Journal of Dermatological Treatment

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ijdt20

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To cite this article: Chenqi Guo, Xiangru Gu, Junchen Li, Yingdong Wang, Xiaoya Liu, Guojing Yang, Min Zhang & Yu Zhang (2024) Efficacy and safety of compound glycyrrhizin combined with topical minoxidil for alopecia areata: a systematic review and meta-analysis of randomized controlled trials, Journal of Dermatological Treatment, 35:1, 2381766, DOI: 10.1080/09546634.2024.2381766

To link to this article: https://doi.org/10.1080/09546634.2024.2381766

JOURNAL OF DERMATOLOGICAL TREATMENT
2024, VOL. 35, NO. 1, 2381766
https://doi.org/10.1080/09546634.2024.2381766

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RESEARCH ARTICLE

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Efficacy and safety of compound glycyrrhizin combined with topical minoxidil for alopecia areata: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Alopecia areata (AA) is a common autoimmune skin disease. Our study aimed to systematically evaluate the efficacy and safety of compound glycyrrhizin (CG) combined with topical minoxidil therapy in treating AA.

Methods: We searched the PubMed, EMBASE, Cochrane Library, Web of Science, CNKI, Wanfang, and VIP databases. Randomized controlled trials (RCTs) on CG combined with topical minoxidil therapy compared with topical minoxidil therapy alone for AA were included. The Cochrane Collaborative Network Tool was used to assess the risk of bias. Statistical analysis was completed using RevMan5.3 software and Stata 15.0 software. The GRADE system was used to evaluate the quality of evidence for outcomes.

Result: 11 RCTs and 1189 patients were included. Compared with topical minoxidil therapy alone, CG combined with topical minoxidil therapy was more effective at improving the clinical efficacy (RR = 1.36, 95% CI [1.27, 1.45], $p<0.00001$). The SALT score (MD = −10.09, 95% CI [−12.89, −7.30], $p<0.00001$), serum TNF-α levels (MD=−0.99, 95% CI [−1.19, −0.39], $p<0.00001$), serum IL-12 levels (MD = −8.84, 95% CI [−11.20, −6.47], $p<0.00001$) and serum IFN-γ levels (MD = −7.44, 95% CI [−11.51, −3.37], $p=0.0003$) were reduced, and the serum TGF-β1 levels (MD = 2.40, 95% CI [1.24, 3.57], $p<0.0001$) were increased. There were no significant differences in reported adverse events, including irritant contact dermatitis (RR = 0.51, 95% CI [0.25, 1.01], $p=0.05$),' gastrointestinal reactions (RR = 2.47, 95% CI [0.49, 12.55], $p=0.28$), lower limb edema (RR = 2.60, 95% CI [0.61, 11.06], $p=0.20$), facial edema (RR = 2.33, 95% CI [0.61, 8.93], $p=0.22$), or localized itching (RR = 0.56, 95% CI [0.18, 1.75], $p=0.32$), between the two groups.

Conclusion: The current evidence indicates that CG combined with topical minoxidil therapy is effective and safe for AA. However, owing to the suboptimal quality of the included studies, more high-quality and large-scale RCTs are needed for comprehensive analysis and further validation.

ARTICLE HISTORY
Received 14 April 2024
Accepted 20 June 2024

KEYWORDS
Alopecia areata; compound glycyrrhizin; minoxidil; randomized controlled trials; meta-analysis

Introduction

Alopecia areata (AA) is a common chronic tissue-specific autoimmune disease that is characterized by patchy hair loss on the scalp [1]. AA affects up to 2% of the general population, irrespective of age, race, or sex [2]. It is often considered a cosmetic problem, but it can cause an enormous psychological burden on patients, seriously affecting their daily life and self-esteem [3]. Topical therapy is used as a first-line therapy for alopecia, and topical minoxidil has beed the only FDA-approved over-the-counter drug uesd to treat androgenetic alopecia for over 30 years [4]. It has been used to treat many other types of alopecia, including AA, since its approval. It can slow hair loss by prolonging the growth period and promote hair regeneration by increasing hair diameter and density. Notably, the efficacy of topical minoxidil as a monotherapy is unsatisfactory. Multiple studies have shown that combination therapy can achieve better clinical efficacy [5]. Therefore, we aimed to collect the relevant published literature, evaluate the efficacy of combination therapy on AA, and provide a new alternative therapy for AA.

The compound glycyrrhizin (CG) has anti-inflammatory, anti-allergic and immunomodulatory effects, and can exert glucocorticoid-like effects safely [6]. CG enhances the activity of lymphocytes by promoting the activation of NK cells and T cells, thereby inhibiting the progression of AA, inhibiting phospholipase activity, and exerting antimicrobial effects to promote new hair growth [7]. In recent years, clinical research on the combination of CG and topical minoxidil for treating AA has gradually increased,

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/09546634.2024.2381766.

but the relative effectiveness and safety of this combination therapy have not been systematically analyzed. This study conducted a systematic evaluation and meta-analysis based on relevant RCTs, aiming to comprehensively evaluate the efficacy and safety of CG combined with topical minoxidil therapy for AA and provide a optimized treatment option for AA.

Methods

This study complied with the Preferred Reporting Items for Systematic Review and Meta-analyses Statement (PRISMA) [8]. We registered the protocol in the PROSPERO (ID: CRD42024528846).

Search strategy

A systematic literature search was conducted in 7 databases from their inception to March 28, 2024: PubMed, EMBASE, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang, and VIP databases. The following terms were used for the search: alopecia areata, alopecia, compound glycyrrhizin, glycyrrhizin, minoxidil. The search strategy was slightly modified due to corresponding database. The details can be found in Supplementary Table 1. In addition, we also searched the list of references included in the studies to further identify eligible papers.

Inclusion and exclusion criteria

Randomized controlled trials (RCTs). (2) The recognized diagnostic criteria had to be reported in the included studies, with no restrictions on the clinical types of AA, age, race, and gender of patients. (3) The experimental intervention applied CG combined with topical minoxidil therapy. The control group received the same topical minoxidil as the experimental group. (4) The main outcome measures were Severity of Alopecia Tool (SALT) score [9, 10] and clinical efficacy. The clinical efficacy with specific definitions at home and abroad were all accepted [11, 12], which can divide into clinical cure, marked efficacy, effective and no efficacy. Clinical cure is defined by all new hair grows out, densely distributed, with hair thickness and color similar to normal hair. Marked efficacy is defined by new hair grows by 50% to 99%, with a significant amount of velvety hair turning into coarse hair. We define the number of patients with clinical efficacy = number of "clinically cured" patients + number of "marked efficacy" patients. Secondary outcomes were serum TNF-α, TGF-β1, IL-12, IFN-γ levels and adverse reactions.

Exclusion criteria were as follows: (1) Studies about AA but mixed with other illnesses. (2) Non-RCTs, such as reviews, case reports and conference abstracts. (3) Unable to obtain full-text or data or duplicate published research.

Data extraction

Two researchers (Gu XR and Li JC) extracted the following data separately for all studies meeting the inclusion criteria independently: study characteristics (including first author, country and year of publication), baseline data (including age, gender, sample size and disease course), intervention measures (dose and frequency of CG, usage of minoxidil) and outcome data. All the extracted data were cross-checked. Any disagreements arising during this process were discussed and addressed with the third researcher (Guo CQ).

Assessment of risk of bias

Two researchers (Wang YD and Yang GJ) used the quality evaluation criteria provided in the Cochrane Intervention System Evaluation Manual to evaluate the basic risk of the included literature [13]. Seven evaluation items were evaluated: random sequence generation, allocation concealment, blinding of investigators and/or subjects, blinding of study results evaluators, integrity of results data, selective reporting, and other bias. Each items was classified as having a low, unclear or high risk of bias. Any agreement was resolved by the third researcher (Guo CQ).

GRADE evaluation

The GRADE system is used to evaluate the quality of evidence for outcomes [14]. The degradation factors mainly include five aspects: risk of bias, inconsistency, indirectness, imprecision, and other considerations. The quality definition is classified as extremely low quality evidence (+), low quality evidence (++), medium quality evidence (+++), and high quality evidence (++++).

Statistical analysis

RevMan 5.3 software was used for data analysis. The dichotomous outcomes were expressed as risk ratio (RR), the continuous outcomes were analyzed using the mean difference (MD), and each effect size was expressed as a 95% confidence interval (CI). Heterogeneity was evaluated using the χ2 test and I^2 test. When $p > 0.1$ and $I^2 < 50\%$, a fixed-effects model was selected for the meta-analysis. Otherwise, a fixed-effects model should be adopted. Subgroup analyses were used based on study design if possible. In addition, STATA 15.0 was used for sensitivity analysis to explore potential sources of heterogeneity. A funnel plot for evaluating publication bias was employed if the number of included studies was ≥ 10.

Result

Literature retrieval

A total of 196 studies were retrieved from the 7 electronic databases, and 101 duplicates were removed. Then, after reading the titles and abstracts of the remaining 95 studies, we further excluded an additional 67 irrelevant studies. Next, after reading the full text of the remaining 28 studies, 17 studies were further excluded. Finally, 11 studies were included in this work [15–25]. (Figure 1)

Characteristics of the included studies

11 RCTs included in this work were published between 2009 and 2021, all of which were conducted in China. A total of 1189 participants were involved ($n = 603$ and $n = 586$ from the experimental group and control groups, separately). In each study, the dosage of CG was 3 times daily applications with 50–75 mg per application. For the concentration of minoxidil, 9 studies used 5% and the

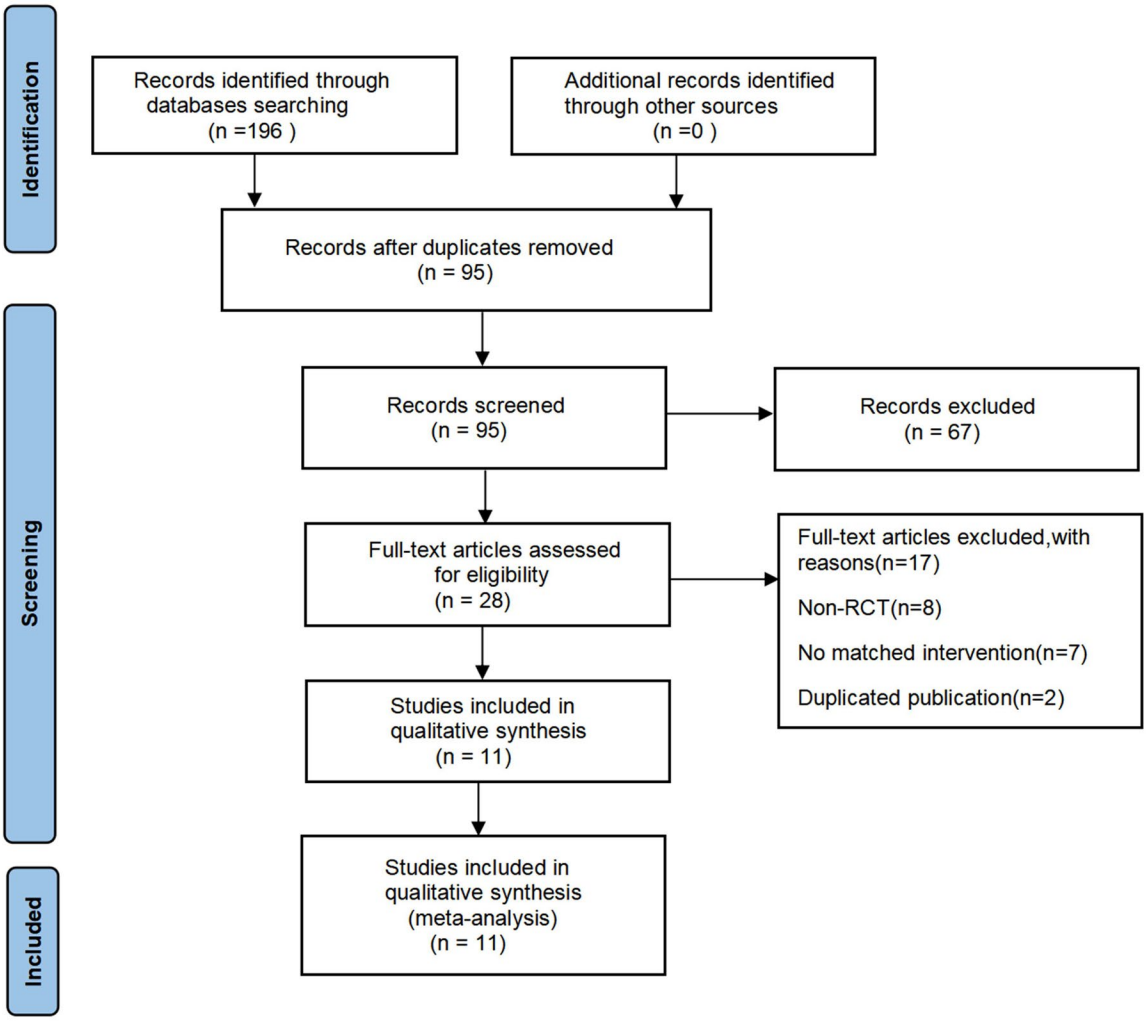

Figure 1. Study selection process.

remained 2 studies were 2%. The treatment course is 2 or 3 months. The characteristics of the included studies are shown in Table 1.

Risk of bias

Three studies [15, 17, 19] reported the use of random number tables, one study [21] reported the order of entering the hospital, and the other studies did not report their detailed randomization generation approach. None of the included studies reported allocation concealment, blinding of participants and personnel or blinding of outcome assessments. Other potential biases mentioned in included studies were unclear due to limited information. The results of the bias risk evaluation are presented in Figure 2.

Clinical efficacy

Eleven studies [15–25] involving 1189 patients reported clinical efficacy. A fixed-effects model was chosen in line with heterogeneous results (I^2=0%, p=0.99). According to the results of a meta-analysis, the combination of CG and topical minoxidil therapy could improve clinical efficacy compared with that of topical minoxidil therapy alone (RR = 1.36, 95% CI [1.27, 1.45], p<0.00001). A subgroup analysis was performed for the treatment course. The clinical efficacy in the CG with a course of 2 months plus topical minoxidil group was better than that in the topical minoxidil alone group (RR = 1.46, 95% CI [1.21, 1.76], p<0.0001). The similar result can be observed at a course of 3 months (RR = 1.34, 95% CI [1.25, 1.43], p<0.00001) (Figure 3).

SALT score

Five studies [15, 17, 19, 21, 22] involving 585 participants reported SALT scores. A random-effects model was chosen in line with heterogeneous results (I^2=97%, p<0.0001). According to the results of a meta-analysis, compared with topical minoxidil therapy alone, CG combined with topical minoxidil therapy significantly reduced the SALT score (MD = −10.09, 95% CI [−12.89, −7.30], p<0.00001) (Figure 4).

Serum TNF-α levels

Two studies [15, 19] involving 230 participants reported serum TNF-α levels. A fixed-effects model was chosen in line with heterogeneous results (I^2=0%, p=0.70). According to the results of a meta-analysis, compared with topical minoxidil therapy alone, CG combined with topical minoxidil therapy significantly reduced the serum TNF-α levels (MD = −0.99, 95% CI [−1.19, −0.39], p<0.00001) (Figure 5).

Table 1. Included studies characteristics.

First Author Year	Country	Sample size (E/C)	M:F	Mean age or age range (E/C)	Disease course (E/C)	Intervention	Treatment course	Outcomes
Du 2021 [25]	China	60/60	71:49	45.71 ± 3.69/44.93 ± 3.72	6.69 ± 1.28m/6.38 ± 1.43m	5% topical minoxidil twice a day + CG 50 mg TID	3m	①②③④⑤
Yang 2021 [26]	China	45/44	57:32	33.15 ± 10.65/32.51 ± 9.87	8.54 ± 2.63m/8.61 ± 2.87m	5% topical minoxidil twice a day + CG 25–75mg TID	3m	①④⑥⑦
Li 2020 [27]	China	75/74	81:68	40.34 ± 10.28/39.18 ± 9.67	9.36 ± 4.17m/9.87 ± 4.03m	5% topical minoxidil twice a day + CG 50 mg TID	3m	①②⑦
Wang 2016 [28]	China	60/60	83:27	19–57/19–59	4–41m/3–39m	5% topical minoxidil twice a day + CG 50 mg TID	2m	①⑦
Chen 2015 [29]	China	55/55	60:50	44.5 ± 15.4/47.5 ± 16.7	6.5 ± 2.5m/6.2 ± 2.0m	5% topical minoxidil twice a day + CG 75 mg TID	3m	①②③④⑤⑦
Yue 2015 [30]	China	55/55	62:48	NR	NR	2% topical minoxidil twice a day + CG 25–50mg TID	3m	①⑦
Fu 2013 [31]	China	60/60	56:64	41.5 ± 13.0/41.9 ± 13.5	5.2 ± 2.0m/5.5 ± 2.6m	5% topical minoxidil twice a day + CG 50 mg TID	3m	①②⑥⑦
Cao 2012 [32]	China	42/44	52:34	12–66/15–64	25d–13y/21d–11.8y	5% topical minoxidil twice a day + CG 75 mg TID	3m	①②
Yu 2012 [33]	China	53/51	59:45	NR	NR	5% topical minoxidil twice a day + CG 75 mg TID	3m	①⑦
Wu 2011 [34]	China	50/50	52:48	NR	NR	5% topical minoxidil twice a day + CG 25–75mg TID	2m	①⑦
Li 2009 [27]	China	48/33	50:31	16–60/17–58	6d–1y/7d–1y	5% topical minoxidil twice a day + CG 50 mg TID	3m	①⑦

Abbreviations: CG: compound glycyrrhizin; M: male; F: female; E: experimental group; C: control group; d: day; w: week; m: month; y:year; NR: not reported; TID: 3 times daily; ①: clinical efficacy; ②: SALT; ③: serum TNF-α levels; ④: serum TGF-β1 levels; ⑤: serum IL-12 levels; ⑥: serum IFN-γ levels; ⑦: adverse reactions.

Serum TGF-β1 levels

Three studies [15, 16, 19] involving 319 participants reported serum TGF-β1 levels. A fixed-effects model was chosen in line with heterogeneous results (I^2=0%, p = 0.88). According to the results of a meta-analysis, compared with topical minoxidil therapy alone, CG combined with topical minoxidil therapy significantly increased the serum TGF-β1 levels (MD = 2.40, 95% CI [1.24, 3.57], p < 0.0001) (Figure 6).

Serum IL-12 levels

Two studies [15, 19] involving 230 participants reported serum IL-12 levels. A fixed-effects model was chosen in line with heterogeneous results (I^2=0%, p = 0.63). According to the results of a meta-analysis, compared with topical minoxidil therapy alone, CG combined with topical minoxidil therapy significantly reduced the serum IL-12 levels (MD = −8.84, 95% CI [−11.20, −6.47], p < 0.00001) (Figure 7).

Serum IFN-γ levels

Two studies [16, 21] involving 209 participants reported serum IFN-γ levels. A random-effects model was chosen in line with heterogeneous results (I^2=86%, p = 0.007). According to the results of a meta-analysis, compared with topical minoxidil therapy alone, CG combined with topical minoxidil therapy significantly reduced the serum IFN-γ levels (MD = −7.44, 95% CI [−11.51, −3.37], p = 0.0003) (Figure 8).

Adverse events

Nine studies [16–21, 23–25] reported adverse events. According to the results of our meta-analysis, there was no signifcant difference in the incidence of irritant contact dermatitis (RR = 0.51, 95% CI [0.25, 1.01], p = 0.05), gastrointestinal reactions (RR = 2.47, 95% CI [0.49, 12.55], p = 0.28), lower limb edema (RR = 2.60, 95% CI [0.61, 11.06], p = 0.20), facial edema (RR = 2.33, 95% CI [0.61, 8.93], p = 0.22), and localized itching (RR = 0.56, 95% CI [0.18, 1.75], p = 0.32) between the two groups. Other adverse reactions included dizziness [16] and mild increase in blood pressure [23]. All of these adverse reactions in the two groups can be resolved spontaneously and did not affect subsequent treatment (Figure 9).

Sensitivity analysis

The sensitivity analyses were performed using the method of omitting individual studies one by one to evaluate the influence on pooled results due to the heterogeneity of the meta-analyses on the clinical efficacy, SALT score, serum TNF-α, TGF-β1, IL-12 and IFN-γ levels. The analyses indicated there were no significant influences on any outcome, suggesting that the sensitivity was low and the results were robust (Figure 10).

Assessment of publication bias

The funnel plot analysis of clinical effective rate showed asymmetry, which indicated potential publication bias (Figure 11).

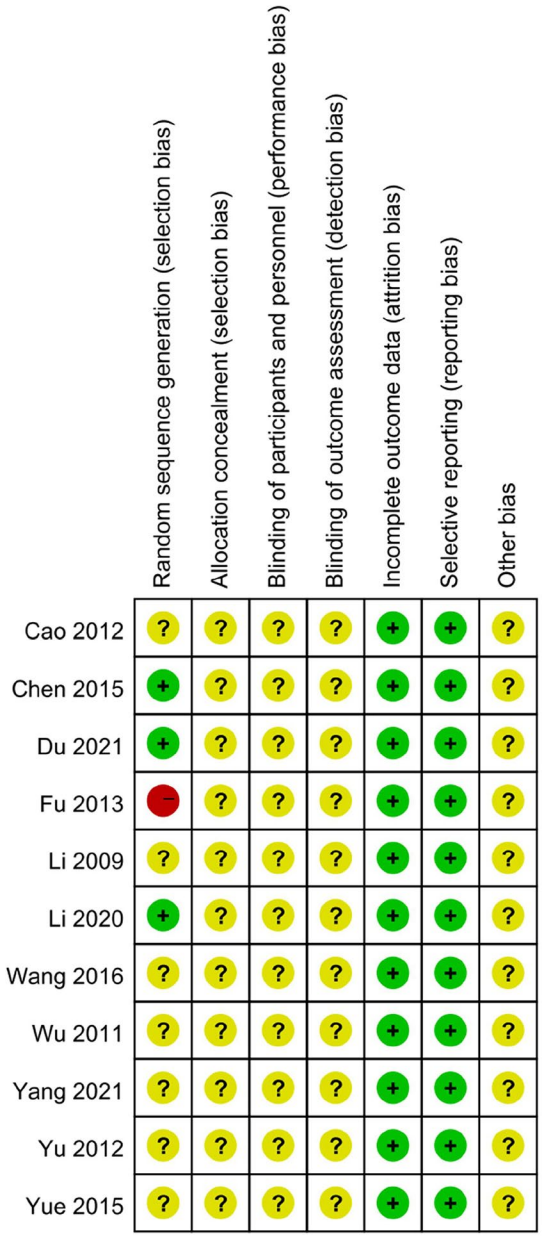

Figure 2. Summary of the risks of bias.

Level of evidence

The evidence of clinical efficacy, serum TNF-α, TGF-β1 and IL-12 levels were identified as "moderate-quality", meanwhile, the equality of evidence for SALT score and serum IFN-γ levels were identified as "low-quality". In conclusion, all of them were moderate or weak recommendations. The details can be found in Supplementary Table 2.

Discussion

AA is characterized by systemic dysregulation of Th1 (TNF-α, IL-12 and IFN-γ), Th2, and Th17 (TGF-β1) cytokines [26]. Studies have shown that patients with AA with a SALT score of ≥ 25% have higher serum TNF-α levels than those with a SALT score of < 25%, and the serum TNF-α levels are positively correlated with the severity of AA [27, 28]. Compared with healthy control individuals, patients with AA have greater expression of IL-12 mRNA in peripheral blood monocytes, and serum IL-12 levels are positively correlated with the severity and duration of hair loss [29, 30]. IFN-γ- induced immune collapse of hair follicles can cause the occurrence of AA [31]. A study showed an increased serum levels of IFN-γ in patients with active AA in comparison with patients with stable AA [32]. TGF-β1 is a pleiotropic cytokine that can regulate the growth cycle of hair follicles and the degradation period of hair growth and also activate hair follicle stem cells to stimulate hair growth [33]. The serum levels of TGF-β1 in patients with AA are lower than those in healthy people, especially in patients with active AA [27, 34].

CG is derived from the traditional Chinese medicine licorice, and as a complementary and alternative TCM treatment method, it has been widely used to treat various skin diseases closely related to autoimmune reactions [35]. CG can inhibit the activity of CD4+ cells, CD8+ cells and related cytokines and enhance the differentiation of extrathymic T cells. Thus, it inhibits the progression of AA and promotes hair regeneration [36]. Our study found that adding CG to topical minoxidil can reduce the levels of multiple Th1 cytokines (TNF-α, IL-12 and IFN-γ). Meanwhile, several studies have shown that CG can increase the levels of IL-10 in patients with AA [16, 37]. And IL-10 is mainly produced by Th2 cells, which can inhibit the production of pro-inflammatory cytokines and inhibit the immune response of Th1 type cells. These indicated that CG may treat AA by regulating the balance of Th1/Th2 cells.

Topical minoxidil can promote the proliferation and differentiation of hair follicle epithelial cells, improve the microvascular circulation around hair follicles, and activate potassium channels on peripheral arterial smooth muscles, inducing cell proliferation. Moreover, it can also increase vascular endothelial growth factor in dermal cells in a dose-dependent manner, stimulate the production of prostaglandin E2, and thus prolong the anagen phase [38]. The combination of oral CG and topical minoxidil is suggested to compensate for the shortcomings of topical application in overall immune regulation, anti-inflammatory and anti-allergic effects, balances helper T-cell function, suppresses autoimmune reactions, reduces local inflammatory reactions in AA, and improves clinical efficacy.

Many research have shown that the evaluation of trichoscopic can help diagnose AA and predict the course of the disease. For example, black dots, broken hairs, and exclamation mark hairs may be related to the activity of AA, while yellow dots may be positively correlated with the severity of AA. Short vellus hairs are adversely correlated with the severity or activity of the AA [39, 40]. Notably, one study we included reported the trichoscopic findings, which revealed that after 12 weeks and 6 months of combined treatment with CG and topical minoxidil, the number of black dots, broken hairs, exclamation mark hairs, and empty follicular openings in AA area significantly decreased, while the number of short vellus hairs increased [16]. Also, it indicated that this combination therapy can improve hair and hair follicle density, as well as reduced recurrence rates.

In this study, we analyzed 11 RCTs and systematically evaluated the efficacy and safety of CG combined with topical minoxidil for the treatment of AA. The results suggested that CG combined with topical minoxidil therapy increased clinical efficacy relative to that of topical minoxidil therapy alone. Moreover, it decreased the SALT score and serum TNF-α, IL-12 and IFN-γ levels and increased the serum TGF-β1 levels. In terms of safety, there was no significant difference in adverse reactions, including irritant contact dermatitis, gastrointestinal reactions, lower limb edema, facial edema or localized itching, between the two groups. These findings indicate that combination therapy does not increase the occurrence of adverse reactions.

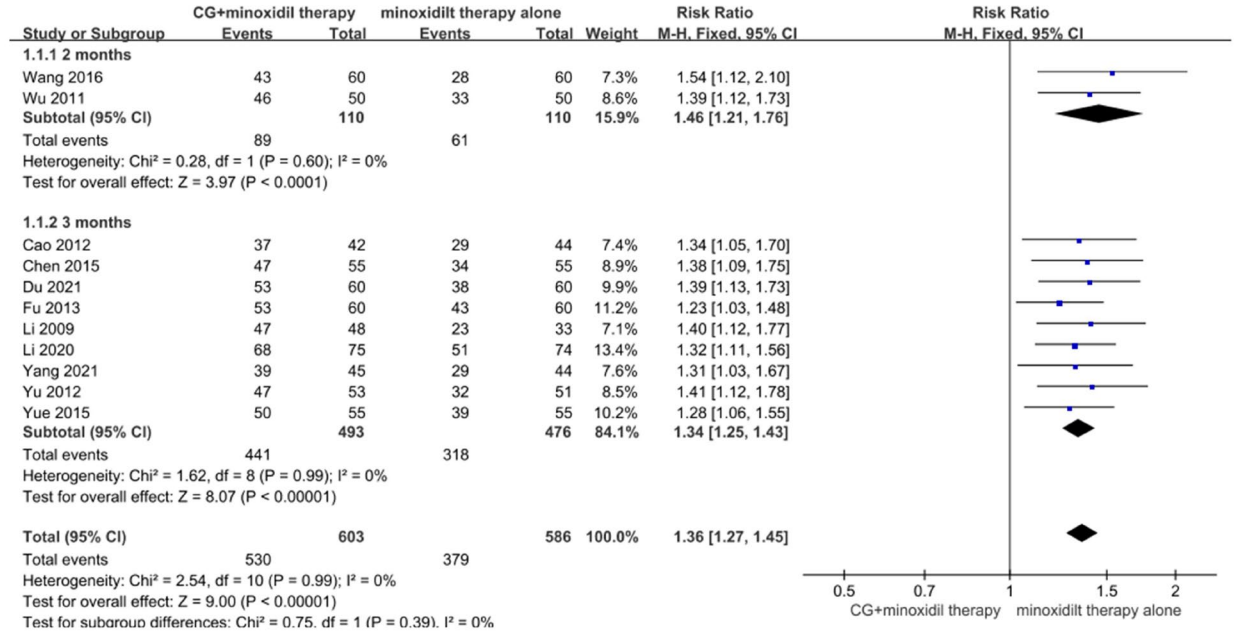

Figure 3. Forest plot for clinical efficacy.

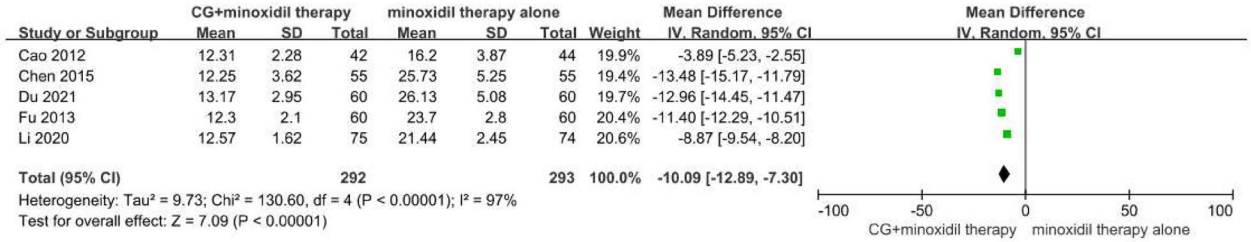

Figure 4. Forest plot for SALT score.

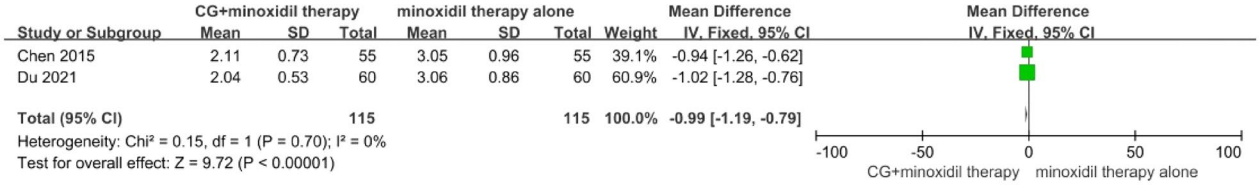

Figure 5. Forest plot for serum TNF-α levels.

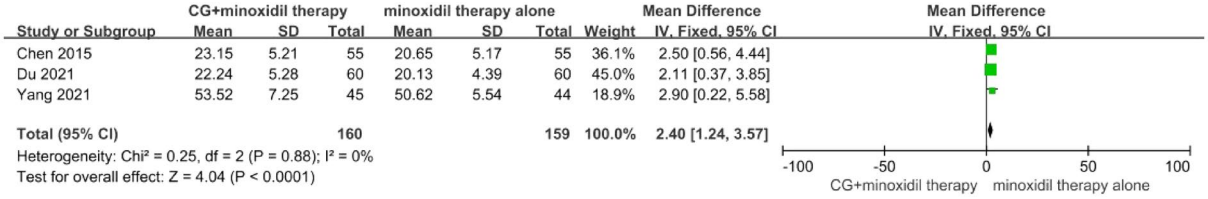

Figure 6. Forest plot for serum TGF-β1 levels.

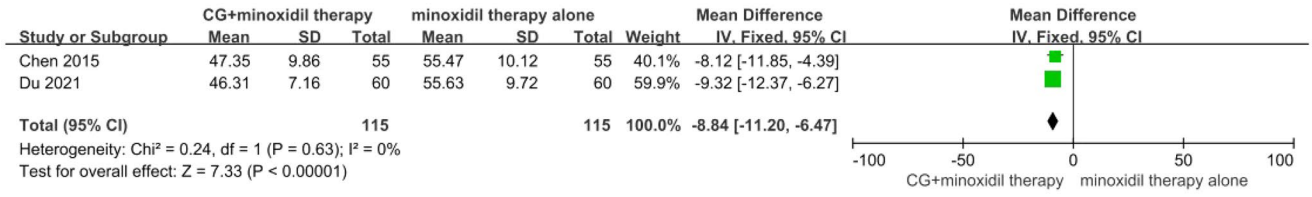

Figure 7. Forest plot for serum IL-12 levels.

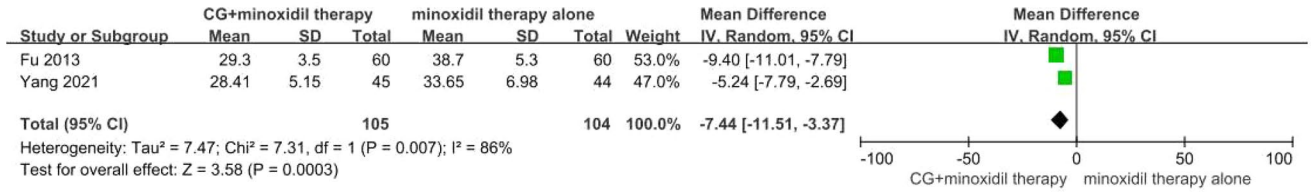

Figure 8. Forest Plot for serum IFN-γ levels.

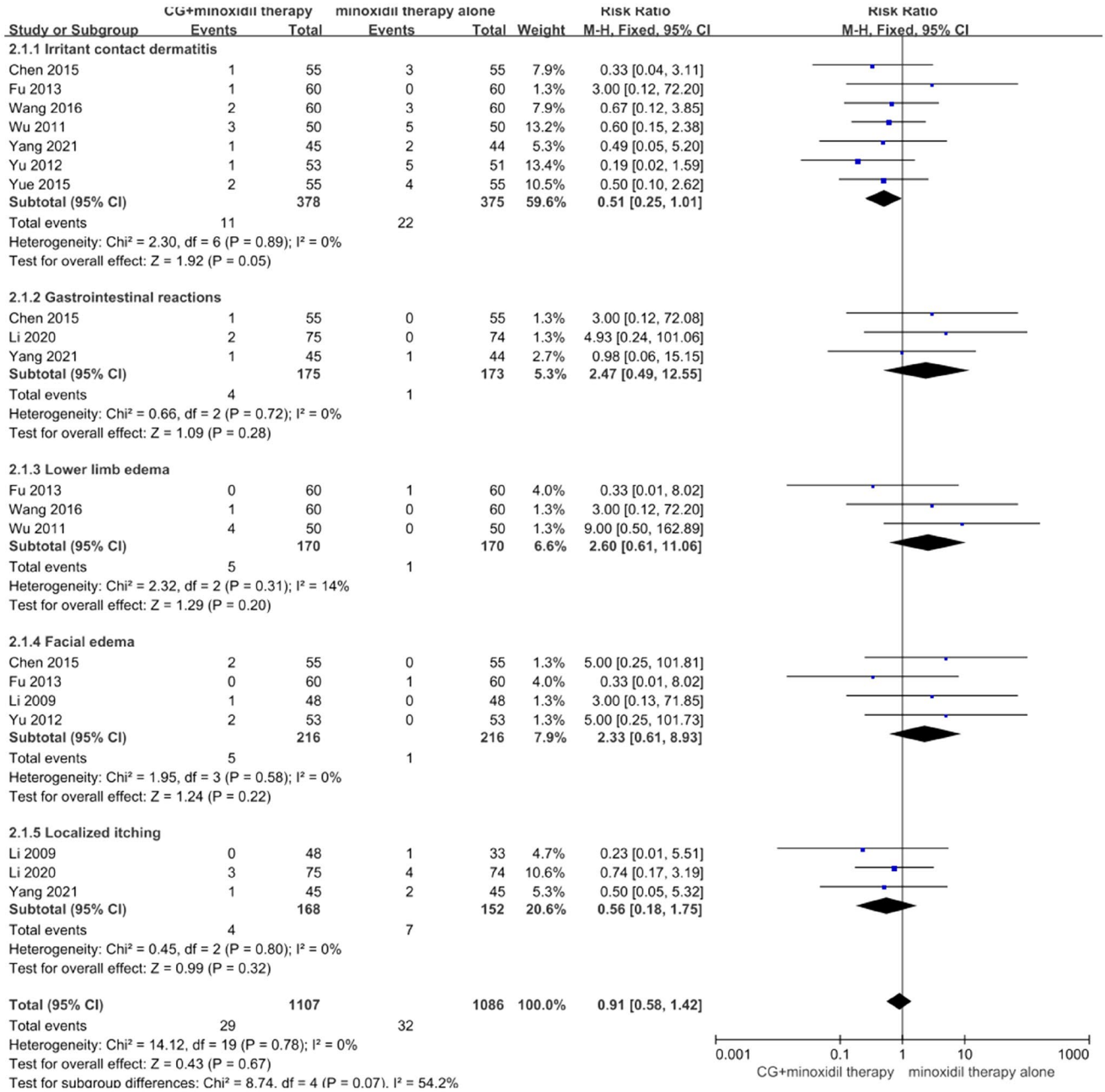

Figure 9. Forest plot for adverse events.

Limitations

The studies analyzed were limited by: First, several factors seemed to have an impact on the degree of treatment response, including patient characteristics and demographics, disease characteristics (such as age of onset, severity, disease course, AA subtype, etc) and prior treatments. Due to the limited information included we reviewed, we were unable to analyze all the above-mentioned factors. Second, the samples sizes of the studies were small. All included studies were conducted in China, and all participants were Chinese, which may cause potential regional or racial differences. Third, only 2–3 studies

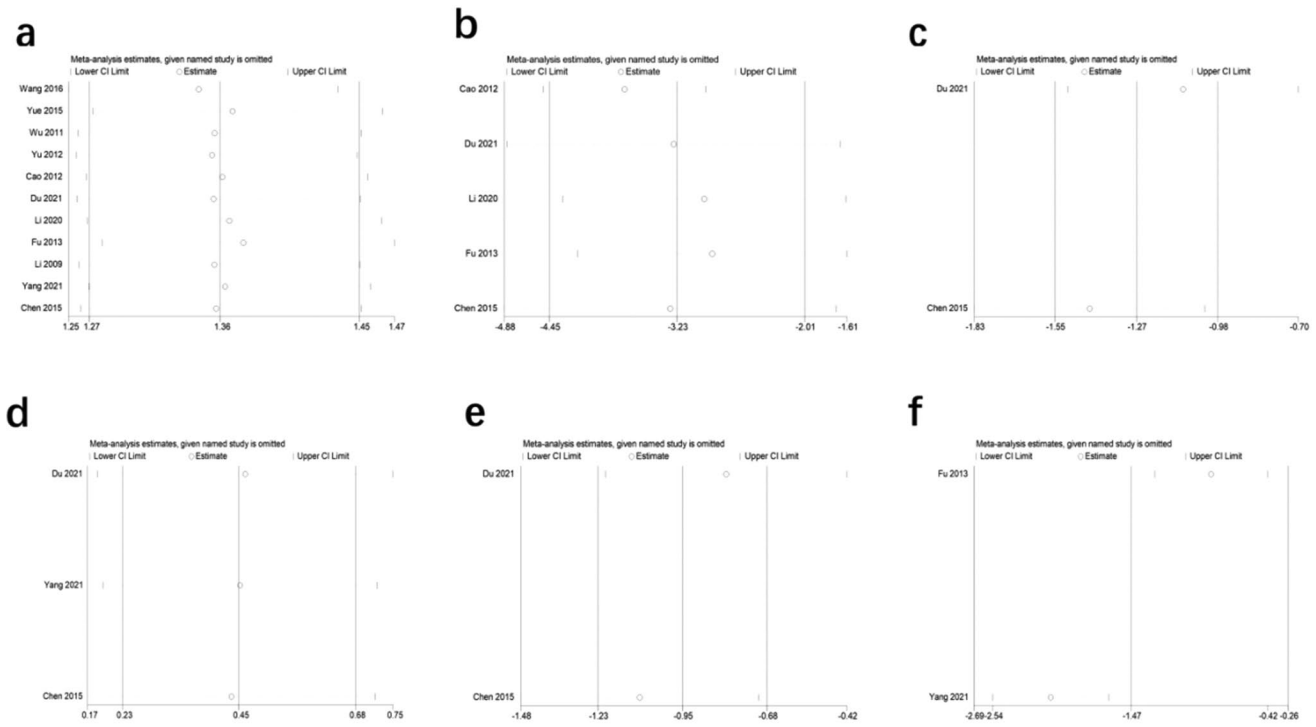

Figure 10. The results of sensitivity analysis. (a)clinical efficacy, (b)SALT score, (c)serum TNF-α levels, (d)serum TGF-β1 levels, (e)serum IL-12 levels, (f)serum IFN-γ levels.

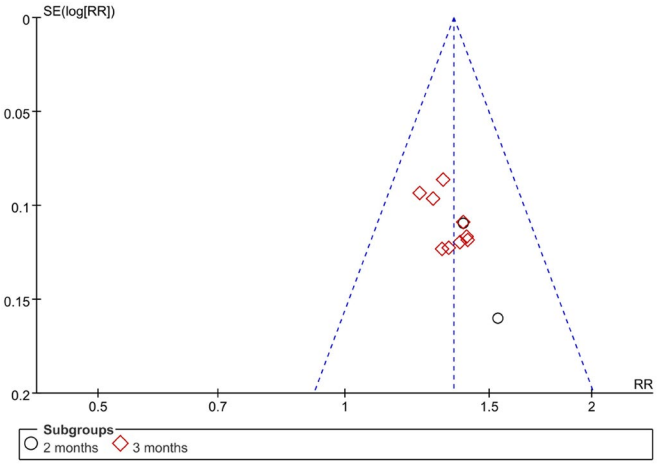

Figure 11. Funnel plot of clinical effective rate.

reported outcome indicators for the serum TNF-α, IL-12, IFN-γ and TGF-β1, reducing the quality of evidence of the results. Fourth, according to the GRADE evaluation system, the quality of evidence in outcome indicators was moderate or low. Consequently, more high-quality studies are needed to verify the effectiveness of CG combined with topical minoxidil therapy for AA treatment.

Conclusion

CG combined with topical minoxidil therapy may be safe and effective but due to the poor quality of evidence provided in the studies we reviewed, more robust studies are needed before this treatment can be recommended.

Ethical statement

This work is based exclusively on published literature and did not require ethics approval.

Author contributions

Chenqi Guo designed the study. Xiangru Gu, Junchen Li and Yingdong Wang collected and analyzed the data. Xiaoya Liu and Guojing Yang involved in writing and revision of manuscript. Min Zhang and Yu Zhang supervised the study. All authors contributed to the article and approved the submitted version.

Disclosure statement

The authors report there are no competing interests to declare.

Funding

This work was supported by the Research project of Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital (grant number 2022010).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

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