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Anti-inflammatory activity and safety of compound glycyrrhizin in ulcerative colitis: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Accumulating evidence suggests that compound glycyrrhizin may have beneficial effects on ulcerative colitis by inhibiting inflammation. However, the credibility of the evidence and safety for this practice are unclear. Therefore, we aimed to perform a systematic review and meta-analysis to evaluate the anti-inflammatory activity and safety of compound glycyrrhizin in the treatment of ulcerative colitis. PubMed, Embase, Cochrane Library, Web of Science, Chinese Biomedical Literature, China National Knowledge Infrastructure, Wanfang Database and CQVIP Database were searched for this review. Twenty-three qualified studies involving 2060 participants were included. There was a significant association of compound glycyrrhizin with TNF-α, IL-6, IL-8, IL-10, IL-17, adverse effects rate and recurrence rate. These results supported the anti-inflammatory activity of compound glycyrrhizin. In addition, compound glycyrrhizin can alleviate the adverse effects of conventional drugs (e.g. sulfasalazine), but it can also lead to edema. Further studies are required on the safety of compound glycyrrhizin and its mitigative effects on the adverse effects of conventional drugs.

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that affects the colon and rectum (Ungaro et al., 2017). Patients with UC usually present with several typical symptoms, such as fatigue, rectal bleeding, abdominal pain, diarrhea, weight loss and tenesmus (Baumgart & Sandborn, 2007; Danese & Fiocchi, 2011). The exact pathogenesis of UC is still unclear, but an increasing amount of evidence indicated that inflammatory disorders are implicated in the pathogenic processes of UC and the associated clinical symptoms (Abraham & Cho, 2009). These findings highlighted the need for appropriate anti-inflammatory therapy. Current studies showed that cytokines have a prominent role in controlling intestinal inflammatory response, including anti-inflammatory and pro-inflammatory cytokines (Neurath, 2014). Pro-inflammatory cytokines, such as IL-6 and TNF-α, could promote the inflammatory process. Indeed, blockade of IL-6 signalling with monoclonal antibody is efficacious in improving chronic intestinal inflammation in animal colitis models (Yamamoto et al., 2000). In addition, anti-TNF treatment is effective in patients with UC and become the first line treatment for moderate to severe UC for more than 15 years (Cohen & Sachar, 2017; Kobayashi et al., 2020). Anti-inflammatory cytokines, such as IL-10, could alleviate inflammatory response. Recent work found that gene-knockout mice deficient for IL-10 are associated with spontaneous colitis (Strober et al, 2002). Hence, cytokines involved in inflammatory response may probably represent crucial therapeutic targets for developing novel drug. However, there are still some problems should be considered. Firstly, cytokines networks in mucosal inflammation are complicated, and it is probable that blockade of a single

Abbreviations: AER, adverse effects rate; Both, female and male; CI, confidence interval; GL, glycyrrhizin; Gly, glycine; ivgtt, intravenous drip; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-17, interleukin-17; L-Cys.HCl, L-cysteine hydrochloride hydrate; NR, no report; Nuclear factor κappa B, NF-κB; po, oral administration; qd, once a day; RR, risk ratio; RER, recurrence rate; SMD, standardized mean difference; SNMC, Stronger Neo-Minophagen C®; tid, three times a day; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis.

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cytokines in UC patients may result in the progression of alternative compensatory pro-inflammatory cytokines pathways (Neurath, 2014). Secondly, the imbalance between anti-inflammatory and pro-inflammatory cytokines that occurs in UC hinders the resolution of inflammation and instead leads to disruption of tissue homeostasis (Neurath, 2014), so the blockade that only targets pro-inflammatory cytokines may not be effective. According to the above findings, the novel treatment for the management of UC is required to produce broad pharmacological effects, which could simultaneously suppress multiple pro- inflammatory cytokines and enhance anti-inflammatory cytokines.

To achieve this, there is a progressive increase in researches focusing on plant-derived bioactive compounds. In comparison with conventional drugs, they do not selectively blockade single molecular target, but exhibit a pleiotropic action profile, which can simultaneously regulate multiple cytokines implicated in the mucosa inflammation (Duan et al., 2021; Meresman et al., 2021). In particular, those plant-derived bioactive compounds that can be used as food may also provide the advantages of low cost, wide availability and fewer adverse effects. Thus plant-derived bioactive compounds represent promising candidates.

Glycyrrhizin (GL), a bioactive triterpenoid saponin, is the major active component of Chinese herbal medicine Gan-Cao (licorice) with anti-inflammatory activity and has been demonstrated to relieve hepatotoxicity, eczema, urticaria and other ailments (Asl & Hosseinzadeh, 2008; Liang et al., 2015; Xu et al., 2020; Wen et al., 2021). In addition, GL could be utilized as dietary supplement in soybean paste, soy sauce and pickles, and is listed as recognized safe substance by the U.S. Food and Drug Administration (Qu & Xiang, 2007). Currently, accumulating evidence suggested that Compound GL has beneficial influence on UC. Several clinical trials showed that Compound GL can alleviate clinical symptoms, such as abdominal pain and diarrhea, through a decrease in the levels of TNF-α, IL-6 and IL-8 (Yao, 2021; Xiao et al., 2018). Moreover, Compound GL may benefit UC by upregulating the expression of IL-10 (Sun, 2018). Results of these relevant clinical trials revealed a protective role of Compound GL in UC patients and suggested that the anti-inflammatory activity was involved in the underlying mechanisms. However, it is insufficient to draw reliable and definitive conclusions about the Compound GL efficacy based on various individual clinical trial because of the small sample size, potential publication bias, small-study effect and other factors. Furthermore, dosage forms can affect the efficacy of drugs. There are three common dosage forms of Compound GL, namely injections, tablets and capsules, but which dosage form has the optimal efficacy is still unknown. In addition, research on drug safety is of great value to clinical medication. Some studies showed that Compound GL may have adverse effects including hypokalemia and muscle cramps (de Putter & Donck, 2014; Deutch et al., 2019). Therefore, it is necessary to systematically review the adverse effects of Compound GL in the treatment of UC. Moreover, publication bias and methodological quality of clinical trials are still unclear, which may exaggerate the Compound GL efficacy.

Systematic review and meta-analysis according to clinical trials could better reply to aforementioned problems. Thus, we performed a systematic review and meta-analysis to assess Compound GL for the treatment of UC. The purposes of this study were to (1) provide empirical evidence to evaluate the anti-inflammatory activity and safety of Compound GL when used in the treatment of UC, (2) discuss which dosage form has optimal efficacy in the treatment of UC, (3) provide an assessment of methodological quality and publication bias of clinical trials, and (4) provide suggestions for future clinical trials and clinical medication.

2. Methods

This systematic review and meta-analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions and reported based on Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. The protocol for this meta-analysis is available in PROSPERO (CRD42021281363).

2.1. Search strategies

Electronic databases including PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Chinese Biomedical Literature, Wanfang Database and CQVIP database were searched for relevant studies from January 2000 to July 2021. The languages were limited to English and Chinese. Medical subject headings (MeSH) terms with free words were employed in English databases. The relevant terms were as follows: colitis, ulcerative [MeSH], UC, ulcer colonitis, ulcerative colitis, colitis gravis; Glycyrrhizic acid [MeSH], glycyrrhizin, glycyrrhizinic acid, dipotassium glycyrrhizate. Chinese databases were searched according to the aforementioned search terms in Chinese. Furthermore, some relevant studies, such as conference proceedings, were searched through other approaches.

2.2. Inclusion criteria

(1) Participants: patients with UC; (2) Intervention: Compound GL with all timings, frequencies and dosages; (3) Control: placebo, treatment registered for use in clinical practice; (4) Outcomes: TNF-α and AER were the primary outcomes, IL-6, IL-8, IL-10, IL-17, NF-κB and RER were the secondary outcomes; (5) Study design: randomized controlled trials; (6) Language: Chinese and English.

2.3. Exclusion criteria

(1) Participants: UC patients who are not suitable for Compound GL treatment; (2) Intervention: Compound GL without batch number; (3) Control: all other control conditions; (4) Study design: case studies, studies without a separate control group and cross-over studies; (5) Not an original research (e.g. review, editorials/letters, abstracts); (6) Studies without full text; (7) Duplicate publication.

2.4. Study selection and data extraction

Study selection was performed in two phases, namely initial screening based on title and abstract, followed by full-text screening of the potentially eligible studies for final determination. Also, in each phase, two reviewers independently screened records for inclusion. Disagreements between individual judgement were resolved through discussion with a third reviewer.

Two reviewers extracted the following data independently from included studies: (1) Basic information: first author's surname and year of publication; (2) Information on participants: gender, number of participants and age in treatment group and control group; (3) Information on intervention: intervention duration, dosage forms, dosage and drug names; (4) Outcome measures: TNF-α, IL-6, IL-8, IL-10, IL-17, NF-κB, AER and RER. For continuous data (e.g. TNF-α, IL-6), the mean and the standard deviation for each intervention group were extracted. For dichotomous data (e.g. AER, RER), the numbers experiencing the outcome and the total numbers for each intervention group were collected. If a trial is included with more than two intervention arms, then the interventions that meet the eligibility criteria were included in the review (Higgins and Green, 2011). In case the data was not reported or showed in the image, we attempted to contact authors by e-mail. Disagreements between reviewers over the data extraction were resolved through discussion with a third reviewer.

2.5. Assessments of risk of bias

The risk of bias of the included studies was assessed according to the Cochrane risk of bias tool for randomized trials (RoB tool). The RoB tool contains 7 entries based on six types of bias: (1) Sequence generation

(selection bias); (2) Allocation concealment (selection bias); (3) Blinding of participants and personnel (performance bias); (4) Blinding of outcome assessment (detection bias); (5) Incomplete outcome data (attrition bias); (6) Selective outcome reporting (reporting bias); (7) Other sources of bias (Other bias). The judgments are expressed simply as 'Low risk', 'High risk' or 'Unclear risk' of bias (Higgins and Green, 2011).

Two reviewers performed assessments of risk of bias independently, and discrepancies were discussed with a third reviewer.

2.6. Statistical analysis

If outcome measures were continuous data (e.g. TNF-α, IL-6), the standardized mean difference (SMD) was considered to describe the effect sizes of the intervention effect. If outcome measures were dichotomous data (e.g. AER, RER), the risk ratio (RR) was employed to express the pooled effect sizes. Random-effects (DerSimonian and Laird) method was implemented for this meta-analysis. The confidence interval (CI) was established at 95 %, and P value < 0.05 was considered to be statistically significant. To evaluate between-study heterogeneity, the chi-squared test and I^2 statistics were used. The chi-squared test with a significance level of $\alpha = 0.1$ was used as statistical measure of heterogeneity, $I^2 > 50\%$ represented a substantial heterogeneity. According to the Cochrane Handbook for Systematic Reviews of Interventions, trials with zero events in both the treatment and the control group were not included in the meta-analysis when RR was calculated. Subgroup analysis was performed to investigate the potential sources of heterogeneity and the influence of several factors on the pooled effect sizes based on following variables if there were adequate studies: combination drugs (sulfasalazine, mesalazine, glutamine), dosage forms (tablet, injection, capsule). Sensitivity analysis was performed to evaluate whether a single study affects the pooled effect sizes by omitting one study at each stage. Publication bias was assessed using the funnel plot as well as the Egger's test (Egger 1997a) if there were at least 10 studies for each outcome. For Egger's test, P value less than 0.05 was considered as statistically significant (Egger et al., 1997). Meta-analysis and subgroup analysis were performed with RevMan 5.4 software, Egger's test were conducted by using STATA 12.0 software.

3. Results

3.1. Study inclusion

A total number of 206 randomized controlled trials were identified through the databases searching for this review. After removing duplicates, 96 records remained. While screening titles and abstracts, 64 studies were excluded due to the following reasons: (1) review article; (2) animal study; (3) not Compound GL or UC; (4) others. Then, full-text selection of the 32 remaining records indicated that 9 records were ineligible due to the following reasons: (1) inappropriate outcome measures (n = 8); (2) duplicates (n = 1). Ultimately, twenty-three eligible studies were included in the present systematic review. The process of study selection was provided in Fig. 1.

3.2. Study characteristics

The twenty-three studies involving 2060 participants were published from 2005 to 2021. The number of all participants in the treatment group was 1031 and that in the control group was 1029. According to gender, 22 studies (96%) of all included both male and female and one study (4%) did not report gender. The age of participants ranged from 18 to 82 years old, two studies (8%) did not report the age. There were three dosage forms of Compound GL in these studies, namely tablet (57%), injection (39%), and capsule (4%).

Three drugs were utilized in combination with Compound GL, namely sulfasalazine (30%), mesalazine (52%) and glutamine (9%), two studies (9%) used Compound GL alone. Control groups mainly included sulfasalazine, mesalazine and glutamine. Eight studies (35%) selected sulfasalazine as control intervention and 13 studies (56%) used mesalazine, the rest 2 studies (9%) used glutamine. The intervention duration ranged from 2 to 4 weeks. One study (4%) applied 2 weeks and twenty-one studies (92%) utilized 4 weeks, the rest one study (4%) did not report intervention duration.

The characteristics of the twenty-three included studies were outlined in Table 1 (Lv et al., 2005; Zhu & Liu, 2007; Xi & Lin, 2008; Ding et al., 2016; Li et al., 2016; Du, 2017; Fan & Liu, 2017; Guan et al., 2017; Lai et al., 2018; Lin et al., 2018; Ma et al., 2018; Sun, 2018; Wang, 2018; Xiao et al., 2018; Gao & Fan, 2019; Hu & Tang, 2019; Li, 2019a; Li, 2019b; Ma & Gou, 2019; Wang, 2019; Zhu, 2020; Lu, 2021; Yao, 2021). In addition, a summary table describing the Compound GL was displayed in Table 2.

3.3. Risk of bias

Random allocation to treatment group and control group was mentioned in nineteen studies (83%), of which twelve studies described random sequence generation process (random number table). In addition, allocation concealment (selection bias), blinding of participants and personnel (performance bias) and blinding of outcome assessment (detection bias) were not mentioned in all studies. All included studies had complete outcome data and reported expected outcome. All studies did not report the protocol of clinical trials, so there was not enough evidence to assess reporting bias. For other sources of bias, twenty-one studies (91%) stated that the baseline characteristic was consistent between treatment group and control group, the rest 2 studies (9%) did not mention it. The risk of bias of included studies was displayed in Fig. 2.

3.4. Effectiveness

TNF-α: Eight studies reported the influence of Compound GL on TNF-α. The pooled results indicated that Compound GL could significantly decrease the level of TNF-α compared with the control group (n = 890, SMD = -2.03, 95 %CI [-2.61, −1.44], $P < 0.00001$; Heterogeneity: $Chi^2 = 85.36$, $P < 0.00001$; $I^2 = 92\%$. Fig. 3).

IL-6: Eleven studies reported the influence of Compound GL on IL-6, and the level of IL-6 in the treatment group was lower than that in the control group (n = 1109, SMD = -2.98, 95 %CI[-3.71, −2.25], $P < 0.00001$; Heterogeneity: $Chi^2 = 176.69$, $P < 0.00001$; $I^2 = 94\%$. Fig. 4).

IL-8: Eight studies reported the impact of Compound GL on IL-8. Compared to the control group, Compound GL could significantly lower the expression of IL-8 (n = 918, SMD = -1.55, 95 %CI[-1.79, −1.30], $P < 0.00001$; Heterogeneity: $Chi^2 = 17.73$, $P = 0.01$; $I^2 = 61\%$. Fig. 4).

IL-10: Three studies mentioned the influence of Compound GL on IL-10. The pooled effect sizes indicated that Compound GL could markedly enhance the expression of IL-10 compared with the control group (n = 240, SMD = 4.14, 95 %CI[3.47, 4.80], $P < 0.00001$; Heterogeneity: $Chi^2 = 4.26$, $P = 0.12$; $I^2 = 53\%$. Fig. 4).

IL-17: Four studies mentioned the influence of Compound GL on IL-17, a significant reduction in IL-17 level was observed after Compound GL, compared to in the control group (n = 343, SMD = -1.70, 95 %CI [-1.95, −1.45], $P < 0.00001$; Heterogeneity: $Chi^2 = 0.54$, $P = 0.91$; $I^2 = 0\%$. Fig. 4).

AER: Eighteen studies reported the AER in the treatment group and control group, and the AER in the treatment group was lower than that in the control group (n = 1380, RR = 0.51, 95 %CI[0.36, 0.73], $P = 0.0002$; Heterogeneity: $Chi^2 = 19.11$, $P = 0.32$; $I^2 = 11\%$. Fig. 5). One study with zero events in both the treatment and the control group, so this study was not included in the meta-analysis (Ding et al., 2016).

RER: Effect sizes for RER were pooled from a total of eight studies. There was a significant association of Compound GL with RER (n = 849, RR = 0.26, 95 %CI[0.17, 0.39], $P < 0.00001$; Heterogeneity: $Chi^2 =$

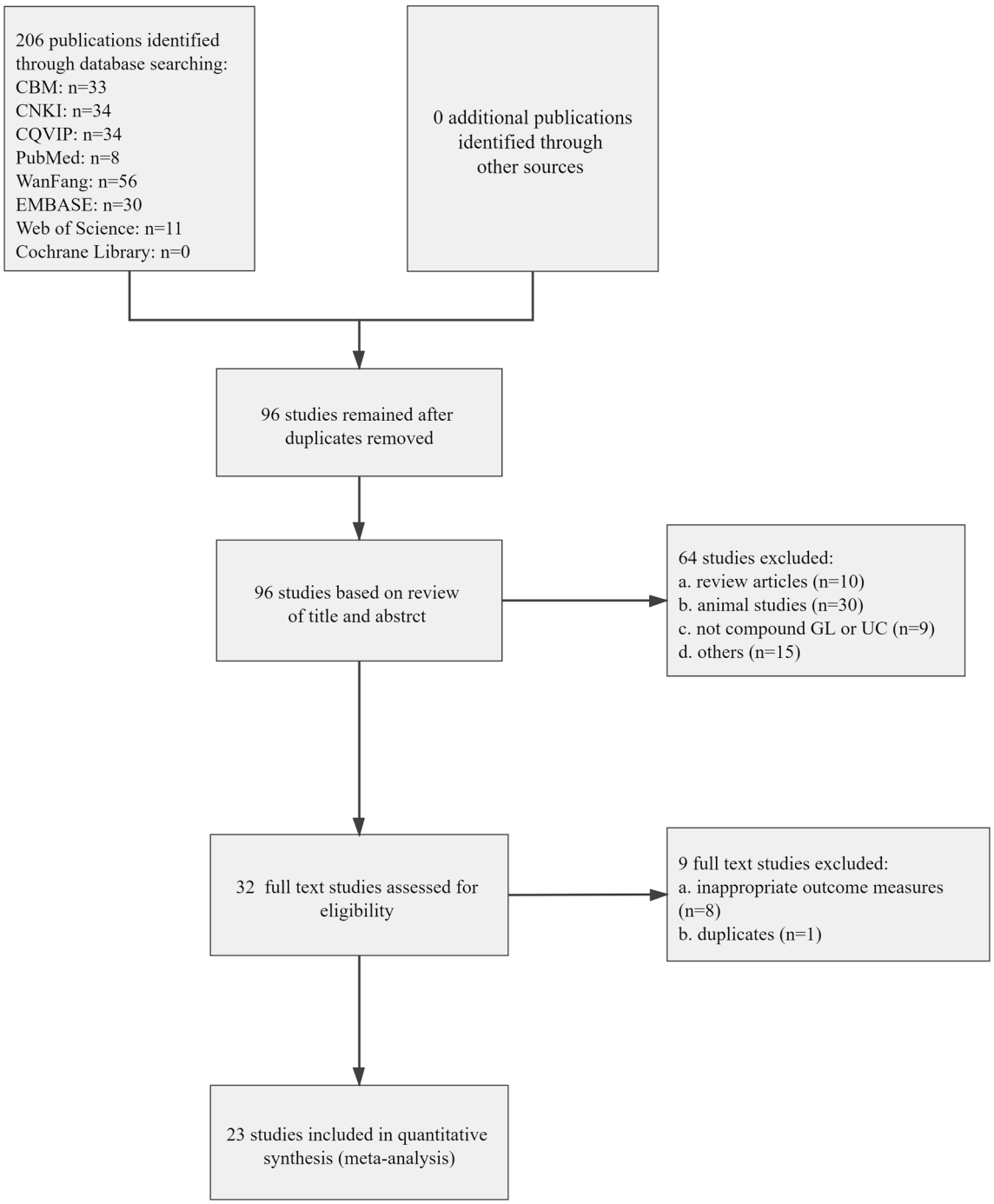

Fig. 1. Flow diagram of the study selection process.

2.39, $P = 0.94$; $I^2 = 0\%$. Fig. 5).

NF-κB: None of the included studies reported the influence of Compound GL on the NF-κB activity.

3.5. Subgroup analysis

(1) TNF-α. The different combination drug ($P = 0.92$) had no significant influence on the level of TNF-α. For dosage forms, more beneficial effects of Compound GL were observed in studies had capsules ($P = 0.0001$) (Table 3).

(2) IL-6. There was no significant difference in pooled effect size relative to different combination drug ($P = 0.14$). For dosage forms, more positive effects were observed when studies had injections ($P < 0.00001$) (Table 3).

(3) IL-8. There was no significant association of Compound GL with UC in the subgroup for combination drug ($P = 0.47$). For dosage forms, compared to the tablets and injections, more beneficial effect was found when studies used capsules ($P = 0.03$) (Table 3).

(4) IL-10. There was a significant difference in effect size relative to dosage forms ($P = 0.04$). Compared to the tablets, more beneficial effects were found when studies used injections (Table 3).

(5) IL-17. There was no significant association of Compound GL with UC in the subgroup for combination drug ($P = 0.72$) (Table 3).

(6) AER. There was no significant difference in pooled effect size relative to different combination drug ($P = 0.25$) and dosage forms ($P = 0.69$) (Table 3).

Table 1
Characteristics of the included studies.

Study year	Sample size(T, C)	Gender	Age (years)	Treatment	Dosage forms of GL	Duration (weeks)	Control	Outcome index
Lv et al., 2005	24, 24	Both	18–65	60 ml/day Compound GL (qd; ivgtt)	Injection	4	Mesalazine	1. AER
Zhu & Liu, 2007	20, 20	Both	18–61	Compound GL (tid; po) + Sulfasalazine	Tablet	4	Sulfasalazine	1. AER 2. RER
Xi & Lin, 2008	32, 32	Both	19–61	60 ml/day Compound GL (qd; ivgtt)	Injection	4	Sulfasalazine	1. AER
Ding et al., 2016	130, 130	Both	17–69	450 mg/day Compound GL (tid; po) + Sulfasalazine	Tablet	4	Sulfasalazine	1. IL-6 2. IL-8 3. TNF-α 4. RER 5. AER
Li et al., 2016	40, 40	Both	23–65	60 ml/day Compound GL (qd; ivgtt) + Mesalazine	Injection	4	Mesalazine	1. IL-10 2. IL-8 3.TNF-α 4. RER 5. AER
Du, 2017	62, 62	Both	21–63	20 ml/day Compound GL (qd; ivgtt) + Glutamine	Injection	4	Glutamine	1. AER
Fan & Liu, 2017	42, 41	NR	NR	30–120 mg/day Compound GL (tid; po) + Sulfasalazine	Tablet	4	Sulfasalazine	1. IL-6 2. IL-8 3. TNF-α 4. AER
Guan et al., 2017	40, 40	Both	18–75	450 mg/day Compound GL (tid; po) + Mesalazine	Tablet	4	Mesalazine	1. IL-17 2. IL-6 3. AER 4. RER
Lai et al., 2018	30, 30	Both	18–70	60 mg/day Compound GL (qd; ivgtt) + Sulfasalazine	Injection	4	Sulfasalazine	1. AER
Lin et al., 2018	40, 40	Both	NR	450 mg/day Compound GL (tid; po) + Mesalazine	Tablet	4	Mesalazine	1. IL-6 2. IL-10 3. TNF-α 4. IL-8 5. AER
Ma et al., 2018	70, 70	Both	30–70	40–60 ml/day Compound GL (qd; ivgtt) + Sulfasalazine	Injection	4	Sulfasalazine	1. IL-6 2. IL-8 3. TNF-α
Sun, 2018	40, 40	Both	23–65	60 ml/day Compound GL (qd; ivgtt) + Mesalazine	Injection	4	Mesalazine	1. IL-8 2. IL-10 3.TNF-α 4. AER
Wang, 2018	25, 25	Both	31–74	30–120 mg/day Compound GL (tid; po) + Sulfasalazine	Tablet	4	Sulfasalazine	1.IL-6 2.TNF-α 3.IL-8 4. AER
Xiao et al., 2018	64, 64	Both	20–66	450 mg/day Compound GL (tid; po) + Mesalazine	Tablet	4	Mesalazine	1. IL-8 2. AER 3. RER
Gao & Fan, 2019	41, 41	Both	21–74	450 mg/day Compound GL (tid; po) + Glutamine	Tablet	2	Glutamine	1. IL-6 2. IL-17 3. AER
Hu & Tang, 2019	52, 52	Both	22–58	Compound GL (tid; po) + Mesalazine	Tablet	4	Mesalazine	1. AER
Li, 2019a	55, 54	Both	23–76	Compound GL (tid; po) + Mesalazine	Tablet	4	Mesalazine	1. IL-17 2. IL-6 3.RER
Li, 2019b	40, 40	Both	22–44	60 ml/day Compound GL (qd; ivgtt) + Mesalazine	Injection	4	Mesalazine	1. IL-8 2. IL-10 3.TNF-α 4. RER 5. AER
Ma & Gou, 2019	50, 50	Both	21–82	90 mg/day Compound GL (tid; po) +Sulfasalazine	Capsule	4	Sulfasalazine	1. IL-6 2. IL-8 3.TNF-α 4. AER
Wang, 2019	30, 30	Both	33–76	Compound GL (tid; po) + Mesalazine	Tablet	NR	Mesalazine	1. AER
Zhu, 2020	18, 18	Both	22–72	40 mg/day Compound GL (qd; ivgtt) + Mesalazine	Injection	4	Mesalazine	1. IL-6 2. AER
Lu, 2021	36, 36	Both	22–69	Compound GL (tid; po) + Mesalazine	Tablet	4	Mesalazine	1. IL-17 2. IL-6 3. RER
Yao, 2021	50, 50	Both	31–69	150–225 mg/day Compound GL (tid; po) + Mesalazine	Tablet	4	Mesalazine	1. TNF-α 2. IL-6

Note: (**AER**, adverse effects rate; **Both**, female and male; **GL**, glycyrrhizin; **ivgtt**, intravenous drip; **NR**, no report; **po**, oral administration; **qd**, once a day; **RER**, recurrence rate; **tid**, three times a day).

(7) RER. There was no significant difference in pooled effect size relative to different combination drug ($P = 0.21$) and dosage forms ($P = 0.61$) (Table 3).

3.6. Sensitivity analysis

For TNF-α, IL-6, IL-8, IL-10, IL-17, AER and RER, the sensitivity analysis was conducted by removing one study at each stage, and the results indicated that no individual study significantly affected the pooled effect sizes.

Table 2
A summary table describing the Compound GL.

Study year	Source	Brand name	Ingredients	Executive standards	SFDA approval number
Lv et al., 2005	Minophagen Pharmaceutical Co. Ltd	Compound Glycyrrhizin Injection (SNMC)	GL (40 mg) + Gly (400 mg) + L-Cys. HCl (20 mg)	JX20100216	J20130071
Zhu & Liu, 2007	NR	Compound Glycyrrhizin Tablets	NR	NR	NR
Xi & Lin, 2008	NR	Compound Glycyrrhizin Injection	NR	NR	NR
Ding et al., 2016	Jiangsu Pengyao Pharmaceutical Co. Ltd	Compound Glycyrrhizin Tablets	GL (25 mg) + Gly (25 mg) + DL-Methionine (25 mg)	NR	H20153162
Li et al., 2016	Xi'an Lijun Pharmaceutical Co. Ltd	Compound Glycyrrhizin Injection (PAI GAN NENG)	GL (40 mg) + Gly (400 mg) + L-Cys. HCl (20 mg)	YBH25192005	H20057478
Du, 2017	Minophagen Pharmaceutical Co. Ltd.	Compound Glycyrrhizin Injection (SNMC)	GL (40 mg) + Gly (400 mg) + L-Cys. HCl (20 mg)	JX20100216	J20130071
Fan & Liu, 2017	Xinjiang Tefeng Pharmaceutical Co. Ltd	Compound Glycyrrhizin Tablets	GL (25 mg) + Gly (25 mg) + DL-Methionine (25 mg)	YBH07542010	H20103804
Guan et al., 2017	Xi'an Lijun Pharmaceutical Co. Ltd	Compound Glycyrrhizin Injection (PAI GAN NENG)	GL (40 mg) + Gly (400 mg) + L-Cys. HCl (20 mg)	YBH25192005	H20057478
Lai et al., 2018	Chengdu Easton Biopharmaceutical Co. Ltd	Compound Glycyrrhizin Injection (SU LAI LE)	GL (20 mg) + Gly (200 mg) + L-Cys. HCl (10 mg)	YBH09712008	H20080538
Lin et al., 2018	Akiyama Jozai Co. Ltd	Compound Glycyrrhizin Tablets (SNMC)	GL (25 mg) + Gly (25 mg) + DL-Methionine (25 mg)	JX20150409	H20080182
Ma et al., 2018	Xi'an Yuanda Detian Pharmaceutical Co. Ltd	Compound Glycyrrhizin Injection	GL (40 mg) + Gly (400 mg) + L-Cys. HCl (20 mg)	YBH18202006	H20066563
Sun, 2018	NR	Compound Glycyrrhizin Injection	GL (40 mg) + Gly (400 mg) + L-Cys. HCl (20 mg)	NR	NR
Wang, 2018	Jiangsu Pengyao Pharmaceutical Co. Ltd	Compound Glycyrrhizin Tablets	GL (25 mg) + Gly (25 mg) + DL-Methionine (25 mg)	NR	H20153162
Xiao et al., 2018	Lepu Pharmaceutical Co. Ltd	Compound Glycyrrhizin Tablets	GL (25 mg) + Gly (25 mg) + DL-Methionine (25 mg)	YBH03002007	H20073723
Gao & Fan, 2019	Xinjiang Tefeng Pharmaceutical Co. Ltd	Compound Glycyrrhizin Tablets	GL (25 mg) + Gly (25 mg) + DL-Methionine (25 mg)	YBH07542010	H20103804
Hu & Tang, 2019	Lepu Pharmaceutical Co. Ltd	Compound Glycyrrhizin Tablets	GL (25 mg) + Gly (25 mg) + DL-Methionine (25 mg)	YBH03002007	H20073723
Li, 2019a	Lepu Pharmaceutical Co. Ltd	Compound Glycyrrhizin Tablets	GL (25 mg) + Gly (25 mg) + DL-Methionine (25 mg)	YBH03002007	H20073723
Li, 2019b	Minophagen Pharmaceutical Co. Ltd.	Compound Glycyrrhizin Injection (SNMC)	GL (40 mg) + Gly (400 mg) + L-Cys. HCl (20 mg)	JX20100216	J20130071
Ma & Gou, 2019	Weifang Zhongshi Pharmaceutical Co. Ltd	Compound Glycyrrhizin Capsules	GL (25 mg) + Gly (25 mg) + DL-Methionine (25 mg)	YBH12282008	H20080677
Wang, 2019	Xi'an Lijun Pharmaceutical Co. Ltd	Compound Glycyrrhizin Tablets (PAI GAN NENG)	GL (25 mg) + Gly (25 mg) + DL-Methionine (25 mg)	YBH00062009	H20093006
Zhu, 2020	NR	Compound Glycyrrhizin Injection	NR	NR	NR
Lu, 2021	Xi'an Lijun Pharmaceutical Co. Ltd	Compound Glycyrrhizin Tablets (PAI GAN NENG)	GL (25 mg) + Gly (25 mg) + DL-Methionine (25 mg)	YBH00062009	H20093006
Yao, 2021	Eisai (China) Pharmaceutical Co., LTD	Compound Glycyrrhizin Tablets	GL (25 mg) + Gly (25 mg) + DL-Methionine (25 mg)	NR	J20130077

Note: (**Gly**, glycine; **GL**, glycyrrhizin; **L-Cys.HCl**, L-cysteine hydrochloride hydrate; **NR**, no report.
SNMC, Stronger Neo-Minophagen C®).

3.7. Publication bias

(1) IL-6. Visual inspection of funnel plots suggested asymmetry for the efficacy of Compound GL on IL-6 level (Fig. 6), while the result of Egger's test was statistically significant (intercept: −7.97, 95 %CI [-12.05.71, −3.88]; $P = 0.002$).

(2) AER. Visual inspection of funnel plots indicated probable symmetrical for the efficacy of Compound GL on AER (Fig. 6), and this result was supported by Egger's test (intercept: −0.10, 95 %CI [-1.26, 1.06]; $P = 0.859$).

Publication bias was not performed on TNF-α, IL-8, IL-10, IL-17 and RER as less than ten studies were included.

4. Discussion

4.1. Efficacy of Compound GL

The present systematic review and meta-analysis mainly intended to evaluate the anti-inflammatory activity and safety of Compound GL when used in the treatment of UC. The results suggested that Compound GL was significantly associated with a lower level of TNF-α, IL-6, IL-8, IL-17, AER, RER and a higher level of IL-10. In addition, sensitivity analysis that excluded one study at each stage did not alter these results. According to the above findings, our meta-analysis demonstrated that Compound GL could confer protection against UC by inhibiting inflammation. Nevertheless, some adverse effects, such as edema, should be paid attention to in clinical application.

4.2. Implication for further studies

GL, a triterpene glycoside, is the primary active ingredient of Gan-Cao (licorice) and represents about 10% of the liquorice root dry weight (Pastorino et al., 2018; Rizzato et al., 2017). GL consists of two molecules of glucuronic acid (18β-glycyrrhetinic acid-3-O-β-D-glucuronopyranosyl-(1 → 2)-beta-D-glucuronide) and one molecule of 18β-glycyrrhetinic acid (Li et al., 2014). GL has a CAS number of 1405-86-3, a molecular weight of 822.92 and an empirical formula of $C_{42}H_{62}O_{16}$. Pure GL is white needle-like crystal, odorless and extremely sweet. In addition, it could be hydrolyzed into glycyrrhizinic acid and two molecules of glucuronic acid by heating, pressing and diluted acid. Currently, the extraction methods of GL mainly include water extraction, dilute ammonia water extraction, ammonia ethanol extraction,

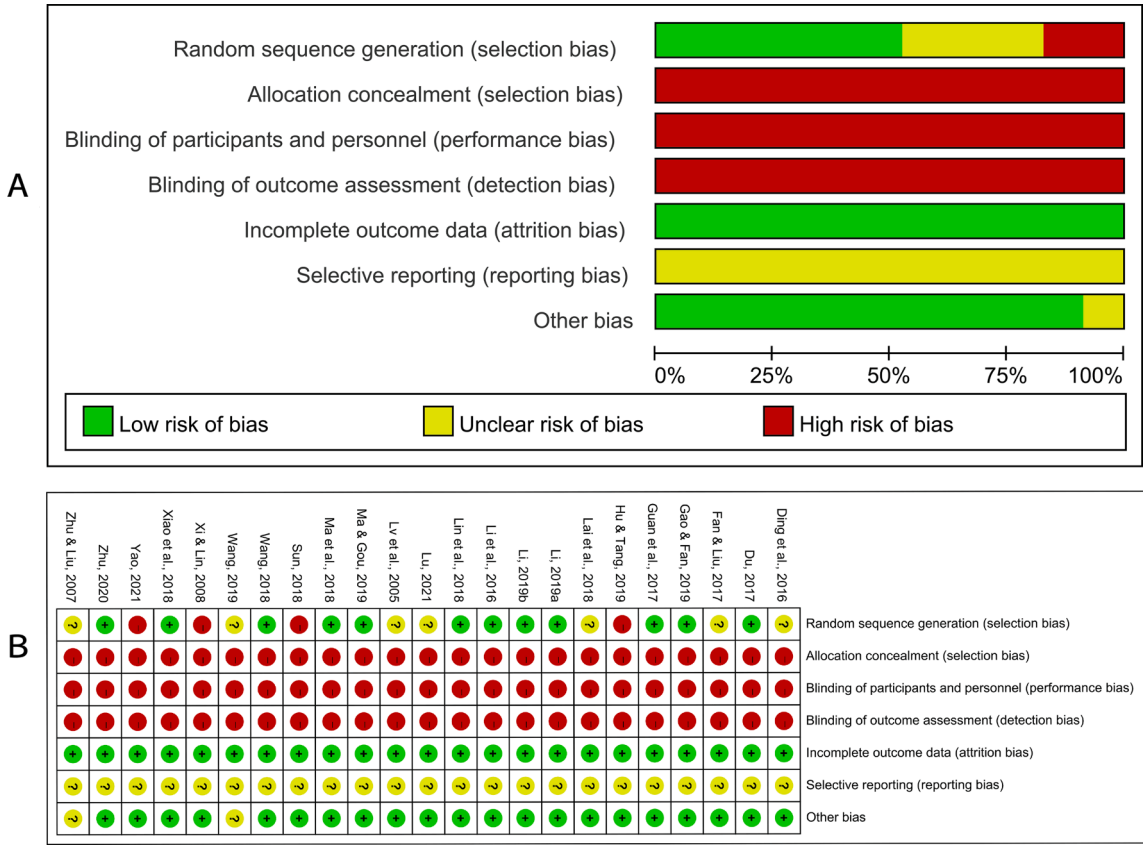

Fig. 2. Risk of bias. (A) Risk of bias graph. (B) Risk of bias summary.

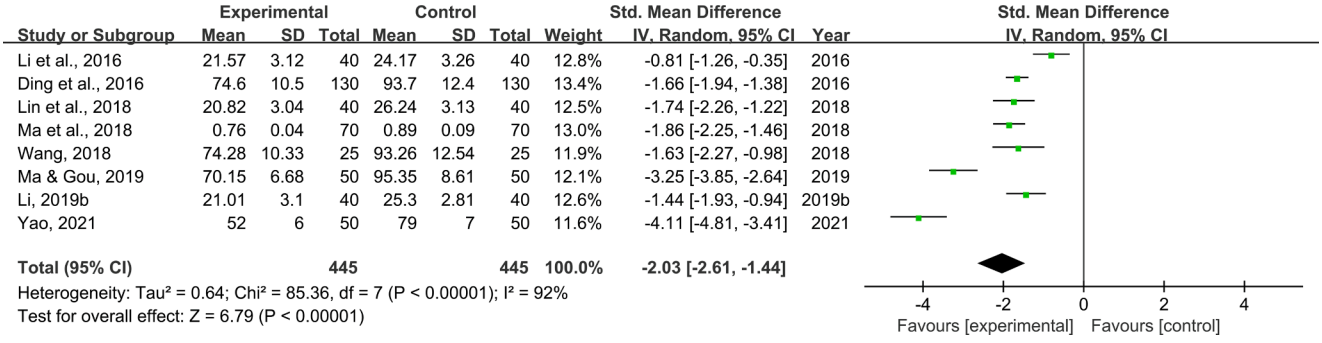

Fig. 3. The effects of Compound GL on TNF-a level.

ultrasonic enhanced extraction, microwave-assisted extraction, and supercritical fluid extraction (Feng et al., 2012). However, shortcomings such as low extraction rate and ammonia leakage exist in the former three extraction methods. The extraction rate of ultrasonic enhanced extraction and microwave-assisted extraction method is high and stable, which can provide theoretical and practical basis for future research on GL extraction, and also provide a meaningful reference for industrial production of GL (Feng et al., 2012). Moreover, a previous study investigated the influencing factors of supercritical fluid extraction and determined the optimal extraction scheme by designing experiments with the extraction rate of GL as an indicator: licorice strips were soaked with 5 ml water and a small amount of 1 mol/L ammonia water, the pressure was 9.5 MPa, the time was 110 min, and 1 ml ethanol was added into CO_2 as modifier (Li et al., 1998). This method has the highest extraction rate, which has been used in large-scale pharmaceutical production companies.

Nowadays, therapeutic drugs made with GL have been on the market for many years, such as Compound GL. Compound GL injection is approved in Japan in 1948. Currently, except for the injections, oral formulations (tablets and capsules) are also marketed as the ethical drugs (Koga & Kikuchi, 2012). With regard to Compound GL injections, the ingredients are GL, glycine and L-cysteine hydrochloride hydrate. Analogously, GL, glycine and DL-Methionine are the compositions in oral formulations. In this meta-analysis, Compound GL was provided by pharmaceutical companies including Minophagen Pharmaceutical Co. Ltd., Tokyo, Japan and Xi'an Lijun Pharmaceutical Co. Ltd., Xi'an, China. Pharmaceutical companies produce Compound GL according to the State Food and Drug Administration executive standards, thus the production methods of Compound GL are basically similar for each pharmaceutical company. Taking injections and tablets as an example, the production processes of Compound GL injections are as follows: raw materials and auxiliary materials → dissolution → concentration → dilute → activated carbon adsorption → filtration (coarse filtration → fine filtration) → separation → sterilization, and the production methods

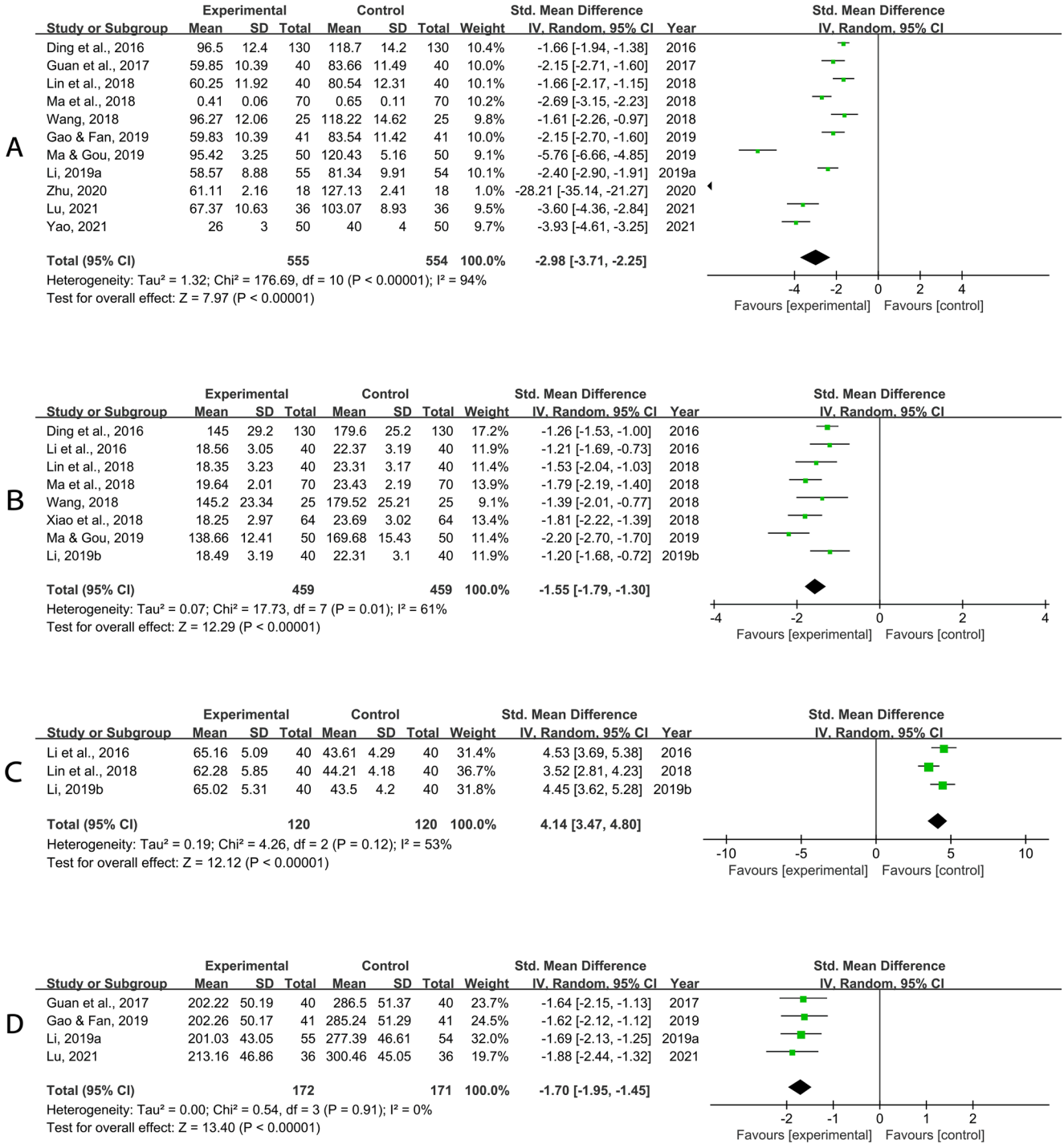

Fig. 4. The effects of Compound GL on (A) IL-6 level; (B) IL-8 level; (C) IL-10 level; (D) IL-17 level.

of Compound GL tablets are as follows: raw materials and excipients → grinding → sieving → weighing → mixing → sieving → granulating → drying → calculating tablet weight → pressing (Sui & Pu, 2018). The executive standards numbers can be found in Table 2.

TNF-α has an indispensable role in pro-inflammatory cytokines, which can increase intestinal permeability and activate the adaptive immune system of the intestine. In addition, excessive production of TNF-α level could lead to epithelial cell apoptosis, epithelial barrier injury and chemokine secretion by colonic epithelial cells (Cho et al., 2011; Vivinus-Nébot et al., 2014). Several reports indicated that Compound GL could significantly decrease the level of TNF-α in the patients with UC (Yao, 2021; Ma & Gou, 2019). In our meta-analysis, it was observed that the level of TNF-α in the Compound GL-treated group was lower than that in the control group. Our results were consistent with previous findings. Modern research showed that dosage form has a certain influence on therapeutic effects, thus it is of great significance to select the appropriate dosage form for patients. Nevertheless, no study reported the influence of Compound GL dosage forms on TNF-α level. In this review, there were three different dosage forms of Compound GL (tablets, injections, capsules), and the optimal effects were recorded in capsule-treated UC patients, which showed significant difference compared with injection-treated patients. These results may suggest that Compound GL capsules have a best therapeutic effect in improving TNF-α level in UC patients. Combination therapy is widely used in the

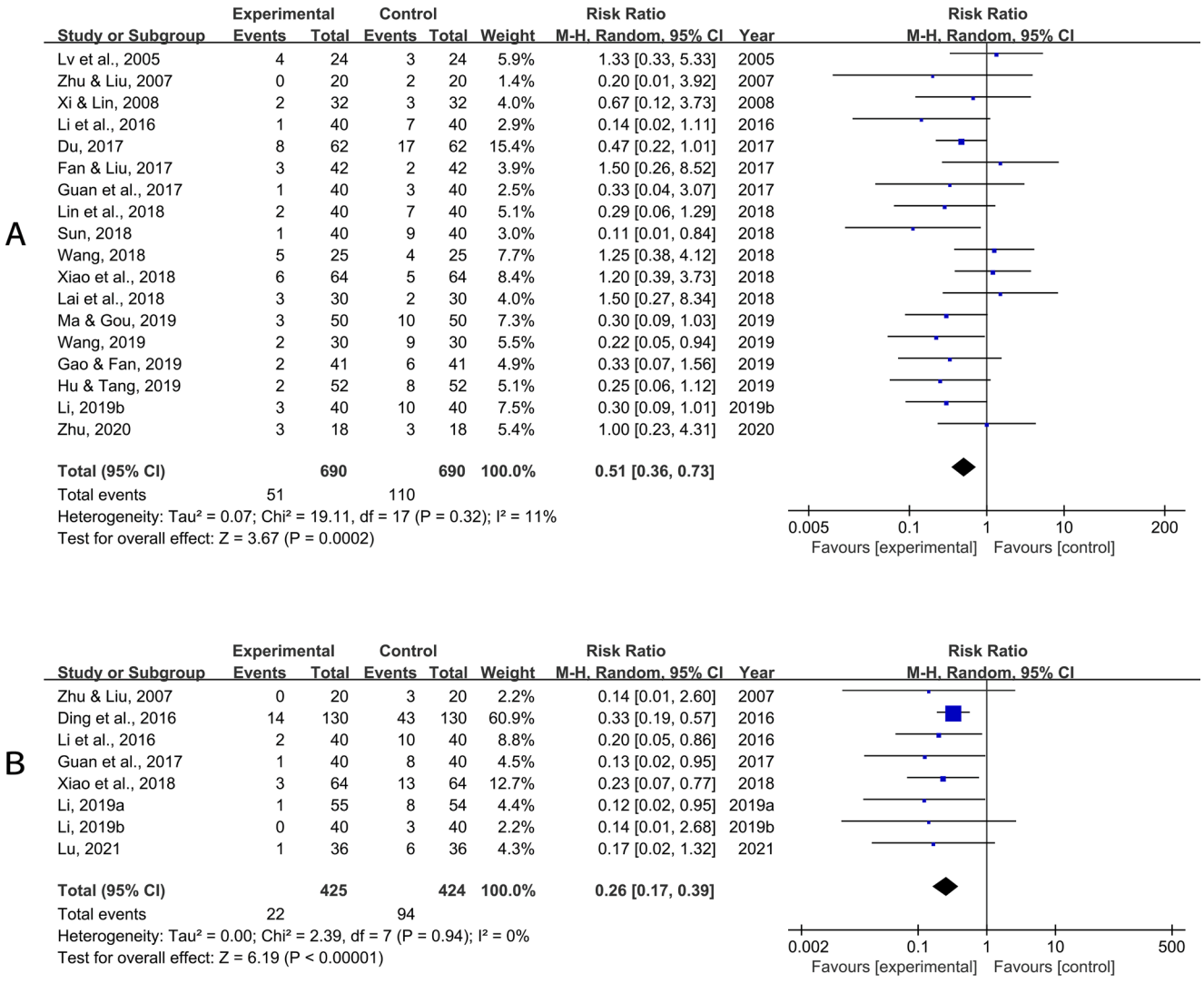

Fig. 5. The effects of Compound GL on (A) AER; (B) RER.

management of UC, such as a combination therapy of Compound GL and conventional drugs (e.g. sulfasalazine, mesalazine), but there were no researches on the difference in efficacy between different combination therapy. In this meta-analysis, there was no significant difference in TNF-α level between Compound GL + sulfasalazine and Compound GL + mesalazine combination ($P = 0.92$). Based on the above findings, we found that there was a crucial problem in numerous clinical trials, most or even all trials focused on the efficacy of Compound GL, but ignored what factors can affect its therapeutic effects, such as dosage forms and combination therapy. Hence, attention should be paid to the following two aspects in the future clinical trials: First, the conclusion that dosage forms have an influence on the efficacy of Compound GL should be confirmed by more prospective evidence. Second, it is necessary to compare the effects of Compound GL in combination with different conventional drugs, and determine which combination treatment is more effective.

IL-6, IL-8 and IL-17 have a fundamental role in driving mucosal inflammation in UC.

IL-6 can exhibit pro-inflammatory functions by activating multiple target cells, such as T cells and antigen-presenting cells, and IL-8 is an important chemokine secreted by monocyte-macrophages after activation, which can drive inflammatory response and the occurrence of UC (Neurath, 2014). Moreover, IL-17 was found to exert pro- inflammatory functions including the recruitment of neutrophils, the increase of TNF-α, IL-6 and IL-8 and the secretion of matrix metalloproteinases by intestinal fibroblasts (Monteleone et al., 2006; Monteleone et al., 2005; Siakavellas & Bamias, 2012). Previous studies found that Compound GL was significantly associated with a lower level of IL-6, IL-8 and IL-17 (Guan et al., 2017; Wang, 2018; Gao & Fan, 2019). In our meta-analysis, IL-6, IL-8 and IL-17 levels were markedly decreased in the treatment group, which further confirmed that Compound GL could inhibit inflammation by suppressing the expression of IL-6, IL-8 and IL-17. However, no study reported the influence of dosage form on the above outcomes. Results reported here showed that different dosage form of Compound GL could affect the efficacy in the level of IL-6 and IL-8, but this conclusion should be further confirmed by preclinical evidence as well as clinical evidence. Nevertheless, there were no sufficient studies to conduct relevant analysis on IL-17. In addition, no significant difference was observed in the IL-6, IL-8 and IL-17 levels between all combination therapy of Compound GL and conventional drugs.

IL-10, as an important anti-inflammatory cytokine in the human body, could inhibit pro-inflammatory cytokine production by T cells and antigen-presenting cells and enhance barrier integrity in the pathogenesis of chronic intestinal inflammation (Neurath, 2014; Chen et al., 2017). Early reports showed that Compound GL could markedly upregulate the expressions of IL-10 in patients with UC (Sun, 2018; Li, 2019b). Their findings were supported by our results. In our meta-analysis, it was observed that the IL-10 production was higher in the

Table 3
Subgroup analysis for each outcome measure.

Variables	No. of Trials	No. of participants	SMD [95 %CI] or RR [95 %CI]	*P* value
TNF-α				
combination drug				
sulfasalazine	4	550	−2.07 [-2.69, −1.45]	0.92
mesalazine	4	340	−2.00 [-3.20, −0.80]	
dosage forms				
tablet	4	490	−2.25 [-3.20, −1.31]	0.0001
injection	3	300	−1.37 [-2.00, −0.75]	
capsule	1	100	−3.25 [-3.85, −2.64]	
IL-6				
combination drug				
sulfasalazine	4	550	−2.87 [-4.19, −1.56]	0.14
mesalazine	6	477	−3.41 [-4.63, −2.20]	
glutamine	1	82	−2.15 [-2.70, −1.60]	
dosage forms				
tablet	8	833	−2.36 [-2.89, −1.83]	<0.00001
injection	2	176	−15.21 [-40.21, 9.79]	
capsule	1	100	−5.76 [-6.66, −4.85]	
IL-8				
combination drug				
sulfasalazine	4	550	−1.65 [-2.08, −1.22]	0.47
mesalazine	4	368	−1.45 [-1.75, −1.15]	
dosage forms				
tablet	4	518	−1.48 [-1.74, −1.21]	0.03
injection	3	300	−1.42 [-1.83, −1.02]	
capsule	1	100	−2.20 [-2.70, −1.70]	
IL-10				
dosage forms				
tablet	1	80	3.52 [2.81, 4.23]	0.04
injection	2	160	4.49 [3.90, 5.08]	
IL-17				
combination drug				
mesalazine	3	261	−1.73 [-2.01, −1.44]	0.72
glutamine	1	82	−1.62 [-2.12, −1.12]	
AER				
combination drug				
sulfasalazine	5	334	0.78 [0.36, 1.70]	0.25
mesalazine	9	728	0.37 [0.22, 0.65]	
glutamine	2	206	0.44 [0.22, 0.87]	
no combination	2	112	1.02 [0.34, 2.99]	
dosage forms				
tablet	9	708	0.54 [0.31, 0.93]	0.69
injection	8	572	0.53 [0.30, 0.92]	
capsule	1	100	0.30 [0.09, 1.03]	
RER				
combination drug				
sulfasalazine	2	300	0.32 [0.18, 0.54]	0.21
mesalazine	6	549	0.18 [0.09, 0.36]	
dosage forms				
tablet	6	689	0.27 [0.17, 0.42]	0.61
injection	2	160	0.19 [0.05, 0.69]	

Note: *P* value for test for subgroup difference.

Compound GL-treated group than that in the control group. In addition, we found that the highest efficacy was documented in Compound GL injection, which showed significant difference compared with Compound GL tablet. Nevertheless, this finding that Compound GL injection tends to have a better effect on IL-10 expression should be demonstrated through increasing sample size. For combination therapy, there were no sufficient studies to preform subgroup analysis to compare different combination treatments on the level of IL-10.

The selection of dosage forms play a substantial role in clinical medication. Therefore, whether the dosage forms of Compound GL influence intervention efficacy should be investigated. Nevertheless, the comparison of the efficacy of different Compound GL dosage forms on inflammatory factors in patients with UC was not explored. In this meta-analysis, Compound GL capsules were most effective in improving the levels of IL-8 and TNF-α compared to injections and tablets. In addition, the injections had the best effects in regulating IL-6 and IL-10 levels. These contradictory results might be due to the small sample size in subgroup analysis. For example, only one study was included in the capsule groups of TNF-α, IL-6 and IL-8. Therefore, the influence of Compound GL dosage forms in anti-inflammatory capacity in the treatment of UC should be further clarified through increasing sample size.

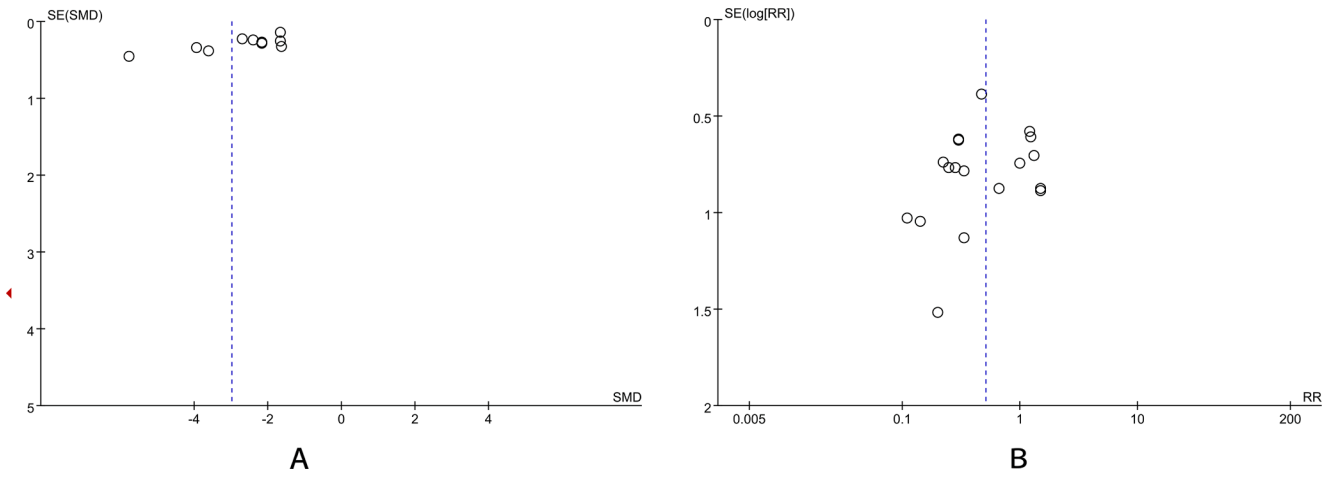

Fig. 6. Funnel plot of effects of Compound GL on (A) IL-6; (B) AER.

NF-κB is first discovered in 1986 by Sen and Baltimore, as a protein factor named NF-κB that specifically binding to the enhanced κB sequence (5′-GGGACTTTCC-3′) of the immunoglobulin K light chain gene in B nuclear extract (Sen & Baltimore, 1986). NF-κB is an important nuclear transcription factors with an extensive range of biological functions, which exists in almost all types of mammal cells (Zhang et al., 2021). The inhibition of various inflammatory cytokines by peroxidase proliferator -activated receptor γ (PPARγ) is mainly accomplished by inhibiting the activation of NF-κB, and the PPARγ ligand could decrease NF-κB activity to alleviate colonic inflammation in mice (Bassaganya-Riera et al., 2004). Except for animal experiments, significant findings were also found in clinical trials. A previous study found that NF-κB P65 expression was enhanced in crypt epithelium and epithelial hyperplasia of the edema area and crypt abscess, and the staining was mainly in the nucleus. The expression of NF-κB P65 mRNA and protein in the colonic mucosal inflammatory tissue of UC patients was increased with the increase of inflammation degree, and was positively correlated with the pathological grade of UC, which suggested that NF-κB P65 plays a key role in the occurrence and development of UC inflammation (Miao et al., 2010). In addition, one research reported that NF-κB DNA binding activity in untreated UC patients was significantly higher than that in drug-treated UC group, and the NF-κB binding activity was positively correlated with IL-1 mRNA and IL-8 mRNA expression levels (Gan et al., 2002). These findings showed that the inflammatory response caused by NF-κB activation is an important pathogenesis of the occurrence and development of UC. In this meta-analysis, no study reported the effects of Compound GL on NF-κB activity. Therefore, NF-κB activity needs to be detected and analyzed in future anti-inflammatory studies in clinical trials.

Every medical intervention comes with the risk, great or small, of adverse effects. All clinicians should comprehensively consider the adverse effects of interventions. In this meta-analysis, the major interventions were Compound GL + conventional drugs (e.g. sulfasalazine, mesalazine) in the treatment group and conventional drugs in the control group. Several adverse effects were found in both the treatment group and control group, such as nausea, emesis, abdominal distension, abdominal pain and dizzy. In addition, it is noteworthy that an adverse effect of edema was occurred in the treatment group but not in the control group. This finding indicated that Compound GL could result in edema. In addition, it is worth paying attention to whether the dosage forms of Compound GL affect the occurrence of adverse effects. According to the clinical application of Compound GL, its injections, tablets and capsules could produce adverse effects such as hypokalemia, edema and elevated blood pressure. A retrospective analysis of 300 patients who received Compound GL injection showed that the incidence rate of elevated blood pressure was 18.67% and hypokalemia was 12.3% (Wang et al., 2021). Another retrospective study found that oral formulations of Compound GL (tablets and capsules) can lead to hypokalemia and rhabdomyolysis (Li et al., 2019). However, it should be noted that the dosage forms may have an effect on the occurrence time of adverse effects. In retrospective study of Compound GL leading to hypokalemia or rhabdomyolysis, adverse effects occurred later in the oral formulation group compared with the injection group. The median time of the injection group was 4 days, and 75% of cases occurred within 7 days or less, and the median time of the oral preparation group was 52 days, and 80% of cases occurred at least 14 days (Li et al., 2019). Therefore, in the clinical application of Compound GL preparation, in addition to strictly follow the usage and dosage prescribed in the drug instructions, the use of large dose and long time should be avoided as far as possible, and the serum potassium level should be monitored in time for patients with long- term use. With regard to AER, in general, the adverse effects of combination therapy are more than that of monotherapy. However, we found that the AER in the treatment group was lower than that in the control group ($P < 0.05$). Pharmacological research indicated that conventional drugs, such as sulfasalazine and mesalazine, could lead to liver toxicity (Li et al., 2020; Li et al., 2011). Also, GL has been demonstrated to have a hepatic protection effect (Li et al., 2021), so Compound GL may alleviate the adverse effects of conventional drugs by protecting the liver. UC is prone to recurrence, results of this study showed that RER in the treatment group was lower than that in the control group ($P < 0.05$). Hence, a combination therapy of Compound GL and conventional drugs is of great value to clinical application, which can improve therapeutic effects and mitigate adverse effects.

4.3. Methodological considerations

Several limitations should be considered in this systematic review and meta-analysis. First, Egger's test and asymmetry of funnel plot suggested that publication bias was existed, which could exaggerate the efficacy of Compound GL. Hence, the positive findings of Compound GL should be interpreted with caution. Second, some included studies were of poor quality. For example, several studies did not report the process of random sequence generation. Third, because of limited number of studies, subgroup analysis of IL-10 and IL-17 were not performed based on dosage form or combination drugs.

5. Conclusion

In this meta-analysis, Compound GL can significantly decrease the levels of TNF-α, IL-6, IL-8 and IL-17 and enhance the expression of IL-10. These findings supported the anti-inflammatory activity of Compound

GL when used in the treatment of UC. In addition, Compound GL can alleviate the adverse effects of conventional drugs (e.g. sulfasalazine, mesalazine), but it can also lead to edema. Further studies are required on the safety of Compound GL and its mitigative effects on the adverse effects of conventional drugs.

6. Ethics Statement

The research did not include any human subjects and animal experiments.

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CRediT authorship contribution statement

Hengchang Hu: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Yuanhong Lei:** Data curation, Methodology, Writing – original draft, Writing – review & editing. **Wei Zhang:** Data curation, Writing – original draft, Writing – review & editing. **Peiyu Xiong:** Data curation, Writing – original draft, Writing – review & editing. **Li Song:** Investigation, Writing – original draft, Writing – review & editing. **Xiaoqiong Luo:** Conceptualization, Formal analysis, Supervision, Validation, Writing – original draft, Writing – review & editing. **Bo Jia:** Project administration, Writing – original draft, Writing – review & editing. **Fenghua Zhang:** Funding acquisition, Project administration, Resources, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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