

Diuretic and anti-diarrheal potential of four fruit extracts of *Capsicum annum* L.

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Abstract: Capsicum has been an important part of diet since centuries and has been widely used traditionally for ailments. The objective of the present analysis was to determine the diuretic and antidiarrheal potentials of four variations of *Capsicum annum* L. fruits available in local market of Karachi, Pakistan. It belongs to family Solanaceae and extracts were prepared in 95% ethanol and was given in doses of 200 and 400mg/kg and the activity was correlated with commonly used diuretics and anti-diarrheal further reinforcing its conventional use. Fruits extracts were evaluated for anti-diarrheal properties in castor-oil induced diarrhea to confirm its activity. The diuretic activity of the 95% ethanolic extracts of *Capsicum annum* L. was assessed based on diuresis of 24 hr. collected through metabolic cage. Urinary excretion of water and electrolytes (Na⁺ and K⁺) is significantly increased by the standard diuretic drug furosemide, which is comparable with the extract. The anti-diarrheal effects of 95% ethanolic extracts of *Capsicum annum* L. were examined by castor oil induced diarrhea and all varieties of *Capsicum annum* L. significantly inhibited the number of defecations.

Keywords: Capsicum, bell pepper, capsaicin, diuretic, anti-diarrheal.

INTRODUCTION

Diarrhea is the prime source of mortality and morbidity in children in countries which are in developing phase, which contributes majorly in worldwide healthcare problems (Nithya, 2021). Similarly, in adults, heart failure, kidney problems, high blood pressure, edema, liver problems and glaucoma are emerging to be very common. Many people belonging to the low socio-economic class cannot afford medicine that can cure such diseases. Hence, they wait for the cure to come to them naturally, without any therapeutic intervention (Maramag, 2013).

The traditional use of natural products that involves medicinal plants has enormously upgraded the pharmacotherapy of various diseases and provided principal compounds that have substantial therapeutic worth in different pathological conditions (Khan *et al.*, 2020). There has been an increasing pattern of prevalence of pathologies such as cancer, diabetes and cardiovascular disease. Several studies exhibited that there has been an association between utilization of vegetables and fruits and the progression of such ailments (Yahia *et al.*, 2011). Epidemiological investigations disclosed that fruits and vegetables contain antioxidant compounds which can eliminate a free radical chain reaction. Consequently, it has the potential to avert chronic diseases (Basma *et al.*, 2011). Metabolites such as phenolic acid, alkaloid,

flavonoid, capsaicinoid and carotenoid are plant's secondary metabolites (Biswas *et al.*, 2011).

Numerous medicinal plants that hold antidiarrheal activity are accessible all over the world (Ojha and Mahara, 2022). Positive antidiarrheal properties of these plants are due to the occurrence of different plant compositions which includes flavonoids, alkaloids, saponins, terpenoids, steroids, and tannins. Remarkably, occurrence of tannins and flavonoids in herbs may help in augmented reabsorption of colon water and electrolytes (Yacob *et al.*, 2016, Mehesare *et al.*, 2019). Likewise, there are various plants that cause diuretic potential (de Souza *et al.*, 2021) and plants that showed diuretic activities were found to be rich in flavonoids, saponins and polysaccharide (Fu *et al.*, 2014). It is known to possess plentiful biological qualities inclusive of being diaphoretic and diuretic. Metabolite outlining of aqueous concentrate of such plants was executed by liquid chromatography. This guided to the isolation of numerous bioactive plant chemicals associated with several categories of metabolites like phenolic acids, phenolic glycosides, flavonoids and anthocyanin (Sulaiman *et al.*, 2020).

Capsicum annum L. is the major part of Mediterranean Diet, which has gains its important due to the presence of high percentages of carotenoid and flavonoid content and regarded as the most powerful food that is effective against chronic diseases and ageing (Wang *et al.*, 2014). Universally pepper is acknowledged for its elevated

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nutritional worth, health and therapeutic value (Aguilar-Meléndez *et al.*, 2021) also, it is abundant in vitamins and minerals, has anti-infective and antineoplastic properties. Chili pepper has protective and therapeutic profile for many disorders such as diverse form of cancer, rheumatoid arthritis, rigid joints, bronchitis, flu and headache, arthritis, cardiac arrhythmias and many other diseases (Saleh *et al.*, 2018). Research has shown that capsicum fruit has anti-oxidants in abundance (Faustino *et al.*, 2007) as well as rich in capsaicinoids. This article will investigate the role of *Capsicum annum* L. specie as anti-diuretic and antidiarrheal.

MATERIALS AND METHODS

Plant Materials

Four variations of fruit of *Capsicum annum* L. (Bell pepper) were procured from local shop in Karachi. Numerous varieties were identified by a taxonomist and kept safe and separated with voucher numbers [Green bell pepper or *Capsicum annum* (CAG / 01-15), red bell pepper (CAR / 02-15), Orange bell pepper (CAO / 03-15), Canary belt, yellow bell pepper (CAY / 04-15). 98% EtOH (Ethanol) was used to soak all 1 kg of above-mentioned varieties of *Capsicum annum* L. for 7 days, the filtration of the EtOH extract was carried out to attain concentrated crude extract by using rotary evaporator, percentage yield was 5.5-7.5% of each extract.

Animals

Either sex male or female Wistar albino rats (150-180g) were used. Rats were acquired from animal house managed at the Department of Pharmacology, University of Karachi at 26.5±2°C temperature and 45-55% relative humidity. Animals were assimilated for 7 days in cages. Food and water were provided to the animals at 25±1°C with a 12-hour light dark cycle. Institutional guidelines were followed for the use of animals. Animals were allocated to various sets so that treatment can be carried out in experiment.

Ethical approval

The study was approved by Institutional Bioethical Committee through Ethical approval No.IBC KU-210 / 2021 of University of Karachi.

Chemicals

Substances used in the experiment are: Castor oil, Loperamide (Janssen-Cilag), Furosemide (Pfizer)

Preparation of extracts

The four kinds of capsicum (1Kg each) were separately washed carefully and cut in small fragments and were then soaked in 3L 98% ethanol solvent individually for seven days. The subsequent mixtures were filtered with Whatman's filter paper (Azmir *et al.*, 2013). Filtered mixture was dried at 40°C under vacuum with the help of rotary evaporator. The ethanol extracts were stored at 8°C

and kept at room temperature for execution of pharmacological actions on animals (Walum, 1998).

Acute toxicity test

Ethanol extracts of *Capsicum annum* are designated as practically non-toxic (5-15g/kg body weight) (Lagu and Kayanja, 2013). Acute toxicity testing of the extracts was executed in mice as done by OECD Guideline 423 (Schlede, 2002). Seven mice were selected randomly and fasting was carried out overnight. Furthermore, Mice in each group were given doses 1000, 2000 and 3000 mg/kg of the ethanol extracts orally. Control group of mice was administered with normal saline (10ml/kg) PO. Toxicity and mortality were observed for 6h and 24 h respectively.

Diuretic activity

Rats were administered with (Sodium Chloride 0.9%, 5ml/100 g), to bring about uniform diuresis (Kau *et al.*, 1984). Extracts were given to seven group of rats (n=7). Vehicle (0.1mL/100 g, p.o.) was administered to control group and positive control group was given Furosemide (10mg/kg, p.o.). At the end of the treatment procedure, each metabolic cage was used to keep the animals individually and volume of urine was gauged after 30, 60, 90, 120 min and at 12th and 24th hour.

Antidiarrheal activity

Overnight fasting of Wistar rats (180-200) g was carried out. The likely antidiarrheal agents (Loperamide) and test samples (*Capsicum annum* extracts, 200 & 400 mg/kg) to be analyzed were orally administered by gavage. One hour after administration of the drug/extract, 1 ml of castor oil was orally given for the induction of diarrhea. Floors were covered with non-wetting paper sheets and animals were kept in cages. Hourly change of non-wetting paper sheets was done, and observations are recorded up to 6th hour. The stools were collected through gravity. A numeric score was designated for the consistence of stool. Normal stool was assigned the value of (1) while semi-solid was (2) and similarly watery stool was (3) (Singh *et al.*, 2013).

The mean total number of feces (dry and wet diarrheal droppings) was assessed and equated with the negative control group. The total score of diarrheal feces for the negative control group was taken as 100%. The percent inhibition of total defecation and that of diarrhea were calculated using the following formulas:

$$\begin{aligned} \text{\% inhibition of defecation} &= \frac{\text{Total No. of feces in negative control} - \text{Total No. of feces in treated group}}{\text{Total No. of feces in negative control}} \times 100 \end{aligned}$$

STATISTICAL ANALYSIS

Data were described as mean ± standard error of mean (SEM). Statistical analysis was carried out through Statistical Package for the social sciences (SPSS), version

20 (SPSS Inc. Chicago, IL, USA). Data were evaluated by one-way analysis of variance (ANOVA) along with Tukey HSD. Values were considered significantly different when $*=p < 0.05$ (significant), $**=p < 0.01$ (more significant), $***=p < 0.001$ (highly significant)

RESULTS

Acute toxicity results

Capsicum annum and its varieties extracts exhibited no toxicity as no incidents of mortality were seen till the dose 3000mg/kg. So, all four extracts were deemed innocuous and used in the doses of 200mg/kg and 400mg/kg for the comparative pharmacological activities.



Fig. 1: Varieties of *Capsicum annum* L., 1.CAG, 2. CAR, 3. CAO, 4. CAY.

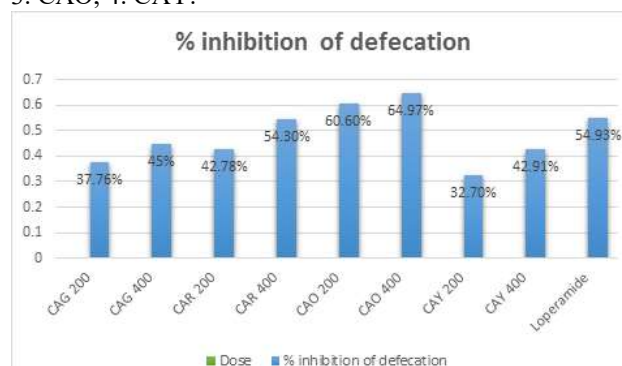


Fig. 2: Shows the percentage inhibition of defecation when compared with the control

Diuretic activity

Most substantial diuretic activity was shown by CAY at 200 mg/kg dose which initiated at 60 min and persisted for 24 hrs. CAP and CAR exhibited substantial results at 120 min till 24hr. (table 1). Similar effect was detected at 400mg/kg dose. Urine volume was remarkably increased after 24 hrs.

Anti-diarrheal activity

All extracts in both doses (200 & 400mg/kg) revealed significant antidiarrheal effect and showed dose dependent activity (table 2).

On comparison with control, the most substantial effect was displayed by CAO in all extracts, which was found to be more effective than standard drug at 200 mg/kg. Whereas by titrating the dose up to 400mg /kg the activity enhanced.

Anti-diarrheal activity of CAR was found to be dose dependent as it was significant as compared to the control at 200mg/kg and found to be more effective by increasing the doses till 400mg/kg which is closely related to the activity of Loperamide.

Percentage inhibition of feces is relatively high at high doses of all varieties of *Capsicum* as compared to low doses which clearly indicates the dose dependent response.

DISCUSSION

Diuretics are majorly used for the modulation of volume of body fluids and its composition and are majorly used for variety of medical indications including cirrhosis, heart failure, hypertension and nephritic syndrome. Diuretics derived from plants or Natural sources are used widely due to its low toxicity and considered as a safe and cost effective alternative as compared to synthetic dosage forms (Amuthan *et al.*, 2012, Bhat and Sharma, 2022).

Apart being used as a food ingredient, bell pepper is utilized widely in age old and alternative medicine particularly for the treatment of various symptoms such as diarrhea, dysentery and stomach ache (Tchiegang *et al.*, 1999, Boxman *et al.*, 2007, Akram *et al.*, 2021), indicating that it might exhibit diuretic and anti-diarrheal activity. However, scientific evidence is still missing so the current research was directed to screen the diuretic and anti-diarrheal action of the different variations of bell pepper. For the conduction of this study ethanolic extracts of four species of *Capsicum annum* L. (bell pepper), Including green (CAGG), red (CARR), orange (CAOO) and yellow (CAYY) extracts were prepared and further investigated for the possible diuretic and anti-diarrheal potential. Metabolic cage was used to assess diuretic effect, whereas, castor oil induced diarrhea was used to indicate the anti-diarrheal activity of the extracts.

Metabolic cage method has been widely used worldwide as a consistent examining approach for diuretic agents that is grounded upon the selection of a group of homogenous rats with a same water and electrolytes excretory pattern (Kau *et al.*, 1984). The method is employed widely for determining the diuretic activity of medicinal plants, number of medicinal plants have been reported till date which exerts a dose dependent diuretic activity (Gupta and Arya, 2011).

Natural diuretics known to exert their actions by increasing the electrolyte concentration of urine along with urinary output, and the oral administration of all the extracts of *Capsicum annum* L. were found to have diuretic potential as compared to the negative control when tested in metabolic cage. The diuresis onset of action was found to be at 12h for most of the peppers

Table 1: Diuretic activity of *Capsicum annum* varieties in rats

Group	Dose mg/kg	Urine in ml					
		30 min	60 min	90 min	120 min	12 Hrs.	24 Hrs.
Control		0.00	0.35±0.16	0.20±0.07	0.40±0.07	0.56±0.14	0.90±0.20
CAG	200	0.00	0.00	0.00	0.45±0.13	3.30±0.14**	5.68±0.10**
CAG	400	0.00	0.16±0.10	0.33±0.11	0.66±0.15	6.26±0.13**	10.80±0.20**
CAR	200	0.00	0.75±0.18	1.00±0.13	1.38±0.21**	8.66±0.66**	15.36±0.40**
CAR	400	0.00	0.00	0.16±0.11	0.75±0.18	4.93±0.19**	9.60±0.26**
CAO	200	0.00	0.00	0.00	0.00	4.58±0.30**	9.86±0.21**
CAO	400	0.00	0.50±0.06	2.08±0.24**	2.63±0.18**	8.13±0.22**	16.31±0.49**
CAY	200	0.00	1.83±0.21**	2.25±0.38**	4.01±0.43**	8.14±0.71**	14.15±0.39**
CAY	400	0.31±0.20**	1.75±0.21**	4.00±0.58**	4.66±0.42**	13.9±0.35**	22.91±0.58**
Furosemide	40	0.56±0.01	0.87±0.02	0.89±0.30	0.98±0.13	1.89±0.15	44.11±0.15**

Observations at 30 min, 60 min, 90 min, 120 min, 12h, 24h, Values are mean ± SEM, N=7, *= $p < 0.05$, **= $p < 0.01$, *** = $p < 0.001$

Table 2: Anti-diarrheal activity of *Capsicum annum* varieties in rats

Group	Dose (mg/kg)	Number of feces	
		Total number of feces at 6 h	% inhibition of defecation
Control		23.33±0.58	
CAG	200	14.50±0.34**	37.76%
CAG	400	12.83 ± 0.17**	45%
CAR	200	13.33±0.56**	42.78%
CAR	400	10.66 ± 0.33**	54.30%
CAO	200	9.16±0.40**	60.60%
CAO	400	8.16 ± 0.60**	64.97%
CAY	200	15.66±0.42**	32.7%
CAY	400	13.33 ± 0.49**	42.91%
Loperamide	10	10.50±0.22	54.93%

Values are mean ± SEM, N=7, *= $p < 0.05$, **= $p < 0.01$, *** = $p < 0.001$

which remained significant till 24 hours for all bell peppers. However, CAR 200 showed onset of action at 120 min, CAO 400 at 90 min and CAY showed onset on action at 30 min at both doses which remain significant up till 24h respectively. (CAY 400>CAY 200>CAO 400>CAR 200>CAG 400>CAR 400>CAG200). The results clearly indicate that the diuretic action produced by all bell pepper were more significant to the standard diuretic furosemide at 12h., which remain significant at 24h when compared with the control.

The flavonoid contents in different species of *Capsicum annum* L. is very high and it is believed that flavonoid compounds exhibited significant diuretic effect (Nayak *et al.*, 2017). Ethanolic extracts of the four varieties of *Capsicum* species utilized in this study indicated a high content of flavonoids with considerable variation in the flavonoid content of the different varieties (Olatunji and Afolayan, 2019). Therefore, it may be said that the principal difference in diuretic activity might be the reflection of differential flavonoid contents of bell pepper.

There is a complicated set of interrelationships is present between the cardiovascular system, the kidneys, the CNS

(Na⁺, appetite and thirst regulation) and the tissue capillary beds (distribution of extra cellular fluid volume), so that agitation at one of site can influence all the remaining sites. The diuretic effect of *Capsicum annum* L. might result in regional blood flow stimulation or vasodilation which is initial or by tubular water reabsorption inhibition of water and anions, the result in both cases being diuresis and it can be co-related that its strong hypertensive action is contributed to the increased amount of excretion of sodium and water. All the varieties of *Capsicum annum* L. exhibited confirmed diuretic effect and the present study supports its ethno pharmacological use as diuretic.

Moreover, we demonstrated for the very first time the anti-diarrheal effects of four kinds of *Capsicum annum* L. by castor oil induced diarrhea. Traditionally, the roasted capsicum and shallots leaves are widely used to treat diarrhea in Indonesia (Yamamoto and Girsang, 2021). The constituents which are responsible for potent antidiarrheal activity of medicinal herbs are tannins, alkaloids, flavonoids and terpenoids (Komal and Rana, 2013, Kritis *et al.*, 2020). The diarrheal activity of Castor oil is attributed to ricinoleic acid which encourages

irritation and inflammation of the intestinal mucosa, which causes prostaglandin release. This brings about a change in mucosal fluid and transport of electrolytes, thereby inhibiting the reabsorption of NaCl and water, thereby causing hyper secretory response and diarrhea (Gaginella and Phillips, 1975).

The antidiarrheal activity of *Capsicum annum* L. Species by castor oil induced diarrhea is displayed in table 2 and percentage inhibition of defecation is shown in fig. 2. Both the positive control (Loperamide) and treatment groups (administered different varieties of bell pepper, i.e., CAGG, CARR, CAO and CAYY), decline the number of defecation and the highest % inhibition of defecation is found to be significantly high at the both doses of CAO which is more significant than positive control group. Also, CAO showed dose dependent effect, the increment of dose up to 400 mg/kg the value is found to be more significant than the positive control group (Loperamide). CAO is reported to have greater amount of flavonoids when compared to CAY and CAG, which might be responsible for its highly significant anti-diarrheal potential (Sun *et al.*, 2007).

The antidiarrheal activity of all varieties of *Capsicum annum* L. may be credited to the presence of flavonoids as they have intestinal motility inhibition ability and hydro-electrolytic discharges that are modified in this intestinal condition. *In vitro* and *in vivo* studies indicate that flavonoids has a profound ability to hinder the intestinal secretory response instigated by prostaglandins E2 (de Medina *et al.*, 1997). Furthermore, flavonoids have found to be high antioxidant potential which is assumed accountable for the inhibitory effects wielded upon numerous enzymes that are involved in arachidonic acid metabolism (Dias *et al.*, 2021). In addition, occurrence of tannins in bell pepper might also be accountable for the anti-diarrheal effects. Earlier studies have established antidiarrheal activity of tannin comprising plant extracts (Sairam *et al.*, 2003). The antidiarrheal action of tannins is attributed to denaturing proteins resulting in protein tannates, further making the intestinal mucosa more impervious and reduces secretion (Esteban *et al.* 2009). Phytochemical investigation of the extract by means of diverse methods showed the existence of flavonoids and tannins, which may be partly accountable for the antidiarrheal activity of ethanol extracts of bell pepper.

Our study justifies the diuretic and anti-diarrheal possibility of four variations of *Capsicum annum* L. which was not reviewed before. There are no epidemiological studies showing intake of bell pepper may be beneficial for diuretic and anti-diarrheal potential, despite our data showing prominent effects of bell pepper as diuretic and anti-diarrheal, Capsicum intake may be advantageous in various human diseases related to urine retention and diarrhea.

CONCLUSION

The present experimental study explains for the very first time the potential diuretic and anti-diarrheal activities of native Pakistani variety of *Capsicum annum* L.

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