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RESEARCH ARTICLE

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Efficacy and safety of compound glycyrrhizin in patients with alopecia areata: a systematic review and meta-analysis

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ABSTRACT

Background: Although compound glycyrrhizin (CG) has been widely used to alopecia areata (AA) in China, its efficacy and safety remain unclear. This systematic review and meta-analysis aimed to evaluate the efficacy and safety of CG for AA.

Materials and methods: Eight literature databases were retrieved from their inceptions to 29 February 2024 to identify the eligible randomized controlled trials comparing CG plus conventional treatments with conventional treatments alone for the treatment of AA. Risk ratio (RR), mean difference and 95% confidence interval (CI) were used to estimate the pooled results. RevMan 5.4 (Cochrane Collaboration, Copenhagen, Denmark) and Stata 12.0 software (StataCorp., College Station, TX) were used for statistical analysis.

Results: A total of 23 eligible studies with 2219 patients were included. The pooled results revealed that CG plus conventional treatments was superior to conventional treatments alone in cure rate (RR = 1.60, 95%CI [1.47, 1.74], $p < .001$), total efficacy rate (RR = 1.37, 95%CI [1.29, 1.45], $p < .001$) and the Severity of Alopecia Tool (SALT) score, regardless of different conventional treatments, treatment courses and doses of CG. In terms of safety, a few patients suffered from adverse events (AEs), including oedema, elevated blood pressure and gastrointestinal tract discomfort, and the incidence of oedema was higher in the patients receiving CG (RR = 2.53, 95%CI [1.04, 6.19], $p = .04$).

Conclusions: The combination of CG and conventional treatments was effective and safe for patients with AA, and CG could promote hair regrowth with mild AEs.

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Adverse reactions; alopecia areata; compound glycyrrhizin; effectiveness; meta-analysis

Introduction

Alopecia areata (AA) is a common immune-mediated disease characterized by non-scarring hair loss involving the scalp and/or body. AA affects 2% of the global population, and the prevalence of AA is increasing over time [1]. Due to hair loss, depression and anxiety are common in patients with AA, and their life qualities are also significantly damaged [2,3]. In addition, the frequent outpatient visits and high medical costs cause substantial incremental healthcare costs [4]. In the treatments of AA, topical corticosteroid (TCS) is the first-line treatment for children and adults with AA, and topical minoxidil is widely used to accelerate hair regrowth. Intralesional corticosteroid (ILC) is also recommended for adults with mild to moderate AA. In addition, oral corticosteroid, intramuscular corticosteroid, cyclosporin, methotrexate, azathioprine and baricitinib could be used for severe AA [5–7]. However, only 56–81% patients receiving TCS alone and 81–87% patients receiving ILC alone could achieve significant hair regrowth [8–11]. Meanwhile, those systematic drugs are not applicable for patients complicated with liver dysfunction, renal dysfunction, malignancy or infectious diseases, and the long-term use of them might increase the incidences of some adverse reactions, such as liver and renal dysfunctions, hypertension and malignancy [12,13].

In China, compound glycyrrhizin (CG) is an immunomodulatory drug containing the active ingredients extracted from the root of *Glycyrrhiza*. The oral formulations of CG include tablet and capsule, and there are 25 mg of glycyrrhizin, 25 mg of glycine, and 25 mg of methionine in a tablet or capsule. In the

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past decades, CG has been widely used to treat some skin diseases, including eczema, chronic urticaria, psoriasis and AA [14–16]. Some studies showed that CG could regulate different T lymphocyte subsets (e.g. T helper (Th) 1, Th2, Th17 and T regulatory (Treg) cells) and their cytokines expression. When eczema patients were treated with CG, their levels of serum interleukin (IL)-4 and immunoglobulin E (IgE) were significantly reduced, while the level of serum interferon (IFN)-γ and the ratio of Th1/Th2 were significantly increased [17,18]. Moreover, CG could decrease the level of serum IL-17 and the percentage of Th17 and increase the level of serum IL-10 and the proportion of Treg in patients with psoriasis [19,20]. In addition, for the treatment of chronic urticaria, CG was also able to reduce the levels of serum IL-4 and IgE and improve the level of serum IFN-γ [21]. Therefore, due to the immunomodulatory effect, CG has been recommended to combine with conventional treatments to improve the clinical efficacy in patients with these inflammatory skin diseases [22,23]. In terms of the treatment of AA, some clinical trials demonstrated that CG plus conventional treatments could accelerate hair regrowth in comparison with conventional treatments alone, and no serious adverse reactions were reported [24,25]. Based on a survey for dermatologists in the southwest China, more than 60% of dermatologists recommended CG to treat AA, and 31% of them chose it due to low economic burden. Moreover, 46% of dermatologists confirmed the safety of CG for the treatment of AA [26].

To the best of our knowledge, although CG has been approved for AA in China, it is not strongly recommended in the Chinese guideline on the treatment of AA [27]. One meta-analysis on the efficacy and safety of CG plus topical minoxidil for AA was published in 2020 [28]; however, it did not illustrate the definition of outcomes, and some conventional treatments were not included, such as TCS and ILC. Therefore, in order to guide the clinical application of CG for AA, this systematic review and meta-analysis collected the latest studies and provided the reliable evidence on the efficacy and safety of CG for AA.

Materials and methods

This systematic review and meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement [29]. The protocol was registered in the PROSPERO (registration number: CRD 42022347287).

Search strategy

Eight literature databases were searched from their inceptions to 29 February 2024, including China National Knowledge Infrastructure (CNKI), Wanfang database (Wanfang), Chinese Scientific Journal Database (VIP), Chinese Biomedical Literature (SinoMed), PubMed, Cochrane library, Web of Science, and OVID. The search strategy combined titles, abstracts and Medical Subject Headings (MeSH) term. The following items were modified in different databases to retrieve studies: (alopecia areata [MeSH terms] OR alopecia areata [Title/Abstract]) AND (compound glycyrrhizin [Title/Abstract]). In addition, the grey literatures, such as dissertations and conference papers, were also screened. The detailed search strategies of different databases are shown in Supplementary Table 1.

Inclusion and exclusion criteria

Inclusion criteria

Inclusion criteria were constructed by using the participants, intervention, comparison, outcomes and study design (PICOS) format.

Types of participants: Based on the Chinese guideline for AA [27], the patients were diagnosed with AA which commonly presented as round or oval patches of nonscarring hair loss and occasionally presented as loss of all scalp hair. There were no restrictions on age, gender, AA subtype, disease severity and disease course.

Types of interventions and comparisons: The experimental groups were treated with CG combined with conventional treatments, including TCS, topical minoxidil and ILC, while the control groups were treated with conventional treatments alone. There were no limitations on the form, concentration, dose and treatment course of each drug.

Types of outcomes: In consistence with some clinical trials [30,31], the primary outcome was cure rate defined as the proportion of patients achieving 100% hair regrowth. In addition, the secondary outcomes included total efficacy rate defined as the percentage of patients achieving ≥50% hair regrowth, the Severity of Alopecia Tool (SALT) score and adverse events (AEs).

Types of study design: Randomized controlled trials (RCTs) published in Chinese or English were included.

Exclusion criteria

Abstracts, duplicates, and studies without detailed data were excluded, such as the lack of the age range of patients, the number of patients in each group, the concentration of topical drugs, and the dose of CG.

Study selection

Two reviewers (ML and YL) independently screened the titles and abstracts of all retrieved studies and excluded the irrelevant studies. Furthermore, the full texts of the rest were read to identify the eligible studies. The third reviewer (LJX) helped to settle any disagreements about the study eligibility.

Data extraction

Two reviewers (ML and YL) read the included studies and collected the data in an independent way. The data contained the first author, publication year, sample size, gender, age range, disease course, intervention, comparison, treatment duration and outcomes. Any discrepancies were resolved by discussing with the third reviewer (LJX).

Quality assessment

Two independent reviewers (ML and YL) assessed the qualities of all included studies by using the Cochrane Collaboration risk assessment tool [32]. It included the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. In this study, the disease severities of AA between two groups were regarded as the source of other bias. The risk of bias of each domain was judged as low, unclear or high. Any disagreement between two reviewers was addressed by consulting with the third reviewer (LJX).

Quality of evidence

Two reviewers (ML and YL) independently used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system to assess the quality of evidence [33]. The quality of evidence has the following four levels: very low, low, moderate and high, and it is evaluated based on five factors, including study limitations, inconsistency of results, indirectness of evidence, imprecision and reporting bias. The third reviewer (LJX) dealt with any disagreement between two reviewers.

Statistical analysis

Review Manager 5.4 (Cochrane Collaboration, Copenhagen, Denmark) and Stata 12.0 (StataCorp., College Station, TX) were used to synthesize and analyse the data. For dichotomous outcomes, risk ratio (RR) plus 95% confidence interval (CI) were used to calculate the effect size. For continuous outcomes, mean difference (MD) plus 95%CI was applied to express the effect size. Heterogeneity among studies was measured by Chi-square test and I^2 statistic. If $I^2 \leq 50\%$ or $p \geq .1$, there was no significant heterogeneity, and a fixed-effect model was used. When $I^2 > 50\%$ or $p < .1$, which indicated a significant heterogeneity, the potential source was explored by using subgroup analysis, such as different conventional treatments, treatment courses, and doses of CG, and if the source was not found, a random-effect model was applied. In addition, sensitivity analyses were conducted to examine the robustness of the pooled results by using leave-one-out method. If one outcome included 10 studies or more, funnel plot and Egger's test were used to assess the risk of publication bias. A p value of <.05 was considered as significant.

Results

Study selection

A total of 974 studies were retrieved from eight literature databases. After removing 620 duplicates, 354 studies were screened. Due to ineligible titles and abstracts, 300 studies were excluded. After scanning the full texts, 31 of the remaining 54 studies were excluded, including two abstracts, six non-RCTs, 16 duplicates and seven studies without sufficient data. Finally, 23 studies were included in this meta-analysis [34–56] (shown in Figure 1).

Characteristics of the included studies

All included studies were single centre clinical trials conducted in China, and all of them were published in Chinese from 2008 to 2021. A total of 2219 patients were enrolled and their ages ranged from 5 to 70 years old. Among them, 16 studies compared CG plus topical minoxidil with topical minoxidil alone [34–49], three compared CG plus topical minoxidil and TCS with topical minoxidil and TCS [50–52] and four compared CG plus ILC with ILC alone [53–56]. Moreover, six [36,41,47,48,55,56] and 17 studies [34,35,37–40,42–46,49–54] were conducted for 2 and 3 months, respectively. The basic characteristics of all included studies are shown in Table 1.

Risk of bias assessment

The methodological quality of all included studies is summarized in Figure 2. Although all studies mentioned the randomization, only two used random table number to generate random number and were judged

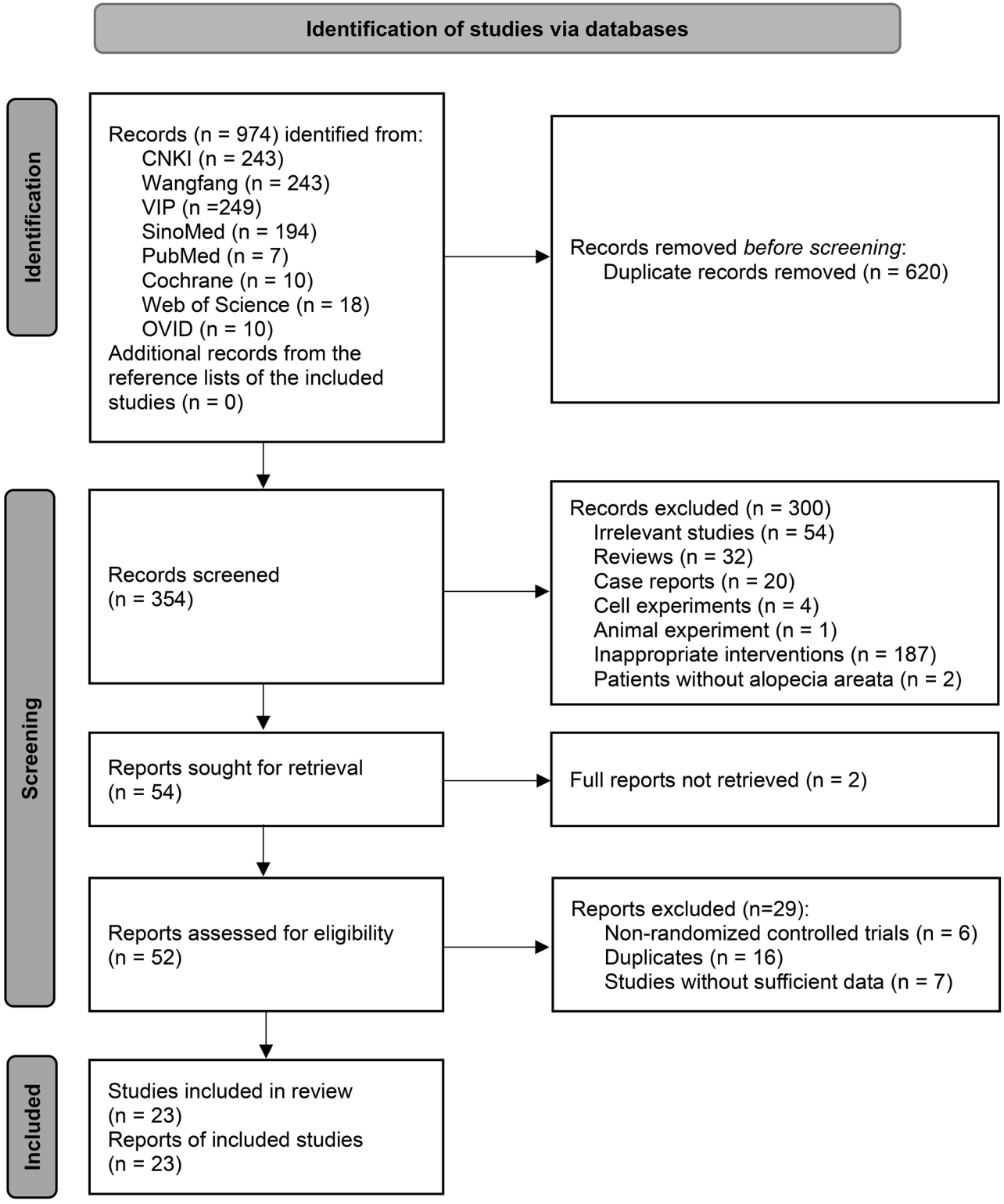

Figure 1. Flow diagram of the study selection.

as low risk [34,35], while the rest were rated as unclear risk due to the lack of information. Because all studies did not provide the information, they had unclear risks of bias in allocation concealment and blinding. There were no missing outcome data in all studies, and all studies reported the predetermined outcomes; therefore, their risks of bias in incomplete outcome data and selective reporting were low. In terms of other bias, 10

Table 1. The basic characteristics of the included studies.

Study	Patients (male/female)		Age (years)		Disease course (months)		Intervention		Treatment duration (months)	Outcomes
	E	C	E	C	E	C	E	C		
Du et al. [34]	60 (35/25)	60 (36/24)	≥18	≥18	6.69 ± 1.28	6.38 ± 1.43	CGT 150 mg/d + ICG	5% minoxidil tincture Bid	3	①②③
Li [35]	75 (41/34)	74 (40/34)	19–62	19–60	1–18	1–18	CGC 150 mg/d + ICG	5% minoxidil tincture Bid	3	①②③④
Wang [36]	60 (42/18)	60 (41/19)	19–57	19–59	4–41	3–39	CGT 150 mg/d + ICG	5% minoxidil solution Bid	2	①②④
Yang [37]	50 (30/20)	50 (31/19)	17–64	20–58	1–38	1–37	CGT 225 mg/d + ICG	5% minoxidil gel Bid	3	①
Zhu [38]	60 (32/28)	60 (29/31)	20–60	20–60	0.25–18	0.17–16	CGT 150 mg/d + ICG	5% minoxidil liniment Qd	3	①②④
Yue and Jiang [39]	55	55	5–17	5–17	0.67–24	0.67–24	CGT 75–150 mg/d[a] + ICG	2% minoxidil liniment Bid	3	①②④
Xie [40]	40 (23/17)	40 (26/14)	17–54	19–54	0.07–4	0.2–5	CGT 225 mg/d + ICG	2% minoxidil liniment Bid	3	①④
Zhang and Ma [41]	43	43	14–62	14–62	0.47–18	0.47–18	CGT 225 mg/d + ICG	2% minoxidil solution Bid	2	①②④
Yu and Yuan [42]	53	51	15–58	15–58	1–36	1–36	CGT 225 mg/d + ICG	5% minoxidil tincture Bid	3	①②④
Cao [43]	42 (25/17)	44 (27/17)	12–66	15–64	0.83–156	0.7–141.6	CGT 225 mg/d + ICG	5% minoxidil tincture Bid	3	①②③④
Wang et al. [44]	42	42	18–55	18–55	0.03–3	0.03–3	CGT 225 mg/d + ICG	2% minoxidil solution Bid	3	①④
Li [45]	60	60	10–45	10–45	0.23–6	0.23–6	CGT 150 mg/d + ICG	2% minoxidil tincture Bid	3	①④
Li [46]	40 (18/22)	40 (19/21)	15–58	17–57	0.5–12	0.5–11	CGT 225 mg/d + ICG	2% minoxidil gel Bid	3	①④
Wu [47]	50	50	8–56	8–56	0.3–36	0.3–36	CGT 75–225 mg/d[b] + ICG	5% minoxidil solution Bid	2	①②④
Huang [48]	38 (26/12)	30 (18/12)	13–60	12–62	0.5–12	0.47–12	CGT 225 mg/d + ICG	2% minoxidil tincture Bid	2	①②④
Li et al. [49]	48 (28/20)	33 (22/11)	16–60	17–58	0.2–12	0.23–12	CGT 150–100 mg/d[c] + ICG	5% minoxidil tincture Bid	3	①②④
Yang and Qi [50]	39 (24/15)	39 (25/14)	24–45	25–46	1–5	1–6	CGT 150 mg/d + ICG	5% minoxidil liniment Bid + 0.05% desonide cream Bid to Qid	3	④
Duan [51]	40 (21/19)	40 (20/20)	12–70	12–70	0.23–48	0.23–48	CGT 75–225 mg/d[d] + ICG	2% minoxidil liniment Bid + 0.05% desonide cream Bid to Qid	3	①②④
Jiang et al. [52]	45 (26/19)	40 (23/17)	18–50	18–50	0.03–3	0.03–3	CGC 150 mg/d + ICG	2% minoxidil liniment Bid + 0.05% desonide cream Bid	3	①②④
Kong and Yuan [53]	52 (25/27)	36 (20/16)	13–47	12–50	NA	NA	CGC 150 mg/d + ICG	Intralesional compound betamethasone injection Qm	3	①②
Yang [54]	40	40	23–45	23–45	2–24	2–24	CGT 150 mg/d + ICG	Intralesional prednisolone acetate injection once per 10 days	3	①④
Gong et al. [55]	60 (26/34)	60 (32/28)	18–59	18–60	0.17–48	0.03–36	CGT 225 mg/d + ICG	Intralesional compound betamethasone injection Qm	2	①②④
Zhang et al. [56]	40	40	16–52	16–52	0.13–36	0.13–36	CGT 150–100 mg/d[e] + ICG	Intralesional compound betamethasone injection Qm	2	①②④

E: experimental group; C: control group; CGT: compound glycyrrhizin tablet; CGC: compound glycyrrhizin capsule; ICG: the intervention in the control group; Bid: twice daily; Tid: three time daily; Qd: once daily; Qid: four times daily; Qm: once per month.
①: cure rate; ②: total efficacy rate; ③: SALT score; ④: adverse events.
[a]CGT 75 mg/d for children aged 5–12 years old and CGT 150 mg/d for adolescents above 12 years old.
[b]CGT 75 mg/d for children and adolescents aged 8–18 years old and CGT 225 mg/d for adults above 18 years old.
[c]CGT 150 mg/d in the 1st month and CGT 100 mg/d in the 2nd and 3rd months.
[d]CGT 75 mg/d for adolescents aged 12–16 years old and CGT 150–225 mg/d for adolescents above 16 years old and adults.
[e]CGT 150 mg/d in the 1st month and CGT 100 mg/d in the 2nd month.

studies did not report the disease severities before the treatments, and they were assessed as unclear risk [36–39,41,46,48,51,53,54]. The remaining 13 studies were rated as low risk due to the similar disease severities between two groups [34,35,40,42–45,47,49,50,52,55,56].

Primary outcome

A total of 22 studies (n = 2141) evaluated cure rates [34–49,51–56]. Due to no significant heterogeneity (I^2 = 0%, p = .77), a fixed-effect model was used. The

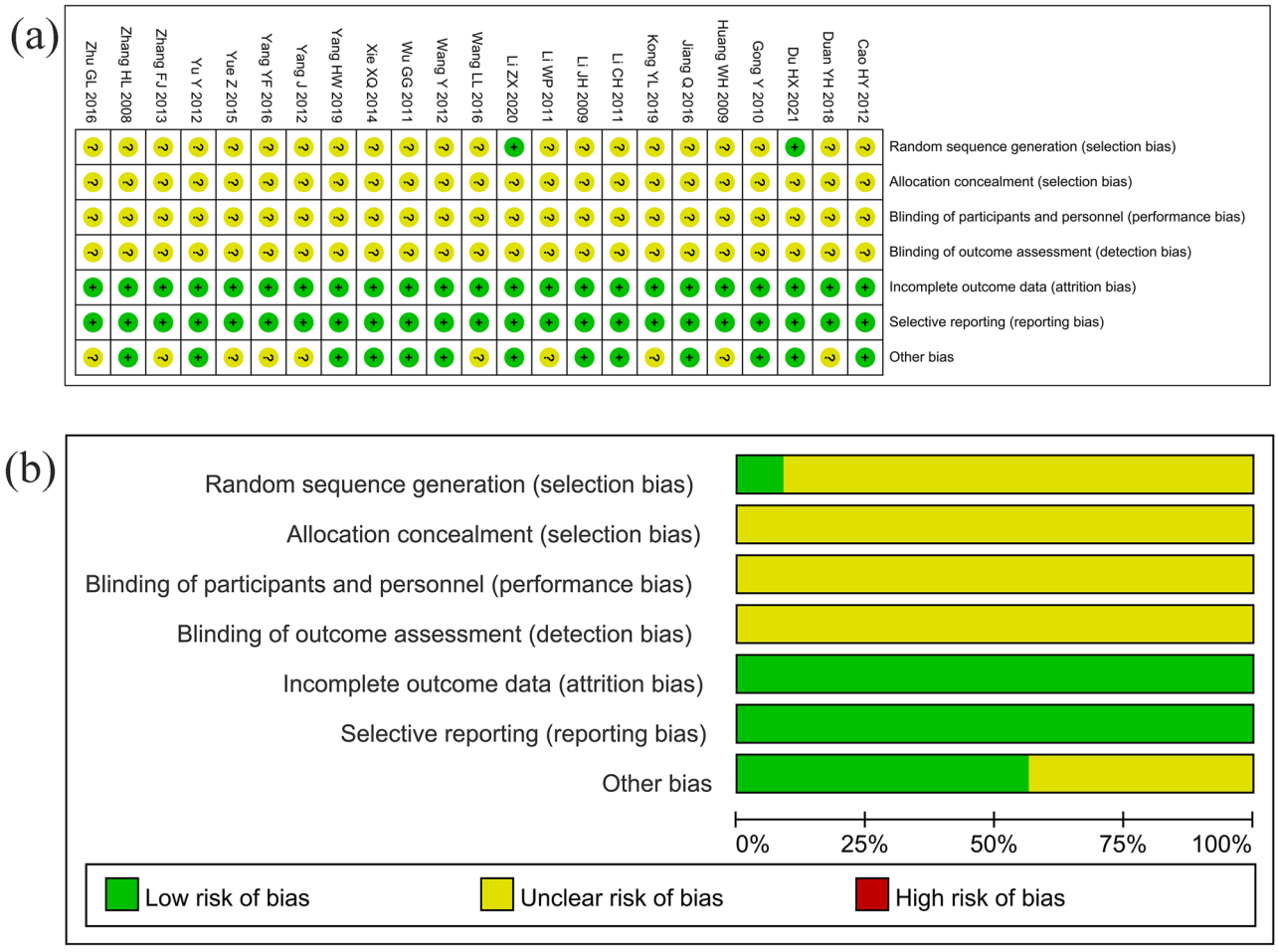

Figure 2. Risk of bias summary (a) and risk of bias graph (b) of the included studies.

pooled result showed that CG plus conventional treatments could significantly improve cure rate in comparison with conventional treatments alone (RR = 1.60, 95%CI [1.47, 1.74], $p < .001$) (shown in Figure 3(a)).

Furthermore, subgroup analyses were performed on the basis of different conventional treatments, treatment courses, and doses of CG (shown in Figure 3(b)). First, CG as an add-on treatment was superior to topical minoxidil alone (RR = 1.62, 95%CI [1.47, 1.78], $p < .001$, $I^2 = 0\%$) [34–49], topical minoxidil and TCS (RR = 1.71, 95%CI [1.16, 2.52], $p = .007$, $I^2 = 0\%$) [51,52] or ILC alone (RR = 1.49, 95%CI [1.24, 1.80], $p < .001$, $I^2 = 0\%$) [53–56] in cure rates. Second, the cure rates of the combination therapy groups were significantly higher than those of the monotherapy groups after 2 months of treatment (RR = 1.60, 95%CI [1.37, 1.87], $p < .001$, $I^2 = 19\%$) [36,41,47,48,55,56] and 3 months of treatment (RR = 1.60, 95%CI [1.45, 1.76], $p < .001$, $I^2 = 0\%$) [34,35,37–40,42–46,49,51–54]. Finally, because three studies [39,47,51] treated children and adults with different doses of CG due to the different ages, they were not included in the subgroup analysis. The remaining 19 studies used fixed dose of CG, and they were divided into low dose groups with CG 150 mg or less daily [34–36,38,45,49,52–54,56] and high dose groups with CG 225 mg daily [37,40–44,46,48,55]. The result displayed that both CG 150 mg or less daily (RR = 1.59, 95%CI [1.40, 1.81], $p < .001$, $I^2 = 0\%$) and CG 225 mg daily (RR = 1.68, 95%CI [1.47, 1.92], $p < .001$, $I^2 = 0\%$) combined with conventional treatments could significantly improve cure rates in comparison with conventional treatments alone.

Secondary outcomes

Total efficacy rate

Total efficacy rates were reported in 16 studies ($n = 1597$) [34–36,38,39,41–43,47–49,51–53,55,56]. Because of no significant heterogeneity ($I^2 = 0\%$, $p = .87$), a fixed-effect model was conducted. The pooled results displayed that total efficacy rates of the combination therapy groups were significantly higher than those of the monotherapy groups (RR = 1.37, 95%CI [1.29, 1.45], $p < .001$) (shown in Figure 4(a)).

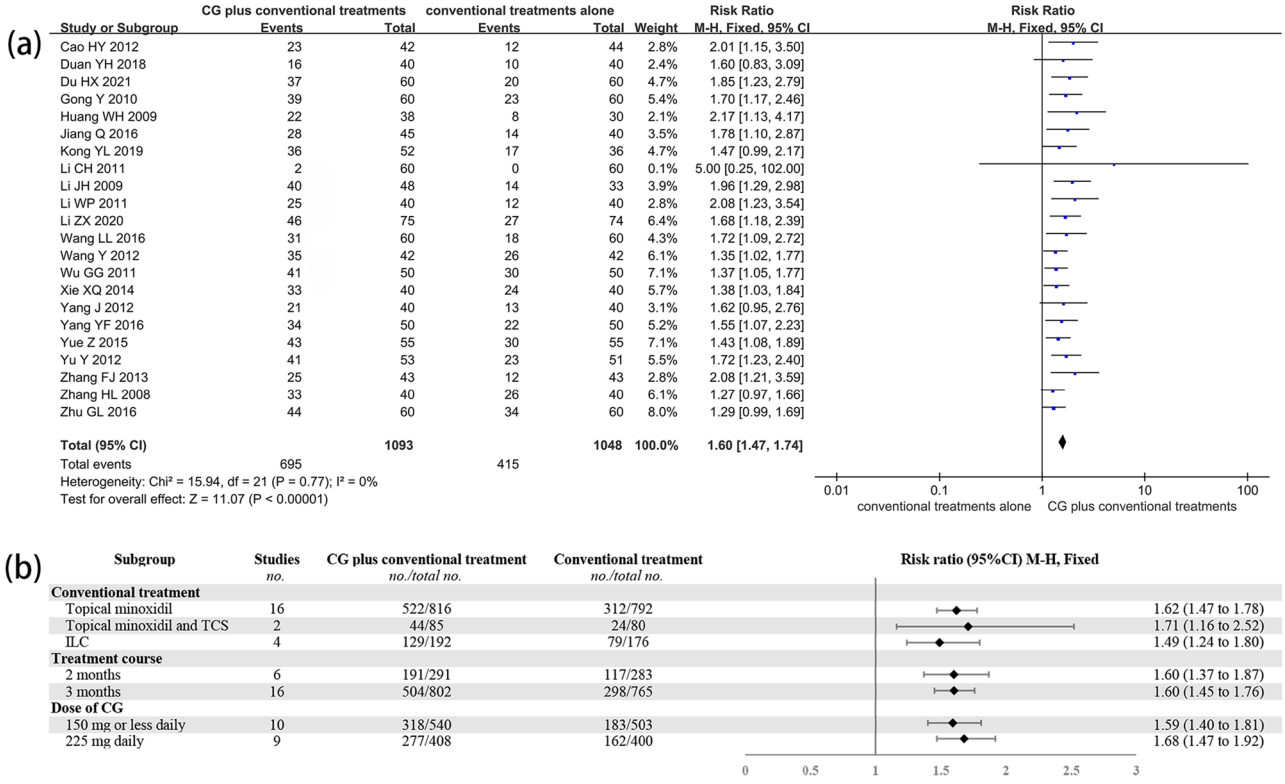

Figure 3. Comparison between CG plus conventional treatments and conventional treatments alone for cure rate (a) and subgroups analyses of cure rate (b).

In addition, subgroup analyses were also conducted based on the above subgroups (shown in Figure 4(b)). First, CG as an add-on treatment significantly improved total efficacy rates in comparison with topical minoxidil alone (RR = 1.38, 95%CI [1.29, 1.48], $p < .001$, $I^2 = 0\%$) [34–36,38,39,41–43,47–49], topical minoxidil and TCS (RR = 1.47, 95%CI [1.18, 1.84], $p < .001$, $I^2 = 31\%$) [51,52] and ILC alone (RR = 1.28, 95%CI [1.14, 1.43], $p < .001$, $I^2 = 0\%$) [53,55,56]. Second, the combination therapy groups had obviously higher total efficacy rates than the monotherapy groups after 2 months of treatment (RR = 1.43, 95%CI [1.28, 1.59], $p < .001$, $I^2 = 0\%$) [36,41,47,48,55,56] and 3 months of treatment (RR = 1.34, 95%CI [1.25, 1.43], $p < .001$, $I^2 = 0\%$) [34,35,38,39,42,43,49,51–53]. Finally, because children and adults received different doses of CG based on their different ages, three studies were excluded in the subgroup analysis [39,47,51]. According to the different fixed doses of CG, the rest were divided into the CG 150 mg or less daily groups [34–36,38,49,52,53,56] and the CG 225 mg daily groups [41–43,48,55]. The result displayed that different doses of CG could significantly improve total efficacy rates, no matter CG 150 mg or less daily (RR = 1.32, 95%CI [1.23, 1.42], $p < .001$, $I^2 = 0\%$) or CG 225 mg daily (RR = 1.43, 95%CI [1.27, 1.61], $p < .001$, $I^2 = 0\%$).

SALT score

Three studies ($n = 355$) measured SALT scores between CG plus topical minoxidil and topical minoxidil alone after 3 months of treatment [34,35,43]. Because of a significant heterogeneity ($I^2 = 98\%$, $p < .001$) among them, the subgroup analysis was conducted based on different doses of CG. The results showed that CG as an add-on treatment significantly reduced the SALT scores in comparison with monotherapy, whether CG 150 mg or less daily (MD = −10.86, 95%CI [−14.87, −6.85], $p < .001$, $I^2 = 98\%$) or CG 225 mg daily (MD = −3.89, 95%CI [−5.23, −2.55], $p < .001$) (shown in Figure 5).

AEs

A total of 20 studies ($n = 1911$) reported AEs during the treatments [35,36,38–52,54–56], and all AEs of the included studies are listed in Table 2. Among them, irritative dermatitis, erythema and pruritus were the common skin AEs, and they occurred in both two groups from those studies which used topical minoxidil as the control treatment. In addition, one case with skin atrophy in the CG plus ILC group and one case with folliculitis in ILC alone group were reported.

On the other hand, oedema was another common AE, and most of them were reported in the patients

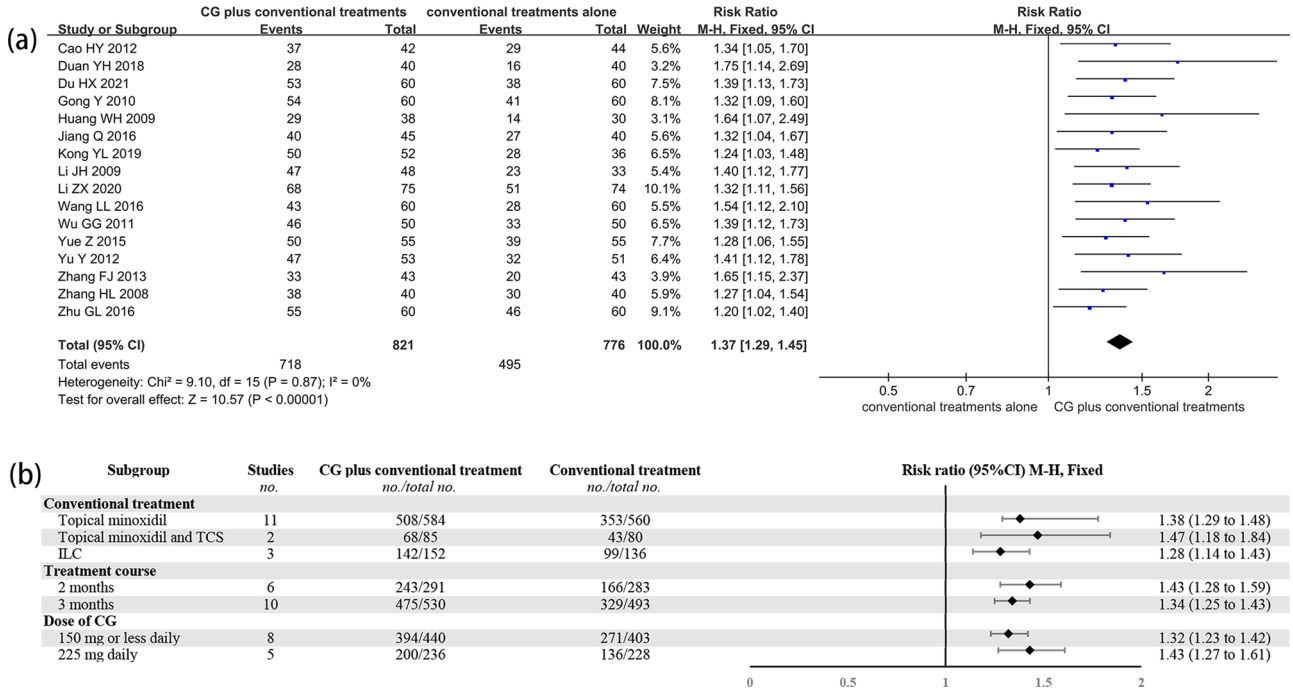

Figure 4. Comparison between CG plus conventional treatments and conventional treatments alone for total efficacy rate (a) and subgroups analyses of total efficacy rate (b).

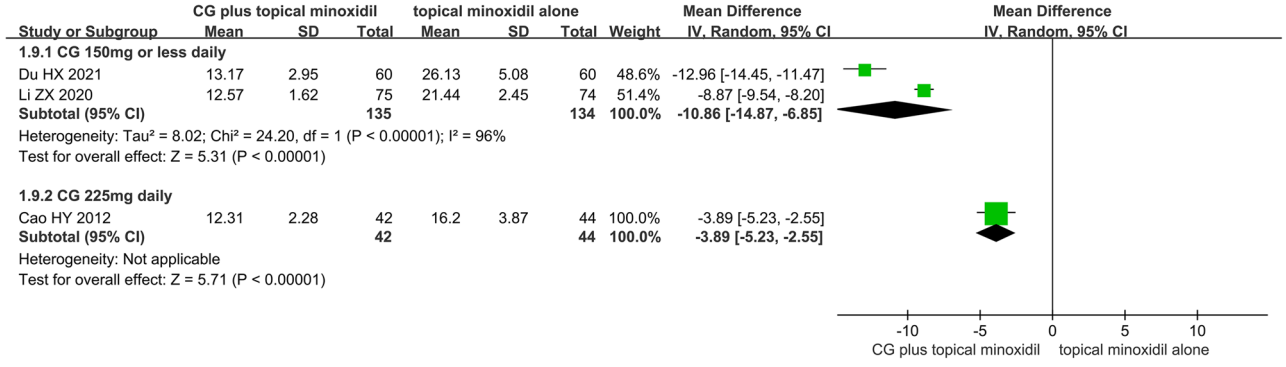

Figure 5. Comparison between CG plus conventional treatments and conventional treatments alone for SALT score.

receiving CG. The pooled results showed that the incidences of oedema in the combination therapy groups were significantly higher than those in the monotherapy groups (RR = 2.54, 95%CI [1.04, 6.22], p = .04, I^2 = 0%) (shown in Figure 6). Meanwhile, five cases with elevated blood pressure and six cases with gastrointestinal tract discomfort were observed in the combination therapy groups, while no similar case occurred in the monotherapy groups. The incidences of elevated blood pressure (RR = 3.47, 95%CI [0.73, 16.47], p = .12, I^2 = 0%) and gastrointestinal tract discomfort (RR = 6.96, 95%CI [0.87, 55.73], p = .07, I^2 = 0%) between two groups were not significantly different (shown in Figure 6). In addition, two cases with headache, two cases with increased weight, and one case with myalgia were reported in the patients treated with CG. These discomfort symptoms were mild and did not discontinue the treatments.

In terms of laboratory tests, five studies (n = 480) [35,42,48–50] measured serum electrolytes, and only one of 253 patients receiving CG suffered from hypokalaemia. Blood routine, urinary routine, liver function and renal function were tested in four studies (n = 402) [35,42,48,49], and no abnormal results were reported in the 214 patients receiving CG. Moreover, one trial (n = 68) [48] monitored electrocardiogram, and no clinically significant changes were observed in all patients.

Table 2. Adverse events of the included studies.

Study	Adverse events	
	Experimental group	Control group
Li [35]	3 cases with skin pruritus and 2 cases with gastrointestinal tract discomfort	4 cases with skin pruritus
Wang [36]	2 cases with irritant dermatitis and 1 case with low limb oedema	3 cases with irritant dermatitis
Zhu [38]	2 cases with erythema and pruritus and 1 case with elevated blood pressure	6 cases with erythema and pruritus
Yue and Jiang [39]	2 cases with irritant dermatitis	4 cases with irritant dermatitis
Xie [40]	1 case with scalp pruritus	3 cases with scalp pruritus
Zhang and Ma [41]	1 case with erythema and pruritus	None
Yu and Yuan [42]	1 case with irritant dermatitis, 2 cases with facial oedema and 1 case with elevated blood pressure	5 cases with irritant dermatitis
Cao [43]	None	None
Wang et al. [44]	None	4 cases with scalp pruritus
Li [45]	2 cases with burning sensation and 4 cases with gastrointestinal tract discomfort	3 cases with burning sensation
Li [46]	2 cases with lower limb oedema	None
Wu [47]	3 cases with irritant dermatitis and 1 case with lower limb oedema	5 cases with irritant dermatitis
Huang [48]	1 case with rash and pruritus	1 case with rash and pruritus
Li et al. [49]	2 cases with facial oedema	1 case with erythema and pruritus
Yang and Qi [50]	2 cases with oedema, 1 case with elevated blood pressure and 1 case with hypokalemia	3 cases with oedema and 2 cases with skin pruritus
Duan [51]	1 case with myalgia	None
Jiang et al. [52]	2 cases with lower limb oedema and increased weight	None
Yang [54]	2 cases with headache and elevated blood pressure	None
Gong et al. [55]	None	None
Zhang et al. [56]	1 case with skin atrophy and 2 cases with lower limb oedema	1 case with folliculitis

Sensitivity analysis

The pooled results of cure rates, total efficacy rates, SALT scores and the incidences of elevated blood pressure and gastrointestinal tract discomfort did not materially change after sequentially excluding one trial at a time. Therefore, these results were relatively stable and credible. On the other hand, when some studies were excluded one by one [36,42,46,47,49,52,56], the incidences of oedema between two groups became not statistically significant. Therefore, the pooled result of the incidences of oedema might not be robust (shown in Supplementary Figure 1).

Publication bias

More than 10 studies were included in both total efficacy rate and cure rate, and their publication biases were evaluated. The asymmetrical funnel plots and the positive Egger tests ($t = 5.54$, $p < .001$, for cure rate; $t = 7.89$, $p < .001$, for total efficacy rate) indicated that their risks of publication bias were significant (shown in Figure 7).

GRADE evaluation

Due to poor methodological qualities and significant risks of reporting bias, the evidence levels of cure rate and total efficacy rate were low. Meanwhile, the evidence level of SALT scores between different doses of CG were very low to low because of poor methodological qualities, small sample size or significant heterogeneity. In terms of the incidences of some AEs, the evidence levels of them were moderate due to poor methodological qualities. The GRADE evaluation is shown in Table 3.

Discussion

AA is a common inflammatory hair loss, and CG has been widely used to inhibit disease progress and promote hair regrowth in China. This comprehensive meta-analysis assessed the efficacy and safety of CG in patients with AA. The results of this study were as follows: (1) in comparison with topical drugs or ILC alone, CG as an add-on treatment could significantly improve cure rate and total efficacy rate. Moreover, CG could accelerate hair regrowth after 2 months of treatment, and both low and high doses of CG were effective on AA. (2) A few patients experienced AEs during the treatment of CG, and most of them were mild, such as oedema, elevated blood pressure, gastrointestinal tract discomfort, headache, increased weight, myalgia and hypokalaemia. Notably, the incidence of oedema was higher in the patients receiving CG.

A previous meta-analysis identified 20 articles and found that CG plus topical minoxidil was more effective than topical minoxidil on AA [28]. However, this meta-analysis contained both RCTs and case-control studies, and lacked other conventional treatments. Moreover, it only evaluated the incidence of all AEs, and some AEs associated with CG were not assessed. Therefore, the current meta-analysis contained the latest RCTs, and more conventional treatments were considered, such as TCS and ILC. Furthermore, the subgroup analyses were conducted based on different conventional treatments, treatment durations, and

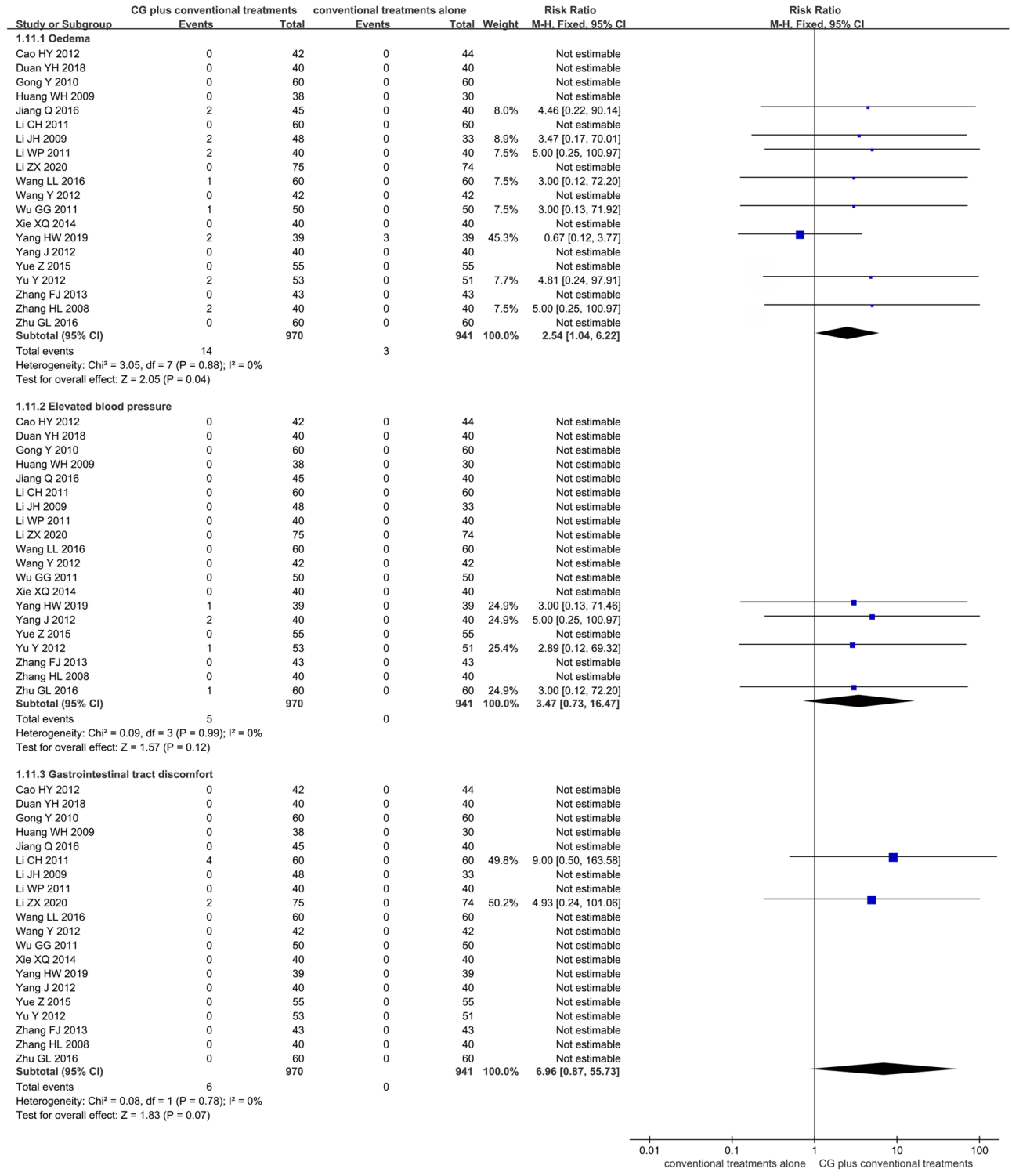

Figure 6. Comparison between CG plus conventional treatments and conventional treatments alone for the incidences of some adverse events.

doses of CG, and the incidences of different AEs were also explored.

In term of the pathogenesis of AA, the altered functions of different Th cells and defected functions of regulatory T cells play important roles in the initiation and progression of AA. IFN-γ and CD8+NKG2D+T cells could promote hair follicle immune privilege collapse and facilitate the autoimmune attack on hair follicles [57]. Some studies reported that in comparison with healthy people, patients with AA had higher serum levels of IL-2, IFN-γ, IL-12, IL-13, tumour necrosis factor (TNF)-α, and IL-17A and lower serum levels of IL-4 and

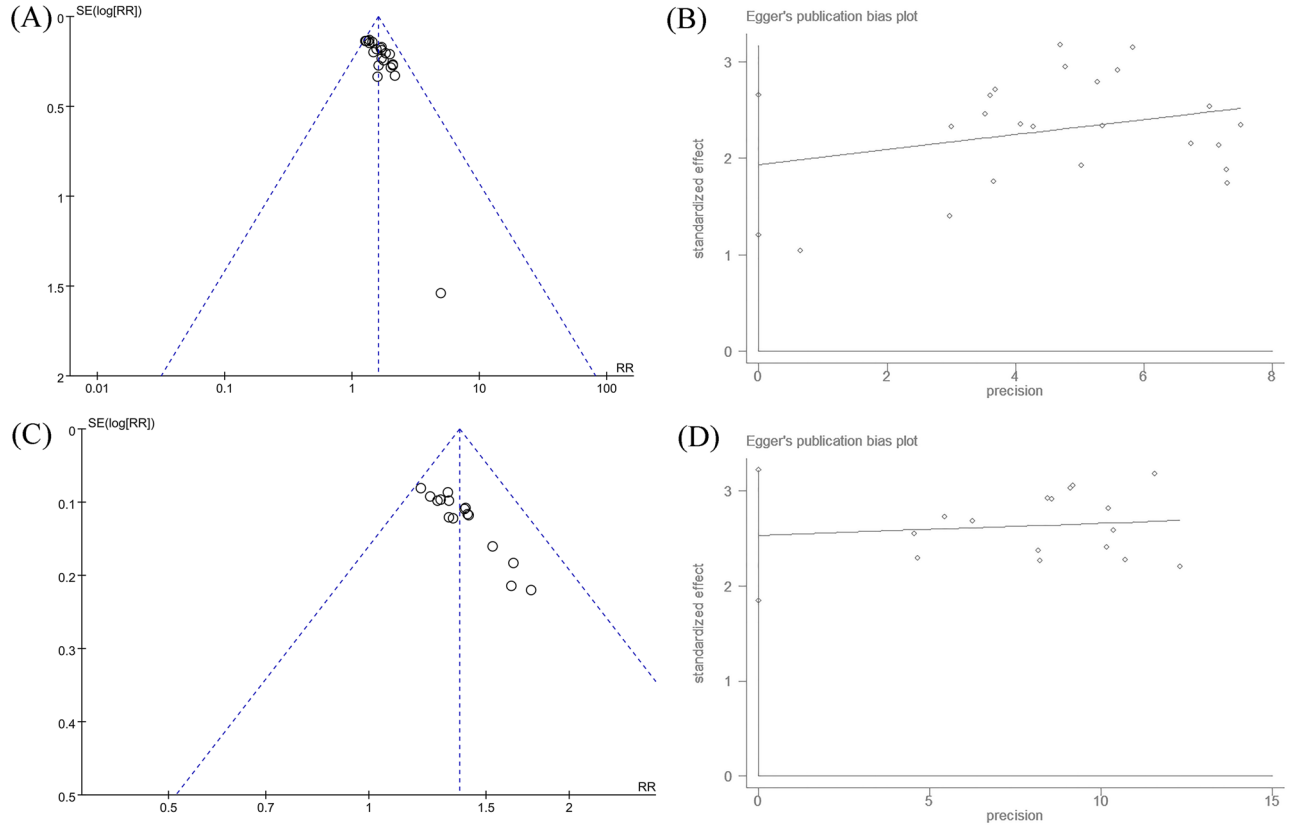

Figure 7. Results of publication bias for funnel plot of cure rate (a), Egger's test of cure rate (b), funnel plot of total efficacy rate (c) and Egger's test of total efficacy rate (d).

Table 3. The qualities of outcomes assessed by GRADE system.

Outcomes	Relative/absolute effect	Number of participants (number of studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of the evidence
Cure rate	RR = 1.60, 95%CI [1.47, 1.74]	2141 (22 studies)	Serious[a]	No serious	No serious	No serious	Reporting bias[b]	⊕⊕◯◯ Low
Total efficacy rate	RR = 1.37, 95%CI [1.29, 1.45]	1597 (16 studies)	Serious[a]	No serious	No serious	No serious	Reporting bias[b]	⊕⊕◯◯ Low
SALT score of CG 150 mg or less daily	MD = −10.86, 95%CI [−14.87, −6.85]	269 (2 studies)	Serious[a]	Serious[c]	No serious	Serious[d]	None	⊕◯◯◯ Very low
SALT score of CG 225 mg daily	MD = −3.89, 95%CI [−5.23, −2.55]	86 (1 study)	Serious[a]	No serious	No serious	Serious[d]	None	⊕⊕◯◯ Low
The incidence of oedema	RR = 2.54, 95%CI [1.04, 6.22]	1911 (20 studies)	Serious[a]	No serious	No serious	No serious	None	⊕⊕⊕◯ Moderate
The incidence of elevated blood pressure	RR = 3.47, 95%CI [0.73, 16.47]	1911 (20 studies)	Serious[a]	No serious	No serious	No serious	None	⊕⊕⊕◯ Moderate
The incidence of gastrointestinal tract discomfort	RR = 6.96, 95%CI [0.87, 55.73]	1911 (20 studies)	Serious[a]	No serious	No serious	No serious	None	⊕⊕⊕◯ Moderate

CG: compound glycyrrhizin; CI: confidence interval; GRADE: the Grading of Recommendations, Assessment, Development and Evaluation; MD: mean difference; RR: risk ratio; SALT: Severity of Alopecia Tool.
[a]Suboptimal methodological quality.
[b]Significant risk of reporting bias.
[c]The significant heterogeneity between the studies.
[d]Total number of patients with less than 400.

transforming growth factor (TGF)-β1 [58–61]. With regard to the mechanisms of CG for AA, some studies showed that CG could decrease serum levels of IFN-γ, TNF-α, IL-12 and IL-17A, and increase serum levels of TGF-β1 and IL-4 in patients with AA [34,50]. Moreover, the proportion of CD8+ T cells in serum were decreased in AA patients treated with CG [24,25]. On the other hand, an *in vitro* study collected dermal papilla cells (DPCs) from neurosurgical patients and showed that CG could promote the proliferation of DPCs in a dose-dependent manner within the concentrations of 0.5–20 mg/L [62]. Therefore, CG could treat AA through regulating immune function and stimulating DPCs proliferation.

In consistence with the previous meta-analysis [28], this meta-analysis demonstrated that in comparison with topical minoxidil, CG plus topical minoxidil significantly improved both cure rate and total efficacy rate and decreased SALT score. Moreover, this meta-analysis also revealed that CG plus topical minoxidil and TCS or ILC was also superior to topical minoxidil and TCS or ILC alone in both cure rate and total efficacy rate. Therefore, CG as an add-on treatment is effective in AA patients with different treatment needs, such as patients who are afraid of injection therapy and the AEs of ILC or patients who do not regularly use topical drugs. On the other hand, two significantly higher rates of CG after 2 months of treatment demonstrated that CG was able to rapidly promote hair regrowth. In addition, the pooled results confirmed that both low and high doses of CG could significantly improve two rates in AA patients, which indicated that the dose of CG could be adjusted for AA patients based on their complications. Besides AA, CG also had the indication for liver dysfunction, while the levels of blood pressure and serum potassium might fluctuate during the treatment of CG. Therefore, high dose of CG could be used in AA patients complicated with liver dysfunction to decrease the elevated liver enzymes, while low dose of CG might be more suitable for AA patients accompanying hypertension or heart diseases.

Safety is as important as efficacy for a drug. In this meta-analysis, no serious AEs were reported during the treatments, and the symptoms were mild. Irritative dermatitis, erythema and pruritus were common AEs during the treatments. Because they occurred in both two groups receiving topical minoxidil, they were considered as the adverse reactions of topical minoxidil. Similarly, one case with skin atrophy and one with folliculitis might be resulted from ILC. On the other hand, the pooled results revealed that CG as an add-on treatment significantly increased the incidence of oedema, and a few patients receiving CG experienced elevated blood pressure, gastrointestinal tract discomfort, headache, increased weight, myalgia and hypokalaemia. These symptoms might be related to the effect of glycyrrhizin. Because glycyrrhizin metabolites inhibit 11-β-hydroxysteroid dehydrogenase (11-β-HSD), while 11-β-HSD could decompose cortisol into inactive cortisone in the distal nephron, glycyrrhizin metabolites indirectly increase the level of cortisol and mineralocorticoid receptor activity, and ultimately induce pseudoaldosteronism. The clinical features of pseudoaldosteronism include sodium and water retention, hypokalaemia, high blood pressure, headache and fatigue [63,64]. In accordance with this meta-analysis and some clinical trials [14–16,24,25], the incidences of these AEs were low, and most of them were mild. These discomfort symptoms could gradually disappear after withdrawal of CG. However, some cases with serious AEs induced by CG haven been reported, such as heart failure, rhabdomyolysis and acute renal injury [65,66]. Some studies found several factors related to the adverse reactions of CG, including older age, higher dose, long-term use, hypertension and concomitant medications [67,68]. Therefore, it is necessary to inform patients of the potential adverse reactions prior to the treatment of CG, especially for elderly and patients with concomitant diseases, such as hypertension. Moreover, blood pressure and serum potassium could be regularly monitored during the treatment. On the other hand, because no abnormal results of blood routine, urinary routine, or hepatic and renal functions were reported in this meta-analysis, CG might have no damage on blood, liver and kidney. In clinical practice, due to the indication for liver dysfunction, CG is widely used to treat hepatic injury related to virus and alcohol consumption [69,70]. Moreover, it had no damage on the ability of immune system resistant to pathogens. Therefore, CG is an alternative drug for some AA patients who could not use systematic corticosteroid, cyclosporin or baricitinib, including patients suffered from liver or renal dysfunction, anaemia, leukopenia, chronic hepatitis B or latent tuberculosis infection.

This meta-analysis revealed that CG plus conventional treatments was more effective than conventional treatments alone in promoting hair regrowth, and there were a few AEs during the treatment of CG. Therefore, CG might be recommended for physicians and patients in the following clinical conditions: first, CG as an add-on treatment could be used for AA patients who want to accelerate hair regrowth and shorten treatment course. Second, CG provides a safe treatment option for AA patients complicated with liver dysfunction, renal dysfunction or some infectious diseases, such as chronic hepatitis B and latent tuberculosis infection. Finally, because CG is also effective in

the treatment of eczema, psoriasis and chronic urticaria, it could be applied for patients with both AA and these skin diseases.

However, there were some limitations in this meta-analysis. First, all included studies were conducted in China, and the conclusions might not be directly generalized to patients from other countries. Second, due to the suboptimal methodological qualities and the limited sample sizes, the reliability of the conclusions was reduced, and researchers need to conduct more high-quality RCTs to rule out the placebo effects in the future. Third, only one study recruited child patients, and most studies included both children and adults; therefore, this meta-analysis did not conduct subgroup analysis to explore the efficacies of CG between children and adults. Fourth, due to the lack of relevant studies, the efficacies among CG and other oral drugs, such as cyclosporin and baricitinib, were not explored. Finally, because the treatment durations of all studies were not beyond 3 months, the long-term efficacy of CG was not evaluated.

Conclusions

This meta-analysis showed that CG as an add-on treatment was effective in the treatment of AA, regardless of different conventional treatments, treatment courses, and doses of CG, and a few mild AEs were observed during the treatment of CG, including oedema, elevated blood pressure and hypokalaemia. Due to the suboptimal methodological qualities, more well-designed RCTs are needed to confirm and update the above results.

Author contributions

Concept and design: Ming Li and Yan Li; database search, study selection and data extraction: Ming Li, Lujing Xiang and Yan Li; statistical analysis: Ming Li and Yan Li; drafting of the manuscript: Ming Li and Lujing Xiang; revision of the manuscript: Yan Li; All authors read and approved the final manuscript.

Ethical approval

Ethical approval was not required for this study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The original data in the study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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