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Original Article

Improved choleretic effect of Benachio-F®-based formula enriched with fennel extracts

Hye Jin Cho[1], Jun Su Im[1], Yong Sam Kwon[2], Kyung Soo Kang[3] and Tae Min Kim[1,4,*]

[1]Graduate School of International Agricultural Technology, Seoul National University, Pyeongchang 25354, Korea
[2]Research Center, Dong-A Pharmaceutical Co., Ltd., Yongin 17073, Korea
[3]Department of Bio Life Science, Life & Environment Field, Shingu College, Seongnam 13174, Korea
[4]Institute of Green-Bio Science and Technology, Seoul National University, Pyeongchang 25354, Korea

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***Correspondence**
Tae Min Kim
E-mail: taemin21@snu.ac.kr

Author's Position and Orcid no.
Cho HJ, MS student,
https://orcid.org/0000-0003-1804-117X
IM JS, MS student,
https://orcid.org/0000-0002-4609-7990
Kwon YS, Research fellow,
https://orcid.org/0000-0001-5312-4777
Kang KS, Assistant professor,
https://orcid.org/0000-0002-5547-7215
Kim TM, Associate professor,
https://orcid.org/0000-0003-0015-2701

ABSTRACT Functional dyspepsia (FD) is a gastrointestinal disorder with diverse symptoms but no structural or organic manifestations. Benachio-F® (herein named 'BF-1') is an over-the-counter liquid digestive formulated with multiple herbal extracts, which has been reported to improve symptoms of FD. A total two experiments were conducted. First, we examined whether BF-1 can modulate the progression of FD through two experimental rat models. A total of three doses (0.3x, 1x, 3x of the human equivalent dose) were used. In the gastric emptying model, both 1x (standard) or 3x (3-fold-concentrated) BF-1 enhanced gastric emptying was compared with that of vehicle-treated animals. In a feeding inhibition model induced by acute restraint stress, treatment with 1x or 3x BF-1 led to a similar degree of restoration in food intake that was comparable to that of acotiamide-treated animals. Among the constituents of BF, fennel is known for its choleretic effect. Thus, we next investigated whether a novel BF-based formula (named 'BF-2') that contains an increased amount of fennel extract (3.5-fold over BF-1), has greater potency in increasing bile flow. BF-2 showed a superior choleretic effect compared to BF-1. Furthermore, the postprandial concentration of serum secretin was higher in animals pretreated with BF-2 than in those pretreated with BF-1, suggesting that the increased choleretic effect of BF-2 is related to secretin production. Our results demonstrate that BF-1 can modulate the pathophysiological mechanisms of FD by exerting prokinetic and stress-relieving effects, and that BF-2 has a better choleretic effect than BF-1.

Keywords: choleresis, feed inhibition, functional dyspepsia, gastric emptying

INTRODUCTION

Functional dyspepsia (FD) is a gastrointestinal dysfunction with various recurrent symptoms in the upper abdomen, even without structural or organic lesions. The symptoms of FD include upper abdominal pain, bloating, postprandial fullness, heartburn, and belching (Tack and Talley, 2013). Its etiology is not yet known; however, studies have shown that the pathophysiology of FD is multi-factorial, among which delayed gastric emptying, psychological/physiological stress, dysfunctional gastric accommodation, and visceral hypersensitivity are the main causes (Talley and Ford, 2015; Ye et al., 2018). FD can be subdivided into post-prandial distress syndrome (PDS), which can be characterized by meal-induced satiety, and epigastric pain syndrome (EPS), characterized

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by epigastric pain or burning (Noh et al., 2010). A meta-analysis revealed that the global prevalence of uninvestigated FD reaches 20.8%, depending on geographical location, and certain criteria including the duration of symptoms (Ford et al., 2015). Although the effect of BF in the treatment of FD has been well-studied (Shim et al., 2015), its detailed function in animal models remains largely uncharacterized (Poudel et al., 2015).

Benachio-F® (BF) is an over-the-counter drug approved by the Korea Food and Drug Administration (KFDA). It consists of seven herbs, including Foeniculi Fructus, Corydalis Tuber, Atractylodis Rhizoma, Cinnamomi Cortex, Glycyrrhizae Radix, Zingiberis Rhizoma, and Citri Unshiu Pericarpium. These herbs have been used in Oriental medicine to treat gastrointestinal dysfunction or pain (Shim et al., 2015). Specifically, fennel has been traditionally used as a culinary ingredient, as well as for medical purposes, mainly because of its diverse role in the gastrointestinal (GI) tract, and its stimulatory, carminative, stomachic, and emmenagogue effect (Platel and Srinivasan, 2004). It has been reported that fennel seeds have a laxative function as well as a stimulatory effect in peristaltic motion, leading to an increased production of gastric juice (Poudel et al., 2015). In addition, it is a well-known herbal medicine used to increase choleretic activity. For example, Platel and Srinivasan demonstrated that fennel increased bile acid and bile solids either as a dietary supplement (8-week study) or as a single oral dosage (Platel and Srinivasan, 2000). In addition, an *in vitro* study also showed that Foeniculi Fructus powder led to an increase in the activity of lipase *in vitro* (Rao et al., 2003). Collectively, fennel can be used as a potent compound for developing choleretic peptics to stimulate key digestive hormones in order to relieve various symptoms of digestive disorders. Based on the aforementioned pharmacological effects, we recently developed a modified BF product with a 3.5-fold-increased amount of fennel extract (herein named 'BF-2').

In this study, we examined whether BF-1 can modulate some of the pathophysiological mechanisms of FD and whether BF-2 has an increased choleretic effect over BF-1. The potential mechanism underlying the increased choleretic function of BF-2 was also investigated.

MATERIALS AND METHODS

Reagents

BF-1 and BF-2 were obtained from Donga Pharmaceutical. Co. Ltd. The formulation of BF is available at the Korea Pharmaceutical Information Center (Seoul, Korea) (http://www.health.kr/searchDrug/result_drug.asp?drug_cd=2014021300002). Semi-solid chow was prepared by thoroughly mixing the conventional mouse chow (Purina Mouse Diets, #38057) in saline (at a ratio of 2 g of chow in 5 mL of saline).

Animal experiments

All experiments were approved by the Institutional Animal Care and Use Committee (IACUC) of Seoul National University (SNU-200121-1-1) and Dong-A Pharmaceutical Co. Ltd. (I-1904079, I-1905097). All procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (Institute for Laboratory Animal Research, 2011).

All animals were purchased from Koatech Inc. (Pyeongtaek, Korea) and housed at 23-24℃ with a 12/12-hr light/dark cycle. To examine the effect of BF-1 on the gastric emptying time, rats were fasted for 16 hours and then orally administered the following: vehicle (3% HPMC; (hydroxypropyl methylcellulose), cisapride (10 mg/kg), and various dosages of BF-1; 2.25 mL/kg (0.3x of standard dosage), 7.5 mL/kg (standard dosage), and 22.5 mL/kg (3x of standard dosage). After 1 h, the rats were orally fed semi-solid chow. After 30 min, the animals were euthanized by CO_2 asphyxiation, after which their stomachs were excised. The gastric emptying rate was calculated as follows: 100 × [(1-a)/b], where a is the weight (g) of the net meal remaining in the stomach, and b is the weight (g) of gastric contents before they enter the small intestine. The value b was calculated in a preliminary experiment by subtracting the weight of the empty stomach from the total weight of the stomach (1.69 ± 0.58g, N = 3).

To induce acute stress-induced feeding inhibition, rats were fasted for 16 hours and then fed vehicle (3% HPMC), acotiamide (10 mg/kg), and various dosages of BF-1; 2.25 mL/kg (0.3x of standard dosage), 7.5 mL/kg (standard dosage), and 22.5 mL/kg (3x of standard dosage). After the rats were kept in a restraint chamber for 2 h, they were given two pieces of chow that had been weighed (10 g) to monitor the initial net gram of pellet. Subsequently,

the amount of food intake was calculated by subtracting the weight (g) of the remaining pellet from the initial weight (g).

To analyze bile flow, male Sprague Dawley (SD) rats weighing 300-320 grams were fasted for 12 h and randomly assigned to six groups: (1) vehicle (3% HPMC), (2) UDCA (ursodeoxycholic acid; 30 mg/kg) (Sokolovic et al., 2013), (3) BF-1 (7.5 mL/kg), and (4) BF-2 (7.5 mL/kg). The dosages of BF-1 and BF-2 were determined based on the guidelines for converting dosages between animals (Nair and Jacob, 2016). After 30 min of oral administration, the animals were orally fed with semi-solid chow (1 mL). After another 30 min, the animals were anesthetized with 4% isoflurane/oxygen in a chamber. After surgical anesthesia was confirmed under 2% isoflurane/oxygen, the rats underwent laparotomy under a dissecting microscope (SMZ445, Olympus), and the skin was shaved and a midline incision was made. Subsequently, a hole was made in the proximal bile duct using a blade (FEATHER Safety Razor Co., Ltd, Japan) and the beveled tip of a silicone SoloCath catheter (3 Fr) was inserted into the bile duct. To fix the catheter, a suture was made around the beads (6-0 silk, Ethicon). After the intestine was repositioned into the peritoneal cavity, the peritoneal and muscle layers were closed with a continuous suture (Vicryl 5-0, Ethicon) while ensuring that the free end of the catheter protruded out of the closure. Bile was steadily collected for 15 min into a 1.7 mL tube. The animals were euthanized by CO_2 asphyxiation.

To measure the secretion of secretin, rats were fasted for 16 h and then orally administered the following: vehicle (3% HPMC), UDCA (30 mg/kg), BF-1 (7.5 mL/kg), or BF-2 (7.5 mL/kg). After 20 min of treatment, animals were orally fed semi-solid chow (1 mL) and whole blood (0.5 mL) was collected after 30 or 45 min from the tail vein. The animals were euthanized by CO_2 asphyxiation. The concentration of secretin was measured using a rat secretin ELISA kit (Novus Biologicals, USA) according to the manufacturer's instructions.

RESULTS

The effect of BF-1 on gastric emptying

Delayed gastric emptying is one of the pathophysiological causes of FD; thus, we tested whether BF-1 has a prokinetic effect. Fasted animals were fed with various dosages of BF-1 (0.3x, 1x, and 3x of standard dosage) and subsequently administered a semi-solid meal, and the change in the weight of the stomach was monitored. As shown in Fig. 1, animals treated with cisapride (a 5-HT_4 agonist), a positive control, showed enhanced gastric emptying. BF-1 of both standard and concentrated dosages stimulated gastric emptying compared to vehicle ($p < 0.005$). No differences were found between rats treated with standard and concentrated BF-1.

The effect of BF-1 on restoring restraint-induced acute stress

Acute stress is known to induce gastrointestinal disorders, including FD (Kim et al., 2018). Thus, we examined whether acute stress induced by restraint can be alleviated by BF-1 at various dosages (0.3x, 1x, and 3x the standard dosage). Food intake was increased in rats that received original or concentrated dosages of BF-1 (Fig. 2; $p < 0.05$), but not in animals that were administered dilute (0.3x) product, compared to animals treated with vehicle (Fig. 2). No difference was found between animals treated with standard and concentrated dosages of BF-1.

The effect of BF-2 on bile flow

As shown in Fig. 3, UDCA, which was used as a positive control, led to an increase in bile compared to the vehicle. We next evaluated whether BF-2 has an enhanced choleretic effect compared to BF-1. BF-2 showed a greater effect on bile flow than BF-1 ($p < 0.0001$), and only BF-2

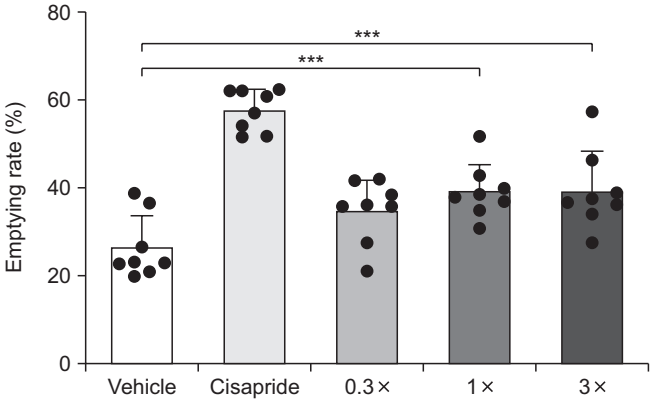

Fig. 1. The effect of BF-1 on the rate of gastric emptying. Standard (1x), diluted (0.3x; 0.3-fold of standard dosage) and concentrated (3x; 3-fold of standard dosage) BF-1 was tested. Vehicle and cisapride were used as negative and positive controls, respectively. Values are mean ± S.D. ***$p < 0.005$.

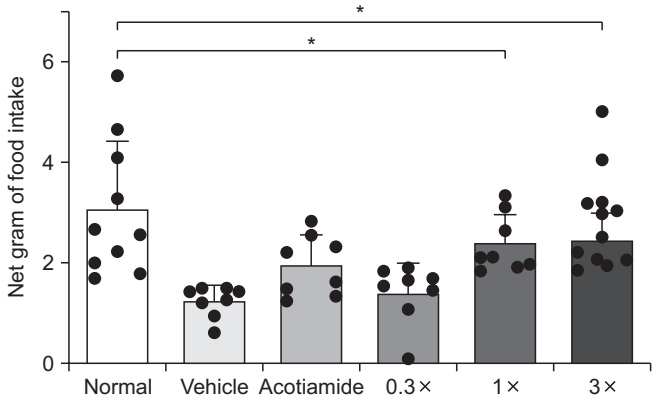

Fig. 2. The effect of BF-1 on food intake after restraint-induced stress. The net gram of food intake was measured by calculating the change of food weights before and after the voluntary intake. Standard (1x), diluted (0.3x; 0.3-fold of standard dosage) and concentrated (3x; 3-fold of standard dosage) BF-2 was tested. Among stress-induced rats, non (negative)- and acotiamide-treated animals were used as negative and positive controls, respectively. Values are mean ± S.D. *$p < 0.05$.

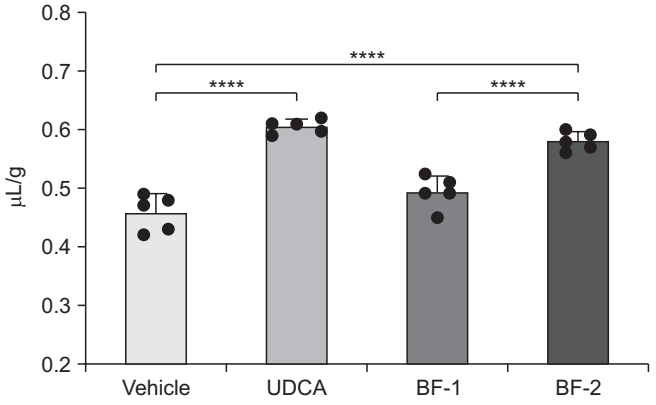

Fig. 3. The effect of BF-2 treatment on bile flow (volume per body weight). BF-2 indicates a BF-1-based product that has a higher (3.5-fold) amount of fennel extract. Vehicle and UDCA were used as negative and positive control, respectively. Values are mean ± S.D. ****$p < 0.0001$.

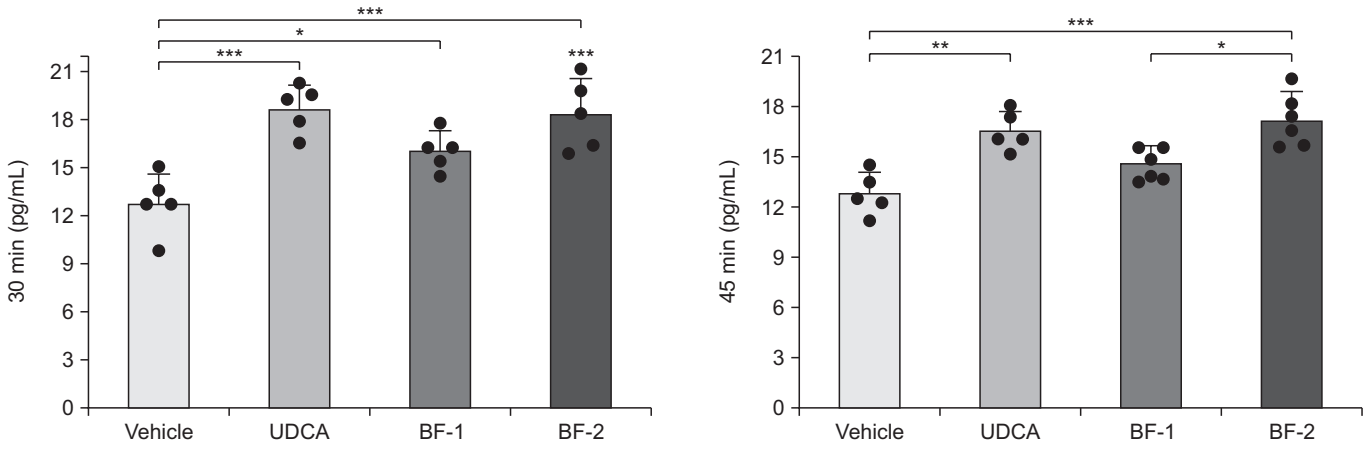

Fig. 4. The effect of BF-2 on concentration of serum secretin. Serum was collected after 30 and 45 minutes of food intake. Vehicle and UDCA were used as negative and positive control, respectively. Values are mean ± S.D. *$p < 0.05$, **$p < 0.01$, ***$p < 0.005$.

showed enhanced choleresis compared to vehicle ($p < 0.0001$). The effect of BF-2 was comparable to that of the positive control (UDCA). The choleretic effect of BF-1 was minimal.

The effect of BF-2 on the concentration of serum secretin

Secretin is known to promote choleresis (Björn, 1994). To identify the underlying mechanisms of increased bile flow by BF-2 treatment, we tested whether BF-2 is superior to BF-1 in elevating serum secretin levels. After 30 min of feeding, both BF-1 and BF-2 enhanced the level of plasma secretin as compared to the vehicle (Fig. 4; $p < 0.05$ and $p < 0.005$ in BF-1 and BF-2, respectively). No differences were observed between BF-1 and BF-2 at this timepoint. However, at 45 min after feed administration, BF-2 led to an increase in plasma secretin ($p < 0.005$), while BF-1 did not show such an effect. Lastly, an enhanced level of secretin was observed in BF-2 compared with BF-1 ($p < 0.05$). No difference was observed between animals treated with UDCA and those treated with either BF-1 or BF-2 (Fig. 4).

DISCUSSION

The gastroprokinetic effect of BF-1, which is an oft-used pharmaceutical agent (Poudel et al., 2015), was evident. BF-1 contributed to an increase in gastric emptying compared to vehicle, although no dose-dependent effect was found between standard and 3-fold increased dosages, suggesting that a standard dosage is sufficient to yield the effect. Dopamine or serotonin receptors can affect gastric emptying. Specifically, 5-HT_4 receptor agonists such as Cisapride® and Tegaserod®, or dopamine D_2 receptor antagonists, including Itopride®, have been developed for FD (Brun and Kuo, 2010). Other drugs also act as D_2 antagonists or 5-HT_4 agonists, such as tetrahydroberberine or Motilitone® (a compound consisting of Corydalis Tuber and Pharbitidis Semen), which can alleviate the inhibition of food uptake by acting via 5-HA_{1A}. Motilitone® also stimulates 5-HA_{4A} and α-2 adrenergic pathways (Kwon and Son, 2013). The mechanism underlying stress-induced impairment of gastric accommodation remains largely unknown; however, it has been reported that neuropeptides such as corticotropin-releasing factor (CRF) can play a role (Nakade et al., 2005). Thus, further investigation into the relationships between the chemical components of BF-1 and neuropeptides, or its cognate agonistic receptors (dopamine, serotonin, or adrenergic) in the GI tract, is needed to better clarify the underlying mechanism by which BF-1 enhances gastric emptying.

Fennel is a perennial herb, and has been reported for its various systemic and local pharmacological effects on human health, especially in the gastrointestinal tract (Badgujar et al., 2014). Fennel seeds have a laxative effect, as shown by the stimulation of peristaltic motion, providing roughage; enhancing the production of bile and gastric juices; and promoting excretion (Poudel et al., 2015). Faith et al. demonstrated that pretreatment of rats with an aqueous extract of fennel significantly reduced the severity of ethanol-induced gastric damage, which was also associated with an increase in GSH, nitrite, and ascorbic acid, and a reduction in malondialdehyde (MDA), indicating that fennel has antioxidant effects, while reducing lipid peroxidation (Birdane et al., 2007). In addition to its effect on the GI system, fennel has been used for various other purposes, such as to treat dysmenorrhea and pain (Uusitalo et al., 2016). Also, its anti-spasmodic effect was effective in reducing pediatric colic and respiratory disorders (Özbek et al., 2003; Savino et al., 2005). In addition, fennel oil has antibacterial and antiviral activities, while fennel extract exhibits an antioxidant effect and also potently reduces the symptoms of cognitive disorders in mice (Ruberto et al., 2000; Oktay et al., 2003; Joshi and Parle, 2006).

We found that BF-2 treatment increased bile volume in rats. One possible mechanism for this effect may involve the increased, stabilized, or prolonged effect of fennel on bile production. In line with these results, it was previously demonstrated that dietary treatment with fennel led to an increased secretion of bile salts, and that oral administration also markedly increased bile acid secretion in rats (Platel and Srinivasan, 2000). Fennel contains various compounds such as monoterpenoids, sesquiterpenes, phenylpropanoids, coumarins, fatty acids, and essential oils, as well as some minor constituents, including tannins and flavonoids (Lal and Meena, 2018). Thus, it will be important to investigate whether any of these components affect pathways of bile acid synthesis (Russell, 2009). Bile helps to emulsify large fat particles into fine ones, so that the surface can be digested by lipase from pancreatic juice. Bile is also essential for excreting waste products as well as for the absorption of other small molecules, including fatty acids, lipids, and cholesterol (Hylemon et al., 2009). Therefore, the stimulation of bile flow by BF-2 could be a major mechanism that can contribute to promoting digestion in digestive disorders, including FD. It was also found that spices other than fennel, for example, a mixture of coriander, turmeric, red chilli, and curcumin, led to a significant increase in the activities of digestive enzymes (pancreatic lipase, chymotrypsin, and amylase) as well as in bile flow and bile acid secretion (Platel et al., 2002). Accordingly, investigating the synergistic effect between fennel and other spices could lead to the development of phytomedicinal products with enhanced choleretic effects.

Secretin is a gastrointestinal peptide hormone secreted by S cells present in brain neurons and the small intestine (Afroze et al., 2013). Besides its well-known function in regulating the acidity of duodenal content by inhibiting gastrin release, secretin acts on the liver to stimulate bile flow (Fukumoto et al., 1992; Úrlz et al., 2011). We observed that the serum concentration of secretin increased after 45 min of BF-2 administration. However, the mechanism by which secretin concentration was increased

by BF-2 remains unclear, because the production and secretion of secretin are affected by multiple factors. For example, secretin is released in an acidic environment due to the presence of hydrochloric acid in the chyme. In addition, its secretion is augmented by digested fat and proteins (Nakamachi, 2016). Thus, in-depth studies are needed to determine the relationship between the choleretic effects of BF-2 and secretin production.

Although the function of fennel on digestive function has been previously reported, no dose-dependent results on its choleretic effect has been shown. Our results from two experimental animal models showed the *in vivo* efficacy of BF-1, which further validated its pharmaceutical function. In addition, modifying BF-1 constituents by increasing the fennel was sufficient to increase the bile flow and post-prandial secretin level, which suggest that BF-2 has better potential for a liquid digestive with an increased choleretic activity. Our data may contribute to developing a novel phytomedicine-based choleretic and gastroprokinetic agent.

CONCLUSION

BF-1 can modulate the pathophysiological mechanisms of FD by exerting prokinetic and stress-relieving effects, and that BF-2 has a better choleretic effect than BF-1.

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Ethical Approval: All experiments were approved by the Institutional Animal Care and Use Committee (IACUC) of Seoul National University (SNU-200121-1-1) and Dong-A Pharmaceutical Co. Ltd. (I-1904079, I-1905097).

Consent to Participate: Not applicable.

Consent to Publish: Yes.

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