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Mechanistic Study of Trimebutine Combined with Berberine Hydrochloride in PI-IBS Rat Intervention via the Brain–Gut–Microbiota Axis

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Abstract: This study explored the therapeutic effect of trimebutine maleate dispersible tablets combined with berberine on PI-IBS rats with liver depression and spleen deficiency. Fifty male rats were divided into five groups: normal, model, berberine (XB), trimebutine (QM), and combination (XB+QM). The PI-IBS model was established using maternal separation, TNBS perfusion, and chronic restraint. After 20 days of drug intervention, DAI, CMDI, TDI, AWR scores, histopathology, and expression levels of c-Fos, VIP, NOS, and CHAT in the hippocampus and colon were assessed. The model group showed significant gut and brain changes, while the combination group (XB+QM) improved fecal characteristics, reduced inflammation, regulated brain-gut peptide expression, and alleviated visceral hypersensitivity and colon tissue damage ($P < 0.05$).

Keywords: Postinfectious irritable bowel syndrome; Brain-gut bacterial axis; Trimebutine; Berberine

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1. Introduction

Irritable bowel syndrome (IBS) is a functional disease of the digestive system that affects an average of 22 % of the general population [1]. The incidence rate in China is 5.2–12% [2]. Its etiology and pathogenesis are still unclear. Domestic and foreign studies have pointed out that post-infectious irritable bowel syndrome (PI-IBS) is a common type of IBS . IBS may be caused by infectious gastroenteritis identified as PI-IBS. The prevalence of PI-IBS in patients with infectious gastroenteritis is 4–36 % [3]. The phenotypic frequency of PI-IBS is composed of mixed IBS (IBS-M) 24 %, diarrhea-type IBS (IBS-D) 63 %, and constipation-type IBS (IBS-C) 13 % [4]. The Rome IV diagnostic criteria provide a new definition for PI-IBS, but the exact mechanism leading to PI-IBS is not yet fully understood. At present, it is generally believed that there is low-grade inflammation or no inflammation in the intestine after gastrointestinal infection, and it is in a state of continuous immune activation, resulting in the symptoms of IBS. The etiology may involve intestinal

motility disorders, visceral hypersensitivity, brain-gut axis disorders, intestinal flora imbalance, psychosocial stress, genetics, and diet. At present, most scholars believe that brain-gut axis regulation disorder is an important pathological basis of IBS [5–7]. In recent years, the impact of intestinal flora imbalance on IBS has received increasing attention. The intestinal flora and the brain-gut axis undergo complex and subtle interactive regulation, and the concept of " brain-gut-enteric microbiota axis " (BGMA) has been proposed [8].

Trimebutine (QM) regulates digestive tract motility by modulating smooth muscle activity. It can either stimulate or inhibit movement by affecting K^+ and Ca^{2+} channels, leading to changes in cell excitability. It also acts on nerve receptors: inhibiting adrenaline release to enhance slow motility, or reducing acetylcholine release to calm excessive activity. Because of the above pharmacological properties, trimebutine maleate has become one of the therapeutic drugs for IBS and some other gastrointestinal motility disorders [9, 10]. Berberine is an isoquinoline alkaloid extracted from the rhizome of the plant of the genus Coptis in the Ranunculaceae family. Traditional Chinese medicine suggests that it has a certain therapeutic effect on intestinal infections and inflammations [11]. Recent studies show that trimebutine can inhibit intestinal smooth muscle excitation and relieve abdominal pain, with proven clinical effectiveness in treating IBS. Combined with berberine, it shows significant patient benefits, though the exact mechanisms and targets remain unclear.

The brain-gut axis regulates the gastrointestinal tract via brain-gut peptides—small molecules found in both the brain and gut. These peptides, such as 5-HT, Ach, CHAT, NOS, VIP, and others, modulate motility, sensation, and secretion. Acting as both hormones and neurotransmitters, they mediate communication between the gut and central nervous system. Changes in gastrointestinal function in IBS patients are caused by the disorder of brain-gut peptide regulation in the brain-gut axis [12]. c-Fos is considered to be a key effector of intracellular signaling cascades and can amplify noxious stimulus signals during stress [13]. With the deepening of our understanding of its biological functions, c-FOS has gradually become an important tool for studying abnormal visceral sensitivity, neural pathways for gastrointestinal noxious signal transmission, how the spinal cord and higher centers regulate, and the origin of key active substances [14]. VIP is widely present in the central and peripheral nervous systems, especially in the myenteric and submucosal plexuses of the gut. As a key neurotransmitter in the brain-gut axis, it is released from neuron endings to regulate intestinal motility, secretion, and blood flow, mainly by inhibiting gastrointestinal movement through neurotransmitter release [15].

2. Experimental materials and methods

2.1. Experimental equipment and reagent models, and numbers

(1) Rotary slicer: model Leica-2016, Germany
(2) Fully automatic closed tissue dehydrator: model TSJ-II, Changzhou Zhongwei
(3) Embedding machine: model BMJ-III, Changzhou Zhongwei
(4) Pathological tissue bleaching and drying instrument: model PHY-III, Changzhou Zhongwei
(5) Electric constant temperature drying oven: model 202-2AB, Tianjin Test
(6) Fume hood: model VD-TGF-06, Guangzhou Ruizhi
(7) Microwave oven: model PTOF20L-DG (S0), Galanz
(8) Upright microscope: model DM500, Leica (Germany)
(9) Pure water manufacturing system: model YL-100BU, Yiliyuan (Shenzhen)
(10) Drug refrigerator: model YPG-260, Qingdao Olex

(11) Tissue embedding box: Item number 31050102W, Jiangsu Shitai
(12) Slide: 24mm × 76mm × 1.2mm, Jiangsu Shitai
(13) Cover glass: 24mm × 24mm, Jiangsu Shitai
(14) High-efficiency section paraffin: 500 g/box, Sinopharm
(15) Paraformaldehyde: 500g/bottle, Sinopharm
(16) PBS phosphate buffer (0.01MPH7.2–7.4): Item number P1010, Solarbio
(17) SPRabbit&MouseHRPKit(DAB): Item number CW2069S, CWBIO (Jiangsu)
(18) 30% hydrogen peroxide: Item number 10011208, Sinopharm
(19) Anhydrous methanol: Comeo (Tianjin)
(20) Anhydrous ethanol: Comeo (Tianjin)
(21) Xylene: Comeo (Tianjin)
(22) Sodium citrate buffer (0.01MPH6.0): Item number C1010, Solarbio (Beijing)
(23) Hydrochloric acid: Item number 81013, Chongqing Chuandong
(24) Hematoxylin dye: Item number G1005-1, Servicebio (Wuhan)
(25) Ultra-clean quick-drying sealing glue: Item number G1404-100ML, Servicebio (Wuhan)

2.2. Methods for animal modeling and intervention

2.2.1. Modeling method (Trimmed to Two-Thirds)

(1) Mother-child separation: Ten male rats are selected. From day 14, they are separated from their mothers for 3 hours daily until weaning on day 22. The normal group is not separated. At over 6 weeks of age and > 220g, rats proceeded to TNBS modeling.
(2) TNBS colonic perfusion: Rats fasted for 18 hours (with water). Under anesthesia, 0.3ml of 0.02ml TNBS in 50% ethanol is administered via a 2mm, 12cm enema tube inserted 8–10cm into the colon. Rats are inverted for 30 seconds before being returned to their cages.
(3) Chronic restraint stress: Two weeks after TNBS perfusion, rats are restrained in a homemade frame for 3 hours daily (9:00–12:00) over 3 weeks. The control group received no restraint and normal feeding.

Figure 1. Binding method

2.2.2. Drug treatment

Trimebutine maleate dispersible tablets combined with berberine are given at a dose of 0.06 g/ kg.d and 0.09 g/kg.d, respectively. Rats in the normal group and the model group are given 15 mL/kg.d of normal saline by gavage, once a day, and the drug intervention lasted for 20 days.

2.3. Model evaluation indicators

2.3.1. General observation

The general condition of the rats (coat color, diet, spirit, activity, and stool) is observed every day, and the body weight is measured and recorded. After one week of drug intervention, the DAI (Disease Activity Index) score is performed, DAI = body weight loss score + stool characteristics score + blood in stool score (**Table 1**).

Table 1. DAI scoring criteria

Weight loss	Stool characteristics	Occult blood or blood in stool	Rating/points
0	Normal	Negative	0
1–5%	Loose stools	Negative	1
6–10%	Loose stools	Positive	2
11–15%	Diarrhea	Positive	3
>15%	Diarrhea	Positive	4

*Note: Normal stool: formed stool; Loose stool: mushy stool that does not stick to the anus; Diarrhea: watery stool that sticks to the anus.

2.3.2. CMDI and TDI scores of colon tissue

The CMDI (colon mucosal injury index) score is based on the Luketal standard (**Table 2**). Dieleman's criteria for TDI (colon histopathology score) scoring is shown in **Table 3**.

Table 2. CMDI scoring criteria

Macroscopic observation of colonic mucosal morphology	Rating/points
No damage to the colon	0
Mild congestion and edema of mucosa, no ulcers	1
Mucosal congestion and edema with thickened intestinal wall, no ulcers	2
A single small ulcer forms, about 0–1 cm in diameter	3
Large ulcer, about 1–2 cm in diameter, but no adhesion between the intestine and surrounding organs	4
The ulcer is about 1–2cm in diameter, the intestine is thickened, and it is severely adhered to the surrounding organs.	5

Table 3. TDI scoring criteria

Pathological changes of colonic mucosa	Rating/points
Normal mucosa	0
1/3 of the basal crypt is missing	1
2/3 of the basal crypt is missing	2
Crypts are absent, leaving only the surface epithelium, with inflammatory cell infiltration	3
Mucosal erosion and ulceration with massive inflammatory cell infiltration	4

2.4. HE staining and immunohistochemistry

The fixed tissue is dehydrated in an automatic dehydrator (dehydration time: 75% alcohol 4h, 85% alcohol 2h,

95% alcohol 1h, 100% alcohol 0.5h, 100% alcohol 0.5h, 100% alcohol 0.5h, 100% alcohol 0.5h, xylene 10min, xylene 10min, paraffin 1h, paraffin 2h, paraffin 3h), embedded, and then sectioned and performed the following operations:

(1) Oven at 60°C, bake for 30 minutes.
(2) Dewaxing in xylene for 20 min (2 times); soaking in anhydrous ethanol for 10 min (2 times) → soaking in 95% ethanol for 5 min → soaking in 85% ethanol for 5 min → soaking in 75% ethanol for 5 min → soaking in pure water for 5 min.
(3) After dewaxing and rehydration, immerse in 3% methanol-hydrogen peroxide at room temperature for 5 min.
(4) Wash with PBS three times, 5 min each time.
(5) The slices were immersed in 0.01 M citrate buffer (PH 6.0), heated in a microwave oven at high temperature for 2 min, and then repeated 5 times after a 5-min interval. After cooling, they were washed twice with PBS, each time for 5 min.
(6) Add goat serum blocking solution and incubate at room temperature for 20 min.
(7) Add primary antibody and incubate at 4°C overnight.
(8) Add biotinylated secondary antibody and incubate at 37°C for 30 min.
(9) Wash with PBS 3 times, 5 min each time.
(10) DAB color development: Use the DAB color development kit, mix the reagent and drop it onto the slice, color at room temperature, control the reaction time under the microscope, generally about 2 minutes, and wash with distilled water.
(11) The slides are lightly counterstained with hematoxylin, dehydrated, transparented, and mounted with neutral gum.
(12) The above specimens are all processed according to the SOP procedures of pathological examination, including dehydration, trimming, embedding, sectioning, staining, sealing, etc., and finally, microscopic examination.

2.5. Image acquisition

An upright microscope (DM500) produced by Leica Microsystems of Germany is used to collect images of the slices. The entire tissue of each slice is first observed at 200 times magnification, and then 2–3 fields of view are selected to collect 400 times microscopic images.

2.6. Data analysis

The Image-Pro Plus 6.0 image analysis system is used to measure the integrated optical density (IOD) and area (Area) of all the collected images, and the mean optical density (MD) of each image is calculated. The average optical density of three images is used to calculate the average to obtain the mean optical density of each sample. SPSS 17.0 statistical analysis software is used to perform one-way ANOVA on the average, and the data are expressed as mean ± standard deviation ($\overline{x}$ ± SD).

3. Results

For the results, * represents comparison with the normal group, # represents comparison with the model group.

3.1. Effects of trimebutine combined with berberine on the expression of c-Fos protein in hippocampal tissue and colon tissue of model rats

Table 4 shows that compared with the normal group, c-FOS, and VIP protein expression in the hippocampus and colon increased significantly (*$P < 0.05$) in other groups. Drug-treated groups showed a significant decrease ($^{\#}P < 0.05$) compared to the model group. The QM+XB group had significantly lower c-FOS and VIP levels than the XB group ($^{\triangle}P < 0.05$) and the QM group ($^{\$}P < 0.05$). The QM group alone showed no significant change ($P > 0.05$).

Table 4. Statistical results of average optical density of c-FOS and VIP $\bar{x}$ in different tissues of rats in each group (±SD)

Group	Rat	c-FOS		VIP	
		Hippocampal tissue	Colon tissue	Seahorse	Colon
	N (only)	OD ($\bar{x}$ ±SD)	OD ($\bar{x}$ ±SD)	OD ($\bar{x}$ ±SD)	OD ($\bar{x}$ ±SD)
Normal group	10	0.1377 ± 0.0046	0.1705 ± 0.0040	0.1336 ± 0.0039	0.1693 ± 0.0046
Model group	10	0.2094 ± 0.0092 *	0.2597 ± 0.0102 *	0.1899 ± 0.0079 *	0.2683 ± 0.0102 *
XB group	10	0.1866 ± 0.0105 *#	0.2280 ± 0.0106 *#	0.1802 ± 0.0096 *#	0.2274 ± 0.0091 *#
QM group	10	0.1794 ± 0.0144 *#	0.2187 ± 0.0112 *#	0.1721 ± 0.0083 *#	0.2219 ± 0.0074 *#
QM+XB group	10	0.1545 ± 0.0040 *#△$	0.1946 ± 0.0061 *#△$	0.1448 ± 0.0085 *#△$	0.1874 ± 0.0046 *#△$

Note: Compared with the normal group, * P <0.05; compared with the model group, $^{\#}P$ <0.05; compared with the XB group, $^{\blacktriangle}P$ <0.01; QM+XB group $^{\triangle}P$ <0.05 ; compared with the QM group, QM+XB group $^{\$}P$ <0.05.

3.2. Effects of trimebutine combined with berberine on NOS protein expression and CHAT expression in hippocampus and colon in model rats

Table 5 showed that compared with the normal group, NOS and CHAT protein expression in the hippocampus and colon of other groups significantly decreased (*$P < 0.05$). Compared with the model group, drug-treated groups showed significant changes in NOS and CHAT expression ($^{\#}P < 0.05$). The QM+XB group had significant changes compared to the XB group ($^{\triangle}P < 0.05$), while the QM group alone showed no significant changes ($P > 0.05$). Compared with the QM group, the QM+XB group showed significant increases in NOS and CHAT expression ($^{\$}P < 0.05$).

Table 5. Statistical results of the average optical density of NOS and CHAT in different tissues of rats ($\bar{x}$ ±SD)

Group	Rat	NOS		CHAT	
		Seahorse	Colon	Seahorse	Colon
	N (only)	OD ($\bar{x}$ ±SD)	OD ($\bar{x}$ ±SD)	OD ($\bar{x}$ ±SD)	OD ($\bar{x}$ ±SD)
Normal group	10	0.2212 ± 0.00 55	0.2990 ± 0.0100	0.2150 ± 0.00 46	0.2743 ± 0.0 107
Model group	10	0.1597 ± 0.0054 *	0.1709 ± 0.00 46 *	0.1502 ± 0.0043 *	0.1699 ± 0.0063 *
XB group	10	0.1846 ± 0.00 39 * #	0.2125 ± 0.007 4 *#	0.1767 ± 0.00 78 * #	0.2222 ± 0.00 62 *#
QM group	10	0.1801 ± 0.00 48 * #	0.2185 ± 0.0 184 *#	0.1820 ± 0.006 4 * #	0.2272 ± 0.00 90 *#
QM+XB group	10	0.2014 ± 0.00 67 *#△$	0.2545 ± 0.006 6 *#△$	0.2032 ± 0.00 59 *#△ $	0.2512 ± 0.00 93 *#△$

Note: Compared with the normal group, *$P < 0.05$; compared with the model group, #$P < 0.05$; compared with the XB group, $^{\blacktriangle}P < 0.01$; QM+XB group $^{\triangle}P < 0.05$; compared with the QM group, QM+XB group $^{\$}P < 0.05$.

3.3. Effect of trimebutine combined with berberine on TDI, DAI, and CMDI scores of model rats

Based on **Table 6**, there were significant differences between the Model group, QM group, XB group, QM combined with XB group and normal group ($P < 0.05$). There were significant differences between QM group, XB group, QM combined with XB group, and the Model group ($P < 0.05$). There was a significant difference between QM group and QM combined with XB group ($P < 0.05$). There was no significant difference between QM group and XB group ($P > 0.05$).

Table 6. TDI score results after different drug interventions

Project	TDI	DAI	CMDI
Group	Rating /points	Rating /points	Rating /points
Control group	0	0	0
Model group	4.7 ± 0.483	4.7 ± 0.483	4.7 ± 0.483
QM group	3.3 ± 0.483	3.6 ± 0.699	3.5 ± 0.707
XB group	3.1 ± 0.568	3.4 ± 0.699	3.3 ± 1.059
QM Joint XB group	2.5 ± 0.527	2.6 ± 0.966	2.5 ± 0.527

Note: Compared with the normal group, $^{**}P < 0.05$; compared with the model group, $^{\#\#}P < 0.05$; compared with the QM combined with XB group, $P < 0.05$.

3.4. Effect of trimebutine combined with berberine on the abdominal withdrawal reflex score of model rats

Based on **Table 7**, the Control group, the scores of the Model group, QM group, and XB group at the pressure of 1, 1.5, and 2 ml were significantly increased, with significant differences ($P < 0.05$), and there was no significant difference between the QM combined with XB group and the Control ($P > 0.05$). Compared with the Model, the scores of the QM group and the XB group at the pressures of 1, 1.5, and 2 ml were reduced, with no significant difference ($P > 0.05$). Compared with the Model group, the scores of the QM combined with XB group at the pressures of 1, 1.5, and 2 ml were significantly reduced, with significant differences ($P < 0.05$). Compared with the QM group, the scores of the QM combined with XB group at the pressures of 1, 1.5, and 2 ml were significantly reduced, with significant differences ($P < 0.05$).

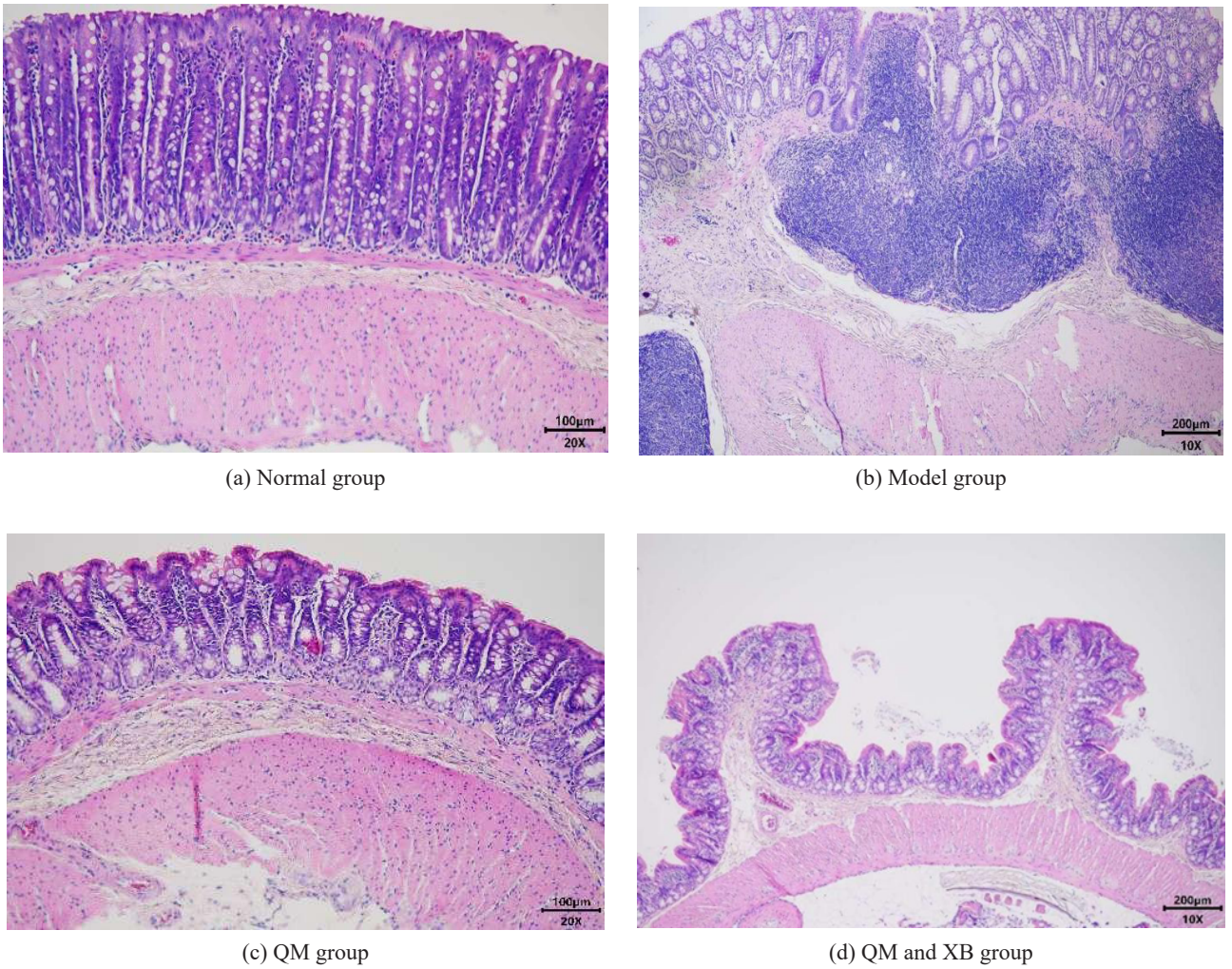
Table 7. AWR score results after different drug interventions

Group	1ML score /point	1.5ML score /point	2ML score /points
Control group	0.5 ± 0.527	1.4 ± 0.516	2.4 ± 0.516
Model group	1.7 ± 0.483	2.7 ± 0.483	3.7 ± 0.483
QM group	1.6 ± 0.516	2.6 ± 0.516	3.5 ± 0.527
XB group	1.4 ± 0.516	2.4 ± 0.516	3 .3 ± 0.483
QM Joint XB group	0.8 ± 0.422	1.8 ± 0.632	2.7 ± 0.483

Note: Compared with the normal group, $^{**}P < 0.05$; compared with the model group, $^{\#\#}P < 0.05$; compared with the QM group, $P < 0.05$.

3.5. Effect of trimebutine combined with berberine on colonic tissue pathological morphology in model rats

HE staining showed the normal group had intact colon mucosa with orderly epithelial cells and no lesions. The model group exhibited mucosal erosion, ulcers, inflammatory infiltration, and crypt atrophy. The QM group had significantly fewer inflammatory cells, regular crypt surfaces, and relatively intact mucosa. The QM+XB group showed notably thickened crypt bases and marked colon tissue improvement compared to QM and XB groups. Refer to **Figure 2** for details.



(a) Normal group

(b) Model group

(c) QM group

(d) QM and XB group

Figure 2. Colon tissue morphology of rats in each group (HE staining, × 100)

4. Discussion

This study found that compared with the normal group, the model group showed increased c-FOS and VIP protein expression in the hippocampus and colon, but decreased NOS and CHAT expression in both regions. Disease indices (TDI, DAI, CMDI) and AWR scores were significantly higher, with mucosal erosion, ulcers, inflammatory infiltration, and crypt atrophy observed. Compared to the model group, the drug-treated groups showed decreased c-FOS and VIP levels, reduced NOS and CHAT expression, lowered disease indices and AWR scores, fewer

inflammatory cells, more regular crypts, and improved mucosal integrity. The QM+XB group had thicker crypt bases and better colon tissue recovery. The study concludes that trimebutine combined with berberine improves intestinal flora and regulates abnormal brain-gut peptide expression, enhancing intestinal barrier integrity and alleviating PI-IBS symptoms.

5. Conclusion

The combination of trimebutine maleate dispersible tablets and berberine demonstrated significant therapeutic efficacy in PI-IBS rats with liver depression and spleen deficiency. The XB+QM group effectively improved fecal characteristics, reduced colonic inflammation, regulated brain-gut peptide expression (c-Fos, VIP, NOS, CHAT), and alleviated visceral hypersensitivity and colon tissue damage compared to the model group ($P < 0.05$). These findings suggest that the combined therapy may offer a promising approach for managing PI-IBS by targeting both gut and brain pathways.

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Disclosure statement

The authors declare no conflict of interest.

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