Systematic Review and Meta-Analysis

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Efficacy and safety of bifid triple viable plus aminosalicylic acid for the treatment of ulcerative colitis

A systematic review and meta-analysis

Mu-yuan Chen, MM[a], Zhen-wen Qiu, PhD[a], Hong-mei Tang, PhD[a], Kun-hai Zhuang, PhD[a], Qing-qun Cai, MM[a], Xin-lin Chen, PhD[b,*], Hui-biao Li, MM[a,*]

Abstract

Objective: Ulcerative colitis (UC), one of the most stubborn diseases, is mainly treated by aminosalicylic acid (ASA). However, the side effects of ASA include vomiting, nausea, rash, diarrhea, headache, etc, which seriously affect life-quality of UC patients. Probiotics such as bifid triple viable (BTV) could reduce drug-induced adverse reactions and has a good clinical effect on UC. Therefore, we aimed to evaluate the clinical efficacy and safety of BTV plus ASA in treating UC.

Methods: PubMed, Cochrane Library, Embase, Chinese Biomedical Literature Database, Chinese Scientific Journal Database, Chinese National Knowledge Infrastructure, and Wanfang databases were searched from the inception dates to October 12, 2018. Randomized controlled trials (RCTs) were included by comparing BTV plus ASA programs with ASA alone in patients with UC. Methodological quality was assessed by 2 independent researchers according to the inclusion criteria and exclusion criteria. Meta-analysis was performed by using the Review Manager 5.3 Software. Risk ratios (RRs), 95% confidence interval (CI), and standardized mean difference were calculated.

Results: Sixty RCTs involving 4954 participants were selected for final review. Compared with ASA, BTV plus ASA significantly improved the clinical effect rate [RR = 1.23, 95% CI (1.20, 1.26), $P < .00001$]; reduced the relapse rate [RR = 0.34, 95% CI (0.18, 0.62), $P = .0005$]; and adverse effect rate [RR = 0.66, 95% CI (0.53, 0.82), $P = .0002$]. Compared with the controls, levels of tumor necrosis factor-α, interleukin-6 (IL-6), IL-8, C-reactive protein (CRP), hypersensitive CRP, erythrocyte sedimentation rate, and malondialdehyde were reduced; levels of IL-10, CD3+, CD4+, and superoxide dismutase were increased in BTV plus ASA group.

Conclusions: BTV plus ASA has positive therapeutic effects on UC, and it might be a safe way to treat UC. However, comprehensive clinical trials are needed to obtain high level of clinical evidence.

Abbreviations: 5-ASA = mesalazine, ANOVA = analysis of variance, ASA = aminosalicylic acid, bid = bis in die, BTV = bifid triple viable, CI = confidence interval, CRP = C-reactive protein, DAI = Disease Activity Index, ESR = erythrocyte sedimentation rate, Hs-CRP = hypersensitive C-reactive protein, IL-6 = interleukin-6, MDA = malondialdehyde, OSLS = olsalazine, po = peros, RCT = randomized controlled trial, RR = risk ratio, SASP = sulfasalazine, SMD = standardized mean difference, SOD = superoxide dismutase, tid = ter in die, TNF-α = tumor necrosis factor-α, UC = ulcerative colitis.

Keywords: aminosalicylic acid, bifid triple viable, meta-analysis, ulcerative colitis

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MYC, ZWQ, and HMT equally contributed to this study.

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[a] The First Affiliated Hospital, [b] School of Basic Medical Science, Guangzhou University of Chinese Medicine, Guangdong, China.

[*] Correspondence: Xin-lin Chen, School of Basic Medical Science, Guangzhou University of Chinese Medicine, Guangzhou 510000, Guangdong, China (e-mail: chenxlsums@126.com); Hui-biao Li, The First Affiliated Hospital, Guangzhou University of Chinese Medicine, Guangzhou 510405, Guangdong, China (e-mail: gzzyydx2011@163.com).

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1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of colonic mucosa. It is caused by a loss of homeostasis between intestinal immune system and gut microbiota in genetically predisposed individuals.[1] Symptoms of UC include abdominal pain, rectal bleeding, reduced stool consistency, increased stool frequency, and urgency of bowel movements.[2] Patients with UC have a high risk to get colorectal cancer.[3]

UC is associated with industrialization. As shown in epidemiological studies, incidence rates of UC vary considerably, ranging from 8.8 to 23.14 per 100,000 in North America, 0.97 to 57.9 per 100,000 in Europe, 0.19 to 6.76 per 100,000 in South America, and 0.15 to 6.5 per 100,000 in Asia.[4] Hence, the rates of UC incidence were obviously lower in developing area than the rates in developed countries. The rate of UC incidence in Asia is, however, increasing dramatically with industrialized development.[5] In urbanized areas, large-scale use of antibiotics in medicine and agriculture is common. Changes in diet and their impact on intestinal microflora during urbanization, reduced intake of carbohydrates (including natural fibers), and increased consumption of animal proteins, fats, and food additives, such as emulsifiers and artificial sweeteners, all of which can lead to a decrease in gut microbial diversity. Exposure to air pollution, which coincides with urbanization, has been shown to increase susceptibility to UC through changes in intestinal microflora. Therefore, diet, socioeconomic status, changes in hygiene status, early-life microbiota exposure, pollution, and other environmental factors have long-term effects on the human gut microbiota and influence tolerance of the host to environmental exposures, which may increase the risk of UC during urbanization.[6]

It has been largely accepted that aminosalicylic acids (ASAs) are the first-line pharmacotherapy for the treatment of UC. Adverse events caused by ASA, however, included pancreatitis, hepatotoxicity, inflammatory reactions, sexual dysfunction, cardiotoxicity, nephropathies, respiratory symptoms, and musculoskeletal complaints.[7] Patients taking ASA should be monitored for the development of new-onset organ dysfunction and UC deterioration.[7]

Bifid triple viable (BTV) has several commercial forms as capsules/powder (Bifico, Shanghai Sine Pharmaceutical, China), and enteric-coated capsules (Bifido, Jincheng Health Pharmaceutical, China). Bifico and Bifido were approved as over-the-counter drugs by State Food and Drug Administration in China, which consist of *Bifidobacterium*, *Lactobacillus*, and *Enterococcus faecalis*. This probiotic combination is effective in ameliorating diarrhea induced by intestinal flora disturbance or enteritis.[8] Pharmacological studies had shown that Bifico, given orally, could restore body weight, colon weight, and colon length in mice; alleviate intestinal inflammations; upregulate the level of interleukin-2 (IL-2), IL-4, and IL-10 in colonic tissues; enhance the expression of Treg cells such as $CD4^+$, $CD25^+$, and $Foxp3^+$ in mesenteric lymph nodes; downregulate proinflammatory factors such as tumor necrosis factor-α (TNF-α) and Interferon-γ; and ameliorate the amount of beneficial flora and harmful flora such as *Lactobacillus* and *Escherichia coli*.[8–10] Furthermore, Bifico can improve colitis-associated cancer in mice by intervening with the possible link between *Mucispirillum*, *Lactobacillus*, *Desulfovibrio*, *Odoribacter*, and CXCR2 signaling.[10]

In recent years, more and more attention has been paid to the application of BTV plus ASA in the treatment of UC.[11–19] Clinical meta-analysis had demonstrated that, compared to mesalazine administration, mesalazine combined with bifico could increase the total effective rate of UC; raise IL-10 and superoxide dismutase (SOD) levels; restrain TNF-α, IL-8, C-reactive protein (CRP), and malondialdehyde (MDA) levels; and attenuate the clinical symptom score, endoscopic score, relapse rate, and adverse effects.[20–22] Published meta-analysis literatures of bifico,[20–22] however, had incomplete data, error data, or included with nonrandomized controlled trials (RCTs), or made no adjudgment of recognized diagnostic criteria. To provide more evidence-based advising for clinical protocols making, a meta-analysis of RCTs of BTV plus ASA program versus ASA program in the treatment of UC was conducted to assess its efficacy and safety.

2. Methods

2.1. Selection strategy

Seven major electronic databases, including PubMed, Embase, Cochrane Library, the Chinese National Knowledge Infrastructure, the Chinese Biomedical Literature Database, the Chinese Scientific Journal Database, and the Wanfang database were searched from inception to October 12, 2018, by 2 investigators (MC and ZQ) independently.

The retrieval strategy for subject words or free words was as follows: ("lived combined *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* capsules" OR "bifid triple viable" OR "bacillus bifidus trigeminy viable-organism" OR "triple viable bifidobacterium" OR "bifidobacterium lactobacillus and enterococcus" OR "Bifico" OR "Bifido" OR "Peifeikang" OR "Beifeida") AND ("inflammatory bowel disease" OR "ulcerative colitis"). References of retrieved literatures were checked to collect potentially relevant studies.

2.2. Inclusion and exclusion criteria

Studies were included if they met the following criteria: study type: RCTs were included; participants: all patients were diagnosed as UC[23] with no restrictions regarding ethnicity, age or sex; interventions: both the treatment and control groups received conventional therapies, on the basis of this, the treatment group was administered BTV combined with ASA including mesalazine (5-ASA), sulfasalazine (SASP) or olsalazine (OSLS), whereas the control group was orally administered ASA alone. Conventional therapies and ASA should be consistent in both groups. No limitations were set on dosages and durations of the treatment. Outcomes: one or more outcome indicators of the following should be involved: clinical efficacy, adverse effects, relapse rate, inflammation factor level, T lymphocyte subsets level, Disease Activity Index (DAI) score, endoscopic score, and lipid peroxide level.

We excluded overview, animal researches, no drug duration trials, no recognized diagnostic criteria, duplicated publications, trials with wrong data, or data missing. We only included the most recent one with the largest number of patients or longer follow-up when several trials by the same authors were identified as duplicates.

2.3. Data extraction

Two researchers (MC and ZQ) independently reviewed and extracted the following information from each study: author's

name; publication year; participant number; dose of BTV, ASA, or other preparations; duration of treatment; outcomes; and adverse reactions. Any disagreements were resolved through discussion, and if necessary, arbitrated by a third reviewer (KZ).

2.4. Bias assessment

The Cochrane risk-of-bias criteria[24] was used by 2 reviewers (MC and ZQ) to assess the quality of included studies independently. The Cochrane criteria include the following items: random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, blinding of outcome assessment, selective reporting, and other bias. Other bias was defined as trials with different baseline characteristics between different intervention groups. The researches were graded as high risk, low risk, and unclear risk.

2.5. Data analysis

Data analysis was performed using Review Manager 5.3 software. Meta-analysis to risk ratio (RR) and its 95% confidence interval (CI) of BTV plus ASA on UC for dichotomous data was performed. For continuous data, standardized mean difference (SMD) and its 95% CI were calculated.

Heterogeneity was evaluated by Q-statistic and I^2 test. If the statistical heterogeneity between summary data was $P < .05$ or $I^2 > 50\%$, the random-effects model was used to pool the data. Otherwise, a fixed-effects model was applied ($P > .05$ or $I^2 < 50\%$). Sensitivity analysis of clinical efficacy was performed by the "leave-one-out" approach. If the group included >10 trials, publication bias was examined by funnel plot analysis, and Egger regression intercept was calculated using the Stata 12.0 software. Subgroup analyses were carried out based on different drug combinations, doses, and durations.

3. Results

3.1. Study identification

According to our literature retrieval strategy, 474 relevant articles were initially identified in 7 electronic databases. After excluding duplicate trials, 266 articles were selected for further analysis, and 120 articles which did not meet the inclusion criteria were excluded. A total of 146 articles were examined for the full texts and 86 were excluded. Finally, 60 RCTs met the inclusion criteria.[11–19,25–75] The flowchart of study selection is shown in Figure 1.

3.2. Study characteristics

The included studies were conducted from 2003 to 2018 and involved a total of 4954 patients, with 2496 in the BTV plus ASA

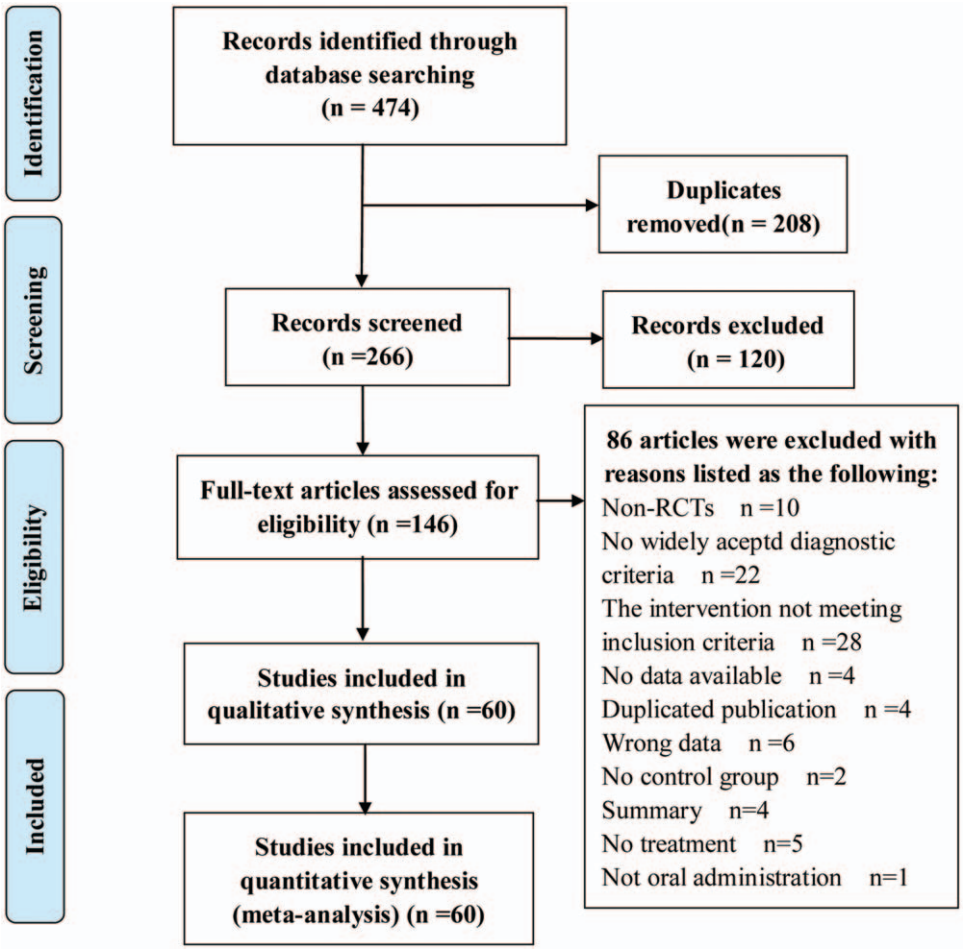

Figure 1. Flow diagram of study selection and identification.

Table 1

The characteristic of the eligible trials.

Trials	Sample size	Intervention measures: Treatment group	Intervention measures: Control group	Treatment time, days	Outcomes
Li et al, 2003[25]	21/20	5-ASA (po, 1.0 g, tid) + BTV (po, 630 mg, bid)	5-ASA (po, 1.0 g, tid)	56	CE, IFL
Qiao, 2018[11]	32/32	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	60	TLSL
Wang and Shi, 2016[12]	40/40	Astragalus granules (po, 4 g, tid) + 5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	Astragalus granules (po, 4 g, tid) + 5-ASA (po, 1.0 g, qid)	56	CE, AE
Xu, 2013[26]	76/78	5-ASA (po, 1 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1 g, qid)	56	CE, AE
Wang et al, 2012[27]	40/38	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, AE, DAI
An, 2011[28]	19/19	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	60	CE, DAI, LPL, IFL
He and Chen, 2013[29]	63/62	5-ASA (po, first 4 weeks 1.0 g, qid; last 4 wk 0.5 g, tid) + BTV (po, 420 mg, tid)	5-ASA (po, first 4 wk 1.0 g, qid; last 4 wk 0.5 g, tid)	56	CE, RR, AE, RR
Luo and Huang, 2017[13]	40/40	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, AE, DAI, IFL
Liu, 2012[30]	50/50	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	28	CE, AE, DAI, ES
Xing and Wang, 2015[31]	40/40	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, AE
Xu, 2017[14]	34/34	5-ASA (po, 1.0 g, tid) + BTV (po, 420–840 mg, bid)	5-ASA (po, 1.0 g, tid)	28	CE, AE, DAI, IFL
Deng and Liu, 2013[32]	36/36	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	49	CE
Yuan et al, 2007[33]	39/36	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, AE
Zhang et al, 2014[34]	43/43	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, AE
Zhao and Hao, 2018[15]	40/40	5-ASA (po, 1.0 g, tid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, tid)	56	CE, DAI, LPL, IFL
Wang, 2017[16]	62/62	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, bid (moderate), tid (severe))	5-ASA (po, 1.0 g, qid)	28	CE, IFL
Zhao and Yi, 2017[17]	42/42	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, IFL, CIL
Mao, 2017[18]	38/38	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	60	CE, AE, LPL
Zhang, 2017[19]	68/68	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, bid (moderate), tid (severe))	5-ASA (po, 1.0 g, qid)	28	CE, DAI, ES, IFL
Ding, 2015[35]	39/39	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, AE, LPL
Luo, 2008[36]	25/28	5-ASA (po, 0.5–1.0 g, tid) + BTV (po, 420 mg, tid)	5-ASA (po, 0.5–1.0 g, tid)	56	CE, RR
Fan, 2013[37]	25/25	5-ASA (po, 0.5–1.0 g, tid) + BTV (po, 420 mg, tid)	5-ASA (po, 0.5–1.0 g, tid)	56	CE, RR, AE
Chen et al, 2016[38]	64/64	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	60	CE, AE, IFL, LPL
Zhang, 2018[39]	43/43	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, AE
Zhou and Hu, 2014[40]	45/45	5-ASA (po, 1.0 g, qid) + BTV (po, 630 mg,bid)	5-ASA (po, 1.0 g, qid)	56	CE, AE, IFL
Wu, 2017[41]	55/55	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	30	CE, IFL, TLSL
An, 2014[42]	20/20	5-ASA (po, 1.0 g, qid) + BTV (po, 840 mg, bid)	5-ASA (po, 1.0 g, qid)	28	CE
Shi, 2011[43]	30/30	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	28	AE, DAI, ES, IFL
Wu, 2017[44]	36/36	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	49	CE
Lu et al, 2017[45]	45/45	5-ASA (po, first 1 mo 1.0 g, qid; last 2 mo 0.5 g, tid) + BTV (po, 840 mg, bid)	5-ASA (po, first 1 mo 1.0 g, qid; last 2 mo 0.5 g, tid)	90	IFL, LPL, TLSL
Chen, 2018[46]	50/50	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, qid)	5-ASA (po, 1.0 g, qid)	60	CE, AE, IFL
Feng et al, 2018[47]	54/54	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, AE, IFL
Hu et al, 2018[48]	28/27	5-ASA (po, 1.0 g, qid) +B TV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, AE, IFL
Zhang and Zhou, 2014[49]	46/46	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, DAI, ES
Ren et al, 2017[50]	50/50	5-ASA (po, 1.0 g, qd) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qd)	60	CE, AE, LPL, CIL, IFL
Su and Wei, 2017 [51]	38/37	5-ASA (po, 1.0 g, tid) + BTV (po, 420 mg, bid–tid)	5-ASA (po, 1.0 g, tid)	28	CE, AE, DAI, ES
Chen et al, 2014[52]	59/59	5-ASA (po, 1.0 g, qid) +B TV(po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	60	CE, DAI, LPL, IFL
Zhang and Zhang, 2013[53]	68/51	5-ASA (po, 1.0 g, qid) + BTV po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, AE
Tang et al, 2017[54]	40/40	5-ASA (po, 1.0 g, tid) + BTV (po, 0.5 g, tid)	5-ASA (po, 1.0 g, tid)	90	IFL, TLSL
Gao and Xue, 2016[55]	40/40	5-ASA (po, 1.0 g, qid) + BTV (po, 1.0 g, tid)	5-ASA (po, 1.0 g, qid)	56	CE, LPL, IFL
Wang, 2017[56]	48/48	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, AE, IFL
Sun, 2013[57]	20/18	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, AE
Jia, 2017[58]	47/47	5-ASA (po, 1.0 g, tid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, tid)	60	CE, AE, DAI, ES, IFL
Wang and Yin, 2016[59]	48/48	5-ASA (po, 1.0, qid) + BTV (po, 840 mg, bid)	5-ASA (po, 1.0, qid)	84	CE, DAI, IFL
Zhang et al, 2017[60]	43/43	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	56	CE, IFL, TLSL
Gong et al, 2015[61]	40/40	5-ASA (po, 1.2 g, tid) + BTV (po, 630 mg, bid)	5-ASA (po, 1.2 g, tid)	56	CE, AE, DAI, IFL
Liu and Tan, 2010[62]	30/28	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	28	CE, AE, RR, IFL
Li, 2017[63]	71/71	5-ASA (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, qid)	28	CE, AE, IFL
Zhang, 2015[64]	30/26	5-ASA (po, 1.0 g, tid) + BTV(po, 420 mg, tid)	5-ASA (po, 1.0 g, tid)	56	CE, AE, DAI, ES
Li et al, 2012[65]	41/41	5-ASA (po, 1.0 g, bid) + BTV (po, 420 mg, tid)	5-ASA (po, 1.0 g, bid)	56	AE, DAI, ES
Shi et al, 2007[66]	27/25	SASP (po, 1.0 g, qid) + BTV (po, 630 mg, tid)	SASP (po, 1.0 g, qid)	56	CE, IFL

(*continued*)

Table 1

(continued).

Trials	Sample size	Intervention measures: Treatment group	Intervention measures: Control group	Treatment time, days	Outcomes
Jiang et al, 2015[67]	53/53	SASP (po, 1.0 g, qid) + BTV (po, 630 mg, tid)	SASP (po, 1.0 g, qid)	84	AE
Shi et al, 2010[68]	47/45	SASP (po, 1.0 g, qid) + BTV (po, 630 mg, tid)	SASP (po, 1.0 g, qid)	56	CE, AE, IFL
Tian et al, 2010[69]	34/32	SASP (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	SASP (po, 1.0 g, qid)	28	CE, AE, IFL
Xie, 2016[70]	41/42	SASP [po, 1.0 g, qid (acute), tid (relief)] + BTV (po, 420 mg, tid)	SASP [po, 1.0 g, qid (acute), tid (relief)]	30	CE, RR, IFL, TLSL
Zhu, 2011[71]	23/22	SASP (po, 1.0 g, tid) + BTV (po, 420 mg, tid)	SASP (po, 1.0 g, tid)	28	CE
Hong et al, 2010[72]	35/33	SASP (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	SASP (po, 1.0 g, qid)	56	CE, AE, IFL
Huang and Chen, 2014[73]	33/33	OSLS (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	OSLS (po, 1.0 g, qid)	60	CE
Liu, 2009[74]	22/21	OSLS (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	OSLS (po, 1.0 g, qid)	56	CE
Wei, 2010[75]	40/40	OSLS (po, 1.0 g, qid) + BTV (po, 420 mg, tid)	OSLS (po, 1.0 g, qid)	56	CE

ASA = aminosalicylic acid, 5-ASA = mesalazine, AE = adverse effect, Astragalus granules = Chinese patent medicine, bid = bis in die, CE = clinical efficacy, DAI = Southerland Disease Activity Index Score, ES = endoscopy score, g = gram, IFL = inflammation factor level, LPL = lipid peroxide level, mg = milligram, OSLS = olsalazine, po = peros, qid = quater in die, RR = relapse rate, SASP = sulfasalazine, tid = ter in die, TLSL = T lymphocyte subsets level.

group and 2458 in the ASA group. All studies were performed in China with all Chinese participants involved. A 2-arm design (1 treatment group vs 1 control group) was shown. In the control group, ASA was administered as 5-ASA in 50 trials,[11–19,25–65] SASP in 7 trials,[66–72] and OSLS in 3 trials.[73–75] Patients were treated with BTV plus ASA in the treatment groups. The main characteristics of the 60 studies are summarized in Table 1.

3.3. Risk of bias

Overall, 20 trials[13,15,17,19,28,34,38,41,46–50,52,55,58,60,63,65,70] were categorized as low risk of bias which mentioned the method of random number table, and the rest of the studies were unclear risk. One trial[25] reported number of drop-out, with 4 cases in treatment and 8 cases in control, and was assessed as low risk. Allocation concealment, blinding, selective outcome reporting, and other sources were assessed as unclear risk of bias. Figures 2 and 3 show the details of the risk of bias.

3.4. Clinical remission rate

Fifty-four studies[12–19,25–42,44,46–53,55–64,66,68–75] reported clinical remission in patients with UC. The meta-analysis showed that there was significant beneficial effect on the BTV plus ASA group compared with ASA using alone (RR = 1.23; 95% CI 1.20–1.26), with no significant heterogeneity between study results ($P = .86$, $I^2 = 0\%$). The effect estimates are shown in Figure 4.

3.4.1. Subgroup analysis of different drug combinations. Subgroup analysis was used to evaluate the efficacy of different drug combinations. Compared with ASA alone, BTV plus 5-ASA,[12–19,25–42,44,46–53,55–64] BTV plus SASP,[66,68–72] and BTV plus OSLS[73–75] had significant improvements of clinical remission, with RR = 1.22 (95% CI = 1.19, 1.26, n = 45), RR = 1.27 (95% CI = 1.16, 1.38, n = 6), and RR = 1.24 (95% CI = 1.09, 1.41, n = 3), respectively (Fig. 4). There was no significantly different ($P = .99 > .05$) in the 3 ASA groups by using analysis of variance (ANOVA) of t test.

3.4.2. Subgroup analysis of different durations. Subgroup analysis was used to evaluate the efficacy of different durations. As shown in Table 2, compared with ASA alone, BTV plus ASA durations of 28 days (n = 10),[14,16,19,30,42,51,62,63,69,71] 30 days (n = 2),[41,70] 49 days (n = 2),[32,44] 56 days (n = 31),[12,13,15,17,25–27,29,31,33–37,39,40,47–49,53,55–57,60,61,64,66,68,72,74,75] 60 days (n = 8),[18,28,38,46,50,52,58,73] and 84 days (n = 1)[59] all had

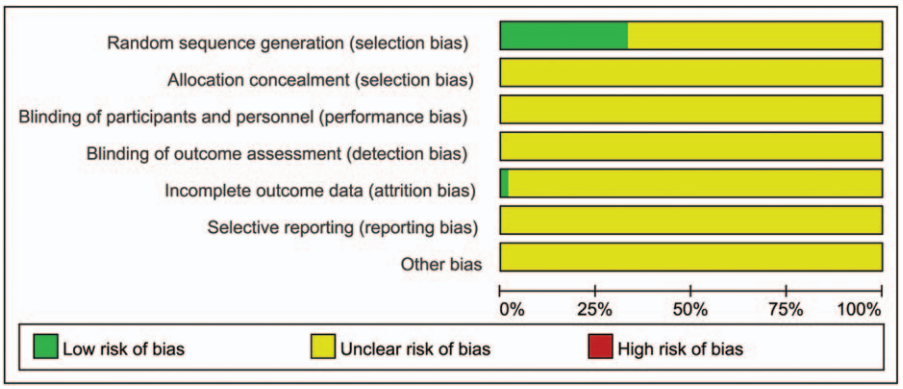

Figure 2. Risk of bias graph.

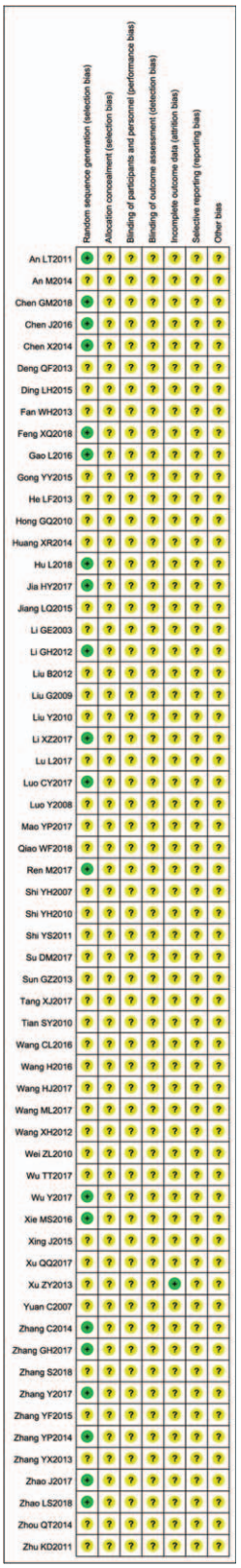

Figure 3. Risk of bias summary.

significant improvements of clinical remission, with RR of 1.17, 1.18, 1.43, 1.26, 1.18, and 1.21, respectively, and $P < .05$ in each subgroup. The duration of 49 days showed a better remission. Notably, the small sample proportion was considered to mostly affect the accuracy of the subgroup analysis, hence, the duration of 30, 49, and 84 days was removed, and ANOVA of *t* test was performed in the durations of 28, 56, and 60 days, there was no significant difference among the 3 groups ($P = .08$).

3.4.3. Subgroup analysis of different doses. Compared with ASA alone, BTV plus ASA with doses of 420 mg [peros (po), ter in die (tid)],[12,13,15,17,18,26–39,41,44,47–50,52,53,56–58,60,62–64,69–75] 630 mg [po, bis in die (bid)],[25,40,61] 630 mg (po,tid),[66,68] and 840 mg (po,bid)[42,59] in their durations all had significant improvements of clinical remission, as shown in Table 2. According to the results, the dose of 630 mg (po,tid) had a better efficacy. The effect was enhanced with increasing daily dose, but ANOVA of *t* test showed that there was no statistically significant difference in efficacy between the 4 doses.

In summary, it indicates that BTV plus ASA has better potential clinical efficacy than ASA used alone. There was no significant difference between 3 drug combinations (BTV plus 5-ASA, BTV plus SASP, and BTV plus OSLS), 3 durations (28, 56, and 60 days), and 4 doses [420 mg (po, tid), 630 mg (po, bid), 630 mg (po, tid), and 840 mg (po, bid)].

3.5. Effects of BTV plus ASA on DAI

Seventeen trials[13–15,19,27,28,30,43,49,51,52,58,59,61,64–66] compared the reduction of DAI. Significant heterogeneity was found in the studies ($I^2 = 88\%$; $P < .00001$). Therefore, pooled RR and their corresponding 95% CIs were calculated using a random-effects model. According to result, we found that the reduction of DAI between the 2 groups was significant different [RR = −1.41, 95% CI (−1.76, −1.05), $P < .00001$] (Fig. 5).

3.6. Effects of BTV plus ASA on endoscopy score

Seven trials[19,30,43,49,51,58,64] compared the reduction of endoscopy score. Significant heterogeneity was found among studies ($I^2 = 85\%$; $P < .00001$). The random-effects model was applied. The pooled RR for endoscopy score was −1.13 [95% CI (−1.58, −0.68), $P < .00001$], which indicated that the reduction of endoscopy score between the 2 groups was significant different (Fig. 6).

3.7. Effects of BTV plus ASA on inflammation factor level

Inflammation factor level was evaluated in 31 trials.[13–19,28,35,38,40,41,43,45,46,48,50,52,54–56,58–63,68–70,72] The meta-analysis results showed that the treatment groups were significantly better than the controls by decreasing the TNF-α, IL-6, IL-8, CRP, hypersensitive C-reactive protein (Hs-CRP), erythrocyte sedimentation rate (ESR), and increasing the IL-10 (Fig. 7).

3.7.1. Tumor necrosis factor-α,. Nineteen trials[13,15,16,19,28,38,40,41,43,45,46,48,52,54,55,58,60,68,70] evaluated the expression of TNF-α between the 2 groups. TNF-α was significantly decreased in the BTV plus ASA group when compared with ASA alone [$P < .00001$, SMD = −1.21, 95% CI (−1.85, −0.57)] (Fig. 7).

3.7.2. Interleukin-6. Eleven trials[16,38,41,45,48,52,54,55,58,68,70] evaluated the expression of IL-6 between the 2 groups. IL-6 was significantly decreased in the BTV plus ASA group when compared with ASA alone [$P = .02$, SMD = −1.34, 95% CI (−2.44, −0.24)] (Fig. 7).

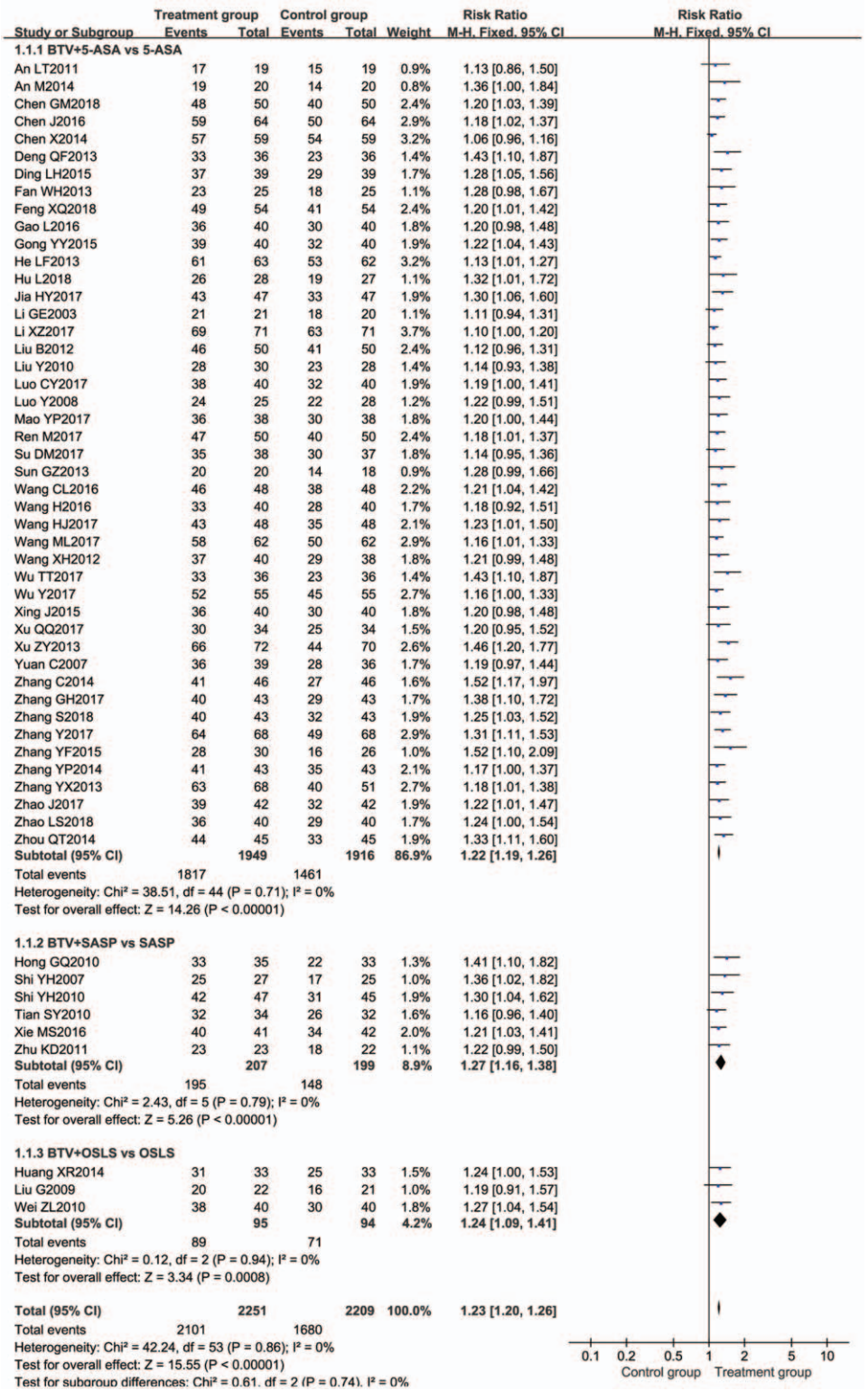

Figure 4. Meta-analysis of clinical remission rate of subgroup analysis of different medicine. BTV = bifid triple viable, CI = confidence interval, OSLS = olsalazine, SASP = sulfasalazine.

Table 2

Subgroup analysis of association between clinical efficacy, durations, and doses.

Duration/dose	No. trials	No. participants		Clinical efficacy rate, RR (95% CI)	*P*
		Treatment group (effect-rate)	Control group (effect-rate)		
Duration					
28 days	10	404/430	339/424	1.17 (1.11, 1.24)	<.00001
30 days	2	92/96	79/97	1.18 (1.06, 1.31)	.002
49 days	2	66/72	46/72	1.43 (1.19, 1.73)	.0002
56 days	31	1155/1245	891/1208	1.26 (1.21, 1.30)	<.00001
60 days	8	338/360	287/360	1.18 (1.11, 1.25)	<.00001
84 days	1	46/48	38/48	1.21 (1.04, 1.42)	.02
Dose					
420 mg, po, tid	41	1594/1711	1273/1675	1.23 (1.19, 1.26)	<.00001
630 mg, po, bid	3	104/106	83/105	1.24 (1.12, 1.37)	<.0001
630 mg, po, tid	2	67/74	48/70	1.32 (1.11, 1.57)	.002
840 mg, po, bid	2	65/68	52/68	1.25 (1.09, 1.44)	.002

bid = bis in die, CI = confidence interval, mg = milligram, po = peros, RR = risk ratio, tid = ter in die.

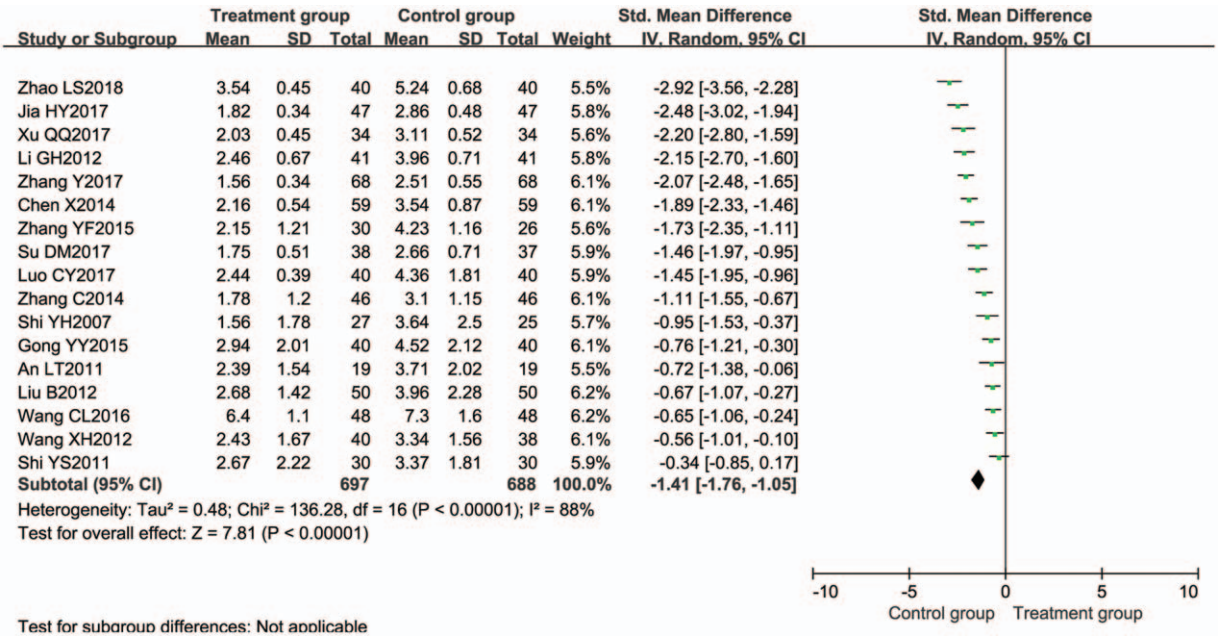

Figure 5. Meta-analysis of Disease Activity Index score. CI = confidence interval, SD = standard deviation.

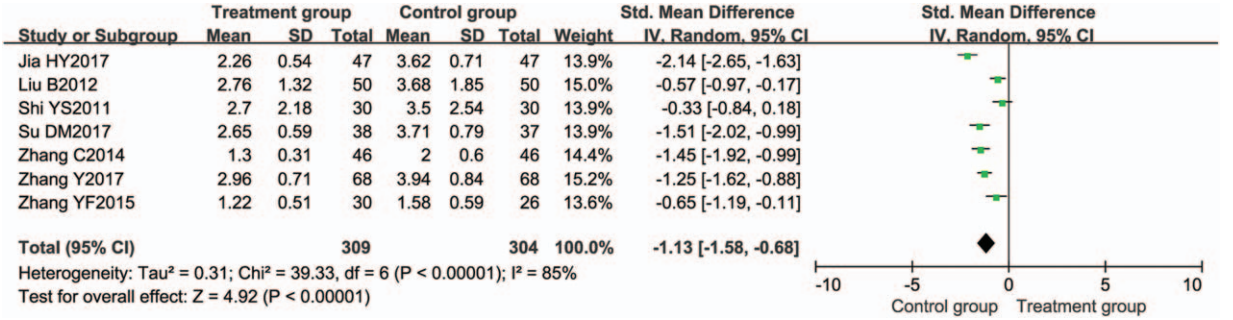

Figure 6. Meta-analysis of endoscopy score. CI = confidence interval, SD = standard deviation.

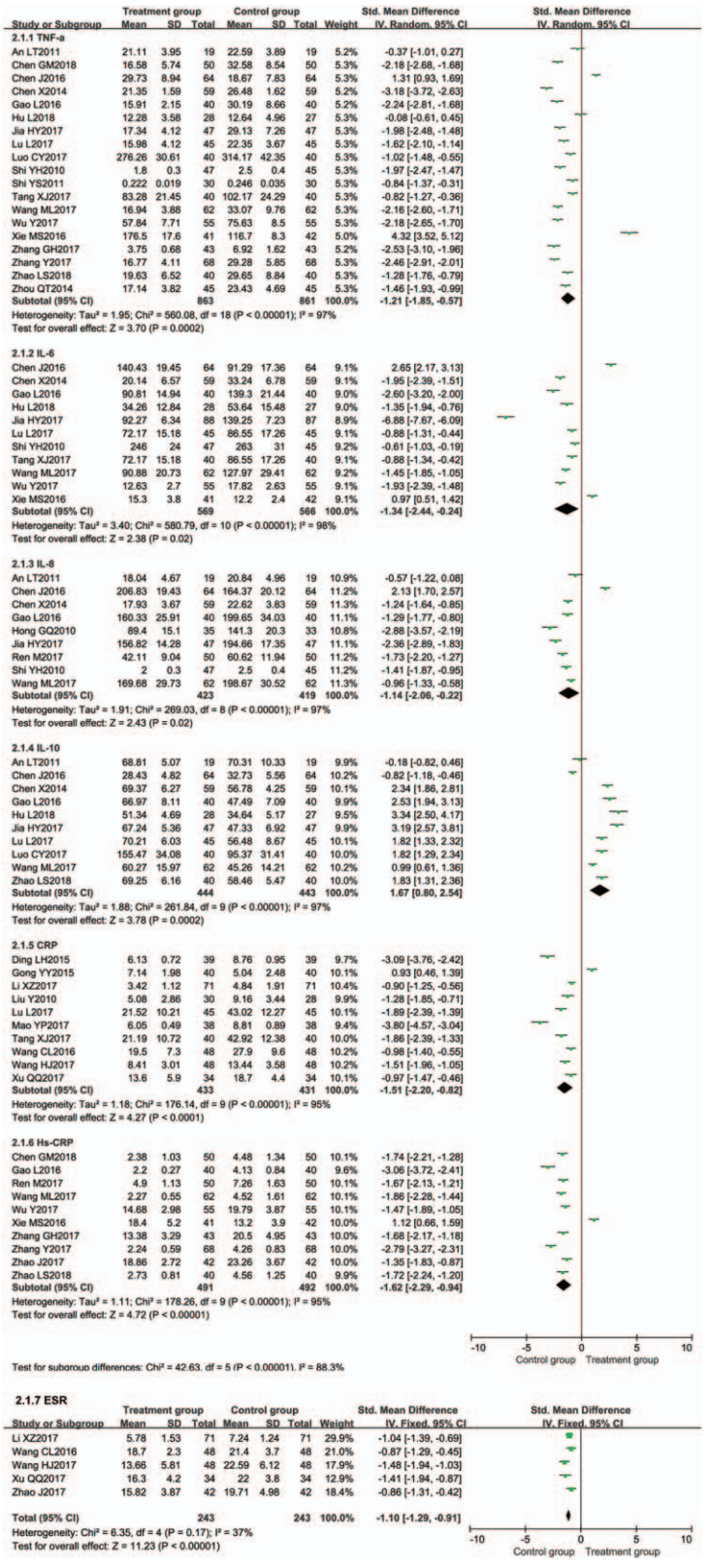

Figure 7. Meta-analysis of effect on inflammation factor level.

3.7.3. Interleukin-8. Nine trials[16,28,38,50,52,55,58,68,72] evaluated the expression of IL-8 between the 2 groups. IL-8 was significantly decreased in the BTV plus ASA group when compared with ASA alone [$P = .02$, SMD = −1.14, 95% CI (−2.06, −0.22)] (Fig. 7).

3.7.4. C-reactive protein. Ten trials[14,18,35,45,54,56,59,61–63] evaluated the expression of CRP between the 2 groups. CRP was significantly decreased in the BTV plus ASA group when compared with ASA alone [$P < .0001$, SMD = −1.51, 95% CI (−2.20, −0.82)] (Fig. 7).

3.7.5. Hypersensitive C-reactive protein. Ten trials[15–17,19,41,46,50,55,60,70] evaluated the expression of Hs-CRP between the 2 groups. Hs-CRP was significantly decreased in the BTV plus ASA group when compared with ASA alone [P < .00001, SMD = −1.62, 95% CI (−2.29, −0.94)] (Fig. 7).

3.7.6. Erythrocyte sedimentation rate. Five trials[14,17,56,59,63] evaluated the expression of ESR between the 2 groups. ESR was significantly decreased in the BTV plus ASA group when compared with ASA alone [$P < .00001$, SMD = −1.10, 95% CI (−1.29, −0.91)] (Fig. 7).

3.7.7. Interleukin-10. Ten trials[13,15,16,28,38,45,48,52,55,58] evaluated the expression of IL-10 between the 2 groups. IL-10 was significantly increased in the BTV plus ASA group when compared with ASA alone [$P = .0002$, SMD = 1.67, 95% CI (0.80, 2.54)] (Fig. 7).

3.8. Effects of BTV plus ASA on T lymphocyte subsets level

Effect on T lymphocyte subsets level was evaluated in 7 trials.[11,41,45,47,54,60,70] The meta-analysis results showed that the treatment groups were superior to the control groups regarding increasing the CD3+, CD4+, and CD4+/CD8+ (Fig. 8).

3.8.1. CD3+. Five trials[11,41,45,54,60] evaluated the expression of CD3+ between the 2 groups. CD3+ was significantly increased in the BTV plus ASA group when compared with control group [$P < .00001$, SMD = 0.65, 95% CI (0.45, 0.84)] (Fig. 8).

3.8.2. CD4+. Seven trials[11,41,45,47,54,60,70] evaluated the expression of CD4+ between the 2 groups. CD4+ was significantly increased in the BTV plus ASA group when compared with

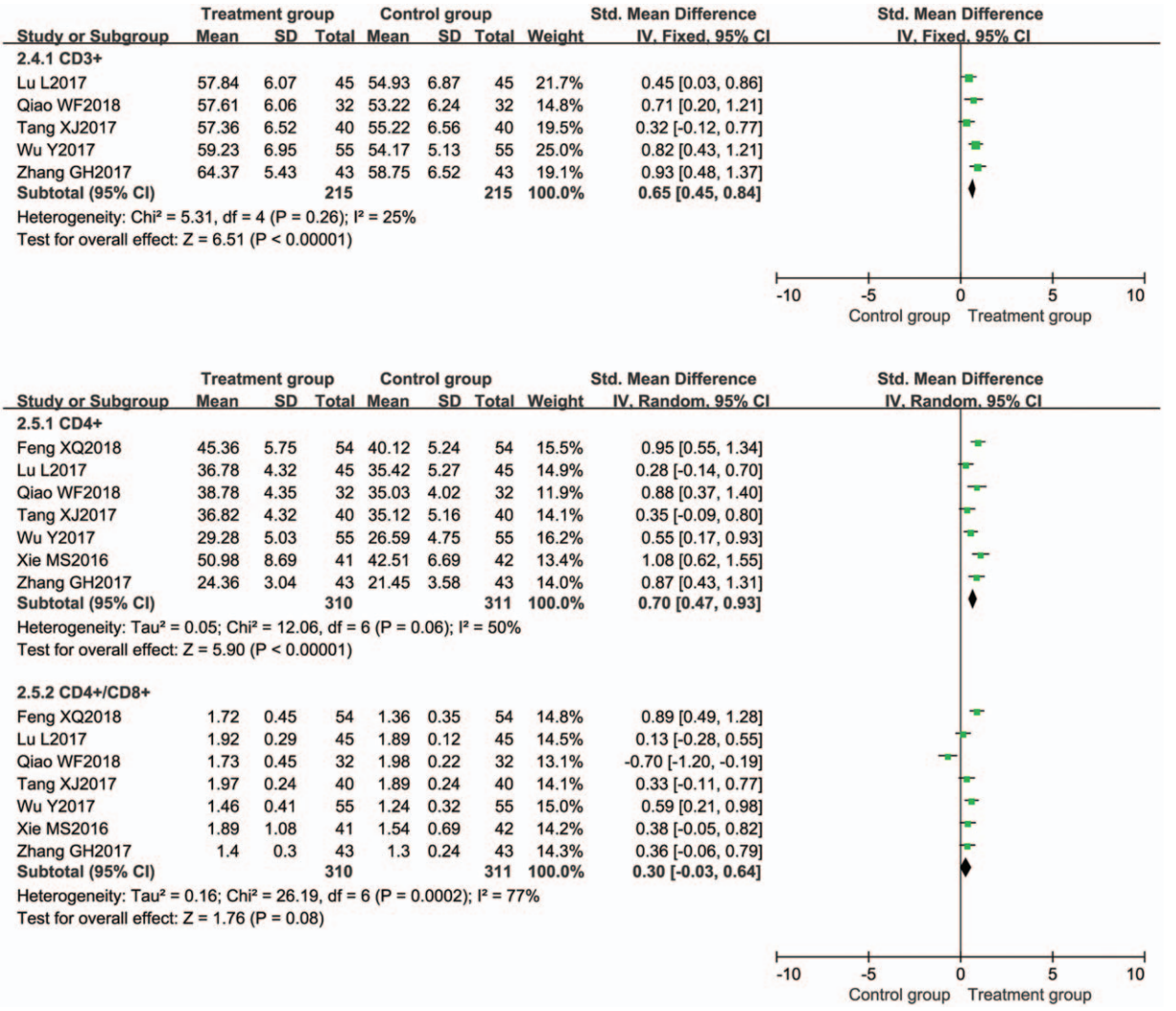

Figure 8. Meta-analysis of effect on T lymphocyte subsets level. CI = confidence interval, SD = standard deviation.

control group [$P < .00001$, SMD = 0.70, 95% CI (0.47, 0.93)] (Fig. 8).

3.8.3. CD4+/CD8+. Seven trials[11,41,45,47,54,60,70] evaluated the ratio of CD4+/CD8+ between the 2 groups. CD4+/CD8+ was significantly increased in the BTV plus ASA group when compared with control group [($P = .08$, SMD = 0.30, 95% CI (−0.03, 0.64)] (Fig. 8).

3.9. Effects of BTV plus ASA on lipid peroxide level

Effect on lipid peroxide level was evaluated in 9 trials.[15,18,28,35,38,45,50,52,55] The meta-analysis results showed that the treatment groups were superior to the control groups regarding reducing the MDA and increasing SOD (Fig. 9).

3.9.1. Malondialdehyde. Nine trials[15,18,28,35,38,45,50,52,55] evaluated the expression of MDA. MDA was significantly reduced in the BTV plus ASA group when compared with control group [$P < .00001$, SMD = −1.55, 95% CI (−1.94, −1.16)] (Fig. 9).

3.9.2. Superoxide dismutase. Nine trials[15,18,28,35,38,45,50,52,55] evaluated the expression of SOD. SOD was significantly increased in the BTV plus ASA group when compared with control group [$P = .0004$, SMD = 2.34, 95% CI (1.03, 3.64)] (Fig. 9).

3.10. Relapse rate of BTV plus ASA

Five trials[29,36,37,62,70] evaluated the effect of relapse rate between the 2 groups. The relapse rate of BTV plus ASA group was 12/184, and that of control group was 36/185. We observed no significant heterogeneity ($P = .98$, $I^2 = 0\%$) for the relapse rate, so the fixed-effects model was used to calculate combined results. The overall estimate indicated that relapse rate in the BTV plus ASA group was significant lower than that in the control group ($P = .0005$), with RR of 0.34 and 95% CI (0.18, 0.62) (Fig. 10).

3.11. Adverse effects of BTV plus ASA

A total of 35 trials[12–14,18,26,27,29–31,33–35,37–40,43,46–48,50,51,53,56–58,61–65,67–69,72] mentioned the occurrence of adverse effects. One trial,[29] however, did not report the number of adverse effects, and 1 trial[61] reported no adverse effects. Thirty-three trials[12–14,18,26,27,30,31,33–35,37–40,43,46–48,50,51,53,56–58,62–65,67–69,72] reported adverse effects rate; adverse effects were reported in both studies, the incidence of adverse events in the BTV plus ASA group (8.3%, 118/1426) was lower than that in the control groups (12.4%, 172/1392), with a summary RR of 0.66 (95% CI 0.53–0.82; $P = .62$; $I^2 = 0\%$) (Fig. 11). The most common adverse events were vomiting, nausea, dry mouth, bloating, rash, dizziness, headache, arthralgia, pyrosis, and so on. It indicated that the safety profile of BTV plus ASA maybe better than ASA alone in the treatment of UC.

3.12. Sensitivity analysis

Sensitivity analysis was adopted to assess the stability of the results. We used leave-one-out method by sequentially omitting each study to assess the impact of individual data on the results. Excluding any study from the clinical remission rate analysis of

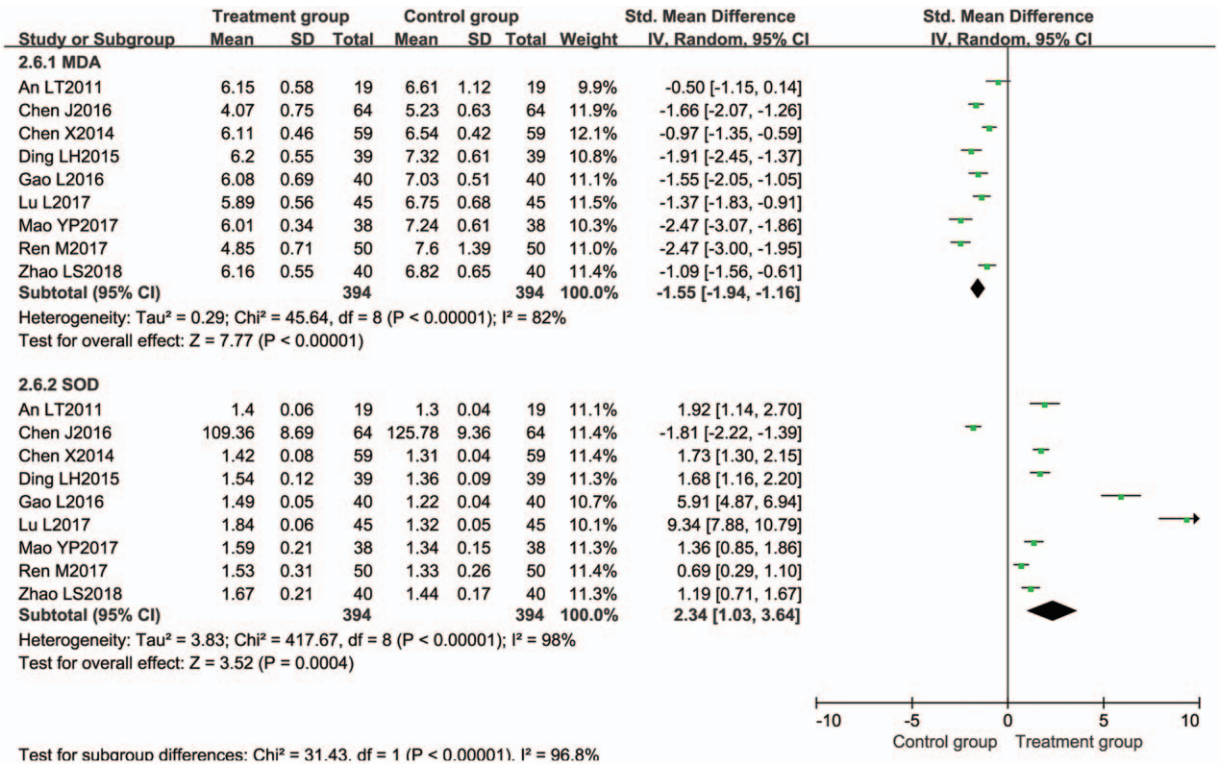

Figure 9. Meta-analysis of effect on lipid peroxide level. CI = confidence interval, SD = standard deviation.

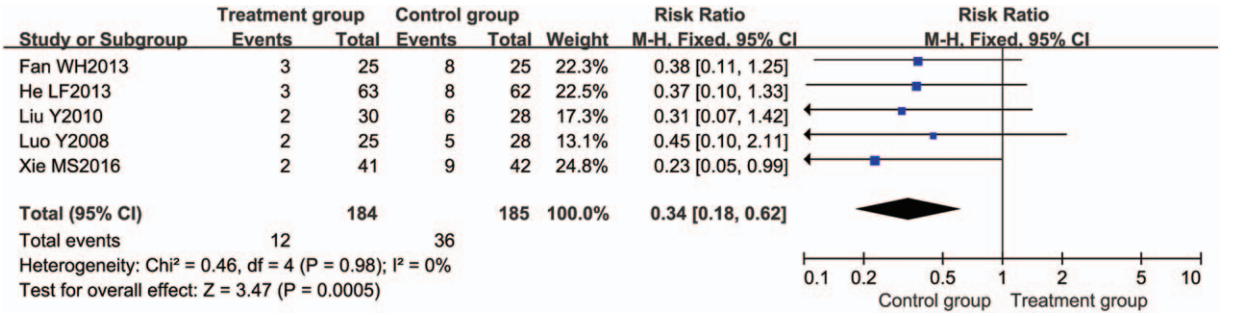

Figure 10. Meta-analysis of relapse rate. CI = confidence interval.

patients with UC did not significantly affect the results. Therefore, the meta-analysis had good reliability.

3.13. Publication bias

A forest plot of comparison of BTV plus ASA program and ASA alone for the outcome of clinical remission rates was depicted with Stata 12.0 software. As shown in Figure 12, publication bias of Egger regression showed that $t=8.32$, $P>|t|=.000<.05$, which revealed that there were obviously evidence of publication bias for clinical remission rates between the treatment group and the control group. The Egger publication bias plot of clinical efficiency is shown in Figure 13, and Egger's publication bias regression in Figure 14.

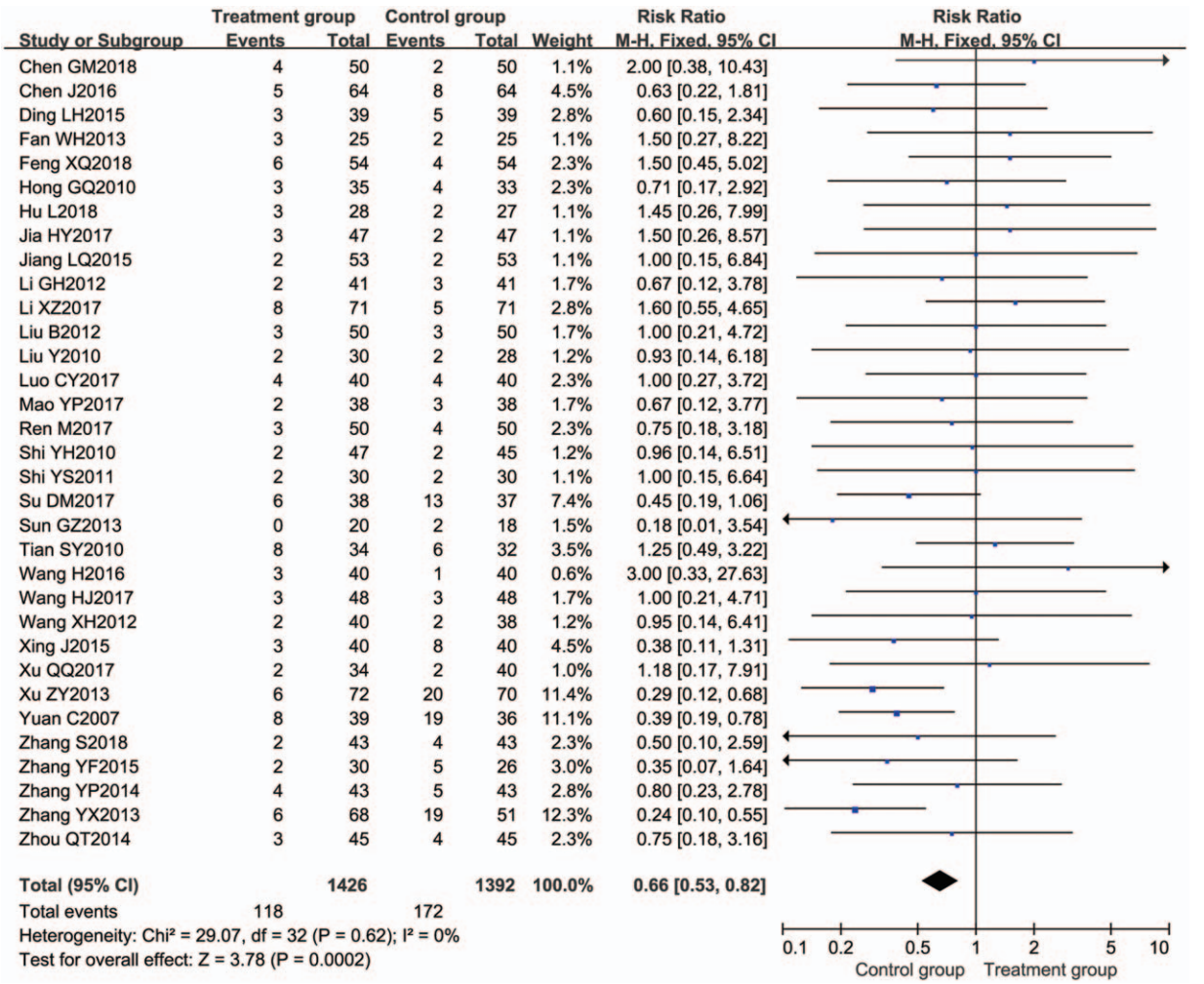

Figure 11. Meta-analysis of adverse reactions. CI = confidence interval.

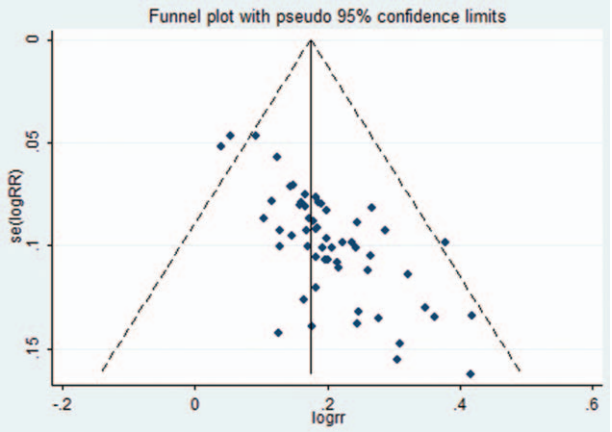

Figure 12. Funnel plot of clinical efficiency. RR = risk ratio.

4. Discussion

It has been largely accepted that the species of microbiota and its stability in patients with UC are different from normal people. The Bifidobacteriaceae family of the Actinobacteria phylum in patients with UC showed lower abundance.[76] Fecal bacteria from patients with UC had higher capacity than those in healthy patients. After fecal bacterial stimulation, the production of multiple cytokines, including TNF-α, IL-6, and IL-12, were higher in UC-active and UC-remission patients.[77,78] Notably, probiotics are associated with bacterial microbiota composition.[77] Evidence was accumulated that probiotics, such as *E coli* Nissle 1917, VSL3, *L acidophilus*, *B breve*, *B bifidum*, *Saccharomyces boulardii*, and so on, had a positive intervention on UC treatment, and improved the clinical efficacy of 5-ASA.[79–82]

Most meta-analysis proved that probiotics combined with mesalazine are beneficial to the treatment of UC.[80,83–85] Most studies, however, used different kinds of probiotics in treating UC, which did not provide sufficient evidence to guide the use of single probiotic. A meta-analysis of Medilac-s capsule plus mesalazine in treating UC, directly provided evidence-based testimony of 1 probiotic for clinic.[86] Since 2016, the strategy of treating UC with BTV + ASA has been increasingly recommended.[11–19,44–48,54–56,58–60,63] Therefore, to demonstrate the efficacy and safety of BTV plus ASA in UC treatment, a meta-analysis was carried out.

4.1. Summary of evidence

As shown in our results, efficacy of BTV plus ASA was 1.23 times that of ASA used alone. Subgroup of efficacy showed that there was no significant difference among 3 drug combinations (BTV plus 5-ASA, BTV plus SASP and BTV plus OSLS) and compared ASA used alone, curative remission rate changed with the duration of treatment, and the best curative effect was achieved in 49 days. But due to the smaller number of trials, it is difficult to draw firm conclusions.[87] After removing the duration of 30, 49, and 84 days with small sample proportion, this lack of an observed duration effect may be due to the small distinction between the duration of 28, 56, and 60 days. More evidence is needed to confirm the differences in different durations. Similar question had been encountered in previous published systematic reviews[87]; the effect was enhanced with increasing daily dose, and dose of 630 mg (po, tid) maybe had a better efficacy. Nonetheless, the number of the studies in doses of 630 mg (po, bid), 630 mg (po, tid), and 840 mg (po, bid) were <5; there may be too few RCTs to draw firm conclusions. More evidence is needed to confirm the differences between high and low doses. The effective dose of probiotics is influenced by many factors, including specific probiotic used, route of administration,

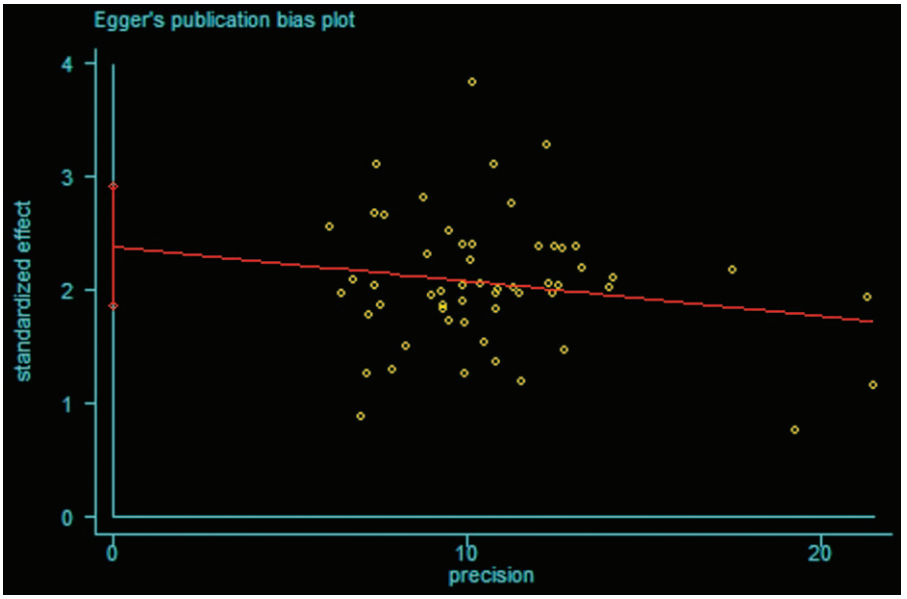

Figure 13. Egger publication bias plot of clinical efficiency.

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.0148411	.0244905	-0.61	0.547	-.063985	.0343027
bias	2.234218	.2685622	8.32	0.000	1.695309	2.773128

Figure 14. Egger publication bias regression of clinical efficiency.

delivery vehicle, and health endpoint. These factors make it difficult to conclude the optimal dose of probiotic.[88]

Furthermore, compared with ASA used alone, BTV plus ASA could significantly reduce the level of TNF-α, IL-6, IL-8, CRP, Hs-CRP, ESR, and MDA; significantly increase the level of IL-10, CD3+, CD4+, and SOD in patients with UC.

4.2. Safety

As shown in our results, adverse effects and relapse rate of BTV plus ASA were 0.66 times and 0.34 times lower than that of ASA used alone, respectively. It reveals that BTV plus ASA program is a safe management on UC.

4.3. Limitations

This study has several limitations should be taken into consideration. First, 60 trials stated random allocation were adopted, nevertheless, two thirds of them did not describe the method of random sequence generation. Secondly, none of the original studies made adequate descriptions of blinding and allocation concealment, which are vitally important elements to ensure methodological quality of clinical trials. The investigators and participants might have been aware of the therapeutic interventions implemented, which could lead to the emergence of false-positive conclusions. Third, only 1 out of 60 trials mentioned drop-out case, and 5 trials reported the relapse rate incidence. The results might have been different if all individuals were tested. Fourth, our meta-analysis only retrieved literatures published in English and Chinese, no reference was made to studies published in other languages, which might result in a certain degree of selective bias. In addition, 60 included trials were all conducted in China; therefore, whether the findings of our analysis could be generalized to broad ranges of regions and ethnic origin was slightly in doubt. Finally, there were subjective biases in the selection of nonquantitative outcomes, such as clinical efficacy, UC symptoms, relapse rate, adverse effects, and so on.

5. Conclusions

In this meta-analysis of RCTs, BTV plus ASA could improve clinical remission, relapse rate, adverse reactions, inflammation factor level, T lymphocyte subsets level, and lipid peroxide level in patients with UC. BTV plus ASA program can be considered to be a new approach for the treatment of UC. Nevertheless, some limitations such as potential selective bias and methodologic flaws might undermine the validity of positive findings. Further RCTs with high-quality and long-term follow-up, are recommended to generate high level of clinical evidence.

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Author contributions

Conceptualization: Hui-biao Li.
Data curation: Mu-yuan Chen, Zhen-wen Qiu.
Formal analysis: Zhen-wen Qiu.
Funding acquisition: Xin-lin Chen.
Investigation: Mu-yuan Chen.
Methodology: Mu-yuan Chen, Kun-hai Zhuang.
Writing – original draft: Mu-yuan Chen, Zhen-wen Qiu.
Writing – review & editing: Mu-yuan Chen, Hong-mei Tang, Qing-qun Cai, Xin-lin Chen, Hui-biao Li.

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