Clinical Trials Study

Effects of Chinese herbal medicine Xiangbin prescription on gastrointestinal motility

Zhi Jiang, Li-Xing Cao, Bo Liu, Qi-Cheng Chen, Wen-Fan Shang, Lu Zhou, Dan-Yan Li, De-An Guo, Zhi-Qiang Chen

Zhi Jiang, Li-Xing Cao, Bo Liu, Qi-Cheng Chen, Wen-Fan Shang, Dan-Yan Li, Zhi-Qiang Chen, Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510120, Guangdong Province, China

Lu Zhou, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Beijing 100005, China

De-An Guo, Shanghai Research Center for Modernization of Traditional Chinese Medicine, Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 201203, China

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Correspondence to: Dr. Zhi-Qiang Chen, Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510120, Guangdong Province, China. zhi57@163.com

Telephone: +86-20-81887233
Fax: +86-20-81867705

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Abstract

AIM
To investigate the effects of Xiangbin prescription (XBP), a Chinese herbal concoction, on gastrointestinal motility.

METHODS
Forty healthy volunteers were recruited for this randomized controlled trial of XBP. Antroduodenojejunal manometry was used to monitor gastrointestinal...
motility in these subjects. After the subjects had fasted for at least 12 h, XBP (n = 30) or placebo (n = 10) was orally administered and gastrointestinal motility was recorded for 4 h. Plasma motilin and ghrelin were measured by enzyme-linked immunosorbent assay.

RESULTS

Oral administration of XBP significantly increased the amplitude of duodenal contractions [19.5 (13.0-26.7) vs 16.9 (12.3-23.9), P < 0.05], jejunal contractions [18.3 (15.3-25.0) vs 15.4 (11.7-23.9), P < 0.01], and the motility index of duodenal contractions [522.0 (146.0-139.0) vs 281.0 (76.5-1006.0), P < 0.01] in phase II of the migratory motor complex (MMC), which subsequently initiated the MMC cycle [74.0 (30.0-118.0) vs 116.5 (24.0-219.0), P < 0.05], shortened the duration of phase I of the MMC [42.0 (0.0-90.0) vs 111.5 (42.0-171.0), P < 0.01], and lengthened the duration of phase II of the MMC [120 (21-240) vs 58 (16-170), P < 0.01] compared to the duration before XBP administration. There were significant differences in the amplitude of jejunal contractions [19.8 (14.0-30.0) vs 18.0 (13.0-28.5), P < 0.05], the motility index of jejunal contractions [236.0 (115.0-306.0) vs 195.0 (109.0-310.0), P < 0.05], and jejunal contractions [214.0 (95.0-403.0) vs 178.0 (55.0-304.0), P < 0.01] in phase III of the MMC. Oral administration of XBP greatly increased plasma motilin (57.69 ± 9.03 vs 49.38 ± 8.63, P < 0.01) and ghrelin (279.20 ± 55.38 ± 8.63, P < 0.01) concentrations compared to concentrations after oral administration of the placebo.

CONCLUSION

XBP can stimulate duodenal and jejunal motility and increase the concentrations of plasma motilin and ghrelin. The clinical applicability of XBP in treating DGIM deserves investigation.

Key words: Antrotroduodenojejunal manometry; Gastrointestinal motility; Migrating motor complex; Xiangbin concoction; Motilin; Ghrelin

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Core tip: Disorders of gastrointestinal motility are heavy medical burdens to patients and the society, and development of effective and safe drug treatments for these disorders has proven challenging. Xiangbin prescription is an effective prokinetic Chinese herbal concoction. The core of this randomized, double-blind study is to investigate the effects of Xiangbin prescription on gastrointestinal motility in 40 healthy volunteers.

INTRODUCTION

Many diseases of the digestive system are associated with disorders of gastrointestinal motility (DGIM), such as gastroesophageal reflux disease, gastroparesis, diarrhea, adhesive bowel obstruction, postoperative ileus, and chronic constipation. DGIM is a worldwide medical burden that affects about 20%-50% of adults in the Western world and 60% of adults in China. Studies on DGIM date back to around a century ago, but the development of effective and safe drug treatments for DGIM has always proven challenging, and prokinetic drugs for the treatment of DGIM are still not widely available in China. Migratory motor complexes (MMC) are waves of electrical activity observed in the gastrointestinal system during fasting, which are well characterized by the appearance of gastrointestinal contractions in the interdigestive state, and are believed to be physiologically important for normal digestive functions; various studies have indicated that DGIM is partly associated with disruptions in MMC rhythm. Antrotroduodenojejunal manometry is a valuable clinical tool for evaluating MMC and has been used to investigate motility patterns in normal people and patients.

Traditional Chinese medicine (TCM), which is fully integrated into the modern healthcare system of China, is characterized by the use of a blend of several herbal ingredients to treat illnesses based on patients’ symptoms. Xiangbin Prescription (XBP) is a TCM concoction created on the basis of TCM theory and clinical experience. Clinical studies on using Chinese herbal medicine for the treatment of DGIM have shown some efficacy, but many of them lack standard protocols and objective indicators. Moreover, the molecular mechanisms underlying the drug action of Chinese herbal medicine are currently hot topics of research in TCM.

Motilin and ghrelin are gastrointestinal hormones that play major roles in regulation of gastrointestinal motility, but the possible effects of XBP on these hormones have not been reported.

In this study, we conducted a randomized, placebo-controlled, double-blind study to assess the effects of XBP on a variety of gastrointestinal motility variables monitored using antrotroduodenojejunal manometry and plasma motilin and ghrelin levels. This provided a comprehensive, objective evaluation of the effects of XBP on gastrointestinal motility.

MATERIALS AND METHODS

Ethical approval

All study procedures were approved by the Ethical...
Committee of the Second Affiliated Hospital, Guangzhou University of Chinese Medicine. Written informed consent was obtained from all volunteers, and the study conformed to the ethical principles set forth by the Declaration of Helsinki.

Participants
This study was conducted from October 2013 to December 2014 at the Second Affiliated Hospital of Guangzhou University of Chinese Medicine. Forty healthy volunteers were recruited by the first author and randomly assigned to a control (placebo) group (n = 10) or an XBP group (n = 30) by the second author, which can be seen in the flow diagram illustrated in Figure 1. A third party was responsible for double blind implementation. The randomization number was put in an envelope, and the same number was affixed to the envelope. The investigator did not know which group the subject would be in, and the color, appearance and drug packets were identical. The subjects of this study had no medical history of gastrointestinal or chronic diseases, psychological disorders, regular drug use, or the use of a gastrointestinal prokinetic agent for more than one week before study. Participants were asked to stop drinking tea, coffee, and alcohol for at least 12 h and to stop smoking cigarettes for at least 1 h before testing. All volunteers underwent electrocardiographic examination as well as hepatic and renal function tests before and after the experiment.

Preparation of XBP and placebo
XBP is a mixture of five crude herbs: 6 g of amomum volosolium lour, 10 g of lindera aggregate (Sims) kosterm, 10 g of prunus persica, 9 g of panax ginseng, and 10 g of aeca catechu to produce a 200-mL concoction, prepared by use of a TCM protocol. Briefly, the weighed herbs and 500 mL of tap water were placed in a heat-resistant glass pot with a lid and boiled on a heater for 60 min before being passed through a paper filter. The herbs were provided by Kangmei Pharmaceutical Co., Ltd. Two hundred milliliters of filtrated Xiangbin concoction were sterilized packed. The placebo consisted of licorice powder (2 g), caramel powder (0.2 g), bitterant (0.1 g) and starch (3 g)[7]. Two hundred milliliters of placebo concoction were prepared by the same method as XBP and had the same color and smell. The above ingredients were used for placebo because: (1) literature search showed no reports of licorice and bitterant having a measurable effect on gastroduodenal movements; and (2) preliminary experiments using these placebo ingredients in healthy volunteers showed no significant effect on gastrointestinal motility compared with 0.9% saline.

Antroduodenoejunal manometry
Antroduodenoejunal manometry was performed with a Solar GI HRM-High Resolution manometer with a 21-channel silicone water-perfused catheter (Enschede, the Netherlands) after subjects had fasted overnight for at least 12 h. The 21-channel catheter was connected to capillaries, then each channel was perfused with water at a rate of 0.3 mL/min. The pressure curve was converted into digital data. The participants laid in a lateral position, and the catheter was inserted into the duodenum under fluoroscopic guidance. After the catheter was fixed, antroduodenoejunal manometry was performed in all participants for 4 h under fasting conditions, followed by the administration of 200 mL XBP or placebo at phase I when the pressure curve was steady with no strong contractions. Antroduodenoejunal manometry was recorded for 4 h after administration of XBP or placebo.

Gastrointestinal motility variables
MMC, which is well characterized by the periodic appearance of gastrointestinal contractions in the interdigestive state[13,14], consists of four phases. Phase I is a quiescent period with no or few contractions. Phase II consists of intermittent and irregular low amplitude contractions. Phase III consists of short bursts of regular high amplitude contractions (3-5 contractions per minute in the stomach; 10-12 contractions per minute in the duodenum). Phase IV is a short transition period back to the quiescence of phase I. Only a pressure fluctuation more than 10 mmHg is designated a contraction[9,15]. The full cycle of the MMC was measured from the end of the first MMC phase IV to the end of the second MMC phase IV. The duration of the MMC was measured from the beginning of the MMC phase III to the end of the same MMC III phase. Motility index (MI; mmHg/min) was quantified according to the contraction amplitude (mmHg) × the number of contractions per minute. The baseline gastrointestinal motility variables were...
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Table 1  Demographic characteristics of the XBP and placebo groups

| Gender | XBP (n = 30) | Placebo (n = 10) | t  | P value |
|--------|-------------|-----------------|----|---------|
| Male   | 21          | 5               | 0.677 |         |
| Female | 9           | 5               |      |         |

Demographic characteristics and baseline motility variables
declared according to internationally recognized, unified conceptual descriptions in the gastrointestinal motility field.\(^{[16]}\)

The pressure curve was recorded by Solar GI HRM-High Resolution Manometry (Medical Measurement System software, MMS). This software can automatically save all original data regarding pressure curves and gastrointestinal motility indicators and general information about the volunteers; calculations can be completed with this software. The total MMC cycles, the mean MMC cycle duration, the duration of phase I and phase II, and the duration of the MMC of the distal stomach, duodenum and jejunum, mean contraction frequency, amplitude, and MI of phase II and phase III were recorded.

Measurement of plasma motilin and ghrelin

Venous blood was collected 15 min before and after oral administration of XBP or placebo and immediately centrifuged at 3000 rpm at 4 °C. Plasma aliquots were frozen at -80 °C until analysis. Plasma motilin concentrations were measured by the use of human Motilin (MTL) ELISA Kit (Wuhan Huamei Biotech Co., Ltd, China), and human total plasma ghrelin was measured by the use of human Ghrelin ELISA Kit (EMD Millipore Corporation, Billerica, MA 01821 United States). ELISA was performed according to the manufacturer’s instructions.

Statistical analysis

Sample size was determined based on the expense of data collection and the need to have sufficient statistical power. Data are presented as mean ± SE, median, or range depending on their distribution and analyzed with PASW Statistics 18.0 (IBM SPSS Inc, Armonk, New York, United States). These means were used for pairwise comparisons between groups using the Wilcoxon signed-rank test. P-values < 0.05 were considered statistically significant.

RESULTS

Demographic characteristics and baseline motility variables

The demographic characteristics of the study subjects are given in Table 1. Ten participants received placebo and 30 participants received XBP. No participants were lost from the study, and data were collected from all participants and analyzed. There were no statistical differences in gender, age, or BMI between subjects who received XBP and those who received placebo.

All catheters were successfully positioned, and a full MMC cycle was recorded in each subject. There were no differences in baseline motility variables between the two groups. The average duration of one complete MMC cycle for all subjects combined was 96 min; the average duration of phase I was 43 min, phase II 38 min, phase III 4 min, and phase IV 11 minutes. Distal stomach contractions of phase III were regular and strong at 2-3 contractions per minute, with an amplitude of more than 40 mmHg. Phase III contractions in the duodenum and jejunum had a frequency of 10-12 contractions per minute.

Effects of XBP or placebo on gastrointestinal motility

The effects of XBP or placebo on the gastrointestinal motility variables are illustrated in Table 2 and Figure 2. Before the administration of either placebo or XBP, the motility variables in the two groups of subjects were similar (P > 0.05). Also, the administration of placebo had no significant effect on these measurements.

After the administration of XBP, the MMC cycle became 36% shorter [116.5 (24.0-219.0 min) to 74 (30.0-118.0 min)], the duration of phase I became 49% shorter [82.5 (25.0-180 min) to 42.0 (0.0-90.0 min)], and phase II became 140% longer [50.0 (15.0-134.0) to 120.0 (21.0-240.0) min] (P < 0.05). In the distal stomach, the duration, frequency, and amplitude of phase III increased slightly after the administration of XBP but did not reach statistical significance (P > 0.05), and the MI decreased slightly. In the duodenum, the duration, contraction frequency, and MI of phase III increased by 12.5%, 2%, and 7%, respectively (P < 0.05). After the administration of XBP, in the jejunum, the duration, amplitude, and MI of phase III increased by 7%, 10%, and 20%, respectively (P < 0.05); the amplitude of phase II in the duodenum and jejunum increased by 15% and 19%, respectively (P < 0.05); and the MI of phase II in the duodenum and jejunum increased by 66% and 114%, respectively (P < 0.05). Oral administration of XBP significantly increased the amplitude (15%) and MI (mmHg/30 min) (176%) (P < 0.05), subsequently shortened the MMC cycle (32%, P < 0.05) and the duration of phase I (165%), and lengthened the duration of phase II (52%) compared to placebo values (P < 0.01). Differences in the amplitude of phase III in the distal stomach (increased by 65%, P < 0.05), in the MI of phase III in the duodenum (increased by 22%, P < 0.05), and in the amplitude (increased by 8%, P < 0.05) of phase II and MI (mmHg/30 min) (increased by 158%, P < 0.01) in the jejunum were observed between the XBP and placebo groups.
Table 3 presents the effect of XBP and placebo on plasma motilin and ghrelin levels. Whereas placebo had no effect on these hormones ($p = 0.179$), concentrations of both had increased compared to the baseline values after the administration of XBP ($p < 0.01$).

**Adverse events**

The subjects’ electrocardiographic recordings and tests of hepatic and renal function were normal before and after the experiments, and no recognizable adverse events occurred during the study.

**DISCUSSION**

In the present study, XBP was found to significantly increase the contractions of the duodenum and jejunum with minimal effects on the distal stomach. The main findings were: (1) XBP significantly shortened the duration of a complete MMC cycle, shortened the duration of phase I of the MMC cycle, and increased the duration of phase II of the MMC cycle; (2) XBP significantly increased the motility of the duodenum and jejunum at phase III of the MMC cycle, such as increasing the duration, contraction frequency, and MI of phase III; and (3) XBP significantly increased the plasma concentrations of motilin and ghrelin. This study provided a comprehensive evaluation of the effects of XBP on gastrointestinal motility and documented that XPB, a TCM concoction, can significantly affect motility of the normal human gastrointestinal tract, a finding which raises the possibility of XBP having therapeutic value in the treatment of diseases or conditions associated with gastrointestinal dysmotility. Our study is also the first to report the effects of XBP on plasma...
Table 2 Gastrointestinal motility variables before and after placebo or Xiangbin prescription administration

| MMC          | Before placebo (n = 10) | After placebo (n = 10) | Before XBP (n = 30) | After XBP (n = 30) |
|--------------|-------------------------|------------------------|---------------------|-------------------|
| Number       | 2.0 (1.3-3)             | 1.5 (1.3-3)            | 2.0 (1.3-3)         | 2.0 (1.3-4)       |
| Cycle (min)  | 125.0 (30.0-178.0)      | 70.0 (51.0-104.0)      | 116.5 (24.0-219.0)  | 74.0 (30.0-118.0) |
| Duration of phase I (min) | 81.0 (40.0-168.0) | 111.5 (42.0-171.0)  | 82.5 (25.0-180.0)  | 42.0 (0.0-90.0)  |
| Duration of phase II (min) | 56.5 (21.0-154.0) | 58.0 (16.0-170.0)  | 50.0 (15.0-134.0)  | 120.0 (21.0-240.0) |
| Duration of phase III (min) | Distal stomach | 3.2 (2.0-4.0) | 2.7 (1.3-3.7) | 3.0 (2.1-7.1) |
|              | Duodenum                | 2.8 (2.2-3.9) | 2.5 (1.3-4.9) | 3.2 (1.5-8.2) |
|              | Jejunum                  | 2.9 (1.5-3.9) | 2.8 (1.3-3.9) | 2.4 (1.4-6.2) |
|              | Frequency of phase III   | Distal stomach       | 2.8 (2.3-3.4) | 2.7 (2.3-2.9) | 2.7 (2.4-3.1) | 2.9 (1.2-4.7) |
|              | Duodenum                | 10.1 (8.8-11.1) | 9.9 (8.9-10.9) | 10.0 (6.9-11.4) | 10.2 (8.4-11.5) |
|              | Jejunum                  | 10.0 (8.1-12) | 9.9 (8.9-10.9) | 10.1 (4.2-11.1) | 10.5 (7.8-19.0) |
|              | Amplitude of phase III (mmHg) | Distal stomach | 31.5 (24.0-50.3) | 29.1 (21.0-41.5) | 46.4 (30.0-60.7) | 49.5 (33.7-72.7) |
|              | Duodenum                | 21.5 (14.0-25.7) | 19.0 (13.7-27.0) | 21.0 (14.5-28.0) | 21.3 (13.5-28.0) |
|              | Jejunum                  | 17.8 (16.0-22.7) | 17.3 (14.3-27.0) | 18.0 (13.0-28.5) | 19.8 (14.0-30.7) |
|              | MI                      |                         |                      |                  |
|              | MI of phase III (mmHg/min) | Distal stomach | 140.0 (74.0-220.0) | 96.5 (55.0-117.0) | 134.5 (51.0-224.0) | 132.0 (48.0-218.0) |
|              | Duodenum                | 197.0 (125.0-324.0) | 120.0 (74.0-312.0) | 195.0 (109.0-310.0) | 226.0 (115.0-306.0) |
|              | Jejunum                  | 202.0 (129.0-325.0) | 151.0 (101.0-295.0) | 178.0 (55.0-304.0) | 214.0 (95.0-403.0) |
|              | Amplitude of phase II (mmHg) | Distal stomach | 20.0 (14.0-24.0) | 16.3 (13.0-18.0) | 18.7 (14.0-22.9) | 19.0 (12.5-56.7) |
|              | Duodenum                | 18.2 (14.0-20.0) | 19.5 (14.3-22.0) | 16.9 (12.3-23.9) | 19.5 (13.0-26.7) |
|              | Jejunum                  | 15.3 (13.7-20.8) | 16.9 (15.1-18.0) | 15.4 (11.7-23.9) | 18.3 (15.3-25.0) |
|              | MI                      |                         |                      |                  |
|              | MI of phase II (mmHg/30 min) | Distal stomach | 170.0 (13.0-480.0) | 128.0 (90.0-204.0) | 157.5 (24.0-444.0) | 169.0 (20.0-1080.0) |
|              | Duodenum                | 264.5 (154.0-432.0) | 189.0 (57.0-403.0) | 281.0 (76.5-1006.0) | 522.0 (146.0-1929.0) |
|              | Jejunum                  | 378.0 (126.0-456.0) | 187.0 (59.0-447.0) | 226.0 (51.0-1099.0) | 483.0 (100.0-2076.0) |

*a P < 0.05, *a,b P < 0.01 vs before XBP; *a,c,d P < 0.05, *a,b,c,d P < 0.01 vs after placebo. XBP: Xiangbin prescription; MMC: Migratory motor complex; MI: Motility index.

Table 3 Plasma concentrations of motilin and ghrelin before and after Xiangbin prescription or placebo administration (pg/mL)

|                      | XBP     | Placebo            |
|----------------------|---------|--------------------|
|                      | Before  | After              | Before  | After              |
|                      | P value |                    | P value |                    |
| Motilin              | 51.37 ± 6.60 | 57.69 ± 9.03 | < 0.001 | 50.11 ± 9.9 | 49.38 ± 8.63 | 0.179 |
| Ghrelin              | 229.1 ± 83.27 | 279.20 ± 104.31 | < 0.001 | 232.45 ± 97.38 | 238.73 ± 111.59 | 0.293 |

ghrelin concentrations. It was reassuring that the study subjects experienced no untoward side effects of XBP.

The pharmacology of XBP is incompletely understood; although various beneficial effects have been ascribed to its herbal components[17], its therapeutic efficacy has not been validated in rigorous studies. Some of the reputed effects are: amomum villosum lour and lindera aggregate (Sims) kosterm recuperate gastrointestinal function; panax ginseng enhances disease resistance and promotes the recovery of gastrointestinal function motility; prunus persica accelerates blood flow and repairs surgical injuries in the gastrointestinal tract; and areca catechu stimulates gastrointestinal motility[17]. A previous study demonstrated that XBP may be a promising prokinetic agent for DIGM and can improve postoperative bowel motility[18].

Various herbs in XBP may have various activities. For example, arecoline is an effective component of areca, and areca can stimulate the motility of isolated colonic smooth muscle strips[18,19]; several studies have described areca as a prokinetic herb[20,21]. Ginsenoside, one of the active ingredients of panax ginseng, exerts a physiological and pharmacological effect on gastrointestinal motility[22]. Ginsenoside Rf regulates intestinal motility by modulating the pacemaker potential of interstitial cells of Cajal, an effect that is mediated by activating non-selective calcium channels and chloride channels, through a mechanism involving intracellular Ca\(^{2+}\) mobilization[23]. Slow waves and spike potential are generated by sets of interstitial cells of Cajal, which intermingle with gastric smooth muscle cells[22]. The possibility that XBP exerts a prokinetic effect through the action on the intestinal cells of Cajal should be considered. Amomifructus has been widely used to treat gastrointestinal dysmotility and gastroparesis[19,20]. Semen persicae has a positive role in regulating blood flow and relaxing the bowels[21].

Our finding that XBP can increase plasma motilin and ghrelin concentrations may have important implications. A previous study suggested that gastrointestinal hormones and neural factors mediate the initiation...
of the MMC\cite{24}. Motilin, a 22-amino-acid peptide, is a gastrointestinal hormone released by the endocrine Mo cells of the duodenal and proximal jejunum mucosa during fasting. Motilin is closely associated with the appearance of the MMC and intestine phase III contractions\cite{25}. It is conceivable that XBP promotes plasma motilin release and enhances motilin secretion through Mo cell receptors. Ghrelin, the closest family member of motilin, is an endogenous ligand of the growth hormone secretagogue receptor, discovered in the rat stomach. Ghrelin has emerged as a functional hormone with important effects on gastrointestinal motility and accelerating gastric emptying\cite{24,26}. In our study, the increase of ghrelin concentrations induced by XBP correlated with increased frequency, amplitude, and MI of phase II contractions of the duodenum and jejunum. It has been reported that ghrelin is important for phase II contraction and that coordination of motilin and ghrelin is necessary for initiating phase III contraction of the MMC\cite{27}. The mechanisms of XBP's actions on gastrointestinal motility require further investigation, but the possibility that XBP helps coordinate the actions or secretion of motilin and ghrelin to create a prokinetic effect is intriguing.

This study has limitations. It is a short-term study, so the long-term effects of XBP on gastrointestinal motility and its possible side effects are unknown. Also, the studies were conducted only in the fasting state, so the postprandial effects of XBP are also unknown. Finally, although effects of XBP on gastrointestinal motility could be demonstrated by high resolution manometry, whether these effects reflect clinically useful prokinetic activity remains to be determined. The safety profile of XBP must be evaluated in longer term studies.

Nonetheless, since disorders of gastrointestinal motility, including postoperative gastrointestinal dysfunction (ileus), are common, and treatments are often inadequate, investigation of novel agents such as TCM is worthy of pursuit.

In conclusion, this short-term study of fasting, healthy human subjects documented that the Chinese traditional herbal concoction XBP safely stimulated duodenal and jejunal motility. XBP also increased plasma concentrations of motilin and ghrelin, which suggests that XBP helps coordinate the actions or secretion of motilin and ghrelin to promote MMC activity and a prokinetic effect. Although this study implicates that XBP may have a potential value in the treatment of DGIM and other diseases or conditions associated with gastrointestinal dysmotility, the clinical applicability of these observations and thorough pharmacological characterizations of the components of XBP responsible for its effect on gastrointestinal motility deserve further investigation.

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