 mg/kg, p.o.
VI-	Standard	Valdecoxib	5 mg/kg, p.o.

The activity of different extracts of *Benincasa hispida* were evaluated by using carrageenan induced hind paw edema model. The wistar albino rats of either sex were divided into six groups comprising six animals in each group (n=6) as shown in Table 1. Inflammation of the hind paw was induced by injecting 0.05 ml of 1% w/v carrageenan suspension sub-planterly to the left hind paw[14].

All the treatments were given one hour before the carrageenan injection. The measurement of paw volume was accomplished immediately by displacement technique using plethysmometer before the carrageenan injection and at 1, 2, 4 and 5 hours after the carrageenan injection. The average feet swelling in test as well as standard groups were compared with that of control and the % inhibition of paw edema volume was calculated using the formula:

Percentage Inhibition = [1-{(Vd-Vp)/(Vc-Vp)}] × 100
Where,
Vd-Vp = Difference in paw volume after carrageenan and initial paw volume for drug treated animals.
Vc-Vp = Difference in paw volume after carrageenan and initial paw volume for control animals.

Histamine- induced paw edema in mice

Table 2
Experimental design for anti-inflammatory studies in rats

	Group	Treatment	Dose
I-	Control	Aqueous suspension of 1% w/v sodium CMC	10 ml/kg; p.o.
II-	Test 1	Petroleum ether extract of *Benincasa hispida*	300 mg/kg, p.o.
III-	Test 2	Methanolic extract of *Benincasa hispida*	300 mg/kg, p.o.
IV-	Standard	Cetrizine	20mg/kg, p.o.

The activity of different extracts of *Benincasa hispida* were evaluated by using histamine-induced paw edema model. The swiss mice of either sex were divided into four groups comprising six animals in each group (n=6) as shown in Table 2. The animals were starved overnight and deprived of water only during the experiment. After 1 h of drug administration, Histamine (0.1% w/v in normal saline) was injected sub-planterly into the left hind paw of each mice at a dose of 0.05 ml to induce edema. The paw volume was measured at 0 min, 10 min, 20 min, 30 min and 40 min respectively. The anti inflammatory effect was expressed as percent inhibition of edema (As above formula).

Cotton pellet-induced granuloma formation in rats[15, 16]

Table 3
Experimental design for anti-inflammatory studies in rats

Group		Treatment	Dose
I.	Control	Aqueous suspension of 1% w/v sodium CMC	10 ml/kg; p.o.
II.	Test 1	Petroleum ether extract of *Benincasa hispida*	300 mg/kg, p.o.
III.	Test 2	Methanolic extract of *Benincasa hispida*	300 mg/kg, p.o.
IV.	Standard	Diclofenac sodium	5 mg/kg, p.o.

The activity of different extracts of *Benincasa hispida* were evaluated by using Cotton pellet-induced granuloma formation in rat model.The wistar albino rats of either sex were divided into four groups comprising six animals in each group (n=6) as shown in Table 3. Autoclaved cotton pellets (50±1 mg), soaked in 0.2 ml of distilled water containing ciprofloxacin, were implanted subcutaneously, one on each side above the scapula region, under ether anesthesia using aseptic precautions. Drugs or vehicle were administrated orally for 7 consecutive days starting from the day of surgery. On day 7^{th}, animals were killed and the pellets along with granuloma were removed and dried in oven in 60^0C until a constant weight was obtained. The weight of cotton pellet before implantation was subtracted from the weight of the dried dissected pellets. The mean weight was calculated for pellets from the groups of rats receiving drugs and compared with the mean values for the control.

STATISTICAL ANALYSIS

*The data obtained were analysed using One-*way analysis of variance (ANOVA) followed by Tukey's multiple range test. $P<0.05$ was considered statistically significant.

RESULT

(1) Carrageenan-induced paw edema in rats

In this model, different extracts of *Benincasa hispida* were tested against carrageenan-induced paw edema in rats. Among these different extracts, petroleum ether and methanolic extract showed maximum inhibition in inflammation (0.270 ± 0.063, 0.307 ± 0.043 respectively) as compared to control group (1.27 ± 0.059), which was comparable with that of standard, valdecoxib (0.247 ± 0.033) (Table 4).

Table 4
Effect of different extracts of Benincasa hispida on Carrageenan-induced rat paw edema model

Group	Dose (mg/kg) (p.o.)	Edema Volume at 3h (ml)	% Inhibition
1% w/v sodium CMC	10ml/kg	1.265 ± 0.059	---
Petroleum ether extract	300	0.270 ± 0.060*	78.66
Methanolic extract	300	0.307 ± 0.043*	75.73
Ethyl acetate extract	300	0.560 ± 0.056*	55.73
Aqueous extract	300	0.697 ± 0.040*	44.90
Valdecoxib	10	0.247 ± 0.033*	80.47

All values represent Mean ± SEM, n=6 in each group.
** p<0.05, when compared with the control group (ANOVA, followed by Tukey's multiple range test); F_{tab} (5, 30) = 2.53; F_{cal} = 61.67 (Edema volume in ml at 3h).*

(2) Histamine-induced paw edema in mice

Further, petroleum ether and methanolic extract showed maximum inhibition in histamine-induced paw edema (62.86% and 54.84% respectively) as compared to control group, which were comparable with that of standard drug cetrizine (95.24%) (Table 5).

Table 5
Effect of active extracts of Benincasa hispida on histamine-induced paw edema in mice

Group	Dose (mg/kg) (p.o.)	Edema Volume at 30 min (ml)	% Inhibition
1% w/v sodium CMC	10ml/kg	0.930 ± 0.043	---
Petroleum ether extract	300	0.345 ± 0.009*	62.86
Methanolic extract	300	0.420 ± 0.030*	54.84
Cetrizine	10	0.044 ± 0.003*	95.24

All values represent Mean ± SEM, n=6 in each group.
** p<0.05, when compared with the control group. (ANOVA, followed by Tukey's multiple range test); F_{tab} (3, 20) = 3.10; F_{cal} = 189.98 (Edema volume at 30 min).*

(3) Cotton pellet-induced granuloma formation in rats

Petroleum ether and methanolic extracts showed slight reduction in granuloma tissue formation in cotton pellet implanted rats. However, the % inhibition of granuloma formation with methanolic extract (12.8%) and petroleum ether extract (16.5%) were not significant when compared with that of standard drug diclofenac sodium (63.8%) (Table 6).

Table 6

Effect of active extracts of Benincasa hispida on cotton pellet-induced granuloma in rats

Group	Dose (mg/kg) (p.o.)	Weight of dry cotton pellets granuloma (mg)	% Inhibition
1% w/v sodium CMC	10ml/kg	146.9 ± 7.91	---
Petroleum ether extract	300	122.7 ± 6.26	16.5
Methanolic extract	300	128.1 ± 4.46	12.8
Diclofenac sodium	05	53.2 ± 5.72*	63.8

All values represent Mean ± SEM, n=6 in each group.
** p<0.05, when compared with the control group. (ANOVA, followed by Tukey's multiple range test); F_{tab} (3, 20) = 3.10; F_{cal} = 43.61(Weight of dry cotton pellets granuloma in mg).*

DISCUSSIONS

The observations of the present study suggest significant anti inflammatory activity of petroleum extract and methanolic extract of *Benincasa hispida* against Carrageenan and histamine induced paw edema while no significant effect against cotton pellet induced granuloma in rats.

The carrageenan-induced paw edema test is widely accepted as a sensitive phlogistic tool for investigating potential anti-inflammatory agents, particularly the non-steroidal type[17]. The time course of edema development in carrageenan-induced paw edema model in rats is generally represented by a biphasic curve. The first phase occurs within an hour of injection and is partly due to the trauma of injection and partly due to the release of histamine, 5-HT and kinins[18, 19]. Platelet activating factor and arachidonic acid metabolites also play a role during this phase[20]. Prostaglandins (PGs) play a major role in the development of the second phase of reaction which is measured around 3 h times[21, 22]. The presence of PGE_2 in the inflammatory exudates from the injected foot can be demonstrated at 3 h and period thereafter. It has been reported that the second phase of edema is sensitive to the most clinically effective anti-inflammatory agents[23]. The carrageenan-induced paw edema model in rats is known to be sensitive to cyclooxygenase inhibitors and has been used to evaluate the effect of non-steroidal anti-inflammatory agents which primarily inhibit the cyclooxygenase involved in prostaglandins synthesis[24, 25].

In our study, all four extracts, petroleum ether, methanolic, ethyl acetate and aqueous extract possess significant anti inflammatory action as compared to control group. But maximum effect is observed in case of methanolic and petroleum ether extract after 3 h. Hence in the further model only these two extracts were selected for screening. This result indicates that both the extract can prevent the release of inflammatory mediators like histamine, kinin and prostaglandin or may be antagonizing the activity of the mediators after their release.

Histamine exists in bound form in granules (mast cell or basophils) and in free form during

inflammatory process[26, 27]. The H1R-PKC-ERK pathway may play crucial roles in eliciting cytokine production from bronchial epithelial cells stimulated by histamine, leading to airway inflammation[28]. Upon injury to a tissue, histamine causes local vasodilatation and leakage of plasma containing mediators of acute inflammation (Complement, C–reactive protein), antibodies, and inflammatory cells (Neutrophils, eosinophils, basophiles, monocytes and lymphocytes). Injection of histamine causes rapid rise in edema and peak was observed at 30 min. Activation of H_1-receptor may lead to activation of the phosphatidylinositol cycle and associated with inflammatory reactions. So H_1- receptor antagonist can be act as anti-inflammatory agent.

In our study, both petroleum ether and methanolic extract showed significant reduction in paw volume after 30 min of histamine injection which was also comparable with the standard drug Cetrizine (H_1- receptor antagonist). This result indicates that both the extract possess anti-histaminic potential.

The cotton pellet test is considered a model for studies on chronic inflammation[29], and inflammatory granuloma is considered as a typical feature of established chronic inflammatory reaction[30]. This method has been useful for evaluation of steroidal and non-steroidal drugs[31].

In the cotton pellet granuloma model, inflammation and granuloma develops during a period of several days. This model is an indication for the both exudative and proliferative phases of inflammation[32]. Multiplications of small blood vessels; infiltration of macrophages, neutrophils and proliferation of fibroblasts are the characteristic features at the repair phase of inflammation. Such proliferating cells penetrate the exudates, producing a highly vascularized reddened mass known as granulation tissue[33]. Granuloma is a chronic inflammation lesion in the form of a tumor resembling mass[34]. Hence, decrease in granuloma weight indicates the suppression of proliferative phase. Formation of fibrous tissue predominates over fluid accumulation. The inflammatory mass consists of inflammatory cells, area of granulation and fibrous tissue thus representing intermingling of healing and inflammation, which is the main feature of chronic inflammation[34, 35].

In our study, both petroleum ether and methanolic extract failed to inhibit granuloma weight which indicates that both were devoid of anti-proliferative activity and cannot be useful for chronic inflammatory conditions.

In conclude, we can say that both methanolic and petroleum ether extracts of *Benincasa hispida* possess anti inflammatory activity by virtue of inhibiting secondary mediators like thromboxanes and prostaglandins via inhibiting COX enzyme and partly may be due to anti histaminic potential. Due to these effects it can be useful for acute inflammatory conditions. But both the extracts were failed to reduce proliferative action and could not be useful in chronic inflammatory conditions.

ACKNOWLEDGEMENT

We are thankful to Zydus Cadila Healthcare Ltd., Ahmedabad for providing necessary API for the present study as a gift sample.

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