Effect of Banxia Xiexin decoction on Helicobacter pylori-related peptic ulcers and its possible mechanism via the TGF-β/Smad signaling pathway

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Abstract

OBJECTIVE: To investigate the effect of Banxia Xiexin decoction (BXD) on Helicobacter pylori (Hp)-related peptic ulcers (PUs) and the possible mechanism underlying BXD actions via the transforming growth factor-β/smooth muscle actin (TGF-β/Smad) signaling pathway.

METHODS: PU patients with cold-heat complex syndrome were randomly assigned to groups that received Chinese or Western medicines with 20 patients in each group. Serum was collected after 7 d of treatment. The healthy group included 20 individuals. Gastric mucosal epithelial cell line GES-1 was cultured in vitro and randomly divided into the following seven groups: control, model, healthy, Western Medicine, prior treatment, low dosage, and high dosage. After 72 h of treatment with the corresponding serum, the mRNA and protein expression levels of TGF-β1, Smad3, and Smad7 were measured by reverse transcription quantitative polymerase chain reaction and western blotting, respectively.

RESULTS: The mRNA expression levels of TGF-β1 and Smad3 in GES-1 cells were increased after Hp introduction, and these increased levels were reduced by the BXD-containing serum. The protein levels of p-Smad3, but not TGF-β1 or Smad3, were significantly increased in Hp-treated GES-1 cells, and treatment with the BXD-containing serum markedly decreased the protein levels. Smad7 expression was significantly enhanced following treatment with the BXD-containing serum at transcriptional and protein levels in a dose-dependent manner.

CONCLUSION: BXD regulates the TGF-β/Smad signaling pathway by inhibiting the expression of TGF-β1 and Smad3, and increasing the expression of Smad7.
Keywords: Helicobacter pylori; Peptic ulcer; Transforming growth factor beta; Smad proteins; Banxia Xiexin decoction; human drug-containing serum

INTRODUCTION

Peptic ulcers (PUs) are a common disease of the digestive system worldwide, which are characterized by a long disease course and recurrence. PUs are responsible for approximately 301,000 deaths annually. PUs are caused by a imbalance in gastrointestinal mucosal offensive and defensive factors. Gastric acid and pepsin are the major factors in the pathogenesis of PUs. Infection with Helicobacter pylori (Hp) is another major risk factor and responsible for ulcer recurrence. To date, no ideal measures are available to eradicate Hp. Hp-related PUs, particularly Hp positive for cytotoxin-associated gene A (CagA), occur frequently in China. The most frequently used treatments are combinations of two antibiotics and a proton-pump inhibitor, which are occasionally combined with a bismuth compound. The curative rate is high, but relapse can easily occur. Antibiotic resistance has increasingly become recognized as the major cause of treatment failure for Hp infection. Additionally, the high recurrence rate is related to the poor quality of ulcer healing (QOUH). The regenerated epithelium has weakened defenses against the offensive factors.

Recently, Traditional Chinese Medicine (TCM) has been shown to improve the QOUH and reduce the recurrence rate via a variety of mechanisms. Banxia Xiexin decoction (BXD) is a representative formula used to treat PU. BXD regulates the proliferation of gastric mucosal cells, repairs the gastric mucous membrane, and effectively improves the QOUH. To date, the underlying mechanism underpinning BXD effects is still unclear.

Although the pathogenesis of PUs remains elusive, the transforming growth factor-beta/small mothers against decapentaplegic (TGF-β/Smad) signaling pathway plays a role in PU development. According to our recent study, Hp inhibits the proliferation of gastric mucosal epithelial cell lineGES-1, and BXD inhibits the effects of HP and promotes the proliferation of these cells. To determine the possible molecular mechanism of BXD in the treatment of PUs, we employed a serum pharmacological method and detected several factors related to the TGF-β/Smad signaling pathway in the current study.

MATERIALS AND METHODS

Materials and reagents

Dulbecco’s modified Eagle’s medium (DMEM), fetal bovine serum (FBS), and trypsinEDTA were purchased from Thermo Fisher Scientific (Waltham, MA, USA). Penicillin-streptomycin was purchased from the Beyotime Institute of Biotechnology (Shanghai, China). RNA Isolator Total RNA Extraction Reagent, HiScript®ⅡQ RT Supermix for qPCR (+gDNA wiper), AceQ® qPCR SYBR® Green Master Mix, RIPA lysis buffer, and a BCA protein quantification kit were obtained from Vazyme Biotech Co., Ltd. (Nanjing, China). The anti-TGF-β1 polyclonal antibody was purchased from Santa Cruz Biotechnology (Dallas, TX, USA). The following antibodies were purchased from the Proteintech Group (Chicago, IL, USA): anti-Smad3 polyclonal antibody, anti-Smad7 polyclonal antibody, and anti-β-actin monoclonal antibody. The anti-phospho-Smad3 (p-Smad3) antibody was purchased from Cell Signaling Technology (Danvers, MA, USA). The anti-phospho-Smad7 (p-Smad7) antibody was purchased from Bios Biotechnology Co., Ltd. (Beijing, China). Secondary antibodies, including horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG (H + L) and HRP-conjugated goat anti-mouse IgG (H + L), were obtained from Santa Cruz Biotechnology.

Participants

A randomized controlled clinical trial was conducted at the Second Affiliated Hospital of the Fujian University of Traditional Chinese Medicine. The participants included 20 healthy volunteers and 40 patients who were recruited from outpatients and inpatients diagnosed with PU between June and December of 2015.

Diagnosis, inclusion criteria, and exclusion criteria for PU and TCM differentiation

PUs were diagnosed according to the “Consensus on the diagnosis and treatment of PUs by integrative medicine (2011 version)”3 that was established by the Digestive Diseases Society of the Chinese Integrative Medicine Association.

The inclusion criteria for PU patients were: (a) patients whose condition conformed to the diagnosis criteria of PUs; (b) participants who signed an informed consent form; (c) patients who were 20-50 years old. The exclusion criteria were: (a) individuals with severe heart, liver, or kidney diseases; (b) pregnant or lactating women; (c) individuals who could not clearly express their feelings.

The diagnostic criteria for cold-heat complex syndrome (CHCS) of TCM in PU patients have been defined previously. The major features included: (a) burning pain in the epigastrium, which is relieved by warmth and pressure; (b) xerostomia, a bitter taste in the mouth, or vomiting; (c) a pink and tooth-marked tongue with a white, yellow, or greasy tongue coating. The minor features included: (a) frequent belching; (b) gastric discomfort and acid regurgitation; (c) cold limbs; (d) fecal disorders; (e) a taut and thread pulse.
The inclusion criteria for CHCS were: (a) participants exhibiting two major features and one minor feature; (b) cases exhibiting one major feature and two minor features.

**Ethics and consent**
The study was performed in accordance with the Helsinki Declaration and the research regulations for Chinese clinical trials. The study protocols were reviewed and approved by the Ethics Committee of the Fujian University of Traditional Chinese Medicine, and informed consent was obtained from all eligible participants.

**Preparation of drugs**
The components of BXD are shown in Table 1. The Chinese herbs were processed into formula granules by Beijing Tcmages Pharmaceutical Co., Ltd. (Beijing, China). The quality standards of the granules met the Codex standard for enterprise internal control standards as shown in Table 2.

**Preparation of BXD-containing serum**
PU patients who met the CHCS diagnostic criteria were enrolled in this study. All patients were randomly assigned to BXD or Western Medicine groups (n = 20, in each group) by random number table method. Each group included 20 patients. Participants in the BXD group were treated with BXD (Table 1) twice a day with a bag containing BXD at 5:00 h after breakfast and dinner. Patients in the Western Medicine group received the following treatment regimen twice daily: 10 mg clarithromycin (Huiren Pharmaceutical Co., Ltd., Nanchang, China, cat#. 150-2109), and 400 mg metronidazole (Hansen Pharmaceutical Co., Ltd., Yiyang, China, cat#. 1504102). Venous blood was obtained from all cases before and after the treatments for 7 d. In total, 20 healthy volunteers donated their venous blood for this study. The sera were separated by centrifugation and stored at −80 ℃.

**Preparation of Hp**
An international standard strain (NCTC11637) of CagA gene-positive Hp was used in this study. The CagA gene-positive Hp were provided by the Pathogenic Biology Department of Fujian Medical University. Hp bacteria were cultured for 2 d, washed with PBS, re-suspended in DMEM without serum and antibiotics, and adjusted to a concentration of 5 × 10⁶ CFU/mL.

**Cell culture**
The GES-1 human gastric epithelial cell line was obtained from the Advanced Research Center of Central South University (Changsha, Hunan, China). The cells were maintained in DMEM supplemented with 10% (vol/vol) FBS, 100 U/mL penicillin, and 100 μg/mL streptomycin (Beoytime Institute of Biotechnology, Shanghai, China). A humidified incubator with 5% CO₂ was used to maintain the cells at 37 ℃.

**Cell treatment and grouping**
GES-1 cells were randomly divided into the following seven groups by random number table method: control, model, healthy, Western Medicine, prior treatment, low dosage, and high dosage. After culturing the cells for 48 h, Hp and serum were added to the corresponding groups (Table 3). After treatment with the appropriate serum, the mRNA and protein levels of genes related to the TGF-β/Smad signaling pathway were

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**Table 1 Components of Banxia Xiexin decoction**

<table>
<thead>
<tr>
<th>Chinese name</th>
<th>Latin name</th>
<th>Dosage (g)</th>
</tr>
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<tbody>
<tr>
<td>Banxia</td>
<td>Ternate Pinellia</td>
<td>Rhizoma Pinelliae</td>
</tr>
<tr>
<td>Ganjiang</td>
<td>Rhizoma Zingiberis</td>
<td>Rhizoma Zingiberis</td>
</tr>
<tr>
<td>Huanglian</td>
<td>Chinese Goldthread Rhizome</td>
<td>Rhizoma Coptidis</td>
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<tr>
<td>Huangqin</td>
<td>Baikal Skullcap Root</td>
<td>Radix Scutellariae Baicalensis</td>
</tr>
<tr>
<td>Renshen</td>
<td>Ginseng</td>
<td>Radix Ginseng</td>
</tr>
<tr>
<td>Dazao</td>
<td>Common jujube</td>
<td>Fructus Jujubae</td>
</tr>
<tr>
<td>Gancao</td>
<td>Liquorice Root</td>
<td>Radix Glycyrrhiza</td>
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**Table 2 Quality standards of the granules**

<table>
<thead>
<tr>
<th>Granule</th>
<th>Control standards</th>
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<tbody>
<tr>
<td>Banxia (Rhizoma Pinelliae) pinellia</td>
<td>95% ethanol extract</td>
</tr>
<tr>
<td>Ganjiang (Rhizoma Zingiberis)</td>
<td>95% ethanol extract</td>
</tr>
<tr>
<td>Common jujube</td>
<td>95% ethanol extract</td>
</tr>
<tr>
<td>Chinese goldthread rhizome</td>
<td>Berberine</td>
</tr>
<tr>
<td>Baikal skullcap root</td>
<td>Baicalin</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Total ginsenoside Rb1</td>
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<tr>
<td>Liquorice root</td>
<td>Ammonium glycyrrhizinate</td>
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measured by reverse transcription quantitative polymerase chain reaction (RT-qPCR) and Western blot analyses, respectively.

**RT-qPCR analysis**

GES-1 cells were cultured in a 6-well culture plate (Costar, Corning, NY, USA) at a density of $1 \times 10^6$ cells/mL in 2 mL of medium. The cell groups were the same as described above. Each group was treated with serum (Table 3). Following 72 h of treatment with the appropriate serum, total RNA of the cells in each group was isolated using Total RNA Extraction Reagent (Vazyme Biotech Co., Ltd., Nanjing, China). cDNA was synthesized from 1.5 μg total RNA using a cDNA Synthesis Kit (Vazyme Biotech Co., Ltd., Nanjing, China). RT-qPCR was performed using 2 μL cDNA with 0.2 μM of each primer. The reaction was conducted using an Applied Biosystems 7500 Fast Real-Time PCR system (Thermo Fisher Scientific, Inc., Waltham, MA, USA). Relative mRNA expression was calculated by the $2^{-\Delta\Delta C_{\text{t}}}$ method. GAPDH was used as an internal standard. Each result was normalized to the mRNA level of GAPDH (Table 4).

**Western blot analysis**

Following 72 h of treatment with serum, GES-1 cells were lysed with RIPA lysis buffer containing protease and phosphatase inhibitor cocktails (Vazyme Biotech Co., Ltd.). The lysates were separated on an 8% SDS-PAGE gel. After electrophoresis, the proteins were transferred to polyvinylidene fluoride membranes (Millipore, Billerica, MA, USA) using a semidy blotting system. After blocking for 120 min, the membranes were exposed to primary antibodies against TGF-β1 (1: 1000 dilution), Smad3 (1: 1000), p-Smad3 (1: 1000), Smad7 (1: 2000), or p-Smad7 (1: 500) overnight at 4 °C. β-Actin (1: 1000) was used as an internal control for protein loading. The membranes were then incubated with HRP-conjugated antibodies (Vazyme Biotech Co., Ltd., Nanjing, China) at a 1: 5000 dilution for 1 h at room temperature. Finally, antibody-bound proteins were detected by enhanced chemiluminescence. Image analyses were performed using a ChemiDoc XRS + (Bio-Rad Laboratories, Hercules, CA, USA). The grayscale value ratio of the target protein to the internal control was used to measure the

<table>
<thead>
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<th>Table 3 Hp and serum added to each group</th>
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<tr>
<td><strong>Group</strong></td>
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<tr>
<td>Control</td>
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<tr>
<td>Model</td>
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<tr>
<td>Healthy</td>
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<td>Western Medicine</td>
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<td>Prior treatment</td>
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<td>Low dosage</td>
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<td>High dosage</td>
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Notes: control group: treated with 10% FBS alone (no Hp); model group: treated with Hp (cell-to-bacterium, 1: 50) and 10% FBS; healthy group: treated with Hp (cell-to-bacterium, 1: 50) and 10% human serum from the healthy group; Western Medicine group: treated with Hp (cell-to-bacterium, 1: 50) and 10% human serum from the Western Medicine group after treatment; prior treatment group: treated with Hp (cell-to-bacterium, 1: 50) and 10% human serum from the BXD group before treatment; low dosage group: treated with Hp (cell-to-bacterium, 1: 50) and 10% human serum from the BXD group after treatment; high dosage group: treated with Hp (cell-to-bacterium, 1: 50) and 20% human serum from the BXD group after treatment. The cells in each group were treated for 72 h at 37 °C. Hp: Helicobacter pylori; vol: volume; FBS: fetal bovine serum; BXD: Banxia Xiexin decoction.

<table>
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<tr>
<th>Table 4 Primer sequences</th>
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<tr>
<td><strong>Gene</strong></td>
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<tr>
<td>TGF-β1</td>
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<td></td>
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<tr>
<td>Smad3</td>
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<td>Smad7</td>
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<td>GAPDH</td>
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Notes: TGF-β1: transforming growth factor-β; Smad3: small mothers against decapentaplegic 3; Smad7: small mothers against decapentaplegic 7; GAPDH: glyceraldehyde 3-phosphate dehydrogenase.
relative amounts of TGF-β1, Smad3, p-Smad3, Smad7, and p-Smad7.

Statistical analysis
Data are expressed as the mean ± standard deviation. One-way analysis of variance was performed to test differences between groups using SPSS 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA). P < 0.05 was considered as significant.

RESULTS
mRNA expression levels of TGF-β1, Smad3, and Smad7
The mRNA expression levels of TGF-β1 were significantly increased in model and prior treatment groups (P < 0.05 and P < 0.01). The mRNA expression levels of TGF-β1 were significantly lower in low and high dosage groups than in model and prior treatment groups (P < 0.01 and P < 0.05). However, these groups were not significantly different from the control group. The highest mRNA expression level of Smad3 was observed in the prior treatment group. The mRNA expression levels of Smad3 were significantly lower in low and high dosage groups than in the prior treatment group (P < 0.05 and P < 0.01). In low and high dosage groups, the mRNA expression levels of Smad3 were higher than those in the other groups after 72 h of treatment (P < 0.01). In addition, a significant difference in Smad7 mRNA expression was observed between low and high dosage groups (P < 0.01) (Figure 2).

DISCUSSION
PUs are a frequently occurring disease affecting millions of individuals, particularly in developing countries. Patients with PUs relapse easily, and PUs significantly reduce quality of life. The goals of PU treatments are to heal the ulcer lesions, relieve the symptoms, and prevent recurrence and complications. BXD is a representative formula that is used to treat CHCS of various gastrointestinal diseases, which is defined according to Treatise on Febrile Diseases written by Zhang Zhongjing.
BXD is prepared with Banxia (Rhzoma Pinelliae), Ganjiang (Rhzoma Zingiberis), Huanglian (Rhzoma Coptidis), Huangqin (Radix Scutellariae Baicalensis), Renshen (Radix Ginseng), Dazao (Fructus Fuyubatae), and Gancao (Radix Glycyrrhizae). Banxia (Rhzoma Pinelliae) was determined by RTqPCR. GAPDH was used as an internal control. Data are presented as the mean ± standard deviation of three independent experiments. *P < 0.01, **P < 0.05 vs the control group; *P < 0.05, **P < 0.01 vs the model group; *P < 0.05, **P < 0.01 vs healthy group; *P < 0.05, **P < 0.01 vs the Western Medicine group; *P < 0.05, **P < 0.01 vs the prior treatment group; *P < 0.01 vs the low dosage group. TGF-β1: transforming growth factor-β; Smad3: small mothers against decapentaplegic 3; Smad7: small mothers against decapentaplegic 7; GAPDH: glyceraldehyde 3-phosphate dehydrogenase. Hp: Helicobacter pylori; vol: volume; FBS: fetal bovine serum; BXD: Banxia Xixi decoction.
and Ganjiang (Rhizoma Zingiberis) decrease the secretion of gastric juices, inhibit the activity of pepsin, harmonize gastrointestinal functions, and promote tissue repair in the stomach mucosa. These two herbs also have a modulatory effect on the hypothalamo-pituitary-adrenal axis and autonomic nervous functions. The combination of Huanglian (Rhizoma Coptidis) and Huangjin (Radix Scutellariae Baicalensis) has synergistic antibacterial, anti-inflammatory, and anti-gastric ulcer effects. This combination has a high potential for further development into a promising therapeutic approach for the treatment of Hp-related diseases. In addition, Renshen (Radix Ginseng), Dazao (Fructus Jujubae), and Gancao (Radix Glycyrrhiza) improve immune functions. Licorice Root has been reported to have antioxidant, antimicrobial, and antiviral properties. Furthermore, Gancao (Radix Glycyrrhiza) possesses anti-inflammatory, anticancer, and anti-ulcer activities. Fukai et al. demonstrated the anti-Hp effects of Licorice. Moreover, Gancao (Radix Glycyrrhiza) had an anti-Hp effect against a species resistant to clarithromycin. In our previous study, BXD promoted angiogenesis, tissue recovery, and ulcer healing in vivo. Our subsequent study showed that Hp inhibited the proliferation of GES-1 cells in vitro. BXD inhibited the effects of HP and promoted the proliferation of cells. Furthermore, BXD-containing serum had no toxicity in cells and increased cell activity. To further elucidate the possible molecular mechanisms of BXD in the treatment of PU, certain genes in the TGF-β/Smad signaling pathway were analyzed in the current study. The TGF-β/Smad signaling pathway is a research focus in studies exploring the pathogenesis and pathophysiology of PU, because this pathway is involved in diverse cellular processes including proliferation, differentiation, migration, and apoptosis. This pathway also plays a critical role in the development and repair of PUs. TGF-β is one of the main cytokines involved in mediating inflammation and remodeling processes in ulcer tissues. TGF-β activates the downstream Smad signaling pathway. The Smad signaling pathway is essential for most TGF-β responses. The main TGF-β-mediated signal transduction occurs with the involvement of Smads. Smad2 and Smad3 are receptor-regulated Smads (R-Smads) that form complexes with TGF-β receptor I (TGFRI). The activated TGFRI stimulates R-Smad2 and 3 phosphorylation of serine residues. Phosphorylated Smad2 and 3 translocate into the nucleus where they associate and cooperate with DNA-binding transcription factors to regulate
the transcription of target genes. Smad6 and 7 are inhibitory Smads that play roles as inhibitors, form trimers with R-Smads, inhibit R-Smad phosphorylation, and block the ability of R-Smads to induce gene transcription by competing with R-Smads for receptor binding and inducing the degradation of TGF-β. In this study, human serum containing drugs was used to induce changes in GES-1 cells after oral absorption and metabolism of the medicinal compounds, which is closer to the drug metabolism in vivo. The GES-1 cells were cultured with the corresponding human sera for 72 h. The role of TGF-β in gastric ulcer healing has been explored previously. TGF-β and TGF-β II are strongly expressed in tissues of patients with ulcers. In this study, compared with the baseline level, the mRNA expression of TGF-B1 in GES-1 cells was increased after the introduction of Hp, and this increase was reduced by the BXD-containing serum. The protein level of p-Smad3, but not TGF-β1 or Smad3, was significantly increased in Hp-treated GES-1 cells, and treatment with the BXD-containing serum markedly decreased the protein. Thus, the BXD-containing serum down-regulated the expression of p-Smad3, attenuated TGFβ1-induced Smad3 nuclear translocation and protein phosphorylation, and concomitantly inhibited the mRNA expression of Smad3. We speculated that this serum might inhibit phosphorylation of Smad3 or enhance p-Smad3 degradation. The expression of Smad7 was significantly and dose-dependently enhanced by treatment with the BXD-containing serum at transcriptional and protein levels. No significant difference in protein expression of p-Smad7 was found among the groups. In contrast to p-Smad3, the BXD-containing serum had an obvious effect on the total protein content of Smad7, while no effect on the protein activity was observed. Following the BXD treatment, the increased Smad7 protein expression exhibited a feedback inhibition effect on Smad3 mRNA expression and its protein phosphorylation. Therefore, we hypothesize that BXD promotes the proliferation and regeneration of gastrointestinal epithelial cells by regulating factors associated with the TGF-β/Smad signaling pathway, which may be an important mechanism of BXD in the treatment of PUs. Because of the high recurrence rate of Hp-related PUs, particularly in areas with high resistance rates to antibiotics, treatment strategies that add BXD to the triple regimen may be beneficial and should be explored in future studies. Our data provide a better understanding of the effects and mechanisms of BXD in the treatment of Hp-related PUs. However, which components of this classic herbal medicine contribute to the effects remains unclear. Therefore, future studies exploring the individual components of BXD are required. In conclusion, BXD regulates the TGF-β/Smad signaling pathway by inhibiting the expression of TGF-β1 and Smad3, and increasing the expression of Smad7.

REFERENCES


