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Review Article

Meta-analysis of the safety and efficacy of probiotics in the treatment of Crohn's disease

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Abstract: *Background:* The aim of this study was to conduct a systematic evaluation of the safety and efficacy of probiotics in patients with Crohn's disease. *Methods:* A systematic literature search of PubMed, Cochrane Library, Embase, CNKI, VIP, and Wanfang databases limited to January 2005 to March 2017 was conducted. We used terms including 'Crohn's Disease' or 'inflammatory bowel disease', and 'probiotics'. Eligible studies were all randomized controlled trials using probiotic agents as the treatment and a placebo as the control. Extracted data were analyzed with RevMan (version 5.1). *Results:* A total of 9 randomized controlled studies were included, including 358 probiotics-and 355 placebo-treated patients; all studies were of high quality. There were no significant differences between probiotics and placebo in the induced remission rate (RR=0.97; 95% CI=0.70-1.35; P=0.87; I^2=0), relapse rate (RR=1.01; 95% CI=0.78-1.32; P=0.93; I^2=0), recurrence time (SMD=-0.04; 95% CI=-0.65-0.56; P=0.89; I^2=0) or the incidence of adverse reactions (RR=0.83; 95% CI=0.62-1.11; P=0.21; I^2=0). *Conclusions:* Probiotics do not show a therapeutic advantage in the maintenance of remission or remission of Crohn's disease during the active period compared to placebos. Large samples and high-quality clinical trials are required to further determine the efficacy of probiotics in the induction and maintained remission of Crohn's disease.

Keywords: Meta-analysis, probiotics, Crohn's disease

Introduction

Crohn's disease (CD) is a chronic idiopathic inflammatory bowel disease condition with unknown etiology that is characterized by skip lesions and transmural inflammation that can affect the entire gastrointestinal tract from the mouth to the anus [1]. The lesions are segmental and can be involved in any part of the digestive tract; lesions appear to be most common in the terminal ileum [1]. CD is more common in North America and Western Europe, with an annual incidence of approximately 0.1 to 0.2‰; the incidence is rising in Asia and South America [2, 3]. In recent years, the incidence of CD showed a sustained growth trend in China [4]. CD can be caused by environmental factors [3], genetic susceptibility such as the NOD2 mutation [5], interleukin (IL)-23 receptor mutation [6], immune regulation [7], smoking [8], or other factors. Currently, no effective treatment method for CD is known.

The main purpose of CD treatment is to control disease activity, to maintain remission and to prevent complications. Currently, the clinical application of CD treatment drugs are mainly amino salicylic acid preparations, glucocorticoids, immunosuppressive agents, probiotics, Chinese herbal medicine, etc. [1]. Probiotics colonize in the human intestinal tract by competitive exclusion with other bacteria and adjustment of the micro-ecological imbalance to maintain the stability of the host's intestinal micro-ecological balance, thus preventing and treaing diarrhea [9]. In addition, part of their metabolites can also stimulate the body's non-specific immune function and enhance human immunty [9]. Some probiotics have been shown to have anti-inflammatory effects and promote the maintenance of the gut intestinal barrier *in vitro* and in murine models of IBD [9]. In addition, probiotics can regulate intestinal flora, playing a synergistic role in maintaining CD remission [10]. In this paper, the meta-analysis method

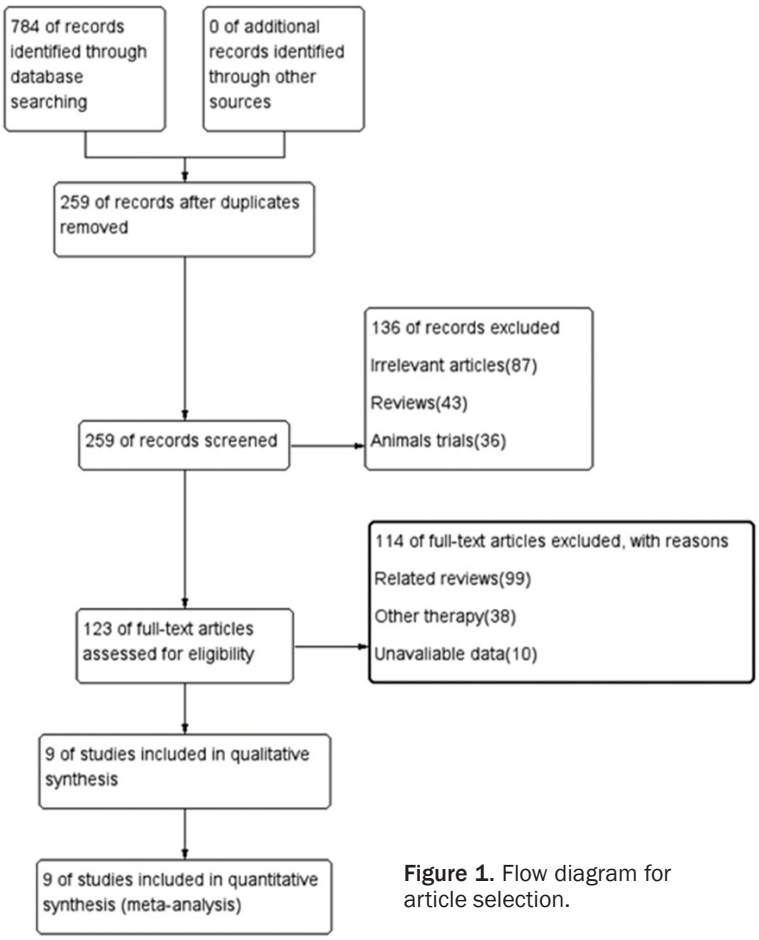

Figure 1. Flow diagram for article selection.

was used to evaluate the efficacy and safety of probiotics in patients with Crohn's disease.

Materials and methods

Data sources and search strategy

All analyses were performed according to PRISMA guidelines [11] and the Cochrane handbook for systematic reviews of interventions. A systematic literature search of PubMed, Cochrane Library, Embase, CNKI, VIP, and Wanfang databases limited to January 2005 to March 2017 was conducted. We used terms including 'Crohn's Disease' or 'inflammatory bowel disease', and 'probiotics'. Eligible studies were randomized controlled trials that used probiotic agents as the treatment and a placebo as the control. Extracted data were analyzed with RevMan (version 5.1). All articles that were selected included only human studies.

Study selection

To be eligible for inclusion in this article, publications had the following inclusion criteria: Patients diagnosed with Crohn's disease by colonoscopy and biopsy pathology and who were induced and/or maintained remission; Test group was treated with probiotics (Bifidobacterium, VSL#3, *Escherichia coli* EcN, synbiotics, or lactic acid bacteria) combined with or without conventional treatment; Measurable outcome indicators were included, such as induction of remission, clinical relapse rate, incidence of adverse events, etc.; Study design was randomized controlled trial (RCT) with newly published data on repeated studies; Available in full text (detail information). Potentially relevant publications were read in full and reviewed independently by two authors.

Studies were excluded if the article was a review or a nonrandom controlled trial or the data were in an unavailable format or the research subjects had serious complications or other intestinal diseases.

Data extraction

Three independent raters examined each retrieved article. The results were compared between raters, and any disagreements regarding inclusion were settled by consensus. The following information was abstracted and tabulated from each paper: author and year of publication, average age of the patients, and quality data of each clinical study (randomization, allocation concealment, blinding, bias, etc.). We used the induced remission rate and recurren ce rate as the main outcome index, the recurrence time as a secondary indicator, and the safety outcome indicators that involved the incidence of adverse reactions.

Quality evaluation

Each individual study was carefully evaluated for strengths, limitations, design, methodology, outcome dissemination, and interpretation. A formal quality assessment was made by using the Cochrane Collaboration Risk of Bias Asse-

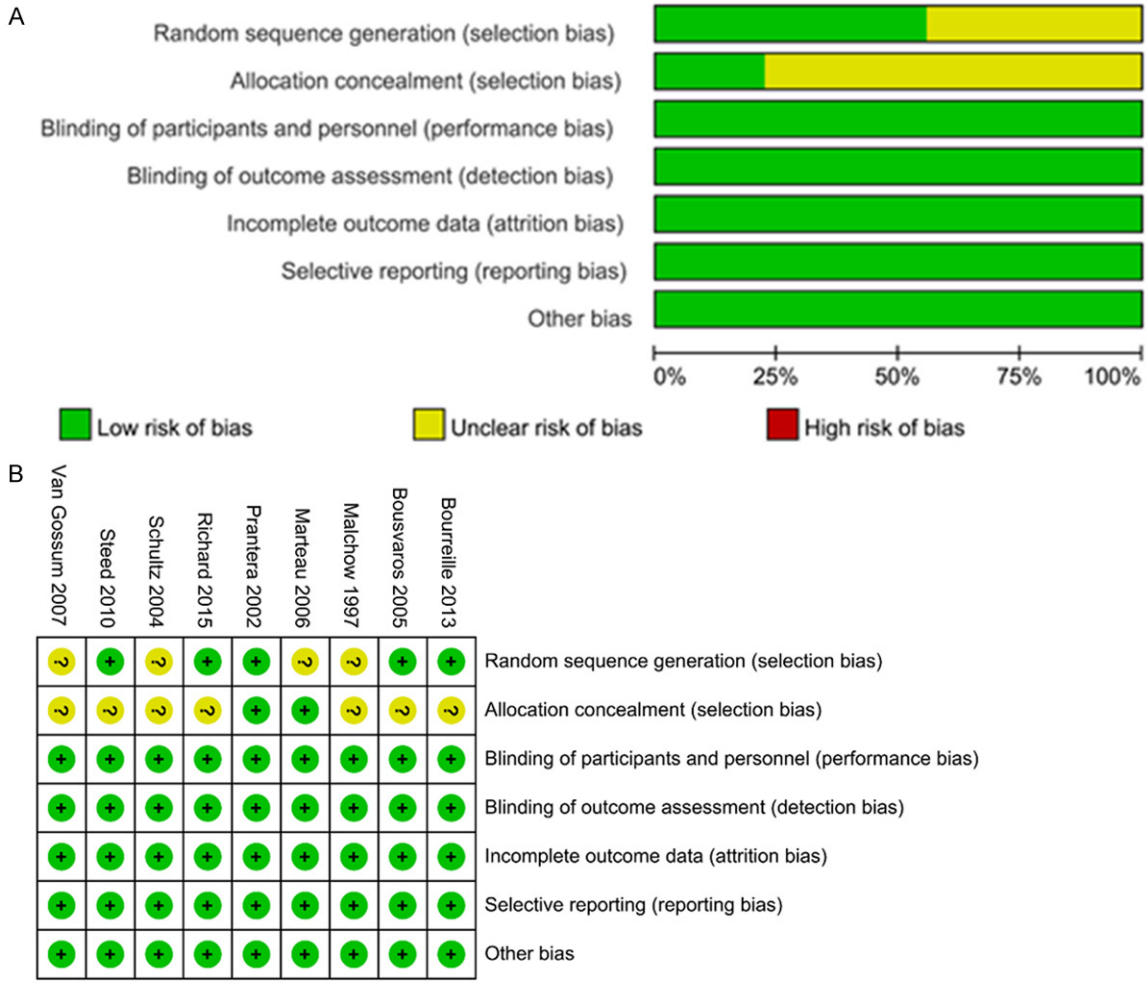

Figure 2. A. Quality evaluation (1). B. Quality evaluation (2).

ssment Tool for the assessment of RCTs, which examines each trial's internal validity and possible bias under "Low" or "High" measures without attempting numerical scores [12].

Statistical analyses

Induced remission rate, recurrence rate, recurrence time, and adverse effects were combined with a random effects meta-analyses in Review Manager (Version 5.1, The Cochrane Collaboration, 2011). Any differences we observed between the two groups were expressed as RR with its 95% CI. Statistical heterogeneity between trials was evaluated by the Cochran chi-square test and was considered to be present when $P \leq 0.1$. In case of the presence of statistical heterogeneity, a random-effect model was used for the analysis. In the absence of statistically significant heterogeneity, only the RR by the fixed-effect model is given. Sensitivity analyses were conducted to ascertain the primary origin of the heterogeneity. The risk of publication bias was assessed using Begger's tests.

Results

A total of 784 articles were retrieved from the Chinese and English databases, including 547 articles in English and 237 Chinese publications. After a check for duplicates and the removal of reviews, 259 publications remained. Of these, the titles and abstracts were screened, and 123 articles were read in full-text. Finally, only nine papers [13-21] were included in the meta-analysis. **Figure 1** shows the study selection procedure.

Results of literature quality evaluation

The quality of the included studies, in general, ranged from medium to high when weighed with the Cochrane Collaboration Risk of Bias Assessment Tool (**Figure 2A, 2B**).

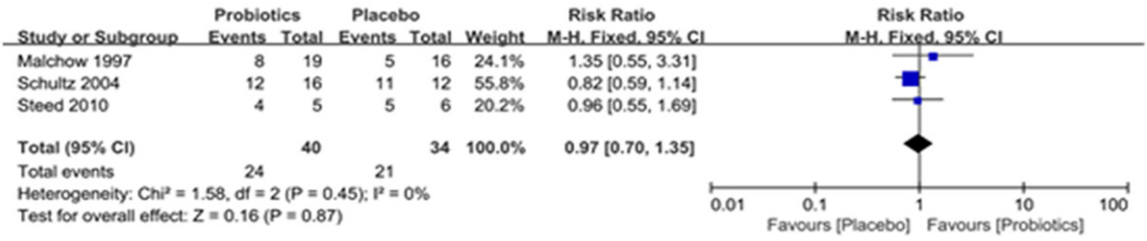

Figure 3. Forest graph showing the difference of induced remission rate between probiotics and placebo. Boxes represent the risk ratio and the line across each box represents 95% CIs. Diamond represents overall effect size of the meta-analysis.

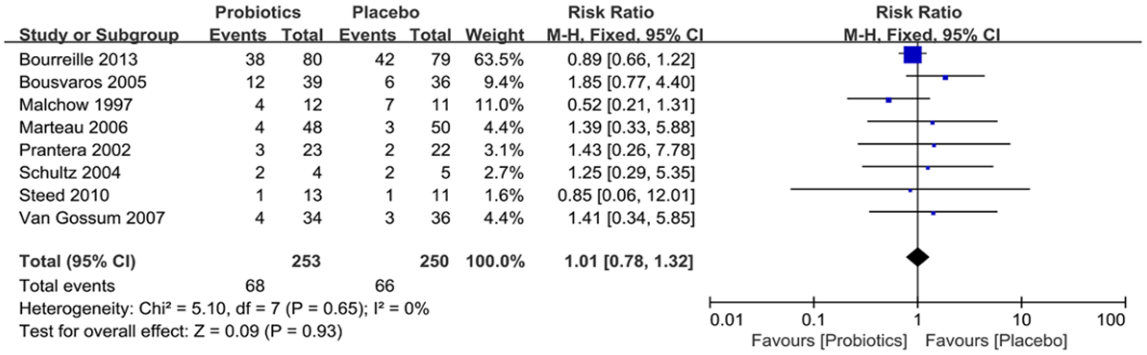

Figure 4. Forest graph showing the difference of recurrence rate between probiotics and placebo. Boxes represent the risk ratio and the line across each box represents 95% CIs. Diamond represents overall effect size of the meta-analysis.

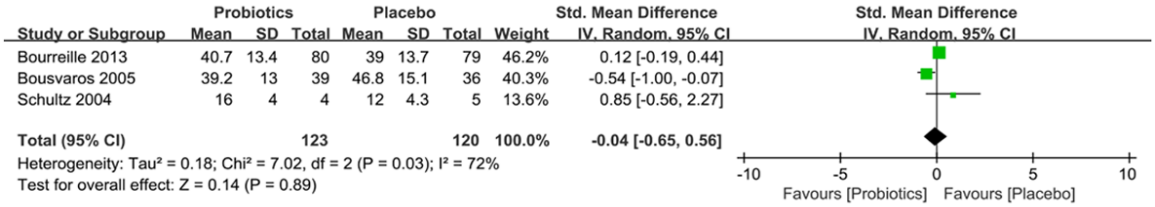

Figure 5. Forest graph showing the difference of recurrence time between probiotics and placebo. Boxes represent the standard mean difference and the line across each box represents 95% CIs. Diamond represents overall effect size of the meta-analysis.

Induced remission rate

A total of three studies reported the outcome of an induced remission rate, with 40 cases in the probiotics group and 34 cases in the placebo group. Meta-analysis showed no significant difference in the induced remission rate between probiotics and placebo (RR=0.97; 95% CI=0.70-1.35; P=0.87; I^2=0) (**Figure 3**).

Recurrence rate

A total of eight studies reported the outcome of the recurrence rate, with 253 cases in the probiotics group and 250 cases in the placebo group. Meta-analysis showed no significant difference in the recurrence rate between probiotics and placebo (RR=1.01; 95% CI=0.78-1.32; P=0.93; I^2=0) (**Figure 4**).

Recurrence time

A total of three studies reported the outcome of the recurrence time, including 123 cases in the probiotics group and 120 cases in the placebo group. Meta-analysis showed no significant difference in recurrence time between probiotics and placebo (SMD=-0.04; 95% CI=-0.65-0.56; P=0.89; I^2=0) (**Figure 5**).

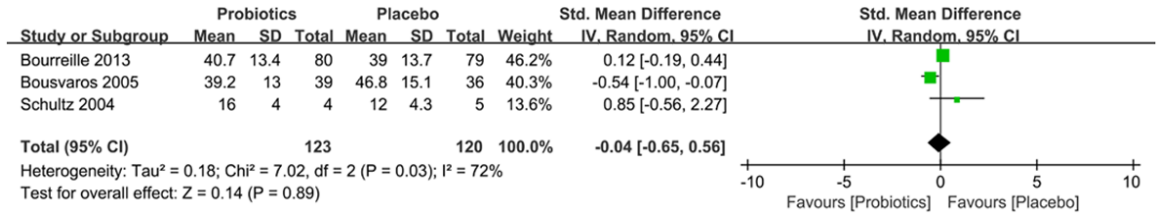

Figure 6. Forest graph showing the difference of adverse effects between probiotics and placebo. Boxes represent the risk ratio and the line across each box represents 95% CIs. Diamond represents overall effect size of the meta-analysis.

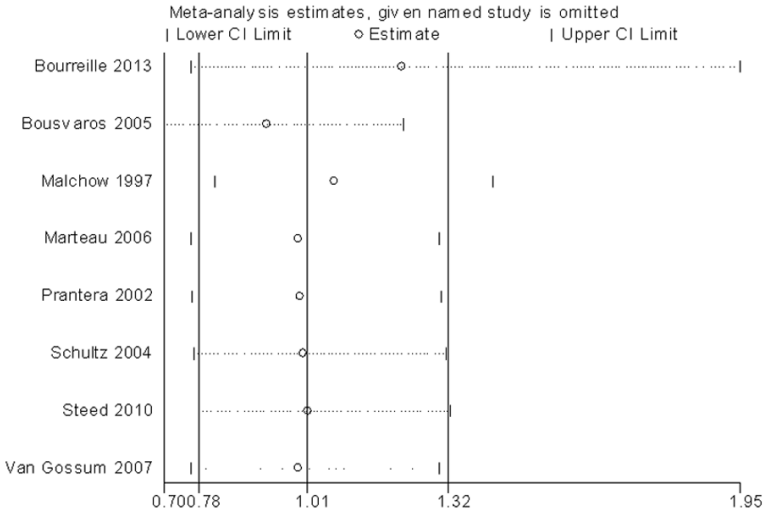

Figure 7. Funnel plot of sensitivity analysis.

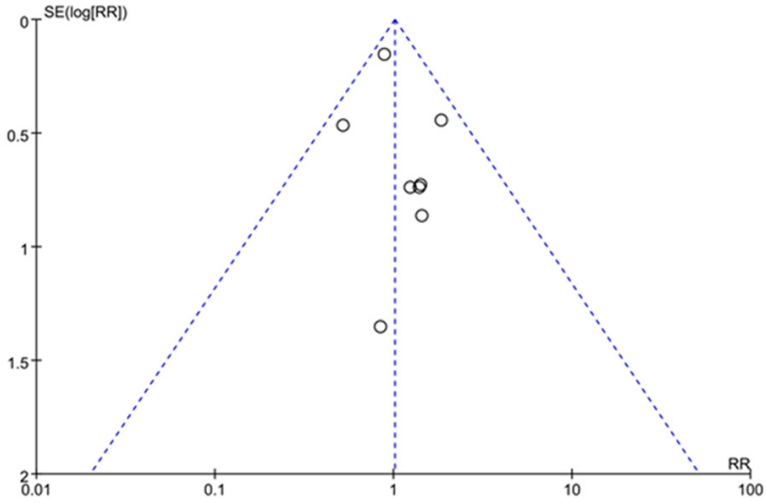

Figure 8. Funnel plot of publication bias.

Adverse effects

A total of four studies reported the outcome of the recurrence time, including 160 cases in the probiotics group and 165 cases in the placebo group. Meta-analysis showed no significant difference in the incidence of adverse effects between probiotics and placebo (RR=0.83; 95% CI=0.62-1.11; P=0.21; I^2=0) (**Figure 6**).

Sensitivity analysis and publication biases

Sensitivity analyses were conducted to ascertain the primary origin of the heterogeneity. For all the included publications, no point estimate of its "omitted" analysis was outside the confidence interval of the "combined" analysis. Its "omitted" meta-analytic estimate differed significantly relative to the "combined" analysis, suggesting that the results of this meta-analysis were stable (**Figure 7**).

A significant risk of publication bias was not detected, as demonstrated by funnel plots (**Figure 8**). The results of Begger's test showed no evidence of publication bias (P>0.05, **Table 1**).

Discussion

Crohn's disease is a chronic, recurrent disease. Patients experience episodes and remission alternately. The purpose of treatment for Crohn's disease is to induce remission, and the primary treatment objective for remission is to avoid recurrence. This study systematically

Table 1. Begger's test results for publication bias

Endpoints	*P* value
Recurrence rate	0.711
Induced remission rate	1.000
Adverse effects	1.000

evaluated the efficacy of probiotics in Crohn's disease. We included nine RCTs related to probiotic-induced remission and Crohn's disease maintenance therapy in this paper. Meta-analysis showed that probiotics did not have a significant effect on CD induction and maintenance remission, and there was no significant difference in adverse reactions when compared with the placebo. In recent years, there have been clinical trials of probiotics in the treatment of Crohn's disease, but the sample sizes are small, so a comprehensive meta-analysis to analyze different clinical research results is required. In the past, meta-analysis was used to study the efficacy of probiotics in the treatment of inflammatory bowel disease. The study showed that compared with the placebo, probiotics significantly improved the clinical remission rate of active ulcerative colitis [22, 23]. This study is the first meta-analysis focusing on Crohn's disease. A recent meta-analysis published by Mahboube *et al.* [24] showed that there was no significant difference in probiotic use in patients with Crohn's disease compared with the placebo; this was consistent with our findings. Compared with this meta-analysis, our meta-analysis included nine clinical studies and made a detailed quality assessment of the included studies; the quality assessment showed that the included studies were of medium or high quality. In addition, we compared the recurrence time after treatment, and the results showed that there was no significant difference in recurrence time between the probiotics group and the control group. We also analyzed the sensitivity of the meta-analysis and published the biased test. The results showed that the stability of this study was good, and no publication bias was found.

The incidence of adverse effects of probiotics was lower, the same as that of the present study. The main adverse effects of probiotics were bloating and diarrhea. The results of this study show that the incidence of adverse events in the probiotics group has not been increased compared with that in the placebo group. Therefore, probiotics can be used safely to treat Crohn's disease.

There were some limitations in this study. Because of the limited number of clinical trials, the small sample sizes, and the different types of probiotics in clinical studies, a certain degree of heterogeneity may have been caused. Thus, a more accurate and credible conclusion requires more rigorous, larger multicenter randomized controlled trials. In the future clinical study of probiotics in Crohn's disease, it should be noted that RCT studies should describe the randomization method and random program concealment, increase the sample size, and unify the probiotics (type, dosage, usage, course of treatment, etc.) in each clinical study.

In conclusion, probiotics do not show a therapeutic advantage in the maintenance of remission or remission of Crohn's disease during the active period. There is still a need for large samples of high-quality clinical trials to further determine the efficacy of probiotic agents in the induction and maintenance of Crohn's disease.

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Disclosure of conflict of interest

None.

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References

[1] Feuerstein JD, Cheifetz AS. Crohn disease: epidemiology, diagnosis, and management. Mayo Clin Proc 2017; 92: 1088-1103.

[2] Ng SC, Bernstein CN, Vatn MH, Lakatos PL, Loftus EV Jr, Tysk C, O'Morain C, Moum B, Colombel JF; Epidemiology and Natural History Task Force of the International Organization of Inflammatory Bowel Disease (IOIBD). Geographical variability and environmental risk factors in inflammatory bowel disease. Gut 2013; 62: 630-49.

[3] Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology 2004; 126: 1504-17.
[4] Qi Z, Ying C. Micro ecological therapy and inflammatory bowel disease. Chinese Journal of Practical Internal Medicine 2006: 974-976.
[5] Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nuñez G, Cho JH. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 2001; 411: 603-6.
[6] Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, Steinhart AH, Abraham C, Regueiro M, Griffiths A, Dassopoulos T, Bitton A, Yang H, Targan S, Datta LW, Kistner EO, Schumm LP, Lee AT, Gregersen PK, Barmada MM, Rotter JI, Nicolae DL, Cho JH. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science 2006; 314: 1461-3.
[7] Bouma G, Strober W. The immunological and genetic basis of inflammatory bowel disease. Nat Rev Immunol 2003; 3: 521-33.
[8] Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc 2006; 81: 1462-71.
[9] Gareau MG, Sherman PM, Walker WA. Probiotics and the gut microbiota in intestinal health and disease. Nat Rev Gastroenterol Hepatol 2010; 7: 503-14.
[10] Zengguo M, Yijing C. Advances in drug treatment for Crohn's disease. Chinese Journal of Trauma and Disability Medicine 2013; 434-435.
[11] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009; 62: e1-34.
[12] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.
[13] Bourreille A, Cadiot G, Le Dreau G, Laharie D, Beaugerie L, Dupas JL, Marteau P, Rampal P, Moyse D, Saleh A, Le Guern ME, Galmiche JP; FLORABEST Study Group. Saccharomyces boulardii does not prevent relapse of Crohn's disease. Clin Gastroenterol Hepatol 2013; 11: 982-7.
[14] Bousvaros A, Guandalini S, Baldassano RN, Botelho C, Evans J, Ferry GD, Goldin B, Hartigan L, Kugathasan S, Levy J, Murray KF, Oliva-Hemker M, Rosh JR, Tolia V, Zholudev A, Vanderhoof JA, Hibberd PL. A randomized, double-blind trial of Lactobacillus GG versus placebo in addition to standard maintenance therapy for children with Crohn's disease. Inflamm Bowel Dis 2005; 11: 833-9.
[15] Malchow HA. Crohn's disease and Escherichia coli. A new approach in therapy to maintain remission of colonic Crohn's disease? J Clin Gastroenterol 1997; 25: 653-8.
[16] Marteau P, Lémann M, Seksik P, Laharie D, Colombel JF, Bouhnik Y, Cadiot G, Soulé JC, Bourreille A, Metman E, Lerebours E, Carbonnel F, Dupas JL, Veyrac M, Coffin B, Moreau J, Abitbol V, Blum-Sperisen S, Mary JY. Ineffectiveness of lactobacillus johnsonii LA1 for prophylaxis of postoperative recurrence in Crohn's disease: a randomised, double blind, placebo controlled GETAID trial. Gut 2006; 55: 842-7.
[17] Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. Gut 2002; 51: 405-9.
[18] Fedorak RN, Feagan BG, Hotte N, Leddin D, Dieleman LA, Petrunia DM, Enns R, Bitton A, Chiba N, Paré P, Rostom A, Marshall J, Depew W, Bernstein CN, Panaccione R, Aumais G, Steinhart AH, Cockeram A, Bailey RJ, Gionchetti P, Wong C, Madsen K. The probiotic VSL#3 has anti-inflammatory effects and could reduce endoscopic recurrence after surgery for Crohn's disease. Clin Gastroenterol Hepatol 2015; 13: 928-35, e2.
[19] Schultz M, Timmer A, Herfarth HH, Sartor RB, Vanderhoof JA, Rath HC. Lactobacillus GG in inducing and maintaining remission of Crohn's disease. BMC Gastroenterol 2004; 4: 5.
[20] Steed H, Macfarlane GT, Blackett KL, Bahrami B, Reynolds N, Walsh SV, Cummings JH, Macfarlane S. Clinical trial: the microbiological and immunological effects of synbiotic consumption-a randomized double-blind placebo-controlled study in active Crohn's disease. Aliment Pharmacol Ther 2010; 32: 872-83.
[21] Van Gossum A, Dewit O, Louis E, de Hertogh G, Baert F, Fontaine F, DeVos M, Enslen M, Paintin M, Franchimont D. Multicenter randomized-controlled clinical trial of probiotics (Lactobacillus johnsonii, LA1) on early endoscopic recurrence of Crohn's disease after lleo-caecal resection. Inflamm Bowel Dis 2007; 13: 135-42.
[22] Shaohui T, Shufen F, Yanfang Y. Meta-analysis of the effect of probiotics on induced remission and maintenance of ulcerative colitis.

Medical Journal of Chinese People's Liberation Army 2010; 521-525.

[23] Jun S, Zhihua R, Jinlu T, Shundong X. Effect of probiotics on remission, relapse and pouchitis in inflammatory bowel disease: meta-analysis. Chinese Journal of Gastroenterology and Hepatology 2008; 114-118.

[24] Ganji-Arjenaki M, Rafieian-Kopaei M. Probiotics are a good choice in remission of inflammatory bowel diseases: a meta analysis and systematic review. J Cell Physiol 2018; 233: 2091-2103.