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BASIC RESEARCH

Elenoside increases intestinal motility

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Abstract

AIM: To study the effects of elenoside, an arylnaphthalene lignan from *Justicia hyssopifolia*, on gastrointestinal motility *in vivo* and *in vitro* in rats.

METHODS: Routine *in vivo* experimental assessments were catharsis index, water percentage of boluses, intestinal transit, and codeine antagonism. The groups included were vehicle control (propylene glycol-ethanol-plant oil-tween 80), elenoside (i.p. 25 and 50 mg/kg), cisapride (i.p. 10 mg/kg), and codeine phosphate (intragastric route, 50 mg/kg). *In vitro* approaches used isolated rat intestinal tissues (duodenum, jejunum, and ileum). The effects of elenoside at concentrations of 3.2 x 10^{-4}, 6.4 x 10^{-4} and 1.2 x 10^{-3} mol/L, and cisapride at 10^{-6} mol/L were investigated.

RESULTS: Elenoside *in vivo* produced an increase in the catharsis index and water percentage of boluses and in the percentage of distance traveled by a suspension of activated charcoal. Codeine phosphate antagonized the effect of 25 mg/kg of elenoside. *In vitro*, elenoside in duodenum, jejunum and ileum produced an initial decrease in the contraction force followed by an increase. Elenoside resulted in decreased intestinal frequency in duodenum, jejunum, and ileum. The *in vitro* and *in vivo* effects of elenoside were similar to those produced by cisapride.

CONCLUSION: Elenoside is a lignan with an action similar to that of purgative and prokinetics drugs. Elenoside, could be an alternative to cisapride in treatment of gastrointestinal diseases as well as a preventive therapy for the undesirable gastrointestinal effects produced by opioids used for mild to moderate pain.

Key words: Elenoside; Gastrointestinal motility; Small intestine preparation

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INTRODUCTION

A great number of arylnaphthalene lignans have been isolated from different species of *Justicia*, many of them exhibiting diverse biological activities including antitumoral[1-4], antiviral[5-7], insecticidal[8], cardiotonic[9,10], antiulcerogenic[11] and anti-inflammatory properties[12,13], and an ability to inhibit lipid peroxidation[14]. Interesting activities also include platelet activating factor antagonism and central nervous system action[15]. Recently it has been observed that magnolol and honokinol, two neolignans, obtained from *Magnolia officinalis* Rehd. et Wils, inhibited the contractility of isolated gastric fundus strips from rats treated with Ach or 5-HT and of isolated ileum from guinea pigs treated with Ach or $CaCl_2$; in each case, the neolignans behaved as non-competitive muscarinic antagonists[16]. However, clinical or experimental studies on the effects of the gastrointestinal activity of lignans obtained from *Justicia* species have not, to our knowledge, been performed.

In a previous paper[17] we reported the isolation from *Justicia hyssopifolia L.* of an arylnaphthalene lignan and its aglycone, now called elenoside and elenin respectively, the former being a β-D-glucoside. Elenoside is a cytotoxic arylnapthalene lignan (NSC 644013-W/1) that displayed cytotoxic activity in the human tumor cell line panel of the US National Cancer Institute[18]. Preliminary screening results suggest that elenoside exerts a sedative, hypnotic barbiturate-type effect[18,19]. In addition, we have found that elenoside has digitalis-like activity similar to that of mammalian lignans[20]. Recently we have also observed that elenoside has central sedative effects and a possible application in anxiety conditions[21]. The current study was designed to investigate the effects of elenoside on gastrointestinal motility.

MATERIALS AND METHODS

Plant material and chemicals

Justicia hyssopifolia L. belongs to the family *Acanthaceae* and is an endemic species in the Canary Islands. Leaves of *J. hyssopifolia* were collected in April 2002 at Punta Cangrejo,

Adeje, Tenerife. A voucher specimen was deposited at the Herbarium of the Department of Botany, Faculty of Biology, University of La Laguna (TFC-28938). The elenoside was extracted and identified in *Centro de Productos Naturales y Agrobiologia, CSIC,* of Tenerife. It was suspended in a mixture of propylene glycol-ethanol-plant oil-Tween80 (40:10:50:2) and administered intraperitoneally in a total volume of 0.5 mL. The control group received vehicle only. An activated charcoal suspension indicator was prepared with 10 g activated charcoal (Panreac, Barcelona, Spain) and 2.5 g Arabic gum dissolved in 100 mL of distilled water. Cisapride was also used (Janssen-Cilag, S.A. Madrid, Spain).

Animals and treatment

Male Sprague Dawley rats weighing 200-250 g were used. The rats were housed under normal laboratory conditions at 22℃ on a standard light-dark schedule (12:12; lighted from 8 am-8 pm) and had free access to standard laboratory chow and water. Animal care complied with the Guide for the Care and Use of Laboratory Animals in accordance with the Guiding Principles in the Use of Animals in Pharmacology. The study protocol was approved by the Local Ethical Committee for animal experimentation at the University of La Laguna.

The standard dosage treatment protocol for each set of experiments described is as follows: rats assigned to randomized groups of 10 each receiving intraperitoneally (i.p.) a solution of propylene glycol-ethanol-plant oil-Tween 80 (40:10:50:2) (vehicle control group), 25 or 50 mg/kg of elenoside in vehicle, or 10 mg/kg cisapride.

Catharsis index

The established index of catharsis is the number of humid boluses produced in 24 h. Masri *et al* found that the majority of humid boluses are produced in the first hours following administration of the substance[22]. Thus, we used their method to study the effect of elenoside. Rats were fasted for 24 h prior to the experiment. Following this period, the rats received the standard dosage treatment protocol (n = 10 per dosage group). Rats were then individually placed in metabolism cages, and the boluses were collected for a 6 h period above blotting paper to facilitate counting.

Water percentage of boluses

Using the standard dosage protocol described above, we tested the water percentage of the boluses. Rats (n = 10 per dosage group) were individually placed in metabolism cages, and the boluses were collected in a methacrylate container for a period of 6 h and deposited in a watch glass. Afterward, the samples were weighed and placed in a heater at 100℃ for 3 h, followed by another weighing to establish the percentage of water in each.

Intestinal transit

This experimental method allows the evaluation of drug action on intestinal transit speed, by measuring the distance travelled by a suspension of activated charcoal when it has been administered intragastrically (po). Rats (n = 10 per dosage group) were fasted for 24 h prior to the experiment. At 15 min following treatment with the standard dosage protocol, the rats received 2 mL of a suspension of activated charcoal po. After 20 min, the rats were anesthetized and sacrificed; their intestines were removed from the pylorus through the ileocecal junction. The migration of activated charcoal from the pylorus to the most distal point of migration was expressed as distance (cm) migration using the stain. The percentage of distance travelled by the activated charcoal suspension established the intestinal transit. This percentage was expressed as % = 100 × l/L, in which *"l"* is the migration distance of the activated charcoal and *"L"* is the distance between the pylorus and the ileocecal junction.

Intestinal transit and codeine antagonism

Using the standard treatment protocol, we studied the effect of elenoside in the presence of codeine phosphate, an opioid with inhibitory activity on intestinal motility. Following administration of the standard dosage treatment, the rats immediately received 50 mg/kg of codeine phosphate po. The method used for the measurement of intestinal transit was the same as that described in the preceding section.

Isolated rat intestine

Rats were anesthetized and sacrificed. The abdomen was opened and a length of duodenum, jejunum and ileum was removed and placed in Tyrode´s solution. Pieces of smooth muscle (1-2 cm) were dissected free from surrounding tissues and mounted in an organ bath with Tyrode´s solution at 37℃, pH 7.4, through which a mixture of 50 mL/L CO_2 and 950 mL/L O_2 bubbled continuously[23]. The isotonic contractions of the preparation were recorded on a Grass Model 7D Polygraph through a Statham force displacement transducer. The load applied to the lever was 1 g. After stabilization, the effect of elenoside was studied for 5 min at the following concentrations: 3.2×10^{-4}, 6.4×10^{-4} and 1.2×10^{-3} mol/L, and cisapride at 10^{-6} mol/L. Ten samples each of duodenum, jejunum, and ileum were used for each concentration.

Statistical analysis

Statistical analysis was performed using the Prism program with two-way analysis of variance (ANOVA) (between group-factor: dose repeated measures factor: time), followed by Tukey´s Multiple Comparison *post-hoc* test. For nonparametric analysis, the Kruskal-Wallis test, was followed by the Mann-Whitney test for catharsis index, water of boluses, intestinal transit, and intestinal transit and codeine antagonism. A probability of 5% or less was considered to indicate a significant difference.

RESULTS

Catharsis index

Table 1 shows the results of cathartic activity for the vehicle control group and groups receiving elenoside at doses of 25 or 50 mg/kg or cisapride at dose of 10 mg/kg. Elenoside produced an increase in the catharsis index compared to the control group. The results of 50 mg/kg group and controls ($P < 0.01$) and of the 50 mg/kg and 25

Table 1 Effect of vehicle control, elenoside (E) and cisapride (C) on catharsis index in rats (n = 10) per treatment group

	Rat weight	Catharsis index
Control	239 ± 4	0.1
E-25 mg/kg	240 ± 3	1.5
E-50 mg/kg	238 ± 3	2.16[a]
C-10 mg/kg	236 ± 2	2.04[a]

Values are mean ± SE for 10 rats. [a]$P < 0.05$ *vs* control.

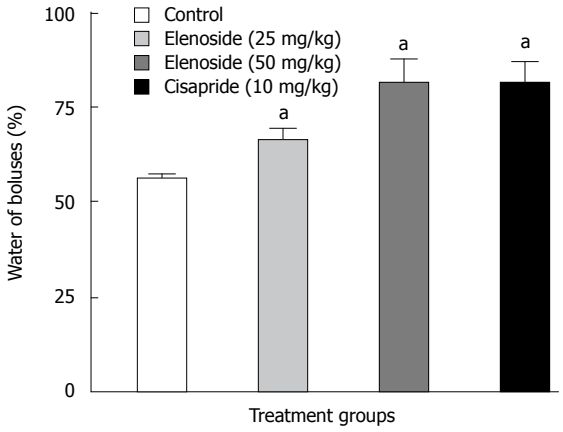

Figure 1 Percentage increase in water of boluses in vehicle control, elenoside, and cisapride. Values are mean ± SE for 10 rats/group. [a]$P < 0.05$ *vs* control.

mg/kg elenoside treatments, respectively, were significantly different from one another. Cisapride produced an increase in the catharsis index compared to the control group ($P < 0.05$), but it did not differ significantly from 50 mg/kg of elenoside in its effects.

Water percentage of boluses

Figure 1 shows the results of the water percentage of boluses analysis for control group, elenoside at doses of 25 and 50 mg/kg, and cisapride at 10 mg/kg. Both concentrations of elenoside produced an increase in water percentage *vs* vehicle control (*vs* 25 mg/kg elenoside, $P < 0.01$; *vs* 50 mg/kg elenoside, $P < 0.01$). Cisapride caused a significant increase in the water percentage versus the control group ($P < 0.01$), an effect similar to that produced by 50 mg/kg elenoside.

Intestinal transit

Figure 2 shows the results of the analysis of the effects of elenoside and cisapride on small intestinal transit (SIT) speed. Both concentrations of elenoside produced an increase in the percentage of distance the suspension of activated charcoal travelled *vs* the vehicle control (*vs* 25 mg/kg elenoside, $P < 0.01$; *vs* 50 mg/kg elenoside, $P < 0.01$). Cisapride produced a significant increase in SIT (control *vs* cisapride 10 mg/kg, $P < 0.05$). There was no difference between cisapride and the 50 mg/kg of elenoside.

Intestinal transit and codeine antagonism

Figure 3 shows the results of SIT analysis for elenoside with codeine phosphate. Codeine phosphate antagonized

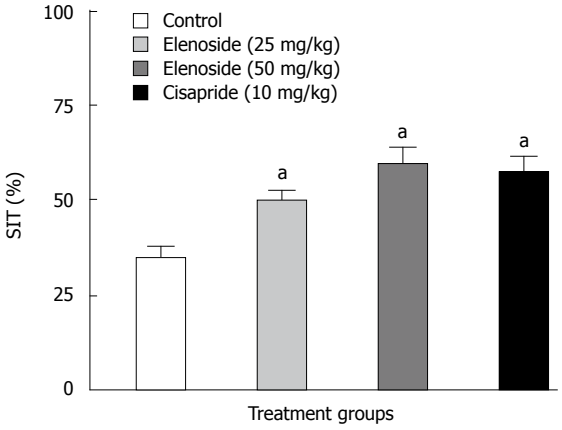

Figure 2 Small intestinal transit (SIT) in vehicle control and elenoside-treated and cisapride-treated animals. Values are mean ± SE for 10 rats/group. [a]$P < 0.05$ *vs* control.

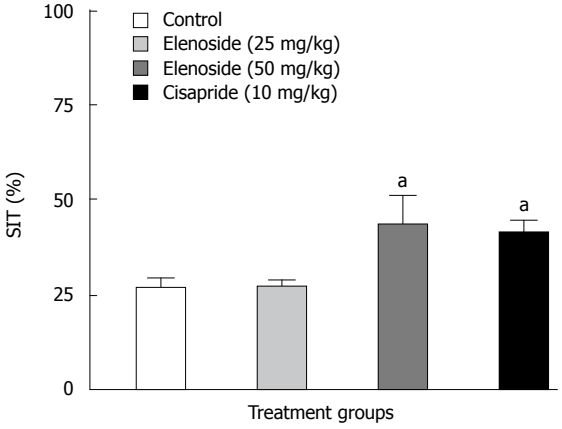

Figure 3 Codeine phosphate induced delay in small intestinal transit (SIT) in vehicle control, elenoside, and cisapride groups. Values are mean ± SE for 10 rats/group. [a]$P < 0.05$ *vs* control.

the effect of 25 mg/kg of elenoside. Moreover, codeine phosphate at 50 mg/kg produced an antagonistic effect on 50 mg/kg of elenoside and 10 mg/kg of cisapride, although this effect was not complete (control *vs* 50 mg/kg elenoside, $P < 0.05$; control *vs* 10 mg/kg cisapride, $P < 0.05$)

Isolated rat intestine

Figure 4 A-C show the results of the concentration force analysis; effects of elenoside and cisapride on duodenum, jejunum and ileum are depicted in Figures 4A, 4B and 4C, respectively. There was a clear dose-effect relationship over the three concentrations of elenoside.

At one minute, elenoside produced a decrease in the contraction force, which continued with increasing concentration from 3.2×10^{-4} mol/L ($P < 0.01$) to 6.4×10^{-4} mol/L ($P < 0.01$) to 1.2×10^{-3} mol/L ($P < 0.01$) during a five-minute assessment. Cisapride produced an effect similar to that of the 6.4×10^{-4} mol/L of elenoside. Elenoside at a concentration of 1.2×10^{-3} mol/L produced a significant increase in contraction force *vs* 3.2×10^{-4} mol/L at 2 ($P < 0.01$), 4 ($P < 0.01$) and 5 ($P < 0.01$) min respectively (Figure 4A).

Elenoside applied to jejunum produced a decrease in the contraction force at one minute, followed by an

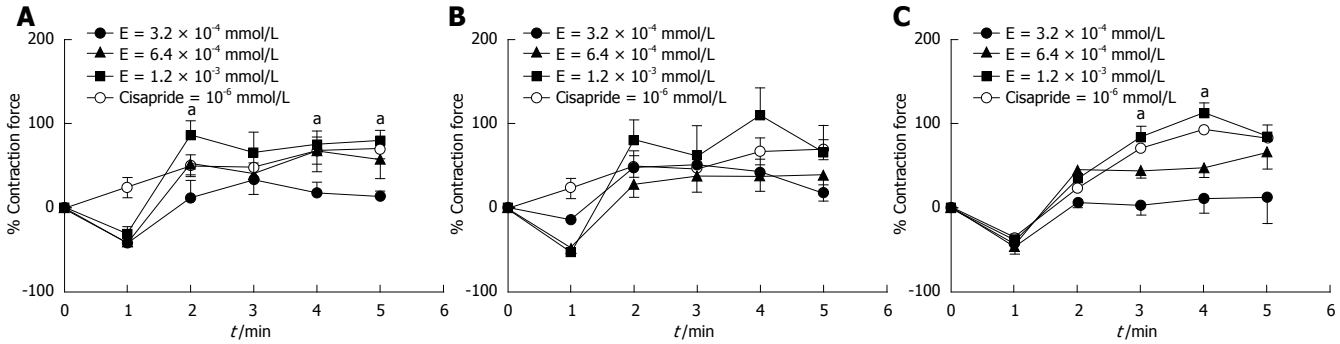

Figure 4 **A**: Time-course of the effects of elenoside and cisapride on contraction force in rat duodenum vs baseline. Values are mean ± SE for 10 duodenum samples during 6 min; $^aP < 0.05$. **B**: Time-course of the effects of elenoside and cisapride on contraction force in rat jejunum vs baseline. Values are mean ± SE for 10 jejunum samples during 6 min; $^aP < 0.05$. **C**: Time-course of the effects of elenoside and cisapride on contraction force in rat ileum vs baseline. Values are mean ± SE for 10 ileum samples during 6 min; $^aP < 0.05$.

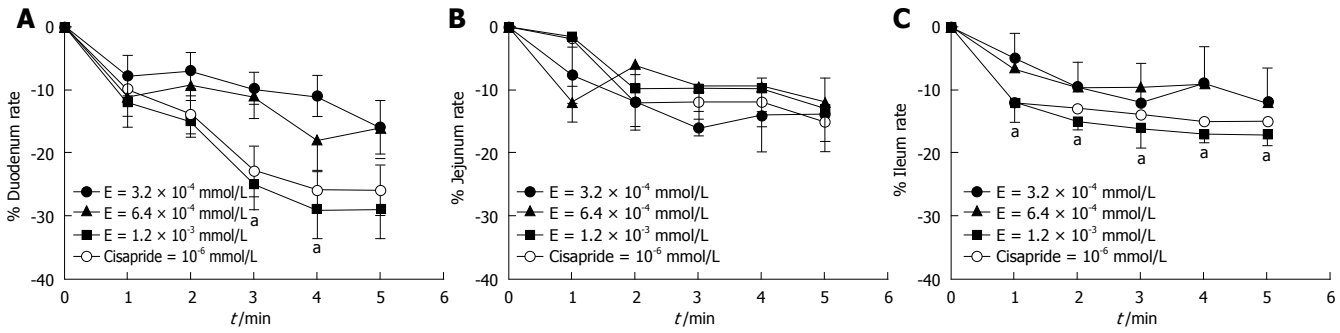

Figure 5 **A**: Time-course of the effects of elenoside and cisapride on intestinal frequency in the rat duodenum vs baseline. Values are mean ± SE for 10 duodenum samples during 6 min; $^aP < 0.05$. **B**: Time-course of the effects of elenoside and cisapride on intestinal frequency in the rat jejunum vs baseline. Values are mean ± SE for 10 jejunum samples during 6 min; $^aP < 0.05$. **C**: Time-course of the effects of elenoside and cisapride on intestinal frequency in the rat ileum vs baseline. Values are mean ± SE for 10 ileum samples during 6 min; $^aP < 0.05$.

increase at concentrations of 3.2×10^{-4} mol/L ($P < 0.01$), 6.4×10^{-4} mol/L ($P < 0.05$), and 1.2×10^{-3} mol/L ($P < 0.01$) at 5 min. Cisapride produced an effect similar to that obtained with elenoside at a concentration of 3.2×10^{-4} mmol/L (Figure 4B).

When elenoside was applied to ileum, a decrease in the contraction force was produced a minute later. In the next minute, the contraction force increased and continued to do so up to five minutes with elenoside concentrations of 6.4×10^{-4} mol/L ($P < 0.01$) and 1.2×10^{-3} mol/L ($P < 0.01$). There was no effect on contraction force with the mid-range concentration of elenoside. Cisapride induced an effect similar to that of elenoside at a concentration of 1.2×10^{-3} mol/L. Elenoside at a concentration of 3.2×10^{-4} mol/L produced a significant increase in the contraction force *vs* 1.2×10^{-3} mol/L elenoside at 3 ($P < 0.05$) and 4 ($P < 0.05$) min, respectively (Figure 4C).

Figure 5A-5C depicts results from the time-course analysis of the effects of elenoside on intestinal frequency of duodenum, jejunum, and ileum respectively. Elenoside produced a decrease in the intestinal frequency of duodenum at concentrations of 6.4×10^{-4} mo/L ($P < 0.05$) and 1.2×10^{-3} mo/L ($P < 0.01$) during the time-course. Cisapride produced an effect similar to that of elenoside at a concentration of 1.2×10^{-3} mo/L. Elenoside at a concentration of 1.2×10^{-3} mo/L produced a significant decrease in the intestinal frequency *vs* 3.2×10^{-4} mo/L at 3 ($P < 0.01$) and 4 ($P < 0.01$) min, respectively (Figure 5A).

Elenoside decreased intestinal frequency in jejunum at all concentrations used during the time-course. No statistical differences among the concentrations of elenoside were observed (Figure 5B).

Elenoside produced a decrease in intestinal frequency in ileum at all concentrations, but only the concentration of 1.2×10^{-3} mo/L ($P < 0.01$) produced a statistically significant decrease (Figure 5C).

DISCUSSION

In this study, elenoside, has been shown to act as a stimulant of gastrointestinal motility. It produced an increase in the catharsis index and in the number of humid boluses at a dose of 50 mg/kg. The water volume of the boluses was also enhanced after treatment with elenoside at the two doses used. These effects of elenoside on the gastrointestinal tract suggest its actions similar to that of purgative drugs.

Another effect of elenoside was the increase in the distance traveled by the charcoal suspension at doses of 25 and 50 mg/kg. The distance traveled by the charcoal suspension has been used in the evaluation of drugs to determine their effects on gastrointestinal motility[24-26]. Elenoside elicited gastrointestinal activity similar to that effected by cisapride at a dose of 10 mg/kg. This effect exerted by elenoside suggested an action similar to that of cisapride, a commonly used prokinetic drug

that acts *via* a mechanism that facilitates cholinergic neurotransmission[27], and of other prokinetic drugs, such as metoclopramide, domperidone, erythromycin, and mosapride[28,29], ghrelin and GHRP-6[30], betanecol[31], and magnolol and honokiol[16]. Other lignans can exert similar effects: Podophyllotoxin and picropodophyllotoxin, lignans isolated from *Podophyllum* species, and produce diarrhea when administered to animals[32]. Herbal remedies with prokinetic activity similar to elenoside are peppermint oil[33], *Cocculus hirsutus*[34], *Zingiber officinale*[35], *Indigofera dendroides*[25], Shundao granules[36], and Banxia-houpo-tang HKT[37].

Codeine phosphate totally antagonized this prokinetic action at the lowest dose of elenoside and partially antagonized it at the higher elenoside dose. In addition, it antagonized the prokinetic action of cisapride. Codeine phosphate is an opium alkaloid with an activity similar to but weaker than that of morphine. It is given mainly orally in the treatment of mild to moderate pain[38]. However, although opioids are given to relieve pain, they exert undesirable gastrointestinal side effects such as nausea, vomiting, and a decreased gastrointestinal transit[39].

Elenoside could be an alternative together with cisapride in the treatment of the undesirable gastrointestinal effects produced by opioid drugs. Increased peristaltic and cathartic activity are parameters of irritant cathartics, according to Fling classification[40].

In isolated rat duodenum, jejunum, and ileum, elenoside produced a decrease in the contraction force followed by an increase. Elenoside applied to duodenum and ileum decreased intestinal frequency, but no significant changes in jejunum were found. Other lignans have been shown to affect contraction force and intestinal frequency[41-43]. Lignans obtained from *Podophylum* species caused a decrease in the initial rate and amplitude of contractions of isolated intestinal preparations followed by an increase in the force of contraction[32]. 2, 3-dibenzil-butirolactone, a lignan obtained from *Carthamus tinctorus* L. (Compositae), was responsible for the cathartic activity of this plant[44]. *Curcuma longa* relaxed spontaneous contractions in isolated rabbit jejunum[45]. On the other hand, some lignans used in the treatment of diarrhea, produced an inhibition in the normal intestine propellant movement[46]. Magnolol and honokiol obtained from *M. officinalis* induced a decrease in contractility of guinea pig ileum[16].

Traditional herbal remedies are used because they can improve the symptoms of gastrointestinal diseases, such as dyspepsia, nausea, vomiting, and abdominal distension. Elenoside obtained from *J. hyssopifolia* could be used to treat these symptoms of gastrointestinal diseases. It produced an increase in the catharsis index or number of humid boluses; an enhancement of the water volume of boluses; and an increase in the distance traveled by the charcoal suspension. In addition, codeine phosphate totally antagonized its prokinetic action; in isolated rat duodenum, jejunum, and ileum, elenoside elicited a decrease in contraction force followed by an increase; and elenoside caused a decrease in intestinal frequency in duodenum and ileum, but not in jejunum.

In conclusion, elenoside in the gastrointestinal tract exhibits activities similar to that of purgative and prokinetics drugs. Elenoside could be an alternative to cisapride in the treatment of gastrointestinal diseases as well as a preventive of the undesirable gastrointestinal effects produced by opioids used for mild to moderate pain.

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