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Original Research Article

Ameliorative effect of *Houttuynia cordata* Thunb (Saururaceae) leaf extract in loperamide-induced constipation in rats

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Abstract

Purpose: *To investigate the efficacy of Houttuynia cordata Thunb (Saururaceae) extract against loperamide-induced constipation in Wistar rats.*
Methods: *Constipation was induced by loperamide (3 mg/kg). The rats were orally treated daily with either 40, 80, 160 mg/kg/day of H. cordata extract or 0.25 mg/kg bisacodyl (positive control) for 7 days, while normal control group received water only. Feed and water intake, body weight, number and water content of fecal pellets were monitored throughout the study period. The biochemical marker activities of aspartate aminotransferase (AST), γ-glutamyltransferase (γ-GT) and lactate dehydrogenase (LDH) were determined in the blood of the animals.*
Results: *The water content of fecal pellets and body weight gain of the constipation rats changed significantly ($p < 0.05$) when compared to the normal control. Serum levels of AST were significantly higher ($p < 0.05$) in the 80 and 160 mg/kg dose groups when compared to normal controls. However, there were no alterations in the levels of γ-GT and LDH across all groups.*
Conclusion: *Treatment of rats with ethanol extract of H. cordata leaf has useful effects against constipation. Therefore, H. cordata leaf may be benefitial as a traditional herbal medicine for the management of constipation.*

Keywords: *Constipation, Houttuynia cordata Thunb, Loperamide, Bisacodyl*

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INTRODUCTION

Constipation is a functional gastro-intestinal disorder affecting 8-15% of the general population [1], characterized by condition of the digestive system where an individual has hard feces that are difficult to expel [2]. The risk has a considerable impact on illness and value of life, which may be categorized by baffling intestinal ache, distress and swelling in link with changed bowel behaviors [3]. The use of synthetic branded drugs such as Correctol, Dulcolax, Ex-Lax, Senokot, and Bisacodyl is actual common as resources of handling constipation [4].

However, the use of these orthodox drugs is limited due to their cost and undesirable side effects [4]. Consequently, most of the affected

persons be sure of on herbal formulations for the usage of the illness [5]. Some therapeutic herbal extracts are known to display antispasmodic effects by water absorption in the intestine [6].

Houttuynia cordata Thunb (Saururaceae, H. cordata), is a natural herb to the area of Southeast Asia. Traditionally *H. cordata* is effective as anti-inflammatory fever reducer, suppurate, diuretic, and detoxifier [8]. Also, it has been used for unceasing dermatosis and diuresis, and as an anti-inflammatory effects in traditional herbal medicine [9]. Studies of *H. cordata* have investigated its properties relative to steroids [10], alkaloids [11], essential oils [12], flavonoids [13]. It also gives a broad range of pharmacological activities, including anti-oxidative [14], anti-cancer [15], anti-microbial [16], and anti-high cholesterol activities [17]. The *H. cordata* is also used traditionally as means of treating constipation however, there is little or no scientific study to substantiate this claim. This study was therefore, designed to evaluate the constipation improve effects of the leaf extract of *H. cordata* on loperamide-induced constipation in rats.

EXPERIMENTAL

Preparation of *Houttuynia cordata*

H. cordata leaves were collected from the Chungcheongbuk-do area in South Korea. The air-dried *H. cordata* was extracted with 10-fold volume of 70% ethanol in distilled water at room temperature for about 72 h. The *H. cordata* extract were collected and concentrated under reduced pressure at 55 ℃. The ethanol extract of *H. cordata* was cleaned with Whatman filter paper (Maidstone, England), and then concentrated exhausting a vacuum evaporator. Finally, the water extract of *H. cordata* was lyophilized (FDU-1100, Eyela Co.) and kept at -20℃ before use.

Animals

Male Wistar rats with an average weight of 125 g were purchased from Orient, Inc (Seoul, Republic of Korea). The animals were kept in a 23 ± 2 ℃ room maintained under 60 ± 5 % humidity and twelve hours in light-dark cycle. They were acclimatized to the animal house condition for seven days during which they were allowed free access to commercial pelleted rat chow and water. All experiments were performed according to National Institute of Heath guidelines (Principles of Laboratory Animal Care) and Dankook University Institutional Animal Care and Use Committee (approval no. DKU-16-043).

Induction of constipation in the rats

Constipation was induced in the experimental rats by the oral administration of 0.5 mL of loperamide (three mg/kg for three days) as a control group [18], while the control rats were administered distilled water only. The rigid and dry fecal pellets marked constipation in the rats.

Experimental design

The animals were allocated into six groups of five rats each. The animals in normal control group and constipated control group were administered using distilled water orally. The constipated *H. cordata* group administered 40, 80 and 160 mg/kg/day of extract of *H. cordata*, and the constipated bisacodyl group administered 0.21 mg/kg/day of bisacodyl for 7 days [19]. All oral processing was done using steel oropharyngeal cannula. The distilled water and feed intake, number of fecal pellets and body weight increase of all the rats were documented for the period of trial dated.

Determine of total number and dehydrated content of fecal pellets

The fecal pellets of experimental rats were collected every day at ten hours throughout the duration of the experiment (7 days). The entire number, dehydrated content of fecal pellets were determined. The distilled water content was calculated as the alteration between dehydrated content of fecal pellets [18].

Preparation of serum samples

At the end of the 7 days treatment period rats were sacrificed under ether anesthesia, after an overnight fast, and blood was collected in a heparinized tube. The collected blood of the experimental rats was centrifuged at 3,000 g for 15 min, and the supernatant was kept at -70 ℃ until assayed.

Determination of serum enzymes

The activities of serum aspartate amino-transferase (AST), γ-glutamyltransferase (γ –GT) and lactate dehydrogenase (LDH) were determined using a Konelab20XT automatic blood analyzer.

Statistical analysis

All experimental data are presented as mean ± standard error of the mean SEM, n = 5). Statistical analysis was performed with SAS

using one-way analysis of difference. $P < 0.05$ was considered statistically significant.

RESULTS

The effect of loperamide on feed and water intake, fecal properties and body weight of constipated rats before treatment

Loperamide significantly ($p < 0.05$) reduced the number of faecal pellets and increased significantly ($p < 0.05$) the body weight of the constipated rats when compared to the normal rats (Table 1). This was an indication of constipation. However, feed intake, water intake and water content of faecal pellets were not significant different ($p > 0.05$) among control and constipated animals.

Table 1: Loperamide effects constipated rats before treatment

Parameter	Normal rats	Constipated rats
Feed intake (g)	14.52±0.58	12.35±0.59
Water intake (mL)	27.53±2.67	28.86±1.96
Number of fecal pellets (n)	53.28±1.23	43.57±2.98*
Water content of fecal pellets (mL)	2.66±0.12	2.23±0.08
Weight of animals (g)	114.58±1.28	128.28±1.79*

Data are mean ± SEM values (n = 5); *$p < 0.05$

The effect of ethanol extract of *H. cordata* on body weight gain, feed and water intake and fecal properties of constipated rats after treatment is shown in Figure 1. There was no significant difference ($p > 0.05$) in the feed and water intake, number of fecal pellets in all the experimental animals. However, water content of fecal pellets and body weight gain of the constipated rats changed significantly ($p < 0.05$) when compared to the normal control. This alteration was counteracted by the administration of ethanol extract of *H. cordata* to the animals.

The effect of the administration of the ethanol extract of *H. cordata* on some serum enzymes activities is shown in Figure 2. There were major differences ($p < 0.05$) in the serum aspartate aminotransferase (AST) among the groups of animals. However, the 40 and 80 mg/kg extract-treated groups may increase better than the 160 mg/kg. The activities of lactate dehydrogenase (LDH) and γ-glutamyltransferase (γ –GT) in the extract treated groups were not significantly different ($p > 0.05$) from the normal control and bisacodyl-treated constipated rats.

DISCUSSION

Constipation is a usual health problem with a drift to cause distress and affect patient of lifespan [20]. The incidence of constipation increases with age and may occur into a long-lasting condition requiring the laxatives used [3]. Constipation may appear from a diversity of causes, including the use of organic compounds such as morphine, nutritional problems and mental pressure [21].

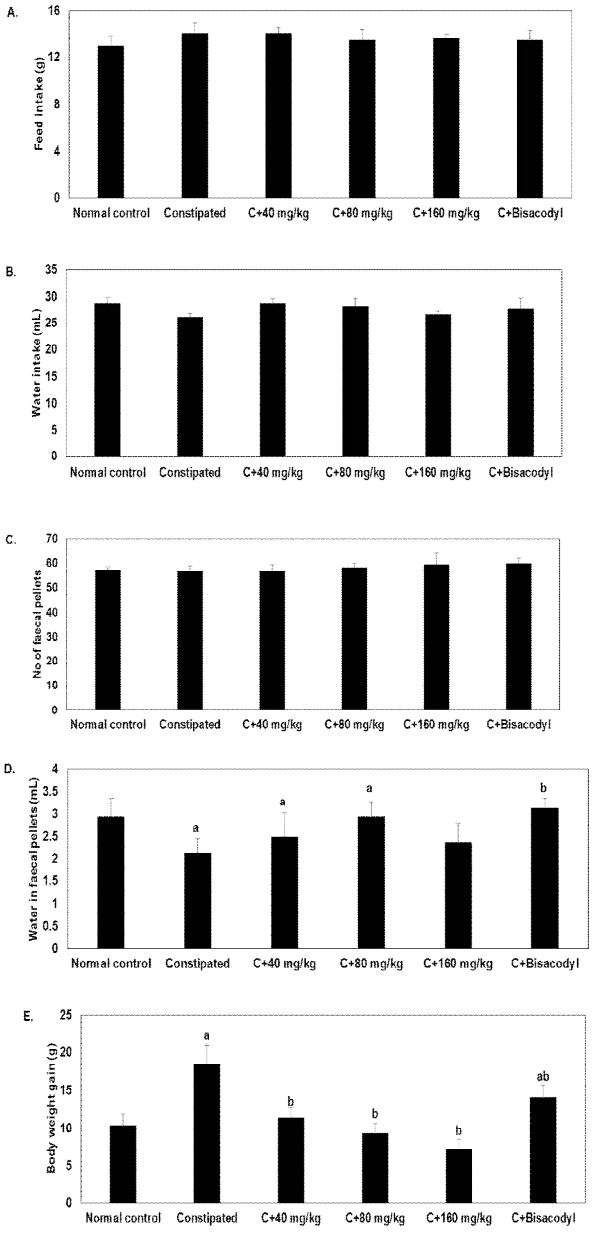

Figure 1: Effect of ethanol extract of *H. cordata on* body weight gain, feed and water intake and fecal properties of constipated rats *on 7 day. Data are mean* ± SEM (n = 5); [a]$p < 0.05$ compared to the normal group; [b]$p < 0.05$ compared to constipated control group

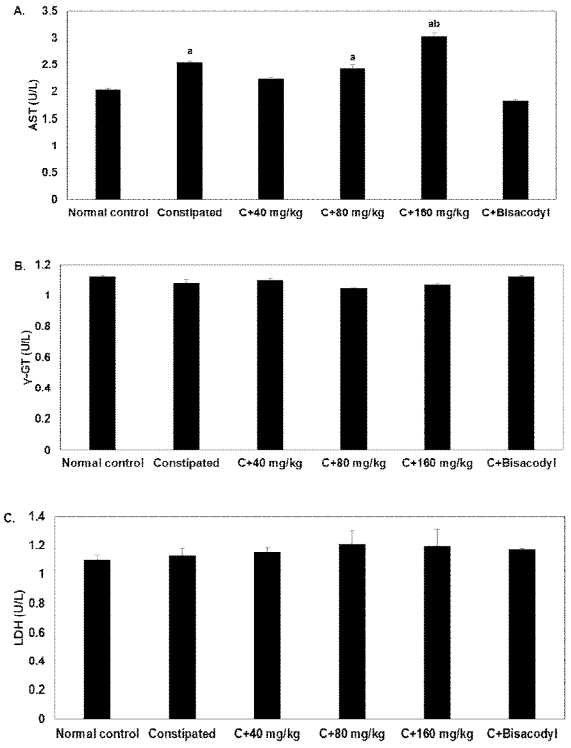

Figure 2: Effect of *H. cordata* on liver function of normal and loperamide-induced constipated rats. Data are mean ± SEM values (n = 5); [a]*p < 0.05* compared to the normal group; [b]*p < 0.05*) compared to constipated control group

Laxatives are the common treatment for constipation caused by irregularities of intestinal behave. Laxatives can be categorized into a form of laxatives, stimulant laxatives, and osmotic laxatives. There are also new drugs such as Tegaserod® and Lubiprostone® [22]. However, the constipation medicines currently have many side effects, including abdominal blow up and vomiting [23]. These kind of side effects limit as the constipation medicines [24]. It is therefore necessary to develop herbal materials which have lower side effects with pronounced results with consider to treating constipation.

The present study has clearly demonstrated that the ethanol extract of *H. cordata* has laxative motion which is similar to bisacodyl, a laxative medicine. Loperamide attached to the morphine receptors of the intestinal membrain, causes the gentle transfer by decreasing instict contractions of the intestinal muscles in abdomen and it also accelerating the water and electrolyte absorption, thereby decreasing the stool liquids [25]. Loperamide induced constipation is therefore deliberated to be a spastic constipation model [26]. The observed fall in the number of fecal pellets and weight resulting treatment with loperamide indicated induction of constipation in the experimental rats. The body weight and water in fecal pellets of the constipated rats changed significantly compared to the normal control treatment of ethanol extract of *H. cordata* on feed and the feed and water intake and number of fecal pellets of all experimental groups.

Taken together, these results indicate that the administration of ethanol extract of *H. cordata* for 7 day increase a dehydration of fecal content, thereby improving the factors of fecal parameters of loperamide-induced constipated rats. These are indications of the laxative property of the plant extract [27]. The presence of terpenoids, sterols, flavonoids, phenolic compounds, tannins and alkaloids have been report to be accountable for laxative activities in plants [28]. Phytochemical screening of ethanol extract of *H. cordata* revealed the presence of flavonoids, polyphenols, and polyterpenes [29,30]. These constituents may be responsible for the laxative activity of ethanol extract of *H. cordata.*

There are various enzymes such as phosphatases, dehydrogenases and transferases that are found in considerable quantities in the serum which did not essentially originate from the extracellular fluid in intestine. To examine whether loperamide treatment could influence of the lipid batteries, alteration of AST, γ –GT, and LDH related to liver function was investigated in serum using a biochemical analysis. Liver toxicity analysis did not show any significant differences in the concentrations of two liver toxicity indicators, γ –GT and LDH, between the normal control group and loperamide-treated group. However, the concentration of AST was slightly increased in the loperamide-treated group than that of the normal control group. Therefore, these results indicate that loperamide may induce some toxicity in the liver of Wistar rats.

CONCLUSION

This study points to a beneficial effect of *H. cordata* in loperamide-induced constipation in rats. It is, however, important to note that the laxative activity was dose-dependent and compares favorably with that of bisacodyl. These also findings lent scientific support for the folkloric use of *H. cordata* as a laxative.

DECLARATIONS

Acknowledgement

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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