



TOPICAL HEXYLRESORCINOL, ALPHA-ARBUTIN, AND TRANEXAMIC ACID FOR MELASMA: A SYSTEMATIC REVIEW AND EVIDENCE MAP OF EFFICACY, SAFETY, AND MECHANISMS

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ABSTRACT

Melasma is a chronic, relapsing facial hypermelanosis sustained by photic exposure, melanocyte hyperactivity, inflammation, oxidative stress, vascular signaling, and dermal remodeling. Interest in non-hydroquinone therapies has increased because irritation and recurrence often limit long-term care. Objective to systematically evaluate the efficacy, safety, formulation characteristics, and mechanistic PubMed/MEDLINE, Scopus, Web of Science, Embase, CENTRAL, ScienceDirect, ClinicalTrials.gov, and WHO ICTRP were searched from database inception to 19 July 2026. The included studies were published between 2012 and 2025. The search identified 455 records; after duplicate removal and screening, 35 full-text reports were assessed for eligibility and 12 studies were included in the qualitative synthesis. Randomized and non-randomized clinical studies evaluating the eligible active ingredients as monotherapy or interpretable combinations were included. Risk of bias was assessed using RoB 2, ROBINS-I, or Joanna Briggs Institute tools, and certainty of evidence was evaluated using GRADE. Clinical and formulation heterogeneity precluded meta-analysis; therefore, structured narrative synthesis and evidence mapping were performed. Twelve studies met the eligibility criteria and were included in the qualitative synthesis. Seven evaluated topical tranexamic acid, three assessed alpha-arbutin-containing interventions, and two investigated hexylresorcinol-containing formulations. Nine studies directly enrolled patients with clinically diagnosed melasma, one included a mixed population of women with melasma or facial dark spots, and two provided indirect evidence from general facial or body hyperpigmentation. Topical tranexamic acid, generally administered at concentrations of 3–5% for 8–12 weeks, showed the most consistent reductions in MASI or mMASI and frequently produced short-term responses that were not significantly different from those obtained with hydroquinone, while generally causing fewer local irritant reactions. Alpha-arbutin-containing regimens improved pigmentation, but most involved co-active ingredients or enhanced-delivery systems. Hexylresorcinol reduced pigmentation in randomized dyspigmentation studies, although melasma-specific evidence remained limited. No factorial trial demonstrated clinical synergy among the three agents. Topical tranexamic acid has the strongest, although low-certainty, evidence. Alpha-arbutin and hexylresorcinol are promising, but ingredient-specific efficacy, durability, and synergy remain unconfirmed.

Keywords: alpha-arbutin; hexylresorcinol; melasma; systematic review; topical therapy; tranexamic acid

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INTRODUCTION

Melasma is a chronic, acquired, and frequently relapsing hyperpigmentary disorder characterized by symmetrical brown-to-gray macules and patches, predominantly affecting the centrofacial, malar, and mandibular regions. Although it does not cause physical disability, its visible facial distribution, persistent course, therapeutic burden, and tendency to recur can substantially impair self-image, social functioning, and quality of life. Melasma occurs most commonly in women of reproductive age and individuals with intermediate-to-dark skin phototypes, although it may affect all sexes and ethnic groups. Its management remains challenging because improvement is often gradual, incomplete, and dependent on sustained treatment and photoprotection (Cassiano et al., 2022; Gan & Rodrigues, 2024).

Melasma is increasingly regarded as a complex photoaging-associated disorder rather than a condition caused exclusively by excessive epidermal melanin production. Ultraviolet radiation is a major initiating and aggravating factor, while visible light may induce or maintain pigmentation, particularly in individuals with darker skin phototypes. Hormonal influences, genetic susceptibility, oxidative stress, inflammatory signaling, mast-cell activation, increased dermal vascularity, basement-membrane disruption, solar elastosis, sebocyte activity, and altered communication among melanocytes, keratinocytes, endothelial cells, and dermal fibroblasts have also been implicated. These interconnected abnormalities create a cutaneous microenvironment in which melanocytes may remain chronically activated even after visible pigmentation has improved, thereby contributing to recurrence and limiting the durability of treatments directed solely at melanogenesis (Gu et al., 2025; Passeron & Picardo, 2018).

Photoprotection is therefore an essential component of melasma management. Broad-spectrum sunscreens that protect against ultraviolet A and B radiation can reduce disease aggravation, while formulations containing visible-light-attenuating pigments, such as iron oxides, may provide additional benefit in susceptible phototypes. Nevertheless, photoprotection alone is generally insufficient for established disease, and topical depigmenting treatment remains a principal therapeutic approach. Hydroquinone and hydroquinone-based triple-combination therapy have the most established conventional evidence, particularly for epidermal and mixed melasma. However, irritant dermatitis, erythema, xerosis, post-inflammatory worsening, poor long-term adherence, regulatory differences, and concerns regarding prolonged unsupervised use have increased interest in non-hydroquinone alternatives. Moreover, recurrence may still occur after treatment withdrawal or renewed photic exposure, even after an initially favorable response (Cassiano et al., 2022; Gan & Rodrigues, 2024).

Among non-hydroquinone agents, tranexamic acid has attracted considerable attention because its activity extends beyond direct inhibition of tyrosinase. Tranexamic acid is a synthetic lysine analogue that inhibits the conversion of plasminogen to plasmin. In the skin, reduced plasmin activity may decrease the release of arachidonic acid, prostaglandins, and other melanocyte-stimulating mediators generated after ultraviolet exposure. Experimental and clinical evidence also suggests possible effects on endothelin-1 signaling, inflammation, vascular activity, and keratinocyte–melanocyte interactions (Kim et al., 2016; Maeda & Tomita, 2007). These mechanisms are consistent with the contemporary understanding of melasma as a disorder involving epidermal, inflammatory, vascular, and dermal components.

Clinical studies have evaluated topical tranexamic acid at concentrations commonly ranging from approximately 3% to 5%, administered through solutions, creams, liposomes, iontophoresis-assisted preparations, and other delivery systems. Several comparative trials have reported reductions in the Melasma Area and Severity Index or modified Melasma Area and Severity Index, with short-term responses that were not significantly different from those obtained with hydroquinone in some populations. For example, 5% topical tranexamic acid has been compared with 3% hydroquinone, whereas 3% tranexamic-acid cream has been evaluated against 4% hydroquinone in individuals with skin of color. These studies generally indicate favorable local tolerability, but their interpretation is limited by modest sample sizes, heterogeneous vehicles, different comparator concentrations, short follow-up periods, and the absence of prospectively defined equivalence or non-inferiority margins (Atefi et al., 2017; Janney et al., 2019; Yasnova et al., 2024).

Alpha-arbutin is another non-hydroquinone candidate with an established antimelanogenic rationale. It is the α -glucoside of hydroquinone and inhibits tyrosinase-dependent melanin synthesis. Alpha-arbutin should not be considered interchangeable with β -arbutin because stereochemical configuration may influence enzyme binding, biological activity, chemical stability, hydrolysis, and formulation behavior. Its clinical performance may also depend on concentration, pH, vehicle

composition, storage conditions, and cutaneous delivery (Boo, 2021; Saeedi et al., 2021; Sugimoto et al., 2004). Consequently, studies reporting only “arbutin” without identifying the isomer provide limited evidence for alpha-arbutin specifically.

Recent clinical evidence supports the therapeutic potential of alpha-arbutin-containing formulations but has not established its independent efficacy. A randomized split-face pilot trial found that a formulation containing 5% alpha-arbutin and 2% kojic acid improved melasma and was associated with fewer adverse effects and less short-term post-treatment rebound than triple-combination cream. However, the presence of kojic acid prevented attribution of the observed effect to alpha-arbutin alone (Tantanasrigul et al., 2025). A separate study using alpha-arbutin-loaded chitosan nanoparticles reported improved cutaneous deposition and clinical outcomes compared with a conventional hydrogel, indicating that carrier design may materially modify treatment performance (Hattem et al., 2022). These findings also highlight a recurring methodological limitation: alpha-arbutin is frequently evaluated as part of a multicomponent formulation or enhanced-delivery system rather than as an independently interpretable monotherapy.

Hexylresorcinol is a substituted phenolic compound with tyrosinase-inhibitory and antioxidant properties. Experimental evidence indicates that it can suppress tyrosinase activity and expression, while randomized clinical studies have demonstrated improvement in general facial or body hyperpigmentation after topical application. A 12-week randomized study reported that 4-hexyl-1,3-phenylenediol improved several measures of pigment appearance and was generally well tolerated (Won et al., 2014). Another randomized split-body comparison found reductions in facial and hand pigmentation with 1% hexylresorcinol and 2% hydroquinone, without a statistically significant between-treatment difference. However, participants were selected for general pigment appearance rather than clinically diagnosed melasma. The available evidence therefore supports the depigmenting activity of hexylresorcinol but remains indirect for melasma-specific effectiveness (Wu et al., 2023).

Interpretation of the three agents is further complicated by formulation and delivery. Tranexamic acid and alpha-arbutin are relatively hydrophilic, and their passive penetration through the stratum corneum may be limited. Liposomes, niosomes, polymeric nanoparticles, iontophoresis, microneedling, and other penetration-enhancing approaches may increase local exposure, but they also produce interventions that differ pharmacologically from conventional creams or solutions. Similarly, multicomponent formulations containing alpha-arbutin, tranexamic acid, niacinamide, kojic acid, antioxidants, sunscreen, or other depigmenting ingredients do not permit the independent contribution of each active to be isolated. Therefore, favorable findings from combination or enhanced-delivery studies should not be generalized directly to conventional monotherapy at the same nominal concentration (Hattem et al., 2022; Kanechorn Na Ayuthaya et al., 2012).

A related issue is the frequent use of the term *synergy* in cosmetic and clinical discussions. Agents that act through different biological pathways may be mechanistically complementary, but complementary mechanisms do not necessarily produce a clinical interaction greater than the expected additive effect. Demonstrating synergy requires an appropriate factorial or multi-arm design containing the relevant monotherapies, their combination, an appropriate control, and a prespecified statistical interaction analysis. The available clinical literature includes monotherapy, active-comparator, carrier-enhanced, and multicomponent studies, but no verified factorial trial has demonstrated clinical synergy among topical hexylresorcinol, alpha-arbutin, and tranexamic acid.

Previous reviews have generally examined melasma treatments broadly, evaluated tranexamic acid across multiple administration routes, or discussed individual depigmenting ingredients separately. Consequently, uncertainty remains regarding the directness of evidence for each agent in clinically diagnosed melasma, the extent to which observed effects arise from the active ingredient rather than

its vehicle or co-intervention, the comparative safety and durability of response, and whether claims of complementary or synergistic activity are supported by appropriate clinical designs.

Accordingly, this systematic review aimed to evaluate the clinical efficacy and safety of topical hexylresorcinol, alpha-arbutin, and tranexamic acid, administered individually or in interpretable combinations, for the management of melasma. Secondary objectives were to examine the influence of concentration, formulation, delivery system, comparator, treatment duration, photoprotection, and study design; synthesize relevant mechanistic evidence; assess risk of bias and certainty of evidence; and determine whether the available literature supports mechanistic complementarity, additive benefit, or true clinical synergy.

METHOD

Review Design and Reporting

This systematic review and evidence map evaluated the efficacy, safety, formulation characteristics, delivery systems, and mechanistic evidence of topical hexylresorcinol, alpha-arbutin, and tranexamic acid for melasma. The review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement, the PRISMA extension for literature searches, and the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2024; Page et al., 2021; Rethlefsen et al., 2021). A protocol specifying the eligibility criteria, search strategy, study-selection process, outcomes, risk-of-bias assessment, and synthesis plan was prepared before study selection but was not prospectively registered.

Eligibility Criteria

Eligibility was defined according to the population, intervention, comparator, outcomes, and study-design framework. The primary clinical synthesis included adolescents or adults with clinically, dermoscopically, histologically, instrumentally, or Wood's lamp-diagnosed melasma. Studies involving other clinically relevant facial or cutaneous hyperpigmentation were retained only as indirect evidence when they provided transferable information on ingredient-specific depigmenting activity, safety, formulation, or skin delivery. Eligible interventions were topical formulations containing hexylresorcinol, including 4-hexylresorcinol or 4-hexyl-1,3-phenylenediol; alpha-arbutin or sufficiently characterized arbutin; and tranexamic acid. Conventional formulations and enhanced-delivery systems, including creams, gels, solutions, liposomes, niosomes, nanoparticles, iontophoresis, and procedure-assisted delivery, were eligible. Combination products were included when their composition and clinical outcomes were sufficiently reported. Studies evaluating only oral, intravenous, or intradermal tranexamic acid were excluded unless topical-arm data could be extracted separately.

Eligible comparators included placebo, vehicle, untreated control, hydroquinone, triple-combination cream, another depigmenting treatment, or an alternative delivery system. Primary outcomes were the Melasma Area and Severity Index, modified Melasma Area and Severity Index, melanin index, colorimetric pigmentation measurements, and investigator-assessed clinical response. Secondary outcomes included patient-reported improvement, satisfaction, quality of life, adherence, adverse events, treatment discontinuation, maintenance of improvement, and recurrence. Randomized controlled trials, split-face or split-body trials, non-randomized comparative studies, and prospective single-arm intervention studies were eligible. Reviews, editorials, case reports, small case series, patents, advertisements, and conference abstracts without sufficient methodological or numerical information were excluded. Experimental studies were considered only in the mechanistic synthesis and did not contribute to estimates of clinical effectiveness.

Information Sources and Search Strategy

PubMed/MEDLINE, Scopus, Web of Science Core Collection, Embase, Cochrane CENTRAL, and ScienceDirect were searched from database inception to 19 July 2026. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were searched for completed, ongoing, and unpublished clinical studies. The studies included in the final qualitative synthesis were published between 2012 and 2025. The search strategy combined controlled vocabulary and free-text terms representing three concepts: (1) melasma or clinically relevant hyperpigmentation; (2) hexylresorcinol, alpha-arbutin/arbutin, or tranexamic acid; and (3) topical formulations or delivery systems. Representative terms included *melasma*, *chloasma*, *facial hyperpigmentation*, *hexylresorcinol*, *alpha-arbutin*, *arbutin*, *tranexamic acid*, *topical*, *cream*, *serum*, *liposome*, *nanoparticle*, and *iontophoresis*. No publication-year or language restrictions were applied at the search stage (Rethlefsen et al., 2021).

Study Selection and Data Extraction

All records retrieved from the databases and trial registers were imported into a reference-management database. Duplicate records were identified using article titles, author names, publication years, DOIs, PubMed identifiers, and other database identifiers, followed by manual verification. Two reviewers independently screened the titles and abstracts of the deduplicated records. Reports considered potentially eligible by either reviewer were retrieved for full-text assessment. The same reviewers independently assessed the full texts against the predefined eligibility criteria. Reasons for exclusion at the full-text stage were recorded as wrong route or absence of a separately extractable topical arm, ineligible population, ineligible study design, uninterpretable multicomponent intervention, insufficient data, or duplicate or secondary publication. Disagreements were resolved through discussion and, when necessary, consultation with a third reviewer. The numbers of records identified, duplicates removed, records screened, reports retrieved, full-text exclusions, and studies included are presented in the PRISMA 2020 flow diagram (Figure 1) (Page et al., 2021).

Two reviewers independently extracted data using a standardized and piloted form. Extracted information included study design, country, sample size, participant characteristics, diagnostic method, melasma subtype, intervention concentration and formulation, delivery system, comparator, treatment duration, photoprotection, outcome measures, numerical findings, adverse events, recurrence, funding sources, and conflicts of interest. For split-face and split-body studies, paired outcomes were prioritized. Alpha-arbutin was distinguished from beta-arbutin and unspecified arbutin. Studies reporting only “arbutin” without isomer identification were classified as isomer-unspecified evidence. Clinical evidence was categorized as direct monotherapy evidence, direct combination evidence, delivery-enhanced evidence, or indirect evidence from other relevant hyperpigmentation conditions. This classification prevented findings from multicomponent formulations, assisted-delivery procedures, or general dyspigmentation populations from being interpreted as evidence of conventional monotherapy efficacy.

Risk-of-Bias Assessment

Randomized parallel-group, split-face, and split-body trials were assessed using the revised Cochrane Risk of Bias 2 tool (Sterne et al., 2019). Non-randomized comparative intervention studies were evaluated using the Risk of Bias in Non-randomized Studies of Interventions tool (Sterne et al., 2016). Prospective single-arm studies were appraised using the relevant Joanna Briggs Institute critical-appraisal checklist (Aromataris & Munn, 2020). Two reviewers independently completed the assessments, and disagreements were resolved through consensus or third-reviewer adjudication. Funding sources and author conflicts of interest were recorded separately. Industry sponsorship was not automatically classified as high risk of bias but was considered when interpreting selective reporting, unclear analyses, or incomplete adverse-event disclosure. Mechanistic studies were assessed separately according to experimental-model

relevance, intervention characterization, control conditions, outcome measurement, replication, and applicability to human topical exposure.

Effect Measures and Data Synthesis

For continuous outcomes measured using the same instrument, treatment effects were summarized as mean differences with 95% confidence intervals when sufficient data were available. Standardized mean differences were considered when comparable constructs were measured using different validated scales. Risk ratios were preferred for dichotomous outcomes, including clinical response, adverse events, and treatment discontinuation. For split-face and split-body studies, paired effect estimates were prioritized.

A statistically nonsignificant difference between interventions was not interpreted as evidence of equivalence or non-inferiority unless the original study used a prospectively defined margin and adequate statistical power. Studies were grouped according to active ingredient, monotherapy or combination treatment, conventional or enhanced delivery, concentration, formulation, comparator, treatment duration, and directness to clinically diagnosed melasma. Substantial heterogeneity in formulations, delivery systems, co-interventions, comparator concentrations, and outcome timing precluded a clinically meaningful meta-analysis. Findings were therefore synthesized using structured narrative synthesis and evidence mapping in accordance with the Synthesis Without Meta-analysis guideline (Campbell et al., 2020).

The synthesis considered the direction and magnitude of effects, precision, consistency, directness, risk of bias, formulation characteristics, tolerability, and durability after treatment withdrawal. Statistical significance alone was not used to determine treatment effectiveness. Mechanistic evidence was synthesized separately from clinical effectiveness. Hexylresorcinol and alpha-arbutin were mapped primarily to tyrosinase-dependent melanogenesis, whereas tranexamic acid was mapped to plasminogen–plasmin inhibition and associated inflammatory, prostaglandin, endothelin, and vascular pathways.

Mechanistic complementarity was defined as activity at different biological targets. Clinical synergy was considered demonstrated only when a factorial or multi-arm study included the relevant monotherapies, their combination, an appropriate control, and a formal interaction analysis. Improvement in a multicomponent formulation without corresponding monotherapy arms was not classified as evidence of synergy.

Certainty of Evidence

The certainty of evidence was evaluated for each intervention–comparator–outcome combination using the Grading of Recommendations Assessment, Development and Evaluation framework (Guyatt et al., 2008). Evidence was assessed for risk of bias, inconsistency, indirectness, imprecision, and publication bias and was categorized as high, moderate, low, or very low certainty. Evidence derived from general hyperpigmentation populations was downgraded for indirectness. Combination and delivery-assisted studies were also downgraded when the independent effect of the eligible ingredient could not be isolated. Mechanistic plausibility was not used to upgrade the certainty of clinical evidence.

Ethics

Ethics approval and informed consent were not required because this review analyzed previously published data and did not involve direct participant recruitment or identifiable individual-level information.

RESULT

Study Selection

The study-selection process is summarized in the PRISMA 2020 flow diagram (Figure 1). The database and trial-register searches identified 455 records, comprising 449 records from electronic databases and six records from trial registers. After the removal of 137 duplicates, 318 records underwent title and abstract screening, of which 281 were excluded. Thirty-seven reports were sought for retrieval, and two could not be retrieved. The remaining 35 full-text reports were assessed for eligibility, of which 23 were excluded because of an ineligible route or absence of a separately extractable topical arm ($n = 7$), ineligible population ($n = 4$), ineligible study design ($n = 5$), uninterpretable combination intervention ($n = 3$), insufficient data ($n = 2$), or duplicate or secondary publication ($n = 2$). Twelve studies met the eligibility criteria and were included in the qualitative synthesis. A quantitative meta-analysis was not performed because of substantial clinical and methodological heterogeneity.

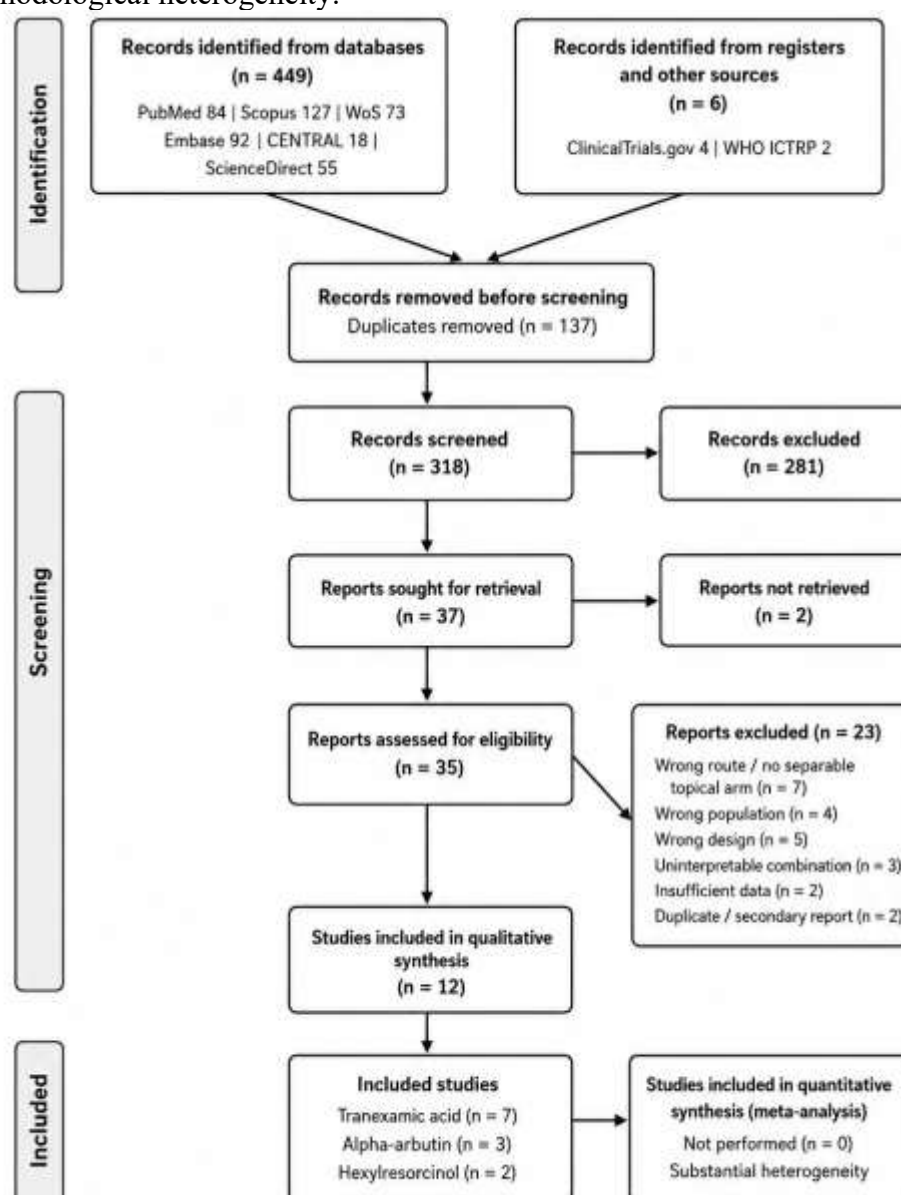


Figure 1. PRISMA 2020 flow diagram of the study identification, screening, eligibility, and inclusion process.

Of the 12 included studies, seven evaluated topical tranexamic acid, three assessed alpha-arbutin-containing interventions, and two investigated hexylresorcinol-containing formulations. Nine studies exclusively enrolled patients with clinically diagnosed melasma, one included a mixed

population of women with melasma or facial dark spots, and two evaluated general facial or body hyperpigmentation and were therefore classified as indirect evidence.

Characteristics of the Included Studies

The included studies were published between 2012 and 2025 and were conducted predominantly in Asian and Middle Eastern populations. Participants were mainly adult women, commonly with Fitzpatrick skin phototypes III–V. Sample sizes ranged from 20 participants in the alpha-arbutin nanoparticle study to 124 participants in the prospective alpha-arbutin combination study. Most interventions were administered for 8–12 weeks, whereas one prospective study used a 90-day treatment period. The evidence base included parallel-group randomized controlled trials, randomized split-face or split-body studies, prospective comparative studies, and one prospective single-arm intervention study. Comparators included vehicle formulations, hydroquinone at concentrations of 2–4%, triple-combination cream, conventional delivery systems, and placebo-assisted procedures.

The most frequently reported outcomes were the Melasma Area and Severity Index, modified Melasma Area and Severity Index, melanin index, colorimetric pigmentation measurements, physician-assessed improvement, standardized clinical photography, and patient satisfaction. Adverse events were reported in most studies, whereas quality of life, treatment adherence, and post-treatment recurrence were assessed less consistently. Interventions were classified as conventional topical formulations or enhanced-delivery interventions. Conventional formulations included creams, solutions, gels, and serums, whereas enhanced-delivery approaches included liposomes, chitosan nanoparticles, and iontophoresis. Findings from enhanced-delivery studies were interpreted as evidence for the complete intervention and were not generalized to conventional formulations containing the same nominal concentration.

Topical Tranexamic Acid

Seven studies evaluated topical tranexamic acid in patients with clinically diagnosed melasma. Concentrations ranged from approximately 3% to 5%, and treatment was generally administered for 8–12 weeks. Kanechorn Na Ayuthaya et al. (2012) conducted a double-blind randomized trial comparing 5% topical tranexamic acid with vehicle. Melasma severity improved during treatment, although the small sample and participant attrition reduced the precision of the findings. The study provided early evidence of clinical activity but did not demonstrate a clear advantage over vehicle.

Ebrahimi and Fatemi Naeini (2014) compared topical tranexamic-acid solution with a combination solution containing hydroquinone and dexamethasone. Both interventions reduced melasma severity, whereas local adverse reactions were less frequent with tranexamic acid. Interpretation was limited by incomplete reporting of randomization procedures, outcome variability, and formulation characteristics. Banihashemi et al. (2015) compared liposomal tranexamic acid with 4% hydroquinone. Both groups showed improvement in clinical pigmentation, and the liposomal formulation demonstrated favorable tolerability. Because the intervention used a penetration-enhancing carrier, the observed effect represented the combined influence of tranexamic acid and liposomal delivery. Atefi et al. (2017) randomized 60 women with melasma to receive either 5% topical tranexamic acid or 2% hydroquinone for 12 weeks. Significant reductions in MASI and melanin measurements occurred in both groups. No statistically significant between-group difference in effectiveness was identified, whereas satisfaction and tolerability favored tranexamic acid. The relatively low concentration of hydroquinone and modest sample size limited the comparative interpretation.

Janney et al. (2019) compared 5% tranexamic-acid solution with 3% hydroquinone cream in 100 participants over 12 weeks. Mean baseline MASI scores were 12.39 ± 3.34 in the tranexamic-acid group and 11.63 ± 3.72 in the hydroquinone group. MASI decreased by 27.0% and 26.7%,

respectively. Patient satisfaction favored tranexamic acid, while irritation occurred in three hydroquinone-treated participants and in none of the tranexamic-acid-treated participants. However, the study did not use a prespecified non-inferiority margin and therefore did not formally establish equivalence.

Yasnova et al. (2024) compared 3% tranexamic-acid cream with 4% hydroquinone cream in a double-blind randomized split-face trial involving patients with mixed-type melasma and skin of color. Both sides improved significantly during the eight-week intervention, with no statistically significant difference between treatments. Local tolerability favored tranexamic acid. The short treatment duration and limited follow-up prevented assessment of long-term effectiveness and recurrence.

Guo et al. (2024) evaluated tranexamic-acid essence administered with iontophoresis in a randomized, double-blind, placebo-controlled trial. Tranexamic acid combined with iontophoresis produced greater improvements in MASI and skin luminance than placebo iontophoresis. Because the intervention incorporated device-assisted delivery, the findings were interpreted as evidence for iontophoresis-assisted tranexamic acid rather than passive topical application alone. Overall, topical tranexamic acid consistently reduced short-term melasma severity. However, direct numerical pooling was inappropriate because of differences in concentration, vehicle, delivery enhancement, comparator strength, treatment duration, photoprotection, and outcome measurement.

Alpha-Arbutin-Containing Interventions

Three studies evaluated alpha-arbutin-containing interventions. Two exclusively enrolled patients with melasma, whereas one included women with either melasma or facial dark spots. None provided a placebo-controlled evaluation of alpha-arbutin monotherapy in a conventional vehicle. Tantanarigul et al. (2025) conducted an evaluator-blinded randomized split-face pilot trial comparing a formulation containing 5% alpha-arbutin and 2% kojic acid with hydroquinone-based triple-combination cream. Thirty participants were randomized, and 27 completed the 12-week intervention and four-week post-treatment follow-up. Both sides showed reductions in mMASI and melanin index. Triple-combination cream produced a faster physician-assessed response during active treatment, but erythema and stinging were more frequent. Greater post-treatment rebound was observed on the triple-combination side. Because kojic acid was included as a co-active ingredient, the independent contribution of alpha-arbutin could not be determined.

Hatem et al. (2022) evaluated alpha-arbutin-loaded functionalized chitosan nanoparticles in a prospective split-face study involving women with epidermal melasma. The nanoparticle hydrogel produced greater reductions in mMASI and epidermal melanin measurements than a conventional alpha-arbutin hydrogel. Ex vivo analysis also demonstrated increased epidermal deposition of alpha-arbutin. The small clinical sample limited the precision and generalizability of the findings. Gabhane et al. (2025) evaluated a 90-day regimen containing 10% trihydroxybenzoic acid glucoside and 2% alpha-arbutin combined with sunscreen in Indian women with melasma or facial dark spots. Improvements were reported in clinical pigmentation, photographic color difference, skin brightness, and skin-tone evenness. The intervention was generally well tolerated. However, the single-arm design, mixed population, sunscreen co-intervention, and additional depigmenting ingredient prevented attribution of the observed effect to alpha-arbutin alone. Overall, alpha-arbutin-containing interventions showed favorable short-term depigmenting activity and tolerability. However, all three studies used either a co-active ingredient or an enhanced-delivery system, limiting conclusions regarding alpha-arbutin monotherapy.

Hexylresorcinol-Containing Interventions

Two randomized studies evaluated topical hexylresorcinol-containing interventions. Neither exclusively recruited patients with clinically diagnosed melasma; therefore, both were classified as

indirect evidence. Won et al. (2014) investigated 4-hexyl-1,3-phenylenediol in experimental models and a randomized clinical study. Twelve weeks of treatment improved overall skin lightening, cheek-spot appearance, pigmentation size, and contrast between pigmented lesions and surrounding skin. Experimental findings also demonstrated inhibition of tyrosinase activity and expression without evidence of melanocyte cytotoxicity. Direct applicability to melasma was limited because participants were recruited for general hyperpigmentation. Wu et al. (2023) randomized 32 women to a double-blind split-body comparison of 1% hexylresorcinol and 2% hydroquinone applied twice daily for 12 weeks. Twenty-nine participants completed follow-up. Colorimetric and clinically assessed pigmentation improved significantly with both treatments at weeks 4 and 12, with no statistically significant between-treatment difference. No major adverse effects were reported. However, participants were selected for facial and hand pigmentation rather than clinically diagnosed melasma. The two studies supported the short-term depigmenting activity and tolerability of hexylresorcinol. Nevertheless, the evidence was insufficient to determine its effects on MASI or mMASI, melasma-related quality of life, or post-treatment recurrence.

Comparative Effectiveness

Topical tranexamic acid had the largest and most directly applicable evidence base. Concentrations of approximately 3–5% generally produced measurable reductions in MASI or mMASI over 8–12 weeks. Several studies found no statistically significant difference in effectiveness compared with hydroquinone, while tolerability and patient satisfaction frequently favored tranexamic acid. However, these trials were not designed to formally establish equivalence or non-inferiority. Alpha-arbutin-containing interventions also improved clinical and instrumental pigmentation outcomes, but their independent effects could not be separated from kojic acid, trihydroxybenzoic acid glucoside, sunscreen, or nanoparticle delivery. Hexylresorcinol improved general dyspigmentation, but the absence of melasma-specific trials prevented direct comparison with topical tranexamic acid or alpha-arbutin.

Safety and Tolerability

Short-term tolerability was generally favorable for all three ingredients. Topical tranexamic acid was associated primarily with transient erythema, dryness, burning, or irritation and was often better tolerated than hydroquinone. No thromboembolic events were reported in the included topical trials; however, the sample sizes and follow-up durations were insufficient to exclude uncommon systemic adverse events. Alpha-arbutin-containing interventions produced relatively few adverse reactions. In the randomized split-face trial, erythema and stinging were more frequent with triple-combination cream than with the alpha-arbutin–kojic acid formulation. Hexylresorcinol studies reported no major adverse reactions during 12 weeks of treatment. A quantitative comparison of adverse-event incidence was not performed because definitions, surveillance procedures, treatment durations, and reporting practices differed across studies.

Recurrence and Durability

Long-term durability was inadequately evaluated. Most studies ended after 8–12 weeks of active treatment and did not include a standardized treatment-free follow-up period. The alpha-arbutin–kojic acid trial included four weeks of post-treatment observation and reported greater pigment rebound on the triple-combination side. However, this follow-up period was insufficient to determine sustained disease control. No included hexylresorcinol study evaluated melasma recurrence, and recurrence data for conventional topical tranexamic acid were insufficient for a comparative conclusion.

Risk of Bias

The randomized trials generally raised some concerns rather than demonstrating uniformly low risk of bias. Common limitations included inadequately described allocation concealment, difficulty blinding visibly different formulations, incomplete reporting of prespecified analyses, participant

attrition, and short follow-up. Split-face and split-body designs reduced between-participant variability but required paired statistical analyses that were not always fully reported. The single-arm alpha-arbutin study was judged to have a high risk of confounding because improvement could have resulted from sunscreen use, the additional active ingredient, natural variation, regression to the mean, or observer expectancy. The hexylresorcinol trials used randomized designs but were affected by substantial indirectness because their populations were not limited to patients with melasma. Several formulation studies also involved industry funding, increasing the need for transparent reporting and independent replication.

Certainty of Evidence

Using the GRADE framework, the certainty of evidence for topical tranexamic acid versus hydroquinone in improving short-term MASI or mMASI was judged to be low because of concerns related to risk of bias, heterogeneity in formulations, and imprecision. The certainty of evidence for alpha-arbutin-containing interventions ranged from very low to low, mainly due to small sample sizes, the frequent use of co-active ingredients, the inclusion of non-randomized evidence, and the difficulty in isolating the independent effect of alpha-arbutin. Evidence for the melasma-specific effectiveness of hexylresorcinol was rated as very low because the available clinical evidence was largely indirect. The certainty of evidence regarding recurrence and long-term durability was also considered very low, as follow-up periods were generally short and recurrence was inconsistently defined across studies. In addition, the evidence was considered insufficient to support clinical synergy among the three agents because no factorial trial directly compared the relevant monotherapies, their combination, and a prespecified interaction effect.

DISCUSSION

Principal Findings

This systematic review identified substantial differences in the quantity, directness, and certainty of evidence supporting topical tranexamic acid, alpha-arbutin, and hexylresorcinol for melasma. Topical tranexamic acid had the most developed melasma-specific evidence, including randomized comparisons with vehicle and hydroquinone and studies using conventional and enhanced-delivery formulations. Alpha-arbutin was primarily evaluated in multicomponent products or specialized delivery systems, whereas hexylresorcinol was assessed mainly in participants with general facial or body dyspigmentation rather than clinically diagnosed melasma (Atefi et al., 2017; Hatem et al., 2022; Janney et al., 2019; Tantanarigul et al., 2025; Wu et al., 2023).

The evidence therefore supports a hierarchy based not only on the magnitude of pigmentation improvement but also on population directness, study design, intervention interpretability, risk of bias, and certainty of evidence. Topical tranexamic acid currently has the strongest clinical basis among the three agents. Alpha-arbutin remains promising, but its independent therapeutic contribution has not been adequately isolated. Hexylresorcinol demonstrates credible antimelanogenic activity, although its evidence for melasma remains substantially indirect (Boo, 2021; Saeedi et al., 2021; Won et al., 2014).

Interpretation of the Tranexamic Acid Evidence

Topical tranexamic acid produced relatively consistent short-term improvement across different clinical designs. Concentrations of approximately 3–5% administered for 8–12 weeks generally reduced MASI, mMASI, melanin index, or investigator-assessed pigmentation. Comparative studies also frequently reported fewer irritant reactions and greater patient satisfaction than hydroquinone-based regimens (Atefi et al., 2017; Janney et al., 2019; Yasnova et al., 2024). Janney et al. (2019) reported MASI reductions of 27.0% with 5% tranexamic-acid solution and 26.7% with 3% hydroquinone cream after 12 weeks. Although the numerical responses were similar, the result should not be interpreted as formal therapeutic equivalence because the study did not employ a prospectively defined non-inferiority or equivalence margin. A nonsignificant between-group

difference may reflect genuinely similar effects, inadequate statistical power, substantial variability, or a combination of these factors. The appropriate interpretation is therefore that no superiority was demonstrated rather than that equivalence was established.

Atefi et al. (2017) similarly reported significant improvement with both 5% topical tranexamic acid and 2% hydroquinone, with tolerability and satisfaction favoring tranexamic acid. However, the relatively low hydroquinone concentration may have influenced the comparison. Yasnova et al. (2024) found significant improvement with both 3% tranexamic-acid cream and 4% hydroquinone in a split-face trial, while local tolerability favored tranexamic acid. The eight-week duration, however, limited assessment of maximum response, maintenance, and recurrence. The clinical activity of tranexamic acid is pharmacologically plausible. Tranexamic acid inhibits plasminogen activation and may consequently reduce plasmin-mediated release of arachidonic acid, prostaglandins, and other melanocyte-stimulating mediators following ultraviolet exposure. It may also influence endothelin-1 signaling, inflammation, vascular activity, and keratinocyte–melanocyte interactions (Kim et al., 2016; Maeda, 2022; Maeda & Tomita, 2007). These mechanisms are consistent with current models of melasma as a disorder involving epidermal, vascular, inflammatory, and dermal components rather than isolated epidermal melanogenesis (Cassiano et al., 2022; Passeron & Picardo, 2018). Nevertheless, mechanistic plausibility cannot overcome limitations such as small samples, heterogeneous vehicles, incomplete blinding, inconsistent photoprotection, and short follow-up. Topical tranexamic acid may therefore be regarded as an evidence-supported non-hydroquinone alternative, but the certainty of evidence remains low.

Formulation and Delivery

The included studies demonstrate that topical tranexamic acid cannot be regarded as a single uniform intervention. Creams, aqueous solutions, liposomes, essences, and iontophoresis-assisted preparations differ in cutaneous penetration, local retention, stability, applied dose, and irritation potential. Because tranexamic acid is hydrophilic, passive diffusion through the stratum corneum may be limited, making delivery technology an important determinant of clinical performance (Banihashemi et al., 2015; Guo et al., 2024). Banihashemi et al. (2015) reported clinically relevant improvement with liposomal tranexamic acid compared with hydroquinone. However, this outcome represented the combined effects of tranexamic acid and liposomal delivery. Similarly, Guo et al. (2024) demonstrated improvement when tranexamic-acid essence was administered with iontophoresis, but the result cannot be generalized directly to passive application of a conventional serum or cream. Formulation heterogeneity also explains why meta-analysis was not clinically appropriate. Pooling studies with different concentrations, vehicles, co-interventions, devices, comparators, treatment durations, and outcome instruments could have produced a statistically precise but clinically misleading summary estimate. Under such conditions, structured narrative synthesis is preferable to indiscriminate statistical pooling (Campbell et al., 2020).

Interpretation of the Alpha-Arbutin Evidence

Alpha-arbutin has a strong mechanistic rationale but a less interpretable clinical evidence base. It inhibits tyrosinase-dependent melanin production, although its performance may depend on stereochemical identity, concentration, formulation pH, chemical stability, hydrolysis, and cutaneous delivery (Boo, 2021; Saeedi et al., 2021; Sugimoto et al., 2004). Tantanasrigul et al. (2025) found that a formulation containing 5% alpha-arbutin and 2% kojic acid improved melasma and produced fewer irritant reactions than triple-combination cream. The formulation also showed less short-term rebound after treatment discontinuation. However, kojic acid is itself an active tyrosinase inhibitor, preventing attribution of the observed effect exclusively to alpha-arbutin. Hatem et al. (2022) reported greater improvement with alpha-arbutin-loaded functionalized chitosan nanoparticles than with a conventional alpha-arbutin hydrogel. These findings support the importance of epidermal deposition and local retention but primarily demonstrate the value of the carrier system rather than the efficacy of alpha-arbutin against placebo or an active comparator in

an identical vehicle. The prospective regimen evaluated by Gabhane et al. (2025) also improved pigmentation outcomes. However, the formulation contained trihydroxybenzoic acid glucoside, alpha-arbutin, and sunscreen. The single-arm design and multiple co-interventions prevented separation of the treatment effect from photoprotection, the additional active ingredient, natural variation, or regression to the mean. Current evidence therefore supports alpha-arbutin-containing formulations as promising alternatives, particularly when local tolerability is prioritized. Nevertheless, its optimal concentration, independent efficacy, comparative effectiveness, and long-term durability remain uncertain.

Interpretation of the Hexylresorcinol Evidence

Hexylresorcinol demonstrated consistent short-term depigmenting activity in the two randomized studies. Won et al. (2014) reported improvement in skin lightening, cheek-spot appearance, pigmentation size, and contrast between pigmented lesions and surrounding skin. Experimental findings also indicated inhibition of tyrosinase activity and expression without evidence of melanocyte cytotoxicity. Wu et al. (2023) found significant improvement with both 1% hexylresorcinol and 2% hydroquinone over 12 weeks, without a statistically significant between-treatment difference or major adverse effects. These results support the clinical depigmenting potential of hexylresorcinol. However, both studies were limited by population indirectness. Participants were recruited for general facial, hand, or body pigmentation rather than clinically diagnosed melasma. General dyspigmentation cannot be assumed to have the same hormonal, inflammatory, vascular, epidermal, and dermal characteristics as melasma (Cassiano et al., 2022; Passeron & Picardo, 2018). Improvement in general pigment appearance therefore does not necessarily establish reductions in MASI, melasma-related quality-of-life burden, or disease recurrence. The absence of a statistically significant difference from hydroquinone should also not be interpreted as equivalence. The available studies did not use prespecified equivalence margins and were not sufficiently powered to exclude clinically important differences. Hexylresorcinol should therefore be described as promising rather than established for melasma.

Mechanistic Complementarity and Clinical Synergy

Hexylresorcinol, alpha-arbutin, and tranexamic acid act through partially different biological pathways. Hexylresorcinol and alpha-arbutin primarily affect tyrosinase-dependent melanogenesis, whereas tranexamic acid acts further upstream through plasminogen–plasmin inhibition and associated inflammatory, prostaglandin, endothelin, and vascular pathways (Boo, 2021; Maeda, 2022; Won et al., 2014). These differences provide a biologically plausible rationale for combination treatment. However, mechanistic complementarity does not establish clinical synergy. Synergy requires evidence that the effect of a combination exceeds a prespecified additive expectation, generally assessed through factorial or multi-arm trials containing the relevant monotherapies, their combination, an appropriate control, and a formal statistical interaction test. None of the included studies directly compared hexylresorcinol, alpha-arbutin, and tranexamic acid as individual treatments and as a three-agent combination. Improvements observed with multicomponent products may result from additive pharmacological activity, enhanced penetration, optimized vehicles, photoprotection, or improved adherence. Consequently, the current evidence supports mechanistic complementarity but does not demonstrate additive benefit or clinical synergy.

Safety and Durability

All three agents generally demonstrated favorable short-term local tolerability. Topical tranexamic acid was associated mainly with mild erythema, burning, dryness, or irritation and was often better tolerated than hydroquinone (Atefi et al., 2017; Janney et al., 2019; Yasnova et al., 2024). No thromboembolic events were reported, although the included studies were too small and too short to exclude uncommon systemic adverse events. Alpha-arbutin-containing formulations were also generally well tolerated. Irritation, erythema, and stinging occurred more frequently with triple-combination cream than with the alpha-arbutin–kojic acid formulation (Tantanasrigul et al., 2025).

However, alpha-arbutin safety depends on formulation stability, pH, storage conditions, and control of hydrolysis or degradation products (Scientific Committee on Consumer Safety, 2023). The hexylresorcinol studies reported no major adverse effects during approximately 12 weeks of treatment (Won et al., 2014; Wu et al., 2023). Nevertheless, long-term tolerability and sensitization risk remain inadequately evaluated. Durability was one of the weakest areas of evidence. Most studies ended after 8–12 weeks and lacked a standardized treatment-free follow-up phase. This limitation is clinically important because melasma is chronic and recurrent, and short-term pigment reduction does not necessarily indicate sustained disease control (Cassiano et al., 2022; Gan & Rodrigues, 2024). The four-week post-treatment assessment reported by Tantanarigul et al. (2025) suggested less rebound with the alpha-arbutin–kojic acid formulation than with triple-combination cream, but the interval was insufficient to establish long-term maintenance.

Clinical Implications

Topical tranexamic acid currently appears to be the most evidence-supported of the three reviewed non-hydroquinone agents. Concentrations of approximately 3–5% may represent an alternative for patients who cannot tolerate hydroquinone, provided that clinicians recognize the low certainty of evidence and the importance of formulation-specific differences. Current studies support short-term improvement but do not establish a universally optimal concentration, vehicle, or maintenance regimen. Alpha-arbutin-containing products may be considered promising alternatives or maintenance formulations, particularly when tolerability is prioritized. However, patients and clinicians should recognize that most evidence involves alpha-arbutin combined with another active ingredient or enhanced-delivery system. Hexylresorcinol may have value in general dyspigmentation, but its melasma-specific use remains supported mainly by indirect evidence. All three agents should be incorporated into comprehensive management that includes ultraviolet and visible-light photoprotection, identification of aggravating factors, adherence support, and monitoring for irritation and recurrence. Photoprotection should also be standardized in future clinical trials because it may independently influence treatment response and recurrence (Cassiano et al., 2022; Gan & Rodrigues, 2024).

Strengths and Limitations

A major strength of this review was the separation of direct melasma evidence from indirect evidence derived from general hyperpigmentation. It also distinguished conventional monotherapy from multicomponent formulations and separated passive topical application from carrier- or device-assisted delivery. This approach reduced the risk of attributing the effect of a complete intervention to a single active ingredient. The review was limited by small study samples, heterogeneous concentrations and vehicles, inconsistent photoprotection, short follow-up, limited representation of different skin phototypes, incomplete adverse-event reporting, and frequent use of co-active ingredients. Publication bias could not be meaningfully assessed because fewer than 10 sufficiently comparable studies were available for any intervention–comparator–outcome combination. Narrative synthesis was therefore required because quantitative pooling of clinically dissimilar interventions could have produced a misleading summary estimate (Campbell et al., 2020).

Future Research

Future research should prioritize adequately powered, multicenter randomized controlled trials of alpha-arbutin and hexylresorcinol monotherapy in patients with clinically diagnosed melasma. Studies should use identical vehicles, standardized photoprotection, blinded outcome assessment, and validated outcomes including mMASI, melanin index, standardized photography, MELASQoL, patient satisfaction, and recurrence. Tranexamic-acid trials should directly compare concentrations and delivery systems while maintaining otherwise identical formulation components. Comparisons with hydroquinone should use prospectively justified non-inferiority margins. Factorial trials are required to determine whether combinations of hexylresorcinol, alpha-arbutin, and tranexamic acid

are complementary, additive, or genuinely synergistic. Longer follow-up, representation across Fitzpatrick phototypes I–VI, inclusion of male participants, transparent funding disclosure, prospective trial registration, and publication of statistical-analysis plans would substantially improve the certainty and clinical applicability of future evidence.

CONCLUSION

Topical tranexamic acid currently has the strongest and most direct clinical evidence among the three reviewed agents for the management of melasma. Formulations containing approximately 3–5% tranexamic acid administered for 8–12 weeks generally reduced MASI or mMASI scores and produced short-term outcomes that were not statistically significantly different from hydroquinone in several small comparative trials. However, the certainty of this evidence remains low because of heterogeneous vehicles, delivery systems, comparator concentrations, limited sample sizes, and short follow-up periods. Alpha-arbutin-containing formulations showed promising improvements in pigmentation and tolerability, but the available evidence was largely derived from combinations with kojic acid or other depigmenting ingredients and from specialized delivery systems. Consequently, the independent clinical effect of alpha-arbutin has not yet been established. Hexylresorcinol demonstrated consistent depigmenting activity and favorable short-term safety in randomized studies of general facial or body dyspigmentation, but direct evidence in clinically diagnosed melasma remains insufficient.

The distinct molecular targets of hexylresorcinol, alpha-arbutin, and tranexamic acid support mechanistic complementarity; nevertheless, no eligible factorial trial demonstrated additive benefit or clinical synergy among these agents. Their combined use should therefore not be described as synergistic without direct interaction testing. Future studies should employ adequately powered randomized designs, identical vehicles, standardized ultraviolet and visible-light photoprotection, validated clinical and patient-reported outcomes, diverse skin phototypes, and long-term assessment of maintenance and recurrence. Overall, topical tranexamic acid may presently be considered the most evidence-supported non-hydroquinone option, whereas alpha-arbutin and hexylresorcinol remain promising but incompletely validated alternatives.

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