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Research Article

Antidiarrheal Activity of Aqueous Fruit Extract of *Phoenix dactylifera* (DATE PALM) in Wistar Rats

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Abstract: Diarrhea is one of the main causes of morbidity and mortality in children under age of 5 years. In view of this problem, the World Health Organization has encouraged studies for treatment and prevention of diarrhoeal diseases depending on traditional medicinal practices. Extracts of *Phoenix dactylifera* (date palm) are widely used in traditional medicine for the treatment of various disorders. In this study, the antidiarrhoeal activity of the aqueous fruit extract of *Phoenix dactylifera* was investigated by castor oil- induced diarrhoea, enteropooling and gastrointestinal motility activity in Wistar rats. Like the standard drug (5mg/kg loperamide), the extract (1000 and 1500mg/kg body weight) elicited a significant decrease in the severity of diarrhoea. The extract significantly ($p<0.05$) reduced the frequency of defaecation and as well decreased gastrointestinal motility. In the enteropooling study, the extract administered at 1000mg/kg had greater anti-enteropooling effect than the standard drug (5mg/kg loperamide). The result obtained shows that the aqueous fruit extract of *Phoenix dactylifera* may contain some pharmacologically active substances with antidiarrhoeal properties. This may be the basis for management of gastrointestinal disorders.

Keywords: Antidiarrheal, castor oil, enteropooling, gastrointestinal transit, *Phoenix dactylifera*, wistar rat

INTRODUCTION

Diarrhea remains the second leading cause of death among children under five globally (WHO, 2011). It is one of the leading causes of mortality in developing countries and the major cause of this malnutrition. The World Health Organisation (WHO) has encouraged studies for treatment and prevention of diarrhoeal diseases depending on traditional medicinal practices (WHO, 1978, 1999; Cynthia *et al*., 2008).

Date palm (*Phoenix dactylifera*) fruits, an important component of diet in the arid and semiarid regions of the world (Biglari *et al*., 2008) are a good source of energy, vitamins, and a group of elements like phosphorus, iron, potassium, and a significant amount of calcium (Abdel-Hafez *et al*., 1980; El-Gazzar *et al*., 2009). Dates contain at least six vitamins including a small amount of vitamin C, and vitamins B_1 (thiamine), B_2 (riboflavin), nicotinic acid (niacin) and vitamin A (Al-Shahib and Marshall, 1993) and are widely used in traditional medicine for the treatment of various disorders e.g., memory disturbances, fever, inflammation, paralysis, loss of consciousness, nervous disorders (Nadkarni, 1976) and as a detersive and astringent in intestinal troubles. It is also used in the treatment for sore throat, to relieve fever, cystitis, gonorrhea, edema, liver and abdominal troubles and to counteract alcohol intoxication (Barh and Mazumdar, 2008; Al-daihan and Bhat, 2012). It possesses anticancer, antimutagenic, antihyperlipidemic, nephroprotective, and *in vivo* antiviral activities, and the ability to increase the concentration of testosterone, follicle stimulating hormone and luteininzing hormone (Bahmanpour *et al*., 2006). Many researchers have also documented the antioxidant property of *Phoenix dactylifera* (Mohamed and Al-Okbi, 2004; Allaith and Abdul, 2005; Al-Qarawi *et al*., 2008).

The aim of this study was to investigate the antidiarrhoeal effect of aqueous fruit extract of *Phoenix dactylifera* (AEPD) in Wistar rats.

MATERIALS AND METHODS

Plant material: *Phoenix dactylifera* fruits were obtained from a local Market in Zaria, Kaduna, Nigeria. Authenticated and deposited in the Herbarium unit of the Department of Biological Sciences, Faculty of Sciences, Ahmadu Bello University, Zaria, Kaduna State, Nigeria with the Voucher Specimen Number of 7130.

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Preparation of *Phoenix dactylifera*: Fruit extract was conducted in the Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Kaduna, Nigeria. The flesh of the dried *P. dactylifera* fruits were manually separated from the pits and pulverized into powder. About 650g of the powder was soaked in 2 liters of cold distil water. After 24 h, the solution was filtered and evaporated to dryness using H-H Digital Thermometer Water Bath (Mc Donald Scientific International-22050Hz1.0A International Number) at 60 ^{o}C. A yield of 21.28% of the extract was obtained.

Experimental animals: Wistar rats of either sex (170-200g), obtained from Pharmacology Animal House Center, Faculty of Pharmaceutical sciences, Ahmadu Bello University, Zaria, Kaduna, Nigeria, were housed in wired cages in the animal house of the Department of Human Anatomy, Faculty of Medicine, Ahmadu Bello University, Zaria, and were acclimatized for two weeks prior to the commencement of the experiments. The animals were housed under standard laboratory condition, light and dark cycles of 12 h, and were provided with standard rodent pellet diet and water *ad libitum*. The animals were categorized into control and experimental groups. The experimental groups were administered, in addition to feed and water, aqueous fruit extract of *P. dactylifera* or standard drug (loperamide hydrochloride) for a period of three (3) days.

Drugs: Castor oil (finest cold drawn castor oil), loperamide hydrochloride (Aaron Healthcare and Export PVT Ltd, Uttarahand, India), activated charcoal and gum acacia (Sigma, USA).

Antidiarrhoeal activity studies:

Castor oil-induced diarrhea in rats: Castor oil-induced diarrhea was determined by the method of Awouters *et al*. (1978). A total number of 25 Wistar rats of either sex (170-200g) were randomly distributed into five groups of five rats each. Group 1 served as the control administered distilled water (1mL/kg) orally by gavage and groups 2-5 as the experimental. Groups 2, 3 and 4 were administered AEPD orally by gavage at doses of 1000mg/kg, 1500 and 2000 mg/kg, respectively, while group 5 was administered the standard drug, loperamide hydrochloride (5mg/kg). After two days of AEPD or loperamide hydrochloride administration, all the animals (groups 1-5) were fasted for 18 h before the third's day treatment. After 1 h of treatment with distilled water, AEPD or standard drug on the third day, diarrhea was induced by administration of 1 mL of castor oil orally to each rat. Each animal was placed in an individual cage, the floor of which is lined with absorbent paper and observed for 4 h. The frequencies of characteristic diarrhoeal droppings were noted on the absorbent paper placed beneath the individual rat. The floor lining (absorbent paper) was changed at every defecation (Izzo *et al*., 1992; Mukherjee *et al*., 1995; Karim *et al*., 2010). The percentage inhibition was calculated as follows (Sule *et al*., 2009; Akuodor *et al*., 2011):

$$\% \text{ of inhibition} = 100 - \{(FNE/ FNC) \times 100\}$$

where,
FNE = Mean fecal number of each experimental group
FNC = Mean fecal number of the control group

Gastrointestinal transit test: Gastrointestinal transit in Wistar rats was tested using the charcoal method (Abdulla, 2008). A total number of 25 Wistar rats of either sex (170-200g) were obtained and distributed into five groups of five rats each. Group 1 served as control and groups 2-5 as experimental. The experiment was for a period of three days. Group 1 (control) received distilled water (l mL, orally); groups 2, 3 and 4 were treated with AEPD (1000, 1500 and 2000mg/kg, respectively, orally), while group 5 was administered loperamide hydrochloride (5 mg/kg, orally) as a standard drug for three days. Prior to the third's day treatment, animals in all groups (1-5) were fasted for 18 h, but allowed free access to water. The animals were treated with distilled water, AEPD or standard drug, and after 1 h, each animal was administered 1 mL of castor oil. 1 mL of marker (10% charcoal suspension in 5% gum acacia) was given orally by gavage to all groups 1h after castor oil administration. All the animals were sacrificed after 1 h of marker administration and the small intestine was rapidly dissected out and placed on a clean surface. The intestine was carefully inspected and the distance travelled (traversed) by charcoal meal plug from the pylorus to caecum was measured. The length of the whole intestine was also measured. The distance travelled by the charcoal plug from the pylorus to the caecum was expressed as a percentage of the total length of the small intestine (Mascolo *et al*., 1994; Rao *et al*., 1997; Rani *et al*., 1999; Karim *et al*., 2010).

Percentage of inhibition: Compared with the control group was determined by using the following equation (Abdulla, 2008; Bakare *et al*., 2011):

$$IP\ \% = (LM/LSI) \times 100$$

$$\% \text{ Inhibition} = IP\ \% \text{ (control)} - IP\% \text{ (treatment)}/ IP\ \% \text{ (control)}$$

where,
PI = Peristaltic index
LM = Length of charcoal meal
LSI = Length of small intestine

Castor oil-induced enteropooling studies: Enteropooling was determined by the method of Robert *et al*. (1976). A total number of 25 Wistar rats of either sex (170 to 200g) were obtained and distributed into five groups of five rats each. Group 1 served as control and groups 2-5 as experimental. The experiment was for a period of three days. Group 1 (control) received distilled water (1 mL, orally); groups 2, 3 and 4 were treated with AEPD (1000, 1500 and 2000mg/kg, respectively, orally), while group 5 was orally administered loperamide hydrochloride (5 mg/kg) as a standard drug for three days. Prior to the third's day treatment, animals in all groups were fasted for 18 h, but allowed free access to water. The animals were treated with distilled water, AEPD or standard drug, and after 1 h, each animal was administered 1 ml of castor oil. After 2 h of castor oil administration, the rats were sacrificed. The two ends of intestine were tied with thread and the intestine was removed. The intestinal content was removed by milking and the content measured.

The percentage of inhibition was calculated as follows (Abdulla, 2008; Akuodor *et al*., 2011):

$$\% \text{ of inhibition} = 100 - \{(ICE/ ICC) \times 100\}$$

where,

ICE = Mean volume intestinal content of each experimental group

ICC = Mean volume intestinal content of the control group

Data analysis: Results obtained were analysed using the statistical soft ware, Statistical Package for Social Scientist (SPSS *version* 18.0) and results were expressed as mean ± S.E.M and presence of significant differences among means of the groups were determined using one way ANOVA with LSD post hoc test for significance. Values were considered significant when $p \leq 0.05$.

RESULTS

Castor oil induced diarrhea: The aqueous fruit extract of *P. dactylifera* significantly ($p<0.05$) inhibited the frequency of defaecation (number of wet faeces) dose-dependently, except for the group that received 2000 mg/kg AEPD, when compared with the control (group 1). Treatment with 2000 mg/kg AEPD was not statistically effective in inhibiting the frequency of defaecation (Table 1).

Castor oil induced gastrointestinal transit: The aqueous fruit extract of *P. dactylifera* and standard drug treatments significantly slowed down the propulsion of charcoal meal through the gastrointestinal tract. The aqueous fruit extract of *P. dactylifera* treatment doses (except 2000 mg/kg AEPD) significantly ($p<0.05$) slowed down the propulsion of charcoal meal through the gastrointestinal tract when compared to the control (group 1). The inhibitory activity (decrease in the propulsive movement and the intestinal length travelled by charcoal meal) of the extract dose (1000 mg/kg AEPD) was statistically ($p<0.01$) equivalent to the activity produced by the standard drug (5 mg/kg loperamide) (Table 2).

Table 1: Effect of *Phoenix dactylifera L* fruit extract on castor oil induced diarrhoea in Wistar rats

Group	Treatment	Number of wet faeces	% Inhibition of defaecation
1	Distilled water (1 ml/kg)	5.00±0.00	–
2	*Phoenix dactylifera L.* (1000 mg/kg)	3.80±0.73	24*
3	*Phoenix dactylifera L.* (1500 mg/kg)	2.40±0.24	52***
4	*Phoenix dactylifera L* . (2000 mg/kg)	4.40 ±024	12
5	Loperamide hydrochloride (5 mg/kg)	2.40±0.24	52***

n = 5, values are means±SEM; * = p<0.05; *** = p<0.001; Significant difference when compared with the control using LSD test

Table 2: Effect of *Phoenix dactylifera L* fruit extract on castor oil induced gastrointestinal transit in Wistar rats

Group	Treatment	Peristaltic index (PI) (%)	Inhibition (%)
1	Distilled water (1 mL/kg)	71.48± 1.30	-
2	*Phoenix dactylifera L.* (1000 mg/kg)	77.76 ±4.93	15.38**
3	*Phoenix dactylifera L.* (1500 mg/kg)	63.73 ±3.49*	10.59*
4	*Phoenix dactylifera L.* (2000 mg/kg)	71.24 ±7.27	7.97
5	Loperamide hydrochloride (5 mg/kg)	60.79 ±1.24**	14.81**

n = 5, values are means ± SEM. * = p<0.05; ** = p<0.01, significant difference when compared with the control using LSD test

Table 3: Effect of *Phoenix dactylifera L* fruit extract on castor oil induced enteropooling in Wistar rats

Group	Treatment/ dosage	Volume of intestinal content (ml)	% inhibition
1	Distilled water (1 ml/ kg)	1.46 ± 0.05	-
2	*Phoenix dactylifera L.* (1000 mg/kg)	0.59 ± 0.31*	59.30***
3	*Phoenix dactylifera L.* (1500 mg/kg)	0.70 ± 0.10***	52.00**
4	*Phoenix dactylifera L.* (2000 mg/kg)	1.74 ± 1.43	82.48***
5	Loperamide hydrochloride (5 mg/kg)	0.70 ± 0.10***	52.00**

n = 5, values are means ± SEM. * = p < 0.05; ** = p< 0.01; *** = p<0.001, significant difference when compared with the control using LSD test

Castor oil induced enter opooling: The aqueous fruit extract of *P. dactylifera* and standard drug treatments had statistical significant ($p<0.01$) inhibitory effect against the activity of castor oil-induced enteropooling when compared to the control (group 1). The treatment with 1000mg/kg AEPD produced statistically ($p<0.001$) more effective anti-enteropooling activity than the standard drug (5mg/kg loperamide). Statistically significant ($p<0.05$) decrease in intestinal fluid volume was observed in the extract treated groups, except in 2000 mg/kg AEPD treatment dose, when compared with the control (Table 3).

DISCUSSION

Castor oil was used in this study to induced diarrhoea. It is well documented that castor oil produces diarrhea due to its most active metabolite, ricinoleic acid by hypersecretory response, which stimulates peristaltic activity in the small intestine, leading to changes in the electrolyte permeability of the intestinal mucosa (Zavala *et al*., 1988; Hardman and Limbird, 2001; Bakare *et al*., 2011). Its action also stimulates the release of endogenous prostaglandins E and F which cause stomach cramp and diarrhea due to the effect on the smooth muscle and secretion (Galvez *et al*., 1993; Saito *et al*., 2002). Among the several mechanisms proposed to explain the diarrhoeal effect of castor oil are activation of adenylate cyclase or mucosal CAMP mediated active secretion (Capasso *et al*., 1994), stimulation of prostaglandin formation (Capasso *et al*., 1992) and nitric oxide (Mascolo *et al*., 1996; Uchida *et al*., 2000).

In this study, loperamide was adopted as the standard drug, which is at present one of the most efficacious and widely employed antidiarrhoeal drugs (Niemegeers *et al*., 1974; Awouters *et al*., 1993; Balogun *et al*., 2011). Loperamide, apart from regulating the gastrointestinal tract, is also reported to slow down transit in the intestine, reduce colon flow rate, and consequently any effect on colonic motility (Theoderau *et al*., 1991). The therapeutic effect of loperamide is believed to be due to its antimotility and antisecretory properties (Couper, 1987).

The inhibition of experimental diarrhea and the reduction in fecal output by a substance are the basis of the pharmacological evaluation of a potential antidiarrhoeal agent (Watson and Gordon, 1962; Ammon and Thomas, 1974).

In this study, there was a statistically significant reduction in the incidence and severity of diarrhoeal stool produced in the experimental animals. The aqueous fruit extract of *P. dactylifera* significantly inhibited the frequency of defaecation (number of wet faeces) in a dose dependent manner except for the 2000 mg/kg AEPD treatment group. 1500 mg/kg AEPD treated group like the standard drug (5mg/kg loperamide) significantly inhibited the frequency of defecation droppings compared to control. This result is in accordance with previous claims in respect of antidiarrhoeal herbs. Antidiarrhoeal plants are known to reduce number of wet stools as reported for *Eremomastax speciosa* and *Momordica charantia Linn* (Oben *et al*., 2006; Bakare *et al*., 2011).

The doses of aqueous fruit extract of *P. dactylifera* inhibited gastrointestinal propulsion in the castor oil induced transit except for the 2000 mg/kg AEPD treated group when compared to the control. The 1000 mg/kg AEPD treatment was of equivalent effect with the standard drug (5 mg/kg loperamide). This study demonstrates that the administration of 1000mg/kg AEPD is as effective as the standard drug. Gastrointestinal propulsion inhibitory activity of the extract is in line with reports of studies on antidiarrhoeal herbs as reported on *Cochlospermum planchonii* (Hook f) (Ezeja and Anaga, 2010); the property of reducing intestinal contractions (and consequently, intestinal transit) is demonstrated by most antidiarrhoeal agents (Bruton, 1996).

The aqueous fruit extract of *P. dactylifera* inhibited gastrointestinal propulsion in the castor oil induced transit. This makes it beneficial as a preventive agent. Antidiarrhoeal treatment in patient is achieved through the objective of the therapy which includes increasing resistance to flow (segmental contraction and decrease propulsion) and increased mucosal absorption or decreasing secretion (Burks, 1991). This is indicative of the ability of the plant to alter normal peristaltic movement and hence decrease the movement of materials in the intestinal tract allowing greater time for absorption (Couper, 1987; Karim *et al*., 2010). Flavonoids has been ascribed with ability to inhibit intestinal motility and hydro-electrolytic secretion; flavonoids have been ascribed the ability to inhibit contractions induced by spasmogenics (Di Carlo *et al*., 1993; Akuodor *et al*., 2011). It is possible that the flavonoids present in the aqueous fruit extract may be responsible for the antidiarrhoeal activity.

In the castor oil induced enteropooling study, the aqueous fruit extract of *P. dactylifera* significantly reduced the intraluminal fluid accumulation (enteropooling) when compared to the control. This result is in concordance with reports of studies in respect to antidiarrhoeal plants; antidiarrhoeal plants are known to decrease intraluminal fluid accumulation as reported for *Verbena hastate, Manniophyton africanum* and *Momordica charantia Linn* (Akuodor *et al*., 2010;

Ezeigbo *et al*., 2010; Bakare *et al*., 2011). The extract also significantly reduced the volume of intestinal content as manifested in the 1000 mg/kg AEPD and 1500mg/kg AEPD treated groups. This implies that, extract treatment at dose 2000mg/kg AEPD is not effect as an anti-enteropooling agent, although demonstrated remarkable percentage inhibition when compared to the control (the mean intestinal volume of 2000 mg/kg AEPD treated group is higher than that of the control as such percentage inhibition tends to be high by computation).

In this study, it was observed that the inhibitory effect of the extract dose 1000mg/kg AEPD on castor oil induced enteropooling was statistically more effective than the standard drug (5 mg/kg loperamide) in Wistar rats. This study also demonstrates that the administration of the extract at a dose of 1000mg/kg decreases intestinal fluid volume. This is in accordance with previous claims on the vital role played by indigenous remedies which are more effective, safe and inexpensive (Katewa *et al*., 2004).

The significant inhibition of the castor oil- induced enteropooling in rats suggests that the extract produced relief in diarrhea by spasmolytic in vivo and anti-enter opooling effects (Akuodor *et al*., 2010). The extract also significantly reduced the volume of intestinal content. This may promote reabsorption of materials in the intestine due to decrease propulsion of material in the intestinal tract, and the extract might have exerted its antidiarrhoeal action by antisecretory mechanism. It is also possible that flavonoids present in the aqueous fruit extract may be responsible for the antidiarrhoeal activity (Akuodor *et al*., 2010).

CONCLUSION

The result of the present study suggests that the aqueous fruit extract of *P. dactylifera* possess significant antidiarrhoeal activity, at doses of 1000 and 1500 mg/kg, due to its effect on reduction of number of diarrhea stool, delayed in gastrointestinal propulsion and inhibition of fluid accumulation in the intestinal tract of rats. Further studies are ongoing to determine the exact compound(s) responsible for its antidiarrhoeal action.

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