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Combination therapy for postinflammatory hyperpigmentation: A systematic review

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Abstract

Background: Post-inflammatory hyperpigmentation (PIH) poses a considerable dermatological concern, affecting individuals of various ethnic backgrounds, with a notably higher prevalence among those with darker skin tones. The intricate pathophysiology of PIH, which involves inflammatory mediators and melanogenic pathways, necessitates a multifaceted treatment approach to achieve the best possible clinical results.
Purpose: This systematic review evaluates the effectiveness, safety, and clinical outcomes of various combination therapies for managing post-inflammatory hyperpigmentation (PIH), with a focus on their synergistic effects and suitability for diverse skin types.
Method: A systematic review with article selection guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The systematic review process begins with the formulation of clinical questions relevant to the topic. Before this, the authors establish PICOS criteria, which stand for: P (problem, patient, or population), I (intervention, prognostic factor, or exposure), C (comparison or control), O (outcome), and S (study design). For this article, P: Individuals of any age and skin type diagnosed with post-inflammatory hyperpigmentation (PIH), I: Any combination therapy involving two or more active ingredients or treatment methods, C: Single therapy, alternative combination therapies, or placebo, O: Clinical improvement in PIH, patient satisfaction, adverse effects, and treatment duration, S: Randomized controlled trials. The article search was conducted systematically using the keywords: “post-inflammatory hyperpigmentation” AND “combination therapy” AND “hyperpigmentation treatment” AND “topical therapy” AND “skin pigmentation” AND “melanin” AND “tyrosinase inhibitors” AND “retinoids” AND “kojic acid” AND “hydroquinone” AND “tranexamic acid” AND “niacinamide” AND “Boolean operators”.
Results: The review of eight studies found that combination therapies were more effective than monotherapy for treating post-inflammatory hyperpigmentation (PIH). Dual treatments, such as glycolic acid cream with peeling and TCA with PRP, showed notable improvements. Combining chemical peels with topical agents was especially effective for stubborn cases. Success depended on proper patient selection, personalized plans, and timing. Overall, targeting multiple pigmentation pathways improved outcomes and was safe, particularly for darker skin types (Fitzpatrick IV–VI).
Conclusion: Combination therapy is the most effective approach for treating PIH, as it utilizes synergistic treatment methods tailored to individual patient factors like skin type and PIH severity.

Keywords: Dermatology Treatment; Hyperpigmentation; Laser Therapy; Topical Agents.

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INTRODUCTION

Post-inflammatory hyperpigmentation (PIH) is a widespread and challenging dermatological condition that affects individuals from diverse ethnic backgrounds, with a significantly higher prevalence among those with darker skin tones. Characterized by the abnormal darkening of the skin following inflammation or injury, PIH has become a major concern in dermatology, impacting both patients' quality of life and psychological well-being. The growing awareness of PIH's complexity and its profound psychosocial effects has led to advancements in treatment strategies, with combination therapy emerging as a highly effective approach for optimal management (Ren, & Zhao, 2022).

The development of PIH involves a complex interaction between inflammatory mediators and melanogenic pathways, resulting in excessive melanin production and uneven distribution within the epidermis and dermis. When the skin undergoes inflammation due to conditions such as acne, eczema, or physical trauma, it triggers a series of inflammatory responses that stimulate melanocytes to increase melanin synthesis. This process is especially pronounced in individuals with Fitzpatrick skin types IV-VI, where melanocytes exhibit heightened sensitivity to inflammatory stimuli. A deeper understanding of these mechanisms has become essential in designing effective treatments that target multiple aspects of the pigmentation process (Sowash, & Alster, 2023).

Traditional monotherapy approaches, although somewhat beneficial, often yield suboptimal results and require prolonged treatment durations, leading to patient dissatisfaction and reduced adherence. These limitations have prompted a shift towards combination therapy, which simultaneously targets multiple pathways involved in PIH development. Recent clinical research indicates that combining different therapeutic agents produces synergistic effects, accelerating the resolution of PIH while reducing the likelihood of adverse effects (Tan, Kim, Jo, Nabieva, Kirshen, & Ortiz, 2022).

The effectiveness of combination therapy lies in its ability to address various aspects of PIH pathophysiology at once. While some treatments focus on inhibiting tyrosinase activity and reducing melanin synthesis, others enhance melanin dispersion, promote epidermal turnover, or exert anti-inflammatory properties. For example, combining topical retinoids with tyrosinase inhibitors has demonstrated significant efficacy in clinical trials. This dual approach not only suppresses melanin production but also enhances cellular turnover and minimizes inflammation, leading to more comprehensive treatment outcomes (Roggenkamp, Dlova, Mann, Batzer, Riedel, Kausch, & Kolbe, 2021).

Multiple combination regimens have been explored, including hydroquinone with retinoids, kojic acid with glycolic acid, and newer formulations incorporating niacinamide and tranexamic acid. A multicenter study conducted across various Asian countries found that patients treated with a triple combination of hydroquinone, tretinoin, and a mild corticosteroid achieved faster and more significant improvements compared to those receiving monotherapy. Furthermore, the combination therapy group experienced fewer side effects, highlighting its superior safety profile when used appropriately (Lupon, Laloze, Chaput, Girard, Cetrulo, Lantieri, & Lellouch, 2022).

Recent advancements in formulation and delivery technologies have further transformed combination therapy for PIH. Innovations such as liposomes, nanoparticles, and microemulsions have improved the stability and penetration of active ingredients, enhancing treatment efficacy. These novel delivery systems allow for the development of more sophisticated combination products that ensure the stability of multiple active compounds while optimizing their absorption into target tissues. Both clinical trials and real-world applications have demonstrated the effectiveness of these advancements, particularly in managing resistant cases of PIH (Kashetsky, Feschuk, & Pratt, 2024).

Despite the promising results of combination therapy, its success depends on careful consideration of patient-specific factors such as skin type, PIH severity, and prior treatment history. Selecting the most suitable treatment combinations and protocols is essential to maximize effectiveness while minimizing potential side effects. Additionally, educating patients on sun protection and appropriate skincare routines remains crucial, as UV exposure can exacerbate PIH and undermine therapeutic

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progress (Maghfour, Olayinka, Hamzavi, & Mohammad, 2022).

Recent studies have emphasized the crucial role of addressing inflammation in post-inflammatory hyperpigmentation (PIH) through combination therapy. Integrating anti-inflammatory agents into treatment regimens has been shown to effectively reduce PIH recurrence and accelerate the fading of existing hyperpigmentation. Research indicates that early intervention with combination therapies that include anti-inflammatory components can significantly lower the risk of PIH developing after inflammatory skin conditions or dermatological procedures (Mathe, Balogun, & Yoo, 2021).

Looking forward, advancements in PIH treatment continue to emerge with the introduction of new therapeutic agents and combination strategies. Ongoing research into specific inflammatory mediators and melanogenic pathways presents promising opportunities for future targeted interventions. Additionally, the integration of artificial intelligence and machine learning in analyzing treatment responses may soon enable more precise and personalized combination therapy protocols (Bhattacharya, Dsouza, & Dhaka, 2024).

RESEARCH METHOD

A systematic review with article selection guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The systematic review process begins with the formulation of clinical questions relevant to the topic. Before this, the authors establish PICOS criteria, which stand for: P (problem, patient, or population), I (intervention, prognostic factor, or exposure), C (comparison or control), O (outcome), and S (study design). For this article, P: Individuals of any age and skin type diagnosed with post-inflammatory hyperpigmentation (PIH), I: Any combination therapy involving two or more active ingredients or treatment methods, C: Single therapy, alternative combination therapies, or placebo, O: Clinical improvement in PIH, patient satisfaction, adverse effects, and treatment duration, S: Randomized controlled trials.

The article search was conducted systematically using the keywords: “post-inflammatory hyperpigmentation” AND “combination therapy” AND “hyperpigmentation treatment” AND “topical therapy” AND “skin pigmentation” AND “melanin” AND “tyrosinase inhibitors” AND “retinoids” AND “kojic acid” AND “hydroquinone” AND “tranexamic acid” AND “niacinamide” AND “Boolean operators”.

The inclusion criteria inquired randomized controlled trials, prospective and retrospective cohort studies, case control studies, and systematic reviews, only studies published in English and article between 2020 – 2025. The exclusion criteria included case reports or small case series with fewer than 10 participants, animal or in vitro studies, conference abstracts without full-text availability, studies focused exclusively on other forms of hyperpigmentation (e.g., melasma, solar lentigines).

The initial search resulted in 72 articles from Pubmed, 41 from Scopus, 56 from Web of Science, 78 from EMBASE and 62 from Cochrane library. After screening and filtering based on the predefined criteria, 8 articles met the inclusion criteria and were selected for further analysist.

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RESEARCH RESULTS

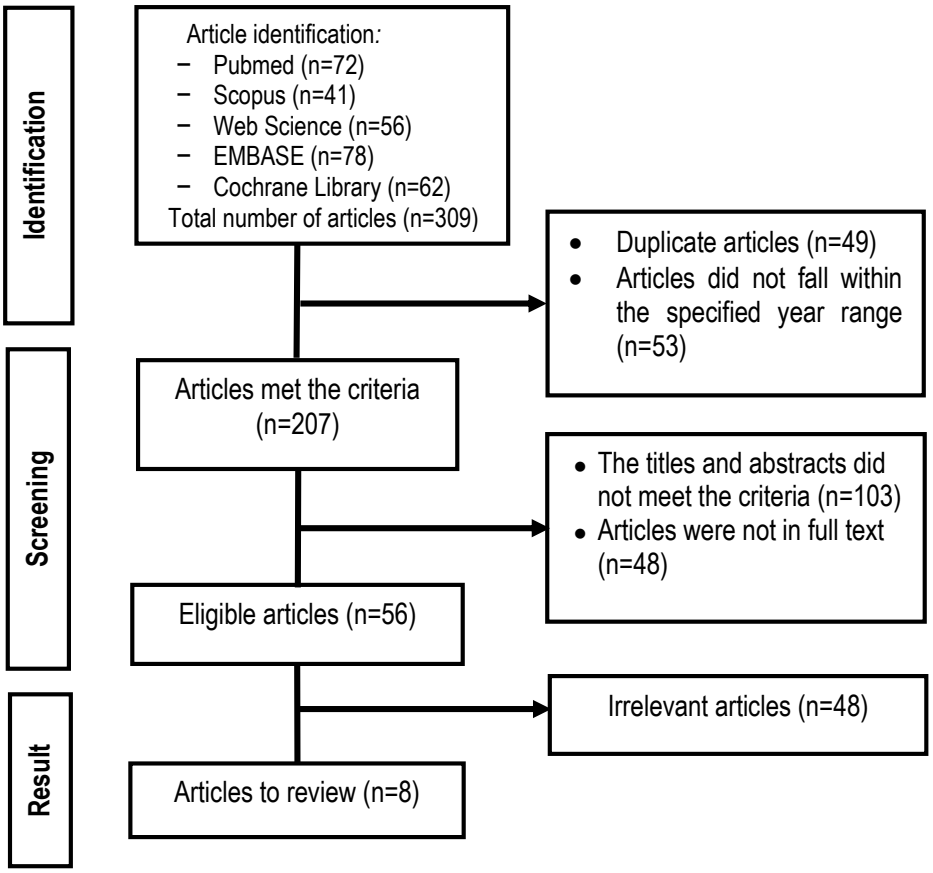


Figure 1. PRISMA Flow Diagram

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Table Main Characteristics of the Included Studies

(Author, Year) (Country)	Purpose	Method	Results
(Murlistyarini et al., 2022) (Indonesia)	Evaluate the efficacy of combined glycolic acid cream and peeling in axillary post-inflammatory hyperpigmentation (PIH)	The lesion was photographed and assessed using Von Luschan's Chromatic Scale by 3 independent assessors. Therapies that have been given were 8% glycollic acid (GA) cream every night and peeling 15% GA 2 times with an interval of 4 weeks. The assessment was done at zero weeks, third week, and eighth week. After 8 weeks there was a decrease in Von Luschan's Chromatic Scale score. The 15% GA peeling is included in superficial chemical peels. One indication of superficial chemical peels is hyperpigmentation of the skin. In axillary hyperpigmentation, superficial chemical peels such as 15% GA can be used and for more optimal results it added daily home care with 8% GA cream In both patients there was a clinical improvement after therapy	GA 8% cream combined with GA 15% chemical skin peeling has been shown to reduce axillary skin hyperpigmentation.
(Tazakka et al., 2023) (Indonesia)	Assess the efficacy and safety of lactic acid and phytic acid chemical peels for melasma	Dermatological examination on the malar showed multiple hyperpigmented macules and patches with Fitzpatrick's skin type IV. On Wood's lamp examination, the first patient was diagnosed with epidermal type melasma and the second patient with mixed type melasma. Both patients were given 0.05% tretinoin cream every night, SPF 45 sunscreen twice a day, and chemical peeling combination of lactic acid (LA) and phytic acid (PA) was performed four times every four weeks. There were no side effects such as burning, skin redness, or pain. Observation showed improvement in epidermal lesions. The superficial penetration of LA and PA remarkably reduced superficial lesions in both patients.	Two melasma patients with Fitzpatrick's skin type IV who received combined LA and PA chemical surgery experienced improvement in epidermal lesions and MASI scores. The safety and comfort of LA and PA combination chemical surgery therapy in both patients were good. Thus, the use of a combination of LA and PA is an interesting new combination for further research and can be given as an alternative adjuvant therapy in melasma cases with Fitzpatrick's skin type IV.

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(Author, Year) (Country)	Purpose	Method	Results
(Lubis et al., 2024) (Indonesia)	Review treatment options for intertriginous hyperpigmentation, including PIH	Prevention can be done by eliminating the possibility of hyperpigmentation. Topical treatments include hydroquinone (alone or in combination with other agents), desonide, retinoids, azelaic acid, kojic acid, arbutin, and niacinamide. Chemical peels can use glycollic acid, salicylic acid, trichloroacetic acid (TCA), lactic acid, tretinoin, and resorcinol.	Laser therapy is effective for hyperpigmentation by showing clinical improvement that lasts longer
(Suyanto et al., 2023) (Indonesia)	Explore the effectiveness of laser and intense pulsed light (IPL) in treating hyperpigmentation	Before starting the laser procedure, the doctor must perform a physical check and document the patient's medical history to identify possible contraindications or precautions to minimize side effects. Photographs before each laser procedure are mandatory to show the results. It is also important that patients are informed about side effects, realistic expectations of each procedure, and wound care after the procedure. All such information must be in writing.	IPL has also been shown to be effective for superficial hyperpigmented lesions with minimal side effects, but with a larger number of sessions due to its broad wavelength spectrum.
(Sunur et al., 2023 (Indonesia)	Discuss the challenges of treating ochronosis caused by long-term hydroquinone use	One method of OE combination therapy is topical therapy and intense pulsed light (IPL). Topical methods are used to remove epidermal pigment and help the therapy penetrate the dermis to be more effective. Topical therapies include non-hydroquinone depigmentation agents such as kojic acid, azaleic acid, and retinoic acid. Intense pulsed light is a filtered nonlaser device that uses a flashlamp to emit polychromatic, broad-spectrum, and divergent light. The mechanism of action of IPL is selective photothermolysis. The thermal radiation of IPL causes localized damage to the pigment targets of the epidermis and dermis so that IPL can be used to treat pigmentation lesions.	The management of exogenous ochronosis (OE) remains a challenge in dermatology. The main therapeutic outcome of OE is to discontinue the use of the pathogenic agent. In general, it is important to stay out of the sun and use photoprotection. Further research is needed to determine the effectiveness of topical therapy, laser and non-laser procedures on OE.

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(Author, Year) (Country)	Purpose	Method	Results
(Aliwardani et al., 2023) (Indonesia)	Evaluate the effectiveness of various treatments for striae, including PIH-associated changes	Treatment modalities for striae vary in terms of type and success rate. They include topical, physical, light/laser, and platelet-rich plasma (PRP) therapies.	Striae therapy is performed to treat aesthetic concerns and the risk of secondary infection in cases of severe striae. Treatment modalities for striae include topical, physical, light/laser and PRP therapy. Topical therapy in the form of topical retinoid 0.05% and chemical peeling TCA 35%; both single and combination gave significant clinical improvement results.
(Suwarsa et al., 2023) (Indonesia)	Assess the immune response to purified protein derivative (PPD) therapy in HPV-induced lesions	This research is one group pre- and post-test design based on an experimental analytic study. The samples were 14 serums of AGWs patients before and after receiving PPD therapy. Serum IL-12 levels meassured by enzyme linked immunosorbent assay.	Results showed serum IL-12 levels before receiving therapy was 45.73±53.186 pg/ml. After receiving PPD therapy, serum IL-12 levels increased by an average of 45.9 pg/ml, became 91.68±79.321 pg/ml (p=0,158). As conclusion, level of IL-12 in the serum of AGWs patients does not increase after receiving PPD therapy.
(Murlistyarini et al., 2023) (Indonesia)	Evaluate the combination of trichloroacetic acid (TCA) peeling and platelet-rich plasma (PRP) for treating periorbital hyperpigmentation	Patients were given 10% TCA peeling combination therapy with PRP atologus injection given for 3 times in an interval of 2 weeks.	Post-action evaluation showed improvement from grade 2 down to grade 1. Assessment of therapeutic improvement assessed by 2 investigators found an improvement of 75% and 80% after 3 procedure sessions. The patient rated very satisfied with a score of 3 for this combination therapy of 10% TCA and PRP injection, which in this case was considered effective in treating periorbital hyperpigmentation.

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DISCUSSION

Post-inflammatory hyperpigmentation (PIH) remains a significant challenge in dermatology, often requiring a multi-modal treatment approach for optimal results. Recent research has highlighted that combination therapies are generally more effective than monotherapies in managing this persistent condition. A review of current literature provides key insights into various combination approaches used for PIH treatment (Kang, Choi, Lee, Kim, Lew, & Kwon, 2024).

Chemical peeling agents have become a cornerstone in the management of post-inflammatory hyperpigmentation (PIH). The efficacy of glycolic acid in varying concentration specifically an 8% topical cream combined with a 15% chemical peel for treating axillary hyperpigmentation. Over an eight-week treatment period, significant improvement was documented using the Von Luschan's Chromatic Scale, indicating a measurable reduction in pigmentation intensity. These results support the notion that employing glycolic acid in different concentrations allows for targeted action across multiple layers of the skin affected by PIH. This finding reinforces the broader clinical understanding that a layered and multimodal treatment approach enhances therapeutic outcomes in hyperpigmentation management (Callender, Baldwin, Cook, Alexis, Stein, & Guenin, 2022).

The integration of platelet-rich plasma (PRP) with conventional chemical peeling agents represents an emerging and promising trend in the treatment of post-inflammatory hyperpigmentation (PIH). One notable example is the combination of a 10% trichloroacetic acid (TCA) peel with PRP for managing periorbital hyperpigmentation. After three treatment sessions administered at two-week intervals, significant clinical improvements were observed, underscoring the potential synergistic effects of combining chemical exfoliation with the regenerative properties of PRP. Several studies have reviewed various therapeutic modalities and consistently identified PRP as a valuable treatment option in dermatology, primarily due to its capacity to enhance tissue regeneration and accelerate healing, making it particularly effective when integrated into combination therapy protocols for hyperpigmentation (Markiewicz, Karaman, Mammone, & Idowu, 2022).

Chemical combination therapies have demonstrated notable efficacy in addressing complex cases of hyperpigmentation. For instance, the combination of lactic acid (LA) and phytic acid (PA) has proven effective in treating melasma among patients with Fitzpatrick Skin Type IV. A study reported significant clinical improvements without adverse effects over the course of four monthly treatment sessions, emphasizing both the safety and effectiveness of this regimen particularly crucial for darker skin types, where maintaining a balance between efficacy and the risk of post-treatment pigmentation is essential. The necessity of integrating multiple treatment modalities pharmacological, non-pharmacological, and procedural is increasingly recognized as key to managing resistant hyperpigmentation. This highlights the critical importance of tailoring therapeutic strategies based on the type, severity, and individual patient characteristics to optimize outcome (Wu, Wang, Wu, Cen, Xi, Shang, & Lin, 2022).

A comprehensive framework for managing hyperpigmentation in flexural areas highlights the superiority of combination therapy over monotherapy. This review emphasizes a holistic approach that integrates preventive measures, topical agents (such as hydroquinone, retinoids, azelaic acid, and arbutin), chemical peels (including glycolic acid, TCA, and tretinoin), and laser therapy. Such a multimodal strategy is in line with the current clinical consensus that addressing multiple pathways involved in the pigmentation process results in more effective and sustained therapeutic outcomes (Nayak, Ansari, Salve, & Patil, 2020).

Laser therapy has been extensively discussed as an integral component of combination treatment protocols for post-inflammatory hyperpigmentation (PIH). The significance of selecting appropriate wavelengths in laser and intense pulsed light (IPL) treatments lies in their ability to effectively target both superficial and dermal layers of hyperpigmentation. The study emphasized that careful selection of treatment parameters such as wavelength, energy level, and pulse duration is essential to maximize therapeutic efficacy while minimizing the risk of adverse effects. This is particularly important when laser therapy is used in conjunction with other modalities, as proper calibration ensures both safety

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and enhanced clinical outcomes, especially in individuals with darker skin tones (Puaratanaarunkon, & Asawanonda, 2022).

The immunological effects of purified protein derivative (PPD) therapy offer valuable insights into the underlying mechanisms of skin inflammation. A deeper understanding of these mechanisms is essential for the development of targeted combination therapies that effectively address both the inflammatory and pigmentary components of post-inflammatory hyperpigmentation (PIH) (Bae, Rettig, Weiss, Bernstein, & Geronemus, 2020).

Management of post-inflammatory hyperpigmentation (PIH) through combination therapy places emphasis on the importance of a personalized approach. The selection of combination therapy needs to be customized according to the patient's individual characteristics, such as skin type, severity of PIH, and location of hyperpigmentation lesions. This principle is important to optimize treatment outcomes and minimize the risk of side effects, especially in individuals with dark skin who are more prone to post-treatment hyperpigmentation (Madnani, Deo, Dalal, Benjamin, Murthy, Hegde, & Shetty, 2024).

Safety is also a major consideration, especially in the use of aggressive therapies in highly pigmented skin. Scheduling and setting intervals between procedures in combination therapy must be done carefully so that maximum results are achieved without triggering additional side effects. A holistic treatment strategy includes prevention, active treatment and maintenance therapy to maintain long-term results. Recent studies have shown that combination therapy, which combines various modalities synergistically, is capable of delivering superior results compared to single therapy. As the understanding of the pathophysiology of PIH grows, a “one-size-fits-all” approach becomes irrelevant. The success of combination therapy is that it is able to target multiple pigmentation pathways while allowing for individualized tailoring of treatment plans (Mar, Khalid, Maazi, Ahmed, Wang, & Khosravi, 2024).

CONCLUSION

Combination therapy is now considered the gold standard in managing post-inflammatory hyperpigmentation (PIH), as it provides better clinical outcomes than monotherapy. By combining treatments such as chemical peels, platelet-rich plasma (PRP), topical agents, and lasers, this approach effectively targets multiple pigmentation pathways, especially in resistant or darker skin types.

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