



Tranexamic Acid for Melasma Treatment: An Updated Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

In this systematic review and meta-analysis of randomized controlled trials (RCTs), we investigated the efficacy and safety of tranexamic acid (TA) in treating melasma. Out of 546 articles initially screened, 63 RCTs met the inclusion criteria. The efficacy was evaluated using the meta-analysis's standardized mean differences (SMDs). The analysis showed that oral TA significantly improved melasma severity in patients receiving long-term treatment, particularly by weeks 8 and 12. Topical TA also demonstrated beneficial effects, with noticeable improvements in melasma indices starting from week 8. Subgroup analyses further supported the effectiveness of TA in reducing MASI index across different treatment modalities. Although some adverse events were reported, TA was generally well tolerated. This study suggests that TA should be widely applied in the treatment of melasma because of its significant improvements.

Keywords Tranexamic acid · Melasma · Randomized controlled trials · Systematic review · Meta-analysis

Introduction

Tranexamic acid (trans-4-(aminomethyl) cyclohexane carboxylic acid; TA) belongs to the class of antifibrinolytic drugs [1]. It is commonly used to treat or prevent excessive bleeding in various medical conditions, such as menstrual bleeding, nosebleeds, postoperative bleeding after dental surgery, and certain bleeding disorders [1]. Recently, TA has also been applied in the treatment of melasma, a common skin condition characterized by dark patches on the face [2]. Melasma is often triggered by hormonal changes, such as

those occurring during pregnancy or hormonal contraceptive use, as well as by sun exposure and genetic factors [2].

The exact mechanism of TA action remains under investigation, but one possible explanation is that it inhibits melanin production, which is often overproduced in patients with melasma [2, 3]. TA can help lighten dark patches and improve the overall appearance of the skin by reducing melanin production. Furthermore, when administered orally or topically, TA may help control melasma owing to its anti-inflammatory and skin-brightening properties [2, 3].

Recently, randomized controlled trials (RCTs) have been conducted worldwide to evaluate the efficacy of applying TA in the treatment of melasma. The efficacy of this therapy has been extensively assessed through several systematic reviews and meta-analyses of these RCTs [4–7]. However, previously published meta-analysis that included only a limited number of eligible studies may have underestimated to the true effects [8–10]. Given the increasing number of RCTs on this topic, this updated systematic review and meta-analysis was designed to access a larger and higher-quality dataset to provide more precise and reliable results. In this study, clinical data were systematically summarized and analyzed using meta-analysis techniques to provide an overview and statistical evaluation of TA's therapeutic potential for melasma. Moreover, this study assessed the effectiveness of TA in improving the clinical symptoms of

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melasma and evaluated the risk of TA-related side effects compared with the control groups receiving either routine treatment or placebo.

Materials and Methods

Literature Search Strategy

According to the “Preferred Reporting Items for Systematic Reviews and Meta-analysis” (PRISMA) protocol 2009 [11], this study performed a literature search on the efficacy of TA in the treatment of melasma and obtained relevant articles published until 2025. The registration number is CRD42023418180, which PROSPERO has approved. English language databases included the Cochrane Library, MedRxiv, PubMed, Elsevier, and EMBASE. The keywords used in the literature search included oral TA, topical TA, melasma, melasma area and severity index (MASI), melanin index (MI), erythema index (EI), microneedling with TA, intradermal injection of TA, intralesional injection of TA, laser therapy with TA, and RCTs.

Study Selection and Data Extraction

Study Selection

All studies that investigated the efficacy and safety of oral or topical TA treatment for improving melasma symptoms—particularly focusing on reductions in MASI, MI, and EI scores in patients with melasma, were included in this study. All RCTs that included at least one participant and one matched participant in the control group were considered, provided that the positive effects of TA on melasma treatment showed no significant differences between comparable groups. Individual studies with multiple trial arms were deemed eligible if they directly compared the control and treatment groups with the correct components included in the meta-analysis. These RCTs reported the results as the mean $\pm$ standard deviation (SD), regardless of whether it was the primary outcome. There were no restrictions regarding the type of treatment or control group, the route of TA administration (oral or topical), study designs, or geographical region. All the included articles were written in English.

This study excluded all non-RCTs related to TA use in melasma treatment (in vitro, in vivo, and cohort studies). Conference abstracts, reviews, presentations, animal studies, basic research articles, and articles not written in English were excluded from this analysis. Articles that were entirely or partially duplicated from different studies were also excluded, and in cases of duplicate publications, only the most recent one was included.

Data Extraction

Three independent reviewers screened each included RCT and extracted the data for a systematic review and meta-analysis. The extracted data included the author’s name, publication year, region of study, trial design, number of participants, ages (years), treatment and control protocols, adverse events, and primary outcomes (mean $\pm$ SD values).

Meta-analysis

For all continuous outcomes, the mean and SD of the preliminary results of each trial in the TA treatment and control groups were analyzed using a random-effects model and expressed as the standardized mean difference (SMD) with a 95% confidence interval (CI) [12]. SMD was obtained by dividing the mean difference (MD) between the two groups by the pooled variance and adjusting for small samples. If the value of 0 was not within the 95% CI, the pooled SMD was considered statistically significant at the 5% significance level. SMDs were considered small, moderate, and large if the pooled SMDs were ≤ 0.2 , $0.2-0.8$, and ≥ 0.8 , respectively [12]. The extent to which the observed variability between the studies was because of actual differences was quantified using the I^2 statistic. Heterogeneity was considered small when $I^2 < 25\%$, moderate when $25-50\%$, and significant when $> 50\%$ [12]. A p-value ≥ 0.1 was considered indicative of heterogeneity, and potential publication bias was assessed using a funnel plot.

All analyses were performed using Review Manager [13] (version 5.3, Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014).

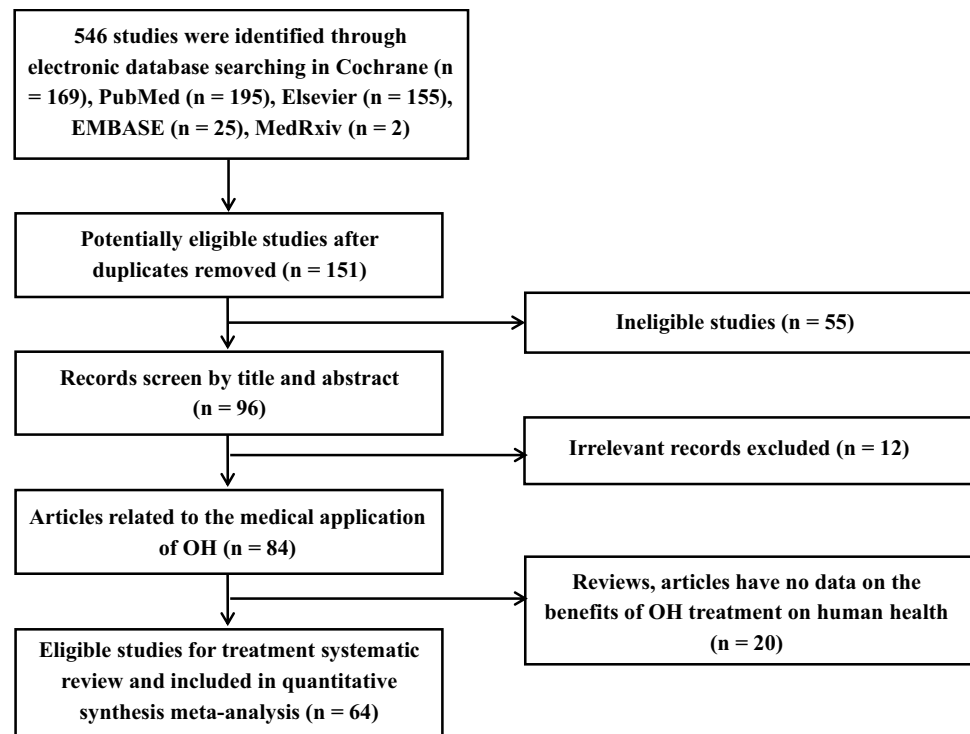
Quality Assessment of Included Studies

The validities of eligible RCTs (risk of bias) were explored by assessing the bias of the random sequence generation, selective reporting, allocation concealment, blinding of participants, blinding of outcome assessment, and incomplete outcome data according to three levels (low, high, and uncertain) following the Cochrane guideline [13] in which low and high risk of bias may indicate a lack of information and uncertainty over the potential for bias, respectively [13].

Results

Characteristic of Included Studies

Figure 1 shows a flowchart of the screening process for qualified studies. In this study, 546 publications were screened by searching their titles and abstracts in the aforementioned

Fig. 1 Systematic screening process of the literature review

databases. After carefully reviewing these articles on the efficacy of TA in melasma treatment (reducing MASI, MI, and EI values), 64 RCTs were selected for the quantitative meta-analyses.

Description of Included Studies

The clinical designs, geographic regions, participant characteristics, treatment and control parameters, treatment durations, measurement outcomes, and adverse events of all 64 RCTs randomly assigning patients with melasma to the TA versus routine treatment or placebo groups are briefly summarized in Table S1 (Supplementary Information I). These trials were conducted worldwide, ensuring broad geographic representation, including Oceania ($n=3$), Asia ($n=47$), South America ($n=4$), and Europe ($n=10$).

A total of 3,640 patients encountered in routine clinical practice typically presented with mild-to-severe melasma. The classification of melasma severity was based on three aspects: the extent of the affected area, intensity of pigmentation, and homogeneity of distribution (Supplementary Information II) [14]. These investigations were performed using a variety of designs, including blinded RCT ($n=15$) [3, 6, 15–27], prospective interventional RCT ($n=3$) [28–30], split-face RCT ($n=24$) [4, 31–53], and open-label RCT ($n=22$) [5, 54–74]. The effectiveness of oral and topical TA in melasma treatment was evaluated in 26 and 38 RCTs, respectively.

For oral TA, patients received 250 mg oral TA twice daily for at least four weeks. The control groups were treated with a triple-combination cream (fluocinolone acetonide 0.01%, tretinoin 0.05%, and hydroquinone 2%); placebo; or topical depigmenting agents such as hydroquinone, kojic acid, and azelaic acid 20% twice daily. Conversely, topical TA were administered at concentrations of 2%–5% and 4 mg/mL, typically applied twice daily. The control treatments included 4–5% or 4 mg/mL hydroquinone or placebo (normal saline solution), while some studies also incorporated microneedling, intradermal injection, intralesional injection, and laser treatment.

The treatment durations ranged from 4 to 24 weeks, in which participants were commonly administered TA for approximately eight weeks ($n=18$) [21–24, 26, 31, 32, 40, 41, 46, 53, 57–59, 63, 69, 71, 73] and 12 weeks ($n=36$) [4, 5, 15–18, 20, 25, 27, 28, 30, 34–39, 42, 45, 47–52, 54–56, 61, 62, 64, 66, 67, 70, 72, 74]. Three RCTs lasted about 4 weeks [29, 44, 60]; one extended to 16 weeks [43], and five continued for approximately 24 weeks ($n=5$) [3, 6, 33, 65, 68].

Numerous clinical trials included follow-up measurements after the treatment period, typically at 12 weeks, to assess the melasma recurrence [3, 5, 6, 15, 16, 20, 26, 27, 31, 33, 35–37, 43, 44, 47, 49–52, 54–58, 65, 72, 74]. Participants who had received melasma treatments or laser therapy within 1–6 months before enrollment were not eligible. Moreover, the use of topical/oral TA or other depigmentation agents (e.g., retinoids, steroids, hydroquinone,

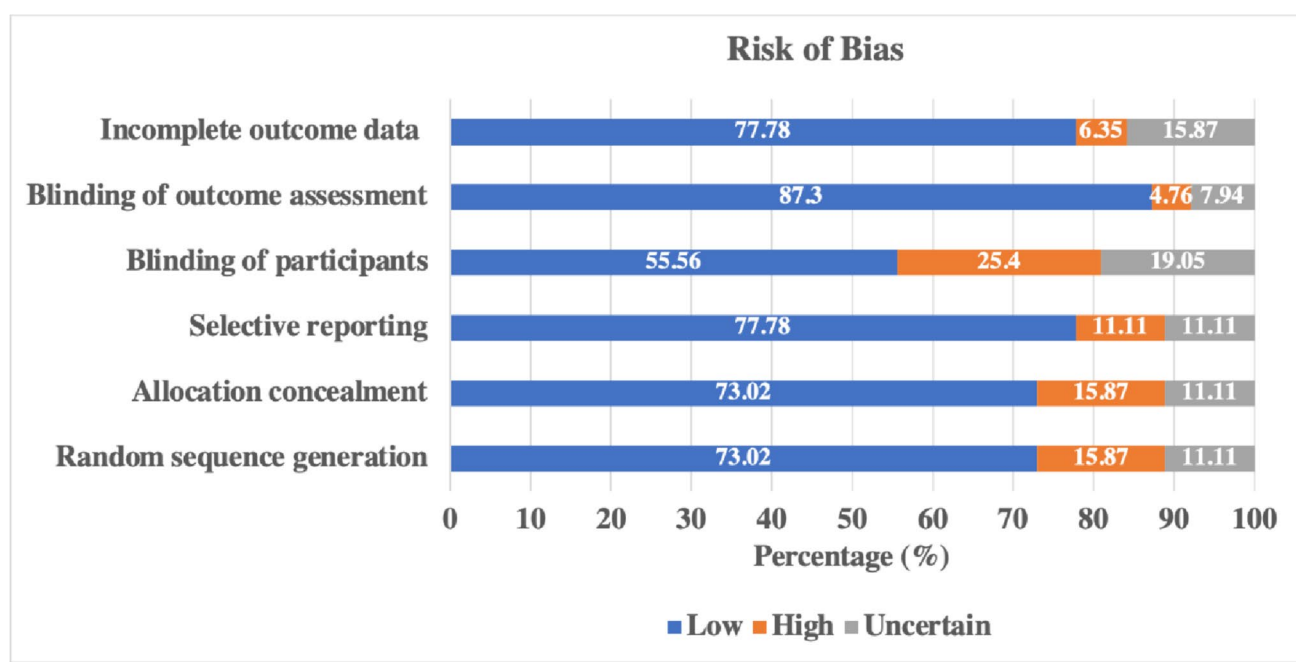


Fig. 2 Quality assessments of included randomized controlled trials (RCTs)

vitamin A) within 1–3 months before study initiation was also prohibited.

The primary outcomes were the MASI, MI, and EI scores. To accurately analyze the efficacy and safety of TA treatment, these values were pre-calculated into the change of MASI, MI, and EI from baseline to the measurement points (4th, 8th, and 12th weeks), and subsequently analyzed using meta-analysis software.

Although adverse events were reported in some RCTs involving TA application and combination therapies, TA was generally considered safe and well tolerated for melasma management.

Bias Risk

Bias risk was evaluated by assessing the biases of the random sequence generation, selective reporting, blinding of participants, allocation concealment, incomplete outcome data, and blinding of outcome assessment corresponding to three levels (low, high, and uncertain) following the Cochrane guidelines [13]. The results showed that all RCTs were of moderate to good quality with a low risk of bias for the relevant outcomes of interest (Table S2 and Fig. 2). It can be seen that the low risks of bias also contributed to improved statistical significance.

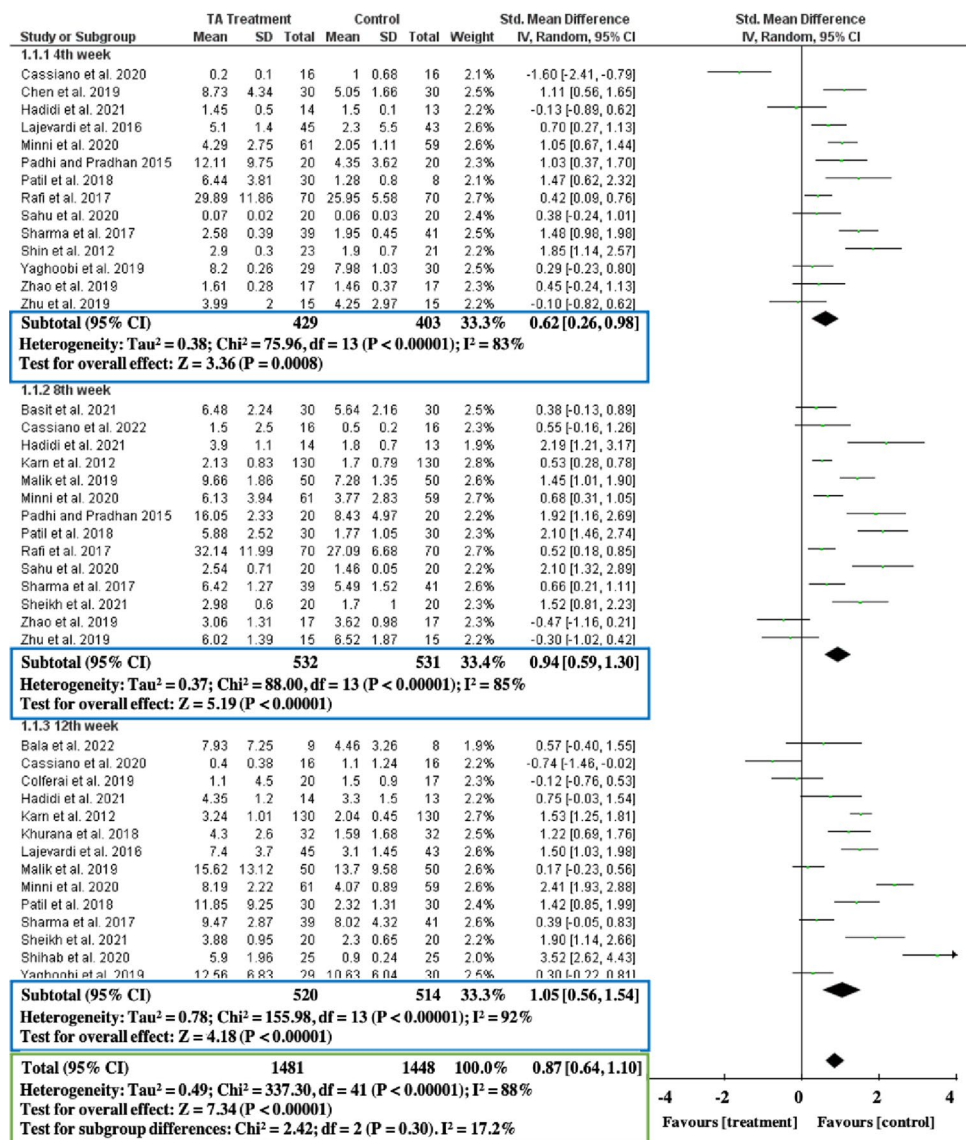
Table 1 Pooled standardized mean differences (SMDs) between Tranexamic acid (TA) and control groups across included studies

Oral TA		SMD	I ²	p
Change in MASI	4th week	0.62 [0.26, 0.98]	83%	<0.00001
	8th week	0.94 [0.59, 1.30]	85%	<0.00001
	12th week	1.05 [0.56, 1.54]	92%	<0.00001
Change in MI	4th week	−0.78 [−2.97, 1.41]	97%	<0.00001
	8th week	0.37 [−0.61, 1.35]	88%	<0.00001
	12th week	0.37 [−0.67, 1.42]	90%	<0.00001
Topical TA		SMD	I ²	p
Change in MASI	4th week	0.05 [−0.05, 0.15]	95%	<0.00001
	8th week	0.23 [0.10, 0.37]	92%	<0.00001
	12th week	0.45 [0.34, 0.55]	92%	<0.00001
Change in MI	4th week	0.10 [−0.18, 0.38]	97%	<0.00001
	8th week	1.11 [0.64, 1.58]	98%	<0.00001
	12th week	4.36 [3.82, 4.90]	74%	0.01

Oral TA for Melasma Treatment

Reducing MASI Score

The change in MASI from baseline to the measurement time point during oral TA administration was analyzed using subgroup comparisons based on the assessment periods (4th, 8th, and 12th weeks) (Table 1; Fig. 3). The results indicated significant differences in the changes in MASI between the orally administered TA and control groups during the three treatment periods. The treatment group achieved an increased reduction in MASI scores in patients with melasma.

Fig. 3 Reduction in MASI score between oral tranexamic acid (TA) and control groups

Notably, the SMD between the two groups was moderate week 4 (0.62 [0.26, 0.98]), while the reductions became more pronounced and statistically significant at week 8 and 12 (0.94 [0.59, 0.98] and 1.05 [0.56, 1.54], respectively). According to the subgroup comparison results, the efficacy of oral TA in reducing MASI was related to the duration of use, where long-term treatment (12 weeks) was more likely to reduce MASI than short-term treatments (4 and 8 weeks). Although oral TA treatment consistently MASI scores, the analysis did not achieve statistical significance owing to considerable heterogeneity across all three subgroup comparisons.

Sensitivity analyses were performed to evaluate the robustness of the pooled effects and to identify potential sources of heterogeneity across different time points (Figure S1). At 4 weeks, heterogeneity was moderate ($I^2 = 73\%$). Excluding Cassiano et al. (2020) [21] or Shin et al. (2012)

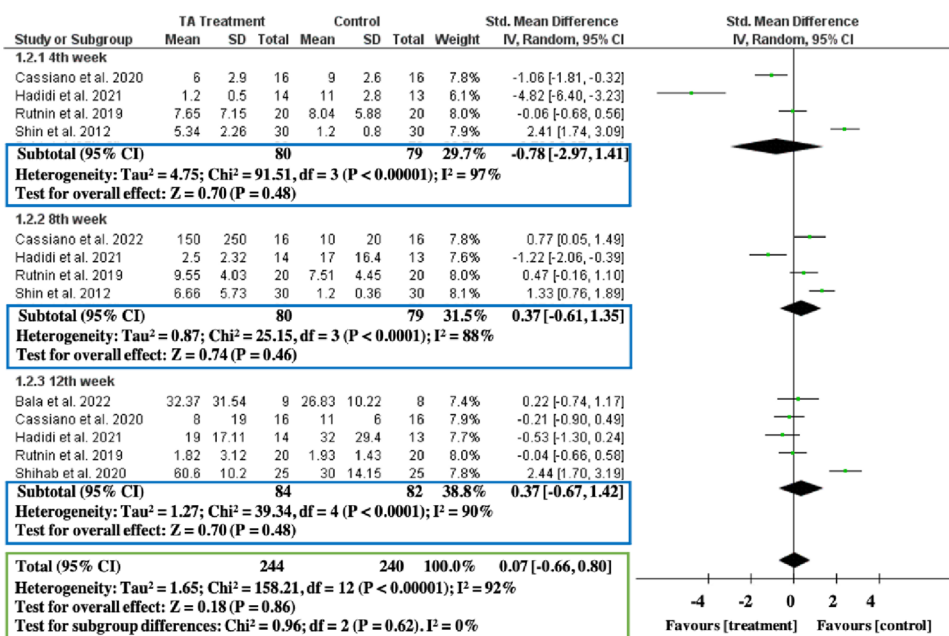
[29] led to the greatest reduction in heterogeneity ($I^2 \approx 60\%$) while the overall treatment effect remained positive and statistically significant. At 8 weeks, heterogeneity was substantial, but omission of Hadidi et al. (2021) [26] or Patil et al. (2018) [70] markedly reduced it ($I^2 \approx 60\%$) without altering the magnitude or direction of the pooled estimate. Finally, at 12 weeks, a large overall treatment effect was accompanied by considerable heterogeneity ($I^2 = 92\%$). Excluding Shihab et al. (2020) [3] or Minni et al. (2020) [15] most effectively decreased heterogeneity ($I^2 \approx \text{mid-60\% range}$), yet the pooled effect remained robust and statistically significant. Collectively, these findings indicate that heterogeneity across time points was mainly driven by a small number of high-effect studies, whereas the overall treatment effects of tranexamic acid remained consistent and reliable.

Reducing MI Score

The benefits of oral TA on melasma therapy were evaluated by analyzing the change in MI values after the administration, compared to the control arm (Fig. 4 and Table 1). The analysis was divided into three subgroup compartments based on the measurement times (4th, 8th, and 12th weeks). The results showed that the changes in MI values were not a significant difference between the two groups, corresponding to the terms of administration. The assessment of the change in MI also did not reach statistical significance because of the high heterogeneity ($I^2 > 88\%$).

Sensitivity analyses were conducted to assess the robustness of MI outcomes across different time points (Figure S2). At 4 weeks, very high heterogeneity was observed ($I^2 = 97\%$). Excluding Hadidi et al. (2021) [26] or Shin et al. (2012) [29] most effectively reduced heterogeneity, suggesting that a few extreme-effect studies largely contributed to the observed variability. At 8 weeks, substantial heterogeneity was again noted ($I^2 = 88\%$); omitting Hadidi et al. (2021) [26] or Shin et al. (2012) [29] reduced heterogeneity ($I^2 \approx 55\%$), but did not alter the nonsignificant overall effect. At 12 weeks, the exclusion of Shihab et al. (2020) [3] markedly decreased heterogeneity; yet, the overall pooled effect remained nonsignificant. Collectively, these findings suggest that heterogeneity was primarily driven by a small number of influential studies, particularly Hadidi et al. (2021) [26] and Shin et al. (2012) [29], and that the overall evidence for improvement in MI remains inconclusive.

Fig. 4 Reduction in MI score between oral TA and control groups



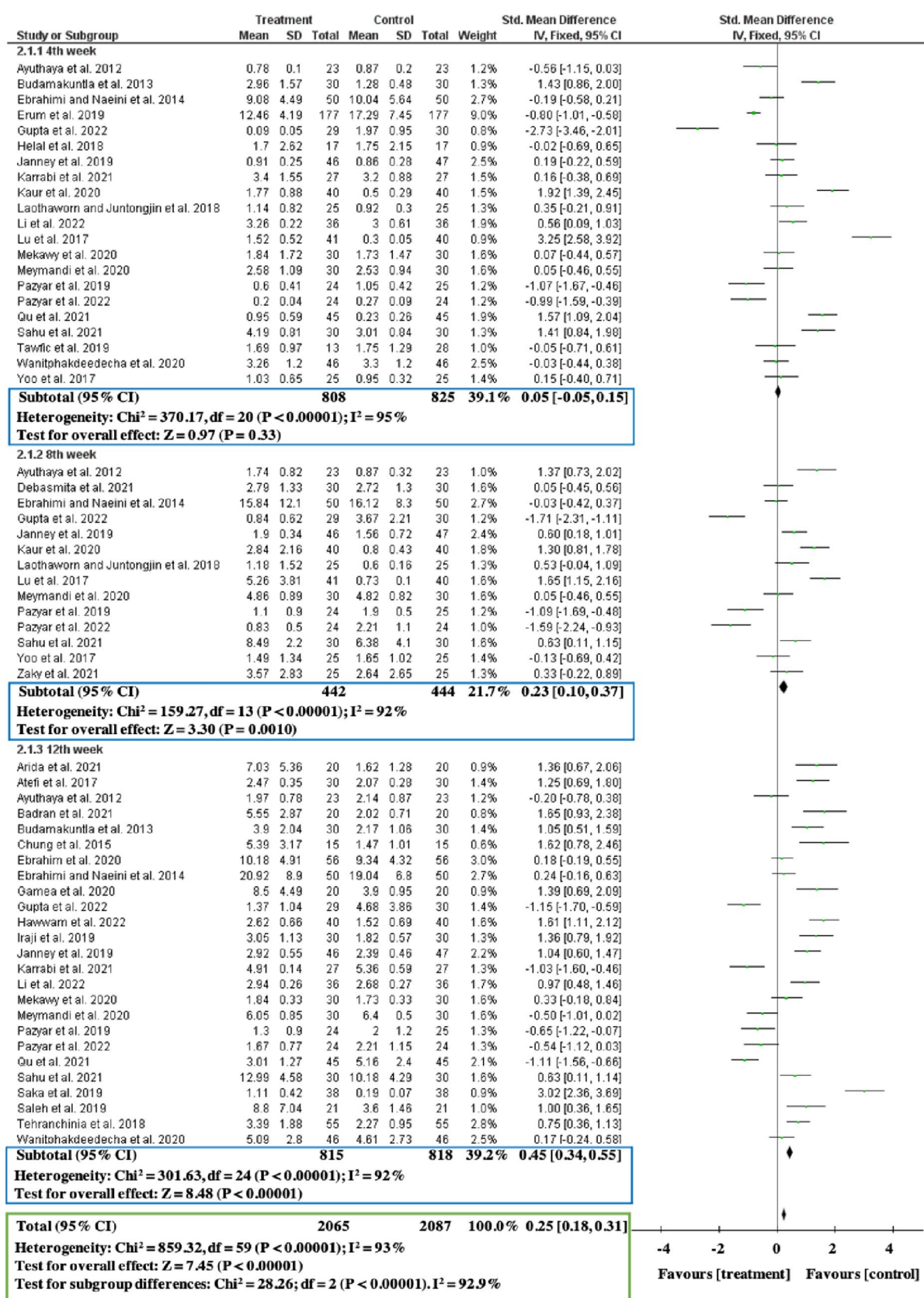


Fig. 5 Reduction in MASI score between topical TA and control groups

particular, the reduction in MASI at week 12 was approximately twice that at week 8 (SMD=0.45 [0.34, 0.55] and 0.23 [0.10, 0.37], respectively). However, the analysis did not reach statistical significance because significant heterogeneity existed across these comparisons.

Sensitivity analyses were performed to evaluate the robustness of MASI outcomes across different time points (Figure S4). At the 4th week, leave-one-out analyses indicated that excluding Gupta et al. (2022) [62] or Lu et al. (2017) [63], and to a lesser extent Kaur et al. (2020) [52], Qu et al. (2021) [37], and Erum et al. (2019) [60], resulted in the greatest reductions in heterogeneity; however, the pooled effect remained small and statistically non-significant in all cases. At the 8th week, substantial heterogeneity was observed ($I^2 = 92\%$). Excluding Gupta et al. (2022) [62], Pazyar et al. (2019, 2022) [35, 36], Ayuthaya et al. (2012) [4], or Lu et al. (2017) [63] led to the most pronounced decreases in heterogeneity, although the pooled fixed-effect estimate consistently remained positive. By the 12th week, heterogeneity reached an extreme level ($I^2 = 92\%$). Studies by Saka et al. (2019) [4], Badran et al. (2021) [5], Hawwam et al. (2022) [5], Chung et al. (2015) [47], Arida et al. (2021) [42], and Gamea et al. (2020) [61] were identified as the main contributors to heterogeneity. Nevertheless, the pooled effect remained positive and stable across all sensitivity tests. Overall, these findings suggest that the observed heterogeneity was primarily driven by a small number of studies with extreme effects, while the overall conclusions regarding MASI outcomes remained consistent.

Reducing MI Score

Changes in MI between the treatment and control groups were observed using side-by-side comparisons across the

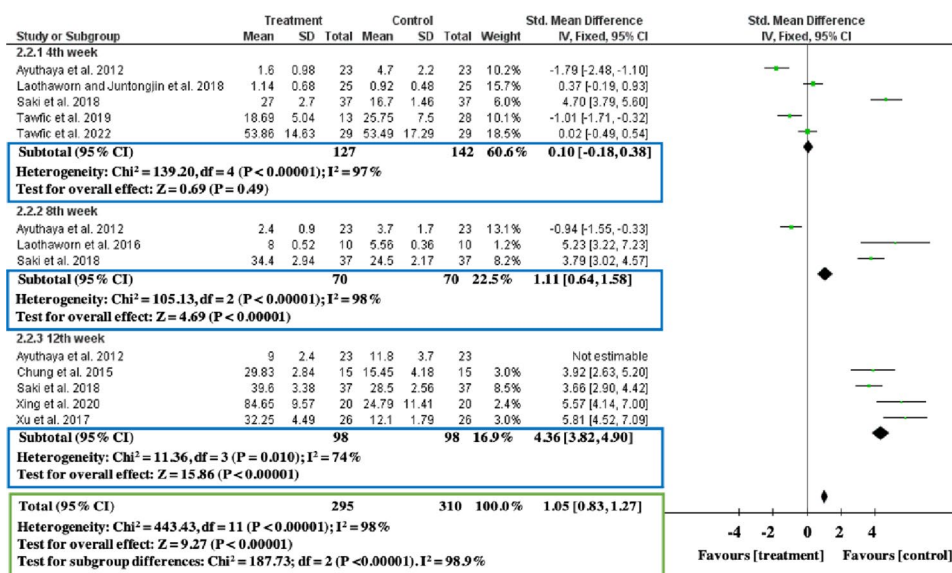
treatment periods (4th, 8th, and 12th weeks). In the short-term, topical TA did not effectively inhibit melanin production compared to the control arm, with an SMD of 0.10 [−0.18, 0.38]. In contrast, long-term treatment with topical TA showed a potential melanin inhibition ability by significantly reducing MI in the treatment group at the 8th and 12th-week measurements. In particular, the inhibitory effect on melanocyte activity appeared to increase with the duration of topical application (Table 1 and Fig. 6).

At the 4th week, heterogeneity was extreme ($I^2 = 97\%$). Leave-one-out analyses indicated that Saki et al. (2018) [39], which reported a very large positive effect, was the dominant source of heterogeneity, with additional contributions from Ayuthaya et al. (2012) [4] and Tawfic et al. (2019) [40]. Excluding any single study did not materially alter the overall conclusion.

At the 8th week, Laothaworn et al. (2016) [32] and Saki et al. (2018) [39] were identified as the major contributors to heterogeneity; removal of either substantially affected the pooled estimate, although heterogeneity remained high. These findings suggest that the overall conclusion is largely influenced by a small number of studies reporting disproportionately large effects.

At the 12th week, heterogeneity remained high ($I^2 = 74\%$). Excluding higher-effect studies such as Xing et al. (2020) [67] or Xu et al. (2017) [45] led to the largest reductions in the pooled SMD, whereas removing lower-effect studies such as Ayuthaya et al. (2012) [4] or Chung et al. (2015) [47] increased it. Overall, these results indicate that heterogeneity was primarily driven by studies reporting larger treatment effects (Figure S5).

Fig. 6 Reduction in MI score between topical TA and control groups



Subgroup Analysis Based on Treatment Modality

To explore potential sources of heterogeneity, subgroup analyses were performed based on treatment modality. The analyses compared the reduction of MASI and MI scores after topical TA treatment with placebo, intradermal injection, microneedling, laser therapy, and other topical treatments (Figure S6). The results indicated that topical TA significantly reduced MASI scores compared with placebo treatment, intradermal injection, and laser therapy with low heterogeneity ($I^2 < 50\%$). However, comparisons with microneedling and other topical treatments did not yield statistically significant and exhibited high heterogeneity ($I^2 = 87\%$ and 95% , respectively).

In addition, subgroup analysis assessing the reduction of MI scores showed that topical TA treatment was associated with a significant decrease in MI index compared to microneedling, intradermal injection, and placebo, with low heterogeneity values ($I^2 = 0\%$, 37% , and 33% , respectively).

Effectiveness of TA Treatment after Treatment Periods

Most clinical trials monitor the recurrence of melasma after treatment, typically at a 12-week follow-up. In total, fourteen clinical trials reported the change in MASI under oral administration [3, 6, 15, 20, 26, 27, 31, 54–57, 65, 72, 74],

and another fourteen reported the change after topical TA treatment [5, 16, 33, 35–37, 43, 44, 47, 49–52, 58]. This study performed a meta-analysis to compare the change in MASI score between the treatment and the control groups after the follow-up period (Fig. 7).

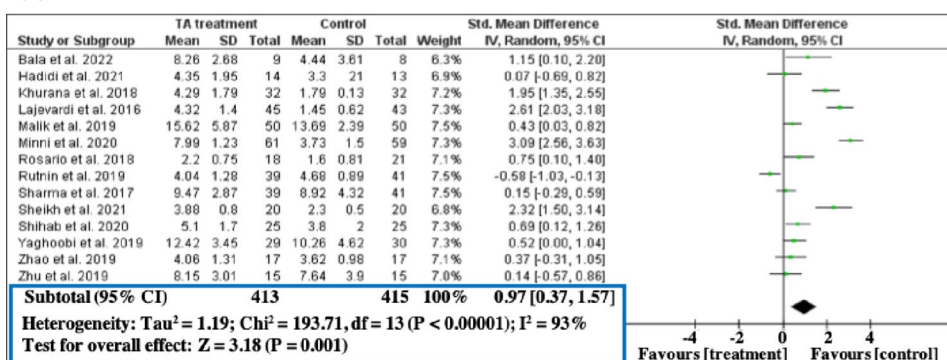
The results revealed a significant reduction in MASI in the oral TA treatment compared with the control groups at follow-up. Similarly, the topical TA treatment showed a remarkable reduction in MASI scores relative to control groups (SMD = 1.28 [1.13, 1.43]). It was observed that there was no recurrence of melasma in patients up to 12 weeks after treatment. However, the analysis did not achieve high statistical significance owing to the considerable heterogeneity. Therefore, larger, well-designed trials are warranted to validate and strengthen these findings.

Risk of Bias

Funnel plots were constructed to determine publication bias (Fig. 8). The results indicated that almost all possible publications existed in the outcome. All funnel plots were symmetrical and tended to include not only positive outcomes but also negative outcomes for each aspect analyzed. Therefore, this systematic review and meta-analysis summarized sufficient and high-quality RCTs to reduce publication bias.

Fig. 7 Reduction in MASI score between TA treatment and control groups after 12 weeks: (a) oral TA; (b) topical TA

(a) Oral TA administration



(b) Topical TA administration

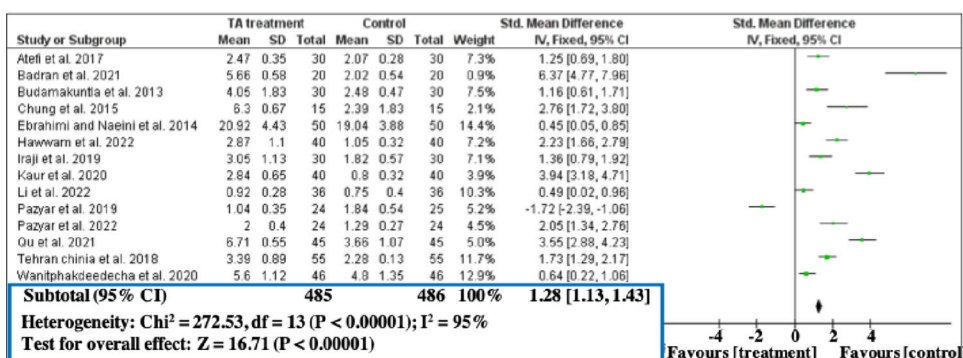
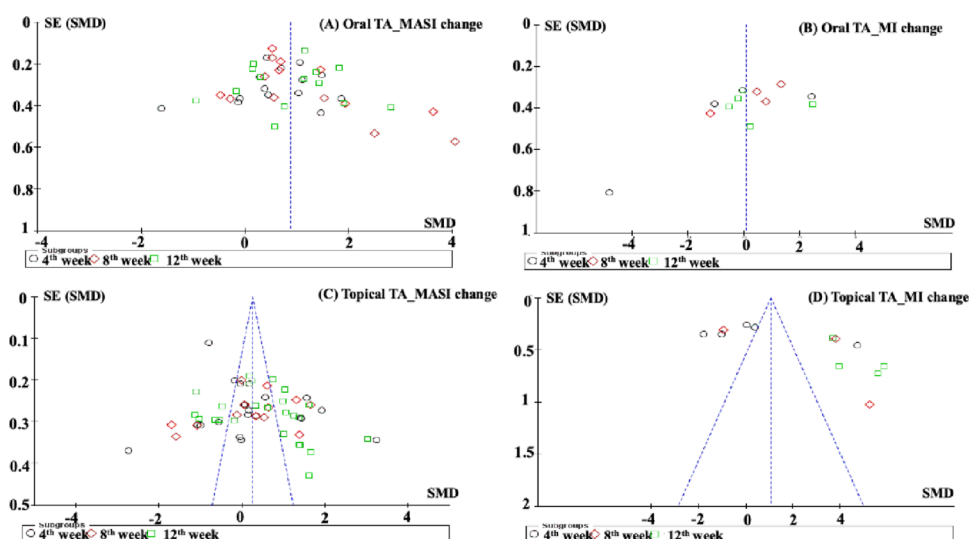


Fig. 8 Funnel plots of included RCTs comparing oral and topical TA with control treatments



Adverse Events

Therapeutic safety is considered one of the most critical criteria for clinical trials in medical and cosmetic applications. Several RCTs have addressed the safety of oral/topical TA and reported that side effects occur because of TA and placebo or routine treatments (Table S1). Almost all investigations reported that no serious adverse events occurred during TA treatment.

Regarding oral TA, the common side effects included nausea, abdominal pain, hair loss, blurred vision, xerosis cutis, pigmentation, gastrointestinal, hypomenorrhea, oligomenorrhea, and vomiting and diarrhea [21, 24–26, 28, 54–56, 69, 71, 72, 74]. Common adverse events associated with topical TA comprised erythema, skin irritation, dryness, a burning sensation, itching, and hyperpigmentation [17, 30, 43, 47, 48, 52, 58, 60, 61, 64].

The meta-analysis of adverse events associated with TA revealed a heterogeneous profile, with some reactions showing significant increases and others showing no meaningful differences compared with control (Table S3). For erythema, the pooled estimate (RR=1.23, 95% CI 0.79–1.89, $P=0.36$) using a random-effects model due to high heterogeneity ($I^2 = 93\%$) indicated no statistically significant difference. The result suggests that the effect of TA on erythema is inconsistent, potentially influenced by differences in study populations, administration routes, dosages, or assessment methods.

In contrast, itching and irritation were consistently and significantly increased in patients receiving TA. The risk of itching was approximately three times higher than control (RR=3.01, 95% CI 1.78–5.11, $P<0.0001$), and the risk of irritation was similarly elevated (RR=3.02, 95% CI 1.93–4.72, $P<0.00001$), with both outcomes showing no heterogeneity ($I^2 = 0\%$). These results indicate that itching

and irritation are reproducible and clinically meaningful adverse effects of TA, likely related to local hypersensitivity reactions or histamine release. Clinicians should be aware of these potential reactions, particularly in patients with a history of allergic skin conditions, and monitor or counsel patients accordingly.

For burning, hyperpigmentation, and dryness, the meta-analysis showed no significant differences between TA and control groups (RR=0.78 [0.23–2.59], 1.16 [0.61–2.20], and 1.00 [0.95–1.06], respectively), all with $I^2 = 0\%$. The CI values for burning and hyperpigmentation were relatively wide, indicating some uncertainty, whereas dryness was precisely estimated with a narrow CI. It can be seen that TA is not associated with meaningful changes in the risk of burning, hyperpigmentation, or dryness, supporting its general safety regarding these adverse events.

Discussion

In the present study, the therapeutic efficacy of TA for melasma was assessed via a systematic review and meta-analysis of 64 RCTs. The potential benefits of oral and topical TA were evaluated using pooled meta-analytic data. These results suggest that several forms of TA, including oral and topical, are potential approaches for improving melasma. Regarding oral TA, the results showed that administration could effectively decrease the MASI score with treatment durations exceeding eight weeks, whereas no significant improvement was observed in the MI. In contrast, topical TA effectively reduced the MASI and MI scores during long-term treatment (8 and 12 weeks). Notably, the magnitude of reduction in MASI and MI scores increased with longer treatment duration, suggesting a dose-time-response relationship for TA therapy.

The intracellular mechanism through which TA improves melasma has been confirmed in several clinical trials and in vitro studies. TA was found to inhibit the activity of tyrosinase, an enzyme involved in the production of melanin, a pigment that impairs the color of the skin. Due to its structural similarity to tyrosinase, TA can competitively block tyrosinase activity, thereby reducing melanin synthesis and lightening hyperpigmented skin lesions. Second, TA possesses anti-inflammatory and anti-angiogenic properties that contribute to its depigmentation action. In particular, ultraviolet (UV)-induced plasmin activates precursors of phospholipase A2, which promotes the production of arachidonic acid, a precursor substance of prostaglandin E2, leukotrienes, and melanogenic paracrine factors (ET-1, α -MSH, and SCF) [2]. These inflammatory mediators then activate melanogenesis. Moreover, plasmin plays an essential role in releasing basic fibroblast growth factor (b-FGF), a potent melanocyte stimulator, may convert vascular endothelial growth factor (VEGF) into its free form, resulting in angiogenesis. Therefore, as a plasmin inhibitor, TA, with its strong anti-angiogenic and anti-inflammatory effects, can prevent skin pigmentation and improve melasma caused by UV light [3]. Another proposed mechanism is the inhibition dermal angiogenesis. Kim et al. (2016) reported that topical TA could reduce erythema in melasma-affected skin by decreasing the number of vessels (e.g., human peripheral blood-derived CD31⁺ vessels) in the dermis, diminishing the visibility of hyperpigmented patches [2].

Recently, numerous meta-analyses dealing with this topic have been designed to analyze data extracted from several studies, including case controls, RCTs, cohort-match controls, individual studies, and unpublished studies. Feng et al. (2021) determined the efficacy and safety of TA for treating adult melasma in twenty-four RCTs [8]. This study compared the changes in MASI scores pre- and post-treatment, and between TA-based and conventional therapies. The results demonstrated that the reduction in MASI scores between TA adjuvant and routine treatment was significant at the 4th, 8th, 12th, and 16th weeks, with SMDs of -0.43 [-0.79 ; -0.08], -0.81 [-1.09 ; -0.54], -1.10 [-1.78 ; -0.43], and -1.12 [-1.51 ; -0.74], respectively [8]. Oral TA was therefore suggested as an effective and safe alternative for melasma management [8]. In contrast, Zhang et al. (2018) performed a systematic review and meta-analysis of 21 RCTs examining TA administration in melasma treatment [10]. The results revealed that oral TA treatment alone induced a significant reduction of MASI point, while topical TA as an adjuvant treatment did not yield a statistically significant improvement [10]. In addition, TA treatment significantly decreased MI scores before and after treatment (SMD = -0.69 [-1.22 ; -0.16]) [10]. A systematic review reported that the adverse effects of oral TA were mainly

gastrointestinal reactions, such as heartburn, nausea, abdominal pain, and epigastric discomfort [10]. Kim et al. (2017) evaluated the effectiveness of TA treatment in melasma based on 11 studies (three RCTs, seven before-after comparisons, and one retrospective cohort study) [9]. A decrease in MASI was observed after treatment with TA, with an SMD of 1.6 [1.2 ; 2.0]. Adding TA to routine treatment modalities also further reduced the MASI score to 0.94 [0.1 ; 1.79]. The side effects were minor, with a few patients reporting mild abdominal discomfort, hypomenorrhea, and transient skin irritation [9]. However, most existing meta-analyses included a limited number of small RCTs, which may not have provided sufficient power to accurately estimate effect sizes or detect significant differences between the treatment and control groups. Compared with current meta-analyses, our study exhibits some novelty. First, it included the most extensive dataset for oral and topical TA treatments (3,640 patients with melasma) and up-to-date relevant information, such as the study region, clinical trial designs, treatment and control parameters, primary outcomes, and side effects. Consequently, this study provides stronger analytical reliability and enhances the quality of evidence for the efficacy and safety of TA in melasma treatment compared to published meta-analysis articles.

Limitations

This meta-analysis had several primary limitations. First, this study included only RCTs, which may have limited the comprehensiveness of the evidence regarding the efficacy and safety of TA for melasma treatment. Second, the results showed substantial heterogeneity, which reduced the statistical precision of the pooled estimates. This heterogeneity likely stemmed from variations in study regions, follow-up durations, treatment modalities and dosages of TA, as well as differences in control group parameters. As a result, the pooled SMDs inevitably reflected this variability. Despite these limitations, this systematic review and meta-analysis provides a snapshot of the best level of evidence currently available on the use of TA in managing melasma. Third, despite the inclusion of many RCTs, some analyses were limited by missing or insufficient data. In particular, comparisons involving changes in MI and EI scores could only be performed using a small subset of studies, which may have led to underpowered or underestimated results. Additionally, this study primarily included Asian participants, and detailed data on Fitzpatrick skin type or ethnic background were not consistently available across the included studies. This limitation may reduce the external validity and generalizability of the findings to populations with different skin phototypes. Future clinical trials should adopt standardized

reporting of Fitzpatrick skin type and ethnicity to enable more comprehensive subgroup analyses and enhance the applicability of results across diverse populations.

Conclusion

This study evaluated the practicality and safety of TA for the treatment of melasma based on the outcomes of 64 RCTs. The findings suggested that oral and topical TA could effectively reduce one of the critical melasma parameters, the MASI score, after long-term treatment (8 and 12 weeks). Prolonging the treatment duration appeared to be more effective than increasing the TA dosage in improving clinical outcomes. In addition, although adverse reactions during the treatment have been reported in some RCTs, TA was considered safe as a routine treatment or placebo control, which dermatological institutions have approved. However, because the number of RCTs is gradually increasing, updated systematic reviews and meta-analyses need to be repeated to evaluate a larger dataset and obtain an up-to-date statistical result.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11814-025-00624-9>.

Declarations

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