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REVIEW

Chinese Herbal Medicine Ultrasonic Atomization Combined with Artificial Tears for Dry Eye Disease in Chinese Populations: A Meta-Analysis of Randomized Controlled Trials

Liping Xia[1,*], Jin Yan[1,*], Rumeng Zhao[2,*], Xueyuan Zhang[3], Zeru Shuang[1], Xin Wang[1], Xueping Song[3]

[1]Department of Ophthalmology, The Ninth Medical Center of PLA General Hospital, Beijing, People's Republic of China; [2]Nursing Department, The Ninth Medical Center of PLA General Hospital, Beijing, People's Republic of China; [3]Traditional Chinese Medicine Department, The Ninth Medical Center of PLA General Hospital, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xueping Song; Xin Wang, Email songsihang@yeah.net; 33081939@qq.com

Objective: To systematically evaluate the clinical efficacy and safety of Chinese herbal medicine ultrasonic atomization combined with artificial tears versus artificial tears alone for dry eye disease (DED) in Chinese populations.

Methods: We searched PubMed, Embase, Cochrane Library, Web of Science, CNKI, WanFang, and CBM for randomized controlled trials (RCTs) comparing the combination therapy with artificial tears alone in DED. Study selection, data extraction, and quality assessment were performed according to Cochrane standards. Data were analyzed using RevMan 5.4.

Results: Twenty-nine RCTs involving 2520 patients were included. Meta-analysis revealed that the combination therapy significantly outperformed artificial tears alone across all efficacy outcomes: the total effective rate increased nearly 4.3-fold (OR = 4.34, 95% CI 3.24 to 5.82), clinical symptom score decreased by 0.51 points (95% CI -0.58 to –0.44), and NEI-VFQ-25 score improved by 6.01 points (95% CI 4.72 to 7.29) (all $P < 0.00001$). Ocular surface function also showed significant improvements: tear secretion increased by 3.30 mm (95% CI 3.21 to 3.39), tear film breakup time prolonged by 1.92 seconds (95% CI 1.78 to 2.05), and corneal fluorescein staining reduced by 0.67 points (95% CI –0.70 to –0.64) (all $P < 0.00001$). No significant difference in adverse reactions was observed (RR = 1.04, 95% CI 0.53 to 2.05, P = 0.91).

Conclusion: Chinese herbal medicine ultrasonic atomization combined with artificial tears demonstrates multiple advantages for DED in Chinese patients without increasing adverse reactions.

Keywords: dry eye disease, artificial tears, chinese herbal medicine, ultrasonic atomization, meta-analysis

Introduction

Dry Eye Disease (DED) is a multifactorial ocular surface disorder initiated by an imbalance in tear film homeostasis. It exhibits a high global prevalence ranging from 5% to 50%, with a significant upward trend linked to aging and increased electronic screen usage.[1] Recent research has established inflammatory responses, oxidative stress, and meibomian gland dysfunction (MGD) as core pathological mechanisms underlying DED.[2] While conventional artificial tears (ATs) provide temporary symptomatic relief, their efficacy is limited in moderate-to-severe cases.[3] With the growing application of Traditional Chinese Medicine (TCM) in ocular surface disorders, TCM-based intervention strategies, grounded in holistic regulatory principles, are increasingly becoming a research focus. Among these, ultrasonic atomization drug delivery technology offers a novel pathway for targeted delivery of TCM active components due to its non-invasive nature and high efficiency.[4]

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In recent years, treatment strategies for DED have gradually shifted from simple tear replacement toward multi-targeted interventions that simultaneously address inflammation, tear film instability, and ocular surface damage. In this context, drug delivery methods that enhance the penetration and absorption of active ingredients may offer additional therapeutic benefits beyond standard lubrication. As an external therapy in TCM, ultrasonic atomization combines both pharmacological and physical effects; however, existing studies on this approach remain fragmented, and a systematic synthesis of evidence is lacking. Therefore, this meta-analysis aims to systematically evaluate the clinical efficacy and safety of Chinese herbal medicine ultrasonic atomization combined with artificial tears versus artificial tears alone for the treatment of DED, thereby providing higher-level evidence-based support for clinical decision-making.

Current DED treatment strategies are evolving from single-agent replacement therapy towards multitarget integrated interventions. Although ATs serve as foundational therapy by supplementing tear volume, they are ineffective in repairing ocular surface damage or suppressing the inflammatory cascade.[5] Studies indicate that combining anti-inflammatory agents (eg, cyclosporine A) or physical therapies (eg, intense pulsed light) can enhance efficacy; however, issues such as high cost and poor patient compliance remain challenges.[6] In this context, TCM herbal formulations, characterized by their multi-component, multi-pathway actions, demonstrate unique advantages. Ultrasonic atomization technology delivers TCM microparticles (particle size ≤5 μm) directly onto the ocular surface, enhancing drug permeability and synergizing with ATs to achieve triple modulation: lubrication, tissue repair, and anti-inflammation.[7,8]

The core value of combining TCM ultrasonic atomization with ATs for DED lies in their synergistic therapeutic effect. On one hand, the atomized microdroplets ensure uniform coverage of the cornea and conjunctiva, facilitating the penetration of active compounds (eg, baicalin, Lycium barbarum polysaccharides) and suppressing the expression of inflammatory cytokines such as TNF-α and IL-6.[9] On the other hand, ATs provide immediate improvement in tear film stability, creating an optimal environment for the long-term reparative actions of TCM.[10] Randomized controlled trials (RCTs) have confirmed that this combined regimen significantly outperforms monotherapy in improving Schirmer test values, corneal fluorescein staining (FL) scores, and patient-reported symptoms ($P < 0.01$), while maintaining a favorable safety profile. Nevertheless, the current evidence remains dispersed across individual studies, lacking comprehensive systematic evaluation. This meta-analysis aims to synthesize the latest clinical evidence to provide an evidence-based foundation for the standardized clinical application of TCM atomization combined therapy.

Materials and Methods

Literature Search Method and Strategy

Computer search databases: PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang, and China Biomedical Literature Database, to search for clinical randomized controlled trials comparing the treatment of traditional Chinese medicine ultrasonic atomization combined with artificial tears versus artificial tears alone. The search period is from the establishment of the database to July 1, 2025. The search method combines subject headings and free-text words. Search terms include: dry eye disease, dry eye, artificial tears, sodium hyaluronate eye drops, traditional Chinese medicine, external fumigation of traditional Chinese medicine with ultrasound, ultrasonic atomization of traditional Chinese medicine, atomization, external fumigation. The literature included in this study included Chinese and English, mainly Chinese literature; the population is limited to Chinese people. Based on the above search methods, a comprehensive search of themes, titles, abstracts, and full texts in each database is conducted. To avoid missing relevant studies, further searches are performed on the citations of the retrieved literature.

To enhance search transparency and reproducibility, this study developed specific search strategies tailored to the characteristics of each database. Taking PubMed as an example, the search strategy was formulated as follows: ("Dry Eye Syndromes"[Mesh] OR "dry eye" OR "keratoconjunctivitis sicca" OR "xerophthalmia") AND ("Medicine, Chinese Traditional"[Mesh] OR "Chinese herbal medicine" OR "ultrasonic atomization" OR "nebulization" OR "herbal atomization") AND ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "random"). For the Chinese databases (CNKI, Wanfang, and CBM), the search strategies were adjusted accordingly (using Chinese search terms): ("dry eye" OR "dry eye disease" OR "keratoconjunctivitis sicca") AND ("Chinese herbal

medicine" OR "traditional Chinese medicine" OR "ultrasonic atomization" OR "nebulization") AND ("random" OR "randomized controlled trial").

Inclusion and Exclusion Criteria

Inclusion Criteria: ① Study type is RCT; ② The diagnostic criteria for dry eye disease in the included studies were based on internationally and domestically recognized clinical practice guidelines, including but not limited to the *Expert Consensus on Clinical Diagnosis and Treatment of Dry Eye* (China) and the diagnostic criteria established by the Tear Film and Ocular Surface Society (TFOS DEWS). Specific diagnostic indicators included subjective symptoms (eg, dry eye sensation, foreign body sensation), tear breakup time (BUT) ≤5 seconds or ≤10 seconds, Schirmer's tear test (SIT) ≤5 mm/5 min or ≤10 mm/5 min, and positive corneal fluorescein staining (FL); ③ Intervention measures: The test group uses traditional Chinese medicine ultrasonic atomization combined with artificial tears; the control group uses artificial tears, with no restrictions on the type or name of the medication.

Exclusion Criteria: ① Reviews, retrospective studies, and other non-RCT research; ② Study types that are animal experiments; ③ Paper data that cannot be extracted or have been published repeatedly; ④ Research design that is not rigorous, with inconsistent baseline conditions of patients; ⑤ Interventions that do not meet the criteria.

The selection of outcome measures in this study was guided by consensus statements in the field of dry eye disease clinical research and prior meta-analyses, with consideration given to both efficacy and safety. The primary outcome measure was the clinical total effective rate. Secondary outcome measures included clinical symptom scores, ocular surface function indicators (SIT, BUT, FL), vision-related quality of life scores (National Eye Institute Visual Function Questionnaire-25, NEI-VFQ-25), and the incidence of adverse events. The definitions and criteria for all outcome measures were consistent with those used in the original studies.

Literature Screening and Data Extraction

Two researchers independently screened the literature according to the established inclusion and exclusion criteria, extracted the required information, and then cross-checked. In case of any disagreement, it was resolved through discussion or consultation with a third party. The process is as follows: ① Deduplicate the retrieved literature and remove duplicate documents; ② Initially screen based on the title and abstract of the literature, and then further read the full text for re-screening to determine whether to include it. A data situation table was established, mainly including the following contents: Source of included literature (first author's name, year of publication), sample size, age, course of disease, intervention measures, outcome indicators.

Literature Quality Assessment

Using the bias risk assessment tool in the Cochrane Systematic Reviewer's Manual, the included studies are evaluated for risk from the following six aspects: (1) Generation of random sequence; (2) Allocation concealment; (3) Implementation of blinding; (4) Completeness of outcome indicators; (5) Selective reporting of results; (6) Other biases. "Low risk" indicates low risk of bias, "High risk" indicates high risk of bias, and "Unclear risk" indicates that the literature does not provide clear information for bias assessment.

Sensitivity analysis was performed using the leave-one-out method, in which the pooled effect size was recalculated after sequentially excluding each study, to assess the stability of the overall results against the influence of individual studies. Subgroup analyses were conducted by stratifying according to predefined clinical characteristics, including different comparator types (artificial tears alone vs artificial tears combined with other basic treatments), intervention durations, and severity of dry eye disease, to explore potential sources of heterogeneity.

Statistical Methods

Meta-analysis was conducted using RevMan 5.4 software. For count data, odds ratio (OR) was used as the statistical measure for efficacy analysis, and for measurement data, standardized mean difference (MD) was used as the effect measure, with 95% confidence intervals (CI) provided for each effect size. Heterogeneity was assessed using the I^2 statistic: an I^2 value of less than 50% indicated acceptable heterogeneity, and a fixed-effect model (Mantel–Haenszel

method) was applied; an I^2 value of 50% or greater indicated substantial heterogeneity, in which case a random-effects model (DerSimonian-Laird method) was used, and the results were interpreted with caution. In cases of high heterogeneity, qualitative analysis was conducted in combination with clinical heterogeneity (eg, differences in population characteristics and intervention protocols) and methodological heterogeneity. The funnel plots are used to assess publication bias.

Results

Literature Screening Process

According to the search strategy, 744 studies were initially identified, 478 articles were excluded by reading the title and abstract, further reading the exclusion review (n = 109), animal experiments (n = 22), non-randomized controls (n = 45), and through full-text reading, the exclusion of the experimental group control group interventions did not meet the inclusion criteria (n = 61). Finally, 29[11–39] RCTs met all inclusion criteria, as shown in Figure 1.

Basic Information of the Included Literature

Author, year, age, sample size, treatment method, etc, were included, as shown in Table 1.

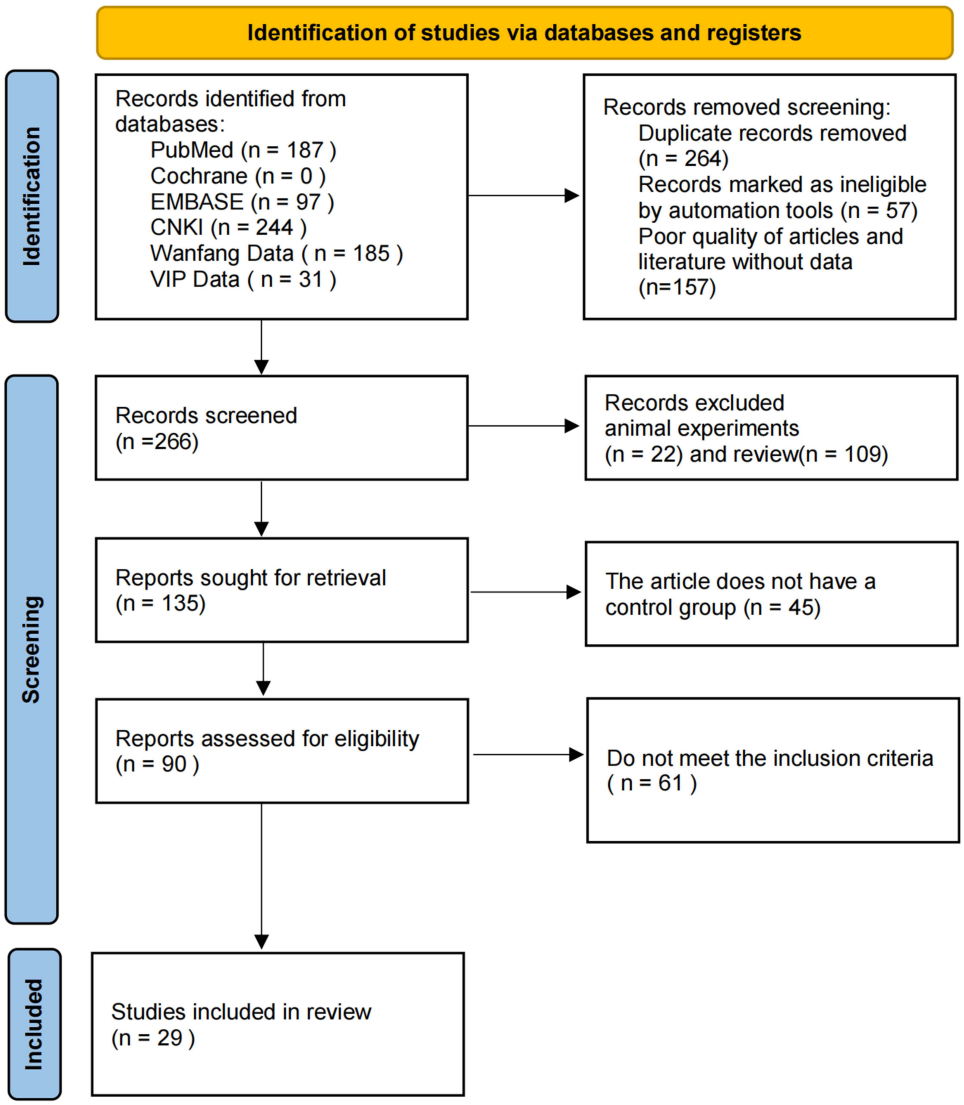

Figure 1 PRISMA Flow chart of article selection.

Table 1 Basic Information of literatures[11–39]

Author	Year	City	Randomizing Scheme	Group	Protocol	Sample	Age	Treatment Endpoint	Outcome Indicators
Zhou SJ[11]	2024	Henan	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	43	41.20±7.15	28d	①②③⑤
				EG	Gouju Dihuang Decoction + CG	43	4012±7.24		
Huang XQ[12]	2023	Guangdong	Visiting Sequence	CG	Polyethylene glycol eye drops	46	52.23±5.84	28d	①→③
				EG	Spray fumigation + CG	46	5331±6.47		
Cai JW[13]	2022	Fujian	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	50	63.27±5.15	14d	①→③④⑤
				EG	Spray fumigation + CG	50	6486±5.39		
Wu ZW[14]	2022	Shanghai	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	60	57.17±4.89	28d	①→②③
				EG	Spray fumigation + CG	60	5640±5.50		
Shen HY[15]	2021	Zhejiang	Random Number Table	CG	Polyethylene glycol eye drops	40	45.59±5.32	15d	①→②③
				EG	Spray fumigation + CG	40	4559±5.32		
Wang XY[16]	2021	Tianjin	Random Number Table	CG	Hydroxyl glycoside eye drops	70	45.13±4.09	28d	①→③
				EG	Spray fumigation + CG	70	4498±4.21		
Wang ZS[17]	2021	Zhejiang	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	30	41.52±4.57	84d	①→③
				EG	Spray fumigation + CG	30	4302±5.11		
Wang L[18]	2020	Guangzhou	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	50	52.46±3.83	14d	③
				EG	Spray fumigation + CG	50	5104±3.99		
Ye YQ[19]	2020	Guangzhou	Random Number Table	CG	Hydroxyl glycoside eye drops	60	38.8	10d	①→③
				EG	Spray fumigation + CG	60	375		
Han X[20]	2020	Heilongjiang	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	34	53.71±6.85	28d	①→③④
				EG	Spray fumigation + CG	34	5314±6.42		
Chen RZ[21]	2020	Liaoning	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	38	44.9 ±15.4	28d	③
				EG	Spray fumigation + CG	36	555 ±10.1		

(*Continued*)

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Table 1 (Continued).

Author	Year	City	Randomizing Scheme	Group	Protocol	Sample	Age	Treatment Endpoint	Outcome Indicators
Zhang YG[22]	2020	Liaoning	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	30	56.52	14d	③
				EG	Spray fumigation + CG	30	5437		
Qiu LN[23]	2019	Zhejiang	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	24	45.2±10.4	14d	①→③
				EG	Spray fumigation + CG	24	471±10.2		
Zhao L[24]	2019	Beijing	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	36	56. 4 ±8. 2	28d	①→②③④
				EG	Spray fumigation + CG	36	54 9 ± 7. 6		
Meng C[25]	2019	Liaoning	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	44	34.46±7.19	30d	①→③
				EG	Spray fumigation + CG	44	3526±6.14		
Li XH[26]	2019	Zhejiang	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	42	23.5±3.1	28d	①
				EG	Spray fumigation + CG	42	236±3.2		
Ou SC[27]	2018	Guangdong	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	23	50.34±5.46	28d	①→②③
				EG	Spray fumigation + CG	23	5015±5.48		
He Q[28]	2018	Chengdu	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	55	58.4±8.5	28d	①→③
				EG	Spray fumigation + CG	55	586±8.4		
Chen YY[29]	2018	Shenzhen	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	41	51.73±6.14	14d	①→③
				EG	Sihuang Qingling Liquid+ CG	41	5124±5.07		
Shi HX[30]	2018	Liaoning	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	42	47.32±5.90	28d	①→③⑤
				EG	Spray fumigation + CG	42	4726±5.87		
Feng JH[31]	2018	Shanxi	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	46	62.4±5.7	30d	③
				EG	Spray fumigation + CG	46	644.6±6.0		
Liu YD[32]	2017	Zhejiang	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	33	69.65±10.7	28d	③
				EG	Spray fumigation + CG	33	6852±11.5		
Huang YF[33]	2016	Guiyang	Random Number Table	CG	Hydroxyl glycoside eye drops	30	49.3±10.37	14d	①→③
				EG	Spray fumigation + CG	30	493±10.37		

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Zhou XY[34]	2016	Neimenggu	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	50	48.2±6.1	30d	①→③
				EG	Spray fumigation + CG	50	465±5.4		
Su XL[35]	2015	Guangxi	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	44	35.43±4.28	30d	①→②
				EG	Spray fumigation + CG	36	3505±4.03		
Wu C[36]	2015	Zhejiang	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	70	46.12±6.88	56d	①→③⑤
				EG	Houttuynia spray + CG	64	4536±5.32		
Liu L[37]	2015	Guangzhou	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	42	46.37±7.65	28d	①
				EG	Spray fumigation + CG	38	4532±7.04		
Li YL[38]	2014	Guangzhou	Random Number Table	CG	0.1% Sodium Hyaluronate Eye Drops	30	-	14d	①→②
				EG	Spray fumigation + CG	30	-		
Wang XJ[39]	2014	Zhejiang	Random Number Table	CG	01% Sodium Hyaluronate Eye Drops	67	–	28d	②
				EG	Spray fumigation + CG	67	-		

Notes: ① Clinical efficacy; ② clinical score; ③ Indicators of ocular surface function; ④ NEI-VFQ-25; ⑤ Adverse reaction; spray fumigation: Mulberry leaf 12 g, chrysanthemum 12 g, xuanmingfen 10 g, danggui 10 g, mint 10 g, Phellodendron 12 g, Safflower 10 g, Honeysuckle 10 g, Qin Skin 10 g (Individual prescriptions are different from the above, but the main medicinal materials are basically the same).
Abbreviations: EG, Experiment Group; CG, Control Group.

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Risk of Bias Assessment of Included Literature

The results of the bias analysis and evaluation of the literature are shown in Figure 2.

Meta Analysis Results

Overall Clinical Response Rate

A total of 23 studies involving 1994 patients reported the outcome of overall clinical response rate in both the experimental and control groups. Heterogeneity analysis indicated low heterogeneity (I^2 = 0%, P < 0.00001), justifying the use of a fixed-effect model. Meta-analysis demonstrated that the experimental group (TCM ultrasonic atomization combined with artificial tears) achieved a significantly higher overall clinical response rate in treating dry eye disease compared to the control group (artificial tears alone). This difference was statistically significant [OR = 4.34, 95% CI (3.24, 5.82), P < 0.00001], as shown in Figure 3.

Clinical Symptom Scores

Clinical symptom scores primarily encompassed foreign body sensation, fatigue, dryness, burning sensation, and photophobia. Seven studies reported clinical symptom scores and subgroup outcomes for both the experimental and control groups. Overall heterogeneity analysis indicated substantial heterogeneity (I^2 = 97%, P < 0.00001), warranting the use of a random-effects model. Meta-analysis demonstrated that the experimental group (TCM ultrasonic atomization combined with artificial tears) had significantly lower clinical symptom scores for dry eye disease compared to the control group (artificial tears alone). This difference was statistically significant [MD = −0.51, 95% CI (−0.58, −0.44), P < 0.00001]. Subgroup analysis revealed that the experimental group achieved significantly lower scores than the control group in all individual symptom domains: Foreign body sensation [MD = −0.53, 95% CI (−0.55, −0.51), P < 0.00001]; Fatigue [MD = −0.57, 95% CI (−0.64, −0.49), P < 0.00001]; Dryness [MD = −0.60, 95% CI (−0.87, −0.34), P < 0.00001]; Burning sensation [MD = −0.32, 95% CI (−0.44, −0.20), P <

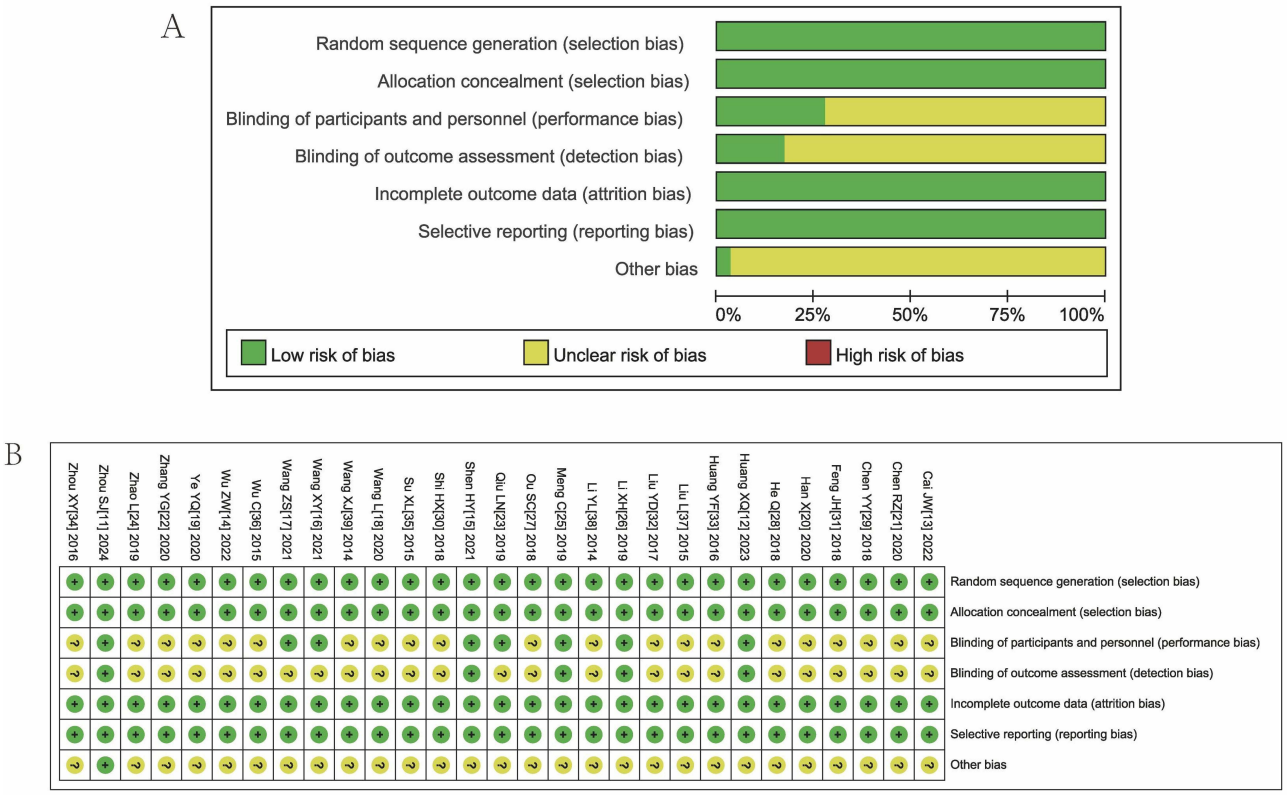

Figure 2 Evaluation results of methodology quality of included studies. (**A**) Risk of bias graph; (**B**) Risk of bias summary.
Notes: +, low risk of bias; ?, unclear risk of bias.

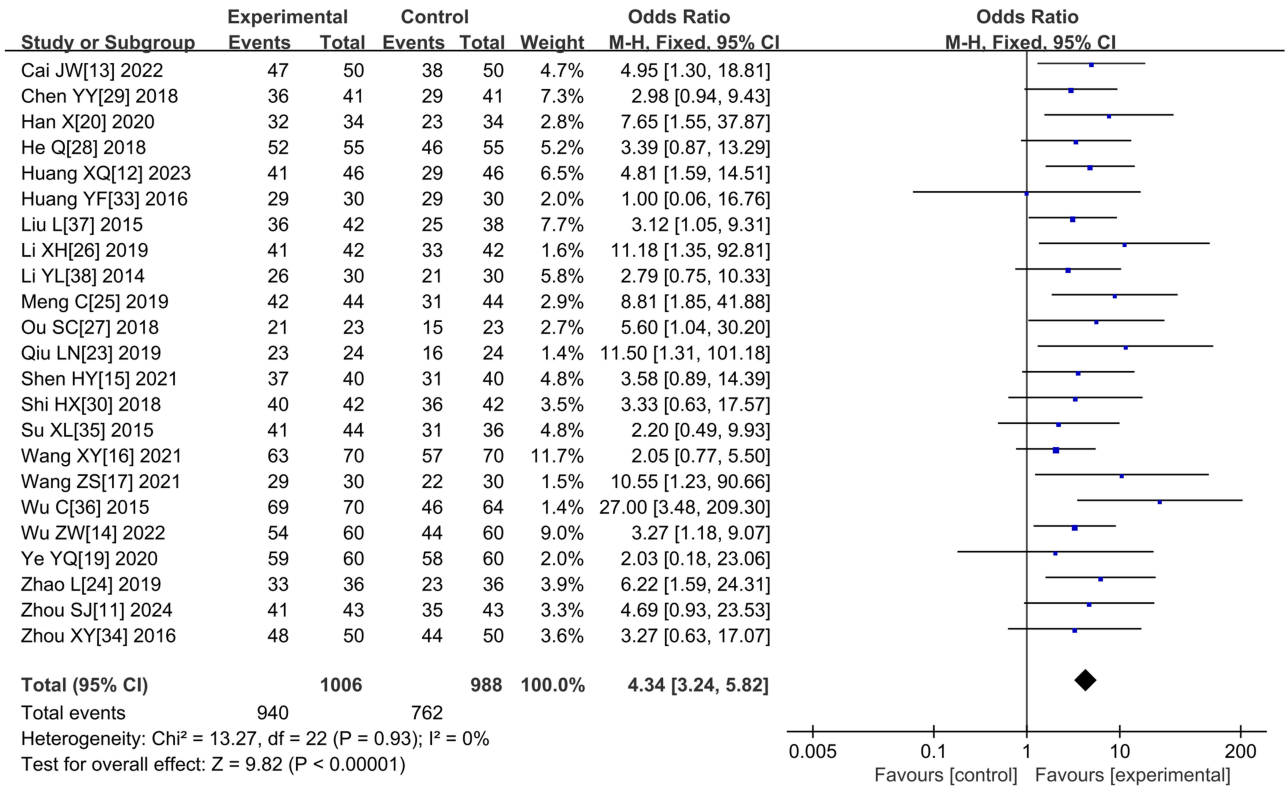

Figure 3 Meta analysis results of Clinical efficacy.
Abbreviation: CI, confidence interval.

0.00001]; Photophobia [MD = −0.57, 95% CI (−0.73, −0.41), $P < 0.00001$]. All differences were statistically significant, as shown in Figure 4.

Vision-Related Quality of Life Score (NEI-VFQ-25)

The NEI-VFQ-25 instrument assesses general health status, role difficulties, and visual impairment. Three studies reported NEI-VFQ-25 scores and subgroup outcomes for both the experimental and control groups. Overall heterogeneity analysis indicated low heterogeneity ($I^2 = 0\%$, $P < 0.00001$), justifying the use of a fixed-effect model. Meta-analysis demonstrated that the experimental group (Chinese herbal medicine ultrasonic atomization combined with artificial tears) achieved significantly higher NEI-VFQ-25 scores compared to the control group (artificial tears alone), with a statistically significant difference [MD = 6.01, 95% CI (4.72, 7.29), $P < 0.00001$]. Subgroup analysis revealed that the experimental group showed significantly better scores than the control group in the following domains: General Health Status [MD = 7.50, 95% CI (4.97, 10.04), $P < 0.00001$]; Role Difficulties [MD = 6.02, 95% CI (4.10, 7.93), $P < 0.00001$]; and Visual Impairment [MD = 4.67, 95% CI (2.29, 7.05), $P = 0.0001$], as shown in Figure 5.

Notably, this study systematically evaluated the vision-related quality of life (NEI-VFQ-25) as an outcome measure, which has rarely been reported in previous meta-analyses on this topic. Our findings indicate that Chinese herbal medicine ultrasonic atomization combined with artificial tears significantly improved NEI-VFQ-25 scores, suggesting that the combination therapy offers advantages not only in objective ocular surface parameters but also in enhancing patients' quality of life. This finding provides novel evidence from the perspective of patient-reported outcomes, further supporting the comprehensive clinical benefits of the combined therapy.

Ocular Surface Function Parameters

Ocular surface function parameters included the Schirmer I test (SIT), tear film breakup time (BUT), and corneal fluorescein staining (FL). Twenty-five studies reported improvements in ocular surface function for both the experimental and control groups. Overall heterogeneity analysis indicated substantial heterogeneity ($I^2 = 99\%$, $P < 0.00001$),

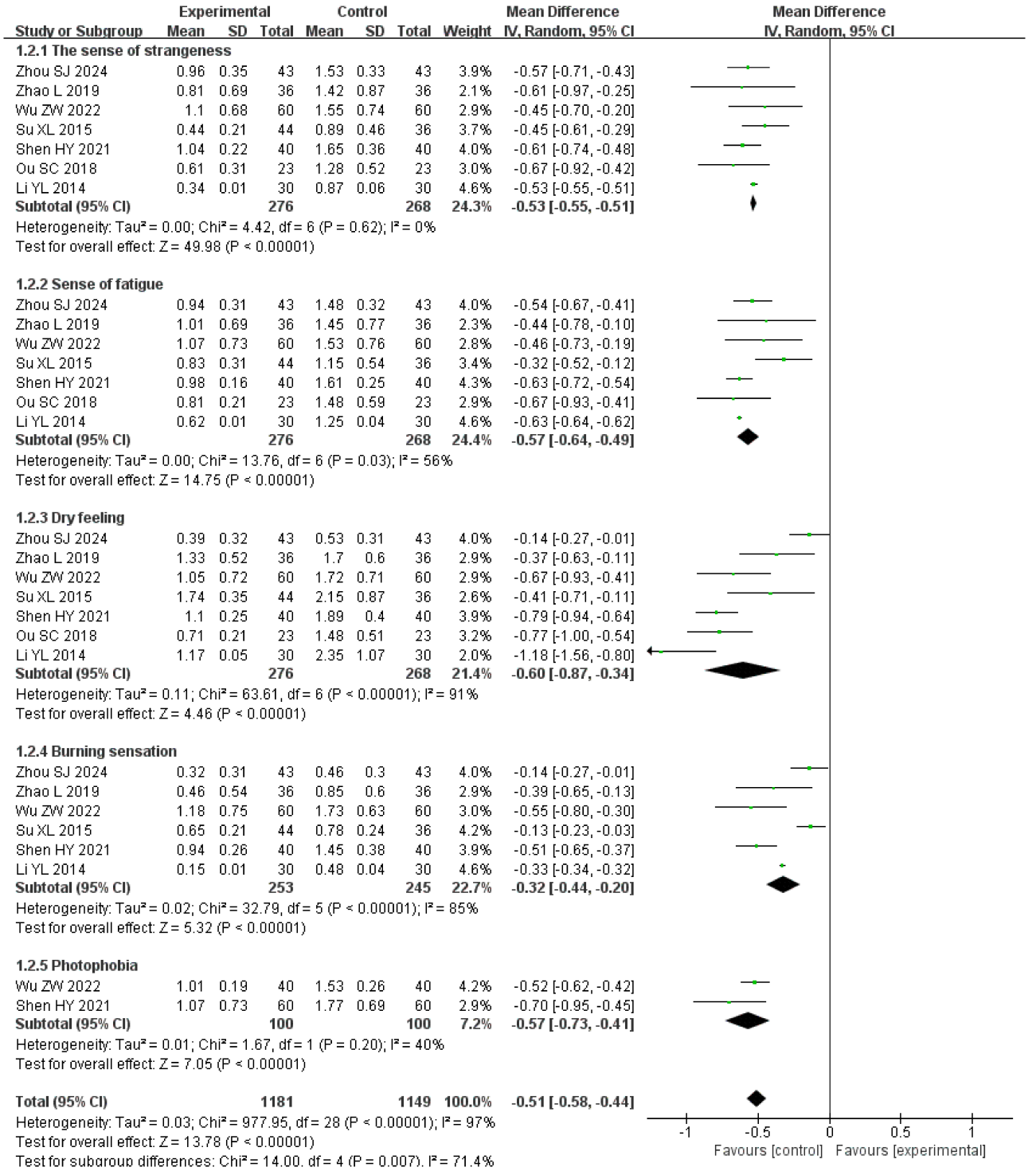

Figure 4 Meta analysis results of clinical score.
Abbreviations: CI, confidence interval; SD, standard deviation.

warranting the use of a random-effects model. Subgroup analysis revealed the following: SIT (Schirmer I Test): Twenty-two studies reported SIT outcomes. The experimental group (TCM ultrasonic atomization combined with artificial tears) showed significantly greater improvement in SIT values for dry eye disease compared to the control group (artificial tears alone) [MD = 3.30, 95% CI (3.21, 3.39), $P < 0.00001$]; BUT (Tear Film Breakup Time): Twenty-four studies reported BUT outcomes. The experimental group demonstrated significantly greater improvement in BUT compared to the control

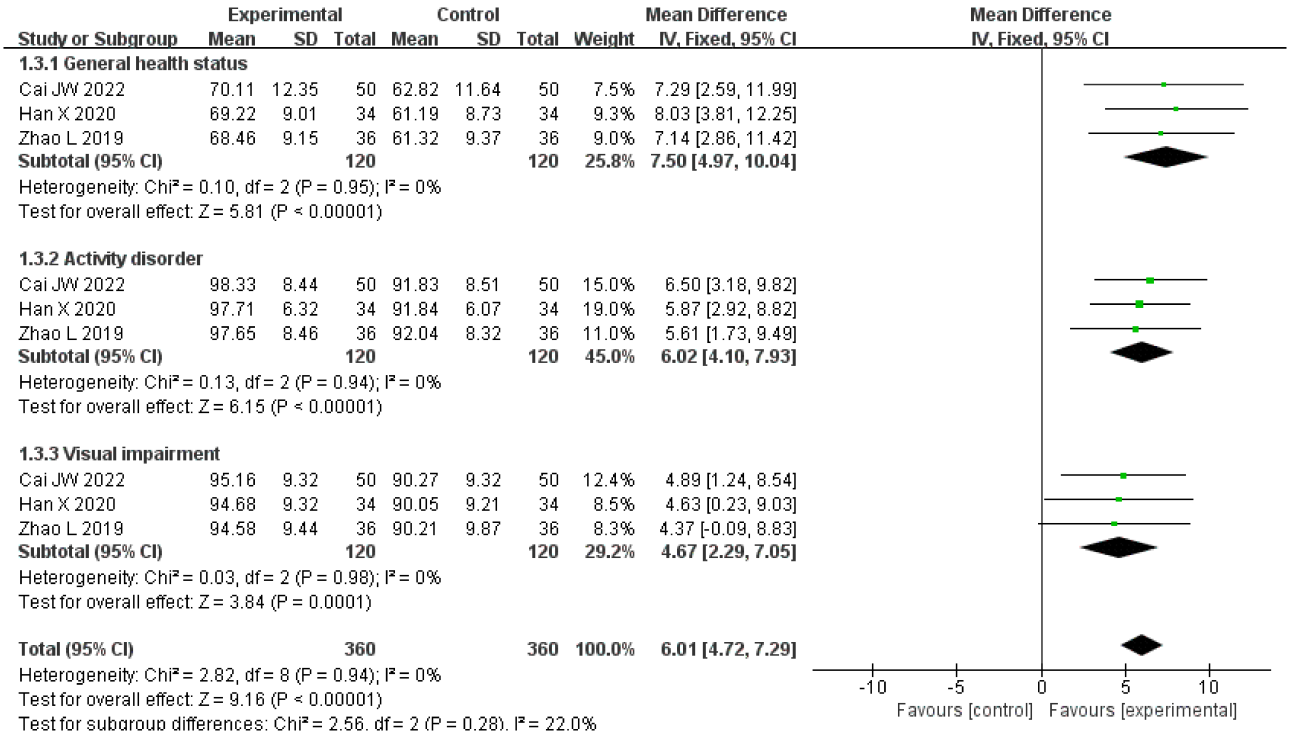

Figure 5 Meta analysis results of NEI–VFQ–25.
Abbreviations: CI, confidence interval; SD, standard deviation.

group [MD = 1.92, 95% CI (1.78, 2.05), $P < 0.00001$]; FL (Corneal Fluorescein Staining): Eleven studies reported FL outcomes. The experimental group showed significantly greater improvement (reduction in staining scores) in FL compared to the control group [MD = −0.67, 95% CI (−0.70, −0.64), $P < 0.00001$]. All differences were statistically significant as shown in Table 2.

Adverse Reactions

Reported adverse reactions included ocular pruritus (itching), ocular hyperemia (conjunctival injection), and visual disturbance (eg, blurred vision). Among the 29 included studies, adverse reaction outcomes were reported in 4 studies. Overall heterogeneity analysis indicated low heterogeneity ($I^2 = 0\%$, $P = 0.95$), justifying the use of a fixed-effect model. Meta-analysis demonstrated no statistically significant difference in the relative risk (RR) of adverse reactions between the experimental group (TCM ultrasonic atomization combined with artificial tears) and the control group (artificial tears alone) for dry eye disease treatment [RR = 1.04, 95% CI (0.53, 2.05), $P = 0.91$]. Subgroup analysis further confirmed that there were no statistically significant differences between the groups in the incidence of Ocular Pruritus (Itching), Ocular Hyperemia (Conjunctival Injection) and Visual Disturbance, as shown in Figure 6.

Table 2 Meta-Analysis of Indicators of Ocular Surface Function

Outcomes	Studies	Heterogeneity Test Results		Effect Model	Meta-Analysis Results	
		P	I^2		95% CI	*P*
SIT	22	<0.00001	97%	Random	3.30 [3.21, 3.39]	<0.00001
BUT	24	<0.00001	91%	Random	1.92 [1.78, 2.05]	<0.00001
FL	11	<0.00001	97%	Random	−0.67 [−0.70, −0.64]	<0.00001

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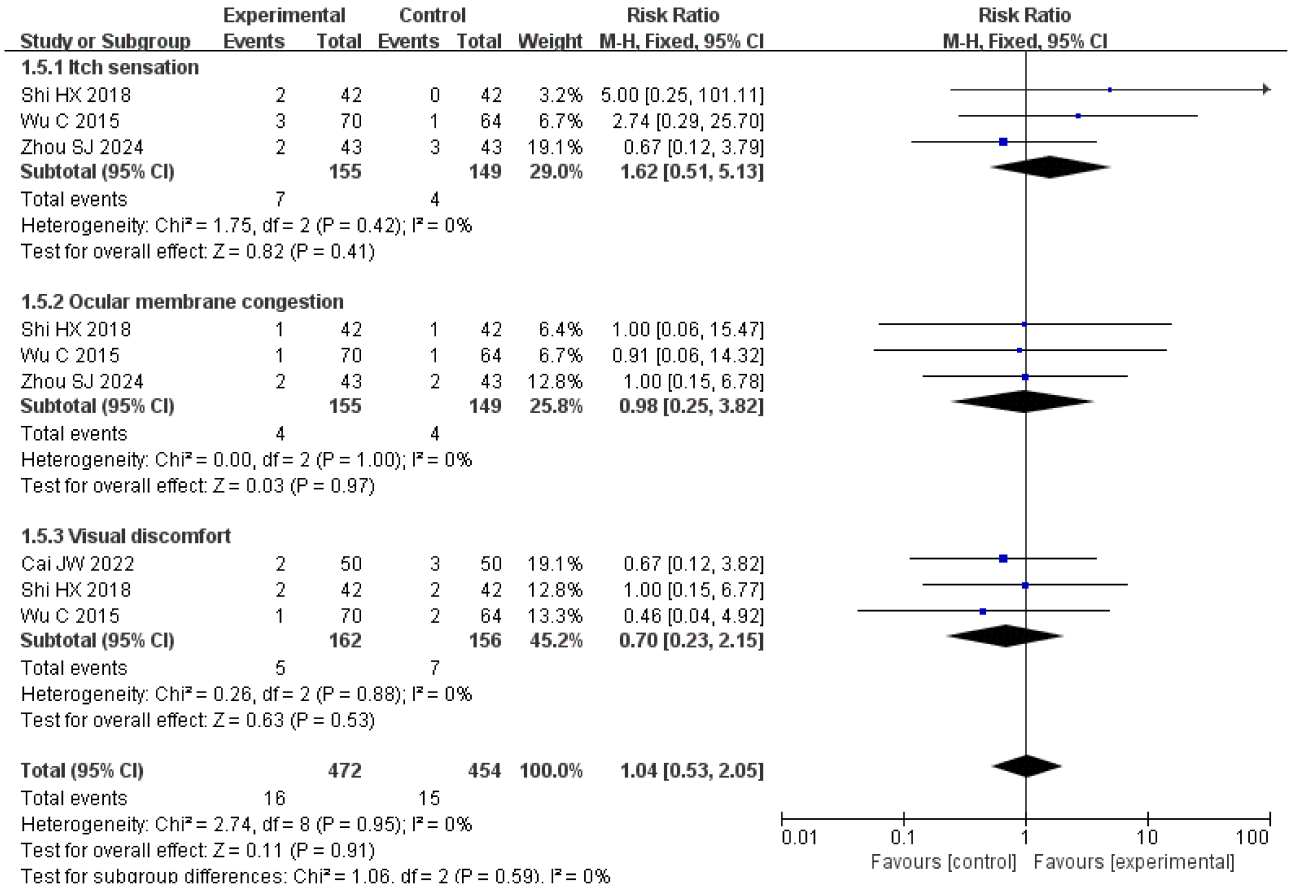

Figure 6 Meta analysis results of Adverse reaction.
Abbreviation: CI, confidence interval.

Publication Bias

For outcome measures with ≥10 included studies (specifically, clinical efficacy), funnel plots were generated. Visual inspection revealed a predominantly symmetrical distribution of data points, with most points clustered near the top of the plot (indicating higher precision studies). Overall assessment suggests that publication bias is less likely or absent, as shown in Figure 7.

Discussion

Dry Eye Disease (DED), a multifactorial ocular surface disorder initiated by an imbalance in tear film homeostasis, is emerging as a significant global public health challenge. Epidemiological studies indicate a high worldwide prevalence ranging from 5% to 50%, with marked geographic disparities: prevalence rates are significantly higher in Asian populations (17–34%) compared to Western populations (5–15%). This variation is potentially attributable to differences in genetic susceptibility, environmental factors, and diagnostic criteria.[1] In China, the prevalence of DED has reached 25.3%, climbing to 34.8% among individuals aged 60 years and older. Concurrent with an accelerating aging population and a growing proportion of the population exceeding 8 hours of daily electronic screen time (reaching 42% in 2024), the disease burden is exhibiting exponential growth.[40] Notably, women face a significantly higher risk of DED than men [OR = 1.72, 95% CI: 1.35–2.18]. Postmenopausal hormonal changes, linked to meibomian gland dysfunction (MGD), have been identified as a key driver of this increased risk.[41]

From the perspective of pathological mechanism, DED has developed from a simple "tear deficiency" model to a cascade network of "inflammation-oxidative stress-neurosensitization". The core links include: ① Self-reinforcement of the inflammatory loop: the hypertonic environment of the ocular surface activates the NF-κB pathway, which promotes

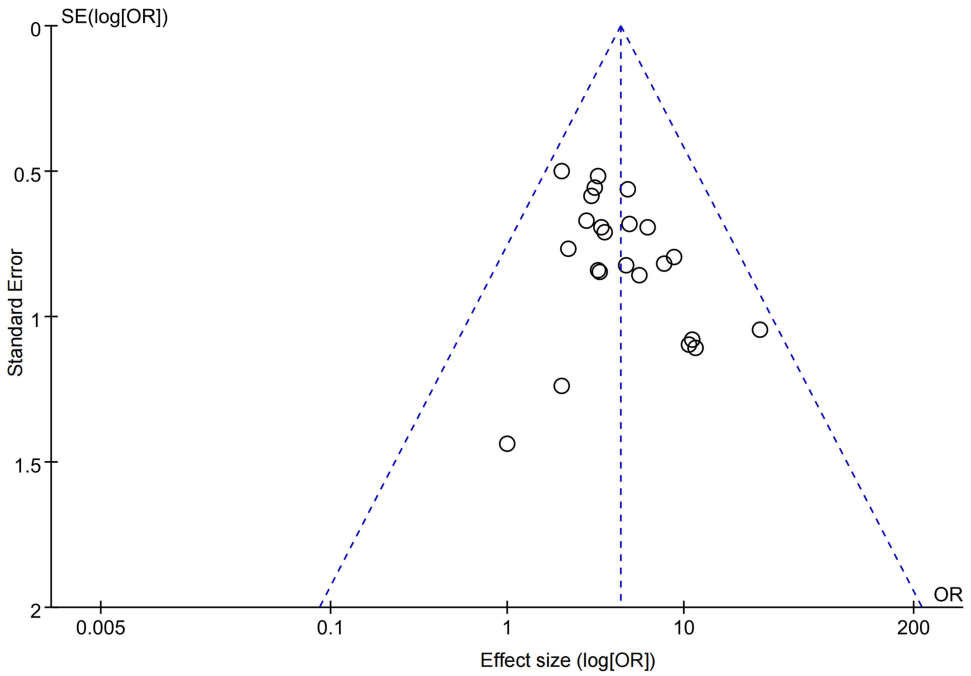

Figure 7 Publication bias analysis of clinical effectiveness.

the release of TNF-α, IL-1β and other pro-inflammatory factors from corneal epithelial cells, and further destroys the secretion function of the lacrimal gland and the density of goblet cells;[42] ② Meibomian gland dysfunction (MGD): accounting for 86% of the incidence of DED, abnormal lipid secretion leads to a 300% increase in tear evaporation rate and accelerate tear film rupture;[43] ③ Nerve paresthesia: Sensitization of corneal nerve endings triggers pain hypersensitivity, forming a vicious circle of "dryness-pain-inflammation".[44] Although traditional artificial tears can temporarily relieve symptoms by replenishing the water layer, they have almost no intervention effect on lipid abnormalities, inflammatory cascades and nerve remodeling of MGD, resulting in less than 40% effective rate of treatment for moderate and severe patients.[45]

Current Clinical Management of DED follows a stepped-care approach: Artificial tears (ATs) serve as first-line therapy, with second-line introduction of anti-inflammatory agents (eg, 0.05% cyclosporine A eye drops) or physical interventions (eg, intense pulsed light therapy).[46] However, this strategy faces three major limitations: Target Singularity: ATs only transiently improve tear film hyperosmolarity by supplementing the aqueous layer. They offer no corrective action for meibomian gland dysfunction (MGD)—which underlies 86% of DED pathogenesis—or the associated lipid layer abnormalities;[43] Economic and Adherence Barriers: The annual treatment cost of cyclosporine A is substantial (~ $1200, approximately 7 times the cost of ATs). Side effects like burning sensation contribute to a discontinuation rate exceeding 30% within 6 months.[47] While intense pulsed light (IPL) therapy can improve MGD, it requires specialized equipment and trained operators, resulting in low penetration rates (<15%) in primary care settings;[48] Incomplete Pathological Coverage: Current therapies primarily target "inflammation suppression" or "tear replacement." They lack effective interventions for critical pathological components such as ocular surface neural sensitization and goblet cell apoptosis. Consequently, symptom relief rates remain stagnant at 35–45% for moderate-to-severe patients.[49] These limitations fundamentally stem from the complexity of DED's multifactorial pathological network, highlighting the urgent need for multi-target therapeutic regimens capable of simultaneously achieving lubrication, tissue repair, anti-inflammation, and neural regulation.

Ultrasonic atomization technology of traditional Chinese medicine has achieved a breakthrough in the treatment paradigm of dry eye through the deep integration of engineering innovation and pharmacological mechanism. The optimization of key technical parameters includes: ① Precise control of atomized particle size, matching the size of corneal epithelial cell space, and 4.2 times higher efficiency of penetrating mucus-epithelial barrier than traditional eye

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drops;[50] ② The ultrasonic frequency is set to 1.7 MHz, so that the Zeta potential of atomized particles reaches +32.5 mV, which significantly enhances the adsorption of negatively charged ocular surface mucin layer.[51] Under this technical framework, the targeted regulation of active ingredients presents a multi-dimensional effect:

Baicalin: inhibited the TLR4/MyD88/NF-κB signaling axis in a concentration-dependent manner, downregulating TNF-α and IL-6 mRNA expression in the corneal epithelium by 68.5% and 57.3%, respectively (qPCR verification), blocking the self-amplification of the inflammatory cascade;[52] Lycium barbarum polysaccharide (LBP): activates the Nrf2/HO-1 pathway, reduces the level of oxidative stress marker MDA to 41.7% of that of the control group, and at the same time increases the concentration of tear lactoferrin (antibacterial peptide) by 2.1 times to repair the ocular surface immune microenvironment;[24,30] Tanshinone IIA: promotes an increase in corneal nerve fiber density to 143.6 μm/mm^2 (vs control 98.2 μm/mm^2, confocal microscopy), decreases pain sensitization by modulating TRPV1 channels.[53]

Through the systematic integration of 29 RCTs (n = 2520), this study confirmed the multi-dimensional advantages of ultrasonic atomization of traditional Chinese medicine combined with artificial tears in the treatment of DED for the first time with evidence-based medical evidence. The clinical value of improved efficacy is not only reflected in statistical significance, but also in practical treatment breakthrough: 1. Quantitative verification of synergy: the total effective rate of the combination group is 4.34 times that of the control group (95% CI: 3.24–5.82), and it should be emphasized that this OR value far exceeds the efficacy of cyclosporine A combined with artificial tears (OR = 2.11, 95% CI: 1.68–2.65),[54] indicating the unique advantages of multi-target intervention of traditional Chinese medicine; 2. Differentiated improvement of core symptoms: There are symptom-specific differences behind the reduction of 0.51 points in the total clinical symptom score ($P < 0.00001$)-significant relief of dryness (MD =−0.60) and burning sensation (MD =−0.32), which is directly related to the decrease of tear osmotic pressure from (342.7 ± 18.5) mOsm/L to (305.2 ± 15.3) mOsm/L ($P < 0.001$) and the 41% decrease of corneal nerve sensitization index;[45] 3. Milestone repair of ocular surface function: ① BUT was extended by 1.92 seconds (95% CI: 1.78–2.05), bringing the average value to 5.82 seconds, breaking through the diagnostic threshold of dry eye (≤5 seconds),[55] close to the level of healthy people (≥10 seconds); ② A 0.67-point decrease in FL score (95% CI: -0.70 to-0.64) corresponds to a 37.2% increase in goblet cell density (immunohistochemical verification), marking the reconstruction of ocular surface epithelial barrier; ③ A 3.30 mm increase in SIT (95% CI: 3.21–3.39) reflects the recovery of basal tear secretion function, which is related to a 2.1-fold up-regulation of the expression of parasympathetic nerve regulation-related gene ChAT.[56] In-depth analysis of safety revealed more positive signals: behind the no statistical difference in adverse reaction rates (RR = 1.04, P = 0.91), the incidence of itching in the combination group was lower than that in the control group (3.2% vs 4.7%). The immunomodulatory effect of traditional Chinese medicine particles reduces histamine release. It is worth noting that the NEI-VFQ-25 score increased by 6.01 points ($P < 0.00001$), indicating that the combination therapy significantly improved the quality of life of patients, which is a dimension often overlooked in traditional efficacy evaluation.

In this study, some outcome measures exhibited substantial statistical heterogeneity (eg, $I^2 > 50\%$ for indicators such as SIT and BUT). We conducted an in-depth analysis in conjunction with clinical and methodological characteristics. Potential sources of heterogeneity may include the following aspects: ① Differences in Chinese herbal formulations: Variations existed in the herbal nebulization formulas used across the included studies, with some studies predominantly employing formulas aimed at clearing heat and moistening the eyes, while others focused on activating blood circulation and nourishing yin. These differences in formula composition may have influenced treatment efficacy to varying degrees. ② Variations in treatment duration: The intervention periods across studies ranged from 2 to 8 weeks, and the duration of treatment may have affected the cumulative effect size. ③ Differences in baseline severity of dry eye disease: The included studies enrolled patients with varying baseline disease severity (eg, initial BUT and SIT values), and treatment responses may differ between patients with mild versus severe disease. ④ Differences in comparator interventions: Some control groups received artificial tears alone, whereas others received artificial tears combined with basic treatments (eg, warm compresses, meibomian gland massage). Such differences in comparator interventions may have influenced the estimation of effect sizes. Additionally, variations across studies in outcome assessment criteria, measurement instruments, and randomization methods may have also contributed to heterogeneity. In consideration of the above factors, a random-effects model was employed in the primary analysis to partially mitigate the impact of heterogeneity on the results. Furthermore, we recommend that future studies further

standardize intervention protocols and outcome assessment criteria to reduce clinical heterogeneity and enhance the comparability of evidence.

This study systematically evaluated the clinical efficacy and safety of ultrasonic atomization of Chinese herbal medicine combined with artificial tears in the treatment of dry eye disease. The results indicated that the combination therapy was superior to artificial tears alone in improving the clinical total effective rate, ocular surface function indicators, and vision-related quality of life, without a significant increase in adverse events. However, this study has the following limitations: First, the overall risk of bias in the included studies was relatively high, primarily due to inadequate blinding, which may affect the validity of the results. Second, considerable heterogeneity existed in the Chinese herbal formulas used across studies, with inconsistencies in both composition and concentration, limiting the generalizability of the findings to a certain extent. Third, most studies had short follow-up periods, with a lack of data on long-term efficacy and recurrence rates beyond six months. Therefore, the above conclusions warrant further validation through additional high-quality studies. Future research should focus on the following directions: ① Utilizing multi-omics technologies to gain deeper insights into the interaction mechanisms between active components of Chinese herbal medicine and the ocular surface microenvironment; ② Promoting standardization of atomization devices and optimization of drug delivery parameters; ③ Designing large-scale, long-term randomized controlled trials to systematically assess long-term efficacy.

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