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Original Research Article

ANTI-INFLAMMATORY, ANTIPYRETIC AND ANALGESIC ACTIVITIES OF ETHANOLIC FRUIT EXTRACT *MOMORDICA CHARANTIA* ON ALBINO RATS

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Abstract: *Diverse natural mechanisms against pain, inflammation, and several other infections are varied for medicinal plants. Inflammation is unique biological defense mechanism against harmful stimuli like infections, harmed cells, or irritants. M. charantia is frequently used to treat a variety of illnesses, including fever, discomfort, and inflammation. The purpose of the current study is to identify the anti-inflammatory, antipyretic, and analgesic properties of ethanolic extract of M. charantia. 30 rats were divided into three groups (control, standard and experimental group). Control and standard group contain 5 rats in each group whereas experimental group contained 20 rats. All rats in three groups were treated with carrageenan for induction of oedema, yeast to induce pyrexia and acetic acid to induce pain. Control group rats were treated with normal saline for all the activities. Standard group rats were treated with diclofenac for anti-inflammatory and analgesic activities and paracetamol for antipyretic activity. The fruit extract was injected into abdominal muscles and intraperitoneal tissues. Carrageenan, an anti-inflammatory substance, was used to assess its ability to reduce spell edema, acetic acid was used to study its ability to cause writhing and yeast, was used to demonstrate its ability to pyrexia. The maximal percentage of fruit extract inhibition in anti-inflammatory action was 31.25%. The maximal percentage of fruit extract inhibition against fever was 83.58%. Maximum percentage of inhibition against stomach pain during analgesic action was 31%. Significant findings in anti-inflammatory, antipyretic and analgesic actions were demonstrated at doses of 200 mg/kg, 50 mg/kg, and 100 mg/kg, respectively, when compared to controls. Our research demonstrates and validates the traditional medical usage of M. charantia. It was concluded that ethanolic fruit extract of M. charantia may decrease inflammation, pyrexia and writhing in albino rats effectively.*

Keywords: Anti-inflammatory, antipyretic, analgesic, *Momordica charantia*, pain, fever, fruit extract, diclofenac, writhing, pyrexia

Introduction

Family Cucurbitaceae includes *Momordica charantia L.* (Jia *et al*., 2017). *Momordica charantia L. (Cucurbitaceae)* commonly known as bitter gourd, Karela (In India) and balsam pear is an important medicinal vegetable crop. The tropics of the old world are thought to be where the Karela first appeared. The world's tropical and subtropical areas, including East Africa, Brazil, China, Colombia, Cuba, Ghana, Haiti, India, Mexico, Malaya, New Zealand, Nicaragua, Panama, the Middle East, Central America, and South America, are all known for their extensive cultivation of *M. charantia* (Alam *et al*., 2015). It is widely produced as a food and medicine in India and other countries on the Indian subcontinent, as well as in Southeast Asia, China, Africa, the Caribbean, and South America (Gupta *et al*., 2011). Earlier, oil extracted from the seed of MC, when applied topically to the patients of spondylitis, rheumatoid arthritis and diabetic neuropathy demonstrated relief from pain (Kaur *et al.*, 2021). Its popular medicinal uses focused research so ever and the last few decades several hundred studies that have been carried with *M. charantia*, using modern tools, credit MC with antidiabetic, antiviral,

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antitumor, antileukemic, antibacterial, anthelmintic, antimutagenic, antimycobacterial, antioxidant, antiulcer, anti-inflammatory, hypocholesterolemic, hypotriglyceridemic, hypotensive, immunostimulant, and insecticidal properties (Alyas *et al*., 2022; Basch *et al*., 2003). *M. charantia* pharmacological properties are attributed to each part of the plant, i.e., seeds, roots, leaves, and particularly the unripe fruits. The juice found application for the treatment of many disorders: for example, it is used for joint pain relief and against chronic fever, in cases of jaundice and illnesses of the liver or the digestive system because of its diuretic, laxative and anti-helminthic actions (Bortolotti *et al*., 2019).

Momordica charantia dietary supplementation has been widely studied to treat several diseases, like T2DM, dyslipidemia, obesity and cancer, thus showing that *M. charantia* extracts possess hypoglycemic and lipid-lowering properties, even if clinical trials conducted so far gave inconclusive results (Alam *et al*., 2015). Chronic inflammation is involved in the pathogenesis of different diseases: a clear association has been established for neurodegenerative diseases, obesity, metabolic syndrome, cardiovascular disease, T2DM, and cancer (Alyas *et al*., 2020; Minihane *et al*., 2015). Several evidence indicate that oxidative stress plays a role in chronic inflammatory diseases. Thus, oxidative stress and inflammation are closely related pathophysiological processes that can activate each other (Biswas, 2016). The fruit extract of *M. charantia* was also having analgesic activity in acetic acid induced writhing test and tail immersion test in mice. The oral administration of *M. charantia* extract significantly inhibited acetic acid induced writhing and tail immersion induced pain at dose 500 mg. Methanolic extract of the seeds from unripe fruits of *M. charantia* has been shown to produce a marked dose-dependent analgesic effect in mice and a much weaker effect in rats by using different test systems for the two species (Bala, 2019). The ethanolic extracts of *M. charantia* fruit showed antipyretic effect in a study that was carried out using yeast-induced pyrexia in rats. The antipyretic activity of *M. charantia* was postulated to be due to individual or combined action of bioactive constituents present in it (Kothar *et al.,* 2015). The extracts of *M. charantia* showed a marked antipyretic effect by causing a reduction in yeast-induced fever. The ethanolic extract showed the effect to the same degree as paracetamol (Tohidpour *et al.,* 2017).

Materials and methods

Sample collection

Healthy and fully ripped fruits of *M. charantia* 5 kg were collected from vegetable market of Lahore Pakistan.

Preparation of fruit extract

Firstly, bitter melons were washed with fresh water and dried with clean towel. Then fruits were cut from the center and seeds were completely removed. Secondly bitter melons were dried in room temperature (37^{o}C) for 4 to 5 days. Position of fruits was changed after 3 hrs to protect from fungus. After 5 days' fruits of bitter melon divided into small pieces and grinded the pieces with the help of grinder. After grinding weight of powder was calculated (345 g). Powder of bitter melon was soaked in 700 ml ethanol for 3 days. Jar with bitter melon powder with ethanol were shake in every 2 hrs. After 3 days' extract was filter from ethanol with the help of funnel and filter paper. 250mL extract was obtained after treated with ethanol. The extracts were dried using a flash rotary evaporator. Evaporate the obtained extract on rotatory vacuum evaporator at temperature 40-45^{o}C and atmospheric pressure 100 mm Hg. The extract obtained after rotatory evaporation was placed in 2 petri dishes and petri dishes placed for 24 hrs at room temperature for solidification of extract. After 24 hrs extract collected in falcon tubes with the help of spatula.

Experimental rats

Four to six-weeks-old, male albino rats (145 g to 170 g) were obtained from Central Animal House of University of Veterinary and Animal sciences (UVAS), Lahore, Pakistan. All procedures for using experimental animals were checked and permitted by the Institutional Animal Ethical Committee UOL. They were housed in cages were kept in polyprolene condition for 5 days. All cages were kept natural environment and feeding was continued.

Drugs used in experiment

- Normal saline 400 µl/L
- Distilled water 100 µl/L
- Acetic acid 400 µl/L
- Standard drug diclofenac 100 mg/ kg
- *M. charantia* fruit extract 400 mg/kg
- Carrageenan 400 µl/L (for inflammation)
- Yeast 400 µl/L (pyrexia)
- Standard drug Paracetamol 400 mg/kg

Anti-inflammatory activity model

Total 30 rats divided into 3 groups. Firstly all rat groups were treated with carrageenan. 0.1ml of 1 % carrageenan was injected into sub planter region of paw. Paws size were measured before and after the injection of carrageenan. Group I was considered as control group and normal saline were given to rats with respective doses of 50, 100, 200, 400 µl/L body weight. Normal saline was injected into right hand paw. Volume of paw was measured in mm. Group II was

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considered as standard group. Rats of standard group treated with diclofenac (50, 100, 200 and 400mg/kg). Group III was considered as experimental group and treated with M. charantia fruit extract were 50, 100, 200 and 400 mg/kg (body weight) injected 3 hour after the carrageenan injection. The volume of paw was measured after the interval of 1hr, 2hrs and 3hrs.

$$\text{Anti - inflammatory} = \frac{(Ct - Co) - (Ct - Co) \times 100\ C}{(Ct - Co)}$$

Where Co = reading of paw before carrageenan, Ct= volume of hind paw after carrageenan (Ct-Co)= Volume of hind paw of treated group after carrageenan injection.

Anti-pyritic activity model

Total 30 rats were divided into 3 groups, 5 rats in control and standard groups and 20 rats in experimental group.In standard and experimental design groups, all rats were treated with brewer's yeast with normal saline (mixture) which was injected below the nape of neck (50 mg/kg, 100 mg/kg, 200 mg/kg, and 400 mg/kg body weight). After the interval of 20 hours, pyrexia developed due to Brewer's yeast injection. Group I was considered as control group. In control group, all rats were treated with normal saline (50, 100, 200 and 400µl/L). Group II was considered as standard group. Standard group was treated with paracetamol injection 50 mg/kg, 100 mg/kg, 200 mg/kg and 400 mg/kg in nape of the neck. Group III was experimental group. The experimental group was treated with fruit extract of *M. charantia* (50 mg/kg, 100mg/kg, 200 mg/kg, and 400 mg/kg) injections. After the interval of 0, 1, 2, 3 and 4 hour, temperature was measured with help of thermometer.

Anti-pyritic activity was calculated by using formula:

$$\text{Percent production} = \frac{B - C_b \times 100}{B - A}$$

Where, B = temperature after pyrexia induction , C_b = temperature after 1-, 2- and 3-hour,A = normal body temperature

Analgesic activity model

Acetic acid induces writing which is used to analysis the potential of ethanolic extract on pain. Firstly, all rats treated with fruit extract of *M. charantia* then rats were treated with acetic acid (50, 100, 200 and 400 mg/kg body weight). After all the injection of acetic acid, rats were immediately placed in separated boxes. A writhe was recorded with the help of stopwatch. Group I was considered as control group. In control group, all rats were treated with normal saline (50, 100, 200 and 400µl/L). Group II was considered as standard group. In standard group all rats were treated with diclofenac (50, 100, 200 and 400 mg/kg body weight). After all the injection of acetic acid, rats were immediately placed in separated boxes. A writhe was recorded with the help of stopwatch. Group III was considered as experimental group. The extracts of fruit of *M. charantia* at the dose 50, 100, 200 and 400 mg/kg were injected 1 hour before. A writhe was recorded with the help of stopwatch.

$$\text{Analgesic activity} = \frac{N_c - N_t \ X100}{N_c}$$

Where N_c = control group writhe, N_t = treated group writhe

Results

Anti-inflammatory activity of Momordica charantia fruit extract

The dose of fruit extract of *M. charantia* (50, 100, 200 and 400 mg/kg) exhibited the most significant ($p < 0.05$) % inhibition. Group I (control) left untreated after carrageenan injection, hence, there is 0 % inhibition in this group. Group II showed ($p < 0.05$) significant 5.29±0.32 mean value with 29.3 % inhibition in the edema at the first hour after injection of drug diclofenac. While group III treated with fruit extract of *M. charantia* showed mean values 5.09±0.11, 5.15±0.23, 5.44±0.28 and 4.87±0.23 with percentage inhibition 26.52%, 27.37%, 31.25% and 23.20% respectively at the end of first hour. The fruit extract of *M. charantia* and the standard drug diclofenac showed significant ($p < 0.05$) % inhibition in induced paw oedema of rats after 1-3hrs compared to the control group (Table I, Figure I). The group that received fruit extract of *M. charantia* at a dose level of 200 mg/kg recorded the highest anti-inflammatory effects, which was 31%, 24% and 19% at 1hr, 2hrs and 3hrs respectively.

Table I: Anti-inflammatory effect of fruit extract of *M. charantia* on carrageenan-induced inflammation in albino rats

Groups	Treatment	Pre-inflammation	Post- inflammation	1hr	2hrs	3hrs
Group-I	**Control group**	3.33±0.17	4.05^{c}±0.12	3.74^{b}±0.11	3.60^{c}±0.09	3.53^{b}±0.09
Group-II	**Standard group**	2.94±0.14	5.65^{a}±0.31	5.29^{a}± 0.32	4.97^{a}±0.33	4.41^{a}±0.21
	Treated at (50 mg/kg)	3.15±0.15	5.79^{a}±0.1	5.09^{a}±0.11	4.79^{a}±0.15	4.35^{a}±0.09

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Group-III	**Treated at (100 mg/kg)**	2.86±0.09	4.84^{b}±0.15	5.15^{a}±0.23	4.61^{ab}±0.12	4.22^{a}±0.1
	Treated at (200 mg/kg)	2.99±0.11	5.40^{ab}±0.33	5.44^{a}±0.28	4.74^{ab}±0.22	4.39^{a}±0.16
	Treated at (400 mg/kg)	2.82±0.13	5.31^{ab}±0.28	4.87^{a}±0.23	4.20^{b}±0.07	4.06±0.03
	p-value	0.1012	0.0001	0.0002	0.0001	0.0002

Transcripts on the different means within column differ significantly at p≤0.05

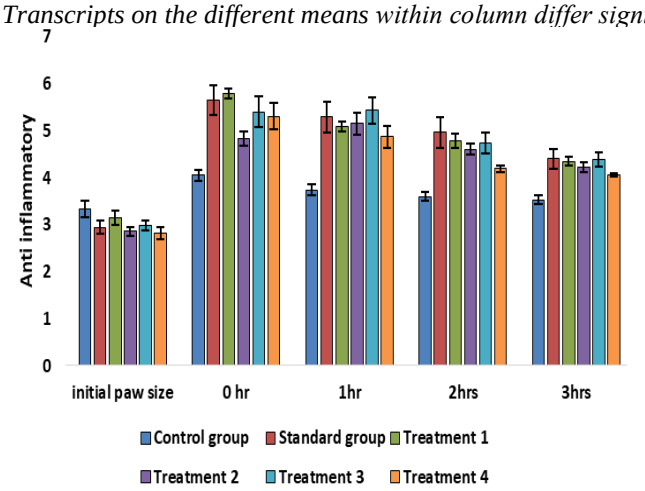


Figure I Anti-inflammatory activity

Paw size of rats (mm); pre-carrageenan and post carrageenan injection at 1-3hrs in Group I, II and III.

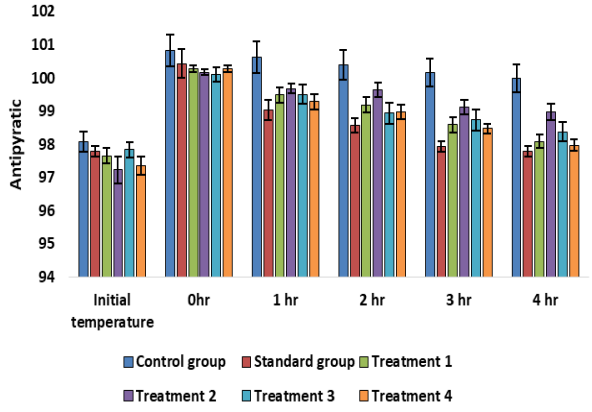
Antipyrectic activity *M. charantia* fruit extract

After one hour of treatment, the groups of albino rats that received paracetamol (100 mg/kg) and *M. charantia* fruit extract dose levels of 50, 100, 200 and 400 mg/kg lowered the rectal temperature to 99.03%, 99.48%, 99.68%, 99.50% and 99.28% respectively (Table II). The *M. charantia* fruit extract at the dose level of 400mg/kg caused the highest antipyretic activity, which reduced pyrexia by 78.76% in the 4th hour. This change was higher than that caused by the reference drug paracetamol which reduced pyrexia . The group that received fruit extract of *M. charantia* at a dose level of 400 mg/kg recorded the highest antipyretic effects, which was 33%, 44% 61% and 78% at 1hr, 2hrs, 3hrs and 4hrs respectively.

Table II : Antipyretic effect of fruit extract of *M. charantia* on yeast-induced pyrexia in Albino rats.

Groups	Treatments	Initial temperature	0hr	1hr	2hrs	3hrs	4hrs
Group-I	**Control group**	98.08±0.3	100.82±0.47	100.62^{a}±0.47	100.40^{a}±0.45	100.15^{a}±0.42	99.98^{a}±0.42
Group-II	**Standard group**	97.77±0.16	100.43±0.44	99.03^{b}±0.3	98.57^{c}±0.22	97.93^{c}±0.17	97.78^{c}±0.17
	Treated at (50 mg/kg)	97.65±0.23	100.27±0.11	99.48^{b}±0.23	99.18^{bc}±0.23	98.58^{bc}±0.24	98.08^{c}±0.2
	Treated at (100 mg/kg)	97.22±0.4	100.17±0.08	99.68^{b}±0.14	99.63^{ab}±0.22	99.12^{b}±0.21	98.97^{b}±0.26
Group-III	**Treated at (200 mg/kg)**	97.83±0.24	100.10±0.23	99.50^{b}±0.29	98.93^{bc}±0.31	98.73^{bc}±0.32	98.37^{bc}±0.29
	Treated at (400 mg/kg)	97.35±0.28	100.27±0.1	99.28^{b}±0.24	98.97^{bc}±0.23	98.47^{bc}±0.15	97.97^{c}±0.17
	p-value	0.279	0.5468	0.0152	0.0017	< 0.0001	< 0.0001

Transcripts on the different means within column differ significantly at p≤0.05



Temperature of rats (F^{o}) at 1-4 hours post yeast injections in control, standard and experimental fruit extract of *M. charantia*

Analgesic activity of *M. charantia* fruit extract

Group I was control group and rats of control group treated with normal saline were shown 18.83±0.91 writhing mean with 0% inhibition. Rats of group II were treated with diclofenic and shown 18.83±0.4 writhing mean with 0% inhibition. Rats of group III treated with fruit extract of *M. charantia* 50, 100, 200 and 400 mg/kg shown 12.83±0.48, 14.33±0.76, 16.00±0.58 and 16.33±0.76

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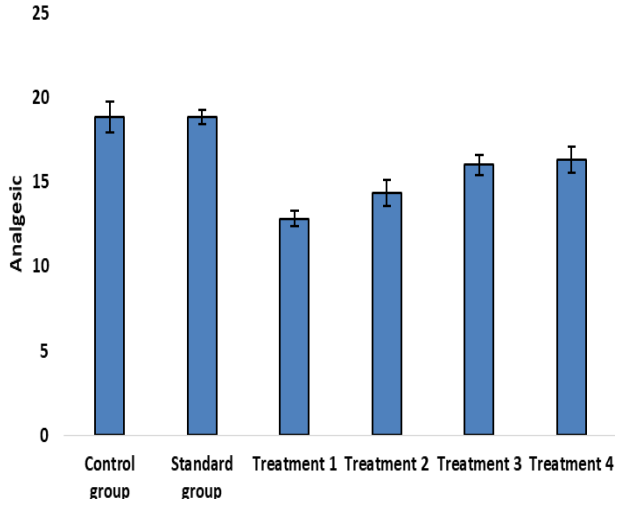
writhing mean with 31.86%, 23.89%, 15.03 and 13.28% inhibition recpectively. The writhe inhibitory effects of the fruit extract of *M. charantia* ranged from 13.28% to 31.86%. The analgesic effect induced by the fruit extract of *M. charantia* was dose-related (50, 100, 200 and 400 mg/kg) lowered writhing 31.86%, 23.89%, 15.03% and 13.28% (Table III). The significant analgesic activity of fruit extract of *M. charantia* was ($p< 0.0001$). The group that received fruit extract of *M. charantia* at a dose level of 50mg/kg recorded the highest analgesic effects, which was 31.86%.

Table III: Analgesic effect of *M. charantia* on acetic acid-induced writhing in albino rats

Treatments	Analgesic Time	Writhing (%)
Control group	18.83_{d}±0.91	0
Standard group	18.83_{a}±0.4	0
Treated at (50 mg/kg)	12.83_{cd}±0.48	31.86
Treated at (100 mg/kg)	14.33_{bc}±0.76	23.89
Treated at (200 mg/kg)	16.00_{b}±0.58	15.03
Treated at (400 mg/kg)	16.33_{b}±0.76	13.28
p-value	< 0.0001	

Transcripts on the different means within column differ significantly at $p \leq 0.05$



Fgure III Analgesic activity

Discussion

The current research aimed to evaluate *M. charantia* fruit extract's anti-inflammatory, antipyretic, and analgesic effects in rats. Inflammation is the body's complex defensive response to dangerous substances such as germs or injured cells (Asija *et al.*, 2014). Our study revealed, the group that received ethanolic fruit extract of *M. charantia* at a dose level of 200 mg/kg recorded the highest anti-inflammatory effects, which was 31%. Previous study evaluated the ability of the extract to reduce the size of oedema produced by carrageenin and formaldehyde, suggests that it contained chemical component (s) that may be active against inflammatory conditions. The inflammatory action induced by carrageenan may be as a result of step-wise release of the inflammatory mediators such as histamine, serotonin and bradykinin which are released in the early phase of inflammatory reaction, and prostaglandins which are released late in the acute phase (Mondal *et al.*, 2021).

Pain is the normal physiological response to a noxious chemical, associated with invasive procedures (Alyas *et al.*, 2020; Oladele *et al.*, 2019). The results obtained from our study showed that the ethanolic fruit extract of *M. charantia* possess a significant analgesic effect on the various pains in rats. In previous study observed a significant inhibitory effect by fruit extract in the writhing test. It was suggested that the analgesic effect of the extract may be peripherally mediated. The extracts also showed a significant effect in the tail-immersion tests (centrally acting analgesic drugs elevate the pain threshold of animals toward heat and pressure). The effect of the extracts on this pain model indicates that it might be centrally acting (Fan *et al.*, 2014)

Fever refers to an increase in body temperature beyond the regulatory set point of 36.5 - 37.5ºC (Kumar and Pathak, 2019). This increase in temperature triggers muscle tone and shivering. Fever signifies several illnesses. Symptoms of fever include sweating, chills, a sensation of cold and other subjective sensations. The absence of these symptoms when the temperature is high can be a pointer to a serious illness (Székely and Garai, 2018). According to our results after one hour of treatment, the groups of albino rats that received *M. charantia* fruit extract dose levels of 400 mg/kg lowered the rectal temperature 99.28%. The *M. charantia* fruit extract at the dose level of 400mg/kg caused the highest antipyretic activity, which reduced pyrexia by 33.90% in the first hour. The extract caused a better hypothermal activity against yeast-induced pyrexia in rats. The ethanolic extracts of *M. charantia* fruit

showed antipyretic effect in previous study that was carried out using yeast-induced pyrexia in rats. The antipyretic activity of *M. charantia* was postulated to be due to individual or combined action of bioactive constituents present in it. Results of present study showed that *M. charantia* fruit extract generally exhibited in vivo antipyretic activities in rats, which was evidenced by a reduction in rectal temperature against fever (Boy *et al.*, 2018).

Conclusion

In light of the results, it was revealed that the ethanolic fruit extract of *M. charantia* have remarkable analgesic, anti-inflammatory and antipyretic activities. The analgesic, anti-inflammatory and antipyretic activity of *M. charantia* may be due to the individual or combined action of bioactive constituents present in it. The findings will be helpful for further phytochemical and pharmacodynamic investigations to find the active constituents responsible for the activity, which may explore some new and promising leads. Therefore, it may presage for future studies to better understand the mechanism of such actions scientifically. Secondary metabolites found in plants will aid in the discovery and isolation of compounds that can be employed in clinical trials in the future.

Conflict of interest

The authors declared absence of conflict of interest.

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