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Efficacy of different topical spironolactone treatments for acne vulgaris: A meta-analysis

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Abstract: **Background**: Topical spironolactone could serve as an alternative to oral therapy for acne vulgaris, but its efficacy requires further validation. **Objectives**: This study aimed to evaluate the efficacy of topical spironolactone monotherapy for acne vulgaris in systemically healthy patients. **Methods**: A PRISMA-compliant meta-analysis was conducted, searching PubMed, Cochrane Library, Embase, and Medline for controlled trials on exclusive topical spironolactone use. **Results**: Four trials (N=212) met criteria. Compared to baseline, the 5% spironolactone gel significantly reduced both Acne Severity Index (ASI; mean difference (MD) = -7.65, 95% CI [-10.63 to -4.67], $p < 0.00001$) and Total Lesion Count (TLC; MD = -13.50, 95% CI [-16.26 to -10.73], $p < 0.00001$). Similar reductions were observed with the 1% spironolactone gel (ASI; MD = -6.02, 95% CI [-7.84 to -4.20], $p < 0.00001$; TLC; MD = -17.60, 95% CI [-21.62 to -13.58], $p < 0.00001$), whereas, the 2% spironolactone solution only showed improvement in ASI (MD = -25.4, 95% CI [-39.61 to -11.91], $p = 0.0005$). Compared to the vehicle control, the 5% gel demonstrated efficacy in reducing both ASI (MD = -6.46, 95% CI [-9.70 to -3.23], $p < 0.00001$) and TLC (MD = -6.82, 95% CI [-11.67 to -1.98], $p = 0.006$). **Conclusion**: This meta-analysis demonstrates that topical spironolactone is an effective and well-tolerated monotherapy for mild-to-moderate facial acne, with its efficacy varying by formulation and concentration. These findings provide clinicians with evidence-based insights for selecting alternative topical treatments. Future studies with larger sample sizes and longer follow-up are warranted to confirm these results.

Keywords: Acne Vulgaris; Formulations; Meta-Analysis; Topical Spironolactone

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INTRODUCTION

Acne vulgaris is a chronic inflammatory disorder exhibiting a significant disease burden. According to the Global Burden of Disease (GBD) Study, acne vulgaris accounts for 12% of the total disability-adjusted life years (DALYs) attributed to dermatological conditions (Huai *et al.*, 2025), ranking as the second most burdensome skin disease globally. The condition affects over 90% of adolescents, with 15% to 20% progressing to moderate-to-severe presentations (Bhate and Williams, 2013; Cruz *et al.*, 2023). Facial acne compromises psychosocial well-being and self-perception, particularly among adolescents, with severe cases associated with a 2.85-fold increased risk of clinical depression and elevated suicidal ideation (Samuels *et al.*, 2020). Despite the absence of globally standardized acne classification systems, the Investigator Global Assessment (IGA) scale prevails as the primary clinical tool for both practitioners and patients. For mild-moderate acne, first-line therapy typically consists of fixed-dose combination topicals (e.g., adapalene 0.3% + benzoyl peroxide 2.5% gel) applied once daily. For moderate-to-severe acne, systemic agents form the therapeutic cornerstone: oral antibiotics (doxycycline 100 mg/day or minocycline 50-100 mg/day) for predominant inflammatory lesions; antiandrogen therapy (spironolactone 50-200 mg/day or combined oral contraceptives) in females with hormonal drivers; isotretinoin (0.5-1.0 mg/kg/day) for nodulocystic/scarring disease or treatment failure (Reynolds *et al.*, 2024). Spironolactone, a synthetic steroidal aldosterone antagonist, was originally indicated for congestive heart failure. Spironolactone exerts its antiandrogen activity primarily through competitive antagonism of cytoplasmic androgen receptors and inhibition of 5α-reductase enzymes (specifically type I and II isoforms). Dermatologists leverage this antiandrogen mechanism to manage androgen-dependent dermatoses, with acne vulgaris in biochemically confirmed hyperandrogenic females representing a key indication (Searle *et al.*, 2020). Retrospective cohort studies indicate that oral spironolactone (50-200 mg/day) demonstrates efficacy in managing moderate-to-severe inflammatory acne or nodular acne in females ≥ 18 years, serving as a guideline-recommended alternative when isotretinoin is contraindicated due to pregnancy potential or psychiatric comorbidities (Grandhi and Alikhan, 2017; Isvy-Joubert *et al.*, 2017; Layton *et al.*, 2017; Reynolds *et al.*, 2024; Roberts *et al.*, 2020; Roberts *et al.*, 2021; Santer *et al.*, 2023).

Additionally, spironolactone has the potential to reduce the antibiotic utilization for acne management, thereby decreasing the occurrence of antimicrobial resistance.

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(Aguilar Medina *et al.*, 2022). Oral spironolactone is generally well-tolerated; however, it may be associated with potential adverse reactions, including menstrual irregularities, hyperkalemia, dizziness, or gynecomastia. (Layton *et al.*, 2017). Several studies have established the efficacy of topical spironolactone in managing acne vulgaris through androgen receptor inhibition.

While some investigations have demonstrated that topical gels reduce Total Lesion Count (TLC) in acne vulgaris, their effects on Acne Severity Index (ASI) have not been consistently demonstrated (Afzali *et al.*, 2012). Furthermore, since various topical formulations and concentrations may elicit divergent therapeutic effects, this study evaluated the effectiveness of topical spironolactone via meta-analysis, incorporating dose-response and formulation-specific analyses.

MATERIALS AND METHODS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two independent reviewers performed the literature search. The protocol was registered in PROSPERO (CRD 42024618207) and revised on February 24, 2025.

Search strategy

The electronic search was conducted from inception to November 19, 2024, across PubMed, Cochrane Library, Embase, and Medline. To enhance sensitivity, "Acne Vulgaris" and "Spironolactone" were employed as key words and MeSH terms, combined using Boolean operators (e.g., AND/OR). The search strategy was designed to be applicable to all four databases. Additionally, reference lists of identified articles were reviewed for relevant studies, with evaluation based on predefined selection criteria.

Acceptance and rejection criteria for the included studies

This study aims to assess the effectiveness of topical spironolactone for acne vulgaris. Included articles reported pre- and post-treatment outcomes of acne severity and specific clinical measures (e.g., ASI, TLC, IGA score). Inclusion criteria were: (1) Randomized-controlled trials (RCTs) or controlled clinical trials on topical spironolactone for acne vulgaris; (2) English-language publications with no restrictions on region, publication year, or patient age. Exclusion criteria encompassed: (1) Overlapping data; (2) Inaccurately extracted data; (3) Non-primary literature (abstracts, book chapters, conference papers, etc.); (4) Non-human studies; (5) Oral administration.

Search results from electronic databases were imported into EndNote 21 for deduplication. Two reviewers independently screened titles/abstracts against predefined criteria. Full texts were retrieved via the Peking Union Medical College Library. After reference-list screening, full texts were assessed for eligibility, with disagreements resolved by a third reviewer. Data extraction was then performed on final included studies.

Information extraction

Data were independently extracted by two reviewers using a piloted, predefined form. Discrepancies were resolved through consensus or third-party adjudication. Extracted elements included: (1) Study metadata (author, year, site, design); (2) Participant demographics (gender, mean age, baseline characteristics); (3) Intervention protocols; (4) Outcomes (ASI and TLC improvements). Textual, tabular, and graphical data were systematically captured.

Assessment of risk of bias

The Cochrane risk of bias tool was independently applied by two authors to each study to assess for bias. Interventions assessment tool including: bias in random sequence generation (selection bias), bias due to allocation concealment (selection bias), bias in blinding of participants and personnel (performance bias), bias due to blinding of outcome assessment (detection bias), bias due to incomplete outcome data (attrition bias), bias in selective reporting (reporting bias), and other bias.

Data integration and evaluation

Outcome data were extracted from both treatment and control groups of the selected studies for meta-analysis. Mean differences (MDs) in changes from baseline to post-treatment values for ASI and TLC were compared between: (1) different treatment groups, and (2) treatment versus control groups. The MD was employed to determine the pooled effect size and the associated 95% confidence interval (CI).

The Cochrane Q statistic and I^2 index were used to assess heterogeneity. When significant heterogeneity was indicated (typically I^2 >50% and/or Q p-value <0.10), a random effects model was applied. For low heterogeneity ($I^2 \leq 50\%$ and Q p-value ≥ 0.10), the pooled effect size with 95% CI was calculated using a fixed effects model with weighting methods appropriate to the outcome type (inverse-variance for continuous data). All analyses were conducted in Review Manager 5.4.

RESULTS

Results of the literature search

A total of 1886 records were retrieved from PubMed, Cochrane Library, Embase, and Medline. After deduplication using EndNote 21 and title/abstract screening, 102 records remained eligible for full-text assessment. Four studies ultimately met the inclusion criteria for meta-analysis, including one additional study identified through manual reference-list screening (Fig. 1).

Features of the included studies

This systematic review included four RCTs (table 1), conducted in Iran, Egypt, and Iraq, and published between 2012 and 2021. The included studies enrolled a total of 212 participants diagnosed with acne vulgaris, comparing the efficacy of topical spironolactone formulations versus placebo or active comparator treatments, with follow-up durations ranging from 6 to 12 weeks.

The included studies employed distinct control methodologies: (1) Afzali *et al.* conducted a standard placebo-controlled trial comparing topical spironolactone against vehicle control; (2) Attwa *et al.* implemented a split-face design with intra-individual placebo comparison; (3) Noaimi *et al.* used clindamycin as active comparator; while (4) Kelidari *et al.* compared different concentration formulations of spironolactone (1% vs 5%). In the single-arm meta-analysis, outcome data were extracted from all treatment groups across included studies. This encompassed both experimental groups (receiving different topical formulations) from the fourth study, which were analyzed as distinct intervention arms (table 2). Additionally, we conducted subgroup analyses using placebo-controlled data from two eligible studies (table 3) (Afzali *et al.*, 2012; Attwa *et al.*, 2019; Kelidari *et al.*, 2016; Noaimi and Al-Saadi, 2021).

Assessment of bias

The high risk of bias included: random sequence generation (selection bias), bias due to allocation concealment (selection bias), bias in blinding of participants and personnel (performance bias), and bias due to blinding of outcome assessment (detection bias). The risk of bias for the other domains (selective reporting, and other bias) was low (fig. 2).

Effects of spironolactone on ASI and TLC

The single-arm meta-analysis, encompassing three studies, demonstrated improvements in both ASI and TLC from baseline across three topical formulations.

ASI changes

- 5% spironolactone gel: MD = -7.65, 95% CI [-10.63 to -4.67], $p < 0.00001$;
- 2% spironolactone solution: MD = -25.4, 95% CI [-39.61 to -11.91], $p = 0.0005$;
- 1% spironolactone loaded nanostructured lipid carrier gel (SP-NLC): MD = -6.02, 95% CI [-7.84 to -4.20], $p < 0.00001$ (fig. 3a).

TLC changes

- 5% spironolactone gel: MD = -13.50, 95% CI [-16.26 to -10.73], $p < 0.00001$;
- 1% SP-NLC gel: MD = -17.60, 95% CI [-21.62 to -13.58], $p < 0.00001$ (fig. 3b).

In the included two-arm studies, encompassing two studies, the 5% spironolactone gel demonstrated improvement in ASI and TLC compared to placebo.

ASI changes

MD = -6.46, 95% CI [-9.70 to -3.23], $p < 0.00001$ (fig. 4a).

TLC changes

MD = -6.82, 95% CI [-11.67 to -1.98], $p = 0.006$ (fig. 4b).

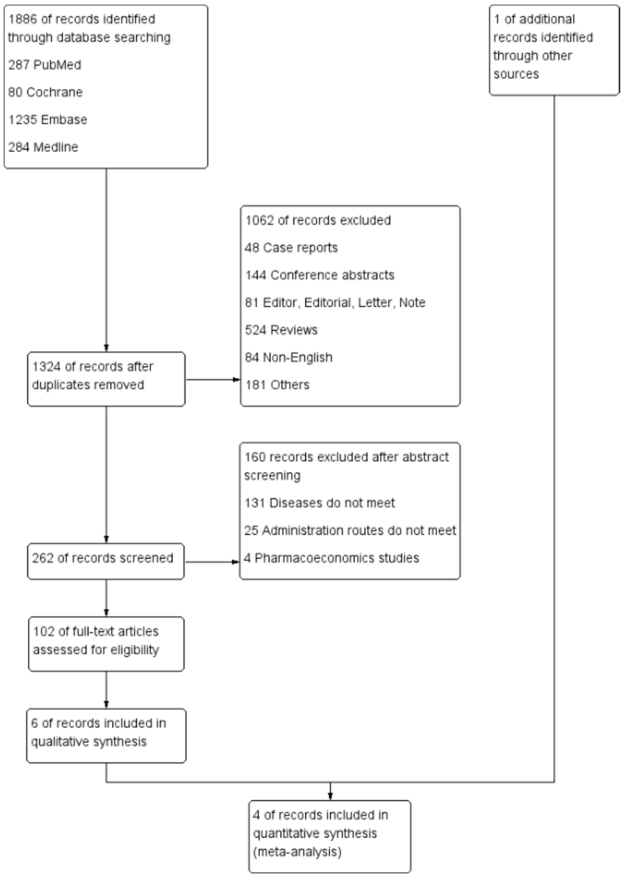


Fig. 1: PRISMA flow diagram reporting the process of the review.

Side effects

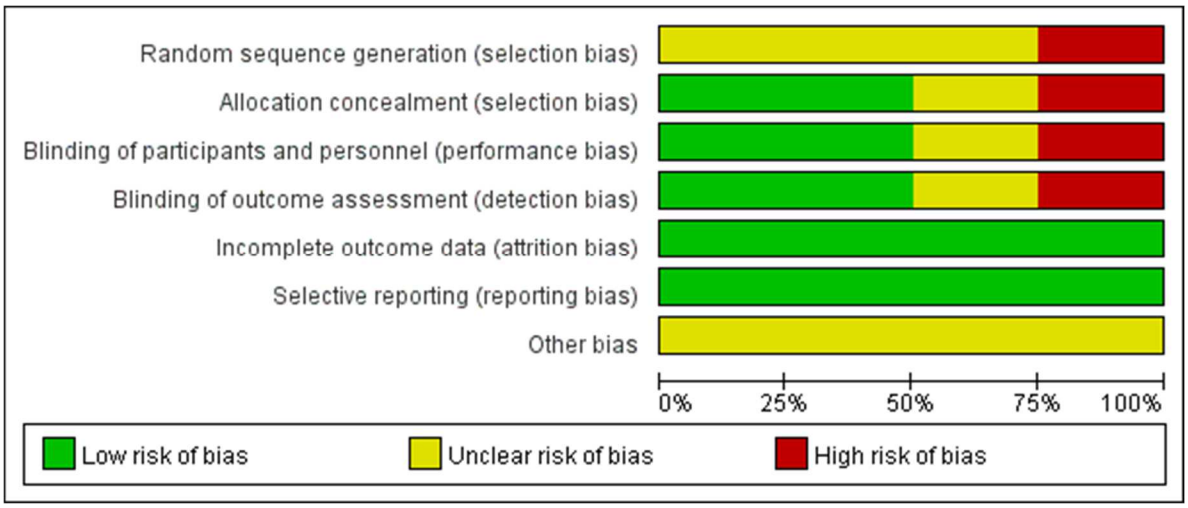
All reported adverse reactions in the included studies were mild, with incidence rates showing no statistically significant difference compared to the control group. None required intervention, including burning sensation, erythema, itching, and peeling.

DISCUSSION

The skin is both a producer of androgens and a significant target organ for them. The well-established role of androgens in acne pathogenesis involves stimulating sebaceous gland proliferation and sebum overproduction, inducing follicular hyperkeratinization and obstruction, ultimately leading to impaired desquamation and acne development. (Searle *et al.*, 2020).

Spironolactone acts as a competitive, reversible antagonist of the aldosterone receptor and inhibits androgen biosynthesis.

A.



B.

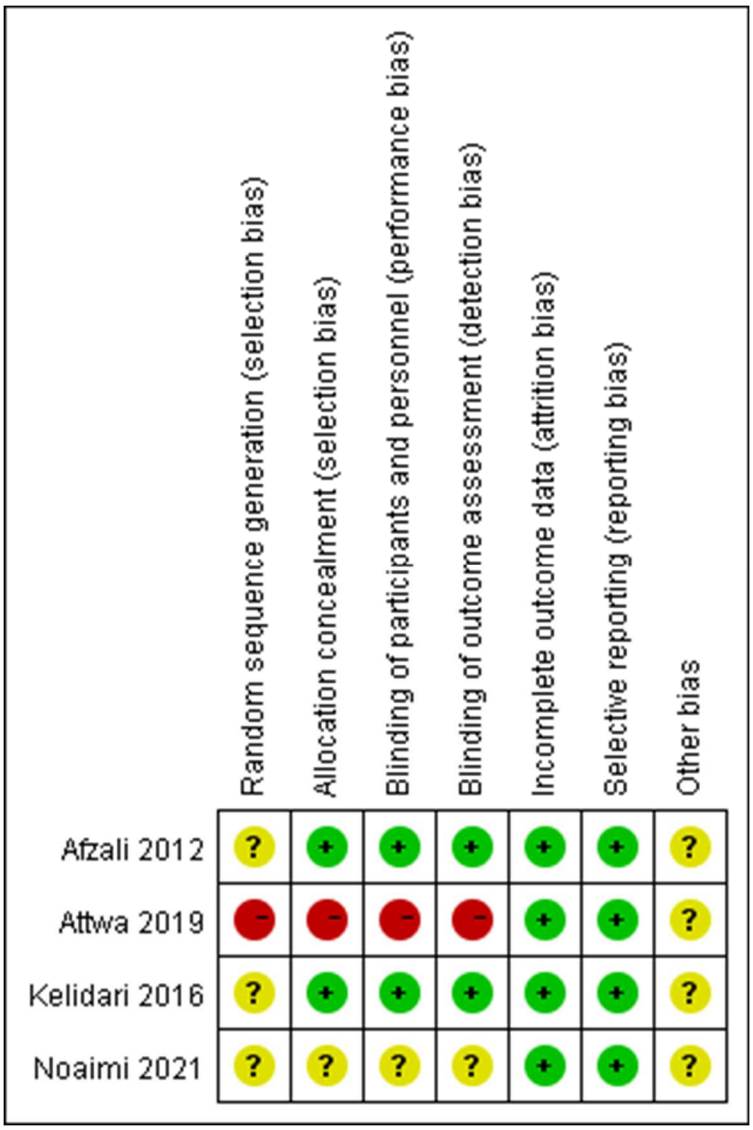


Fig. 2: A. Risk of bias graph: Risk of bias judgments for all studies, shown as percentages. B. Risk of bias summary: Assessments of risk of bias for each study. ?, unclear risk of bias. +, low risk of bias. −, high risk of bias.

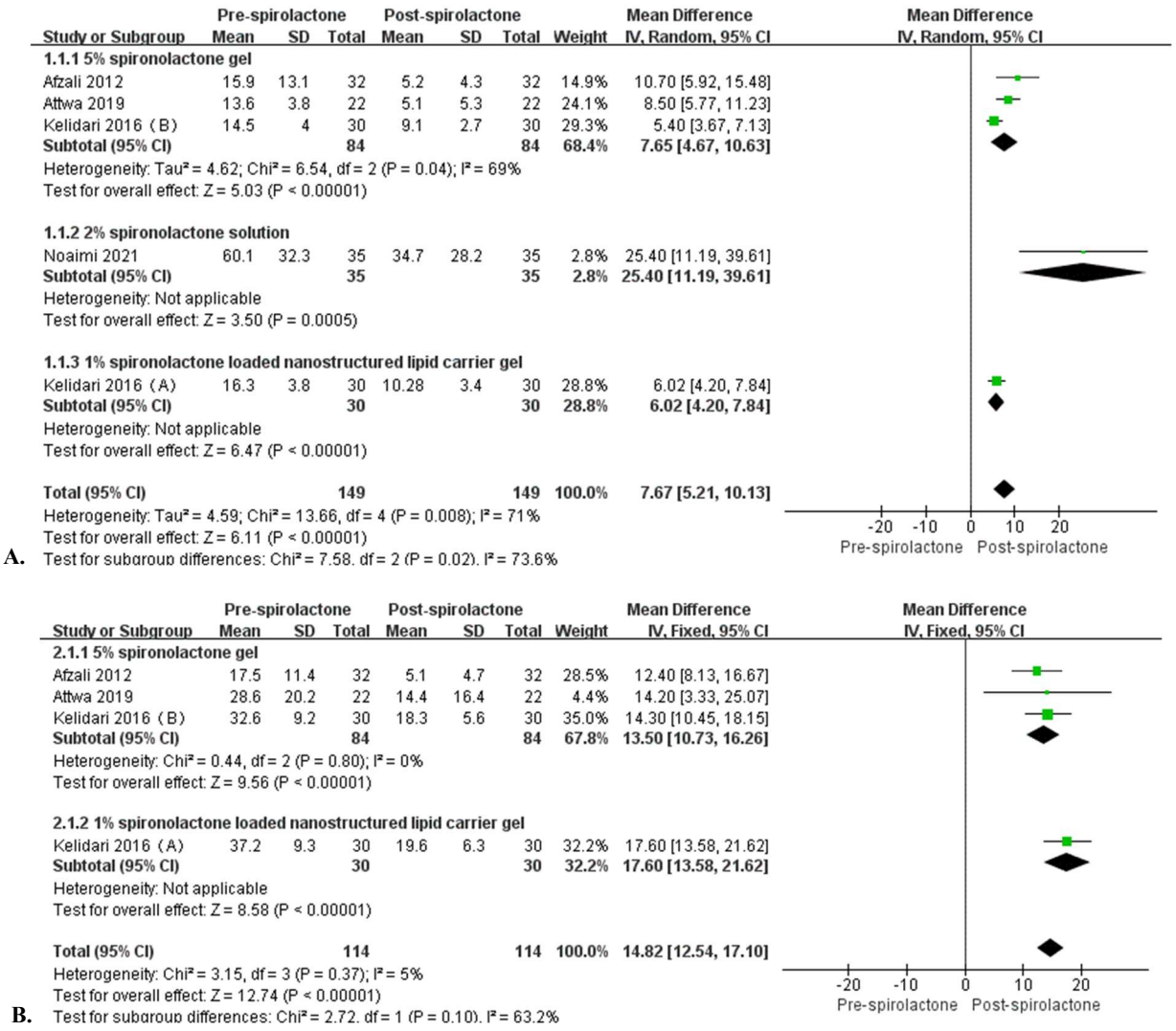


Fig. 3: **A.** Forest plot of Acne Severity Index (ASI) changes from baseline to post-treatment. B. Forest plot of Total Lesion Count (TLC) changes from baseline to post-treatment.

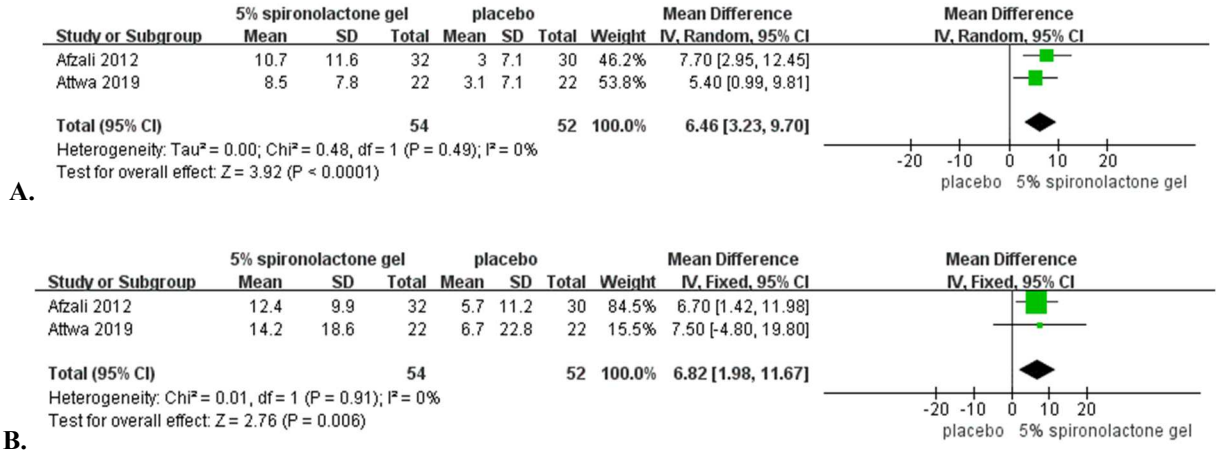


Fig. 4: A. Forest plot of ASI changes between treatment and placebo groups. B. Forest plot of TLC changes between treatment and placebo groups.

Table 1: Features of the included studies.

Publication author and year	Country	Type of study	Number of participants, sex	Age [years]	Treatment methods	control
Afzali 2012	Iran	Clinical trial	62, (The gender ratio of the subjects who ultimately completed the trial is unknown.)	Treatment group:21.5 ± 4.2 Control group:22.03 ± 4.06	5% spironolactone gel	placebo
Attwa 2019	Egypt	Clinical trial	22, 15 females and 7 males	18.2 ± 3.4	5% spironolactone gel	placebo
Noaimi 2021	Iraq	Clinical trial	68, 51 females and 17 males	Treatment group:18.3 ± 4.6 Control grouo:17.8 ± 3.8	2% spironolactone solution	1.5% clindamycin solution
Kelidari 2016	Iran	Clinical trial	60, 55 females and 5 males	Treatment group A: 21.80 ± 5.97 Treatment group B: 20.86 ± 5.36	Treatment A: 1% spironolactone loaded nanostructured lipid carrier gel (SP-NLC); Treatment B: 5% spironolactone alcoholic gel (SP-ALC)	none

Table 2: Data obtained from the treatment groups within the included studies.

Publication author and year	Treatment group	Subjects	ASI Pre-spironolactone	ASI Post-spironolactone	*p*-value	TLC Pre-spironolactone	TLC Post-spironolactone	P-value	Visit time
Afzali 2012	5% spironolactone gel	32	15.9±13.1	5.2±4.3	0.000	17.5±11.4	5.1±4.7	0.000	6 weeks
Attwa 2019	5% spironolactone gel	22	13.6±8.9	5.1±5.3	<0.001	28.6±20.2	14.4±16.4	<0.001	8 weeks
Noaimi 2021	2% spironolactone solution	35	60.1±32.3	34.7±28.2	0.0001	-	-	-	8 weeks
Kelidari 2016	A:1% spironolactone loaded nanostructured lipid carrier gel (SP-NLC)	30	16.3±3.8	10.28±3.4	<0.001	37.2±9.3	19.6±6.3	<0.001	8 weeks

Table 3: Data from the treatment groups and placebo groups within the included studies.

Author and year publication	ASI		TLC		Subjects		Visit time
	5% spironolactone gel	placebo	5% spironolactone gel	placebo	5% spironolactone gel	placebo	
Afzali/2012	10.7±11.6	3.0±7.1	12.4±9.9	5.7±11.2	32	30	6 weeks
Attwa/2019	8.5±7.8	3.1±7.1	14.2±18.6	6.7±22.8	22	22	8 weeks

It suppresses steroidogenesis in both gonadal and adrenal tissues, inhibits 5α-reductase activity, and enhances hepatic hydroxylase activity, thereby increasing testosterone clearance (Dhurat *et al.*, 2020). Furthermore, it increases sex hormone-binding globulin (SHBG) levels, thereby reducing circulating free testosterone concentrations. Collectively, these mechanisms mediate spironolactone's anti-androgenic effects, decreasing sebum production and inhibiting acne pathogenesis (Muhlemann *et al.*, 1986).

Clinical studies have demonstrated the efficacy of oral spironolactone in the treatment of acne vulgaris. Nevertheless, its anti-androgenic properties induce a relative estrogenic excess, resulting in endocrine-related adverse effects. These include hyperestrogenism manifestations such as menstrual irregularities and breast tenderness in female patients, as well as gynecomastia and decreased libido in males (Dhurat *et al.*, 2020; Dréno *et al.*, 2024; Layton *et al.*, 2017). Following oral administration, spironolactone exhibits minimal systemic absorption and undergoes rapid hepatic metabolism to its active metabolites, canrenoic acid and 6β-hydroxy-7α-thiomethylspironolactone (Aguilar Medina *et al.*, 2022). Consequently, topical administration is advantageous as it enables localized action, minimizing systemic absorption and the incidence of adverse reactions. Furthermore, spironolactone is classified as a BCS Class II drug, characterized by high permeability and low solubility. With a molecular weight of 416.57 Da, a melting point of 212°C, and a log *P* value of 2.78, spironolactone presents a suitable candidate for topical delivery. This physicochemical profile facilitates penetration through the stratum corneum and enables effective action via topical application. (Roberts *et al*., 2021) (Saeedi *et al*., 2023).

Our research focused on evaluating clinical trials investigating topical spironolactone for the treatment of facial acne vulgaris. Among the included trials, two employed a vehicle placebo as the control; one of these was a split-face study. The third trial utilized a clindamycin solution control, while the fourth compared two distinct vehicle formulations. Considering the heterogeneity in concentration and formulation among the studies, we conducted subgroup analysis, dividing them into a 5% spironolactone gel group and other formulation groups. In the study by Noaimi *et al.*, we extracted data from the eighth-week follow-up to reduce heterogeneity in follow-up duration among the studies.

The results indicate that different topical formulations may have varying clinical effects. The 2% spironolactone solution demonstrated superior efficacy in improving the ASI compared to other formulations. The observed inverse dose-response relationship may potentially be attributed to variations in the investigated topical formulations. The delivery efficiency of topical dermatological products depends not only on the physicochemical properties and concentration of the active pharmaceutical ingredient (API), but also critically on formulation characteristics such as dosage form, excipients, and penetration enhancers. These factors influence drug release (as measured by *in-vitro* release testing, IVRT) and skin permeation (as measured by *in-vitro* permeation testing, IVPT) profiles, thereby impacting the formulation's overall therapeutic efficacy. Within topical dermatological formulations, solutions and gels represent distinct dosage forms. Compared to gels, solutions generally demonstrate superior spreadability and better conformity to the skin surface. This characteristic facilitates greater contact area between the active pharmaceutical ingredient (API) and the skin, potentially enhancing drug delivery and therapeutic efficacy. Additionally, the 2% spironolactone solution formulation used in the included studies contained approximately 75% alcohol. The alcohol component serves dual functions: acting as both an effective solvent and a well-established chemical penetration enhancer. Mechanistically, ethanol enhances cutaneous permeability primarily through disruption of stratum corneum lipid bilayer organization and extraction of intercellular lipids, thereby facilitating transdermal API transport and potentially improving clinical efficacy. (Barnes *et al.*, 2021; Karande and Mitragotri, 2009; Kuswahyuning *et al.*, 2015). Based on the factors outlined above, the superior improvement in ASI observed with the 2% spironolactone solution compared to the 5% gel formulation can be rationally explained.

The clinical trials included in this study had a maximum follow-up period of 12 weeks, lacking supporting data on long-term maintenance therapy and relapse rates. Notably, in a 2019-2021 RCT (n=342), the spironolactone group (50 mg/day) had significantly higher odds of Acne-QoL

symptom improvement at 24 weeks (82% vs. 63%; OR = 2.72, 95% CI [1.50 to 4.93], $p = 0.001$), but not at 12 weeks (OR = 1.16, 95% CI [0.70 to 1.91]) showed favorable but non-significant differences (Santer *et al.*, 2023). Another RCT (n=133) revealed a time-dependent efficacy profile for spironolactone (150 mg/day), with clinical improvements emerging at 2-4 weeks and demonstrating cumulative benefits through 12 weeks of continuous treatment (Dréno *et al.*, 2024). These findings suggest that while spironolactone treatment may require more than 4 weeks to exhibit measurable effects, its long-term efficacy (≥24 weeks) appears superior to its own short-term outcomes. However, existing evidence remains notably limited regarding the efficacy of topical formulations beyond 12 weeks of continuous treatment.

In the sensitivity analysis performed on the 5% gel subgroup using a leave-one-out approach (sequentially excluding each study), the point estimates for both ASI and TLC outcomes consistently remained within the 95% confidence interval of the pooled effect size, demonstrating the robustness of these findings (detailed data not shown).

Our study has several limitations. The primary constraint is the lack of sufficient research employing topical spironolactone for the treatment of acne, along with the small sample sizes in the included studies. Furthermore, the varying trial protocols, drug formulations, and concentrations used across the studies likely contributed to the observed heterogeneity of the results. In terms of subject demographics, all four included studies involved patients with mild-to-moderate acne vulgaris, including adolescent and adult patients, predominantly female. However, none of the studies reported data on the initial and final outcomes of treatment for subjects of different ages and genders, which prevented further subgroup analyses. We hope that our findings will stimulate broader interest in this topic and encourage the conduct of larger-scale, standardized clinical research.

CONCLUSION

Topical spironolactone demonstrates efficacy in treating mild-to-moderate acne vulgaris, with improvements in TLC and ASI observed across studies. While formulation-dependent efficacy variations were noted, existing evidence supports its therapeutic value. Larger-scale RCTs with extended follow-up are warranted to confirm long-term safety and optimize treatment protocols.

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Authors' contributions
Conceptualization, H.Y.; methodology, W.H. and C.T.; software, B.L. and C.T.; validation, H.Y.; formal analysis, C.T.; investigation, W.H.; resources, B.L.; data curation, C.T.; writing-original draft preparation, W.H.; writing-review and editing, H.Y.; visualization, W.H. and C.T.; supervision, H.Y.; project administration, H.Y. All authors have read and agreed to the published version of the manuscript.

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Data availability statement
All data generated or analysed during this study are included in this published article.

Ethical approval
As a meta-analysis, this study utilized data from original studies that were all conducted in compliance with ethical standards and obtained necessary ethical approvals.

Conflict of interest
The authors declare no conflicts of interest.

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