

## Effects of *Cassia obtusifolia* L. Extract on Loperamide-Induced Constipation in Rats

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### Abstract

*Cassia obtusifolia* L. is commonly used as medicinal foods to treat gastrointestinal disease in many countries. This study evaluated the anti-constipation effects of ethanolic extract of *Cassia obtusifolia* L. in rats with loperamide-induced constipation. Different concentrations of ethanolic extract of *Cassia obtusifolia* L. (0, 10, 250, and 500 mg/kg) was administered to rat orally once daily for 3 weeks following loperamide treatment. Six-week-old Sprague-Dawley rats (N=25) were randomly divided into five groups: normal control and experimental groups and injected loperamide intraperitoneally to induce constipation in the latter four experimental groups. Following the induction of loperamide-induced constipation, a marked decrease was observed in the fecal weight and water content discharged for over 1 week and intestinal transit time while an increase was observed in the number of fecal pellets remaining in the colonic lumen as compared with the normal control group. These conditions were significantly alleviated following the administration of the two doses (250 and 500 mg/kg) of ethanolic extract of *Cassia obtusifolia* L. when compared to the loperamide-treated (constipation control) group. More specifically, the number of fecal pellets in the colon was 3, 5, 4, 2.8, and 1.2 in the five groups, respectively and the corresponding GIT ratio was 70.77, 56.59, 58.67, 66.81, and 72.10%, respectively. The fecal water content, transit distance, and GIT ratio in the high-dose treatment group were significantly higher than that in the medium-dose treatment group, but a significant decrease in the number of fecal pellets in the colon.

In conclusion, the *Cassia obtusifolia* L. extract is suggested to have beneficial effects as a therapeutic and preventive strategy to alleviate constipation and to relieve the symptoms of constipation such as pain, flatulence, distention, bloating, and unpleasant taste.

Key words: *Cassia obtusifolia* L. extract, constipation, loperamide, rat

### Introduction

*Cassia obtusifolia* L. a well-known traditional Chinese medicine, belongs Leguminosae family and is widely used for preventing and curing diseases for centenarians (Zhang et al. 1996, Hong et al. 2012b, Tang et al. 2015); it was recorded in the Compendium of Materia Medica that *Cassia obtusifolia* L. had the functions of clearing the liver, improving vision, and relaxing the bowel.

Pharmacological analysis and clinical observation showed that *Cassia obtusifolia* L. could reduce the content of total cholesterol and triglyceride in serum (Zhang et al. 2012). It can delay and partially reverse the formation of atherosclerotic plaque, significantly decreasing the incidence of and mortality associated with cardiovascular and cerebrovascular diseases. It also used to treat the conjunctival congestion, pain in the eye, photophobia, hyperdacryosis (a condition of excessive tearing of eyes), head

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ache, dizziness, constipation, among others (Li & Luo 2003). Recent research indicated that *Cassia obtusifolia* L. had the function of strengthening immunity and had antiaging properties. In addition, the major active component of *Cassia obtusifolia* L. was identified as anthraquinones; aurantio-obtusin, chrysophanol, rheum, and emodin (Luo et al. 2011, Hong et al. 2012a, Cao et al. 2015).

Constipation, traditionally defined as unsatisfactory defecation with lack of bowel movement for appropriately 72 hours, is a common problem in men and women of all ages, with a chronic gastrointestinal disorder affecting appropriate 20% of the general population (Drossman & Dumitrascu 2006). The symptoms include infrequent bowel movements, difficulty during defecation, lower abdominal discomfort, distension, bloating, vomiting, restlessness, gut obstruction and perforation and the sensation of incomplete bowel evacuation (Wald A 2016). Therefore, constipation is a common health problem with a tendency to cause discomfort and affect patient quality of life.

Constipation commonly occurs during pregnancy, following childbirth or surgery, or after taking medications such as loperamide to alleviate pain resulting from fractures or other musculoskeletal disorders (Wald A 2016). Increase in fluid intake and physical activity do not appear to relieve constipation, except in patients who are dehydrated, but symptoms of constipation typically respond to diet modification alone or in combination with an osmotic laxative (Lembo & Camilleri 2003). While treating constipation, patients' compliance with the use of dietary fiber supplements is poor because of their side effects, like flatulence, distention, bloating, and unpleasant taste. Medications such as osmotic laxative are commonly prescribed for constipation. Laxatives include foods like fruits, especially banana, kiwi-fruit, and prunes and various drugs such as senna, correctol (Docusate sodium), exlax, and senokot that are commonly used to treat constipation (Lembo & Camilleri 2003, Kim et al. 2015). Their use is limited owing to high costs and undesirable side effects. Overuse of laxatives may result in severe dehydration rather than treating of constipation (Lembo & Camilleri 2003).

Loperamide is a medication used to decrease the frequency of diarrhea; it is an agonist of  $\mu$ -opioid receptors and inhibits the release of endogenous acetylcholine granules in the intestine (Sohji et al. 1978). Loperamide-induced delay of colonic transit results in spastic constipation due to the inhibition of stool frequency and increased colonic contractions in humans. The drug inhibits intestinal water secretion and colonic peristalsis, which

extends the fecal evacuation time and delays intestinal luminal transit. Thus, loperamide-induced constipation is considered a model of spastic constipation.

The purpose of this study was to investigate the effects of *Cassia obtusifolia* L. extract on loperamide-induced constipation in rats. In the present study, body weight, fecal weight, fecal water content, and peristalsis (Gastrointestinal Transit Time: GIT) parameters were examined in rats with loperamide-induced constipation.

## Materials and Methods

### 1. Preparation of extract of *Cassia obtusifolia* L.

The seed extract of *Cassia obtusifolia* L. was provided from TEAZEN Inc. (Haenam, KOREA) and the *Cassia obtusifolia* L. was extracted as following; dried *Cassia obtusifolia* L. was extracted twice in 70% ethyl alcohol (w/v, 1:8) at 70°C for 3 h. The extracts were filtered and concentrated in a rotary evaporator under reduced pressure. The concentrate was spray-dried, finally dry weight yield of *Cassia obtusifolia* L. was approximately 20%.

The *Cassia obtusifolia* L. extracts were then validated by analysis of aurantio-obtusin as marker compounds for using HPLC.

### 2. Animals and experimental design

A total of 25 male Sprague-Dawley (SD) rats (aged 6 weeks) were used in this experiments following a 7 days acclimatization period (Damul Science Co., Daejeon, Korea). The animals were fed a commercial chow pellet diet (Samyang Co., Seoul, Korea) containing the following components (g/kg/diet): moisture, 80; protein 230; fat, 35; fiber 50; carbohydrate, 600, and water *ad libitum*. The rats were maintained in a room under the following conditions: temperature, 24±2°C relative humidity, 55±5%; and in an automatically controlled 12-h light and dark cycle with a brightness of 150-300 lux, with *ad libitum* access to feed. All SD rats were randomly grouped into five groups, including normal control, constipated control, constipated-*Cassia obtusifolia* L. extract treated group (10, 250 and 500 mg/kg). This experimental study was conducted in two sessions including an induction session of 6 days and experimental session of 7 days. All animals except the normal control group, were orally administered 2 mg/kg loperamide hydrochloride (Sigma-Aldrich, St. Louis, MO, USA) in a volume of 5 mL/kg (dissolved in saline), once daily for 7 continuous days 1 h before administration of the test agent to induce constipation, as described previously.

The control rats were administered normal saline only.

All animal experimental protocols were performed in accordance with the Korean Food and Drug Administration Guidelines on the Use of Laboratory Animals and were approved by the Committee on the Ethics of Animal Experiments of the Dongshin University (Permit Number: 2016-02-02). All surgeries on rats were performed under sodium pentobarbital anesthesia, and all efforts were made to minimize suffering.

### 3. Body weight gain, food consumption, and water intake

Body weight gain, food consumption, and water intake of all the rats were measured daily after loperamide-induced constipation during the experimental period and treatment was continued for 7 days.

### 4. Measurement of fecal parameter

The excreted fecal pellets of individual rats were collected everyday at 09:30 h throughout the duration of the experiment. Total number, weight and water content of the pellets were determined. The water content was calculated as the difference between the wet and dry weights of the pellet. The water content was calculated as follows: Fecal water content (%) = [(fecal wet weight - fecal dry weight)/fecal wet weight] × 100. The total number fecal pellets remaining in the colon lumen were measured.

### 5. Gastrointestinal transit (GIT) ratio

The GIT ratio was calculated according to the method of Nagakura et al. in 1996. On the last day of extract administration, 1 mL of carmine (3 g suspended in 50 mL of 0.5% carboxymethylcellulose) was orally administered to the rats. One hour after administering the marker, the animals were sacrificed and the small intestines were removed. The distance travelled by carmine and the total length of the small intestine were measured.

The GIT ratio was calculated as the ratio of the distance travelled by the carmine relative to the total length of the small intestine.

## 6. Data analysis

The dependent variables were measured three times, daily for 7 days and the mean values among of seven measurements were used for analysis. Data analysis was performed using SPSS for Windows version 21.0 (IBM Corp., NY, USA). All the data are expressed as mean±standard deviation of 3 replicates. The differences between the groups were tested by one-way analysis of variance (ANOVA), followed by Duncan multiple range test to determine significant differences in all the parameters. A *p*-value <0.05 at a 95% confidence level was considered significant.

## Results

### 1. Intake condition after oral treatment with *Cassia obtusifolia* L. in constipated SD rats

Table 1 shows body weight gain, food intake, and water intake following oral treatment with *Cassia obtusifolia* L. extract in five groups of rats with loperamide-induced constipation. The body weight gain was 19.00 g, 23.00 g, 19.2g, 17.00g, and 16.20 g at normal control, constipated control, low-dose, medium-dose, and high-dose groups respectively. The body weight gain in the constipated control group was significantly higher than in the normal control group, although the values of the other three treatment groups were not significantly different from that of the normal control group. The body weight gain in the medium-dose and high-dose treatment groups was decreased significantly compared to that in the constipated control group. However, the body weight gain in the low-dose treatment group was not significantly different from that in the constipated control group. The body weight gain was not significantly different among the three treatment groups. Food intake was 19.69, 19.71, 19.45,

**Table 1. Body weight, food intake and water intake change following oral treatment with Cassiae Semen extract for loperamide-induced constipation in rats**

Parameters	Normal control	Constipated control	Constipated + <i>Cassia obtusifolia</i> L. extract (mg/kg body weight)		
			10	250	500
Body weight gain (g)	19.00±2.12	23.00±1.41*	19.20±2.17	17.00±1.87†	16.20±2.86†
Feed intake (g/day)	19.69±0.73	19.71±0.68	19.45±0.81	19.48±1.01	18.96±1.06
Water intake (mL/day)	22.91±0.97	17.17±1.17*	18.01±0.97	18.87±0.73	20.09±1.50

Data are mean±S.D. values (n=5). Row values with different superscripts from the control are significantly different (*p*<0.05)\*, *p*<0.05 is the significant level compared with normal control group. †, *p*<0.05 is the significant level compared with constipated control group.

19.48, and 18.96 mL in the five groups respectively, and was not significantly different. Water intake was 22.91, 17.17, 18.01, 18.87, and 20.09 mL in the five groups, respectively. Water intake in the constipated control group was significantly lower than in the normal control group, although those in the other three treatment groups were not significantly different from the values of the normal control group. Water intake was not significantly different among the three treatment groups.

## 2. Fecal parameters after oral treatment with *Cassia obtusifolia* L. in constipated SD rats

To investigate the effect of ethanol extract of *Cassia obtusifolia* L., four fecal parameters were measured, including wet weight, dry weight, water content and fecal pellets in the colon. Wet weight was 6.13, 4.32, 4.63, 4.97, and 5.58 g/24h/rat in the five groups respectively, and significantly decreased in the constipated control group compared to that in the normal control group; however, the wet weight was not significantly different among the other three treatment groups. Dry weight was 3.57, 3.28, 3.38, 3.19, and 3.37 g/24 h/rat in the five groups, respectively, and was not significantly different. Water content was 43.28, 24.00, 26.83, 35.86, and 39.52% in the five groups, respectively, and was significantly different between the constipated control and normal control group; the water content in the medium-dose and high-dose treatment groups were significantly different from that in the constipated control group. Moreover, it was found to increase significantly in the high-dose treatment group but not in the medium-dose treatment group compared to that in the low-dose treatment group. The number of fecal pellets in the colon was 3, 5, 4, 2.8, and 1.2 in the five groups, respectively. This number increased significantly in the constipated control group compared to that in the normal control group, and decreased sig-

nificantly in the medium-dose and high-dose treatment groups compared to that in the constipated control group; the number of fecal pellets in the low-dose treatment group was significantly different from that in the constipated control group. The fecal pellet number in the high-dose treatment group was lower than that in the low-dose treatment group, but was not significantly different between the medium-dose treatment and low-dose treatment group (Table 2).

## 3. Gastrointestinal transit ratio after oral treatment with *Cassia obtusifolia* L. in constipated SD rats

Average length of total small intestine was 104.06, 103.56, 103.56, 104.96, and 102.44 cm in the five groups respectively, and was not significantly different. Transit distance was 73.58, 58.58, 60.78, 69.92, and 73.80 cm in the five groups, respectively, and the corresponding GIT ratio was 70.77, 56.59, 58.67, 66.81, and 72.10%. The transit distance and GIT ratio significantly decreased in constipated control group compared to that in the normal control group, and significantly increased in medium-dose and high-dose treatment groups compared to that in the constipated control group. The high-dose treatment group exhibited a significant increase in transit distance and GIT ratio compared with the low-dose treatment group. However, these parameters were not significantly different between the three treatment groups and the normal control group (Table 3).

## Discussion

The seeds of *Cassia obtusifolia*, it has been used to improve visual acuity and is reputed for its medical value as an antimicrobial, antidiuretic, antiarrhoeal, antioxidant, antihepatotoxic and antimutagenic (Yen et al. 1998, Patil et al. 2004). The bio-

**Table 2. Fecal parameters following oral administration with Cassiae Semen extract in rats with loperamide-induced constipation**

Parameters	Normal control	Constipated control	Constipated + <i>Cassia obtusifolia</i> L. extract (mg/kg body weight)		
			10	250	500
Wet weight (g/24 h/rat)	6.13±0.40	4.32±0.53*	4.63±0.29	4.97±0.40	5.58±0.35†
Dry weight (g/24 h/rat)	3.57±0.35	3.28±0.39	3.38±0.15	3.19±0.24	3.37±0.21
Water content (%)	43.28±2.68	24.00±1.03*	26.83±2.45	35.86±0.34†	39.52±0.44‡
Fecal pellets in the colon (n)	3.00±0.70	5.00±0.70*	4.00±1.00	2.80±1.83†	1.20±0.44‡

Data are mean±S.D. values (n=5). Row values with different superscripts from the control are significantly different ( $p<0.05$ )\*,  $p<0.05$  is the significant level compared with normal control group. †,  $p<0.05$  is the significant level compared with constipated control group. ‡,  $p<0.05$  is the significant level compared with low dose treatment group.

**Table 3. Gastrointestinal transit ratio following after treatment with Cassiae Semen extract in rats with loperamide-induced constipation.**

Parameters	Normal control	Constipated control	Constipated + <i>Cassia obtusifolia</i> L. extract (mg/kg body weight)		
			10	250	500
Total small intestine length (cm)	104.06±6.79	103.56±3.36	103.56±3.67	104.96±3.80	102.44±3.47
Transit distance (cm)	73.58±6.10	58.58±4.42*	60.78±3.02	69.92±6.97 <sup>†</sup>	73.80±6.97 <sup>‡</sup>
Gastrointestinal transit ratio (%)	70.77±4.85	56.59±4.29*	58.67±1.59	66.81±8.53 <sup>†</sup>	72.10±6.80 <sup>‡</sup>

Data are mean±S.D. values (n=5). Row values with different superscripts from the control are significantly different ( $p<0.05$ )\*,  $p<0.05$  is the significant level compared with normal control group. <sup>†</sup>,  $p<0.05$  is the significant level compared with constipated control group. <sup>‡</sup>,  $p<0.05$  is the significant level compared with low dose treatment group.

active constituents of this seeds are anthraquinones, including aurantio-obtusin, emodin, chrysophanol, rhein, physcion etc. (Xue et al. 2018). In this study, five anthraquinones (aurantio-obtusin, emodin, chrysophanol, rhein) have been quantified in raw material of *Cassia obtusifolia*. The anthraquinones analysed in this study, aurantio-obtusin, emodin, chrysophanol, rhein, physcion content each 1.33 mg/g, 0.037 mg/g, 0.063 mg/g, 0.054 mg/g, 0.189 mg/g, respectively.

Also, among the major anthraquinones analysed, aurantio-obtusin, emodin contents of 3.81 mg/g, 0.629 mg/g, respectively, in extract of *Cassia obtusifolia*.

This experimental study was conducted to investigate the effectiveness of *Cassia obtusifolia* L. on body weight gain, food consumption, water intake, fecal characteristics (wet weight, dry weight, water content, and total number of fecal pellets in the colon), and GIT ratio in a rat model of loperamide-induced constipation. The main results of this experimental study were as follows: First, none of the dependent variables in three treatment groups was significantly different from those in the normal control group. Second, in the constipated control group, body weight gain and number of fecal pellets in the colon significantly increased, but water intake, fecal wet weight, fecal water content, transit distance, and GIT significantly decrease compared with the normal control group. Third, none of the dependent variables in low-dose treatment group was significantly different from those in the control group. Fourth, body weight gain and number of fecal pellets in the colon significantly decreased compared with high-dose treatment group. Fifth, fecal water content, transit distance, and GIT ratio significantly increased in the medium-dose and high-dose treatment groups compared to that in the constipated control group. Finally, fecal water content, transit distance, and GIT ratio in high-dose treatment group significantly

higher than that in the medium-dose treatment group, but the number of fecal pellets in the colon significantly decreased.

Constipation is a problem affecting population of all ages causing symptoms like excessive straining, hard stools, feeling of incomplete evacuation and infrequent defecation. Previous studies reported several treatment approaches such as use of dietary fibers (e.g., *Aloe ferox* Mill, *Ficus carica* paste) and medications (e.g., methylnaltrexone, bulk laxative, osmotic laxative, poorly absorbed sugar, stimulant laxative, rectal enema or suppository, cholinergic agent, prokinetic agent) (Wintola et al. 2010, Choi et al. 2014). Wintola and colleagues examined the efficacy of aqueous leaf extract of *A. ferox* Mill. against loperamide-induced constipation in Wister rats; the extract was administered for 7 days, and its effects were comparable with to those of senokot, a standard laxative (Wintola et al. 2010). Mehta and colleagues evaluated the efficacy of methylnaltrexone in the treatment of opioid-induced constipation and discussed the newly developed alternatives and established the current treatment algorithm utilized at our institution (Mehta et al. 2016). Lee and colleagues examined the effects of *Ficus carica* L. paste for the treatment of loperamide-induced constipation in a rat model. They reported that constipation decreased, as indicated by the improved fecal number, weight and water content, and thickness of mucin areas in the distal colon. They also suggested that fig treatment might be a useful therapeutic and preventive strategy for chronic constipation (Lee et al. 2012).

The results of this experimental study were similar to those reported previously. The results of this study show that *Cassia obtusifolia* L. extract has laxative effects and enhance bowel movement. Fecal wet and dry weights, fecal water content, fecal pellets in the colon, transit distance, and GIT ratio were measured. Specially, fecal wet weight and water content, transit distance,

and GIT ratio increased in *Cassia obtusifolia* L. extract-treated rats compared to those in non-treated constipated rats. A similar trend was observed for the number of fecal pellets in the colon. Three doses of *Cassia obtusifolia* L. extract (10, 250 and 500 mg/kg body weight) were used to investigate the optimal dose of the *Cassia obtusifolia* L. extract for the treatment of the loperamide-induced constipation. Animals that received higher dose of *Cassia obtusifolia* L. extract showed more fecal water content, less fecal pellets in the colon, increased intestinal transit distance, and increased GIT ratio. Therefore, the higher dose of *Cassia obtusifolia* L. extract was found to rapidly improve gastrointestinal displacement. Based on the results of this study, the optimal treatment dose of *Cassia obtusifolia* L. extract was 500 mg/kg body weight.

The results of this study corroborate those of previous studies, since effects of *Cassia obtusifolia* L. extract on loperamide-induced constipation were not evaluated at the cellular level. In the present study, increases in the number of discharged fecal pellets and water content were detected with *Cassia obtusifolia* L. extract treatment, and these changes were considered to be direct evidence that *Cassia obtusifolia* L. extract exhibits favorable effect in improving constipation problem. *Cassia obtusifolia* L. extract has been reported to alleviate constipation; improve eyesight; lower hypertension and hyperlipidemia; promote liver, and have also anti-inflammation, anti-diabetic and neuroprotective effects (Li et al. 2003). Recently, several researchers examined the contents of anthraquinones in *Cassia obtusifolia* L. (Chen et al. 2002, Li et al. 2003, Zhang et al. 2008, Luo et al. 2011, Cao et al. 2015). Yang and colleagues reported seven anthraquinones including chrysophanol, emodin, aloe-emodin, rheum, physcion, obtusifolin and aurantio-obtusin in *Cassia obtusifolia* L. (Yang et al. 2015). Cao and colleagues also reported that the quality of *Cassia obtusifolia* L. is the contents of aloe-emodin, aurantio-obtusin and chrysophanol (Cao et al. 2015). These anthraquinones include important drugs such as laxatives, antimalarials, and anti-neoplastics, and natural anthraquinone derivatives tend to have laxative effects. Anthraquinones are almost completely insoluble in water or ethanol near room temperature but soluble in boiling ethanol. This was also observed with the *Cassia obtusifolia* L. extract extract (Cao et al. 2015, Yang et al. 2015). Therefore, the ethanol extract of *Cassia obtusifolia* L. extract has anthraquinone-stimulated laxative effects and relieves loperamide-induced constipation.

In conclusion, this study focused on the effects of ethanol

extract of *Cassia obtusifolia* L. extract on loperamide-induced constipation in an SD rat model. The results of this study showed that loperamide-induced constipation is alleviated by the *Cassia obtusifolia* L. extract and high-dose of *Cassia obtusifolia* L. extract is more effective than low-dose. Therefore, the *Cassia obtusifolia* L. extract is suggested to have beneficial effects as a therapeutic and preventive strategy to alleviate constipation and to relieve the symptoms of constipation such as pain, flatulence, distention, bloating, and unpleasant taste. Further studies are required to examine the effects of the *Cassia obtusifolia* L. extract on the constipation in other model.

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