

Original Article

Effect of shenling baizhu powder on the serum TH1 cytokines of elderly patients with ulcerative colitis complicated by bloody purulent stool

Shuhong Li*, Xuwen Hao*, Yanxia Gong, Simiao Liu, Wei Niu, Jiannan Jia, Yanping Tang

*Department of Gastroenterology, Tianjin Nankai Hospital, Tianjin, China. *Equal contributors.*

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Abstract: Objective: To investigate the role of Shenling Baizhu powder as an adjuvant therapy on the serum TH1 of elderly patients with ulcerative colitis complicated by bloody purulent stool. Methods: A total of 70 elderly patients with ulcerative colitis complicated by bloody purulent stool presenting to our hospital from June 2018 to October 2019 were enrolled and equally randomized. Patients were administered mesalazine enteric-coated tablets in the control group, and patients were additionally treated with Shenling Baizhu powder. The main clinical symptom scores, the relief of bloody purulent stool symptoms, and the serum TH1 levels before and after treatment as well as the clinical efficacy were compared in the two groups, and the ROC curve was plotted to analyze the value of serum TH1 cytokine in predicting disease recurrence. Results: After treatment, the scores in the two groups were decreased significantly, and the decrease in the study group was significant ($P < 0.05$). The total effective rate in the study group (88.57%) was significantly higher than that of the control group (68.57%), and the response rate after treatment in the study group (85.71%) was significantly higher than that of the control group (62.86%). In the two groups, serum IL-2 and IFN- γ levels were decreased significantly before and after treatment, but the decrease in the study group was significant ($P < 0.05$). ROC analysis showed that the area under the curve (AUC) of IL-2 was 0.797, the maximum Jordan index was 0.573, the sensitivity was 61.10%, and the specificity was 96.20%. The AUC of IFN- γ was 0.794, the maximum Jordan index was 0.453, the sensitivity was 55.60%, and the specificity was 72.50%. Conclusion: Shenling Baizhu powder as an adjuvant therapy is a promising option for elderly patients with ulcerative colitis complicated by bloody purulent stool.

Keywords: Shenling Baizhu powder, elderly patients, ulcerative colitis, bloody purulent stool, serum TH1

Introduction

Ulcerative colitis is a typical refractory disease in the Department of Gastroenterology. It often presents with bloody diarrhea, abdominal pain, hematochezia, and weight loss. In severe cases, it can induce complications such as massive hemorrhage, intestinal perforation, and toxic colonic dilatation, which has a serious effect on the quality of life and health of patients [1]. Such patients have mild or insignificant clinical signs in the early stages of the disease, and as the disease progresses, the clinical signs worsen, with increased stool frequency and the presence of purulent blood or mucus. Literature survey [2] showed that infection, allergic reactions, genetic and immune dysfunction may induce ulcerative colitis, and

elderly patients often get complicated by bloody purulent stool. According to the TCM theory, the essence of disease is weakness in constitution and fullness of superficial elements. The former is abundance of dampness due to spleen deficiency, and blood stagnation. The latter is dampness and heat in the intestines and damage to the intestines [3]. Mesalazine is commonly used in the treatment of ulcerative colitis with spleen and stomach qi deficiency. Although it has a some effect, patients are prone to experience adverse reactions such as nausea and headache. Clinical findings [4] revealed that Shenling Baizhu powder has the effect of strengthening the spleen and replenishing qi, and checking diarrhea, and is also effective in patients with spleen and stomach qi deficiency, but it remains to be stud-

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ied whether it affects the serum TH1 levels of patients. Mesalazine is a first-line drug for the clinical treatment of inflammatory bowel disease in western medicine. It mainly acts on the inflammatory part of the intestinal mucosa by activating 5-aminosalicylic acid, which has an anti-inflammatory effect, but it cannot regulate the patient's status as a whole and patients are prone to relapse. Shenling Baizhu powder embodies its inherent advantages through a holistic concept. It can not only adjust body functions, but also take into account the changes in the local area. However, its treatment course is longer, so the combination of the two has no adverse reactions, but they can give full play to their advantages. The aim of this study was to investigate the effect and clinical efficacy of Shenling Baizhu powder as an adjuvant therapy, on the serum TH1 level of elderly patients with ulcerative colitis complicated by bloody purulent stool.

Materials and methods

General data

A total of 70 elderly patients with ulcerative colitis complicated with bloody purulent stool who were treated in our hospital from June 2018 to October 2019 were selected as subjects of the study. Inclusion criteria: (1) be diagnosed by clinical examination, and meeting the diagnostic criteria for ulcerative colitis [5]; (2) aged ≥ 60 years; (3) complicated with bloody purulent stool. Exclusion criteria: (1) complicated with colon cancer or intestinal perforation; (2) the presence of heart, liver and kidney dysfunction; (3) complicated by sepsis and intestinal obstruction; (4) being allergic to the study drug. This study was approved by the Ethics Committee of our hospital.

The patients were randomly divided into a control group ($n=35$, aged 60-75 years) and study group ($n=35$, aged 60-78 years), with a course of disease of 6-30 months.

Methods

All patients underwent routine treatment after admission, quitting smoking and alcohol, and avoiding the consumption of foods to which they were intolerant such as high protein, peppers, and raw or cold food, and their vital signs were monitored. Patients in the control group

initiated treatment with mesalazine enteric-coated tablets (Sunflower Group Jiamusi Luling Pharmaceutical Co., Ltd., SFDA approval number H19980148, strength: 0.25 g*24 s) at a dose of 4-8 s/d, gradually increased to 12-16 s/d for each 30 days, and maintained this dose until the end of the course of treatment, and swallowed with warm water before each meal. Patients in the study group were treated with the addition of Shenling Baizhu powder (Beijing Tong Ren Tang Co., Ltd. Tong Ren Tang Pharmaceutical Factory, SFDA approval number 11020755, strength: 12 g \times 10 bags/box) to mesalazine enteric-coated tablets at a dose of 6 g TID for each 30 days, and swallowed with warm water after each meal. Patients in the two groups were treated for 3 courses of treatment.

Outcome measures

(1) The vital signs of patients during study treatment were observed in the two groups, and the main clinical symptom scores (abdominal distension, diarrhea, abdominal pain, bloody purulent stool and asthenia) before and after treatment were compared. Scoring criteria [6] were as follows: 0 (no symptom), 1 (mild symptoms), 2 (moderate symptoms), and 3 (severe symptoms). (2) The clinical efficacy of patients was compared between the two groups. Evaluation criteria [7]: markedly effective: clinical symptoms disappeared, the mucosa returned to normal by re-examination under colonoscope; effective: clinical symptoms basically disappeared or improved, the lesion mucosa gradually recovered by re-examination under colonoscope; ineffective: clinical symptoms did not improve or aggravate, the lesion mucosa did not recover by re-examination under colonoscope. (3) The relief of bloody purulent stool symptoms before and after treatment was compared between the two groups. (4) The serum TH1 (IL-2 and IFN- γ) levels of patients before and after treatment were compared between the two groups. (5) The value of serum TH1 cytokines in predicting disease recurrence was analyzed by ROC curve.

A total of 5 mL of venous blood was collected from the patients under the fasted conditions in the morning before and after surgical treatment, centrifuged at 12,000 r/min for 10 min ($r=15$ cm) to obtain 100 μ L of serum. Subsequently, it was placed in an EP tube and stored at -20°C for examination. Serum TH1

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Table 1. General data of patients in the two groups [n (%), ($\bar{X} \pm s$)]

Group	n	Male	Female	Mean age (year)	Mean course of disease
Control group	35	21	14	67.23±5.48	11.23±1.65
Study group	35	23	12	66.94±6.15	10.98±1.43
χ^2/t		0.245		0.208	0.677
<i>P</i>		0.621		0.835	0.500

cytokines (IL-2 and IFN- γ) were detected by ELISA kit (Wuhan Cusabio Biotech Co., Ltd.).

Statistical analysis

SPSS 17.0 software was used for data analysis. Normally distributed measurement data were expressed as ($\bar{X} \pm s$), and analyzed by t-test; categorical variables were expressed as constituent ratio (%), and analyzed by χ^2 ; ROC curve was plotted, and $P < 0.05$ was considered a significant difference.

Results

Comparison of general data between the two groups

The General data of patients between the two groups were homogeneous ($P > 0.05$, **Table 1**).

Clinical symptom scores before and after treatment in the two groups

There was no significant difference in the clinical symptom scores before treatment between the two groups ($P > 0.05$); the scores after treatment in the two groups were significantly decreased, and the study group had a more significant decrease than the control group, and there was a significant difference ($P < 0.05$). See **Table 2**.

Comparison of the clinical efficacy between the two groups

The total effective rate (88.57%) was significantly higher in the study group than that in the control group (68.57%), indicating that the difference was significant ($P < 0.05$). See **Table 3**.

Comparison of the relief of bloody purulent stool symptoms after treatment between the two groups

After the treatment, 30 patients in study group were relieved (85.71%), while 22 patients in

control group were relieved (62.86%), and there was a significant difference between the groups ($P < 0.05$). See **Table 4**.

Comparison of the serum IL-2 and IFN- γ levels before and after treatment between the two groups

Before treatment, there was no difference in serum IL-2 and IFN- γ levels between the two groups ($P > 0.05$). Serum IL-2 and IFN- γ levels after treatment were significantly decreased compared with those before treatment, but the serum IL-2 and IFN- γ levels in the study group were significantly decreased compared with those in the control group ($P < 0.05$). See **Table 5**.

Analysis of the value of serum TH1 cytokines in predicting disease recurrence by ROC curve

ROC analysis showed that the area under the curve (AUC) of IL-2 was 0.797, the maximum Jordan index was 0.573, the sensitivity was 61.10%, and the specificity was 96.20%. The AUC of IFN- γ was 0.794, the maximum Jordan index was 0.453, the sensitivity was 55.60%, and the specificity was 72.50% (**Figure 1**).

Discussion

Ulcerative colitis is a chronic non-specific inflammatory disease of the colon and rectum, and its pathogenesis is relatively complex and not yet known. Clinically, it is believed that the disease may be related to genetics, immune function and infection, which in turn causes abnormalities in the immune system of the gastrointestinal mucosa and ultimately leads to inflammatory reactions [8]. With continuous economic development, changes in people's living habits and dietary structure, the incidence of the disease has gradually increased. Ulcerative colitis was characterized by the predominance of abdominal pain, diarrhea, and bloody mucopurulent stool, complicated by various degrees of extraintestinal manifestations (erythema nodosum, oral ulcers); and it changes mucin and disrupts the barrier effect of the intestinal mucosa, making entry of food and intestinal commensal bacteria into the intestinal mucosa difficult, and leads to antigen-specific immune responses and a series of inflammatory changes [9, 10]. Inflammatory cells can release a large number of related cytokines and inflammatory mediators, which

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Table 2. Comparison of clinical symptom scores before and after treatment between the two groups [n (%)]

Group (n=35)		Abdominal distention	Diarrhea	Abdominal pain	Asthenia
Control group	Pre-treatment	2.45±1.28	3.42±1.33	3.32±1.12	1.22±0.53
	Post-treatment	1.76±0.94*	2.25±1.04*	2.14±0.63*	0.87±0.10*
Study group	Pre-treatment	2.41±1.23	3.39±1.28	3.27±1.25	1.19±0.58
	Post-treatment	1.21±0.54#	1.97±0.86#	1.76±0.51#	0.43±0.06#

Note: * was compared with # (P < 0.05).

Table 3. Comparison of clinical efficacy between the two groups [n (%)]

Group	n	Significant	Effective	Ineffective	Overall effective rate
Control group	35	14 (40.00)	10 (28.57)	11 (31.43)	24 (68.57)
Study group	35	19 (54.29)	12 (34.29)	4 (11.42)	31 (88.57)
χ^2					4.158
P					0.041

Table 4. Comparison of the relief of bloody purulent stool symptoms after treatment between the two groups [n (%)]

Group	n	Response	Non-response	Response rate
Control group	35	22 (62.86)	13 (37.14)	62.86%
Study group	35	30 (85.71)	5 (14.29)	85.71%
χ^2				4.786
P				0.029

in turn induce inflammatory lesions and cause tissue destruction, affecting the normal defense function of the intestinal mucosa. At present, the clinical treatment principles for elderly patients with ulcerative colitis are to control the onset of the disease, alleviate the progression of the disease, and reduce the occurrence of complications [11].

In TCM, the disease is classified as “diarrhea” and “blood in the stool”. The causes of the disease are mostly due to exopathogens and six external etiological factors, internal damage, improper diet, which can cause dysfunction of the spleen and stomach in ascending and descending, damage the spleen and stomach, affect the large intestine, breed dampness and heat, obstruct qi and blood, encourage stagnation and pus, with final emergence of anabrosis [12]. The disease mainly occurs in the spleen and stomach, where the dysfunction in transport due to splenic deficiency appears, dampness is internalized, and clearness and turbidity are not differentiated, thus causing

diarrhea. Therefore, ulcerative colitis may also be referred to as ulcerative colitis with spleen and stomach qi deficiency in TCM [13]. In Shenling Baizhu powder, Baizhu is sweet, warm and dry in nature, not only invigorating qi, reinforcing deficiency, but tonifying the spleen and eliminating dampness; Ginseng is sweet and warm; it enters the spleen meridian and is good for tonifying the spleen and stomach; Fu Ling, sweet and bland, is an important medicine for inducing diuresis, tonifying the spleen and improving transport. Coix seed is sweet, bland and mildly cold, tonifying spleen and eliminating dampness. White lentil is sweet, flat

and buzhong, tonifying spleen and eliminating dampness. Fructus amomi is used to remove dampness, invigorate the spleen, move qi, and harmonize the stomach. Common yam rhizome is sweet, flat and tonifying spleen and stomach. Lotus seed is sweet, flat and astringent, tonifying spleen and thickening stomach, astringent to the intestines, stopping diarrhea, invigorating the spleen and increasing appetite. Platycodon grandiflorum is used to release lung-qi and alleviate water retention. Radix glycyrrhizae preparata invigorates qi and harmonizes all herbs. Jujube is good for the spleen and stomach This formula is good for strengthening the spleen and invigorating qi, and it is also effective for patients with chronic diarrhea due to consumptive disease, internal injury, qi deficiency and yang deficiency. Studies have shown [14] that the formula also has antimicrobial, analgesic and anti-diarrhea effects, is effective in inhibiting damage to the intestinal mucosa, and helps to improve antioxidant capacity and modulate immune function.

Table 5. Comparison of serum IL-2 and IFN- γ levels before and after treatment between the two groups ($\bar{X} \pm s$)

Group	n	IL-2 (pg/mL)		IFN- γ (pg/mL)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group	35	35.47 \pm 4.28	28.34 \pm 3.17	24.68 \pm 3.75	21.87 \pm 2.94
Study group	35	34.92 \pm 4.35	21.58 \pm 3.26	24.39 \pm 3.62	13.65 \pm 2.18
t		0.533	8.795	0.329	13.290
P		0.595	< 0.001	0.743	< 0.001

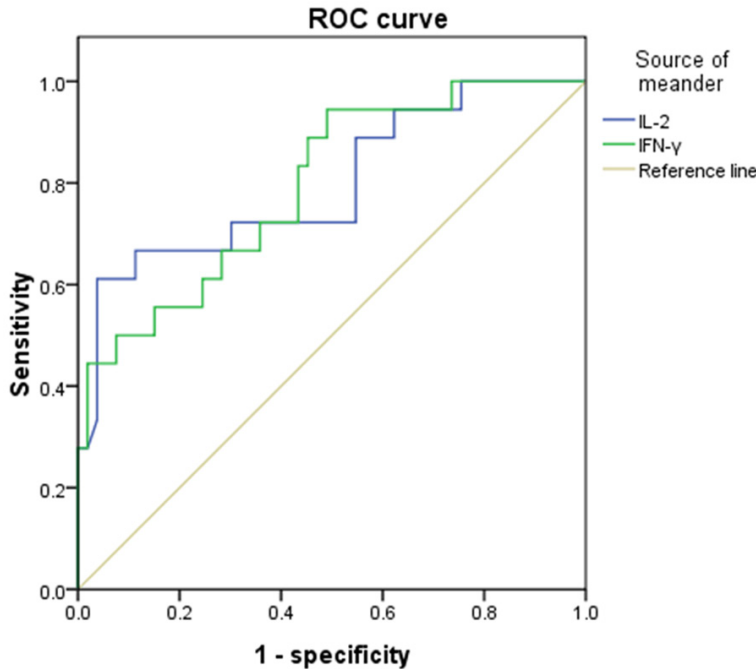


Figure 1. Analysis of the value of serum TH1 cytokines in predicting disease recurrence by ROC curve.

In the study, the total effective rate in the study group (88.57%) was significantly higher than that in the control group (68.57%), and after treatment, the remission rate in the study group (85.71%) was significantly higher than that in the control group (62.86%). It was shown that Shenling Baizhu powder plus mesalazine enteric-coated tablets were administered for ulcerative colitis with spleen and stomach qi deficiency in the study group, which exhibited significant effect and a significant anti-inflammatory and analgesic effect. Besides, after treatment, clinical symptom scores in the two groups were decreased significantly, and the decrease in the study group was more significant than that in the control group ($P < 0.05$). These results indicated that Shenling Baizhu powder can effectively improve the

inflammatory response of patients, control the condition, and alleviate the progression of the disease [15]. The study results showed that in the two groups, serum IL-2 and IFN- γ levels were decreased significantly before and after treatment, but the decrease in the study group was greater than that in the control group, and there was a significant difference ($P < 0.05$). Immune mechanisms are particularly important in the development of ulcerative colitis complicated by bloody purulent stool, a large number of activated T lymphocytes occupy the lesion site of the disease, and the secreted cytokines have an extremely strong inflammatory effect and can exacerbate the condition [16]. Serum TH1 acts as a immunity factor of

the master cell, and its expression factors are mainly IL-2 and IFN- γ . Under normal circumstances, it can antagonize with TH2 cytokines and maintain a dynamic balance; if there is an imbalance, it means that corresponding diseases appear in the body. It has been found that serum TH1 cytokines have an important role in inflammatory diseases. TH1 cytokines are functionally enhanced in patients with ulcerative colitis [17]. IL-2 is a biologically active cytokine that is produced by TH1 cells in response to antigenic stimulation and mitosis and acts by binding to receptors on the surface of monocytes, T cells, and B cells to contribute to the activation and proliferation of T cells and to enhance killing, resulting in increased activity of natural killer cells [18]. IFN- γ is a major synthesis product of TH1 cells

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and can enhance TH1 cell activity. It has the strongest immunomodulatory activity and weak antiviral effect, and can improve antigen presentation, promote T and B cells differentiation, and activate neutrophils, NK cells, and macrophages [19]. Therefore, the serum IL-2 and IFN- γ levels of the patients in the study group were decreased significantly after treatment, indicating that the Shenling Baizhu powder as an adjuvant therapy could inhibit the expression of inflammatory factors, reduce the levels of serum TH1 cytokines, alleviate the damage of colonic mucosa, improve immune function, and promote early recovery of patients.

ROC analysis showed that the AUC of IL-2 was 0.797, the maximum Jordan index was 0.573, the sensitivity was 61.10%, and the specificity was 96.20%. The AUC of IFN- γ was 0.794, the maximum Jordan index was 0.453, the sensitivity was 55.60%, and the specificity was 72.50%. It was shown that serum factors IL-2 and IFN- γ have the value in predicting disease recurrence. After treatment, IL-2 and IFN- γ levels are reduced. If they are increased, it indicates that patients are at risk of recurrence [20, 21]. The limitation of this study is that it did not conduct a multivariate analysis on the factors with higher sensitivity and specificity derived from the ROC curve. Whether this is a risk factor for the disease will be assessed in future studies.

In conclusion, Shenling Baizhu powder as an adjuvant therapy is administered for elderly patients with ulcerative colitis complicated by bloody purulent stool, which can reduce the expression level of serum TH1 cytokine, reduce the inflammatory response, and improve the clinical efficacy in patients.

Disclosure of conflict of interest

None.

Address correspondence to: Yanping Tang, Department of Gastroenterology, Tianjin Nankai Hospital, No. 6 Changjiang Rd, Nankai District, Tianjin, China. Tel: +86-18698087151; E-mail: tangyanping1961@126.com

References

[1] Adams SM and Bornemann PH. Ulcerative colitis. *Am Fam Physician* 2013; 87: 699-705.

- [2] Ordás I, Eckmann L and Talamini M. Ulcerative colitis. *Lancet* 2012; 380: 1606-1619.
- [3] Devlen J, Beusterien K, Yen L, Ahmed A, Cheifetz AS and Moss AC. The burden of inflammatory bowel disease: a patient-reported qualitative analysis and development of a conceptual model. *Inflamm Bowel Dis* 2014; 20: 545-552.
- [4] Rather IA, Majumder R, Alshammari FH, Park JG and Bajpai VK. Review-ulcerative colitis and probiotics: an overview. *Pak J Pharm Sci* 2016; 29: 1877-1880.
- [5] Kappelman MD, Moore KR, Allen JK and Cook SF. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. *Dig Dis Sci* 2013; 58: 519-525.
- [6] Hou JK, Kramer JR, Richardson P, Mei M and El-Serag HB. The incidence and prevalence of inflammatory bowel disease among U.S. veterans: a national cohort study. *Inflamm Bowel Dis* 2013; 19: 1059-1064.
- [7] Shivashankar R, Tremaine WJ, Harmsen WS and Loftus EV Jr. Incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted county, Minnesota from 1970 through 2010. *Clin Gastroenterol Hepatol* 2017; 15: 857-863.
- [8] Li X, Song P and Li J. The disease burden and clinical characteristics of inflammatory bowel disease in the Chinese population: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2017; 14: E238.
- [9] Hou JK, Feagins LA and Waljee AK. Characteristics and behavior of elderly-onset inflammatory bowel disease: a multi-center US study. *Inflamm Bowel Dis* 2016; 22: 2200-2205.
- [10] Shi HY, Chan FK, Leung WK, Li MK, Leung CM, Sze SF, Ching JY, Lo FH, Tsang SW, Shan EH, Mak LY, Lam BC, Hui AJ, Wong SH, Wong MT, Hung IF, Hui YT, Chan YK, Chan KH, Loo CK, Tong RW, Chow WH, Ng CK, Lao WC, Harbord M, Wu JC, Sung JJ and Ng SC. Natural history of elderly-onset ulcerative colitis: results from a territory-wide inflammatory bowel disease registry. *J Crohns Colitis* 2016; 10: 176-185.
- [11] Song EM, Lee HS, Park SH, Kim GU, Seo M, Hwang SW, Yang DH, Kim KJ, Byeon JS, Myung SJ, Yang SK and Ye BD. Clinical characteristics and long-term prognosis of elderly onset ulcerative colitis. *J Gastroenterol Hepatol* 2018; 33: 172-179.
- [12] Charpentier C, Salleron J, Savoye G, Fumery M, Merle V, Laberrenne JE, Vasseur F, Dupas JL, Cortot A, Dauchet L, Peyrin-Biroulet L, Lerebours E, Colombel JF and Gower-Rousseau C. Natural history of elderly-onset inflammatory bowel disease: a population-based cohort study. *Gut* 2014; 63: 423-432.
- [13] Baumgart DC. Crohn's disease and ulcerative colitis: from epidemiology and immunobiology

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- to a rational diagnostic and therapeutic approach. Boston: Springer; 2012. pp. 75-84.
- [14] Yanai H, Salomon N and Lahat A. Complementary therapies in inflammatory bowel diseases. *Curr Gastroenterol Rep* 2016; 18: 62.
- [15] Lang A, Salomon N, Wu JC, Kopylov U, Lahat A, Har-Noy O, Ching JY, Cheong PK, Avidan B, Gamsus D, Kaimakliotis I, Eliakim R, Ng SC and Ben-Horin S. Curcumin in combination with mesalamine induces remission in patients with mild-to-moderate ulcerative colitis in a randomized controlled trial. *Clin Gastroenterol Hepatol* 2015; 13: 1444-1449.
- [16] Singla V, Pratap Mouli V, Garg SK, Rai T, Choudhury BN, Verma P, Deb R, Tiwari V, Rohatgi S, Dhingra R, Kedia S, Sharma PK, Makharia G and Ahuja V. Induction with NCB-02 (curcumin) enema for mild-to-moderate distal ulcerative colitis - a randomized, placebo-controlled, pilot study. *J Crohns Colitis* 2014; 8: 208-214.
- [17] Sandborn WJ, Targan SR, Byers VS, Rutty DA, Mu H, Zhang X and Tang T. *Andrographis paniculata* extract (HMPL-004) for active ulcerative colitis. *Am J Gastroenterol* 2013; 108: 90-98.
- [18] Langhorst J, Wulfert H, Lauche R, Klose P, Cramer H, Dobos GJ and Korzenik J. Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. *J Crohns Colitis* 2015; 9: 86-106.
- [19] Ji J, Huang Y and Wang XF. Review of clinical studies of the treatment of ulcerative colitis using acupuncture and moxibustion. *Gastroenterol Res Pract* 2016; 2016: 9248589.
- [20] Perreault N. Ulcerative colitis-associated carcinoma: epithelial SMAD4-mediated signaling is a key guardian. *Cell Mol Gastroenterol Hepatol* 2018; 6: 350-351.
- [21] Paschos P, Katsoula A, Giouleme O, Sarigianni M, Liakos A, Athanasiadou E, Bekiari E and Tsapas A. Tofacitinib for induction of remission in ulcerative colitis: systematic review and meta-analysis. *Ann Gastroenterol* 2018; 31: 572-582.