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Effects of taranjabin manna on gastrointestinal tract in Wistar rats.

¹Noorbakhsh MF, ²Afkhami Gol A, ²Kazerani HR*

1Graduate School of Veterinary Medicine, 2Department of Pharmacology and Physiology, School of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran.* Corresponding author: kazerani@um.ac.ir

ABSTRACT

Noorbakhsh MF, Afkhami Gol A, Kazerani HR., Effects of taranjabin manna on gastrointestinal tract in Wistar rats, Onl J Vet Res., 21(4):207-215, 2017. Taranjabin manna (wet honey) has been used as a laxative, antipyretic, expectorant and to treat/prevent newborn jaundice. Groups of rats (n=7) were gavaged taranjabin manna or placebo (controls) and number, weight and water content of fecal pellets were determined for 24h. Osmotic laxative effect in rats (n=5) was determined by injecting 0.5ml taranjabin solution, lactulose or saline into separate 4cm jejunum segments and measuring volume of contents in each segment after 1h. Intestinal transit time was evaluated in fasting rats (n=32) given taranjabin or lactulose by the phenol red test. Oral administration of taranjabin increased (p<0.001) number of fecal pellets and their percentage of water, but had no effect on intestinal transit time. Volume of contents in jejunum segments increased (P<0.05) with taranjabin or lactulose compared with placebo. Taranjabin may exert a laxative effect partly via osmotic infiltration of fluids into the intestine partly masked by delayed emptying of cecum contents.

Keywords: Laxative, prokinetic, taranjabin. Normally distributed raw data files provided for independent analyses

INTRODUCTION

Taranjabin is a manna produced on camelthorn (*Alhagi persarum* Boiss), a shrub grown in some deserts in Iran. The manna is believed to be produced by an insect (*Poophilus nebulous*) and has a sweet taste due to existence of sugar (melezitose) in its composition (Askarzadeh MA et al. 2005). Taranjabin has been traditionally used as laxative, antipyretic, expectorant and to treat/prevent newborn jaundice (Zargari A 1992, Ayenechi, Y 1990). However, using scientific methods, only a few reports are available regarding the medicinal effects of the manna. Although a recent study suggests no beneficial effects for the drug in preventing newborn jaundice (Panjvani Z et al 1990), the herbal remedy has been reported to prevent hyperbilirubinemia in mice (Bandegi AR 2002). In another study, the manna did not show significant effects on serum parameters such as urea, creatinine, total bilirubin, alkaline phosphatase (ALP) and alanine aminotransferase (ALT) in healthy adult Syrian mice (Kazerani HR, et al. 2006)). To the best of our knowledge, there is no scientific report regarding the laxative effects of taranjabin. The current research was aimed to verify the possible prokinetic and laxative effects of the manna in rats.

MATERIALS AND METHODS

Wistar rats of either sexes weighing 180-230 g (Razi Vaccine and Serum Research Institute, Mashhad, Iran) were used. The animals were housed and allowed to acclimate in the Animal Unit of the School of Veterinary Medicine, Ferdowsi University of Mashhad at least for one week before beginning of the experiment. High quality taranjabin was purchased from the market. The herbal medicine was confirmed by the Research Center for Plant Sciences, Ferdowsi University of Mashhad to be taranjabin, which is formed on *Alhagi persarum* Boiss (Herbarium no: 18902, FUMH). The manna was dissolved in distilled water and was heated (100°C) for 5 min.

The laxative effects

Laxative effect of taranjabin was studied using two groups of 7 rats. The rats in the test group were gavaged with taranjabin solution at 2.5 g/kg Bwt, while the control rats received placebo. The fecal pellet were counted up to 24 hr in both groups. In order to measure the water content (Crocì T et al. 1996, Freeman DE et al. 1992 and Saito T et al. 2000), pellets were collected every 10 min up to 24 h. To achieve this, the samples were weighed both immediately and after drying (50 °C, 18-20 h). In order to assess the possible effects of the drug on intestinal secretions or osmotic infiltration of fluids into the gut lumen, 5 extra rats were anesthetized with pentobarbital sodium (60 mg/kg), the abdominal cavity was opened, and the jejunum was randomly divided into three segments of 4 cm. Within each segment, taranjabin solution (2.5 or 5 g/kg), lactulose (as positive control; 0.33 g/ml) or placebo (as negative control) were injected (0.5 ml), in a random order. One hour later, the volume of the fluid in each segment was measured.

Gastrointestinal transit time

The effect of taranjabin on gastrointestinal transit time was studied using phenol red as previously described (Firpo et al. 2005, Martinez V et al. 1998 and Kimura T et al. 2000). Briefly, 32 rats in the control and the test groups were deprived from food but had access to drinking water. The test animals received taranjabin at 2.5g/kg by gavage twice, with 18h intervals. The control rats received similar volumes of placebo (distilled water). Thirty minutes after the last medication, all rats were gavaged with phenol red (3mg/ml) and methyl cellulose (15mg/ml). Rats from both

control and the test groups were sacrificed using a CO₂ chamber in groups of 3 at 30min, 1h, 2h and 4h following intragastric injection of phenol red.

The abdominal cavity was opened; the small intestine was divided into 3 equal sections (S1-S3) and was removed. The stomach, the cecum and the colon were also cut out. All segments were washed with 0.9% saline and then were homogenized within 100ml NaOH 0.1N solution. The suspension was allowed to settle at room temperature for 1h, and then 5ml of the supernatant was added to 0.5ml 20% trichloroacetic acid and was centrifuged at 3000 rpm (4°C, 30min). The supernatant was added to 4ml 0.5N NaOH, stirred and the absorbance of the samples were read at 560nm (Jenway, UK). The concentration of phenol red in each segment was calculated according to the standard curve. The geometric center was calculated using the following formula (Firpo et al, 2005):

$$\text{Geometric center} = \Sigma(\% \text{ dye per segment} \times \text{segment number})/100$$

Statistics

Statistical analysis and drawing of the figures were performed using GraphPad Prism v4.0 (GraphPad Software, USA). Statistical comparisons were performed using t-test for fecal pellet count and feces water percentage; two-way analysis of variance (ANOVA) followed by Bonferroni posttests for cumulative phenol red and geometric center; and one-way ANOVA followed by Dunnett's test for osmotic infiltration of fluids into the jejunum. In all cases, $P < 0.05$ was considered as significant. Unless otherwise mentioned, all data are represented as mean \pm SEM.

RESULTS

The laxative and purgative effects

The laxative and purgative effects of taranjabin were studied according to fecal pellet count, fecal weight and fecal water percent up to 24h following treatment. As shown in Figure 1, fecal count was higher in the test group during the second 8h following the treatment. Fecal weight was significantly higher in the test group during the second and the third 8h (Figure 2). The percentage fecal water showed a rather similar pattern, being significantly higher during the second and the third 8h, compared to the control group (Figure 3). The jejunum segments filled with taranjabin solutions at 2.5 and 5 g/kg had significantly higher volumes compared to those filled with placebo (Figure 4). This was consistent to the results obtained with lactulose, used as the positive control.

Gastrointestinal transit time

In order to determine the effect of taranjabin on the transit time of ingesta within the gastrointestinal tract, the percentages of phenol red within the stomach and different parts of the intestines were measured at 30min to 4h following intragastric injection of the dye (Figure 5). Accordingly, the dye was mainly concentrated within the stomach and the second third of the small intestine at 30min. After 1h, the ingesta was mainly distributed within the stomach and throughout the small intestine. Following 2h, the main part of the dye could be detected within the last third of the small intestine. At the end of the experiment (4h), the ingesta were mainly accumulated within the cecum and colon. There were no significant differences between the test and the control groups during the first 3 hours of the experiment. At 4h, however, the ingesta seem to have accumulated in the cecum of the rats received taranjabin.

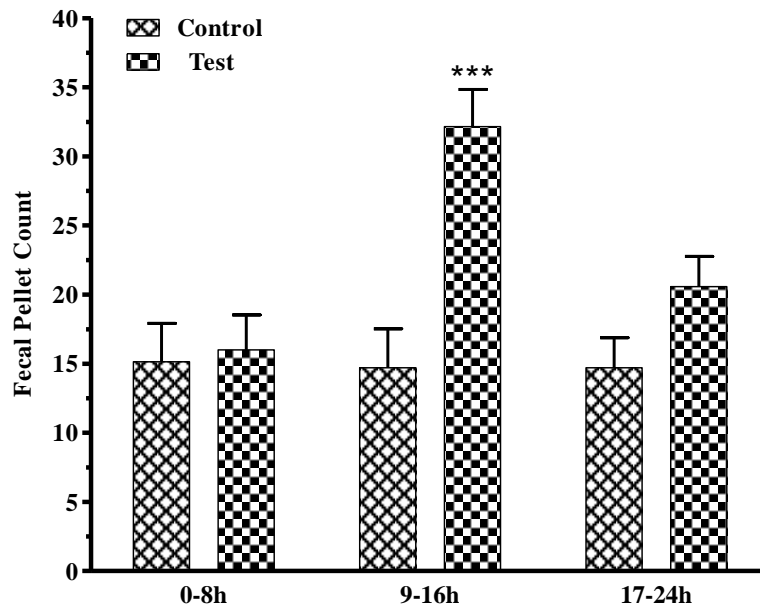


Figure 1 Fecal pellet count up to 24 h following intragastric administration of the taranjabin (2.5 g/kg Bwt, n= 7 each). Data are represented as mean±SEM (***: P < 0.001).

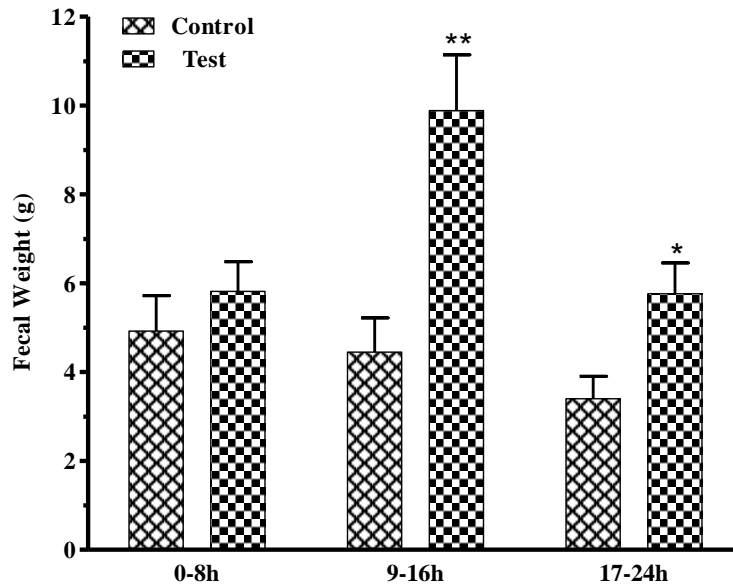


Figure 2 The weight of feces in the test group up to 24 hr following intragastric administration of the solution of taranjabin (2.5 g/kg Bwt, n=7) compared to the control (n=7). Data are represented as mean± SEM (**P<0.01, *p<0.05).

The geometric centers of the ingesta were not significantly different among experimental groups at any of the 4 time-points tested (Figure 6).

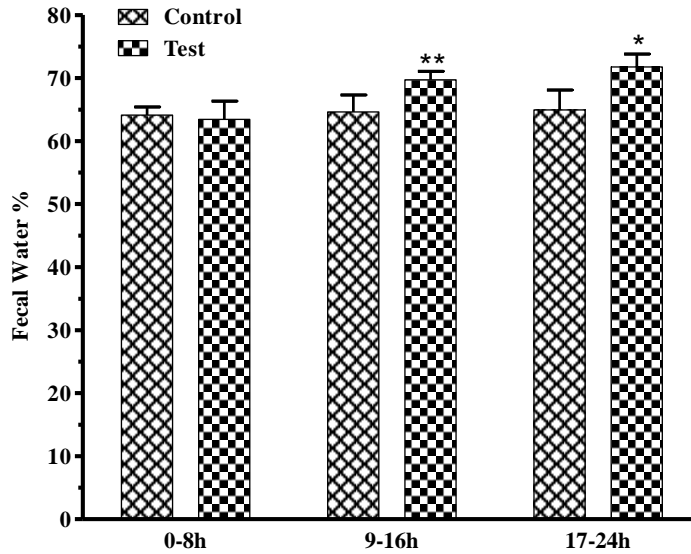


Figure 3 The percentage of feces water content in the test group up to 24 hr following intragastric administration of the solution of Taranjabin (2.5 g/kg Bwt, n=7) compared to the control (n=7). Data are represented as mean±SEM (**P<0.01, *p<0.05).

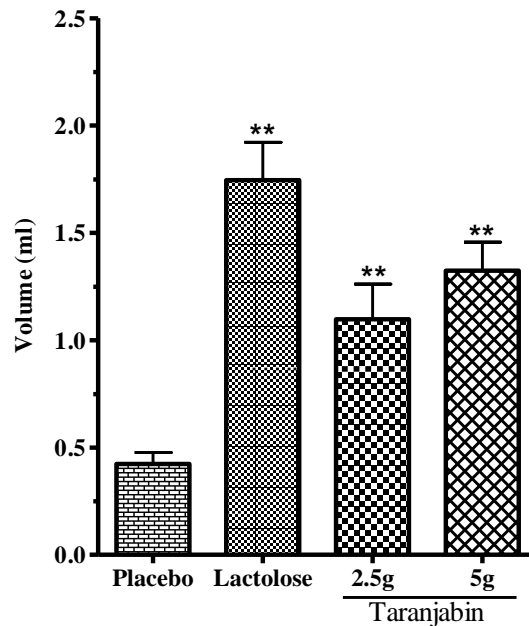


Figure 4 The fluid volumes within jejunum segments (n=7) filled with the solution of Taranjabin (2.5 and 5 g/kg) compared to those filled with placebo (saline) or lactulose (0.33 g/ml). Data are represented as mean±SEM (**P< 0.01).

DISCUSSION

In this research, the laxative/purgative effect of taranjabin, the manna of camelthorn, were investigated. The ability to increased fecal water and the frequency of defecation are among the most important characteristics of laxatives (Gangarosa LM and Seibert DG 2003). Oral gavaging of the solution at 2.5 g/kg Bwt significantly increased both parameters in rats, suggesting laxative effects for the drug.

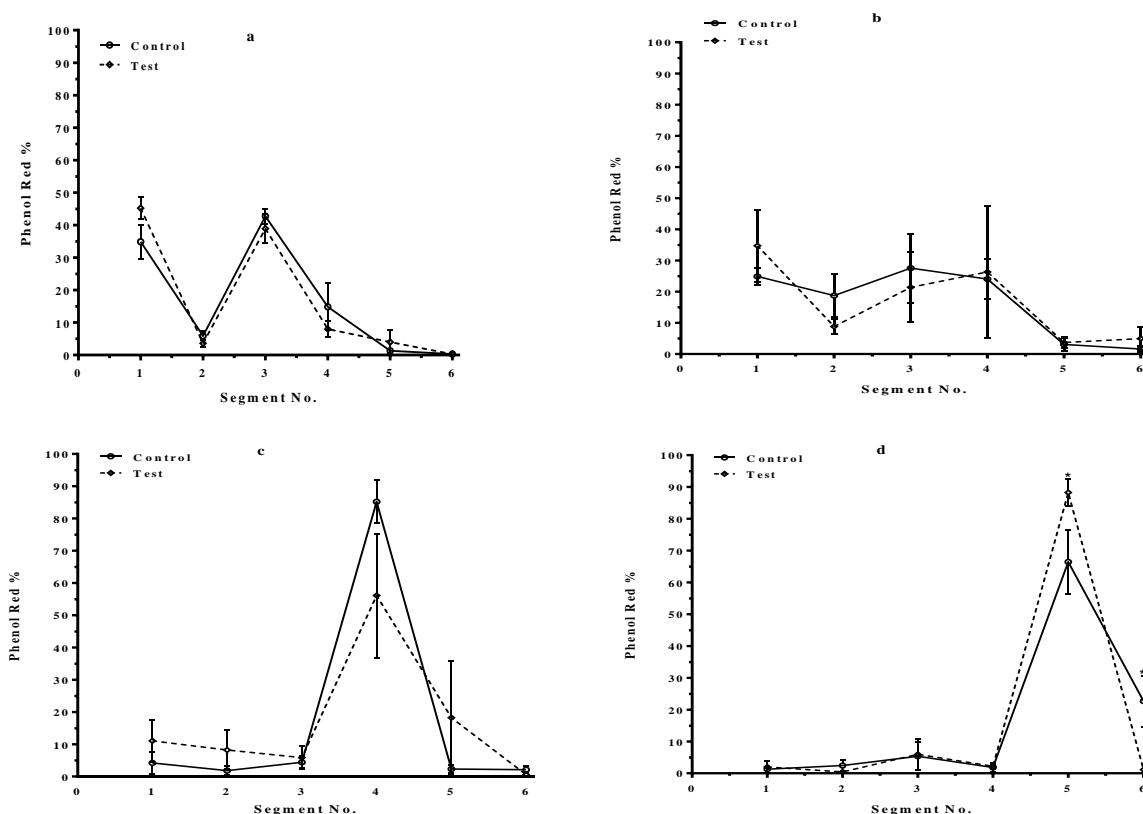


Figure 5 Gastrointestinal transit time. Figures A-D represent the percentage of phenol red within each part of the GI tract 30min, 1h, 2h and 4h, respectively, following ingestion of the dye. Segments 1-6 represent stomach, small intestine (S1-S3), cecum and colon. Data are represented as mean \pm SEM (*P< 0. 1).

Laxatives are among the most widely used drugs. However, their consumption is limited due to insufficient efficacy or their side effects, especially when used continuously or with contraindications. Bloating, cramping, diarrhea, and metabolic disturbances such as hypercalcemia, hyperphosphatemia, hyponatremia, and hypokalemia are among the most common side effects (Harris LA 2006). Cardiotoxic and arrhythmogenic effects have been reported with magnesium purgatives (Qureshi T and Melonakos TK 1996) and cisapride (Washabau RJ 2003). The use of stimulant laxatives such as senna compounds and bisacodyl may be associated with colonic neoplasia (Xing JH and Soffer EE 2001). The search for novel safe laxative drugs seems, therefore, inevitable. A huge category of laxative agents, both with herbal and chemical origin, exert their effect via osmotic infiltration of fluids into the intestinal lumen. These drugs or their

metabolites are slightly, if any, absorbed and increase osmolarity of intestinal contents (Gangarosa LM and Seibert DG 2003). In this research, possible osmotic infiltration of fluids into the intestinal segments of treated animals was studied in comparison with lactulose, a widely used osmotic laxative (Gangarosa LM and Seibert DG 2003) and both significantly increased intestinal fluid contents compared to the placebo (normal saline). This suggests the solution may induce its laxative effects, at least partly, via increased intestinal osmolarity. As an alternative justification, the solution may stimulate intestinal electrolyte secretion. In fact, one category of laxative drugs, known as stimulant or irritant laxatives, including bisacodyl, castor oil, senna, cascara etc, acts via increased electrolyte secretion from intestinal crypts (Gangarosa LM and Seibert DG 2003).

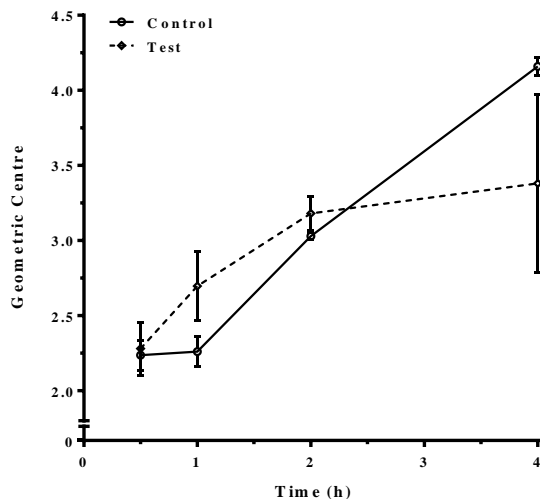


Figure 6 The geometric center of the phenol red within the GI tract 30min-4h following ingestion of the dye.

The laxative/purgative effects may be caused as a result of increased motility, and subsequently, decreased transit time in the intestine. This may arise as a result of enhanced stimulatory effects of neurohumoral substances, or suppressed inhibitory pathways, within the gut wall. Some therapeutic effects of the manna (such as antitussive) in traditional medicine require modulation of neurohumoral pathways (Zargari A 1992). These suggest that taranjabin solution may interfere with a wide variety of regulatory neurohumoral pathways. On the other hand, varying regulatory substances are released from enteric nervous and endocrine systems that affect gastrointestinal movements and secretions (Hansen MB 2003, Barrett KE and Raybould HE 2008). It seems, therefore, conceivable that taranjabin solution may affect gastrointestinal motility via modulating its regulatory neuronal or endocrine pathways. Since different neuroendocrine mechanisms are involved in integration of GI function, the laxative effect of taranjabin may also be mediated via affecting these regulatory pathways. In order to verify the above hypothesis, the present research verified the possible effect of taranjabin on gastrointestinal transit time. Consistently, this study suggest strong inhibitory effect on cecum emptying. Obviously, the above inhibitory effect on cecum is in contrast to laxative properties of the plant observed in this research. It should be noted, however, that different mechanisms may be involved in intestinal smooth muscle cells and there is no report regarding the effects of taranjabin on these cells.

In this research, the solution of taranjabin did not significantly affect intestinal transit time. However, regarding its inhibitory effect on cecum emptying, its laxative effects may be, at least

partly, due to shortening the intestinal transit time. In other words, the effects on intestinal transit time may be masked by delayed cecum emptying. This, however, demands further experiments. This research, did not study the chemical ingredients involved in laxative effects of taranjabin.

In conclusion, The current study showed significant laxative effects for solution of taranjabin in rats. The effect seems to be, at least in part, due to osmotic infiltration of fluids into the intestinal lumen. Intestinal transit time of the marker, phenol red, did not change due to the solution. However, since the effect might have been masked by delayed cecum emptying, further research is required to assess possible prokinetic effects of the solution.

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