



Effects of Funchicórea®, a Traditional Brazilian Herbal Complex, on Intestinal Motility in Healthy and Constipated Rodents

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Authors' contributions

This work was carried out in collaboration among all authors. Authors ACMFV and VLA designed the study, conducted the research, analyzed the results and drafted the manuscript. Authors PMPM and JGFA conducted *in vivo* and *in vitro* experiments and analyzed the results. Authors CZ and JLR provided the herbal product, analyzed the results and helped to review the manuscript. Authors RCV, IGAA and IAM took primary responsibility for the paper, conceived and coordinated the study, responsible for funding acquisition and drafted the manuscript. All authors approved the final manuscript

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ABSTRACT

Ethnopharmacological Relevance: The traditional herbal medicinal product Funchicórea® has been widely used in clinical practice for the treatment of intestinal colic and constipation in newborns. However, no scientific data on the herbal product to prove its efficacy is available.

Aim of the Study: This study aimed to evaluate the laxative and spasmolytic actions of Funchicórea®.

Materials and Methods: Wistar rats (*Rattus norvegicus*) and Swiss mice (*Mus musculus*) of both

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sex, were used. In vivo pharmacological assays were performed to evaluate the stimulating effect on the gastrointestinal tract, and in vitro studies to verify its spasmodic activity.

Results: Funchicórea® increased the motility of the small intestine in male mice at doses of 100 mg/kg (161.66±14.86 %, n=6) and 200 mg/kg (151.04±17.17 %, n=6) compared to control (100.00±10.49 %, n=6). However, this drug did not induce any change in intestinal transit in female mice. The intestinal transit of male mice treated with loperamide (3 mg/kg/day, during three days) was reduced 66.25±7.49 % (n=8) compared to the control group (100.00±5.16%, n=8) and we observed the normalization of the intestinal transit in constipated animals treated with Funchicórea® 100 mg/Kg (98.42±6.33 %, and 200 mg/kg (99.32±8.47%, n=7). Similar results were observed in the quantification for 24 hours of male and female rats faeces constipated by loperamide (3 mg/kg/day three days), however, in both animals groups treated with Funchicórea® 100 mg/kg (1.24±2.90 g, male; 3.60±0.80 g, female, n=6) and 200 mg/Kg (8.70±2.01 g, male, 10.03±1.30 g, female, n=6) the levels of faeces returned to basal values compared to constipated group (4.01±1.43 g, male; 1.70±0.10 g, female, n=6). In addition, Funchicórea® (0.01-1000 µg/mL) elicited relaxation in rat ileum pre-contracted by KCl 40 mM (Emax=97.5±7.0 %, n=7) and carbachol (1 µM, Emax=100.0±7.0 %, n=7).

Conclusion: The results obtained demonstrated that the herbal medicine Funchicórea® acts by stimulating the intestine of rats and mice and has spasmolytic activity in isolated rat ileum.

Keywords: Traditional herbal medicine; Gastrointestinal tract; Loperamide induced constipation; laxative; spasmolytic; calcium.

1. INTRODUCTION

Functional gastrointestinal disorders (FGD) are generalized diseases, more common than hypertension, obesity, or diabetes mellitus [1,2]. About 2.6% to 26.9% of the world population suffers from constipation, a condition more frequent than ever [3,4]. Constipation is an example of FGD, whose simple definition is the condition in which the stools are abnormally hard and difficult to eliminate, regardless of the frequency of bowel movements [5].

Infantile colic is a type of disorder that is important because it affects about 16% to 26% of children in the first months of life and therefore it becomes a frequent problem for both parents and caregivers [1,6–8]. episodes of constipation and colic include excessive and inconsolable crying, bending of the legs, distension, and tension in the abdomen, vigorous exertion, the passage of excessive gas, explosive evacuation and postprandial agitation and discomfort, suggesting that the baby is experiencing abdominal pain that may be similar to that of adults with irritable bowel syndrome [9].

To improve FGD, several plants and secondary metabolites, such as phenolic compounds and flavonoids, can be used, which have pharmacological effects and clinical benefits in the area of gastroenterology [10,11]. Funchicórea®, is a traditional Brazilian herbal medicine used in folk medicine for over 50 years

against intestinal colic and constipation, mainly in newborns and children, which consists of the dry root extract of *Rheum palmatum* L., leaves of *Cichorium intybus* L. and flowers of *Foeniculum vulgare* L.. However, any scientific proof of its effectiveness was found in the literature. Thus, the efficacy of this herbal complex remains questionable and its use is locally restricted [12].

Rheum palmatum L. (family: Polygonaceae), in folk medicine, is known as rhubarb and is widely known for its laxative effect, for treating gastrointestinal disorders and a wide range of diseases, including kidney stones, gout, liver, as well as other intestinal diseases [13,14,15].

Cichorium intybus L, a member of the sunflower family (Asteraceae, Compositae), is a typical Mediterranean plant native to Europe, Western Asia and North America [16]. It is dated that the Egyptians cultivated chicory as a medicinal plant 4,000 years ago [17]. Phytochemical studies have shown that, in addition to inulin, the main storage carbohydrate in many Asteraceae, plants of the genus *Cichorium* produce bitter sesquiterpene lactones, phenolic compounds [18–20] and coumarins [21].

Foeniculum vulgare is a small greenish-brown seed belonging to the Umbelliferae family. It grows in the Mediterranean region and in West Asia. *F. vulgare* seeds alone and in preparations are used to cure various diseases, acting as a carminative, lactagogue and diuretic agent and

used to treat respiratory and gastrointestinal problems [22].

The traditional use of a product should serve as another way of subsidizing their safety and effectiveness, however, it is important to complement these data with toxicological and pharmacological pre-clinical studies [23]. Thus, this study aimed to investigate the preclinical pharmacological effects induced by Funchicórea®, a Brazilian traditional herbal medicinal product, on intestinal transit and fecal output in healthy and constipated animals, besides to evaluate its spasmolytic activity in the isolated rat ileum.

2. MATERIALS AND METHODS

2.1 Drugs and Chemicals

Hydrochloride carbamylcholine (carbachol, Merck), loperamide hydrochloride (Janssen-Cilag), HCl (Nuclear), diethylstilbestrol (Sigma), Carboxymethylcellulose (Sigma), and red phenol (Sigma). The herbal product Funchicórea® was kindly provided by the Laboratory Melpoejo Ltda-Brazil. In the experiments using isolated rat ileum preparations, a Krebs modified solution was used [24] (in mM): NaCl (117.0), NaHCO₃ (25.0) KCl (4.7), MgSO₄.7H₂O (1.3), NaH₂PO₄.H₂O (1.2), CaCl₂ H₂O (2.5) and glucose (11.0), pH 7.4 and bubbled with carbogen (95% O₂ and 5% CO₂, White Martins, LTDA). All salts were from Merck Brazil, LTDA.

2.2 Animals

Wistar rats (*Rattus norvegicus*) and Swiss mice (*Mus musculus*) of both sex, were provided from the animal house "Prof. George Thomas" from the Federal University of Paraíba (UFPB). All experimental protocols were approved by Ethics Committee for Animal Research (CEPA) UFPB, n°0406/11. The animals were housed in individual stainless steel cages at a controlled temperature (21±1 °C), in normal 12-h light and dark cycle with free access to water and balanced feed (type "pellets", Purina®), according to international recommendations [24].

2.3 In vivo Experiments

2.3.1 Analysis and induction of estrus of female rats and mice

The estrous cycle was monitored via vaginal smears at least three consecutive days [25,26]. On the second day, the animals were treated

with diethylstilbestrol (1 mg/Kg body weight, sc) to inducing estrus and after 24h only animals in "estrus" were selected [27].

2.3.2 Induction of constipation in mice and rats

Constipation was induced in the animals by oral administration of loperamide (3 mg/kg body weight/day in 0.9% NaCl for 5 days), while the non-constipated control animals group received saline [28]. The reduction of intestinal transit or decrease of fecal weight indicated constipation in mice or rats, respectively.

2.3.3 Gastrointestinal transit (GIT) ratio in mice non-constipated and constipated

In experiments with non-constipated mice, the animals after fasting (12h) [29] were separated into groups in accordance with sex and each of these was divided into experimental groups with six mice, a first group received saline, a second group received Funchicórea® 100 mg/kg and a third group received 200 mg/Kg Funchicórea®. Animals received Funchicórea® diluted with saline or only saline intragastrically (i.g.) in the dose of 10 ml/kg. After 30 minutes, all animals received a suspension of phenol red (PhR_S, 50 mg suspended in 100 mL of the 1.5% carboxymethylcellulose, 10 ml/kg). 30 minutes later, the animals were euthanized by cervical dislocation, the abdomen was opened and the small intestine was rapidly removed and the measurement of intestinal transit realized.

In experiments with constipated mice, the animals in group 1 (normal control) and group 2 (constipated control) were treated with saline. Groups 3 and 4 comprised constipated mice given Funchicórea® (100 and 200mg/kg, respectively).

Measurement of intestinal transit was evaluated by comparing the distance traveled by the small intestine marker from the pyloric sphincter to the most distal part of the PhR_S bulk (distance traveled by PhR_S), with the total length of the small intestine, measured from the pyloric sphincter to the ileocecal junction. This study was conducted according to the method described by Stickney and Northup [30]. The intestinal transit (% transit) was calculated as a percentage conforming to the following equation % transit =(distance traveled by PhR_S/total length of the small intestine)x100

2.3.4 Determination of fecal elimination over 24 hours in non-constipated and constipated rats

The determination of fecal elimination followed the technique described by Awouters et al. (1975) briefly, the animals were placed in individual metabolic cages, which allowed measurements of water intake, and the feed quantity of faeces eliminated. After the acclimation period, male and female rats were grouped into three of six rats each. The first group of the animals received saline (control), the second and third group received 100 and 200 mg/kg of Funchicórea®, respectively. After 24 hours of treatment, the animals individually were evaluated with respect to body weight, the amount of faeces eliminated and water and feed consumption.

In the next set of experiments, after acclimation, animals of Group 1 (normal control) were treated with saline. Group 2 (constipated control, n=6), Groups 3 (n=6) and 4 (n=6) were constipated with loperamide treatment (3 mg/kg/day). On the third day, while animals of groups 1 and 2 received saline, the animals of groups 3 and 4 received 100 and 200 mg/kg/day of Funchicórea®, respectively. The body weight, water and feed intake, and fecal weight of all rats were recorded after administration of saline and Funchicórea®.

2.4 In vitro Experiments

2.4.1 Pharmacological assays using isolated rat ileum

Rats were sacrificed after 12 h of fasting, the abdomen was opened and the ileum removed. After dissection, segments 2-3 cm of ileum were incubated in an organ bath containing 20 mL of modified Krebs buffer, pH 7.4 and bubbled with carbogen, under the tension of 1 g, at 37°C, and attached to a force transducer (FORT 10, WPI, Sarasota, USA) coupled to acquisition system (Miobath-4, WPI, Sarasota, USA) to obtain registration of isometric tension and kept at rest for 30 min before the beginning of the experimental procedures [31]. During this period, the nutrient solution was replaced every 15 minutes to prevent interference of metabolites [32] and the baseline was adjusted as necessary. After stabilization, contractions were induced in preparations of isolated rat ileum, by the use of constrictor agents such as depolarising solution of 40 mM KCl and carbachol (1 µM) in different

preparations. In the second component of the tonic contraction was added cumulatively Funchicórea® concentrations (1 µg/mL, 3 µg/mL, 10 µg/mL, 30 µg/mL, 100 µg/mL, 300 µg/mL, 1000 µg/mL) to construction of cumulative dose-response curve.

2.5 Statistical analysis

Values are presented as mean±standard error of the mean (S.E.M.). For statistical analysis was used the Student t-test and analysis of variance "oneway" (ANOVA) followed by the Bonferroni test, the difference between values was considered statistically significant when $P<0.05$. All data were analyzed using the statistical program GraphPad Prism 5.0®.

3. RESULTS

3.1 Effect Induced by Funchicórea® on Intestinal Transit of Mice

The intra-gastric administration of Funchicórea® increased the distance traveled by the marker (PhR_S) in the small intestine of non-constipated male mice, at 100 mg/kg (161.66±14.86%, n=6, $P<0.05$) and 200 mg/kg (151.04±17.17%, n=6, $P<0.05$) compared to control group (100.00±10.49%, n=6). There was no difference between the doses. However, any change in intestinal transit of female mice after administration of Funchicórea® could be observed (Fig. 1).

Treatment with loperamide (3mg/kg/day) for three days caused a decline of the distance traveled by the PhR_S in the small intestine of male mice (66.25±7.49%, n=8, $P<0.05$) compared to the control group (100±5.16%, n=8). The treatment with Funchicórea® 100 mg/kg (98.42±6.33%, n=7, $P<0.05$) and 200 mg/kg (99.32±8.47%, n=7, $P<0.05$) significantly reversed the inhibitory effect induced by treatment with loperamide (Fig. 2).

3.2 Effect Induced by Funchicórea® after 24h Faeces Elimination

After 24h, Funchicórea® (100 and 200mg/kg) did not change the parameters assessed (body weight, water and food intake, and elimination of faeces) in non-constipated male and female rats (see Table 1). However, constipated animals obtained different results. Females and males rats when treated with Loperamide (3mg/kg) presented a reduction in fecal elimination (about

50% to males and 40% to females). The treatment with Funchicórea® (100 mg/kg and 200 mg/kg reversed the inhibitory effect induced by Loperamide (3 mg/kg) to normal values (Table 2).

3.3 Effect Induced by Funchicórea® in the Isolated Rat Ileum Pre-Contracted with Carbachol and Depolarizing Solution

In this model of spasmolytic activity, Funchicórea® (1-1000µg/mL) induced relaxation by concentration dependent manner in ileum of rats pre-contracted with KCl (40 mM) ($E_{max}=97.5\pm7.0$, $n=7$) and carbachol (1 µM, $E_{max}=100.0\pm7.0$, $n=7$, Fig. 3). Although a difference in potency has been observed, there

was no difference in maximal effect induced by Funchicórea® in these two constrictor agents.

4. DISCUSSION

This study evidenced the pharmacological results that could show the effectiveness of a traditional herbal complex which already marketed in Brazil for over fifty years, similar to other drugs used in folk medicine, especially preparations containing more than one compound, has not been previously studied on its intestinal motility [33]. The main finding of this study was to demonstrate the effects already reported of this herbal product, performing for this purpose, preclinical pharmacological assays, that were consistent with their traditional uses [9].

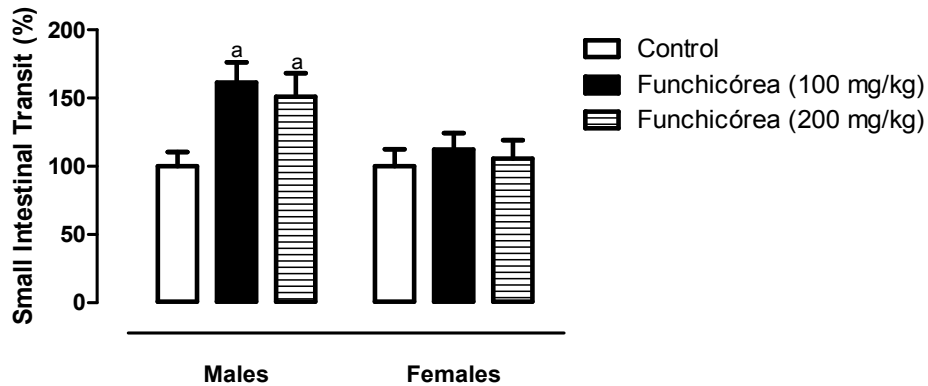


Fig. 1. Effect of Funchicórea on small intestinal transit of male and female mice. Representative bars were normalized to the intestinal transit of control animals (treatment with saline, 100%). Data are expressed as mean±e.p.m. of 6 animals. a= $P<0.05$ compared to control

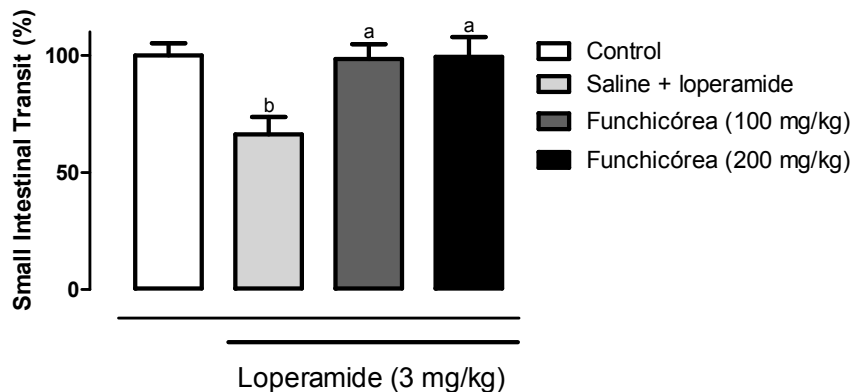


Fig. 2. Funchicórea normalizes the small intestinal transit of mice treated with Loperamide (3 mg/kg). Representative bars were normalized to the intestinal transit of control animals (treatment with saline, 100%). Data are expressed as mean±e.p.m. of 6 animals. a= $P<0.05$ compared to constipated animals (treated with loperamide, 3 mg/kg), b= $P<0.05$ compared to non-constipated animals (control, treated with saline)

Table 1. Effect of Funchicórea on weight, water and feed intake and fecal elimination of non-constipated male and females rats

Groups (females, n=6)	Variation of weight (g)	Ingestion of water (mL)	Ingestion of food (g)	Elimination of feces (g)
Control	0.88±1.43	21.81±2.44	14.60±2.70	5.30±1.23
Funchicórea (100 mg/kg)	0,98±1.67	22.50±3.70	15.73±4.07	5.73±1.40
Funchicórea (200 mg/kg)	-2.61±1.52	16.20±5.54	10.20±4.04	3.70±1.51
Groups (males, n=6)	Variation of weight (g)	Ingestion of water (mL)	Ingestion of food (g)	Elimination of feces (g)
Control	0.97±0.01	16.42±3.23	10.18±6.70	3.00±1.70
Funchicórea (100 mg/kg)	0.98±0.02	17.50±6.0	16.32±8.40	3.80±1.80
Funchicórea (200 mg/kg)	0.95±0.01	12.17±4.40	15.78±9.00	4.48±2.71

Data are presented as mean±epm (n=6/per group)

Table 2. Effect of Funchicórea on weight, water and feed intake and fecal elimination of constipated rats (male and female)

Groups (males, n=6)	Variation of weight (g)	Water intake (mL)	Feed intake (g)	Fecal elimination (g)
Normal Control	1.45±3.01	28.00±4.90	18.28±4.20	8.0±1.01 ^a
Constipated Control	1.55±4.35	30.83±2.55	18.45±4.19	4.0±1.43
Constipated + Funchicórea (100mg/kg)	-4.35±4.70	23.00±13.25	17.47±5.42	11.2±2.90 ^a
Constipated + Funchicórea (200mg/kg)	-3.52±4,20	26.83±6.64	21.38±5.25	8.70±2.01 ^a
Groups (females, n=6)	Variation of weight (g)	Water intake (mL)	Feed intake (g)	Fecal elimination (g)
Normal Control	-2.30±2.70	22.00±3.16	11.73±3.57	8.0±0.75 ^a
Constipated Control	-4.60±2.63	19.50±5.86	11.57±4.86	4.7±0.72
Constipated + Funchicórea (100 mg/kg)	-2.06±1.44	26.00±5.64	20.57±1.09	9.2±2.44 ^a
Constipated + Funchicórea (200 mg/kg)	-0.53±1.11	26.50±4.82	17.88±2.43	10.9±1.54 ^a

Data are presented as mean±epm (n=6/group). a=P<0.05 vs Loperamide (3 mg/Kg)

Funchicórea® is indicated for the treatment of intestinal colic and constipation, especially in newborns. The infant's abdominal pain can be considered similar to the spastic colon, which is a benign relapsing chronic disorder, characterized by altered bowel function and recurrent abdominal pain. In the literature, a few are known preparations containing drugs that have both laxative and spasmolytic effects and may be promising in the treatment of diseases like spastic colon and infantile colic [9,33].

Numerous animal studies demonstrate the bioactivity and effects on the intestinal function of various plants used in the treatment of intestinal disorders. The intestinal transit is usually determined by measuring traversed by a marker,

the phenol red [34]. In the present study, Funchicórea® (100 and 200 mg/kg) significantly increase the peristalsis and motility, only in male mice (Fig. 1) when compared to non-treated animals. No significant change was observed in experiments with females, ever with controlled estrous cycle. Study from Ryan and Cols, 1986 support the hypothesis that colonic transit in female rats is influenced by the circulating levels of the female sex steroid hormones. Specifically, situations that result in increased hormone levels are characterized by decreased transit. In humans, an influence of hormones may exist, but the influence of menstrual hormones on gastrointestinal transit must be small and of doubtful clinical significance [35].

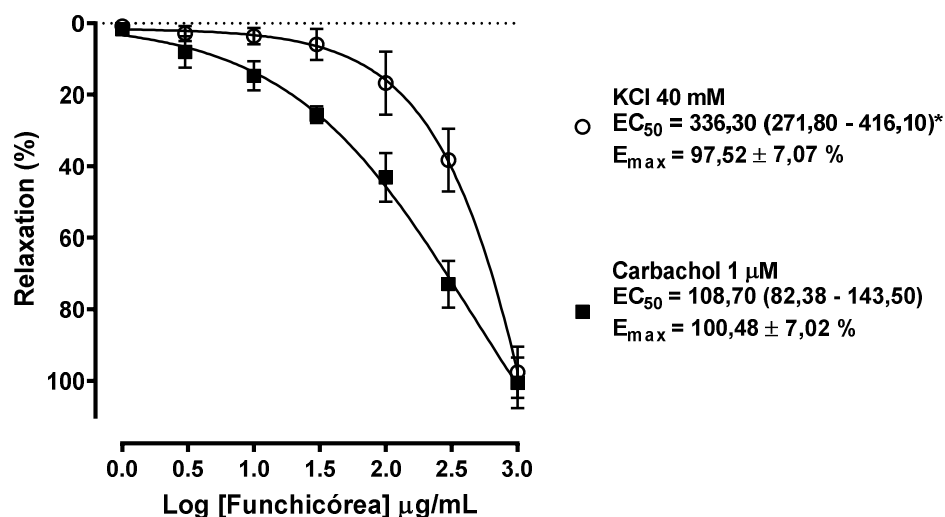


Fig. 3. Concentration-response curve to Funchicórea (1-1000mg/mL) on isolated rat ileum strips pre-contracted with 40 mM KCl (○) or 1 μM carbachol (■)

Attention then turned to evaluate the herbal medicine effect in animal constipated using a documented constipation spastic model induced by Loperamide [36]. This compound promotes an increase in the evacuation time interval in rats, inhibits peristalsis in colon [37] and control the smooth movement of the intestinal wall [38]. This inhibition decreases the intestinal transit causing a delay in faeces elimination [29]. Loperamide has therefore been widely used to identify the cause of constipation and find useful therapeutic agents [38].

In intestinal transit experiments, was observed an inhibitory effect induced by loperamide which presented a decrease in the percentage of the intestine traveled by the phenol red (marker) compared to control groups. Accordingly, administration of 100 and 200 mg/kg of the herbal medicine reversed the constipating effect induced by loperamide, reestablishing the intestinal motility similarly to the control group (Fig. 2).

Since the motility effect was characterized in the small intestine, our group sought to investigate the action of Funchicórea® on entire gastrointestinal transit by assessing the elimination of faeces in a period of 24 hours. This protocol is an excellent tool for acute investigations, which is a practical way to estimate full gastrointestinal motor activity [39]. Funchicórea® (100 and 200mg/kg, *per os*) did not cause changes in analyzed parameters in the

experimental protocol for fecal elimination over 24 hours in both male and female rats (Table 1). However, Funchicórea® tended to increase the number of faeces eliminated at doses studied, additionally was not observed animals with diarrhea, indicating a protection gastrointestinal effect [40,41,42].

In constipated animals, loperamide promoted a decreased amount of faeces eliminated, indicating the induction of constipation in both male and female rats (Table 1). Similar findings were reported by Wintola and collaborators (2010), whose study demonstrated that oral administration of loperamide also induced a decrease in weight of faeces eliminated.

The treatment of constipated animals, male and female, with Funchicórea® returned to basal faeces levels eliminated in 24 hours. This laxative effect induced by Funchicórea® may be due to the presence of hydroxyanthraquinones (emodin), their glucosides (aloe-emodin, emodin and chrysophanol) containing in the root of *R. rhaponticum* [43]. These effects may not require essentially their absorption through the gut barrier, may occur mainly in the intestinal lumen [44]. According to Izzo et al. [40] aloin, a polyphenol found in the root of *R. rhaponticum*, is metabolized by the gut microbiota to reactive aloe-emodin which is responsible for the purgative activity. This compound possibly exerts its action by disturbing the equilibrium between the absorption of water from the intestinal lumen

via an active sodium transport [45] and the secretion of water into the lumen by prostaglandin-dependent mechanism [46,47].

The postulated mechanism in the pathogenesis of infantile colic may be a spasm of the intestinal smooth muscles [22]. In pharmacological trials used to evaluate the spasmolytic activity on isolated rat ileum, Funchicórea® (1-1000 mg/mL) relaxed concentration-dependent manner preparations of isolated rat ileum, pre-contracted by depolarizing Krebs solution (containing 40 mM KCl) and by carbachol (Fig. 3). In a first moment in both conditions, Funchicórea® shows absence of response on 1mg/mL or in lower concentrations. Funchicórea® was more potent when the organ was contracted with Cch (1 µM) shifting the curve to left versus KCl 40 mM curve [42].

Carbachol, a cholinergic agonist binds to receptors M(3) found in the ileum [48]. These receptors are coupled to Gq protein that activates phospholipase C, promoting the synthesis of inositol triphosphate (IP3) which induces the release of calcium from intracellular calcium inventories and calcium influx through voltage-gated calcium channels (Cav), channels activated receptor (ROC), and channels activated by the depletion of intracellular store (SOC). The solutions rich in K⁺ promote depolarization of the membrane and thus opens Cav, causing the influx of Ca²⁺ and muscle contraction [49]. Although a significant difference in potency has been observed, there was no significant difference in the maximal relaxant effect induced by Funchicórea® in response to these two constrictor agents. So, the spasmolytic activity induced by the traditional herbal product may be due to its action on both, muscarinic receptors and/or calcium mobilization. As a matter of fact, a previous study has demonstrated that signal transduction of mAChR M2 and M3 is a molecular mechanism mediating the laxative effects of aqueous extracts of LP [50]. Furthermore, since regulation of the smooth muscles in the small intestine is calcium dependent, the concentration of intracellular calcium is an important factor in the constipation-related signal transduction system. Therefore, the regulation of the intracellular calcium concentration, is an indicator of the therapeutic effect of significant constipation [51].

Taken together, the effects on muscarinic receptors and on calcium movements may

account for its effectiveness against inducing abdominal spasm.

The results obtained from this study were similar to animal experiments have demonstrated by F. vulgare seed oil, which reduces the intestinal spasms and increases the motility of the small intestine [52,53]. Therefore, Funchicórea® can cause relaxation of pre-contracted isolated ileum rat, contributing to the return of the physiological function. A similar mechanism has been found for other substances used in the treatment of constipation, such as magnesium sulfate, a known stimulant laxative whose smooth muscle relaxation of the colon reduces the flow resistance and promotes bowel movement of fecal material along the intestine [40,54].

Finally, Funchicórea®, a traditional herbal medicinal product consisting of different medicinal plants, may lead to the development of several mechanisms of action and various biological effects, in this case, producing laxative and spasmolytic activities. In the literature, there are other drugs that also have this same indication, such as Eucarbon®, which is classified as a stimulant laxative that has a mild laxative effect and spasmolytic action acting by relieving the pain intestinal [32]. Other studies have demonstrated that other laxatives, such as supplementation by fibers, a trend toward reduced intraluminal pressures and normalization of colonic motility of humans with irritable bowel syndrome [9].

5. CONCLUSION

Our findings together, contributed to the preclinical study of Funchicórea® with characterization of their effects on intestinal motility and antispasmodic activity, which corroborate its use for the infantile colic treatment. However, future studies are needed to clarify the possible mechanisms of action involved in the effects induced by this traditional herbal complex.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by

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CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Fornai M, Colucci R, Antonioli L, Ghisu N, Tuccori M, Gori G, Blandizzi C, et al. Effects of a bicarbonate-alkaline mineral water on digestive motility in experimental models of functional and inflammatory gastrointestinal disorders. *Methods Find Exp Clin Pharmacol*. 2008;30(4):26.
2. Foxx-Orenstein A, McNally MA, Odunsi ST. Update on constipation: one treatment does not fit all. *Cleve Clin J Med*. 2008;75(11):813.
3. Peppas G, Alexiou VG, Mourtzoukou E, Falagas ME. Epidemiology of constipation in Europe and Oceania: A systematic review. *BMC Gastroenterol*. 2008;8(1):5.
4. Schmidt FMQ, Santos VLGC. Prevalence of constipation in the general adult population. *J Wound Ostomy Cont Nurs*. 2014;41(1):70-76.
5. Bisanz AK. Bowel management in patients with cancer. In: *Gastrointestinal Cancer*. Springer; 2005:313-345.
6. Crowcroft NS, Strachan DP. The social origins of infantile colic: Questionnaire study covering 76 747 infants. *BMJ*. 1997; 314(7090):1325.
7. Hide DW, Guyer BM. Prevalence of infant colic. *Arch Dis Child*. 1982;57(7):559-560.
8. Rubin SP, Prendergast M. Infantile colic: Incidence and treatment in a Norfolk community. *Child Care Health Dev*. 1984;10(4):219-226.
9. Treem WR, Hyams JS, Blankschen E, Etienne N, Paule CL, Borschel MW. Evaluation of the effect of a fiber-enriched formula on infant colic. *J Pediatr*. 1991; 119(5):695-701.
10. Hur SJ, Kang SH, Jung HS, Kim SC, Jeon HS, Kim IH, et al. Review of natural products actions on cytokines in inflammatory bowel disease. *Nutr Res*. 2012;32(11):801-816.
11. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. *Am J Clin Nutr*. 2004; 79(5):727-747.
12. Kaur GJ, Arora DS. Antibacterial and phytochemical screening of *Anethum graveolens*, *Foeniculum vulgare* and *Trachyspermum ammi*. *BMC Complement Altern Med*. 2009;9(1):30.
13. Xiao P, He L, Wang L. Ethnopharmacologic study of Chinese rhubarb. *J Ethnopharmacol*. 1984;10(3): 275-293.
14. Silveira JPS, Seito LN, Eberlin S, Dieamant GC, Nogueira C, Pereda MCV, et al. Photoprotective and antioxidant effects of Rhubarb: Inhibitory action on tyrosinase and tyrosine kinase activities and TNF- α , IL-1 α and α -MSH production in human melanocytes. *BMC Complement Altern Med*. 2013;13(1):49.
15. Zhang X, Wang L, Chen D-C. Effect of rhubarb on gastrointestinal dysfunction in critically ill patients: A retrospective study based on propensity score matching. *Chin Med J (Engl)*. 2018;131(10):1142.
16. Fernald ML. *Gray's manual of botany 1632* New York. NY Am B Co. 1950;1632.
17. Faraji S, Daneghian S, Alizadeh M. Effects of chicory (*Cichorium intybus* L.) on nonalcoholic fatty liver disease. *Tradit Med Res*. 2020;5(6):476-486.
18. Kisiel W, Michalska K. Root constituents of *Cichorium pumilum* and rearrangements of some lactucin-like guaianolides. *Zeitschrift für Naturforsch C*. 2003;58(11-12):789-792.
19. Papetti A, Daglia M, Aceti C, Sordelli B, Spini V, Carazzone C, et al. Hydroxycinnamic acid derivatives occurring in *Cichorium endivia* vegetables. *J Pharm Biomed Anal*. 2008;48(2):472-476.
20. Shulha O, Zidorn C. Sesquiterpene lactones and their precursors as

- chemosystematic markers in the tribe Cichorieae of the Asteraceae revisited: An update (2008–2017). *Phytochemistry*. 2019;163:149-177.
21. Kumari BDR, Velayutham P, Anitha S. A comparative study on inulin and esculin content of *in vitro* and *in vivo* Plants of Chicory (*Cichorium intybus* L. Cv. Lucknow Local). *Adv Biol Res (Rennes)*. 2007;1(1-2):22-25.
 22. Alexandrovich I, Rakovitskaya O, Kolmo E, Sidorova T, Shushunov S. The effect of fennel (*Foeniculum vulgare*) seed oil emulsion in infantile colic: A randomized, placebo-controlled study. *Altern Ther Health Med*. 2003;9(4):58.
 23. Turolla MSR, Nascimento ES. Informações toxicológicas de alguns fitoterápicos utilizados no Brasil. *Rev Bras Ciências Farm*. 2006;42(2):289-306.
 24. Sun Y-D, Benishin CG. K⁺ channel openers relax longitudinal muscle of guinea pig ileum. *Eur J Pharmacol*. 1994; 271(2-3):453-459.
 25. Marcondes FK, Bianchi FJ, Tanno AP. Determination of the estrous cycle phases of rats: Some helpful considerations. *Brazilian J Biol*. 2002;62(4A):609-614.
 26. Saito T, Ciobotaru A, Bopassa JC, Toro L, Stefani E, Eghbali M. Estrogen contributes to gender differences in mouse ventricular repolarization. *Circ Res*. 2009;105(4):343-352.
 27. McCracken JA, Custer EE, Lamsa JC. Luteolysis: A neuroendocrine-mediated event. *Physiol Rev*. 1999;79(2):263-323.
 28. Bustos D, Ogawa K, Pons S, Soriano E, Bandi JC, Fernández BL. Effect of loperamide and bisacodyl on intestinal transit time, fecal weight and short chain fatty acid excretion in the rat. *Acta gastroenterol latinoam*. Published online 1991:3-9.
 29. Wintola OA, Sunmonu TO, Afolayan AJ. The effect of *Aloe ferox* Mill. in the treatment of loperamide-induced constipation in Wistar rats. *BMC Gastroenterol*. 2010;10(1):95.
 30. Stickney JC, Northup DW. Effect of gastric emptying upon propulsive motility of small intestine of rats. *Proc Soc Exp Biol Med*. 1959;101(3):582-583.
 31. Pessôa HLF, Oliveira RCM, Silva JL V, Santos RF, Duarte JC, Costa MJC, et al. Evaluation of the acute toxicity, cytotoxic and spasmolytic effects of *Pomacea lineata* (Spix, 1827) (Mollusca, Caenogastropoda) 2007;17:76-84.
 32. Altura BM, Altura BT. Differential effects of substrate depletion on drug-induced contractions of rabbit aorta. *Am J Physiol Content*. 1970;219(6):1698-1705.
 33. Hübner WD, Moser EH. Charcoal tablets in the treatment of patients with irritable bowel syndrome. *Adv Ther*. 2002; 19(5):245-252.
 34. Palombo EA. Phytochemicals from traditional medicinal plants used in the treatment of diarrhoea: Modes of action and effects on intestinal function. *Phyther Res An Int J Devoted to Pharmacol Toxicol Eval Nat Prod Deriv*. 2006;20(9):717-724.
 35. Degen LP, Phillips SF. Variability of gastrointestinal transit in healthy women and men. *Gut*. 1996;39(2):299-305.
 36. Kakino M, Tazawa S, Maruyama H, Tsuruma K, Araki Y, Shimazawa M, et al. Laxative effects of agarwood on low-fiber diet-induced constipation in rats. *BMC Complement Altern Med*. 2010;10(1):68.
 37. Shimotoyodome A, Meguro S, Hase T, Tokimitsu I, Sakata T. Decreased colonic mucus in rats with loperamide-induced constipation. *Comp Biochem Physiol Part A Mol Integr Physiol*. 2000;126(2):203-212.
 38. Lee H-Y, Kim J-H, Jeung H-W, Lee C-U, Kim D-S, Li B, et al. Effects of *Ficus carica* paste on loperamide-induced constipation in rats. *Food Chem Toxicol*. 2012;50(3-4):895-902.
 39. Wang X, Zhang F, Liu Z, Feng H, Yu Z-B, Lu Y, et al. Effects of essential oil from *Croton tiglium* L. on intestinal transit in mice. *J Ethnopharmacol*. 2008;117(1):102-107.
 40. Izzo AA, Gaginella TS, Mascolo N, Capasso F. Nitric oxide as a mediator of the laxative action of magnesium sulphate. *Br J Pharmacol*. 1994;113(1):228-232.
 41. Watanabe M, Miyai A, Danjo S, Nakamura Y, Itoh K. The threshold of pentylenetetrazole-induced convulsive seizures, but not that of nonconvulsive seizures, is controlled by the nitric oxide levels in murine brains. *Exp Neurol*. 2013;247:645-652.
 42. Ryan JP, Bhojwani A. Colonic transit in rats: effect of ovariectomy, sex steroid hormones, and pregnancy. *Am J Physiol Liver Physiol*. 1986;251(1):G46-G50.
 43. Raal A, Pokk P, Arend A, Aunapuu M, Jõgi J, Okva K, et al. trans-resveratrol alone and hydroxystilbenes of rhubarb (*Rheum*

- rhaponticum* L.) root reduce liver damage induced by chronic ethanol administration: a comparative study in mice. *Phyther Res An Int J Devoted to Pharmacol Toxicol Eval Nat Prod Deriv.* 2009; 23(4):525-532.
44. Santos-Buelga C, Scalbert A. Proanthocyanidins and tannin-like compounds—nature, occurrence, dietary intake and effects on nutrition and health. *J Sci Food Agric.* 2000;80(7):1094-1117.
45. Ishii Y, Tanizawa H, Takino Y. Studies of Aloe. III.: Mechanism of Cathartic Effect.(2). *Chem Pharm Bull.* 1990;38(1): 197-200.
46. Capasso F, Mascolo N, Autore G, Duraccio MR. Effect of indomethacin on aloin and 1, 8 dioxianthraquinone-induced production of prostaglandins in rat isolated colon. *Prostaglandins.* 1983;26(4):557-562.
47. Collier HO, McDonald-Gibson WJ, Saeed SA. Stimulation of prostaglandin biosynthesis by drugs: effects in vitro of some drugs affecting gut function. *Br J Pharmacol.* 1976;58(2):193.
48. Hishinuma S, Shoji M. Desensitization of depolarization-mediated contractile pathways does not necessarily regulate receptor-mediated excitation–contraction coupling in longitudinal smooth muscle of guinea pig ileum. *Clin Exp Pharmacol Physiol.* 2011;38(4):233-238.
49. Chokri A, Doukali R, El Abida K, Cheikh R Ben. Myorelaxant and spasmolytic effects of *Globularia alypum* L. extract on rabbit jejunum. *Int J Pharmacol.* 2010;6(5):608-615.
50. Kim JE, Lee YJ, Kwak MH, Ko J, Hong JT, Hwang DY. Aqueous extracts of *Liriope platyphylla* induced significant laxative effects on loperamide-induced constipation of SD rats. *BMC Complement Altern Med.* 2013;13(1):333.
51. Somlyo AP, Somlyo A V. Ca²⁺ sensitivity of smooth muscle and nonmuscle myosin II: modulated by G proteins, kinases, and myosin phosphatase. *Physiol Rev.* Published online; 2003.
52. Imaseki I, Kitabatake Y. Studies on effect of essential oils and their components on the isolated intestines of mice. *Yakugaku zasshi J Pharm Soc Japan.* 1962;82:1326.
53. Plant OH, Miller GH. Effects of carminative volatile oils on the muscular activity of the stomach and colon. *J Pharmacol Exp Ther.* 1926;27(2):149-164.
54. Gullikson GW, Bass P. Mechanisms of action of laxative drugs. In: *Pharmacology of Intestinal Permeation II.* Springer. 1984;419-459.

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