

COMPARATIVE STUDY OF 1% TURMERIC, 1% KOJIC ACID, 5% VITAMIN C COMBINED CREAM VS KLIGMAN'S FORMULA CREAM (4% HYDROQUINONE, 0.05% TRETINOIN, 0.01% FLUOCINOLONE ACETONIDE) FOR POST-ACNE HYPERPIGMENTATION IN THAI PATIENTS: A SPLIT-FACE CLINICAL TRIAL

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ABSTRACT

Acne-induced post-inflammatory hyperpigmentation (PIH) significantly impacts the quality of life in patients with darker skin phototypes (Fitzpatrick IV–VI). While Kligman's formula (4% hydroquinone, 0.05% tretinoin, 0.01% fluocinolone acetonide) remains the gold standard, its irritating potential can limit long-term use. This prospective, randomized, double-blinded, split-face trial evaluated the clinical efficacy, safety, and tolerability of a novel combination cream containing (1% turmeric, 1% kojic acid, and 5% vitamin C) versus Kligman's cream for the treatment of acne-induced hyperpigmentation in 18 Thai patients (Fitzpatrick skin types III–VI) over 12 weeks. Outcomes were assessed using the Post-Acne Hyperpigmentation Index (PAHPI), Mexameter® MX 18 melanin index (MI), patient satisfaction scores (quartile grading scale), and side-effect monitoring at weeks 0, 4, 8, and 12. Both treatments significantly reduced PAHPI scores ($p < 0.001$). At week 12, Kligman's cream demonstrated greater overall clinical efficacy (PAHPI reduction of 26.40% vs. 18.62%). However, in Week 4, the intervention cream achieved significantly greater early melanin suppression, indicated by a larger reduction in MI (97.32 vs. 39.90 reduction, $p = 0.021$), even though Kligman's cream maintained a higher overall reduction in PAHPI. Notably, the interventional cream showed an exceptional safety profile with zero adverse events, whereas Kligman's cream caused transient peeling (72.2%), burning, and erythema. These findings suggest that the novel combination cream is a safe, effective alternative for PIH, offering an advantage in rapid melanin reduction and superior tolerability for long-term maintenance.

Keywords: Acne-induced Post-Inflammatory Hyperpigmentation, Kojic Acid, Turmeric, Vitamin C, Kligman's Formula

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INTRODUCTION

Acne vulgaris affects approximately 9% of the global population and is a leading cause of post-inflammatory hyperpigmentation (PIH), occurring in 45.5%–87.2% of acne patients with darker skin tones (Fitzpatrick IV–VI)(Falder et al., 1996; Tan & Bhate, 2015). PIH significantly impairs quality of life and represents a primary reason patients seek dermatological care(Archambault et al., 1995)The condition is driven by epidermal inflammatory responses and pigmentary incontinence, which collectively stimulate excessive melanin production and deposition (Arora et al., 2012).

While Kligman's triple therapy — a combination of 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide — remains the gold standard for PIH management, its clinical use is often limited by adverse effects, including erythema, peeling, and paradoxical irritant-induced PIH (Davis & Callender, 2010). These risks are particularly pronounced in individuals with darker phototypes who are already more susceptible to hyperpigmentation (Thomas et al., 2021). Consequently, there is a growing demand for safer and effective bioactive alternatives. Kojic acid, vitamin C (ascorbic acid), and turmeric (curcumin) have emerged as promising candidates, offering a multimodal approach through tyrosinase inhibition, oxidative stress reduction, and suppression of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) (Bae et al., 2020; Katz et al., 2009; Oram & Akkaya, 2014).

Although these natural agents individually demonstrate lower potency than hydroquinone, their combination may provide synergistic depigmentation with superior tolerability (Callender et al., 2011; Katz et al., 2009). This split-face, randomized, double-blind clinical trial evaluates the efficacy and safety of a novel combination cream (1% turmeric, 1% kojic acid, 5% vitamin C) versus Kligman's formula in Thai patients with acne-induced hyperpigmentation week period.

LITERATURE REVIEWS

Melanogenesis and PIH Pathophysiology

Melanin is synthesized in melanosomes within melanocytes via tyrosinase-catalyzed conversion of L-tyrosine to L-DOPA and subsequently to eumelanin or pheomelanin(Oram & Akkaya, 2014). In PIH, acne-induced inflammation triggers keratinocyte release of cytokines, endothelins, and growth factors that stimulate melanocyte hyperactivation. UV radiation further compounds this by inducing paracrine melanocyte stimulation through bFGF, stem cell factor, and nitric oxide (Dorai et al., 2001). The inflammatory signaling between keratinocytes, fibroblasts, and melanocytes drives excess melanogenesis and abnormal melanosomal transfer to keratinocytes (Archambault et al., 1995; Arora et al., 2012).

Kligman's Formula

The triple therapy cream comprising hydroquinone, tretinoin, and a topical corticosteroid is the most widely studied depigmenting combination. Hydroquinone inhibits tyrosinase and melanin biosynthesis; tretinoin promotes epidermal turnover and enhances hydroquinone penetration to basal melanocytes; the corticosteroid mitigates irritation(Davis & Callender, 2010; Oram & Akkaya, 2014). Clinical data show 20–40% efficacy in darker skin phototypes, though tolerability remains a persistent concern due to erythema, peeling, and potential long-term toxicity from prolonged hydroquinone use (Callender et al., 2011; Thomas et al., 2021).

Natural Depigmenting Agents

Kojic acid (1–4%) competitively inhibits tyrosinase via copper chelation at the active site and is used in cosmeceutical formulations for PIH and melasma (Hollinger et al., 2018). Comparative studies show it matches 4% hydroquinone when combined with emblica extract and glycolic acid (Katz et al., 2009). L-ascorbic acid (vitamin C) is the predominant skin antioxidant, reducing oxidized dopaquinone and competitively inhibiting copper-bound tyrosinase (Oram & Akkaya, 2014). Its instability in aqueous environments limits bioavailability, but combinations with other depigmenting agents have demonstrated efficacy for solar lentigines and UV-induced pigmentation (Callender et al., 2011). Curcumin, the primary bioactive in *Curcuma longa*, inhibits

tyrosinase and modulates post-inflammatory cytokine signaling (TNF- α , IL-1 β , IL-6), with evidence from in vitro studies demonstrating apoptosis induction in melanoma cells and clinical RCT data showing reduction in facial hyperpigmentation and fine lines (Bae et al., 2020; Swanson et al., 2010).

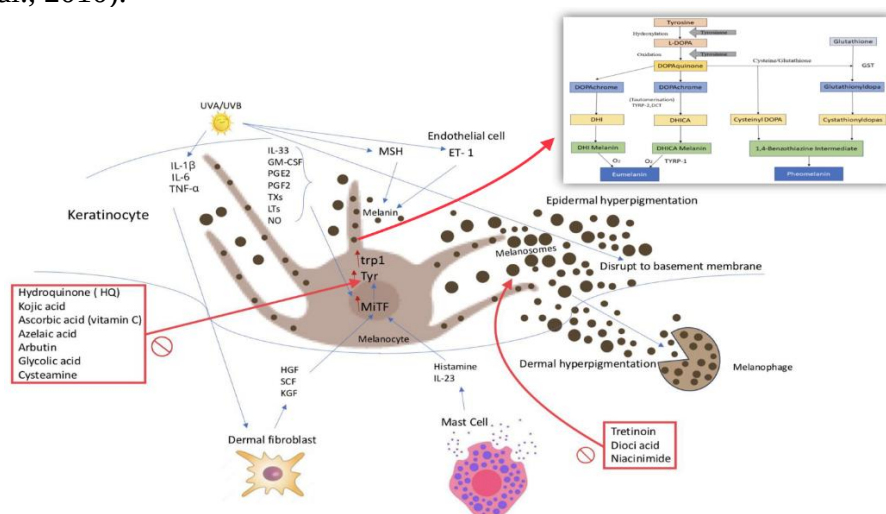


Figure 1: The process of Melanogenesis from UV radiation up-to formation of melanin. (Nandraj et al.,2024)

RESEARCH METHODOLOGY

This prospective, randomized, double-blinded, intra-individual split-face comparative experimental study enrolled 18 Thai males and females aged 18–40 years with Fitzpatrick skin types III–VI and a diagnosis of acne-induced hyperpigmentation (PAHPI score 6–22, with no active inflammatory acne lesions). The study was conducted at Mae Fah Luang University Hospital, Bangkok, Thailand, in compliance with Good Clinical Practice (GCP) guidelines and ICH standards.

Using a Microsoft Excel-generated randomization sequence, the right or left hemiface of each participant was randomly assigned to receive either the intervention cream (1% turmeric, 1% kojic acid, 5% vitamin C) or Kligman's cream (4% hydroquinone, 0.05% tretinoin, 0.01% fluocinolone acetonide). Both creams were applied once daily in the evening, approximately 0.5 g (one fingertip unit), to hyperpigmented areas only, 30 minutes before bedtime. All participants applied SPF 50 PA+++ broad-spectrum sunscreen gel daily to the entire face and were instructed to avoid other depigmenting treatments.

Treatment was administered for 12 weeks (weeks 0, 4, 8) with a final assessment at week 12. The primary outcome was the change in PAHPI score from baseline. Secondary outcomes included the melanin index (Mexameter® MX 18), patient satisfaction (quartile grading scale, 0–4), and adverse event monitoring. PAHPI assessment at follow-up visits was performed by two independent blinded physicians. Statistical analysis used repeated measures ANOVA for continuous outcomes and the Wilcoxon Signed-Rank Test for ordinal satisfaction data (significance $p < 0.05$, SPSS v26.0).

RESEARCH RESULTS

Participant Demographics

The study enrolled 22 Thai participants; 4 participants were lost to follow-up after the baseline assessment. A complete-case analysis (CCA) was performed on the 18 participants who completed the 12-week study and were included in all demographic and outcome analyses. (11 females, 7 males; mean age 30.7 ± 4.7 years; range 23–39 years). All participants were indoor workers, minimizing UV exposure variability. Fitzpatrick skin types were distributed as follows: Type III (n=10), Type IV (n=5), Type V (n=2), and Type VI (n=1). Acne history was mild in 7, moderate

in 10, and severe in 1 participant. Duration of hyperpigmentation: <3 months (n=5), 3–6 months (n=3), 6–12 months (n=4), and >12 months (n=6).

Table 1 Demographic Data (n=18)

Variables	Category	n/value
Age (Mean ± SD)		30.7 ± 4.7
Gender		
	Female	11
	Male	7
Fitzpatrick Type		
	III	10
	IV	5
	V	2
	VI	1
Acne History		
	Mild	7
	Moderate	10
	Severe	1
Duration of Hyperpigmentation		
	<3 months	5
	3-6 months	3
	6-12 months	4
	> 12 months	6
Previous treatment		
	Topical treatment	15
	Combination (Oral & Topical)	3

Note: SD=Standard Deviation; n= Number of participants. N= 18 Total participants

Primary Outcome: PAHPI Score

Both treatment groups demonstrated progressive, statistically significant reductions in PAHPI scores throughout the study ($p < 0.001$ within groups). Kligman's cream achieved a significantly greater overall reduction at Week 4 ($p = 0.013$) and Week 12 ($p < 0.001$), with a 26.40% decrease vs. 18.62% for the intervention cream. Baseline scores were comparable between groups ($p = 1.000$).

Table 2 PAHPI Score — Multiple Comparison with-in group (n=18)

Week	Intervention Cream (Mean±SD)	Degree of reduction from Baseline	Kligman's Cream (Mean±SD)	Degree of reduction from Baseline	p-value
0	10.15 ± 2.50	-	10.57± 2.13	-	1.000
4	9.35 ± 2.21	0.80(7.9%) ↓	9.67 ± 2.12	0.90(8.6%) ↓	0.013*
8	9.02 ± 1.73	1.13 (11.1%) ↓	8.18 ± 1.88	2.39(22.6%) ↓	1.000
12	8.26 ± 1.81	1.89(18.62%) ↓	7.78 ± 1.77	2.79(26.4%) ↓	<0.001*

Note: * Significant at $p < 0.05$. Bonferroni adjustment applied

Secondary Outcomes

Melanin Index (Mexameter® MX 18)

Both groups demonstrated statistically significant within-group improvements in melanin index over time ($p < 0.001$). The intervention cream produced significantly greater early melanin

suppression at Week 4 (mean reduction: 97.32 vs. 39.90 units; $p = 0.021$), suggesting a more rapid initial therapeutic response. At Weeks 8 and 12, Kligman's cream demonstrated numerically greater reductions, though differences did not reach statistical significance ($p = 0.066$ and $p = 0.061$, respectively).

Table 3 Melanin Index — Multiple Comparison with-in group (n=18)

Week	Intervention Cream (Mean±SD)	Degree of reduction from Baseline	Kligman's Cream (Mean±SD)	Degree of reduction from Baseline	p-value
0	336.15 ± 171.15	-	334.79 ± 159.97	-	0.952
4	238.83 ± 123.52	97.32 (28.95%) ↓	294.88 ± 152.42	39.90(11.92%) ↓	0.021*
8	303.46 ± 145.06	32.69(9.73%) ↓	261.97 ± 140.18	72.82(21.75%) ↓	0.066
12	298.80 ± 142.78	37.35 (11.11%) ↓	257.57 ± 141.61	77.21(23.06%) ↓	0.061

Note: * Significant at $p < 0.05$. Within-group $p < 0.001$ for both arms.



Figure 2: Visia Skin Analysis photographs of Participants: Baseline week 0 (Before) and Week 12 (After)

Photos and VISIA skin analysis images before and after treatment. (a1, b1, c1, d1) Before treatment (week0) photograph of the front face. (a2, b2, c2, d2) Before treatment (week0) photograph of the left face. (a3, b3, c3, d3) Before treatment (week0) photograph of the right face. (a4, b4, c4, d4) After treatment (week12) photograph of the front face. (a5, b5, c5, d5) After treatment (week12) photograph of the left face. (a6, b6, c6, d6) After treatment (week12) photograph of the right face

Side Effect Assessment

The intervention cream demonstrated an exceptional safety profile with zero adverse events recorded at any time point. In contrast, Kligman's cream caused transient peeling in 13 participants (72.2%) at Week 4, which resolved by Week 8 (n=2) and Week 12 (n=1). Mild burning sensation

was recorded in 4 participants at Week 4 (persisting mildly at Weeks 8 and 12). Delayed erythema was noted in 6 participants at Week 8, resolving partially by Week 12. No serious adverse events were recorded in either group.

Table 4 Side Effects Assessment (n=18)

Side Effect	Treatment side	Week 4	Week 8	Week 12
Redness / Erythema	Intervention Cream	0	0	0
	Kligman's Cream	0	6	4
Burning Sensation	Intervention Cream	0	0	0
	Kligman's Cream	4	3	4
Peeling	Intervention Cream	0	0	0
	Kligman's Cream	13	2	1

Note: Table 4 summarizes adverse events recorded at Weeks 4, 8, and 12 for both treatment sides.

Patient Satisfaction Level

High levels of patient satisfaction were observed across both treatment groups, indicating favorable overall acceptance of both interventions. Participants treated with Kligman's cream reported a higher proportion of "very satisfied" responses, suggesting greater patient preference and perceived clinical benefit compared with the intervention cream. Overall, both treatments achieved positive patient-reported outcomes and demonstrated good acceptability throughout the study period.

Table 5 Patient satisfaction evaluated by using Global satisfaction Score Ranging from 1-4 (very slightly satisfied (n=18))

Satisfaction Level	intervention Cream	Klingman's Cream
Very Satisfied	5	12
Moderately Satisfied	13	6
Slightly Satisfied	0	0
Very Slightly Satisfied	0	0

Note: Wilcoxon Signed-Rank Test

DISCUSSION & CONCLUSION

The findings of this study indicate that both Kligman's cream and the novel intervention cream containing 1% turmeric, 1% kojic acid, and 5% vitamin C significantly reduced post-acne hyperpigmentation index (PAHPI) scores over a 12-week treatment period. These results confirm that both formulations are efficacious for the treatment of acne-induced hyperpigmentation in Thai patients with Fitzpatrick Skin Types IV–VI (Ali & Al-Niaimi, 2013; Zaenglein et al., 2016). While Kligman's cream achieved greater overall reductions in PAHPI and melanin index by the study's end, the intervention cream demonstrated significantly early melanin suppression at Week 4 and a higher tolerability profile throughout the trial.

The efficacy of Kligman's cream is attributed to the synergistic action of hydroquinone (tyrosinase inhibition), tretinoin (accelerated epidermal turnover and enhanced co-active penetration), and a topical corticosteroid (mitigation of irritation) (Chang, 2009; Kligman & Willis, 1975; Nautiyal & Wairkar, 2021; Zaenglein et al., 2016). Its significant early advantage in PAHPI reduction at Week 4 ($p = 0.013$) likely reflects tretinoin's ability to rapidly induce epidermal turnover, facilitating the delivery of hydroquinone to the melanocyte-rich basal layer (Badreshia-Bansal & Draelos, 2007; Nautiyal & Wairkar, 2021). The 26.40% PAHPI reduction observed at Week 12 aligns with 20–40% efficacy rates reported for triple-combination formulations in darker skin phototypes (Eimpunth et al., 2013; Hollinger et al., 2018; Nautiyal & Wairkar, 2021). Furthermore, the peeling observed in 72.2% of participants at Week 4 mirrors the documented irritation profile of this gold-standard treatment in Asian populations (Briganti et al., 2003; Eimpunth et al., 2013; Kligman & Willis, 1975).

Regarding the impact of UV protection, the lack of significant differences in the melanin index between groups at Weeks 8 and 12 ($p = 0.066$ and $p = 0.061$, respectively) may be explained by the strict UV-protection protocol. Universal daily use of broad-spectrum sunscreen likely suppressed UV-driven paracrine melanocyte stimulation, narrowing the efficacy gap between the two arms. In studies without standardized sunscreen use, hydroquinone's advantage is typically more pronounced, as uncontrolled UV exposure continuously reactivates the melanogenic cascade via keratinocyte-derived mediators such as basic fibroblast growth factor, endothelins, and stem cell factor (Castanedo-Cazares et al., 2014; Hachiya et al., 2001; Halaban et al., 1988; Imokawa et al., 1992; Mahmoud et al., 2010; Sayre et al., 2013).

The intervention cream's early success, evidenced by a superior melanin reduction at Week 4 ($p = 0.021$), suggests a synergistic effect between its components. Kojic acid chelates copper ions at the tyrosinase active site, while vitamin C reduces oxidized melanin intermediates downstream. This dual-pathway inhibition may accelerate melanin suppression faster than either agent could individually (Chang, 2009; Kameyama et al., 1996; Parvez et al., 2006; Picardo & Carrera, 2007). Although kojic acid has traditionally been considered slower-acting than hydroquinone, its combination with 5% vitamin C in this study challenged that paradigm (Hollinger et al., 2018; Kameyama et al., 1996). The efficacy of the vitamin C component may be further enhanced by curcumin, whose antioxidant properties likely protected the ascorbic acid from oxidative inactivation, maintaining its bioavailability (Di Lorenzo et al., 2023; Long et al., 2015; Taylor et al., 2002).

Curcumin, the primary bioactive polyphenol of *Curcuma longa*, interrupts the post-inflammatory cascade by suppressing NF- κ B and pro-inflammatory cytokines (TNF- α , IL-1 β , and IL-6). These mediators are released by keratinocytes during acne-induced injury and directly stimulate melanocytes (Di Lorenzo et al., 2023; Hossain et al., 2021; Long et al., 2015). Prior work by Swanson et al. (2010) and Arct et al. (2014) demonstrated that topical curcumin and *Curcuma longa* extract modulate epidermal pigmentation. By dampening this upstream inflammatory signal, curcumin likely reduced active melanocyte stimulation during the first four weeks, providing the intervention cream with its early advantage. However, this advantage was not sustained through Weeks 8 and 12, likely due to curcumin's pharmacokinetic limitations. Poor aqueous solubility and restricted dermal penetration often constrain curcumin's bioavailability at the dermal-epidermal junction (Di Lorenzo et al., 2023; Taylor et al., 2002). As its anti-inflammatory effect reached a pharmacodynamic ceiling, the sustained tyrosinase inhibition of Kligman's formula led to a progressive divergence in results. Future formulations utilizing nanocurcumin or phospholipid complexes may help sustain this early advantage over longer periods.

The key finding of this study was the intervention cream's safety and tolerability profile, with zero adverse events recorded throughout the 12-week study. In contrast, Kligman's formula caused transient peeling (72.2%), mild burning ($p = 0.046$), and delayed erythema ($p = 0.020$), all resolving by study end (Castanedo-Cazares et al., 2014; Mahmoud et al., 2010; Vashi & Kundu, 2013; Zaenglein et al., 2016). While both regimens were ultimately well tolerated, this difference in early tolerability carries important real-world implications. For patients with Fitzpatrick Types IV–VI, this difference is clinically significant; inflammation from tretinoin and hydroquinone can paradoxically trigger irritant-induced PIH, worsening the condition the therapy is intended to treat (Di Lorenzo et al., 2023; Parvez et al., 2006; Silpa-Archa et al., 2017; Taylor et al., 2002). In routine clinical practice, visible peeling and irritation are the primary drivers of treatment discontinuation. A formulation that provides meaningful depigmentation without side effects is more likely to ensure patient adherence. Moreover, the absence of side effects makes the intervention cream a viable candidate for long-term maintenance therapy, which is essential given the recurrent nature of acne (Kubba et al., 2009).

While the 18.62% PAHPI reduction in the intervention group was numerically lower than Kligman's 26.40%, it still represented a meaningful improvement in lesion darkness. While 66.7% of Kligman's users were very satisfied, 27.8% in the intervention group reported the same high satisfaction without experiencing any discomfort. For patient's intolerant to retinoids or

corticosteroids, or those requiring long-term management, the intervention cream offers a favorable benefit-to-risk profile.

The study has several important limitations that should be considered when interpreting the findings. The 12-week observation period was insufficient to evaluate the long-term durability of depigmentation or recurrence following treatment cessation, particularly because acne-induced hyperpigmentation can persist for 3–24 months without intervention. The borderline significance of melanin index differences at Weeks 8 and 12 suggests that a longer study duration may have provided clearer evidence of treatment effects. Although the split-face design effectively controlled for inter-individual variability, it introduced the possibility of product migration between facial halves and perceptual bias during subjective satisfaction assessments. The absence of a vehicle-only control arm also limited the ability to distinguish treatment-specific effects from those attributable to the cream base, standardized skincare, or the natural resolution of post-inflammatory hyperpigmentation. In addition, the fixed three-component formulation prevented assessment of the individual contribution of each active ingredient and whether the observed efficacy was due to specific components or synergistic interactions.

Generalizability of the findings is also limited because the study population consisted exclusively of Thai patients from a single center, predominantly Fitzpatrick skin Types III and IV, who worked indoors. Differences in melanocyte biology, inflammatory responses, skin barrier function, and UV exposure may influence treatment outcomes in other ethnic groups and settings. Furthermore, the final analysis included only 18 participants who completed the study, reducing statistical power and increasing the risk of type II error. Future research should therefore involve larger, adequately powered multicenter randomized controlled trials with ethnically diverse populations, vehicle-control groups, and longer follow-up periods. Factorial study designs evaluating individual ingredients, their pairwise combinations, and the complete formulation would help clarify the relative and synergistic contributions of each component. Additionally, advanced curcumin delivery systems such as nanocurcumin, phospholipid complexes, solid lipid nanoparticles, and cyclodextrin inclusion complexes should be investigated to improve skin penetration and potentially enhance long-term therapeutic efficacy.

In conclusion, both Kligman's formula and the novel combination cream (1% turmeric, 1% kojic acid, and 5% vitamin C) significantly reduced acne-induced hyperpigmentation over 12 weeks. Kligman's formula cream demonstrated numerically greater reductions in PAHPI and melanin index, achieving higher PAHPI reduction and patient satisfaction. However, the intervention cream demonstrated significantly faster early melanin suppression and an exceptional safety profile with zero adverse events. These results suggest that the novel combined cream is an effective, non-irritating alternative for the treatment of PIH, particularly for patients with sensitive skin or those requiring long-term maintenance therapy.

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