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Evaluation of antiemetic effect of aqueous rhizome extract of *Cynodon dactylon* against all emetogenic stimuli

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This study was an extension of our previous antiemetic work. Many researchers quoted *Cynodone dactylon* as anti emetic agent but none of them have provided strong pharmacological evidence for it, which drove us for its therapeutic evaluation. Crude aqueous rhizome extract of *C. dactylon* was evaluated for anti-emetic activity. Emesis was induced by the oral administration of copper sulphate, fresh aqueous extract of *Brasica compestris* while intravenous Cisplatin was used to induce emesis in fifteen days age chicks of either sex. The anti-emetic activity was determined by calculating the mean decrease in number of emesis in comparison to those of control and standards. *C. dactylon* (50 and 100 mg/kg body weight orally) showed remarkable emesis suppressant activity when compared with standard drugs chlorpromazine, domperidone and metoclopramide. Both the doses showed remarkable antiemetic activity.

Key words: Antiemetic, *Cynodone dactylon,* chick emesis model, domperidone, metoclopramide, chlorpromazine, *Brasica compestris*.

INTRODUCTION

Vomiting is a means by which gastrointestinal tract rids itself of its contents when upper gastro intestinal tract (GIT) excessively irritated, over distend or even over excited (Guyton and Hall, 2011). Irritation on the small area located bilaterally on the floor of the fourth ventricle in or above the area postrema causes vomiting which is

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located in medulla (Shahzad, 2011). Chemorecepter trigger zone gets excited with artificial electrical stimulation and drugs (Morphine, digitalis derivatives and chemotherapeutic agents). Motion sickness and classical migraine quite often excite chemorecepter trigger zone for vomiting (Kumar and Clark, 2002). Cholera toxin, irritable bowel syndrome and gestro-eosophygeal reflux disease (www.bnf.org), partial or complete bowel obstruction, uremia and brain metastases are also contributing factors (www.pakcancer.com). Electrolyte imbalance such as hyponatrremia, hypercalicemia and hyperglycemia induces emesis (www.cancer.org). Muscarinic M_1, histaminic H_1, neurokinin NK_1 and serotonin $5HT_3$ receptors nucleus tractus solitaries are involved while in area postrema dopamine D2, Opioid, serotonin $5HT_3$ neurokinin NK_1 receptors are responsible for ematogenic response (Katzung, 2011).

Cynodon dactylon belongs to the family of Poaceae (Saroja and Annapoorani, 2012). It is said to have many medicinal properties including antihelmentic (Sujon et al., 2008), antidiuretic, antinflammatory and hepatoprotective activity (Singh et al., 2009), efficacious for prostatitis and dysentery (Cheryl, 206). Traditionally, it is used in diabetes (Jarald et al., 2008; Singh et al., 2007), jaundice, kidney problems (Khajavi et al., 2011), urinary disease, constipation and abdominal pain (Das and Dutta, 2011). The whole plant is used for diuretic, dropsy, syphilis, wound infection and piles, anti haemorrhagic, in dysentery and nasal bleeding (Kunja et al., 2012). The juice of the plant is astringent and is applied externally to fresh cuts and wounds. It is used in the treatment of catarrhal opthalmia, hysteria, epilepsy, insanity, and chronic diarrhea (Rad et al., 2011). The plant is folk remedy for anasarca, calculus, carbuncles, cough, hypertension, snake bites, gout and rheumatic affections (Najafi et al., 2008). *C. dactylon* is a valuable herbal medicine and used for first aid for minor injuries (Oudhia et al., 1998). *C. dactylon* is bitter, sharp hot taste, good odour, laxative, brain and heart tonic, aphrodisiac, expectorant, carminative and useful against grippe in children and for pains, inflammations and toothache (Oudhia, 1999a). In homoeopathic systems of medicine, it is used to treat all types of bleeding and skin troubles (Agharkar, 1999). It is reported to have anticonvulsant effect (Oudhia, 1999b). It is also known for its antidiabetic and hypolipidemic effect (Santosh et al., 2007). Its antimicrobial and antifungal potentials were also reported (Kanimozhi and Ratha, 2012). It is also reported as anti inflammatory agent (Garg and Khosa, 2008). New antiemetic agents are the need of the time which effectively counters multiple emetogenic stimuli. *C. dectylone* is known as good antiemetic agent locally but yet do not have strong pharmacological evidence for this, which was the main aim of this evaluation. In this study, the antiemetic activity of aqueous rhizome extract of *C. dactylon* was tested against multiple emetogens.

MATERIALS AND METHODS

Collection of plant material

Indigenous medicinal plant *C. dactylon* is known by its local name of “Dub grass”. The plant was collected from the fields of Multan, Pakistan. The plant material was authenticated by Professor of Pharmacognosy, Dr. Romana Riaz at Multan college of Pharmacy, Multan, Pakistan.

Crude extract

The subterranean parts of *C. dactylon* were washed with fresh water, dried under shade at room temperature and grinded to form coarse powder. The powdered sample (100 g/100 ml) were kept in aqueous solvent (water) overnight at room temperature, filtered through muslin cloth then through Wattman-1 filter paper. The extract was evaporated at 50°C until a paste like consistency was attained (Khan et al., 2014).

Chemicals

They include: Copper (Scharlau Chem-ie S.A. Barcelona, Spain), dimethyl sulfoxide (DMSO) and polyoxy-ethylene sorbitan monooleate (Tween 80) (Darm-stadt, Germany), chlorpromazine and Metoclopramide (GSK Pharmaceutical (pvt). Ltd, Pakistan), Domperidone (Johson & Johnson Pharmaceuticals (Pvt) Ltd. Karachi, Pakistan), cisplatin (Sanofi aventis Pharmaceuticals (pvt) Ltd. Pakistan).

Animals

Chicks of either sex, fifteen days of age, weighing from 332 to 345 g were obtained from Al -Manara poultry traders, Multan. After 12 h fasting (deprived of food but had free access to water), the antiemetic activity was conducted. All chicks were kept under laboratory conditions at room temperature with 12 h light and dark cycles. All animal experiments were carried out in accordance with the acts of the Animal Ethical Committee of Multan College of Pharmacy, Multan, Pakistan (EC. rab /11/2013)

Antiemetic activity

Brasica compestris induced emesis model

Same procedure was adopted for fresh aqueous extract of *Brasica compestris* induced emesis as described by Imran et al. (2014). Chicks were divided into 6 groups, 3 chicks in each group. Each chick was placed in a large separate beaker and left to settle for 10 min. Aqueous extracts of *C. dactylone*. were prepared to a dose of 50 and 100 mg/kg body weight in a volume of 10 ml/kg in 0.9% saline containing 5% DMSO and 1% Tween 80. The doses were administered orally. The control group received vehicle (0.9% containing 5% DMSO and 1% Tween 80). After 10 min, fresh leaves extract of *B. compestris* was administered orally to irritate gastric mucosa. The number of retches was observed during the next 10 min. Chlorpromazine, domperidone and metoclopramide were used as standard antiemetic drugs (150, 100, 50 mg/kg body weight, respectively).

Cisplatin induced emesis model

Cisplatin induced model was used in fifteen days old chicks of

either sex according to Florczyk et al. (1982). Cisplatin 10 mg/kg was given by IV catherter. Other protocol remained same as before.

Copper sulphate induced emesis model

The antiemetic activity was evaluated by using chick emesis model (Khan et al., 2013). Copper sulphate at a dose of 50 mg/kg b.w was used to stimulate peripheral nervous system for emesis. Other protocol remained same before. The percent inhibition was calculated by the following formula:

Inhibition (%) = (A – B / A) × 100

Where A = Frequency of retching in control group and B = Frequency of retching in test group.

Phytochemical study

Phytochemical analysis for the presence of various phytochemical classes was done by the method described by Aziz et al. (2013).

Toxicity study

C. dactylon was evaluated for the toxic effects and toxic dose in albino rats. Albino rats were divided in 4 (a, b, c, d) groups, with each group containing 5 rats. Group 'a' was treated with distilled water while other three were given 1100, 2200, 3300 mg/kg body weight of *C. dactylon*. Physiological, biochemical and haematological parameters were analysed as per standard procedures. *C. dactylon* was found to be safe dose up to 3300 mg/kg body weight in albino rats.

Statistical analysis

Values for antiemetic activity was expressed as mean ± standard error of mean (SEM). The statistical significance was determined by an unpaired Student's *t*-test where *P* values of < 0.05 were considered significant and < 0.01 were highly significant.

RESULTS

Preliminary phytochemical screening detected presence of tannins, phenols, saponins, anthraquinones and coumarins as constituents of the crude aqueous rhizome extract of *C. dactylon* as depicted in Table 1. Results of the antiemetic activity of aqueous extracts of *C. dactylon* at both concentrations are given in Figures 1 to 3. Both the extracts inhibited emesis to an extent greater than chlorpromazine at a dose of 150 mg/kg. At test dose of 50 mg/kg, *C. dactylon* showed more antiemetic activity as compared to the reference drug, chlorpromazine, against brasica and copper sulphate induced models and slightly less in cisplatin induced model as given in Figures 1 to 3, while metoclopramide and domperidone showed more potential in suppression against all induced models in comparison to respective dose 50 mg/kg. At test dose of 100 mg/kg, *C. dactylon* showed almost similar antiemetic activity as metoclopramide and domperidone reference drugs as shown in Figures 1 to 3, respectively. In copper sulphate induced model, highest antiemetic activity showed by *C. dactylon* was 79.41% and the lowest was 52.94%. In fresh *Brasica* aqueous extract induced model, highest antiemetic was observed (81.91%) and lowest (59.57%). In cisplatin induced model, highest antiemetic response was (75.38%) and lowest (60.03%) was observed.

DISCUSSION

Diversified multiple receptors blocking mechanism was most likely to be the cause of such effective suppression of ematogenic stimuli. *C. dactylon* blocked $5HT_3$ receptors of small intestine so entereochromaffin cells failed to release serotonin which is responsible for vagal stimulation which in turn initiates vomiting reflex. Its bronchspasm revealing activity supports this claim (Patel et al., 2013). *C. dactylon* blocked the H_1 receptors of gastric mucosa so that thiocynates of *Brasica* failed to stimulate H_1 receptors and release of histamine by irritation which would in turn stimulate chemotrigger zone of medulla for emesis. Anti allergy activity of *C. dactylon* supports this claim (Subramanian et al., 1986; Anonymous, 1978). Radiation induces emesis by irritating gastric mucosa especially small intestine which is similar to cynates of Brasica, which provides its effectiveness in post radiation induced emesis.

Acetylcholine is one of the neurotransmitter involved in emesis (www.cnnj.org), while *dactylone* antidirrheal activity have already been reported via anticholinergic mechanism which is an effective evidence for antiemetogenic response of it (Oudhia et al., 1998) as anticholinergics are good choice of antemetic medications (Michelle et al., 2011). Although the results are significant but the mode of action is not exactly known. However, proposed mechanisms are as the oral copper sulphate which induces emesis by peripheral action (Hossein et al., 2005) and the extracts were able to effectively prevent its effect, it could be implied that these extracts have a peripheral anti-emetic action. Brasica induces emesis by the toxic effect of its phytoconstituent isothiocynate and betaphenylisothiocynate (Decker, 1971; Mishra et al., 2012) by causing irritation in the gastrointestinal mucosa. This irritation causes release of histamine and serotonin as vomiting centre rich in H_1-histamine receptors (Katzung, 2011), while in other way input to the vomiting centre are generated by vagus and spinal nerves of the gastric mucosa which are rich in $5HT_3$ receptors. This potentiates ematogenic stimuli in the brain by stimulating vagus afferent input to the vomiting centre.

Cisplatin and other chemotherapeutic agents induces emesis by stimulating the 5HT M-receptors located on

Table 1. Pytochemical analysis of aqueous rhizome extract of *C. dactylon*.

S/No	Test	Observations	Result
1	Alkaloid	orange ppt	Positive
2	Steroids	Violet colour	Positive
3	Tannins	Dark green colour	Positive
4	Glycoside	Pink	Positive
5	Saponin	1 cm froth	Positive
6	Phenols	Light purple	Positive
7	Flavanoid	yellow	Positive

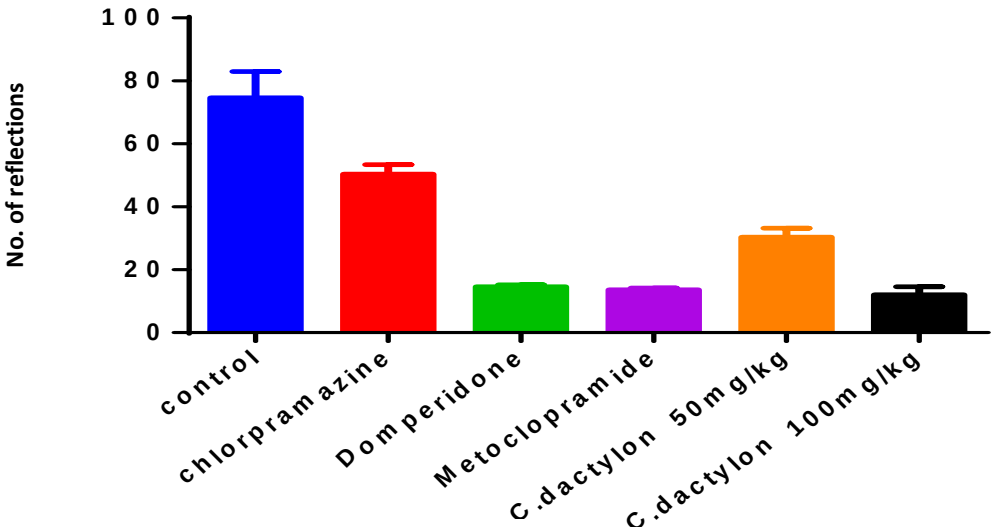

Figure 1. Effect of drugs on copper sulphate emesis. Antiemetic effect, Group-I: Control (Distilled Water); Group-II: Standard drugs (Chlorpromazine, metoclopramide and domperidone); Group-III; *C. dactylon* (50 and 100 mg/kg).

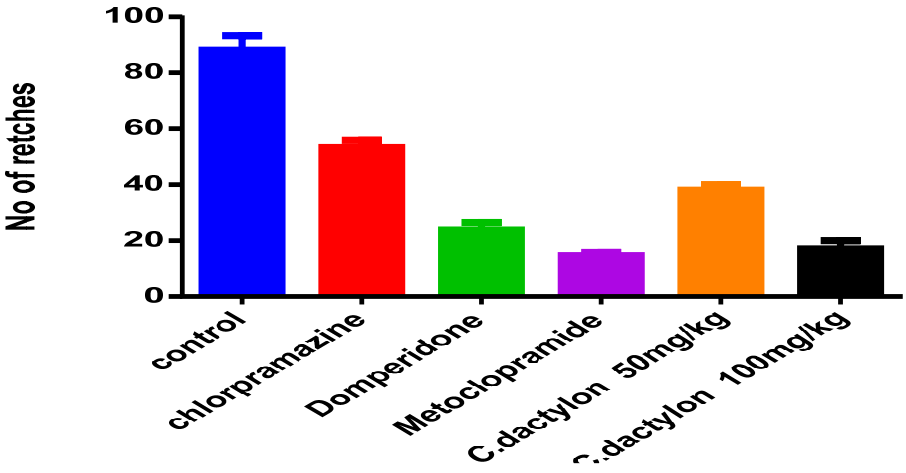

Figure 2. Effects of drugs on Brasica compestris induced emesis. Antiemetic effect, Group-I: Control (distilled water); Group-II: Standard drugs (chlorpromazine, metoclopramide and domperidone); Group-III; *C. dactylon* (50 and 100 mg/kg).

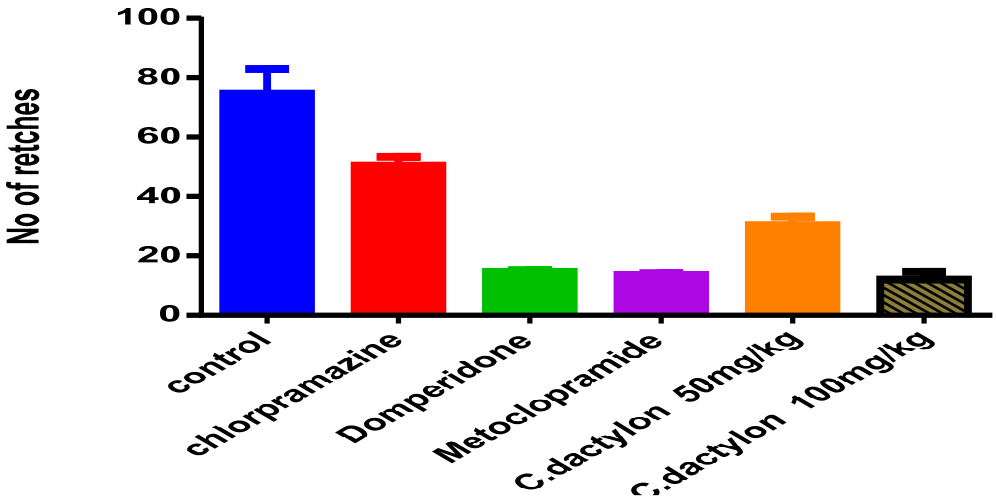

Figure 3. Antiemetic effect, Group-I: Control (distilled water); Group-II: Standard drugs (chlorpromazine, metoclopramide and domperidone); Group-III; *C. dactylon* (50 and 100 mg/kg).

afferent nerve pathways leading from the viscera to the area postrema. Our study verified the results that domperidone are most strongly dopamine receptor mediated in activity but metoclopramide in high dose blocks the 5HT-M receptors which was the cause of chemotherapy induced emesis (Wesley et al., 1986). *Cynodon dactylon* is rich in plant steroids (Abdullah et al., 2012) and steroids are used in combination to prevent emetic stimuli (Katzung, 2012; BNF, 2012) which helps in countering the emetic effect of cisplatin along 5HT-M receptor blockade.

CONCLUSION

From the present investigation it is clear that *C. dactylon* aqueous rhizome extract possess excellent antiemetic activity. Others factors such as the sex, emetogenic stimulation site and type of stimuli did not affect the degree of antiemetic activity due to its multidisciplinary receptor blocking mechanism.

Conflict of interest

The authors have not declared any conflict of interests.

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