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*Cenchrus ciliaris* for multiple gas-  
trointestinal disorders**

# Ethnopharmacological evaluation of *Cenchrus ciliaris* for multiple gastrointestinal disorders

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## Abstract

This study was conducted to rationalize the traditional uses of *Cenchrus ciliaris* in gastrointestinal disorders using *in vivo* and *ex vivo* assays. The antidiarrheal effect was evaluated in rats by the castor oil-induced diarrheal model. *C. ciliaris* (100, 300 and 500 mg/kg) reduced the castor oil-induced diarrhea significantly. Another study carried out in mice to determine the intestinal transit rate showed that *C. ciliaris* (100 and 200 mg/kg) inhibited the transit rate significantly. *Ex vivo* assay demonstrated that *C. ciliaris* (0.01–1 mg/mL) relaxed the spontaneous and K<sup>+</sup> (80 mM)-induced contractions, like verapamil. The crude extract (75, 100 and 150 mg/kg) also exhibited significant antiemetic activity in chicks. These results indicate the presence of antispasmodic, antidiarrheal and antiemetic activities in *C. ciliaris*, thus providing the scientific basis for its traditional uses.

## Introduction

*Cenchrus ciliaris* L. (Poaceae) is a highly nutritious grass famous for its traditional uses as galactagogue, emollient, purgative and diuretic. It is used in renal colic, tumor, wound, and sores, menstrual disorders and urinary tract infections (Mahmood et al., 2011; Ashraf et al., 2013).

Several pharmacological studies showed the presence of antifungal, antibacterial (Singariya et al., 2012; Eloff, 1998), anthelmintic (McGaw et al., 2000), antischistosomal activity (Sparg et al., 2000), COX I and II inhibitory activity (Jager et al., 1996; Zschocke and Van Staden, 2000), dysmenorrheal and uterine relaxing activity (Lindsey et al., 1999). Four steroids named 4,22-stigmastadienen-3-on, fagarsterol,  $\delta$ 4-sitosterol-3-one, and ethyl iso-allochololate were isolated from the *C. ciliaris* (Singarya et al., 2012).

Despite its traditional uses in various ailments such as gastrointestinal, *C. ciliaris* is not well-studied plant in terms of pharmacological exploration.

The present study was aimed to evaluate and provide the therapeutic basis for its use in gastrointestinal ailments and to provide its mechanistic basis using various experimental models.

## Materials and Methods

### Plant collection and extract preparation

A collection of *C. ciliaris* (whole plant) was done in August 2014 from the fields and roadsides of the Bahawalpur, Pakistan, and identified by Dr. Zafar Ullah Zafar, a taxonomist from the Institute of Pure and Applied Biology, Bahauddin Zakariya University. The voucher specimen number Stewart F. West Pak. 116 (9) was deposited there. The plant material was shade dried, removed any foreign material by manual picking and grinded into a coarse powder by an herbal grinder. The powdered plant material was undergone maceration by using 70% ethanol (v/v) at room temperature for 7 days with random shaking. The soaked material was filtered twice, once through a muslin cloth and



secondly through filter paper (Whatman No. 1). The same procedure was repeated thrice and mixed all the three filtrates. The rotary evaporator (Rotavapor, BUCHI Labortechnik AG, Model 9230, Switzerland) was used to evaporate the solvent and to collect the crude extract (dark brown in color) of *C. ciliaris* with percent yield of 28.5%

The solvent-solvent extraction was done according to the method described previously using equal quantities of dichloromethane and water (Bashir et al., 2006). The dichloromethane and aqueous fractions were yielded 12 and 26% respectively. Ethanol crude extract and fractions of *C. ciliaris* were preserved in an amber colored glass container at -20°C.

#### **Animals and housing condition**

Animals including, Sprague-Dawley rats (180-200 g), Balb<sup>c</sup> albino mice (18-24 g, 3-5 weeks old), young chicks (80-90 g, 10-12 days old) and local breed rabbits (1.0-1.6 kg, 8-12 months old), either male and female, were purchased locally and placed in the animal house of the Department of Pharmacy, Bahauddin Zakariya University. Animals were kept under a controlled temperature of 25-28°C with 12/12 dark-light cycle with free access to standard diet and *ad libitum* water. Before the start of experiments, animals were kept on fasting with free access to water. All experiments were performed by approval of the Ethical Committee of the Bahauddin Zakariya University with reference number EC/04PhDL/2013, and studies designed according to the rules of Institute of Laboratory Animal Resources, Commission on Life Sciences (National Research Council, 1996).

#### **Chemicals and drugs**

Atropine sulfate, loperamide and verapamil hydrochloride were purchased from the Sigma Chemical Co. (USA). Chlorpromazine was kindly gifted by Highnoon Pharmaceutical (Pvt.) Ltd. (Pakistan). Copper sulfate was purchased from Scharlau Chemie (Spain). Chemicals of physiological solutions including potassium chloride were from Sigma Chemical Co. Calcium chloride, glucose, magnesium chloride, magnesium sulfate, potassium dihydrogen phosphate, sodium bicarbonate, sodium dihydrogen phosphate and sodium chloride were obtained from the Merck (Germany), ammonium hydroxide, sodium chloride and sodium hydroxide from BDH Laboratory Supplies (England). All the chemicals used were of analytical grade and distilled water was used to made fresh dilutions on the day of the experiment.

#### **Preliminary phytochemical analysis**

The crude extract of *C. ciliaris* was explored for the possible presence of important phytochemical constituents including alkaloids, anthraquinones, coumarins, glycosides, flavonoids, saponins, sterols, tannins, and

terpenes (Tona et al., 1998).

#### **Castor oil-induced diarrhea**

This test was accomplished by following the methods used in earlier available studies (Mehmood et al., 2014). After an overnight fast, rats (♂/♀) were allocated into five groups (n=5/group) and were kept in individual cages. The Group I received 10 mL/kg/p.o of normal saline and served as the control group. The Group II was administered with loperamide 10 mg/kg/p.o and was considered as a standard group. The remaining three groups received the crude extract of *C. ciliaris* in respective doses of 100, 300, and 500 mg/kg, p.o. After an hour of treatment, rats of all groups received castor oil 10 mL/kg orally. Afterwards, enclosures of all animals were examined for the existence of usual diarrheal droppings. The total of wet feces in each cage was noted, and all the five groups were compared to the standard and control.

#### **Charcoal meal transit test**

The study was carried out following a previously established method, using mouse as an experimental animal (Mascolo et al., 1994; Maiti et al., 2007). Mice were kept on overnight fasting, and divided into four groups with n=5. Group A was administered with normal saline (10 mL/kg, p.o.), and Group B was administered with atropine sulfate (3 mg/kg, i.p); these groups were represented as control and standard, respectively. Next, two groups, C and D received the crude extract (100 and 200 mg/kg, p.o.) respectively. After 15 min of treatment each mouse received charcoal meal (0.3 mL p.o.). Charcoal meal comprises of 10% gum acacia, 15% starch, and 10% vegetable charcoal dissolved in distilled water. Mice were euthanized after 30 min of administration of charcoal meal, and dissected to isolate the small intestine. The total length of the small intestine was measured and compared with the distance between the pylorus and front of the charcoal, and charcoal transport percentage was calculated.

#### **Antiemetic activity**

Chick emetic model with slight modification was used to assess the antiemetic activity of the crude extract of *C. ciliaris* (Janbaz et al., 2014). Five groups of chicks were made with n=5 groups. Each chick was located under a large glass beaker to acclimatize for 30 min. Group 1 chicks (control group) received normal saline orally. The Group 2 was administered with chlorpromazine 150 mg/kg/p.o and was considered as a standard group. The chicks of experimental (Group 3, 4 and 5) received an oral dose of crude extract of *C. ciliaris* at the doses of 75, 100 and 150 mg/kg (solubilized in normal saline). After 15 min of treatment, all groups received orally 50 mg/kg of copper sulfate. Then the number of retches (an emetic action without emitting



gastric material) was counted for the next 10 min and the percent inhibition was calculated as:

$$\% \text{ inhibition} = [(A-B)/A] \times 100$$

Where, "A" represents the frequency of retching in control, and "B" represents experimental groups

#### **Isolated rabbit jejunal tissue preparation**

Preparation and calibration of tissue

To evaluate the possible presence of antispasmodic action, and to find out the mechanism of antidiarrheal and antimotility activities of the crude extract of *C. ciliaris*, isolated rabbit jejunal tissue preparations were used. Rabbits were sacrificed, peritoneum cavity incised and the jejunum was resected out. Mesenteries were removed, and small (2-3 cm) segments of jejunum were prepared to mount in isolated tissue baths (Janbaz et al., 2015). These tissues were then attached in isolated tissue bath (10 mL) having Tyrode's solution, aerated with carbogen (95% O<sub>2</sub> and 5% CO<sub>2</sub>), and kept at room temperature i.e. 37°C. A 1 g preload tension was applied and isotonic spontaneous contractions were noted using an isotonic transducer (MLT0015) coupled with the Power Lab data acquisition system (AD Instruments, Australia) attached with a computer using LabChart software version 6.0 (AD Instruments). The tissues were permitted to acclimatize for about 30 min before the addition of any test material.

#### **Effects on spontaneous contractions**

After 30 min of tissue acclimatization, the crude extract and fractions (organic and aqueous) were added in a cumulative manner to find out the presence of gut modulatory effects on spontaneous contractions of the rabbit jejunum. Isolated jejunum preparations showed spontaneous contractions in a rhythm and allowed to test the spasmolytic (relaxant) effect without the use of an agonist (Janbaz et al., 2012). The relaxant effect of test substances was observed as the spontaneous contractions of preparation showed percent change, recorded immediately before and after the addition of test substances.

The mechanism of spasmolytic effect was evaluated by studying the effect of the test substances against K<sup>+</sup> (80 mM)-induced contractions. The concentration-dependent inhibitory responses of the crude extract of *C. ciliaris* were observed by cumulative addition, and the antispasmodic effect was showed as a percentage of the control contractions just prior to the application of the test material.

#### **Effect on the high K<sup>+</sup>-induced contraction**

To assess the mechanism of spasmolytic activity of the test substances, it was mediated through calcium channel blockade, a high concentration of K<sup>+</sup> (80 mM), as KCl, was added to depolarize the tissue preparations (Farre et al., 1991). The added K<sup>+</sup> (80 mM) produced a

sustained contraction. Plant crude extract, fractions, and standard were then added in a cumulative manner to attain concentration-dependent inhibitory responses (Van-Rossum, 1963). The relaxation of intestinal preparations, precontracted with K<sup>+</sup>, was stated as a percent of the control precontraction.

#### **Confirmation of calcium antagonistic activity**

The calcium antagonist effect of the crude extract was further confirmed by allowing the tissue to get stabilized in normal Tyrode's solution, which was then exchanged with calcium-free Tyrode's solution (containing EDTA 0.1 mM) for 30 min to make the tissue calcium free. The solution was further changed with K<sup>+</sup>-rich and Ca<sup>2+</sup>-free Tyrode's solution. Control concentration-response curves (CRCs) of calcium were attained after 30 min of incubation period. After the control calcium CRCs found superimposable (usually after two cycles), the tissue was pretreated with the crude extract for 60 min to test the possible calcium channel blocking effect. The CRCs of calcium (CaCl<sub>2</sub>) were reconstructed in the presence of different concentrations of crude extract.

#### **Statistical study**

The EC<sub>50</sub> value (median effective concentrations) with 95% CI was used to analyze spontaneous and induced contractions in tissue preparations. The concentration-response curves (CRCs) were analyzed by using non-linear regression. The data of *in vivo* activities i.e. antidiarrheal, charcoal meal GIT transit and antiemetic activities were analyzed by using one-way ANOVA followed by Dunnett's t-test, a value of p<0.05 was considered significant.

## **Results**

Phytochemical analysis of *C. ciliaris* ethanolic extract showed the presence of important constituents like alkaloids, anthraquinones, flavonoids, glycosides, phenols, saponins and tannins.

#### **Castor oil-induced diarrhea in rats**

The crude extract of *C. ciliaris* showed marked anti-diarrheal activity at the doses of 100, 300 and 500 mg/kg when tested against castor oil-induced diarrhea in rats in comparison with the control. The control group (saline) showed no protection from diarrhea, while standard group (loperamide) showed 100% protection at 10 mg/kg dose. The rats in groups III, IV, and V pretreated with increasing doses of the plant extract showed 37, 61 and 77% protection at 100, 300 and 500 mg/kg respectively (Table I).

#### **Charcoal meal GI transit activity**

The charcoal meal propulsion in the mice gastrointestinal tract has been reduced by ethanolic extract of

Table I		
Castor oil-induced diarrhea in rats		
Treatments	Average No. of wet feces	% Protection
Saline (10 mL/kg) plus castor oil (10 mL/kg)	12.4	0
Crude extract (mg/kg) plus castor oil (mL/kg)		
100 + 10	7.8 ± 0.2	37.1
300 + 10	4.8 ± 0.1 <sup>a</sup>	61.3
500 + 10	2.8 ± 0.1 <sup>b</sup>	77.4
Loperamide (mg/kg) plus castor oil (mL/kg)		
10 + 10	1.2 ± 0.1 <sup>b</sup>	89.9

Data are presented as mean ± SEM; <sup>a</sup>p<0.01 and <sup>b</sup>p<0.001 vs saline plus castor oil treated group (one-way analysis of variance followed by Dunnett's test)

*C. ciliaris* at the oral doses of 100 and 200 mg/kg, in comparison with the control group. Standard drug i.e. atropine sulfate at the dose of 10 mg/kg showed an alike reduction in the intestinal transit of charcoal meal in mice. The traveled distance in the control group was 36 ± 0.5 (mean ± SEM, n=5) of the full length of small intestine, while the standard group significantly reduced the movement (p<0.001 vs control) of the charcoal meal to 70.8%. The crude extract at the dose of 100 and 200 mg/kg moved the charcoal meal to the level of 39.2% (p<0.01) and 63.9% (p<0.001), respectively when compared with the control group (Table II).

#### Antiemetic activity

The ethanolic extract of *C. ciliaris* showed significant dose-dependent antiemetic effect i.e. 19.9%, 43.8% (p<0.001) and 64.9% (p<0.001) at the doses of 75 mg/kg, 100 mg/kg and 150 mg/kg respectively, comparable to chlorpromazine (150 mg/kg) as standard drug (80.4%; p<0.001) (Table III).

#### Effect of extract on isolated rabbit jejunal preparations

The administration of the ethanolic extract of *C. ciliaris*

Table II		
Charcoal meal gastrointestinal transit test		
Groups	Movement of charcoal meal (cm)	
	Mean ± SEM	% Inhibition
Control (charcoal meal)	36.0 ± 0.5	-
Atropine (3.0 mg/kg)	10.5 ± 0.2 <sup>b</sup>	70.8
Crude extract (100 mg/kg)	21.9 ± 0.1 <sup>a</sup>	39.2
Crude extract (200 mg/kg)	13.0 ± 0.1 <sup>b</sup>	63.9

Values are expressed as mean ± SEM; n=5; <sup>a</sup>p<0.01, <sup>b</sup>p<0.001 when compared with vehicle-control

Table III		
Anti-emetic activity of <i>Cenchrus ciliaris</i>		
Groups	No. of retches ± SEM	Inhibition of emesis (%)
Control (10 mL/kg)	64.4 ± 1.2	Nil
Chlorpromazine (150 mg/kg)	12.6 ± 0.4 <sup>c</sup>	80.4
Crude extract (75 mg/kg)	51.6 ± 0.6 <sup>a</sup>	19.9
Crude extract (100 mg/kg)	36.2 ± 0.8 <sup>b</sup>	43.8
Crude extract (150 mg/kg)	22.6 ± 0.3 <sup>c</sup>	64.9

<sup>a</sup>p<0.05, <sup>b</sup>p<0.01 and <sup>c</sup>p<0.001 vs control showing significant and most significant values by using student's t-test respectively

to the isolated rabbit jejunal preparations exhibited relaxant effect at a tissue bath concentration range of 0.01-1 mg/mL, with EC<sub>50</sub> of 0.149 mg/mL (95% CI: 0.11-0.19; n=5). The crude extract also relaxed K<sup>+</sup> (80 mM)-induced spastic contractions at a concentration of 1 mg/mL with EC<sub>50</sub> of 0.254 mg/mL (95% CI: 0.18-0.34; n=5) (Figure 1A). Among the fractions of *C. ciliaris*, dichloromethane extract also relaxed spontaneous and K<sup>+</sup> (80 mM)-induced contraction at the tissue bath concentration of 0.01-1 mg/mL with EC<sub>50</sub> value of 0.06 mg/mL (95% CI: 0.05 to 0.09; n=5) and 1 mg/mL with EC<sub>50</sub> 0.22 mg/mL (95% CI: 0.20 to 0.24; n=5) respectively (Figure 1B). The aqueous fraction did not show any significant relaxation of spontaneous and K<sup>+</sup> (80 mM)-induced contraction even at the highest tissue bath concentration i.e. 10 mg/mL (Figure 1C). The relaxant effect of crude extract and dichloromethane extract was found similar to the effect of the standard Ca<sup>2+</sup> channel blocker, verapamil, which relaxed the spontaneous and K<sup>+</sup> (80 mM)-induced contractions with respective EC<sub>50</sub> value of 0.213 μM (95% CI: 0.126 to 0.360; n = 4) and 0.158 μM (95% CI: 0.123 to 0.204; n = 5) (Figure 1D).

To evaluate the potential of Ca<sup>2+</sup> antagonistic effect, the crude and dichloromethane extracts were also tested on the control calcium concentration-response curves. The medium was made Ca<sup>2+</sup> free and the spontaneous contractions of the isolated jejunal preparations were eliminated completely but the addition of Ca<sup>2+</sup> (0.1-6.4 mM) in a cumulative manner caused the contractile activity to be restored in tissue and maximal contraction was attained at maximum tissue bath concentration (6.4 mM) of Ca<sup>2+</sup>, which was presumed to be 100%. Subsequently, the jejunal tissue incubated with crude and dichloromethane extract at a concentration of 0.1 and 0.3 mg/mL for 35 min shifted the concentration-response curve (CRC) of Ca<sup>2+</sup> towards right. These effects were found comparable to those produced by verapamil (0.1-0.5 μM), (Figure 2; n=3-4).

## Discussion

*C. ciliaris* showed a dose-dependent protecting effect

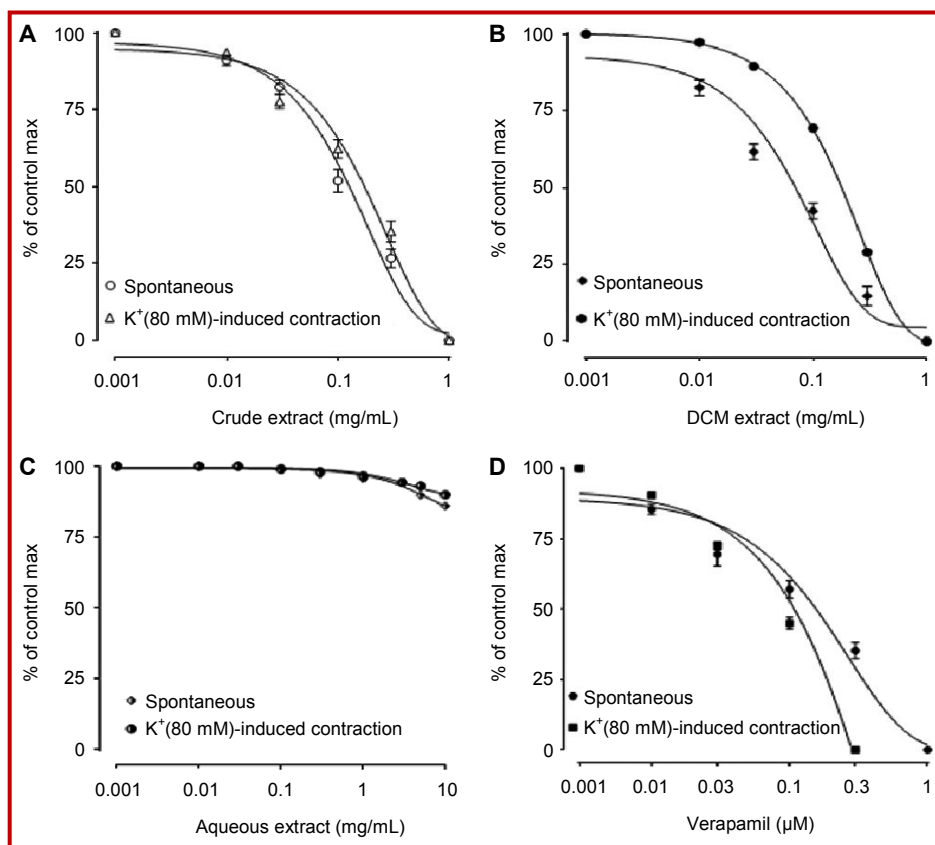


Figure 1: Dose-dependent inhibitory effect of crude extract (A), DCM extract (B) and aqueous extract (C) against spontaneous contractions and K<sup>+</sup> (80 mM)-induced contractions in comparison to verapamil (D) in isolated rabbit jejunum preparations. Values shown are mean  $\pm$  SEM (n=5-6)

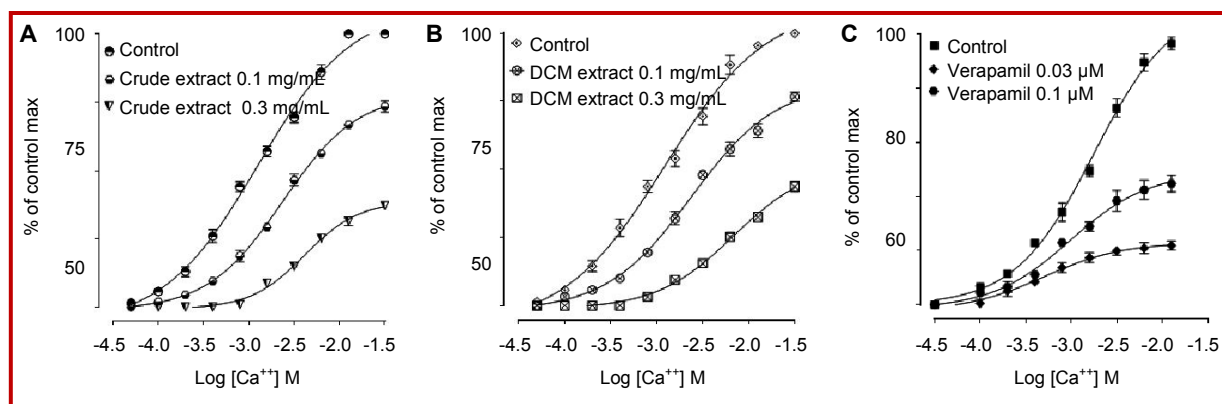


Figure 2: Ca<sup>2+</sup> concentration response curves (CRCs) in the presence of increasing concentrations of crude extract (A), DCM extract (B) and verapamil (C) respectively in isolated rabbit jejunum preparations. Values shown are mean  $\pm$  S.E.M (n=3-4)

against diarrhea and GI motility. The results showed that the crude ethanolic extract significantly inhibited the induced diarrhea in rats. Castor oil produce diarrheal effect by various previously explained mechanisms including a) intestinal Na<sup>+</sup> K<sup>+</sup> ATPase activity inhibited, hence reduced the normal fluid absorption (Gaginella and Bass, 1978), b) initiation of adenylate cyclase/cAMP-mediated active secretion (Capasso et al., 1994), c) formation of prostaglandins

(Galvez et al., 1993), and d) platelet activating factor (PAF) (Pinto et al., 1992). Other studies claimed the contribution of nitric oxide to the diarrheal effect of castor oil (Mascolo et al., 1994; Mascolo et al., 1996). However, it is well discussed that production of diarrhea by castor oil is due to the hypersecretory effect of ricinoleic acid, a most active component (Aleem et al., 2015; Rafique et al., 2016). Antidiarrheal effect of the plant extract was compared with that of loperamide (a

famous antidiarrheal drug).

When administered, crude extract (100 and 200 mg/kg) reduced the propulsive movement of charcoal meal through the small intestine and decreased the intestinal transit, thus supporting the presence of spasmolytic activity in the plant extract, similar to that of atropine, a cholinergic antagonist that is famous to decrease the movement of intestinal contents (Crocì et al., 1997), reduction in gastric emptying could also result in increased GIT transit time (Pierce et al., 1977) The results presented that the extract increased the absorption of water and electrolytes absorption by suppressing the propulsion of charcoal meal.

It is previously reported that the copper sulfate induces emetic effect by acting on the peripheral nervous system (Hosseini et al., 2005) and there is an important role of peripheral 5-HT<sub>4</sub> in this action. The medulla oblongata contains the vomiting center, triggered by irritants directly or indirectly ensuing response from four principal areas, including GIT, cerebral cortex, thalamus, vestibular region, and chemoreceptor trigger zone (CTZ). Blood brain barrier is not responsible for protecting CTZ, located in proximity to the medulla. The detected antiemetic effect of the crude extract can be possibly mediated through CTZ inhibition.

The application of crude extract on the spontaneously contracting isolated jejunal preparations intimidated both the frequency and magnitude of contractions, similar to verapamil. The spontaneous contractions of smooth muscles are dependent on increased cytoplasmic calcium levels, in turn activates the contractile elements. While action potential for maximal depolarization is produced through a rapid influx of Ca<sup>2+</sup> via the VDLCs (voltage-dependent L type channels) or released from sarcoplasmic reticulum calcium stores (Brading and Sneddon, 1980; Karaki et al., 1997; Bashir et al., 2011). The decrease in the spontaneous movements of jejunum by crude extract is assumed to be mediated through Ca<sup>2+</sup> channels blockade (Janbaz et al., 2012), as it was earlier observed that the antispasmodic constituents found in various medicinal plants inhibited the Ca<sup>2+</sup> movement to produce their effect (Gilani et al., 2005a, 2005b). The antispasmodic activity of the crude extract was further concluded by administering on K<sup>+</sup> (80 mM)-induced contractions in isolated rabbit jejunum tissues. The application of the crude extract in cumulative manner cause relaxation of K<sup>+</sup> (80 mM)-induced contractions, recommended that the detected relaxant effect was likely to be produced by blockade of Ca<sup>2+</sup> channels. The crude extract exerted the relaxant effect through Ca<sup>2+</sup> channels blockade and additional inhibition of sequence of actions, i.e., decrease in cytoplasmic concentration of Ca<sup>2+</sup>, reduction in Ca<sup>2+</sup>-calmodulin binding and complex formation, decrease activation of MLCK (myosin light chain kinase) and its phosphorylation, decrease in actin and myosin interaction

and inhibition of contractile response. These responses were further confirmed as pretreatment of isolated rabbit jejunal preparations with crude extract triggered Ca<sup>2+</sup> concentration response curve to shift rightward with suppression of maximal response like verapamil (a standard antagonist of Ca<sup>2+</sup> channels)(Fleckenstein, 1977; Godfraind et al., 1986). The CCBs are a famous group of therapeutic agents being active in the managing of hyperactive gut illnesses.

Further *ex vivo* studies on spontaneous and high K<sup>+</sup> induced contractions in rabbit jejunum were performed on the organic and aqueous fractions to find out the shift of activities in the fractions. The results suggested that the calcium channel blocking activity was more concentrated in the dichloromethane fraction while the aqueous fraction did not show relaxant effect on spontaneous and K<sup>+</sup> (80 mM) induced contractions.

Previous studies suggested that phytochemical classes like, alkaloids, flavonoids, tannins, terpenes and terpenoids possesses smooth muscle relaxant, antidiarrheal and antiemetic activities (Kinoshita et al., 1996; Mehmood et al., 2010; Hassan et al., 2012) and smooth muscle relaxant activity of natural compounds is referred by various different mechanisms including calcium channel blockade (Rafique et al., 2016).

The presence of phytochemical constituents like, alkaloids, flavonoids, tannins and saponins in *C. ciliaris* might be accountable for spasmolytic, antidiarrheal and antiemetic activities.

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## Conclusion

The ethanolic extract of *C. ciliaris* possesses spasmolytic and antidiarrheal activities, possibly by blockade of Ca<sup>2+</sup> channels. It also showed significant antiemetic activity. Both the Ca<sup>2+</sup> antagonistic and antiemetic activities can be accredited to the phytochemical constituents like flavonoids, tannins and alkaloids.

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