Am J Transl Res 2025;17(6):4859-4866
www.ajtr.org /ISSN:1943-8141/AJTR0164661

Original Article

Combination therapy with otilonium bromide and trimebutine maleate demonstrates significant clinical advantages in irritable bowel syndrome patients

Dingfeng Chen, Dongqiong Ni, Haiyan Yang

Department of Gastroenterology, The Affiliated Hospital of Shaoxing University, Shaoxing 312000, Zhejiang, China

Received March 20, 2025; Accepted June 3, 2025; Epub June 15, 2025; Published June 30, 2025

Abstract: Objective: To evaluate the efficacy of combined otilonium bromide (OB) and trimebutine maleate (TM-906) therapy in patients with irritable bowel syndrome (IBS). Methods: Data from 105 IBS patients treated at the Affiliated Hospital of Shaoxing University were retrospectively analyzed. Patients were divided into two groups: the control group (n=50), receiving OB alone, and the observation group (n=55), receiving both OB and TM-906. A comprehensive set of data, including treatment efficacy, safety profiles, clinical symptom improvements, serum markers, and quality of life, were collected from both groups. Results: The observation group exhibited significantly higher treatment efficacy and greater improvement in quality of life compared to the control group ($P<0.05$). The incidence of adverse reactions was similar between groups (7.27% vs. 6.00%, $P>0.05$). Additionally, the observation group experienced faster symptom relief and a more substantial reduction in inflammatory markers post-treatment ($P<0.05$). Conclusions: Combined therapy with OB and TM-906 is a safe and effective treatment for IBS, offering quicker symptom relief and substantial improvement in quality of life.

Keywords: Otilonium bromide, trimebutine maleate, irritable bowel syndrome, efficacy, safety, symptom improvement

Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder marked by symptoms such as abdominal pain, bloating, and changes in bowel habits [1]. The effects of IBS extend beyond the individual, severely affecting quality of life and contributing to increased medical costs and a substantial socioeconomic burden [2]. The pathophysiology of IBS involves complex factors, including dysregulation of the gut-brain axis, gut dysbiosis, abnormal visceral pain signaling, and intestinal immune activation. IBS is influenced by genetic predisposition, environmental factors, stress, inflammation, physical inactivity, and inadequate sleep [3-5]. Epidemiologic data underscore the global prevalence of IBS, with a risk range of 10% to 25% in the United States, affecting all age groups. The incidence is notably higher in women, with a rate of 14.0%, compared to 8.9% in men [6, 7]. Current IBS treatments primarily aim to reduce intestinal inflammation and alleviate symptoms, enhancing patients' quality of life [8]. However, despite ongoing research, there remains a lack of a highly effective, clinically safe treatment that addresses IBS symptoms comprehensively. Thus, there is a pressing need to identify more optimal treatments [9].

Otilonium bromide (OB), a selective inhibitor of ubiquitin-specific protease 28 (USP28), has demonstrated anticancer effects in various human cancer cell lines [10]. Beyond its oncology-related properties, OB is an anticholinergic spasmolytic agent that alleviates abdominal pain by targeting the distal gastrointestinal tract, making it a viable treatment for IBS [11]. In IBS rat models, OB has been shown to prevent chronic water avoidance stress-induced cholinergic alterations in the distal colon, serving as a preventive measure against disease progression [12]. Trimebutine maleate (TM-906), an opioid receptor agonist, is used to treat gastrointestinal dysfunction in IBS by reg-

https://doi.org/10.62347/JFCI2618

ulating abnormal gastrointestinal motility [13]. It also functions as a prokinetic agent, promoting gastric emptying by stimulating the release of motilin and gastrin. Additionally, TM-906 modulates inflammatory signaling pathways, providing anti-inflammatory benefits that are particularly relevant for IBS patients [14].

Despite the individual promise of OB and TM-906, there is limited literature on their combined therapeutic use. This study aimed to evaluate the clinical efficacy and safety of the OB-TM-906 combination in IBS treatment, addressing a significant gap in the current clinical understanding and possibly offering a novel, evidence-based treatment for this prevalent gastrointestinal disorder.

Patients and methods

Case selection

This retrospective study included data from 105 IBS patients admitted to the Affiliated Hospital of Shaoxing University between October 2022 and October 2024. The patients were divided into two groups based on clinical records: the control group (n=50), which received OB treatment alone, and the observation group (n=55), which received a combination therapy of OB and TM-906. This study was approved by the Ethics Committee of The Affiliated Hospital of Shaoxing University, ensuring ethical compliance.

Inclusion criteria: Patients had to meet the established diagnostic criteria for IBS [15], with symptoms such as abdominal distension, abdominal pain, and changes in stool consistency. Participants were treatment-naive, with no prior exposure to relevant therapies for IBS. They also had to avoid medications that could interfere with the study outcomes for at least three months before enrollment. Additionally, participants were required to have no mental illness or cognitive impairment, to complete a three-month follow-up, and to have accurate and comprehensive medical records.

Exclusion criteria: Patients were excluded if they had severe underlying conditions, including cardiovascular, pulmonary, cerebral, or renal insufficiency. Those with co-existing malignancies, structural or functional anomalies of the gastrointestinal organs, a history of gastrointestinal surgery, or allergies to the treatment drugs were also excluded. Pregnant or lactating women were excluded.

Intervention methods

Patients in the control group received OB, administered orally, twice daily, two tablets per dose.

Patients in the observation group received a combination of OB and TM-906. OB was administered as described for the control group, while TM-906 was given orally at a dose of two tablets, taken 30 minutes before each meal, three times a day. Both groups underwent continuous treatment for one month.

Data collection

Efficacy: Efficacy was assessed using the Bristol Stool Form Scale. The criteria for efficacy were as follows: Markedly Effective: Complete resolution of symptoms (abdominal discomfort, stool consistency) with a symptom score reduction of ≥ 80%. Effective: Improvement in symptoms, with a symptom score reduction of 50%-80%. Ineffective: No significant improvement or worsening of symptoms. The total effective rate was calculated as the percentage of patients in the markedly effective and effective categories.

Safety: The incidence of adverse reactions, including dry mouth, nausea, rash, and dizziness, was observed and recorded in both groups. The total adverse reaction rate was calculated as the percentage of patients experiencing these side effects.

Bowel symptom scores: The severity of abdominal pain and diarrhea was categorized as follows: 0 points: No symptoms (normal bowel movements, 1-3 times/day, well-formed stools). 1 point: Mild symptoms (slight abdominal pain, 4-5 bowel movements/day). 2 points: Moderate symptoms (frequent abdominal pain, 6-8 bowel movements/day). 3 points: Severe symptoms (significantly affecting daily life, >8 bowel movements/day).

Stool consistency: Stool consistency post-treatment was observed and categorized as loose stools, mushy stools, watery stools, or well-formed stools.

Table 1. Comparison of general information

General information	Control group (n=50)	Observation group (n=55)	χ^2/t	P
Age (years)	43.34±7.33	41.13±8.20	1.450	0.150
Sex			0.051	0.822
Male	22 (44.00)	23 (41.82)		
Female	28 (56.00)	32 (58.18)		
Disease course (years)	3.38±1.32	3.51±1.60	0.452	0.653
Clinical subtype			1.326	0.515
Diarrhea-predominant	28 (56.00)	25 (45.45)		
Constipation-predominant	15 (30.00)	22 (40.00)		
Mixed-type	7 (14.00)	8 (14.55)		
Marital status			0.040	0.842
Married	39 (78.00)	42 (76.36)		
Unmarried	11 (22.00)	13 (23.64)		

Symptom improvement: The time to improvement in symptoms (abdominal discomfort, stool frequency, stool consistency) was recorded for both groups.

Serum biomarkers: Fasting venous blood (5 mL) was collected in the morning before and after treatment. Serum was obtained after centrifugation, and levels of interleukin (IL)-10, IL-18, and tumor necrosis factor (TNF)-α were measured using the enzyme-linked immunosorbent assay (ELISA) technique.

Quality of life: The Irritable Bowel Syndrome Quality of Life Scale (IBS-QOL) was used to assess patients' quality of life. The IBS-QOL scale includes eight domains: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual function, and relationships. The total score was converted to a range of 0-100, with higher scores indicating better quality of life.

Recurrence rate: A three-month follow-up was conducted by telephone and outpatient consultations. The recurrence rate was recorded during this period.

Statistical methods

Data analysis was performed using SPSS 26.0 software. Continuous variables, such as age and disease duration, were presented as mean ± standard deviation ($\bar{x}$ ± sd). Comparisons between groups were made using an independent-sample t-test. For comparisons of the same variables at two time points, a paired t-test was used. Categorical data, such as treatment efficacy and safety outcomes, were expressed as frequencies and percentages (n(%)). The chi-square (χ^2) test was used to assess statistical significance for categorical data. A significance level of P<0.05 was considered significant.

Results

General information

The control group and the observation group were similar in terms of demographic and clinical characteristics. No significant differences were observed between the two groups in terms of age, gender, disease durations, clinical subtypes, etc. (all P>0.05). See **Table 1**.

Comparison of clinical efficacy

The total effective rate in the control group was 70.00%, whereas the observation group had a rate of 87.27%. The observation group exhibited a significantly higher total effective rate compared to the control group (P<0.05). See **Table 2**.

Comparison of clinical safety

In the control group, the number of cases experiencing dry mouth, nausea, rash, and dizziness were 2, 1, 0, and 0, respectively. In the observation group, the corresponding numbers were 2, 0, 1, and 1. The overall incidence of adverse reactions did not differ significantly between the two groups (7.27% vs. 6.00%, P>0.05). See **Table 3**.

Comparison of bowel symptom scores

Before treatment, no significant differences were observed in the symptom scores for abdominal pain, diarrhea, or other manifestations between the two groups (all P>0.05). After treatment, both groups showed significant reductions in these scores, with the observation group showing significantly lower scores compared to the control group (all P<0.05). See **Table 4**.

Table 2. Comparison of clinical efficacy

Therapeutic efficacy	Control group (n=50)	Observation group (n=55)	χ^2	P
Markedly effective	20 (40.00)	28 (50.91)		
Effective	15 (30.00)	20 (36.36)		
Ineffective	15 (30.00)	7 (12.73)		
Total effectiveness	35 (70.00)	48 (87.27)	4.718	0.030

Table 3. Comparison of clinical safety

Adverse reaction	Control group (n=50)	Observation group (n=55)	χ^2	P
Dry mouth	2 (4.00)	2 (3.64)		
Nausea	1 (2.00)	0 (0.00)		
Rash	0 (0.00)	1 (1.82)		
Dizziness	0 (0.00)	1 (1.82)		
Total	3 (6.00)	4 (7.27)	0.068	0.794

Table 4. Comparison of bowel symptom scores

Bowel symptoms	Control group (n=50)	Observation group (n=55)	t	P
Abdominal pain				
Before	2.02±0.74	2.29±0.81	1.777	0.079
After	1.38±0.73[a]	0.75±0.55[b]	5.022	<0.001
Diarrhea				
Before	2.08±0.72	2.0±0.94	0.486	0.628
After	1.12±0.63[a]	0.82±0.58[b]	2.541	0.013

Notes: [a]P<0.05 and [b]P<0.01 *vs.* the pre-treatment value.

Table 5. Comparison of stool consistency

Stool consistency	Control group (n=50)	Observation group (n=55)	χ^2	P
Loose stools	14 (28.00)	4 (7.27)	7.922	0.005
Mushy stools	12 (24.00)	4 (7.27)	5.674	0.017
Watery stools	7 (14.00)	12 (21.82)	1.080	0.299
Well-formed stools	17 (34.00)	35 (63.64)	9.202	0.002

Table 6. Comparison of symptom improvement

Symptom improvement	Control group (n=50)	Observation group (n=55)	t	P
Abdominal discomfort (d)	9.08±3.06	6.78±1.82	4.731	<0.001
Stool frequency (d)	14.08±3.34	8.71±2.16	9.870	<0.001
Stool consistency (d)	12.56±3.48	8.44±2.44	7.075	<0.001

Comparison of stool consistency

The observation group had significantly fewer cases of loose and mushy stools compared to the control group (P<0.05). The number of cases with watery stools was comparable between the two groups (P>0.05), while the observation group had significantly more cases with well-formed stools (P<0.05). See **Table 5**.

Comparison of symptom improvement

The time to improvement in abdominal discomfort, stool frequency, and stool consistency was significantly shorter in the observation group compared to the control group (all P<0.001). See **Table 6**.

Comparison of serum biomarkers

Before treatment, no significant inter-group differences were observed in serum biomarkers, including IL-10, IL-18, and TNF-α (all P>0.05). After treatment, a significant elevation in IL-10 levels was observed in both groups, along with a down-regulation of IL-18 and TNF-α levels (all P<0.05). Furthermore, the observation group exhibited significantly higher post-treatment IL-10 levels and significantly lower IL-18 and TNF-α levels compared to the control group (all P<0.05). See **Figure 1**.

Comparison of quality of life

Before treatment, the IBS-QOL scores in all dimensions were similar between the control and observation groups (all P>0.05). After treatment, the IBS-QOL scores of both groups significantly improved across all domains, including dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual function, and relationships. Moreover, the ob-

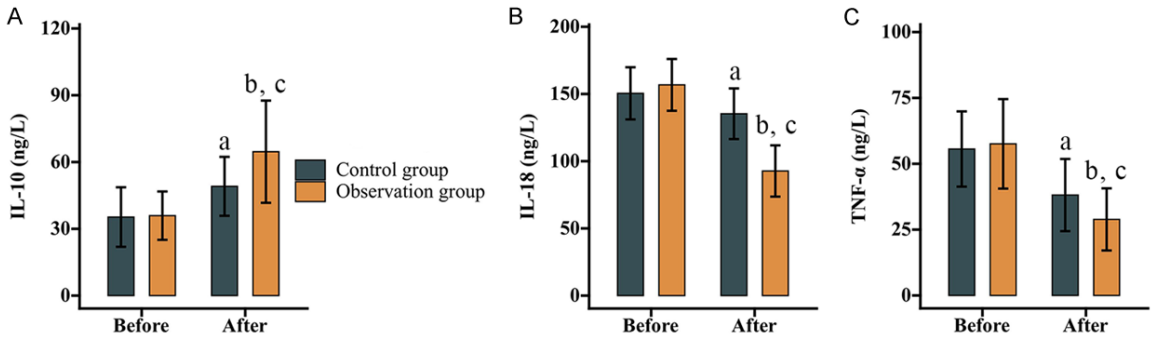

Figure 1. Comparison of serum biomarkers (IL-10, IL-18, and TNF-α) before and after treatment in the two groups. A. Pre- and post-treatment IL-10. B. Pre- and post-treatment IL-18 levels. C. Pre- and post-treatment TNF-α levels. Note: [a]P<0.05 and [b]P<0.01 *vs.* the pre-treatment value; [c]P<0.05 *vs.* Control. IL-10, interleukin-10; IL-18, interleukin-18; TNF-α, tumor necrosis factor-α.

Table 7. Comparison of quality of life

Quality of life	Control group (n=50)	Observation group (n=55)	t	P
Dysphoria				
Before	73.76±8.50	72.47±10.96	0.669	0.505
After	79.58±8.74	83.45±9.13	2.214	0.029
Interference with activity				
Before	65.70±7.77	69.00±10.57	1.808	0.074
After	78.36±9.68	84.47±8.46	3.451	<0.001
Body image				
Before	75.82±6.48	73.64±9.42	1.368	0.174
After	79.96±7.29	84.13±9.46	2.512	0.014
Health worry				
Before	73.16±10.90	73.27±10.44	0.053	0.958
After	82.64±8.04	87.33±8.17	2.960	0.004
Food avoidance				
Before	68.64±9.40	72.18±9.08	1.962	0.053
After	79.08±7.20	83.62±7.18	3.232	0.002
Social reaction				
Before	81.08±8.55	78.96±8.75	1.253	0.213
After	85.08±6.48	89.55±6.36	3.565	<0.001
Sexual function				
Before	83.88±7.55	83.71±7.07	0.119	0.905
After	90.16±6.76	93.13±4.23	2.725	0.008
Relationships				
Before	76.18±7.63	75.78±7.85	0.264	0.792
After	82.70±8.51	86.89±6.76	2.806	0.006

servation group demonstrated significantly higher IBS-QOL scores in all domains compared to the control group (all P<0.05). See **Table 7**.

Comparison of recurrent rate

In the control group, 9 cases experienced recurrence, resulting in a recurrence rate of 18.00%. In contrast, the observation group had only 3 relapsed cases, with a recurrence rate of 5.45%. The recurrence rate in the observation group was significantly lower than that of the control group (P<0.05). See **Figure 2**.

Discussion

Numerous previous studies have persistently explored optimal treatment approaches for IBS patients. For example, Bai et al. [16] reported that Atractylodes macrocephala-Paeonia lactiflora-based prescriptions, a traditional Chinese medicine, were more effective than placebo or western medications in enhancing symptom remission rates and alleviating disease severity in IBS patients. Similarly, Jiabao et al. [17] found that combining traditional Chinese and Western medicine therapies, specifically Weichang'an pills with western drugs, demonstrated superior clinical efficacy in treating gastrointestinal disorders like IBS, without causing severe adverse reactions. These findings have paved the way for new therapeutic interventions for IBS.

In this study, initial results revealed that the combination therapy of OB and TM-906 yielded

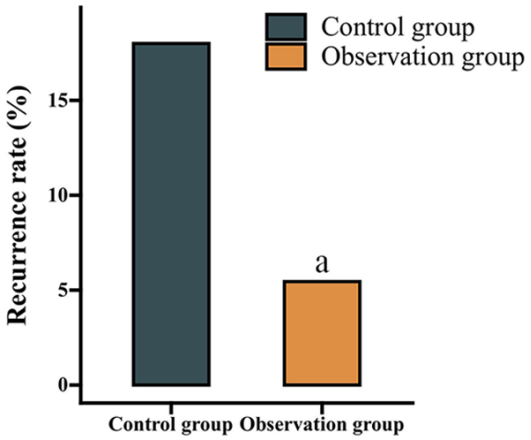

Figure 2. Comparison of recurrence rates. [a]denotes P<0.05 compared to the control group.

a significantly higher treatment effectiveness rate of 87.27%, compared to 70.00% in the control group. A study on an IBS mouse model demonstrated that TM-906 mitigated post-infection colonic muscle hypercontraction, thereby reducing colonic hyper-reactivity [18]. It also selectively inhibited propulsive activity in the proximal two-thirds of the colon, which may partly explain its therapeutic mechanism in IBS patients [19].

In terms of clinical safety, the combination therapy did not significantly increase medication-related side effects (7.27% vs. 6.00%), suggesting that the added drug did not compromise clinical safety. A study by Zhong et al. [20] also showed that TM-906 provided effective relief for functional dyspepsia and diarrhea-predominant IBS, with fewer adverse reactions and lower treatment costs, consistent with our findings. Additionally, TM-906 accelerates gastric emptying and has a low to moderate severity adverse reaction rate of only 12.3% [21]. In this study, IBS patients experienced significant alleviation of abdominal pain and diarrhea, as well as a higher rate of well-formed stools under the combination therapy. Furthermore, this combination therapy significantly shortened the time to improvement in symptoms such as abdominal discomfort, stool frequency, and stool consistency in IBS patients.

TM-906 modulates gastrointestinal motility by regulating calcium and potassium channels, effectively relieving abdominal pain in IBS patients [22]. Chmielewska-Wilkońet al. [23] found that OB alleviated individual and overall clinical symptoms (such as diarrhea frequency and normal stool frequency) within four weeks, consistent with our research findings. After receiving OB and TM-906 combined therapy, IBS patients showed a significant increase in IL-10 levels and a marked reduction in IL-18 and TNF-α, indicating effective improvement in inflammatory imbalance, inhibition of inflammation, and significant anti-inflammatory effects. IL-10, IL-18, and TNF-α are crucial in the pathologic progression of IBS, with IL-10 exerting anti-inflammatory effects, while IL-18 and TNF-α promote inflammation in the context of dysregulated inflammation [24]. In Motawea et al.'s [25] study, TM-906, delivered by nanostructured lipid carriers for acute colitis treatment, significantly reduced disease severity and downregulated TNF-α, supporting our findings.

Regarding quality of life, the combination of OB and TM-906 significantly improved IBS patients' scores in various domains, including dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual function, and relationships. The combination therapy also significantly reduced the risk of recurrence, lowering the recurrence rate from 18.00% to 5.45%. These results demonstrate that OB combined with TM-906 provided significantly better clinical outcomes than OB monotherapy in IBS management.

However, this study had several limitations. First, the relatively small sample size and short follow-up period may have limited the generalizability of our findings. Future multicenter studies with longer follow-up durations are needed to validate the clinical efficacy of this combination therapy. Second, potential confounding factors such as dietary patterns, psychological status, and concomitant medications were not systematically recorded, which may have influenced the outcomes. Future studies should incorporate these variables for a more comprehensive analysis. Lastly, the mechanisms behind the observed improvements remain incompletely understood. Further investigation of the causal relationship between inflammatory biomarkers and symptomatic improvement could provide valuable insights into the therapeutic mechanisms. Future research should aim to address these limitations through more

robust experimental designs and expanded analytical approaches.

In conclusion, the combination of OB and TM-906 significantly enhanced treatment efficacy for IBS patients, achieving an effectiveness rate of 87.27% while maintaining a favorable safety profile. This combination therapy effectively alleviates abdominal pain and diarrhea, increases the rate of well-formed stools, and accelerates improvement in symptoms such as abdominal discomfort, stool frequency, and stool consistency. Additionally, it modulated excessive inflammatory responses and significantly improves patients' overall quality of life. These findings provide a more efficacious and safer treatment alternative for IBS symptom relief, offering valuable insight for clinical practice and future research.

Disclosure of conflict of interest

None.

Address correspondence to: Haiyan Yang, Department of Gastroenterology, The Affiliated Hospital of Shaoxing University, Shaoxing 312000, Zhejiang, China. Tel: +86-0575-88293602; E-mail: 15381676606@163.com

References

[1] Staudacher HM, Black CJ, Teasdale SB, Mikocka-Walus A and Keefer L. Irritable bowel syndrome and mental health comorbidity - approach to multidisciplinary management. Nat Rev Gastroenterol Hepatol 2023; 20: 582-596.

[2] Huang KY, Wang FY, Lv M, Ma XX, Tang XD and Lv L. Irritable bowel syndrome: epidemiology, overlap disorders, pathophysiology and treatment. World J Gastroenterol 2023; 29: 4120-4135.

[3] Aguilera-Lizarraga J, Hussein H and Boeckxstaens GE. Immune activation in irritable bowel syndrome: what is the evidence? Nat Rev Immunol 2022; 22: 674-686.

[4] Okawa Y. A Discussion of whether various lifestyle changes can alleviate the symptoms of irritable bowel syndrome. Healthcare (Basel) 2022; 10: 2011.

[5] Sciberras M, Karmiris K, Nascimento C, Tabone T, Nikolaou P, Theodoropoulou A, Mula A, Goren I, Yanai H, Amir H, Mantzaris GJ, Georgiadi T, Foteinogiannopoulou K, Koutroubakis I, Allocca M, Fiorino G, Furfaro F, Katsanos K, Fousekis F, Michalopoulos G, Camilleri L, Torres J and Ellul P. Mental health, work presenteeism, and exercise in inflammatory bowel disease. J Crohns Colitis 2022; 16: 1197-1201.

[6] Shaikh SD, Sun N, Canakis A, Park WY and Weber HC. Irritable bowel syndrome and the gut microbiome: a comprehensive review. J Clin Med 2023; 12: 2558.

[7] Mayer EA, Ryu HJ and Bhatt RR. The neurobiology of irritable bowel syndrome. Mol Psychiatry 2023; 28: 1451-1465.

[8] Yelencich E, Truong E, Widaman AM, Pignotti G, Yang L, Jeon Y, Weber AT, Shah R, Smith J, Sauk JS and Limketkai BN. Avoidant restrictive food intake disorder prevalent among patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2022; 20: 1282-1289, e1.

[9] Wu J, Lv L and Wang C. Efficacy of fecal microbiota transplantation in irritable bowel syndrome: a meta-analysis of randomized controlled trials. Front Cell Infect Microbiol 2022; 12: 827395.

[10] Xu Z, Wang H, Meng Q, Ding Y, Zhu M, Zhou H, Zhang N and Shi L. Otilonium bromide acts as a selective usp28 inhibitor and exhibits cytotoxic activity against multiple human cancer cell lines. Biochem Pharmacol 2023; 215: 115746.

[11] Shrivastava A and Mittal A. A mini review on characteristics and analytical methods of otilonium bromide. Crit Rev Anal Chem 2022; 52: 1717-1725.

[12] Traini C, Idrizaj E, Biagioni C, Baccari MC and Vannucchi MG. Otilonium bromide prevents cholinergic changes in the distal colon induced by chronic water avoidance stress, a rat model of irritable bowel syndrome. Int J Mol Sci 2023; 24: 7440.

[13] Natoli A, Branca S, Granata A and Lavagnini L. Colonic radiography by double-contrast enema in the elderly patient with the use of trimebutine maleate. Clin Ter 1992; 140: 391-394.

[14] Boziki M, Grigoriadis N, Papaefthymiou A, Doulberis M, Polyzos SA, Gavalas E, Deretzi G, Karafoulidou E, Kesidou E, Taloumtzis C, Theotokis P, Sofou E, Katsinelos P, Vardaka E, Fludaras I, Touloumtzi M, Koukoufiki A, Simeonidou C, Liatsos C and Kountouras J. The trimebutine effect on Helicobacter pylori-related gastrointestinal tract and brain disorders: a hypothesis. Neurochem Int 2021; 144: 104938.

[15] M'Koma AE. Inflammatory bowel disease: clinical diagnosis and surgical treatment-overview. Medicina (Kaunas) 2022; 58: 567.

[16] Bai W, Wang Z, Liang J and Deng H. Atractylodes macrocephala-paeonia lactiflora class formula for the treatment of irritable bowel syndrome: a systematic review with meta-anal-

ysis and trial sequential analysis. Cureus 2023; 15: e49997.
[17] Jiabao W, Lishuang Z, Baihan N, Yajun YU, Fengwen Y, Lin M, Lijuan C, Xinya D, Yingjie S, Yujing W, Lin W, Han Z, Yi W and Lin LI. Efficacy and safety of weichang' an pill combined with western medicine on gastrointestinal diseases: a systematic review and meta-analysis. J Tradit Chin Med 2023; 43: 1057-1067.
[18] Long Y, Liu Y, Tong J, Qian W and Hou X. Effectiveness of trimebutine maleate on modulating intestinal hypercontractility in a mouse model of postinfectious irritable bowel syndrome. Eur J Pharmacol 2010; 636: 159-165.
[19] Frexinos J, Fioramonti J and Bueno L. Effect of trimebutine on colonic myoelectrical activity in IBS patients. Eur J Clin Pharmacol 1985; 28: 181-185.
[20] Zhong YQ, Zhu J, Guo JN, Yan R, Li HJ, Lin YH and Zeng ZY. A randomized and case-control clinical study on trimebutine maleate in treating functional dyspepsia coexisting with diarrhea-dominant irritable bowel syndrome. Zhonghua Nei Ke Za Zhi 2007; 46: 899-902.
[21] Kountouras J, Gavalas E, Papaefthymiou A, Tsechelidis I, Polyzos SA, Bor S, Diculescu M, Jadallah K, Tadeusz M, Karakan T, Bochenek A, Rozciecha J, Dabrowski P, Sparchez Z, Sezgin O, Gulten M, Farsakh NA and Doulberis M. Trimebutine maleate monotherapy for functional dyspepsia: a multicenter, randomized, double-blind placebo controlled prospective trial. Medicina (Kaunas) 2020; 56: 339.
[22] Lee HT and Kim BJ. Trimebutine as a modulator of gastrointestinal motility. Arch Pharm Res 2011; 34: 861-864.
[23] Chmielewska-Wilkon D, Reggiardo G and Egan CG. Otilonium bromide in irritable bowel syndrome: a dose-ranging randomized double-blind placebo-controlled trial. World J Gastroenterol 2014; 20: 12283-12291.
[24] Ismail MH, Molan AL and Abbas SK. Serological levels of cytokines in irritable bowel syndrome (IBS) patients and non-IBS subjects with and without blastocystis spp. infection. Ann Parasitol 2022; 68: 77-85.
[25] Motawea A, Abd El Hady WE and Ahmed El-Emam G. The protective impact of adapted trimebutine maleate-loaded nanostructured lipid carriers for alleviating the severity of acute colitis. Drug Deliv 2022; 29: 906-924.