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REVIEW ARTICLE

Assessing the Safety and Efficacy of Picosecond Alexandrite Lasers in the Management of Melasma: A Systematic Review and Meta-Analysis of Randomised Control Trials

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ABSTRACT

Melasma is a chronic hyperpigmentation disorder that disproportionately affects women and individuals with darker skin types, leading to a significant psychosocial burden. This meta-analysis aims to evaluate the safety and efficacy of the 755-nm picosecond alexandrite laser (PSAL) compared with conventional therapies in the management of melasma. PubMed, Ovid Medline, Embase, Cochrane Library, and Google Scholar were searched from inception to April 10, 2025, in accordance with PRISMA guidelines. Randomised controlled trials (RCTs) assessing PSAL versus control comparators in adults with melasma and reporting Melasma Area and Severity Index (MASI) or Modified MASI outcomes were included. The review was registered prospectively on PROSPERO (CRD420251022381). Risk of bias was assessed using ROB2. Pooled effect sizes were calculated using a random-effects model. Five RCTs ($n = 139$ patients) were included. Change in MASI favoured triple combination cream (TCC) over PSAL therapy (MD = 1.82, 95% CI: 1.11, 2.52, $I^2 = 0\%$). Post-inflammatory hyperpigmentation was more common in the PSAL group compared to topical creams (OR = 6.86, 95% CI: 1.47, 32.07, $I^2 = 0\%$) but had no difference with the *Q*-switched lasers (OR = 4.09, 95% CI: 0.62, 26.97, $I^2 = 0\%$). There was no incidence of hypopigmentation or infection reported. PSAL appears inferior to the TCC in reducing MASI scores. Overall certainty is low due to small, heterogenous trials. Low rates of irreversible adverse events with PSAL may support trials in refractory cases, but long-term RCTs with larger sample sizes are required to evaluate durability and recurrence outcomes.

Abbreviations: DLA, diffractive lens array; HQ, hydroquinone; MASI, melasma area and severity index score; mMASI, modified melasma area and severity index score; PIH, post inflammatory hyperpigmentation; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PSAL, picosecond alexandrite laser; QSND, *Q*-switched Nd: YAG laser; RCT, randomised control trial; ROB2, Cochrane risk-of-bias tool for randomised trials; TCC, triple combination cream; VAS, visual analogue scale (scoring system 1–10).

Kangjie R. Chua and Dilip K. Vankayalapati contributed equally to this work and are recognised as co-first authors.

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1 | Introduction

Melasma is a chronic pigmentation disorder of the face [1]. While benign, it may cause psychosocial distress [2]. It particularly concerns patients with Fitzpatrick skin types III–V and in Asian populations [1]. Traditional treatments, including sun protection, topical lightening agents, and chemical peels, may offer temporary benefit [3]. While oral tranexamic acid (TXA) has been increasingly recognised and used as a safe and effective option [4, 5], other newer laser technologies have also emerged as potential alternatives for refractory cases or where tranexamic acid is contraindicated. As complications such as post-inflammatory hyperpigmentation (PIH), paradoxical worsening, hypopigmentation, and scarring concern about safety persist [6, 7], interest lies in identifying laser therapies that are both safe and effective.

The 755-nm picosecond alexandrite laser (PSAL) intends to provide a safe option for melasma clearance by delivering ultrashort 300–900 ps pulses that generate a photomechanical effect, fragmenting melanin and facilitating phagocytic clearance while limiting collateral thermal damage [8]. Earlier studies were promising, showing reduced Melasma Area and Severity Index (MASI) scores and mostly transient adverse effects [9]. Current literature suggests that PSAL offers similar efficacy to established technologies, like the *Q*-switched nanosecond laser, with a potentially improved safety profile, particularly due to its lower risk of permanent dyspigmentation [10, 11]. Similarly, a systematic review and meta-analysis by Feng et al. reported PSAL outcomes comparable to those of topical depigmenting agents, including hydroquinone (HQ) and triple combination cream (TCC), though the authors encouraged further research to establish its role [9].

Although an Australian review discussed intense pulsed light in combination with topical hypopigmentation agents as an option for refractory melasma [5], no consensus has been reached on the specific role of PSAL. Existing literature on the efficacy of the 755-nm PSAL in treating melasma is limited by small sample sizes, treatment protocols heterogeneity, and lack of long-term follow-up [9]. While some studies assert the effectiveness of PSAL with minimal side effects [10, 11], a comprehensive meta-analysis evaluating its safety and efficacy at the 755-nm wavelength against current treatments is lacking. This meta-analysis aims to address this under-investigated area by systematically assessing the therapeutic impact of PSAL on melasma, focusing on MASI or modified MASI (mMASI) reduction, relapse rates, and adverse events to provide evidence for its use and inform future protocols.

2 | Methods

2.1 | Search Strategy

A comprehensive search of PubMed, Ovid Medliner, Embase, The Cochrane Library, and the search engine Google Scholar up to April 10th, 2025 was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [12]. Controlled vocabulary supplemented with keywords describing PSAL for melasma treatment in adult patients (Item S1) was used. The review was registered with PROSPERO (CRD420251022381).

2.2 | Inclusion and Exclusion Criteria

Eligible randomised controlled trials (RCTs) met: (1) adult ≥18 years treated with PSAL for melasma; (2) control group without PSAL (Table 1); (3) reported MASI and/or mMASI. Reviews, case reports, case series, case–control studies, surveys, guidelines, letters to the editors, discussions and preliminary reports were excluded. No language restriction applied.

2.3 | Data Extraction and Quality Assessment

Screening and data extraction were conducted by two of five assessors (VA, EJBN, KAA, DKV, KRC). Primary outcome was improvement in melasma severity using MASI or its modified version [13]. Data was extracted directly from text or tables, or estimated from graphs via WebPlotDigitizer if unavailable [14]. Study quality was assessed by two authors (V.A., E.J.B.N.) using the Version 2 of the Cochrane risk-of-bias tool for randomised trials (ROB2) (Figure S1) [15]. Conflicts were resolved by consensus with a third author (S.C.L.).

2.4 | Statistical Analysis

Means and proportions were pooled using a random-effects model. Continuous outcomes applied the generic inverse variance method; dichotomous outcomes used Mantel–Haenszel [16]. The DerSimonian and Laird approach was used for one-arm analyses [17]. Heterogeneity was quantified using the *Q* statistic and I^2. When mean and standard deviation (SD) were unavailable, medians were converted using the Cochrane Handbook formulas [18]. Analysis separates subgroups of laser and creams, and used RevMan 5.4 (Review Manager [RevMan] [Computer program]. The Cochrane Collaboration, 2020) [19] and Open Meta-Analyst software [20].

3 | Results

3.1 | Study and Patient Characteristics

Literature search yielded 235 studies. After removing duplicates and screening, five unique RCTs [21–25] involving 139 patients were included (Figure 1). All were single-institutional, Asian cohorts. Mean age ranged 39.5 to 50.7 years; 113 patients (81.3%) were female. Fitzpatrick type ranged III–V. Baseline characteristics are described in Table 1.

3.2 | Clinical and Treatment Characteristics

Among the five included studies, three used a split face comparison (70 patients) [21, 23, 24], two [22, 25] used full face (PSAL 40; control 29). Overall, 110 patients received PSAL; 99 received control therapy. Follow-up was 20–36 weeks across studies (Table S2). PSAL sessions ranged from 3 to 5 sessions at 2–4 week intervals [21–25]. Two studies [21, 23] included adjuvants including 20% azelaic acid and 2% HQ. Two studies [24, 25] used a diffractive lens array (DLA), one a flat optic [22], and two [21, 23] did not report lens used.

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TABLE 1 | Baseline and clinical characteristics of the included studies.

Study, year	Country	Study design	Treatment parameters	PSAL settings	Comparator	*N* of participants and sex ratio (F:M)		Dropout reason (*N*)	Average age ± SD (years)		Fitzpatrick skin type (I, II, III, IV, V)	
						Total (PSAL: control)	Sex ratio (F:M)		PSAL	Control	PSAL	Control
Lai et al. (2024)[c]	China	RCT	3 sessions at 4-week intervals with 20% azelaic acid	Fluence 0.25–0.40 J/cm^2; spot size 8–10 mm; frequency 5 Hz; 2 passes	20% azelaic acid alone	30 → 27 (27:27)[a]	4:26	Noncompliance (3)	43.7 ± 6.9		(0, 0, 7, 23, 0)[f]	
Liang et al. (2025)[b]	China	RCT	3 sessions at 4-week intervals (flat optic)	Fluence 0.40–0.71 J/cm^2; spot size 6–8 mm; frequency 10 Hz	1064-nm *Q*-switched Nd: YAG laser	40 (20: 20) → 38 (19:19)	40:0	Loss of contact (1), unplanned pregnancy (1)	39.5 ± 6.3	41.3 ± 8.3	(0, 0, 4, 16, 0)	(0, 0, 6, 14, 0)
Manuskiatti et al. (2022)[c]	Thailand	RCT	5 sessions with 2-week intervals with 2% HQ cream	Fluence 0.40 J/cm^2; spot size 8 mm; frequency 2.5 Hz; 2 passes	2% HQ cream only	20 (20:20)[a]	20:0	NR (0)	50.7 ± 5.3[d]		(0, 0, 1, 14, 5)[f]	
Wang et al. (2020) (Group A1)[b]	Taiwan	RCT	3 sessions with 4-week intervals (DLA)	Fluence 0.40 J/cm^2; spot size 8 mm	Triple combination cream[e]	18 (9:9) → 15 (9:6)	15:0	NR (3)	40.4 ± NR	50.0 ± NR	(0, 0, 0, 9, 0)	(0, 0, 0, 6, 0)
Wang et al. (2020) (Group A2)[b]	Taiwan	RCT	5 sessions with 4-week interval (DLA)			20 (11:9) → 17 (11:6)	17:0	NR (3)	46.4 ± NR	50.0 ± NR	(0, 0, 0, 11, 0)	(0, 0, 0, 11, 0)
Zhou et al. (2024)[b]	China	RCT	3 sessions at 4-week intervals (DLA)	Fluence 0.71 J/cm^2; spot size 6 mm; frequency 10 Hz	1064-nm *Q*-switched Nd: YAG laser	20 → 17 (17:17)[a]	17:0	Time constraints (3)	40 ± 4.3[f]		(0, 0, NR, NR, 0)[f]	

Note: Group A1: 3 laser sessions at 4-week intervals of PSAL; Group A2: 5 laser sessions at 4-week intervals of PSAL.

Abbreviations: DLA, diffractive lens array; F, female; HQ, hydroquinone; M, Male; MASI, melasma area severity index score; mMASI, modified melasma area severity index score; *N*, number; NR, not reported; PSAL, picosecond alexandrite laser; RCT, randomised controlled trial; SD, standard deviation; TCC, triple combination cream.

[a]Split face comparison.

[b]MASI as primary outcome.

[c]mMASI as primary outcome.

[d]Value estimated from age range or IQR.

[e]TCC: fluocinolone acetonide 0.01%, hydroquinone 4% and tretinoin 0.05%.

[f]Number of PSAL patients equals Control patients with Fitzpatrick Skin Type (I, II, III, IV, V).

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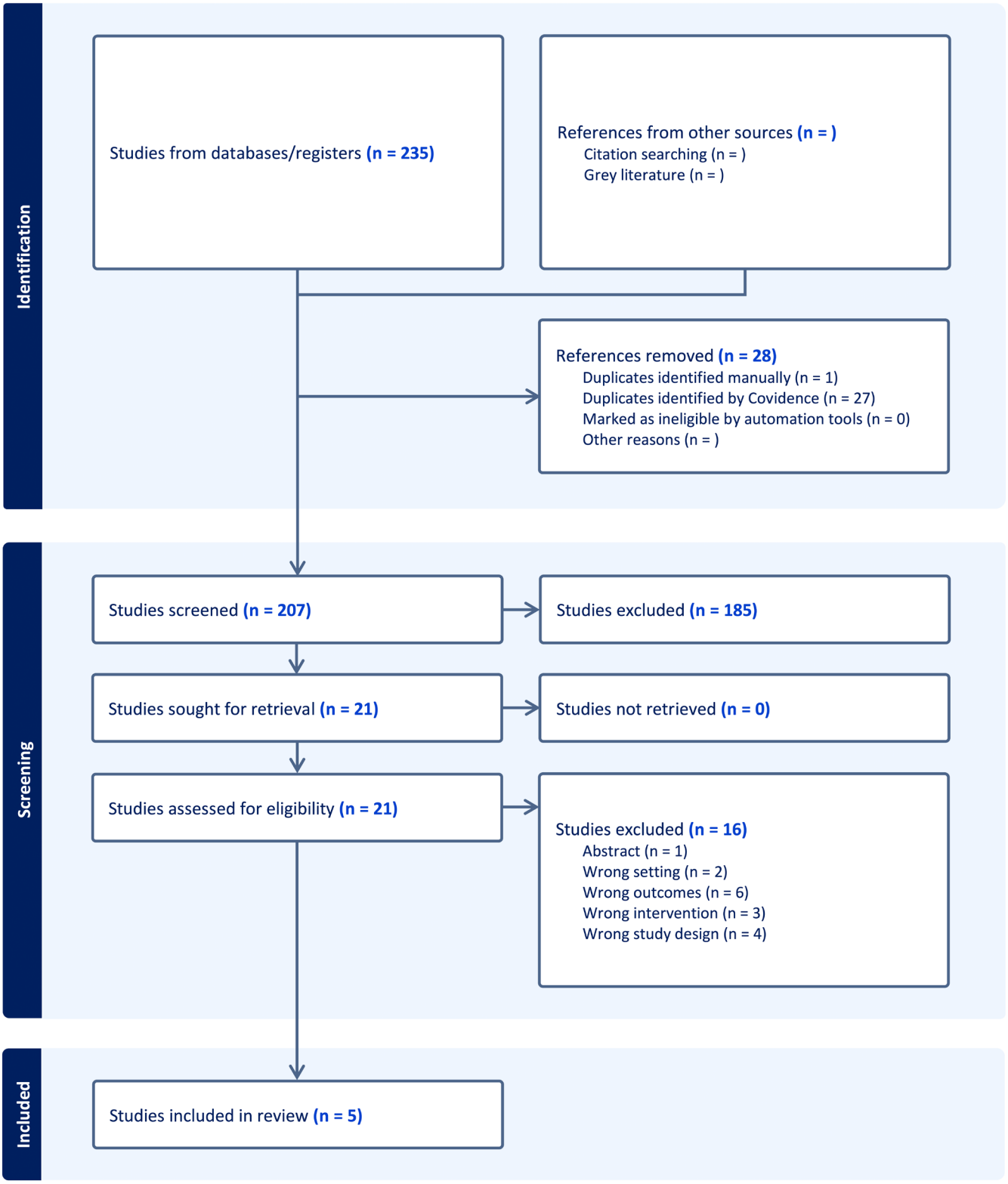


FIGURE 1 | Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart.

Fluence ranged from 0.25–0.71 J/cm^2; spot size 6–10 mm; and frequency 2.5–10 Hz. Topical control interventions included 20% azelaic acid [21], 2% HQ [23], TCC [25], and laser comparator was the 1064-nm *Q*-switched Nd:YAG (QSND) laser [22, 24]. Interventions of the included studies are summarised in Table 1.

3.3 | Risk of Bias

Of five randomised control trials judged via the ROB2 Tool (Figure S1), one had low risk [21], three with some concerns [23–25], and one at high risk [22]. Studies with some concerns primarily demonstrated issues in domains of randomisation

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process, deviations from intended intervention, and missing outcome data. The study at high risk showed concerns in the randomisation process and selection of the reported result. Nevertheless, the included studies were deemed adequate within the selection and compatibility domains.

3.4 | Primary Outcomes

Baseline, final, and the change in MASI scores were contributed from three studies (Tables S1–S3) [22, 24, 25]. There were no differences between groups at baseline (MD = −0.61, 95% CI: −2.13, 0.92, I^2 = 20%; Figure 2A) or at the end of treatment (MD = 0.32, 95% CI: −0.28, 0.92, I^2 = 0%; Figure 2B) when compared against the QSND or TCC. Change in MASI scores involved 62 patients (PSAL n = 56, control n = 48) and favoured the TCC (MD = 1.82, 95% CI: 1.11, 2.52, I^2 = 0%); no difference was noted with the QSND (MD = 0.92, 95% CI: −0.45, 2.30, I^2 = 87%) (Figure 3).

3.5 | Complications

All five studies reported overall adverse events (PSAL 42/107, QSND 3/37, Topicals 19/56; Figure 4; Table S4) [21–25]. There were no differences between groups (OR = 2.20, 95% CI: 0.38, 12.72, I^2 = 78%). Four studies [21–23, 25] including 116 patients reported erythema rates (PSAL 25/90, QSND 2/20, Topicals 6/56; Figure 5; Table S4) with no differences between PSAL and topical interventions (OR = 2.16, 95% CI: 0.13, 35.64, I^2 = 78%).

3.6 | Pigmentation Changes

All five studies [21–25] reported PIH (PSAL 14/107, QSND 1/37, Topicals 0/56; Table S4) and were more common in PSAL when compared against topical interventions (OR = 6.82, 95% CI: 1.17, 39.92, I^2 = 0%) but had no difference with QSND (OR = 4.09, 95% CI: 0.62, 26.97, I^2 = 0%; Figure 6). Hypopigmentation was assessed in four studies [22–25], and infection reported in two studies (Table S4) [23, 25]; no hypopigmentation or infection occurred in either group.

Recurrence was reported in three studies [22, 23, 25] and infrequent (PSAL 2/60, QSND 0/20, Topicals 0/26).

3.7 | Pain

As pain is expected in laser therapy, it was not included as an adverse effect herein. Post-treatment visual analogue scale (VAS) pain was reported in three studies (Table S5) [22–24], was overall mild (mean = 3.65; Figure 7A), and favoured topical interventions over PSAL (MD = 0.72, 95% CI: 0.19, 1.25, I^2 = 12%; Figure 7B).

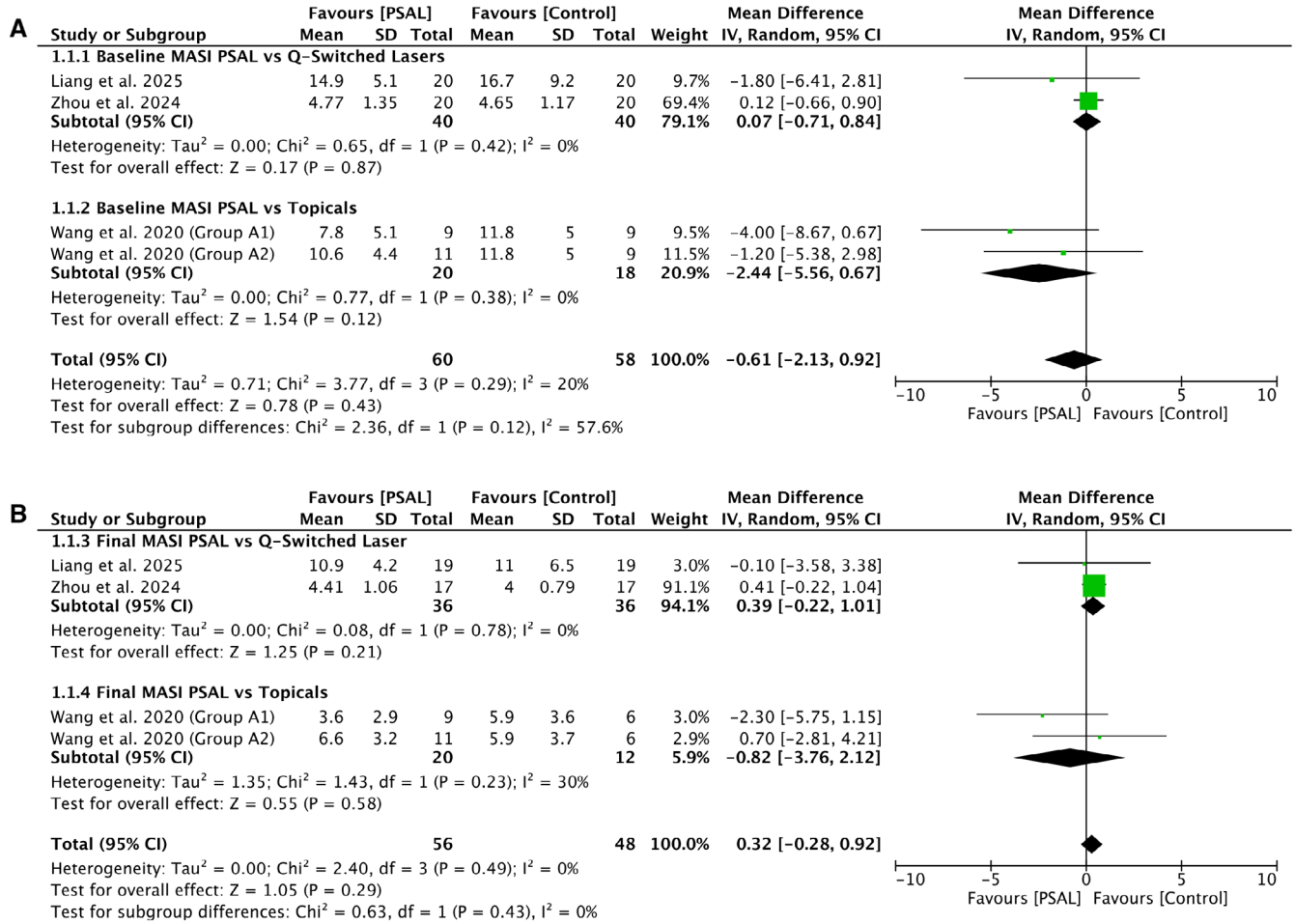


FIGURE 2 | Baseline and final MASI scores for PSAL vs. control (Q-switched lasers vs. TCC).

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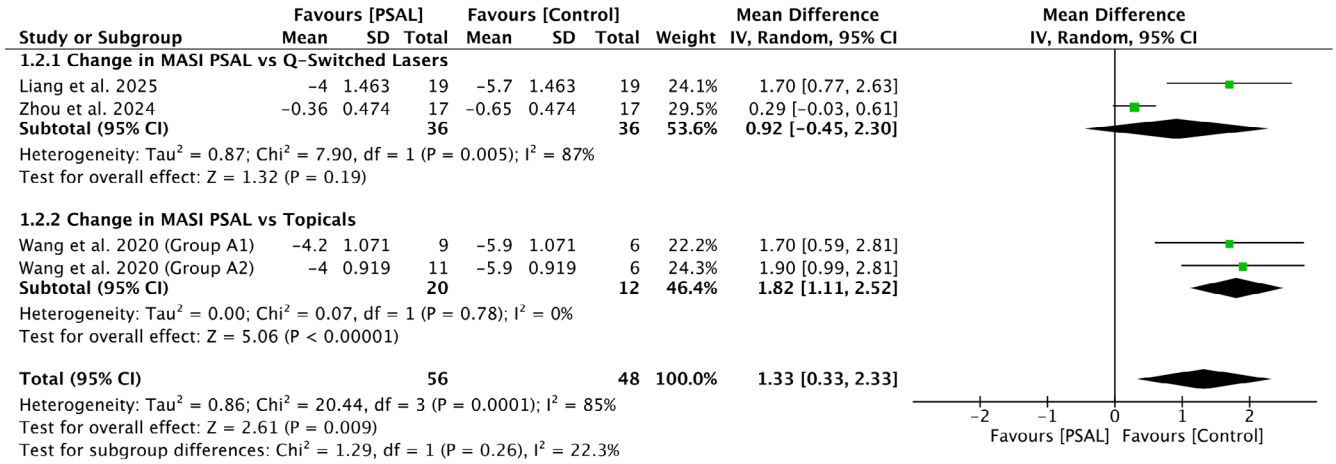


FIGURE 3 | Change in MASI values for PSAL vs. control (*Q*-switched lasers vs. TCC).

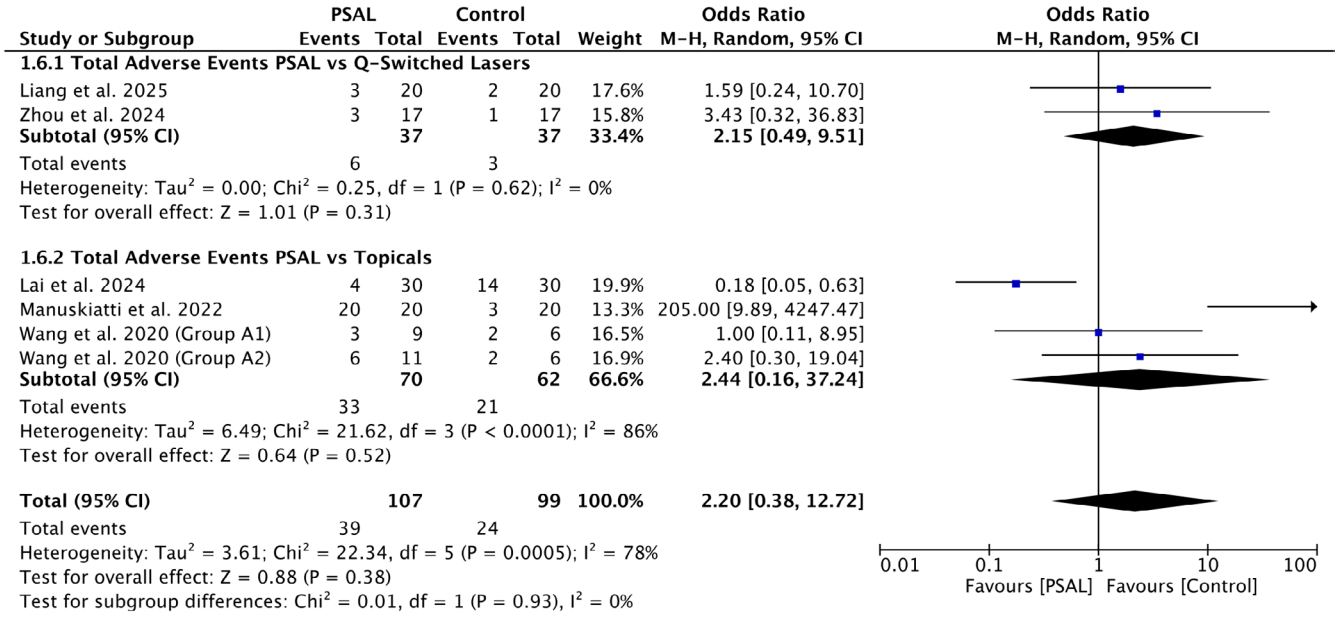


FIGURE 4 | Overall adverse events comparing PSAL vs. control (*Q*-switched lasers vs. Topicals).

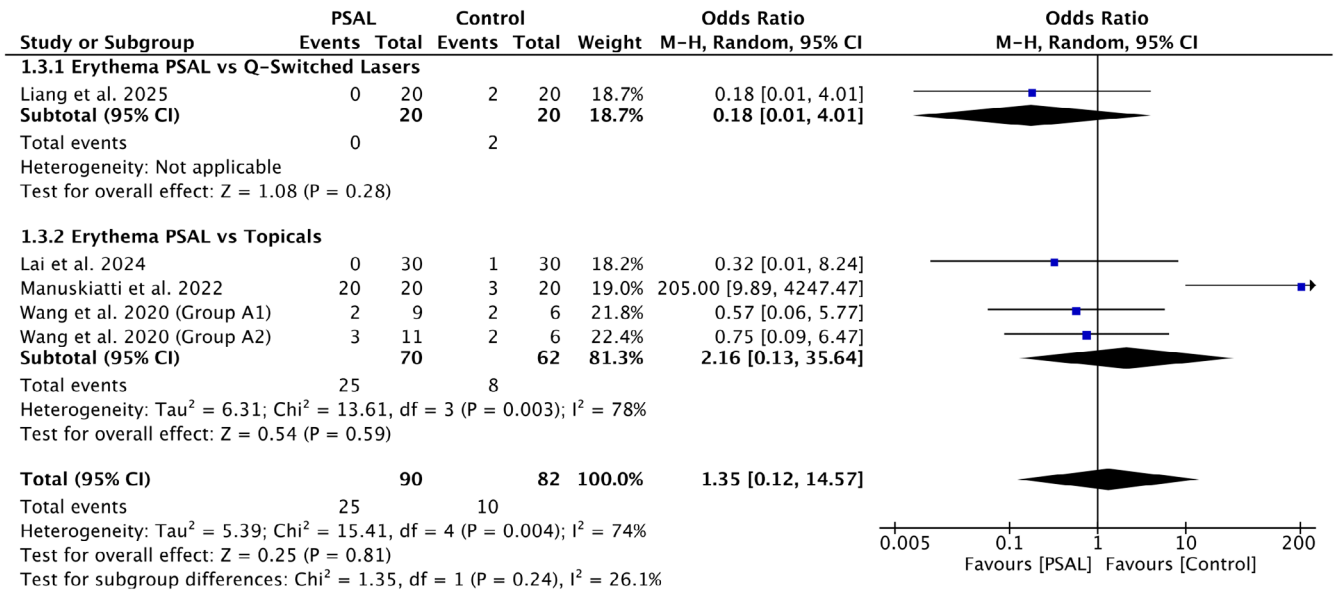


FIGURE 5 | Erythema score for PSAL vs. control (*Q*-switched lasers vs. Topicals).

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3.8 | Patient Satisfaction

Patient satisfaction was assessed in three studies (Figure 8; Table S6) [21, 22, 24]; there were no differences between groups (QSND MD = −0.10, 95% CI: −0.41, 0.21, I^2 = 0%; Azelaic Acid MD = 0.00, 95% CI: −0.27, 0.27, I^2 = 0%).

4 | Discussion

Melasma is a chronic hyperpigmentation disorder disproportionately affecting women and individuals with darker skin phototypes which may cause psychological distress [2, 26]. Despite many therapies available, treatment remains challenging due to recurrence and variable efficacy [1]. In recent years, PSAL has been introduced as a potential therapeutic alternative, with theoretical advantages over nanosecond devices due to shorter pulse durations and greater reliance on photomechanical rather than photothermal effects [8]. The primary aim of this meta-analysis was to evaluate the safety and efficacy of the PSAL for the treatment of melasma in RCTs. Analysis of five RCTs (n = 139) found PSAL inferior to topical interventions for MASI improvement and with a higher risk of PIH.

4.1 | Inferiority of PSAL

The salient finding of this meta-analysis is the inferiority of PSAL when compared with topical interventions in achieving reduction in MASI scores for melasma (Figure 3). This contrasts with early uncontrolled studies and case series suggesting promising outcomes with reports of substantial pigment clearance and fewer sessions required [10, 27, 28]. This discrepancy is best explained by differences in patient selection, treatment protocols, and outcome measures between uncontrolled series and randomised trials. Observational cohorts may have included heterogeneous populations with predominantly epidermal melasma or milder baseline disease [27], both of which are more

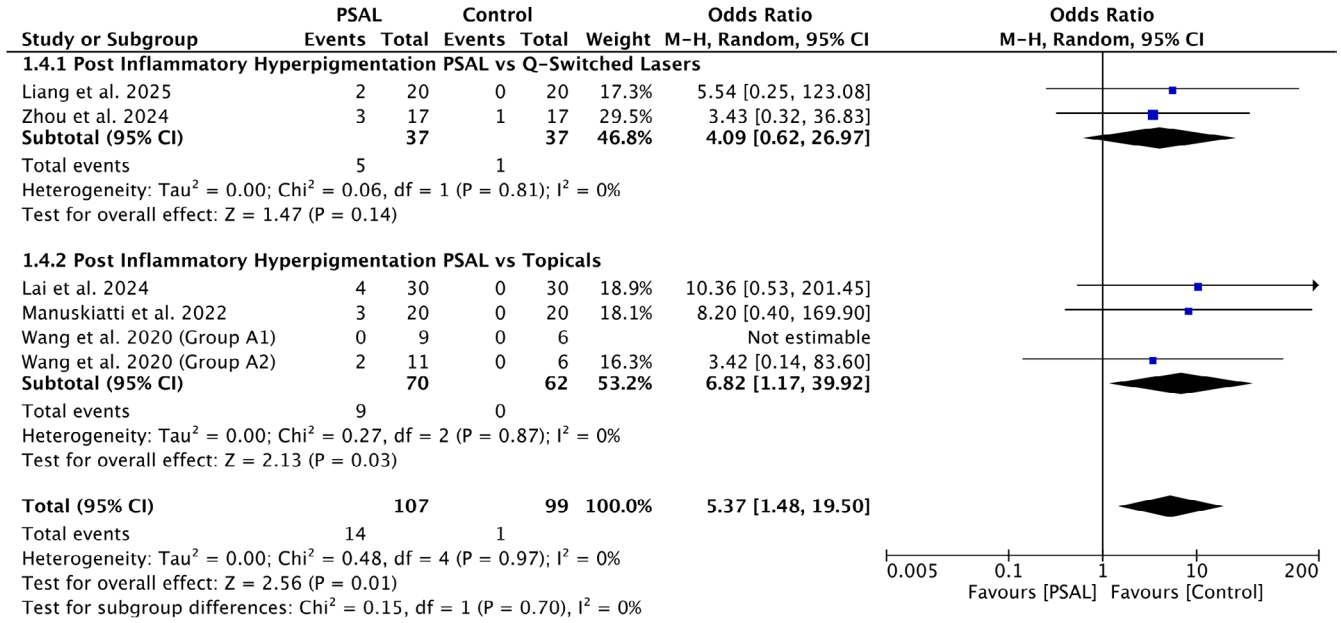


FIGURE 6 | Incidence of post inflammatory hyperpigmentation after treatment with PSAL vs. control (*Q*-switched lasers vs. Topicals).

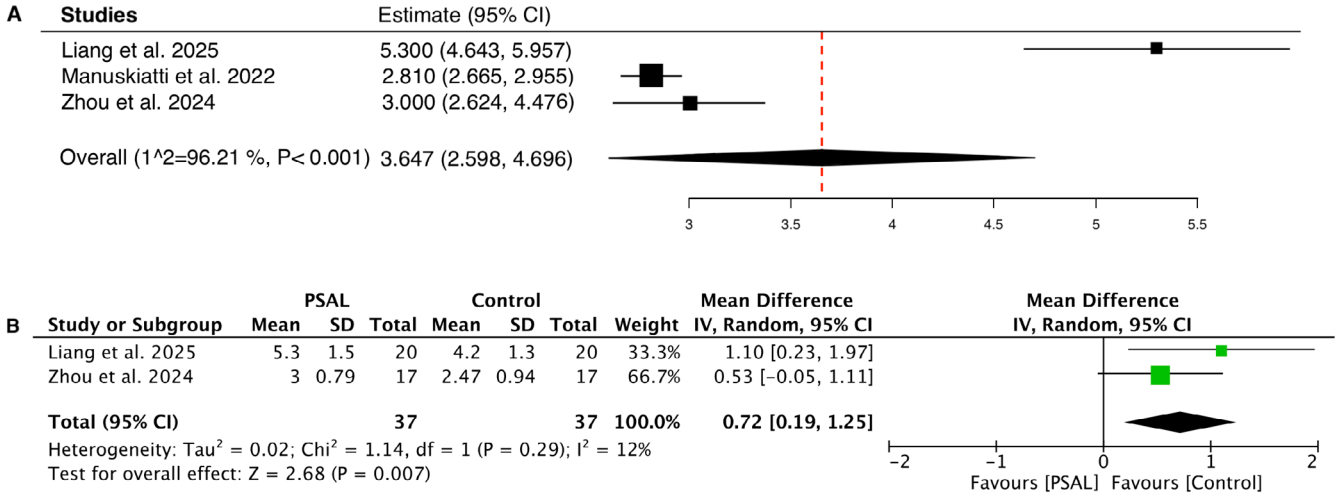


FIGURE 7 | Post PSAL Treatment VAS Pain scores and comparing PSAL vs. QSND.

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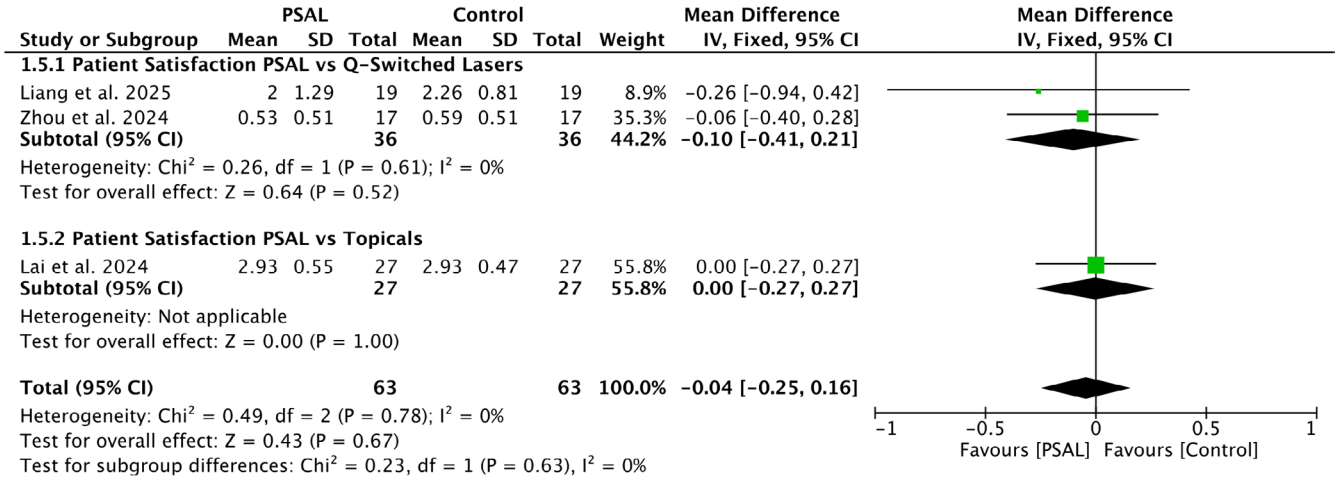


FIGURE 8 | Patient satisfaction scores on follow-up for PSAL vs. control (QSND vs. azelaic acid).

responsive to superficial laser therapy. Treatment protocols in case series also varied widely in fluence, spot size, and number of sessions, and the absence of a comparator group made it impossible to account for placebo effect or natural disease fluctuation [29]. Finally, differences in outcome assessment—such as use of non-validated scales [10] or evaluation at earlier follow-up timepoints [29]—may have artificially inflated treatment responses. Our analysis of RCTs with validated outcome metrics provides higher-level evidence that tempers the initial optimism surrounding PSAL.

4.2 | Mechanistic Consideration

While there was no difference between PSAL and QSND in this analysis, PSAL's ineffectiveness may be explained mechanistically by its limited effects on melanocytes and the dermal-epidermal junction. Melasma is increasingly recognised as a disorder involving not only melanocytic hyperactivity but also dermal inflammation, vascular remodelling, and structural disruption of the basement membrane [30–32]. PSAL's 755-nm wavelength confines effects to the epidermis, and its mechanism—photomechanical fragmentation of melanin [33]—may not adequately address deeper, more complex pathogenic processes [34]. In contrast, QSND lasers, particularly the 1064-nm Nd:YAG, penetrate deeper into the dermis with both photothermal and photomechanical effects [8, 33], inducing subcellular selective photothermolysis, disrupting stage IV melanosomes, and altering melanocyte biology [35]. Mun et al. showed a reduction in dendritic processes and pigment transfer from melanocytes to keratinocytes following QSND exposure [36] in melasma—processes not seen with PSAL [33]. Although it is postulated that QSND devices modulate the pigment production-transfer cycle at multiple levels and PSAL may be limited to superficial pigment fragmentation without significant downstream biological modulation, a difference was not supported in this analysis.

4.3 | Safety and PIH

In addition to limited efficacy, PSAL showed increased PIH risk compared with several topical agents [21, 23, 25]. This is clinically significant as PIH both worsens cosmetic outcomes and may exacerbate patient distress and undermine treatment adherence [26]. PIH is particularly concerning in darker skin phototypes, which represent a large proportion of the global melasma population [1]. Mechanisms underlying PIH after laser therapy may include melanocyte hyperreactivity to sublethal injury, inflammatory mediator release, and post-laser epidermal barrier disruption [37]. Although PSAL theoretically minimises thermal damage, there was no difference in PIH when compared against the QNSD. Additionally, contemporary literature with topical agents report low rates, likely due to their non-ablative, anti-inflammatory mechanisms on melanogenesis without significant disruption to the epidermal barrier [38, 39], making the PSAL a poor option when considering PIH.

Hypopigmentation—a recognised complication of QSND therapy which may manifest as persistent and potentially irreversible mottled hypopigmentation or punctate leukoderma [6]—was not reported in the included studies [22–25]. Similarly, transient erythema and oedema [21–25] were observed but were generally self-limiting and did not require intervention. Wholistically, these findings suggest that although PSAL may not demonstrate a superior overall safety profile with the salient risk of PIH, it may offer an advantage in reducing the risk of clinically significant hypopigmentation. Clinicians should be cognizant of this compromise: PSAL may carry a similar likelihood of temporary hyperpigmentation, but the risk of long-term or irreversible pigmentary change appears substantially lower compared with QSND.

4.4 | Recurrence

Reported recurrence was low across studies but short follow-up durations (< 6 months) such as Wang et al. [25] and Zhou et al. [24] likely underestimate relapse rates. Long-term outcomes or recurrence rates for PSAL in melasma are scarce in the literature, limiting clarity [8, 9, 31, 33, 40].

4.5 | The Use of Short-Pulse Lasers in Melasma

When comparing short-pulse laser modalities for melasma, two critical technical parameters include pulse duration and

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wavelength. Picosecond lasers, such as PSAL, deliver shorter pulses than traditional *Q*-switched lasers, theoretically applying more targeted photomechanical disruption of melanin with less collateral thermal damage [8], making them attractive for pigmentary disorders with a dermal component from a safety perspective. However, melasma predominantly involves the epidermis and superficial dermis, possibly limiting PSAL's advantage. Secondly, wavelength influences tissue penetration; while PSAL uses a 755-nm wavelength, devices such as QSND lasers operate at 1064-nm, allowing for deeper tissue penetration and safer use in darker skin. The interplay between pulse duration and wavelength suggests that no single laser is universally superior; rather, optimal treatment depends on pigment depth, skin type, and treatment goals.

4.6 | The Role of TXA and PSAL in the Current Treatment Landscape

TXA has emerged as one of the most effective and well-tolerated therapeutic options for melasma, supported by multiple randomised trials and meta-analysis [4, 41, 42]. The mechanisms of TXA on the inhibition of melanogenesis via the plasminogen-plasmin pathway and control of vascular components of melasma [4] have contributed to its efficacy and widespread clinical use. While PSAL monotherapy may be a poor therapeutic option, it may have potential in combination with topical tranexamic acid, as a previous meta-analysis has suggested the combination of topical TXA with lasers is more effective than laser monotherapy [43]. Given PSAL's inferiority and higher risk of PIH, it should be reserved for TXA-resistant cases or where TXA is contraindicated.

5 | Limitations

Our findings are subject to several limitations. Foremost is the heterogeneity in treatment protocols, control measures, and outcome measures. Secondly, the limited and mixed quality of studies and small sample size included in this meta-analysis reduce the overall power of the analysis and limit the strength of our claims. Most studies followed patients with variable intervals for less than 27 weeks [21, 22, 24, 25]—a follow up period insufficient to assess the durability of response in a chronic condition like melasma [44]. A limitation in analysis is the baseline score from the first episode of treatment potentially skewing results as it assumes that adjuvant therapy used before the use of PSAL had no effect—particularly relevant in Lai et al. as they used 4 weeks of azelaic acid prior to PSAL therapy [21]. Furthermore, subgroup data stratified by melasma subtype or skin phototype were rarely reported, limiting insights into which patient groups might benefit most from PSAL. Finally, results may not be generalisable as most studies were from East Asia [21, 22, 24, 25].

6 | Conclusion

This systematic review and meta-analysis of RCTs evaluated the safety and efficacy of the PSAL for melasma. This is the most up-to-date and comprehensive meta-analysis focused specifically on PSAL for melasma using high-level evidence. Findings suggest that the PSAL may be inferior to established topical therapies for melasma and is associated with a higher risk of PIH. Limited and heterogeneous data do not support the use of PSAL monotherapy for melasma, particularly for patients with darker phototypes and most vulnerable to pigmentary complications. Our findings lend to the motif that conventional modalities such as the TCC are safer and more effective standards of care, though certainty is limited by the evidence pool.

Future studies should standardise PSAL parameters, include longer follow-up to appropriately capture relapse and other complications, and stratify outcomes by melasma subtype and skin phototype. Investigation of combination approaches, such as PSAL with topical or systemic adjuvants, may clarify whether it has a role within multimodal therapy. It appears that until higher-quality evidence emerges, PSAL should be regarded as investigational rather than first-line treatment for melasma.

Author Contributions

Systematic review conception: D.L., D.K.V., K.R.C. Screening and extraction: V.A., E.J.B.N., K.A.-A., D.K.V., K.R.C. Statistical analyses: S.-Y.C.L. Drafted manuscript: D.K.V., K.R.C., E.J.B.N. Editing and final approval: All.

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The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** Supporting Information.

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