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CAN SEEDS OF JOANNESIA PRINCEPS IMPROVE INTESTINAL MOTILITY IN LOPERAMIDE-INDUCED CONSTIPATION IN RATS?

[1]Juliana Agostinho Lopes, [1]Carolina Alves Giorgi, [1]Cássia Mariano de Oliveira, [1]Fabiana Baldassim Pontelli, [1]Adriano Cressoni Araújo, [1,2]Élen Landgraf Guiguer, [1]Patrícia C. S Bueno and [1,2]Sandra Maria Barbalho

[1]Department of Biochemistry and Pharmacology, School of Medicine, University of Marília, Av. Higino Muzzi Filho 1001, Marília 15525-902, SP, Brazil
[2]Department of Biochemistry and Nutrition, Faculty of Food Technology of Marília (FATEC), Av. Castro Alves, 62, Marília 17506-000, SP, Brazil

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ABSTRACT

Constipation may be considered a public health problem leading to harmful interference on the quality of life. Its prevalence varies from 0.7% to 81% worldwide and may affect adults and children. It is usually treated with laxative drugs. Joannesia princeps is a plant used in popular medicine as a laxative. This work aims to evaluate the potential of J. princeps in reversing the constipation effects produced by loperamide. Animals were divided in Group 1 (Control group that received propylene glycol), Group 2 (treated with J. princeps), Group 3 (treated with loperamide), and Group 4 (treated with J. princeps and loperamide). After 30 minutes, all groups were gavage-fed with activated charcoal. Thirty minutes later, the rats were euthanized with thiopental. After confirmation of death, the intestines were removed along with the stomach, and the length and the distance covered by the activated charcoal was measured. Our results showed that the distance covered by the activated charcoal from the pylorus to the beginning of the caecum was higher in the group treated with J. princeps showing that this plant may revert the constipation pattern produced by loperamide. For these reasons we may suggest that J. princeps seeds could be an alternative treatment for opioid-induced constipation in Wistar rats. Nevertheless, other studies with humans are necessary to evaluate the doses that are required, possible side effects and the effectiveness of the treatment with this plant in constipation opioid-induced.

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INTRODUCTION

Constipation is usually referred as being difficult, persistent, not frequent, and incomplete defecation (Longo *et al*., 2012) leading to harmful interference on the quality of life due to physical symptoms and social and psychological discomfort. It is considered a public health problem, and although it is more frequent in women, it may also affect men in any stage of life (Bantel *et al*., 2018; Reber, McGauvran, Froemming, 2018; Levy *et al*., 2017). The prevalence of constipation varies from 0.7% to 81% worldwide (Yan *et al*., 2017; Mugie *et al*., 2011). In children and adolescent, it may reach between 10% and 23% in North and South America, and 0.7% to 12% in Europe (Fattahi *et al*., 2017; Quigley *et al*., 2009; Lewis *et al*., 2016). The constipation is treated with laxative drugs that are associated with few adverse reactions when used for a short period. However, the continued intake may result in inflammatory and degenerative processes that cause morphological changes in the rectum and colon. These conditions may contribute to the chronic and abusive use of laxatives, thus instituting a vicious circle that can lead to intestinal atony (Camilleri *et al*., 2017).

***Corresponding author:* [1,2]Sandra Maria Barbalho**
[1]Department of Biochemistry and Pharmacology, School of Medicine, University of Marília, Av. Higino Muzzi Filho 1001, Marília 15525-902, SP, Brazil
[2]Department of Biochemistry and Nutrition, Faculty of Food Technology of Marília (FATEC), Av. Castro Alves, 62, Marília 17506-000, SP, Brazil

Table 1. Results for animal weight, bowel length, and distance traveled by the activated charcoal

	G1	G2	G3	G4	*p-value*
Animal weight	172.13±17.11 B	161.13±12.97 B	163.13±13.77 B	138.75±24.58 A	0.004*
Bowel lenght	120.25±6.4 A	116.25±5.95 A	115.85±11.73 A	115.75±9.39 A	0.350
Travelled distance	76.14±29.65 B	102.71±13.00 C	16.25±30.21 A	67.12±37.46 B	<0.001*
% of the travelled distance	66.14±23.74 B	97.93±9.05 C	16.86±28.84 A	57.93±31.74 B	<0.001*

G1: control group; G2: *Joannesia princeps* group; G3: loperamide group; G4: *Joannesia princeps* + loperamide group

Furthermore, the use of laxatives frequently is associated with high costs, abdominal pain, cramps, and bloating (Ford, Suares, 2011). Plants such as senne are traditionally used as exhibiting laxative effects, and several scientific reports confirm these effects. In Brazil, the seeds of *Joannesia princeps* (Euphorbiaceae) are used popularly for this purpose. Araujo *et al*. (2016) showed the potential of this plant as a laxative in animal models (Araujo *et al*., 2016; Seethapathy *et al*., 2014). This work aims to evaluate the potential of *J. princeps* in reversing the constipation effects produced by loperamide.

MATERIALS AND METHODS

Plant material: The seeds of *Joannesia princeps* were obtained from a local market in the city of Marilia, São Paulo state, Brazil. The seeds were dried in air circulation oven under a temperature of 45°C for seven days, and subsequently, they were crushed immediately before the use. After that, the seeds were crushed and mixed with propylene glycol (50mg/mL).

Animal groups: This research had the approval by the Animal Research Ethics Committee of the University of Marília (UNIMAR, Marília, São Paulo State, Brazil). Forty healthy male Wistar rats were used, with approximately 180g to 220g, were maintained in the vivarium at the University of Marilia (UNIMAR, Marília, São Paulo State, Brazil). The animals were housed in cages under a dark/light cycle of 12 hours, with a room temperature of 22 ± 2°C, and relative air humidity about 60 ± 5%. All the animals received water and food *ad libitum*, *and* were cared for according to the recommendations of the Canadian Council's "Guide for the care and use of experimental animals". After the acclimation period to laboratory conditions (seven days) the rats were separated randomly into different groups.

Gastrointestinal motility evaluation: The gastrointestinal motility evaluation was performed according to the model of Michelin, Salgado (2004), with minor modifications. After a 24-hour fast, the groups and were gavage-fed, according to the following treatments:

Group 1: Control group that received 0.2 mL of propylene glycol (10mg/kg);
Group 2: Group that received 0.2mL of the suspension prepared with *J. princeps* and propylene glycol (50mg/kg);
Group 3: Group that received 0.2mL of loperamide (3mg/kg);
Group 4: Group that received 0.2mL of *J. princeps* (50mg/kg) + loperamide (3mg/kg).

After 30 minutes, all groups were gavage-fed 0.2mL of activated charcoal (10%) suspension in gum Arabic (5%).

Thirty minutes after this procedure, the rats were euthanized with thiopental (lethal dose of 200 mg/Kg). After confirmation of death, the intestines were removed along with the stomach, and the length and the distance covered by the activated charcoal was measured.

Statistical analysis: Kruskal-Wallis supplemented with Dunn test were used for the statistical analysis, and the variables are presented as mean and standard deviation, adopting a 5% level of significance.

RESULTS AND DISCUSSION

The results found in Table 1 show that the animals of this study did not present statistically significant differences in body weight. The distance covered by the activated charcoal from the pylorus to the beginning of the caecum was higher in the group treated with *J. princeps*. It is also important to note that the group that was treated with loperamide, significantly reduced the distance covered by the charcoal, notwithstanding, when it is used associated with the plant, we observe a reversion in the constipation pattern produced by that drug. There are also significant differences when we consider the percentage of the distance traveled by the activated charcoal between the control group and the other groups. Constipation is related to considerable expenses with laxatives, and the gastroenterologist's goals for the treatment of problem involve several modifications in the lifestyle, such as an increase in the intake of water and fiber, the practice of regular physical activity and adequate and conscious use of laxatives. (Wilson *et al*., 2015; Hanif-Palla *et al*., 2015). Several researchers have shown that several plants may exhibit laxative potential. The senne is traditionally used in popular medicine for the treatment of constipation.

The presence of different compounds such as flavonoids, sennosides, anthraquinone, naphthalene acetophenones, xanthones, and fatty acids may be related with the improvement of the intestinal motility (Sakulpanich *et al*., 2009; Seethampani *et al*., 2014; Epifano *et al*., 2015). Yan *et al*. (2017) showed that the aqueous Extracts of *Herba Cistanche* also increased the intestinal motility in Loperamide-Induced Constipation Rats. Ren *et al*. (2017) also found similar results with the use of a common marine alga named Enteromorpha. Rtibi *et al*. (2018) also evaluated the effects of plants as laxatives. They showed that *Opuntia ficus-indica* juice and seeds could reverse the effects of loperamide. *J. princeps* exhibits laxative effects as found by Araujo *et al*. (2016) and Sousa *et al*. (2007). However, these authors did not study the effects of the seeds of this plant in reversing the obstipation effects of loperamide that was used to induce constipation in the animals. Adrenergic, muscarinic, dopaminergic and opioid receptors have a significant role in

modifying the bowel motility and transit time. Among the mechanisms most likely to be involved in the pathophysiology of opioid-induced constipation are the reduction of the small intestine and colon peristalsis, increased absorption of water and electrolytes, impaired bowel movements, and increased anal sphincter tone. Our results indicate that the seeds of *J. princeps* could be an alternative treatment for opioid-induced constipation.

Conclusion

The results obtained in this study corroborate the already known laxative activity of *J. princeps* and furthermore, show, for the first time, that its seeds could be an alternative treatment in opioid-induced constipation since its use reversed loperamide-induced constipation in Wistar rats. Nevertheless, other studies with humans are necessary to evaluate the doses that are required, possible side effects and the effectiveness of the treatment with this plant in constipation opioid-induced.

Author Disclosure Statements: Authors declare no conflict of interests.

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