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Antipyretic activity of aqueous ethanolic extract of *Chenpodium album* whole plant in albino rats

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ABSTRACT

The present study was done to evaluate antipyretic activity of aqueous ethanolic extract of *Chenpodium album* (bathua) whole plant against Brewer's yeast induced pyrexia in albino rats. Paracetamol and ibuprofen were used as standard drugs. For evaluation of antipyretic study the animal were divided in seven groups, i.e group-I (Normal control :given normal saline at dose of 10ml/kg/p.o), group-II (Disease control; given 20% Brewer's yeast at dose 10ml/kg/sc) ,group-III (Standard control -I; given paracetamol at dose 100mg/kg/p.o), group-IV (Standard control-II; given ibuprofen at dose 100mg/5ml/p.o), group V-VII (Test groups; were given aqueous ethanolic extract of *Chenpodium album* in 100, 200 and 400mg/kg/p.o doses, respectively). The results indicated that *Chenpodium album* whole plant extract reduced temperature (39.90%) at dose 400mg/kg/p.o as compared to standard control groups. Furthermore, acute toxicity study test did not show any sign of toxicity during 14 days of observation period. Phytochemical screening of aqueous ethanolic extract of *Chenpodium album* revealed the presence of phenolics, flavonoids, alkaloids and glycosides. This was concluded that concentrations of these phytochemical agents in the crude extract contributed in antipyretic activity.

INTRODUCTION

Humanity has three great enemies fever, food crisis and war. Of these, the greatest and the most horrible is fever [1]. Fever is an impressive engine, which nature brings into the world for the take-over of her enemies [2]. In the recent dictionary of thermal physiology (IUPS Thermal Physiology Commission, 2001) fever can be defined as" A state of elevated core temperature (Tc) due to an elevation of the set-point of Tc actively established by heat producing and heat conserving thermo effectors [1]." Today Fever is considered as discomfort for the patient. Since older time's physician have applied different physical method for lowering temperature, in early 1600s, Cinchona bark was used as antipyretic but in the 18th century extreme use of cinchona created shortage and started a search for substitutes. Reverend Stone sent a report from English willow of "feverbark" on antipyretic action in 1763. In 1838 Salicylic acid prepared from the glucoside salicin, which is willow bark active component, in 1853 acetylsalicylic acid (aspirin) was prepared and become available in market as antipyretic drug in 1899. Ever since, various antipyretics have been introduced. Antipyretic effect of acetaminophen is latest. While precursor such as acetanilide and phenacetine were introduced in19th century [3]. Today commonly used antipyretics are acetaminophen, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs).

MATERIALS AND METHODS

Plant Collection

Chenpodium *album* was chosen for the evaluation of antipyretic activity in albino rats. Fresh whole plant was collected from local fields of Lahore Pakistan and its samples were identified and authenticated by Mr. Bashir a botanist at the Institute of Punjab University Lahore, Pakistan. Samples were preserved at the Herbarium of the Laboratory of Riphah international university Lahore Pakistan with Voucher no RIU-Pcol 1-3-2013. Plant material was dried under shade for fifteen days and then ground into coarse powder. The powdered sample was taken in a clean, round bottomed flasks (3 L) and soaked in 70% ethanol. The flask was sealed by aluminum foil and kept for a period of three days with occasional shaking and stirring. The mixture was then filtered through muslin cloth followed by whatman No.1 filter paper and the filtrate was concentrated and evaporated to dryness at 39 °C in rotary evaporator. Semi solid viscous extract so obtained was stored in air tight containers and was kept in refrigerator after proper labeling.

Experimental Animals

Albino Wistar albino rats of either sex weighing 180-200 g were used for this study. The animals were provided by Riphah International University where they were kept under controlled conditions of temperature (23) °C, humidity (50) % and 12 h light-dark cycles. All the animals were acclimatized for seven days before the study. They had free access of standard pellets as basal diet and water.

Drugs and Chemicals

Paracetamol and Ibuprofen raw powders were donated by Abbott's Laboratory, Karachi upon special request. Brewer's yeast was obtained from market. All other reagents used were of analytical grade and were prepared in distilled water.

Equipments

Analytical balance (yoke galvano FA2004B), Vortex mixture (VM-300), Ultraviolet spectrophotometer (1900 yoke galvano), Rotary evaporator (A-1000s japan), Digital thermometer (citizen)

Solubility test

Solubility test was performed with different solvent water, ethanol, normal saline and DMSO in ratio of (1:1) and (1:5).

Phytochemical screening

Different secondary metabolites are present in plant materials which exhibit various pharmacological activities. Crude extract was subjected to phytochemical analysis for identification of Alkaloids, Flavonoids, Phenol, Carbohydrates, Protein, Cardiac glycosides, Steroids, Tannins and Saponins. Following methods were used for analysis

Qualitative tests

Saponin test

Five ml of distilled water was added to the extract in a test tube and was shaken. Foams Formation was indicative for the presence of saponin.

Steroid test

2ml of the ethanolic extract, 2 ml Chloroform and sulphuric acid was added and red color indicated the presence of steroids. 2ml of extract, 2ml chloroform, sulphuric acid and 2ml of acetic acid was added in test tube. Greenish color indicated the presence of steroids.

Terpenoids test

2ml extract and 2ml chloroform was evaporated to dryness. 2ml sulphuric acid was added. Grayish color indicated the terpenoids.

Alkaloids test

Extract and eight ml of 1% hydrochloric acid were added and boiled on water bath for 10 minutes. The mixture was cooled, filtered and divided into four test tubes. Few drops of Mayer's reagent, Hager's reagent, Wagner'reagent and Dragendroff were added to test tubes. Presence of turbidity, yellow color, reddish brown color and precipitate formation indicated alkaloids.

Protein test

2ml Millon's reagent was added to extract in test tube and heated. Red color indicated protein. 2ml Ninhydrin reagent was added to extract. Violet color indicated the presence of protein.

Carbohydrates test

2ml of Benedict's reagent was mixed with extract in test tube. Reddish brown precipitates indicated the carbohydrates. 2ml of Molisch's reagent was added to extract and was shaken and mixed with 2ml of sulphuric acid. Violet ring indicated the presence of carbohydrates.

Phenol and tannins test

2ml of 2% ferric chloride was added to extract in test tube. Bluish green or black colors were considered the presence of phenol and tannins.

Glycosides test

Liebermann's 2ml chloroform and 2ml acetic acid was added to extract and mixture was cooled in ice then added 2ml sulphuric acid. Change in color from violet to blue to green indicated presence of glycosides. Salkowski's 2ml chloroform and 2ml sulphuric acid was added to extract. Reddish brown color indicated presence of glycosides [4].

Flavonoids test

Half gram of the ethanolic extract of the plant was dissolved in 1 ml ethanol and then 1 ml of 1% KOH was added. Dark yellow color indicated the presence of flavonoids. To confirm the result, 1 ml of aluminum chloride was added to the extract. A change of the mixture to yellow color confirmed the results [5].

Acute toxicity

Acute oral toxicity study was carried out as per the guidelines of Organization for Economic Co-operation and Development (OECD425). The rats were divided into four groups with six animals in each group. Single dose of extract (500, 1000, 2000 and 3000mg/kg p.o.) was administered to overnight fasted rats, while control group received normal saline (10mL/kg) [6]. Animal were Observed for 30 min, 1, 2 and 4 hours for skin changes, morbidity, aggressiveness, sensitivity of the sound, pain as well as respiratory movement [7], behavioral and neurological changes such as tremors, convulsions, salivation, diarrhea, sleep, lacrimation and feeding behavior as a sign of acute toxicity. The observation was further extended up to 14 days to see any sign of mortality [6].

Induction of pyrexia

Antipyretic activity test was found by brewer's yeast induced pyrexia model. The rats were injected with brewer's yeast. Due to the presence of pyrogenic substances inside the body, pyrexia/fever occurred in the animals. All Albino rats were randomly divided into six groups containing six rats in each group and fasted overnight before the experiment with free access to water. The normal body temperature of each rat was measured rectally with the digital thermometer at predetermined intervals and observations were recorded. After measuring the basal rectal temperature by digital thermometer, animals were injected subcutaneously with 10 ml/kg of 20% w/v brewer's yeast. Rats were then kept separately in separate cages for 18 hours. Rectal temperatures of the rats were recorded again after 18 hours of brewer's yeast injection. Rats showing increase of temperature of at least 0.5°Cto 1°C were selected for the experiment only [8].

Administration of extract

The animals were divided into seven groups, each group

contained 6 animals. Group I (Normal control) received normal saline (10 mL/kg). Group II was positive control. Group III (standard control I) was given 100 mg/kg/p.o of paracetamol [9]. Group IV (standard control II) received ibuprofen 100mg/5ml/p.o, and group V-VII were administered with ethanolic extract at the doses of 100mg/kg/p.o, 200mg/kg/p.o and 400 mg/kg/p.o, respectively [10]. After the drug was administered, the temperature of all the rats in each group was recorded at 1, 2, 3 and 4 h [9] . The mean temperature was calculated for each group and compared with the positive control group. The percent decrease in pyrexia was calculated with following formula:

% Decrease in pyrexia= T induced-Cn/ T. induced-T Normal ×100

Where T-induced represented body temperature after induction of pyrexia, Cn was body temperature at 1, 2, 3 and 4 h intervals and T normal indicated normal body temperature [11] .

RESULTS

Solubility test

Aqueous ethanolic extract of *Chenpodium album* whole plant was dissolved into distilled water, ethanol, normal saline and DMSO in ratio of 1:1 and 1:5 and results were tabulated in table 1.

Phytochemical analysis of Ca.E

Different constituents were found in extract. The results obtained after analysis are mentioned in table 2.

Effect of Chenpodium album extract (Ca.E) on Brewer's yeast induced hyperpyrexia in rats

Experimental studies indicated that pyrexia level in normal control was 37.03±0.08, 37.15±0.10, 37.28±0.12, 37.13±0.10, 37.10±0.09°C in at 0,1,2,3 and 4hr while in disease control group hyperpyrexia was recorded as 38.60±0.17, 38.48±0.17, 38.43±0.17, 38.40±0.19, 38.18±0.13°C at 0,1,2,3 and 4 hour interval. The body temperature recorded in standard control-I at 0, 1, 2, 3 and 4 hour interval was 38.75±0.21, 38.43±0.21, 38.10±0.20, 37.83±0.17 and 37.65±0.16°C, respectively and in standard control-II it was 38.53±0.11, 38.25±0.12, 37.95±.0.12, 37.67±0.12and 37.43±0.13°C, respectively. The result of Ca.E at 100mg/kg dose at 0hr was 38.42±0.23°C, at 1hr was 38.22±0.23°C, at 2hr was 38.10±0.23°C, at 3hr was 37.97±0.23°C and at 4 hr it was 37.83±0.24°C. The result of Ca.E at 200mg/kg dose was 38.47±0.23, 38.37±0.20, 38.22±0.10, 38.08±0.0.18, 37.85±0.18°C at 0, 1, 2, 3 and 4 hour, respectively. The antipyretic result of Ca.E at 400mg/kg dose was 39.18±0.17, 39.05±0.18, 38.85±0.18, 38.63±0.18, 38.35±0.18 °C at 0, 1, 2, 3 and 4 hour, respectively. Brewer's yeast induced pyrexia in rats.

Table 1. : Solubility of aqueous ethanolic extract of *Chenpodium album* in different solvents

Solvent	Ratio	Presence
Distilled water	1:1	Soluble
	1:5	Soluble
Ethanol	1:1	Not soluble
	1:5	Soluble
Normal saline	1:1	Soluble
	1:5	Soluble
DMSO	1:1	Soluble
	1:5	Soluble

Table 2. : Phytochemical analysis of Ca.E

Phytochemical test	Presence
Saponin	Not present
Steroid	Present
Terpenoid	Not present
Alkaloids	Present in Hager's test Present in Wager's test
Protein	present
Carbohydrate	Present
Phenol and tannin	Present
Glycosides	Present
Flavonoids	Present

Table 3. : Percentage decrease in pyrexia with Ca.E in rats

Groups	Normal rectal temperature (°C) before yeast administration	Induced temperature (°C) 18 hr. after injection (0hr)	Rectal temperature (°C) after drug administration (orally)		%decrease in pyrexia
Standard control I	37.07±0.09	38.75±0.21	1hr	38.43±0.21	19.05%
			2hr	38.10±0.20	38.69%
			3hr	37.83±0.17	54.76%
			4hr	37.65±0.16	65.48%
Standard control II	37.03±0.18	38.53±0.11	1hr	38.25±0.12	18.67%
			2hr	37.95±0.12	38.67%
			3hr	37.67±0/12	57.33%
			4hr	37.43±0.13	73.33%
Ca 100mg/kg	36.67±0.18	38.42±0.23	1hr	38.22±0.23	11.43%
			2hr	38.10±0.23	18.29%
			3hr	37.97±0.23	25.71%
			4hr	37.83±0.24	33.71%
Ca 200mg/kg	36.75±0.06	38.47±0.20	1hr	38.37±0.20	5.81%
			2hr	38.22±0.18	14.53%
			3hr	38.08±0.18	22.67%
			4hr	37.85±0.18	36.04%
Ca 400mg/kg	37.10±0.15	39.18±0.17	1hr	39.05±0.18	6.25%
			2hr	38.85±0.18	15.87%
			3hr	38.63±0.18	26.44%
			4hr	38.35±0.18	39.90%

There was remarkable reduction in pyrexia in standard control groups. It represented that Ca.E reduced the pyrexia at different doses and the percentage decrease in temperature was calculated from formula. The standard control groups reduced the pyrexia with high significance i.e P <0.01 (**). Similarly, Ca.E at 100,200 and 400mg/kg significantly reduced the pyrexia with level of significance i.e. P<0.05(*) when compared to positive control group.

Values were expressed as mean±SEM (n=6) two way ANOVA test was applied and P>0.05 was considered non-significant, P<0.05, significant (*), P<0.01, more significant (**) and P<0.001(***) highly significant. All extract Treated groups and standard groups were compared with positive control group.

Acute toxicity test

Acute oral toxicity study showed that, Ca.E up to 3000mg/kg/p.o body weight did not show any signs of behavioral or neurological toxicity. A normal body weight gain was observed and there was no relative difference in weights of control as well as treated rats. In acute toxicity study, the ethanolic extract of plant did not show lethality up to the dose level of 3000 mg/kg/p.o, which indicated the safety of crude extract.

DISCUSSION

Fever is autonomic, behavioral and endocrine response controlled by the brain. In many clinical conditions, fever may occur due to the presence of the substances called pyrogens that may be endogenous or exogenous. Common pyrogens are microorganisms and toxins. Numerous toxins, infections and other mediators induce endogenous pyrogen. Gram negative bacteria produce endotoxin which is endogenous pyrogen. Cell wall of Gram positive bacteria has peptidoglycan which produces pyrogens. Exogenous pyrogens act mostly by endogenous pyrogens formation through host cells stimulation generally monocytes and macrophages. The endogenous pyrogens produced locally or systemically then enter in the circulation and generate fever. Various interleukins (IL) IL-I, 1L-6, TNF-c (tumor necrosis factor) and INF-c (interferon) are fever producing cytokines. IL-1 is an important pyrogen that induces fever in 10 minutes on reaching the hypothalamus [12]. These cytokines act on brain blood vessels to generate PGE2 [13].

Table 4. : Effect of different doses of Chenpodium album extract (Ca.E) on Brewer's yeast induced hyperpyrexia in rats

Groups	Normal rectal temperature (°C) before drug administration	Induced temperature (°C) 18 h after injection (0hr)	Rectal temperature (°C) after drug administration (orally)			
			1hr	2hrs	3hrs	4hrs
Normal Control	37.00±0.13	37.03±0.07	37.15±0.10	37.20±0.12	37.13±0.10	37.10±0.09
Positive control	37.06±0.10	38.60±0.17	38.48±0.17	38.43±0.17	38.40±0.19	38.18±0.13
Standard I	37.07±0.09	38.75±0.21	38.43±0.21*	38.10±0.20*	37.83±0.17**	37.65±0.16**
Standard II	37.03±0.18	38.53±0.11	38.25±0.12*	37.95±0.12**	37.67±0.12**	37.43±0.13**
Ca100mg/kg	36.67±0.18	38.42±0.23	38.22±0.23	38.10±0.23*	37.97±0.23*	37.83±0.24*
Ca200mg/kg	36.75±0.06	38.47±0.20	38.37±0.20	38.22±0.18*	38.08±0.18*	37.85±0.18*
Ca400mg/kg	37.10±0.15	39.18±0.17	39.05±0.18	38.85±0.18	38.63±0.18	38.35±0.18*

Values were expressed as mean±SEM (n=6), * ($p< 0.05$), ** ($p< 0.01$) significantly different when compared with the corresponding value of positive control group

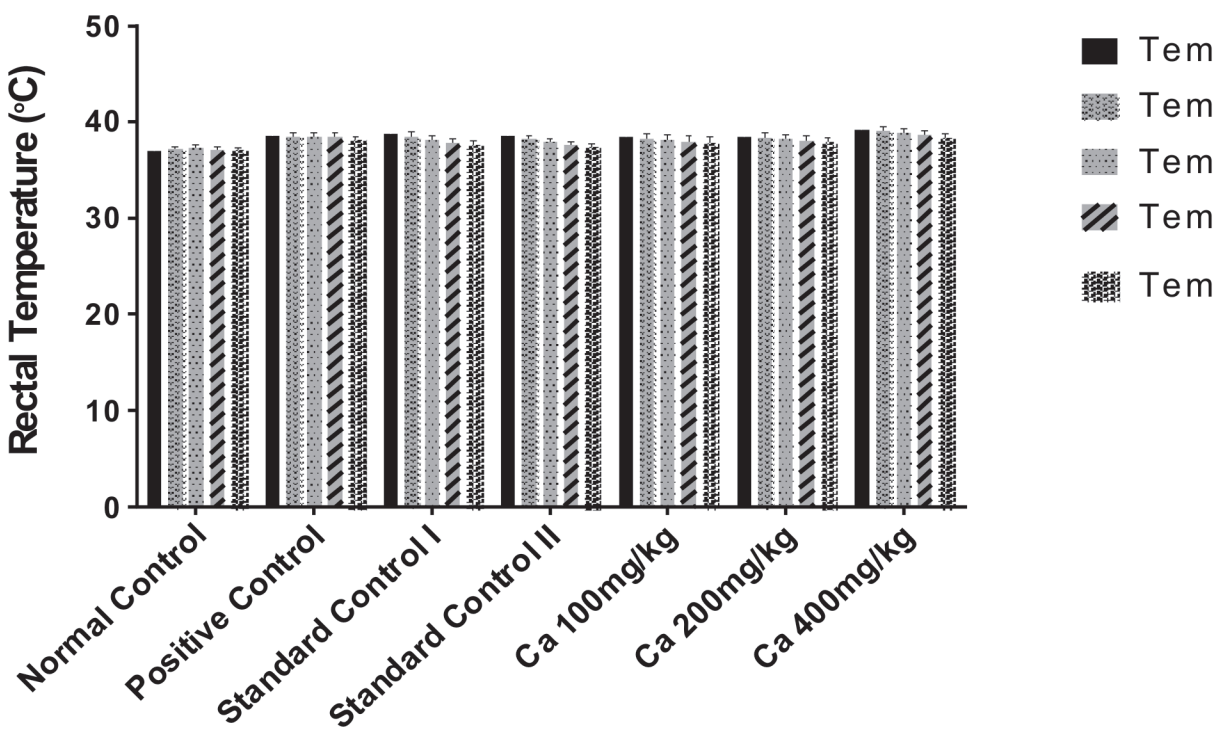

Fig 1. : MEffect of different doses of *Chenpodium album* extract (Ca.E) on Brewer's yeast induced hyperpyrexia in rats

Table 5. : Acute toxicity test of Ca.E on behavioral changes in rats

Days	Behavioral changes	Presence
30minutes	Skin changes	No
1hour	Aggressiveness	No
2hour	Sensitivity to sound	No
4hour	Pain	No
24hour	Sleep	No
	Feeding	No
	Salivation	No
	Breathing	No
7 day	Aggressiveness	No
	Sensitivity to sound	No
	Pain	No
	Sleep	No
	Feeding	No
	Salivation	No
	Breathing	No
	Skin changes	No
14 day	Aggressiveness	No
		No
	Sensitivity to sound	No
	Pain	No
	Sleep	No
	Feeding	No
	Salivation	No
	Breathing	No
	Skin changes	

Yeast-induced pyrexia is called pathogenic fever and its mechanism comprises the prostaglandins production, which effect thermoregulatory neurons and causes increase in body temperature. The prostaglandins production is most effective pyretic agent. The anti-pyretic effect of non-steroidal anti-inflammatory drugs is due to inhibition of synthesis and release of PGE2 near preoptic anterior hypothalamus. A number of plant extracts modify enzymes of cyclooxygenase pathway, which inhibit leukotriene and prostaglandin synthesis by inhibiting COX-1 and COX-2 pathways [9]. In fever this set point elevates and a drug like paracetamol does not influence body temperature when it is elevated by the factors such as exercise or increase in ambient temperature. A commonly available drug such as diclofenac, ibuprofen or mefenamic acid has the therapeutic effect, to reduce inflammation and pyrexia. However, these drugs may produce adverse effect such as hepatotoxicity. Therefore, natural products have been alternative for treatment of hyperpyrexia [14]. Therefore, it is considered that the inhibition of prostaglandin biosynthesis by aqueous ethanolic extract of whole plant of *Chenpodium album* may be the cause for the anti-pyretic activity. Alkaloids like boldine have the ability to block and inhibit the synthesis of prostaglandin E2 [15] similarly, flavonoids like baicalin have been shown to exert antipyretic effect by suppressing TNF [16]. Some secondary metabolites such as flavonoids, tannins, steroids and triterpene also contributed in antipyretic effect [15].

Aqueous ethanolic extract of *Chenpodium album* produced significant ($P<0.05$) antipyretic effect in dose dependent manner. The significant antipyretic effect was observed at 400 mg/kg/p.o which was comparable to standard drugs paracetamol and ibuprofen. Phytochemical screening of aqueous ethanolic extracts of *Chenpodium album* revealed the presence of phenolics, flavonoids, alkaloids and glycosides. Furthermore, flavonoids and tannins are known to inhibit prostaglandin synthesis. The presence of flavonoids, tannins and other chemical component are responsible for the observed antipyretic effect [17].

CONCLUSION

On the basis of results obtained, it is concluded that aqueous ethanolic extract of *Chenpodium album* exhibited antipyretic effect in yeast induced pyrexia in albino rats. There was decreased in fever by the use of the extract in different doses. There were no remarkable behavioral changes in the treated rats, during the acute toxicity study period. No mortality was recorded during the observation period following administration of the extract at the doses of 500, 1000, 2000 and 3000 mg/kg body weight.This study indicated that plant extract can be used in pyrexia condition because this study has scientifically proved the conventional use of this plant in treatment of pyrexia in conventional medicines. However, further phytochemical and toxicological investigations are needed to verify the active ingredients responsible to the

therapeutic effects of and the potential side effects.

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