

Herba Swertiae Benefits the Gastrointestinal System *In Vivo*

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Abstract

Due to the increasing usage of herbal medicines and natural products for the body function management and ailments treatment and the lack of study on the beneficial effect of *Herba Swertiae*, a widely used traditional herbal medicine, this paper aimed to investigate the effect of *Herba Swertiae* on gastrointestinal system *in vivo*. The effect of *Herba Swertiae* on gastric emptying and intestinal propulsion was examined in mice; the effect of *Herba Swertiae* on gastric acid secretion and pepsin activity was tested in rats; and the effect of *Herba Swertiae* on the mobility of ileum was evaluated by *ex vivo* experiments using isolated ileum from guinea pig. The results showed that *Herba Swertiae* markedly enhanced gastric emptying and intestinal propulsion in mice. Also, *Herba Swertiae* remarkably increased the gastric acid secretion, the acidity of gastric acid, and the activity of pepsin in rats. Of note, these effects were comparable to that of positive control. Moreover, *Herba Swertiae* exerted a potent promoting effect on the mobility of ileum of guinea pigs, with a marked increase in the muscular tension force and contraction amplitude in the isolated ileum. Moreover, *Herba Swertiae* excited the isolated ileum that was inhibited by atropine. Taken together, *Herba Swertiae* exerts markable beneficial effects on gastrointestinal system *in vivo*. More studies are warranted for the investigation of the underlying mechanisms for its beneficial effects.

Keywords: *Herba Swertiae*; Gastrointestinal system; Intestinal propulsion; Mobility of ileum

Introduction

There is a wealth of evidence on the use of natural products, in particular, herbal medicine, for the management of body function and the treatment of a variety of ailments [1]. Also, there is a large line of evidence showing that herbal medicine and natural products have been the most productive source for drug discovery and development [2]. There are over 100 compounds/products that are under investigation at different stages or in clinical use [3,4]. They are mainly used in anti-cancer and anti-infective areas, to a lesser extent, neuropharmacological, cardiovascular / gastrointestinal, inflammation, metabolic, skin, hormonal, and immunosuppressant fields [1,5].

Herba Swertiae, also called Dang Yao, is traditionally used for the treatment of diarrhea, poor appetite, hypochondriac pain, jaundice due to dampness and heat [6,7]. The mechanism of action is ascribed to the clearance of damp-heat and strengthening of the stomach [6,7]. *Herba Swertiae* has a complex of components and the major ones include secoiridoids, triterpenoids, and flavonoids [6]. There are only scattered reports regarding the beneficial effects on *Herba Swertiae*, with a focus on the hepatoprotective effect, central nervous system suppressive effect, analgesic effect, and calming effect [6]. However, there is no report regarding the effect of *Herba Swertiae* on the gastrointestinal system.

Thus, in the present study, we aimed to evaluate the effect of *Herba Swertiae* on the gastrointestinal system *in vivo*, with a focus on the examination of the effect of *Herba Swertiae* on the gastric emptying, intestinal propulsion, gastric acid secretion, pepsin activity, and the mobility of ileum.

Materials and Methods

Materials

Herba Swertiae ointment was obtained from Shanghai Longhua Hospital (Shanghai, China). JianWeiXiaoShi pill was purchased from Jiangzhong Pharmaceutical Co. Ltd. (Jiangxi, China). Domperidone

was sourced from Bohua Pharmaceutical Co. Ltd. (Shanghai, China). Pepsin assay kit was bought from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). Sodium chloride, potassium chloride, magnesium sulfate, sodium bisulfate, sodium bicarbonate, calcium chloride, D-glucose, carboxymethylcellulose sodium, acetylcholine chloride (0.01 mg/ml), and atropine sulfate (0.5 mg/ml) were obtained from Sigma-Aldrich (St. Louis, MO, USA).

Reagents preparation

Herba Swertiae ointment was dissolved in distilled water at a stock concentration of 21.48×10^{-3} g/ml and stored at -20°C . Domperidone was dissolved in distilled water at a stock concentration of 0.125×10^{-3} g/ml. The solid meal was made from carboxymethylcellulose sodium, milk powder, D-glucose, and starch and black colored by ink.

Animals

A number of 50 male Sprague-Dawley rats (200-250 g, 6-8 weeks old), 50 male Kunming mice, (18-22 g, 6-8 weeks old), and 10 male guinea pigs (300-500 g, 6-8 weeks old) were provided by the Experimental Animal Center of Shanghai University of Traditional Chinese Medicine, Shanghai, China. The animals were housed in the accredited animal housing facility under controlled temperature ($22 \pm 2^{\circ}\text{C}$) and a 12-hour dark/light cycle. All animals were allowed

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to acclimate for 5–7 days prior to experiments. All experiments were conducted according to the animal protocol approved by the Animal Ethics Committee of Shanghai University of Traditional Chinese Medicine.

Animal experiments

Effect of *Herba Swertiae* on gastric emptying and intestinal propulsive function in mice: The Kunming mice were divided into five groups ($n = 8$), including saline, *Herba Swertiae* (0.215, 0.430, and 0.860 g/kg), and domperidone (positive control) treatment group. All mice were fasted for 24 h prior to the treatment. The mice were received solid meal (0.8 ml) via gavage after treatment for 30 min, and all mice were euthanized after the solid meal for 30 min. The stomach was collected and weighed with cardia and pylori ligated and the total weight was measured. Then, stomach was cut open and cleaned to measure the net weight. The percentage of the gastric emptying rate was calculated. In addition, the small intestine was collected to calculate the intestinal propulsion.

Effect of *Herba Swertiae* on the secretion of gastric acid and the activity of pepsin in rats: The rats were divided into five groups ($n = 8$), including saline, *Herba Swertiae* (0.15, 0.30, and 0.60 g/kg), and JianWeiXiaoShi Pill (positive control) treatment group. All mice were fasted for 24 h prior to the treatment. The rats were anaesthetized before the operation. The ligation was conducted between pylori and duodenum, and the drug was injected into duodenum. The rats were housed for 4 h without access to water and food after the operation. Then, the rats were euthanized and the gastric acid was collected for further analysis.

Effect of *Herba Swertiae* on the function of isolated ileum of guinea pig: The *ex vivo* study was performed to examine the effect of *Herba Swertiae* on the function of isolated ileum of guinea pig. The guinea pigs were fasted for 24 h and euthanized. The ileum was collected for the test of effect of *Herba Swertiae* on muscular tension force, contraction amplitude and frequency as previously described [8].

Results

Herba Swertiae enhances gastric emptying and intestinal propulsive function in mice

First, we examined the effect of the extraction of *Herba Swertiae* on the gastric emptying rate and intestinal propulsion in mice. Mice were dosed with *Herba Swertiae* at different concentrations. The data

showed that *Herba Swertiae* increased the gastric emptying rate and promoted the intestinal propulsive function mice (Figure 1A and 1B). In comparison to the saline-treated group, there was a 1.7-fold elevation in the gastric emptying rate in mice when treated with 0.43 g/kg *Herba Swertiae* ($P < 0.05$; Figure 1A). In addition, the positive group treated with 0.005 g/kg domperidone exhibited a significant increase in the gastric emptying rate and intestinal propulsion in mice (Figure 1A and 1B). On the other hand, there was only a slight increase in the intestinal propulsive in mice after *Herba Swertiae* treatment ($P > 0.05$) Taken together, the results show that *Herba Swertiae* enhances the gastric emptying and intestinal propulsion in mice.

Herba Swertiae promotes the secretion of gastric acid and the activity of pepsin in rats

Following the observation on the promoting effect of *Herba Swertiae* on gastric emptying and intestinal propulsion, we examined its effect on gastric acid secretion and the activity of pepsin in rats. Treatment of rats with different concentrations of *Herba Swertiae* led to a marked increase in the secretion and acidity of gastric acid and the activity of pepsin (Figures 2A-2C). In comparison to the saline-treated group, there was a 1.7-fold rise in the secretion of gastric acid in rats when dosed with 0.60 g/kg *Herba Swertiae* ($P < 0.05$; Figure 2A), which was comparable to the effect of positive control group. Also, there was a 1.4- and 1.8-fold increase in the acidity of gastric acid when the rats were treated with 0.30 and 0.60 g/kg *Herba Swertiae*, compared to the saline-treated group, respectively ($P < 0.001$; Figure 2B). There was a 1.4-fold elevation in the acidity of gastric acid in the positive control group, compared to the saline-treated group ($P < 0.001$; Figure 2B). In addition, *Herba Swertiae* dose-dependently increased the activity of pepsin in rats (Figure 2C). In comparison to the saline-treated group, there was a 1.7-, 1.8-, and 2.5-fold increase in the activity of pepsin in rats when treated with *Herba Swertiae* at 0.15, 0.30, and 0.60 g/kg, respectively ($P < 0.01$ or 0.001 ; Figure 2C). The positive control group also showed a 2.5-fold elevation in the activity of pepsin in rats ($P < 0.001$; Figure 2C). Collectively, the results show that *Herba Swertiae* exerts a potent enhancing effect on the secretion and acidity of gastric acid and the activity of pepsin in rats.

Herba Swertiae enhances the function of isolated ileum of guinea pig

To further examine the effect of *Herba Swertiae* on gastrointestinal

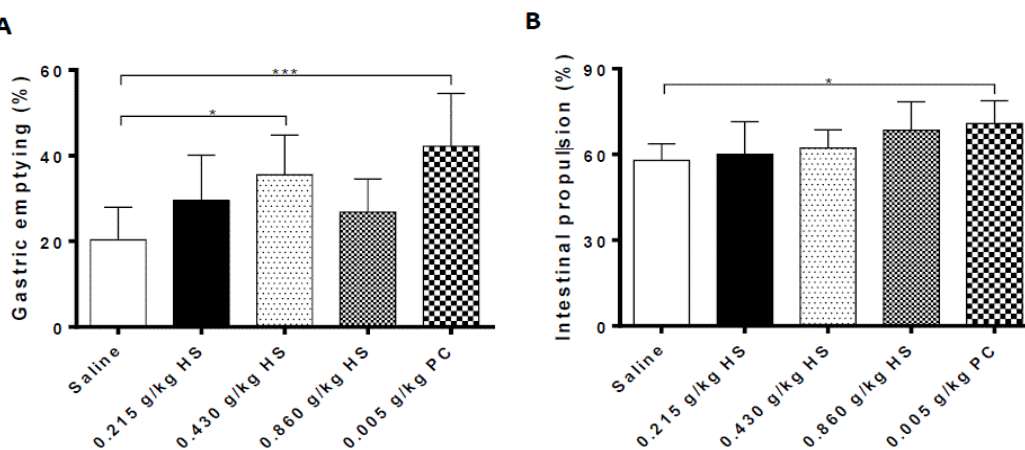
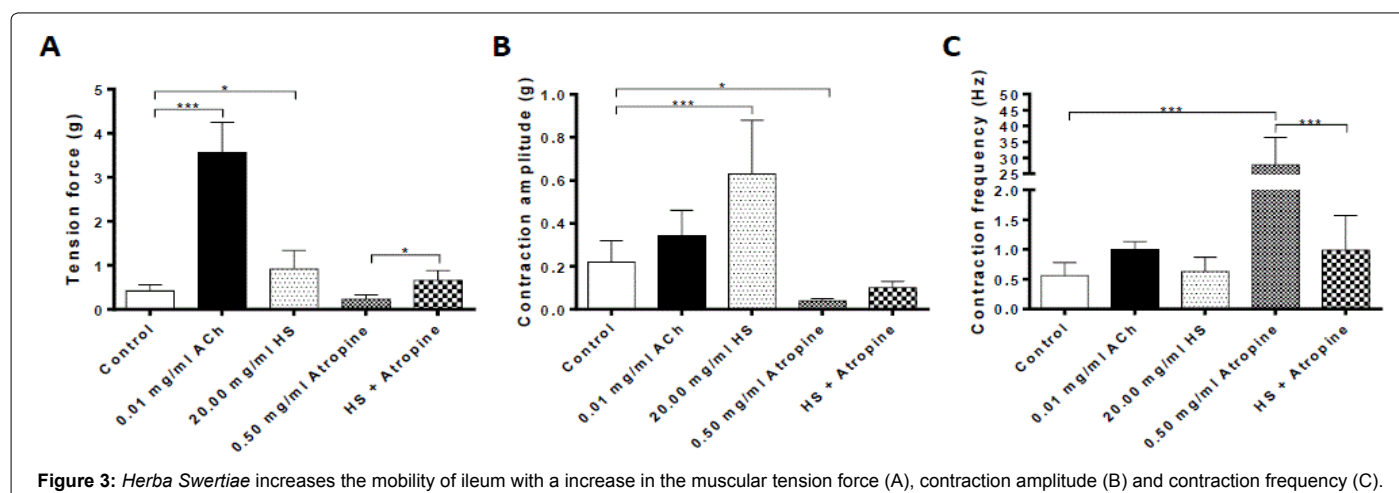
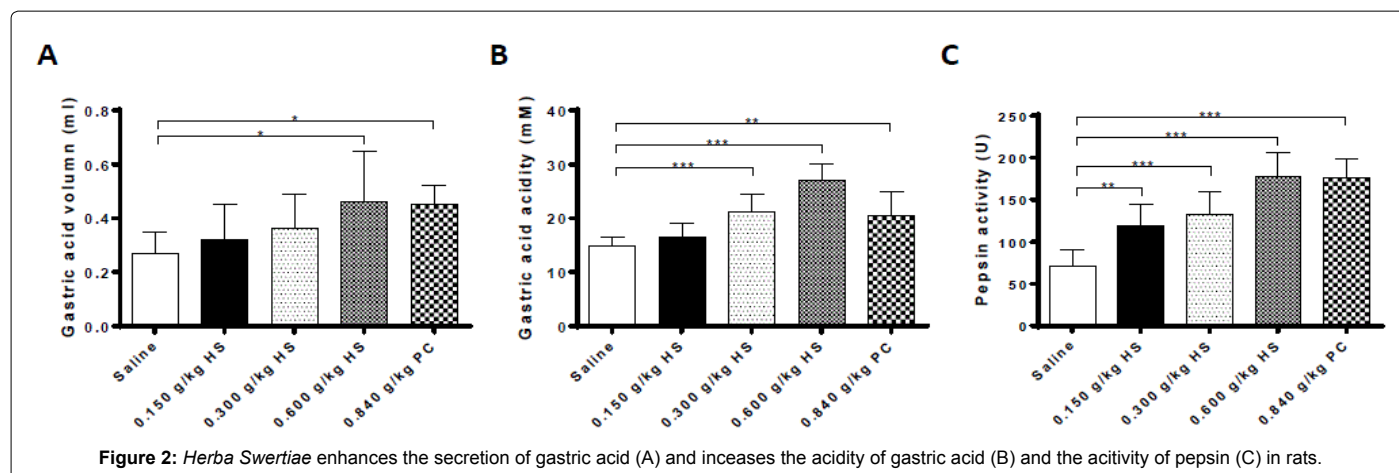


Figure 1: *Herba Swertiae* promotes gastric emptying (A) and intestinal propulsion (B) in mice.



system *in vivo*, we performed *ex vivo* study to test the effect of *Herba Swertiae* on isolated ileum of guinea pig with a focus on muscular tension force, contraction amplitude and frequency. Treatment of guinea pig with 20 mg/ml *Herba Swertiae* enhanced the muscular tension force, contraction amplitude and frequency in isolated ileum (Figures 3A-3C). Compared to the control group, *Herba Swertiae* (20 mg/ml \times 2 ml) increased 2.2-fold in the muscular tension force ($P < 0.05$; Figure 3A); ACh (0.01 mg/ml \times 0.1 ml) enhanced 8.5-fold in the muscular tension force ($P < 0.001$; Figure 3A); atropine (0.5 mg/ml \times 0.4 ml) decreased 45.2% in the muscular tension force ($P > 0.05$; Figure 3A). Of note, *Herba Swertiae* restored atropine-minished muscular tension force with 2.9-fold increase, compared to atropine-treated alone ($P < 0.05$; Figure 3A). For the contraction amplitude, *Herba Swertiae* treatment resulted in a significant increase with 2.9-fold ($P < 0.001$), whereas atropine treatment led to a 81.1% decrease ($P < 0.05$), compared to the control group (Figure 3B). *Herba Swertiae* antagonized atropine-reduced contraction amplitude with 2.5-fold increase, compared to atropine-treated alone ($P > 0.05$; Figure 3B). In addition, although there was slight increase in the contraction frequency in the isolated ileum when treated with ACh and *Herba Swertiae*, there was no significant alteration ($P > 0.05$, Figure 3C). However, atropine dramatically increased the contraction frequency 49.6-fold ($P < 0.001$; Figure 3C). Notably, *Herba Swertiae* abolished the increasing effect of atropine on contraction frequency and normalized it (Figure 3C). In aggregate, *Herba Swertiae* exerts a beneficial effect on the mobility of ileum.

Discussion

A large line of evidence shows that herbal medicines and natural products have been the most productive source for the drug discovery and development and there is a wealth of evidence showing the application of herbal medicines and natural products for body function management and ailments treatment [1,2,4,9,10]. Owing to the multiple bioactive components in herbal medicines and natural products, it can explain the multiple targets effect in their medical applications; on the other hand, it may contribute to the unwanted side effects. Therefore, it needs to fully evaluate the beneficial effect and side effect of herbal medicines and natural products to improve their therapeutic effect and avoid unfavorable effect in clinical practice.

Herba Swertiae is traditionally used for the treatment of diarrhea, poor appetite, hypochondriac pain, and jaundice that can be ascribed to the mechanism of actions of the clearance of damp-heat and the strengthening of the stomach [6,7]. In the present study, we observed potent beneficial effects of *Herba Swertiae* on gastrointestinal system *in vivo*. In clinical settings, the aberrations in gastric emptying and intestinal propulsion are the common causes to gastrointestinal disorders [11,12]. Our study showed a promoting effect of *Herba Swertiae* on gastric emptying and intestinal propulsion in mice, which is similar to the effect of domperidone. It has been demonstrated that domperidone stimulates gastric muscle contraction by antagonizing the inhibitory effects of dopamine on postsynaptic cholinergic neurons

[13]. Therefore, our findings suggest that *Herba Swertiae* may exert similar effect to domperidone on gastrointestinal system via its multiple active components; however, it needs to be further validated in future studies regarding the underlying mechanisms and molecular targets for beneficial effect on the gastrointestinal system.

Furthermore, our findings showed that *Herba Swertiae* dose-dependently enhanced the secretion and the acidity of gastric acid and the activity of pepsin in rats. Such increasing effect is comparable to that of the positive control, which renders *Herba Swertiae* may be a potent agent for the gastrointestinal disorders treatment. Moreover, the *ex vivo* experiment showed that *Herba Swertiae* had the capability of promoting the mobility of ileum of guinea pig with a marked enhancement in the muscular tension force and contraction amplitude. Notably, *Herba Swertiae* was able to antagonize the effect of atropine in the isolated ileum regarding the muscular tension force, contraction amplitude and frequency. On the other hand, *Herba Swertiae* showed a similar effect to that of ACh. Atropine is recognized as a competitive inverse agonist for the muscarinic acetylcholine receptor types M1, M2, M3, M4, and M5 [14]. Also, it has been well recognized that ghrelin is able to stimulate the gastric acid secretion and gastric mobility [15]. Collectively, our results combined with previous findings suggest that *Herba Swertiae* may be a promising agent for the treatment of gastrointestinal disorders. However, the underlying mechanism and the full spectrum of molecular targets of *Herba Swertiae* need to be identified in future study. With the increasing usage of state-of-art computational, molecular biological and analytical chemistry techniques, it will promote the exploration of the pharmacological effect of *Herba Swertiae*.

In conclusion, *Herba Swertiae* is a promising agent with great potential for the treatment of gastrointestinal disorders, owing to its promoting effect on the gastric emptying, intestinal propulsion, gastric acid secretion, pepsin activity, and the mobility of ileum. More studies are warranted to elucidate the underlying mechanism and molecular targets.

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