



# Effect of Bifidobacterium triple live bacteria on inflammatory factors, oxidative stress and T lymphocyte subsets in patients with ulcerative colitis

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## ABSTRACT

**Objective:** To explore the effect of Bifidobacterium triple live bacteria on inflammatory factors, oxidative stress and T lymphocyte subsets in patients with ulcerative colitis (UC). **Method:** A total of 90 patients with UC treated in our hospital were selected and randomly divided into the observation group and the control group each with 45 cases. The control group was given Mesalazin Enteric-coated Tablets 1 g/times, 4 times/d, continuous treatment for 1 **months**; when the clinical symptoms were stable, switched to 500 mg/times, 3 times/d, continuous treatment for 3 months. The observation group on the basis of conventional treatment to give Bifidobacterium triple live bacteria scattered adjuvant therapy (Bifico capsule), 0.84 g/time, 2 times/d, continuous treatment for 3 months. In the two groups, the levels of inflammatory factors (IL-6, IL-10, CRP, TNF- $\alpha$ ), oxidative stress markers (MDA, SOD) and T lymphocyte subsets (CD3<sup>+</sup>, CD4<sup>+</sup>, CD8<sup>+</sup>, CD4<sup>+</sup>/CD8<sup>+</sup>) were compared pre and post treatment. **Results:** The levels of IL-6, CRP, MDA, TNF- $\alpha$ , CD8<sup>+</sup> in both two groups were significantly decreased compared with treatment before; the levels of IL-10, SOD, CD3<sup>+</sup>, CD4<sup>+</sup> and CD4<sup>+</sup>/CD8<sup>+</sup> were significantly increased compared with treatment before. After treatment, the levels of serum IL-6, CRP, TNF- $\alpha$ , MDA and CD8<sup>+</sup> in observation group with the data (72.17 $\pm$ 15.18) pg/mL, (21.52 $\pm$ 10.21) mg/mL, (15.98 $\pm$ 4.12) pg/mL respectively were decreased more significantly than those data in control group which were (86.55 $\pm$ 17.26) pg/mL, (43.02 $\pm$ 12.27) mg/L, (22.35 $\pm$ 3.67) pg/mL, MDA level (5.89 $\pm$ 0.56) nmol/mL in observation group was decreased more significantly than the level in the control group (6.75 $\pm$ 0.68) nmol/mL; CD8<sup>+</sup> level (17.24 $\pm$ 3.06)% in observation group was decreased more significantly than the level (19.01 $\pm$ 2.62)% in the control group. After treatment, IL-10 level (70.21 $\pm$ 6.03) pg/mL in observation group was increased more significantly than the level in the control group (56.48 + 8.67) pg/mL; SOD level (1.84 $\pm$ 0.06) U/mL in observation group was increased more significantly than the level in the control group (1.32 $\pm$ 0.05) U/mL; the levels of CD3<sup>+</sup>, CD4<sup>+</sup>, CD4<sup>+</sup>/CD8<sup>+</sup> in the observation group (57.84 $\pm$ 6.07)%; (36.78 $\pm$ 4.32)%; (1.92 $\pm$ 0.29) were increased more significantly than the level in the control group (54.93 $\pm$ 6.87)%; (35.42 $\pm$ 5.27)%; (1.89 $\pm$ 0.12). **Conclusion:** Bifidobacterium triple live bacteria scattered adjuvant treatment of ulcerative colitis helps regulate oxidative stress and inflammatory cytokines inhibiting inflammatory reaction and improving enhance function, and can effectively improve the clinical symptoms of patients with UC.

## 1. Introduction

Ulcerative colitis (UC) is a common digestive tract inflammatory disease, whose pathogenesis is affected by many factors; and the pathological mechanism of UC is not clear[1–3]. In recent years, the

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incidence of UC has been increasing, which poses a serious threat to people's health. Some studies have found that intestinal flora imbalance plays a certain role in the pathogenesis and progression of UC, so it is helpful to correct the imbalance of intestinal flora to improve therapeutic effects[4]. The triple living bacteria of Bifidobacterium belongs to the microbial preparation, which can improve the environment of the intestinal cavity, thus increase the permeability of the mucosa[5]. Our study has investigated the effect of adjuvant treatment of Bifidobacterium triple viable (Peifeikang capsule) in UC and then analyzed change patterns of relevant inflammatory factors, oxidative stress and T lymphocytes. The results are as follows.

## 2. Materials and methods

### 2.1. Demographic materials

A total of 90 patients with ulcerative colitis treated in Shunyi District Hospital of Beijing from June 2014 to January 2017 were selected and randomly divided into the observation group and the control group. The observation group consisted of 45 cases aged 23-51 years, including 21 males and 24 females. The control group consisted of 45 cases, including 19 males and 26 females, aged 22-54 years. There was no significant difference between the two groups ( $P>0.05$ ).

Inclusion criteria: (1) clinical symptoms, colonoscopy and laboratory examinations agree with the criteria in "Chinese inflammatory bowel disease diagnostic consensus" about active UC related diagnosis and treatment; (2) age: 18-60 years; (3) all the patients have signed the informed consent. Exclusion criteria: (1) severe symptoms (such as fulminant or severe ulcerative colitis); (2) complications: liver, kidney, hematopoietic system, endocrine system and other serious diseases and mental illness; (3) pregnancy or lactation; (4) Mesalazine or Bifidobacterium triple viable fungus allergy; (5) treated by other drugs that could influence the effects of UC treatment.

### 2.2. Treatment

The control group: patients were given the positive health education after admission, like strictly following the schedule and undergoing moderate exercise, reducing the acute period of enteral nutrition; and in remission stage, patients were instructed to have low-fat, low sugar and high protein diet, avoiding eating seafood, spicy, bitter and irritating food. At the same time Mesalazin Enteric-coated Tablets (sunflower Pharmaceutical Group (Jiamusi) Co. Ltd., Zhunzi H19980148) were given (1 g/time, 4 times/d, 1 consecutive months of treatment). The dosage will be 500 mg/ times, 3 times/d during stable stages. Besides, active treatments for complications were performed for 3 months.

Patients in the observation group were given Bifidobacterium triple viable (Peifeikang capsule, Shanghai Xinyi Pharmaceutical Co. Ltd., Zhunzi S10970105) as the adjuvant therapy (0.84 g/time, 2 times/d) for 3 months. Other treatments were the same as the control group.

Table 1.

The comparison for serum inflammatory factor levels ( $n=45$ ).

Group	Time	TNF- $\alpha$ (pg/mL)	CRP (mg/L)	IL-6 (pg/mL)	IL-10 (pg/mL)
Observation Group	Before	33.48 $\pm$ 3.42	81.64 $\pm$ 22.04	211.36 $\pm$ 47.83	28.01 $\pm$ 4.89
	After	15.98 $\pm$ 4.12 <sup>ab</sup>	21.52 $\pm$ 10.20 <sup>ab</sup>	72.17 $\pm$ 15.18 <sup>ab</sup>	70.21 $\pm$ 6.03 <sup>ab</sup>
Control Group	Before	32.86 $\pm$ 3.44	82.89 $\pm$ 23.02	207.83 $\pm$ 45.66	28.67 $\pm$ 4.97
	After	22.35 $\pm$ 3.67 <sup>a</sup>	43.02 $\pm$ 12.27 <sup>a</sup>	86.55 $\pm$ 17.26 <sup>a</sup>	56.48 $\pm$ 8.67 <sup>a</sup>

Comparison in the group before or after the treatment <sup>ab</sup> $P<0.05$ ; Comparison between the group before or after the treatment <sup>a</sup> $P<0.05$ .

Table 2.

The comparison for oxidative stress indicators ( $n=45$ ).

Group	Time	MDA (nmol/mL)	SOD (U/mL)
Observation Group	Before	8.51 $\pm$ 0.64	1.15 $\pm$ 0.05
	After	5.89 $\pm$ 0.56 <sup>ab</sup>	1.84 $\pm$ 0.06 <sup>ab</sup>
Control Group	Before	8.38 $\pm$ 0.72	1.16 $\pm$ 0.05
	After	6.75 $\pm$ 0.68 <sup>a</sup>	1.32 $\pm$ 0.05 <sup>a</sup>

Comparison in the group before or after the treatment <sup>ab</sup> $P<0.05$ ; Comparison between the group before or after the treatment <sup>a</sup> $P<0.05$ .

### 2.3. Observation indicators

(1) Fasting venous blood samples of all patients were collected before and after treatment for inflammation factors and oxidative stress indicators tests through enzyme linked immunosorbent assay (ELISA), including interleukin-6 (IL-6), interleukin -10 (IL-10), C reactive protein (CRP), tumor necrosis factor alpha (TNF-alpha), malondialdehyde (MDA) and superoxide dismutase (SOD), IL-6 IL-10, CRP, SOD, MDA. (Nanjing science and technology limited company, Reagent kit for MDA, SOD). TNF-alpha was tested by radioimmunoassay (Wuhan boster Biological Engineering Co., Ltd., Reagent kit for IL-10 IL-6 and TNF-alpha detection). (2) The comparison of T lymphocyte subsets changes before and after treatment in two groups, including CD3<sup>+</sup>, CD4<sup>+</sup>, CD8<sup>+</sup> and CD4<sup>+</sup>/CD8<sup>+</sup>. (Beckman Kurt flow cytometry (FCM) in the United States)

### 2.4 Statistical methods

SPSS 18.0 was used for the statistical analysis, measurement data was displayed as (Mean  $\pm$  SD), which was subject to normal distribution for t test.  $P<0.05$  was deemed as statistically significance.

## 3. Result

### 3.1. The comparison for serum inflammatory factor levels

After treatment, the levels of serum TNF-alpha, CRP and IL-6 in the observation group and the control group decreased significantly, and the level of IL-10 increased significantly ( $P<0.05$ ). After treatment, TNF-alpha, CRP, IL-6 alpha levels in the observation group were (72.17  $\pm$  15.18) pg/mL and (21.52  $\pm$  10.21) mg/L, 15.98  $\pm$  4.12 (pg/mL), which were significantly lower than those in the control group (86.55  $\pm$  17.26) pg/mL, (43.02  $\pm$  12.27) mg/L, (22.35  $\pm$  3.67) pg/mL, respectively ( $P<0.05$ ).

After treatment, the level of IL-10 in the observation group was (70.21  $\pm$  6.03) pg/mL, which was significantly higher than that in the control group (56.48  $\pm$  8.67) pg/mL ( $P<0.05$ ) (Table 1).

### 3.2 The comparison for oxidative stress indicators

After treatment, the level of MDA in the two groups was significantly lower ( $P<0.05$ ), but the level of SOD increased significantly ( $P<0.05$ ). After treatment, the level of MDA in

Table 3.

The comparison for immunoglobulin levels ( $n=45$ ).

Group	Time	CD3 <sup>+</sup> (%)	CD4 <sup>+</sup> (%)	CD8 <sup>+</sup> (%)	CD4 <sup>+</sup> /CD8 <sup>+</sup>
Observation Group	Before	51.12±6.23	33.92±3.98	22.02±2.21	1.68±0.41
	After	57.84±6.07 <sup>ab</sup>	36.78±4.32 <sup>ab</sup>	17.24±3.06 <sup>ab</sup>	1.92±0.29 <sup>ab</sup>
Control Group	Before	50.36±6.72	34.01±5.82	21.84±2.01	1.68±0.24
	After	54.93±6.87 <sup>a</sup>	35.42±5.27 <sup>a</sup>	19.01±2.62 <sup>a</sup>	1.89±0.12 <sup>a</sup>

Comparison in the group before or after the treatment <sup>a</sup> $P<0.05$ ; Comparison between the group before or after the treatment <sup>ab</sup> $P<0.05$ .

the observation group was ( $5.89 \pm 0.56$ ) nmol/mL, which was significantly lower than that in the control group ( $6.75 \pm 0.68$ ) nmol/mL. Moreover, the level of SOD in the observation group was ( $1.84 \pm 0.06$ ) U/mL, which was significantly higher than that in the control group ( $1.32 \pm 0.05$ ) U/mL ( $P<0.05$ ) (Table 2).

### 3.3 The comparison for immunoglobulin levels

After treatment, the levels of CD3<sup>+</sup>, CD4<sup>+</sup> and CD4<sup>+</sup>/CD8<sup>+</sup> in the observation group and the control group were significantly increased ( $P<0.05$ ), and the level of CD8<sup>+</sup> was significantly decreased ( $P<0.05$ ). After treatment, CD3<sup>+</sup>, CD4<sup>+</sup>, CD4<sup>+</sup>/CD8<sup>+</sup> levels in the observation group were ( $57.84 \pm 6.07$ )%, ( $36.78 \pm 4.32$ )%, ( $1.92 \pm 0.29$ ) respectively, which were significantly higher than those in the control group ( $54.93 \pm 6.87$ )%, ( $35.42 \pm 5.27$ )%, ( $1.89 \pm 0.12$ ) respectively.

CD8<sup>+</sup> level in the observation group was ( $17.24 \pm 3.06$ )%, which was significantly lower than that in the control group ( $19.01 \pm 2.62$ )% ( $P<0.05$ ). (Table 3)

## 4. Discussion

UC occurs frequently in all ages. It is one of the common diseases in digestive tracts. It has a long process and a high rate of canceration. The complication rates and recurrence rates are somewhat high, which imposes great harm to patients' bodies and minds[6,7]. Long term clinical study showed that patients with UC not only had diarrhea, abdominal pain, bleeding, but also experienced other gastrointestinal symptoms and even systemic symptoms, like fever, emaciation, anemia and hypoproteinemia. Severe symptoms are as follows: colonic polyp, intestinal bleeding, colorectal cancer, and skin lesions[8]. Timely and effective treatments are important in improving the prognosis. Mesalazine is commonly used, and Mesalazine is a kind of amino salicylic acid. Mesalazine can reduce the levels of inflammatory factors; moreover, it has small side effects and obvious curative effects, which help to promote the recovery of colonic mucosa of patients with UC. Besides, Mesalazine can improve the abdominal pain, diarrhea and other symptoms of sepsis in UC patients[9]. The study found that stools from patients in the active stage, had lower proportions of Lactobacillus and other anaerobic bacteria than normal people; and in the recovery stage, proportions of Lactobacillus and other anaerobic bacteria increased significantly, indicating that intestinal microflora disorders may play a role in the initiation and progression of UC[10]. Bifid Triple Viable Capsules, which consists of Bifidobacterium, Enterococcus and Lactobacillus acidophilus, can improve the activity of macrophages, decrease the level of tumor necrosis factor, and improve intestinal microflora environment to treat UC[11].

It is reported that the pathogenesis of inflammatory diseases will release a large amount of oxygen free radicals, of which the activation of inflammatory mediators is the main cause of inflammatory disease; inflammatory factors maintained a high level in active UC patients and is the key factor for complications and systemic symptoms; at the same time, a significant reduction of

immune function in UC patients will result in a higher incidence of infectious diseases[12,13]. Tumor necrosis factor (TNF- $\alpha$ ) is an important inflammatory mediator, mainly produced by activated monocytes and macrophages[16]. TNF- $\alpha$  plays a leading role in inflammatory factors. TNF- $\alpha$  directly damages the intestinal mucosa and causes abdominal pain, diarrhea and other symptoms in UC patients[14,15]. IL-10 can inhibit inflammatory factors and it is one of the important anti-inflammatory factors. Because the IL-10 could inhibit the chemotaxis of macrophage and neutrophil, which would reduce macrophage and neutrophil aggregation in the site of inflammation, thus reducing the level of IL-10 would lead to the decrease of inflammatory factors[17]. In our study, the levels of TNF- $\alpha$ , CRP and IL-6 in the two groups decreased, and the level of IL-10 increased ( $P<0.05$ ), and the change in the observation group was significantly higher than that in the control group ( $P<0.05$ ). The results showed that the two groups had significant therapeutic effects (the control group with Mesalazine only, and the observation group with Mesalazine and Bifidobacterium triple viable treatment) to reduce inflammation in UC patients. And the therapeutic effects of the observation group were better than the control group. The observation of changes in T cell subsets indicated that blood CD3<sup>+</sup>, CD4<sup>+</sup> and CD4<sup>+</sup>/CD8<sup>+</sup> levels were significantly increased in the two groups after treatment, but CD8<sup>+</sup> levels were significantly decreased ( $P<0.05$ ). Besides the change in the observation group was significantly higher than the control group ( $P<0.05$ ). The reasons might be that triple viable Bifidobacterium could increase the phagocytosis of macrophages in the gastrointestinal tracts and stimulate the secretion of large amounts of IgA, IgG to prolong the survival of T cells, and thus mediating phagocytosis and inhibiting the release of TNF- $\alpha$ , IL-6, CRP, thereby increasing the intestinal mucosal cell immune ability to alleviate inflammation in UC patients[20]. At the same time, the activity of probiotic Bifidobacterium triple viable could be multiplied in the intestinal tract, which increased the beneficial bacteria ratio in the colorectal to inhibit the proliferation of pathogenic bacteria and reduce adverse effects of pathogens. This process would alleviate the inflammatory reaction caused by pathogenic bacteria with certain benefits[11].

Because of the increase in the level of oxygen free radicals, the stimulation of peroxidation is also an important factor for UC[23]. MDA is one of the important products of membrane lipid peroxidation. Oxygen free radicals triggered lipid peroxidation for polyunsaturated fatty acids on the cell membrane to form MDA[24]. The higher the MDA level is, the more serious the tissue damage is. Studies[25] showed that serum levels of MDA were significantly higher in UC patients than healthy controls after excluding other confounding factors, suggesting that intestinal mucosal lesions might be associated with elevated MDA levels. SOD is an important antioxidant enzyme in organisms that can scavenge oxygen free radicals and oxygen free radicals in vivo to prevent damages to the body. By detecting of the level of SOD patients, we can indirectly understand the injury status of oxygen free radical on the intestinal mucosa; and the reduced activity of SOD is not advantageous to the control of the disease[26]. In this study, the levels of MDA in two groups after treatment were significantly decreased, SOD levels were significantly increased ( $P<0.05$ ); the MDA level in the observation

group after treatment was significantly lower than that in the control group, and the level of SOD was significantly higher than that in the control group ( $P < 0.05$ ). The results showed that the drugs administered by both group strengthened the ability to scavenge oxygen free radicals to improve the level of oxidative stress, reducing the damage to the intestinal mucosa by oxygen free radicals; and curative effect in the observation group is more significant than the control group. Our results agreed with He Jia Yu's[9] and Han Jinli's studies[18]. The reason might be that triple viable Bifidobacterium is a kind of probiotics used in the treatment of digestive tract diseases in recent years. It shows the resistance of digestive enzyme digestion, adhesion and colonization in the intestinal mucosa. Besides it can restore the balance of intestinal flora to protect and restore the damaged intestinal mucosa[19]. In addition, Bifidobacterium, Lactobacillus acidophilus and Enterococcus faecalis played important roles in intestinal mucosal surface adhesion to promote the secretion of mucus in intestinal mucosal epithelial cells to form a protective barrier. Finally, it can promote wound recovery in UC to delay the recurrence[21,22]. The recovery of intestinal mucosal wound can reduce the release of oxygen free radicals, regulate the redox balance and alleviate oxidative stress reaction.

In conclusion, Bifidobacterium triple viable treatment can yield adjuvant therapy effects to improve clinical symptoms, control the inflammatory factors' levels, protect the intestinal mucosa, and improve the antioxidant capacity in UC patients in addition to the common treatments. Thus, it is recommend to be applied in clinical practices.

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