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Retrospective Evaluation of the Efficacy and Tolerability of a Combination Cream Containing 3% Kojic Acid, 10% Liposomal Azelaic Acid, 1% Tranexamic Acid, 3% Glycolic Acid, and 1.5% 4-n-Butylresorcinol for the Treatment of Melasma

Bikash Kar [1], R. D. Kharkar [2], Sharmistha Basu [3], Rahul Pathak [4], Shruti Pal [4]

1. Dermatology, Venereology, and Leprosy, Institute of Medical Sciences and SUM Hospital, Siksha 'O' Anusandhan (SOA) University, Bhubaneswar, IND 2. Dermatology, Venereology, and Leprosy, Dr. Kharkar's Skin Clinic, Mumbai, IND 3. Pediatric Medicine, Maharaja Jitendra Narayan Government Medical College, Cooch Behar, IND 4. Medical Affairs, Indchemie Health Specialities Pvt Ltd, Mumbai, IND

Corresponding author: Rahul Pathak, rahulp@indchemie.in

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Abstract

Background

Melasma is a chronic acquired hyperpigmentary disorder characterized by symmetrical facial pigmentation and substantial psychosocial impact. Despite available treatments, outcomes remain variable, highlighting the need for therapies targeting multiple melanogenesis pathways. This study evaluated the clinical effectiveness, safety, and patient satisfaction of a combination cream containing 3% kojic acid, 10% liposomal azelaic acid, 1% tranexamic acid, 3% glycolic acid, and 1.5% 4-*n*-butylresorcinol in patients with melasma.

Methods

This retrospective, multicenter observational study included 3,090 patients with melasma treated across 383 dermatology centers in routine practice. Baseline demographic and disease characteristics were extracted from medical records. Clinical effectiveness was assessed by changes in the Melasma Severity Scale at one and two months. Secondary outcomes included physician- and patient-reported satisfaction and safety. Longitudinal changes were analyzed using generalized estimating equations with an ordinal multinomial distribution and cumulative logit link; subgroup associations were evaluated using chi-square tests with Cramér's V.

Results

The mean age of the 3,090 patients was 34.38 ± 7.20 years, and 1,981 (64.1%) were female. The mean disease duration was 17.56 ± 14.53 months. Melasma severity progressively improved during treatment, with mean score changes of −0.42 ± 0.76 at one month and −1.01 ± 1.23 at two months. Clinical improvement was observed in 1,443 (46.7%) patients at one month and 2,086 (67.5%) patients at two months. Severity scores improved significantly over time ($p < 0.001$), with progressive shifts toward lower severity categories. Treatment response was significantly associated with baseline clinical characteristics, including Fitzpatrick skin type, melasma subtype, disease duration, and lesion distribution ($p < 0.001$). At two months, 1,343 (43.5%) patients had minimal residual disease on physician assessment, while 180 (5.8%) patients remained severely affected. Patient and physician satisfaction was high, and the treatment was generally well tolerated, with predominantly mild local adverse reactions and minimal treatment discontinuation.

Conclusion

In this large real-world study, the combination cream produced significant, progressive improvement in melasma severity with a clear time-dependent effect and high patient and physician satisfaction. Treatment response varied by baseline characteristics, with greatest benefit in Fitzpatrick skin types V-VI. Despite mild local adverse reactions, the formulation containing 3% kojic acid, 10% liposomal azelaic acid, 1% tranexamic acid, 3% glycolic acid, and 1.5% 4-*n*-butylresorcinol demonstrated favorable safety and tolerability, supporting its use as a multi-mechanistic topical therapy for melasma.

Categories: Therapeutics, Family/General Practice, Dermatology
Keywords: 10% liposomal azelaic acid, 1.5% 4-n-butyl resorcinol, 1% tranexamic acid, 3% glycolic acid, 3% kojic acid, hyperpigmentation, melasma, retrospective study, skin disorders, topical therapy

Introduction

Melasma is a common acquired hyperpigmentary disorder characterized by symmetric, irregularly bordered brown to grey-brown macules and patches, predominantly affecting sun-exposed areas of the face such as the cheeks, forehead, upper lip, and chin. Although benign, melasma significantly impacts patients' quality of life due to its chronic, relapsing course and cosmetic disfigurement. Histopathological studies have demonstrated increased melanin deposition in the epidermis and/or dermis, along with ultrastructural changes in melanocytes, keratinocytes, and dermal components, highlighting the complex and multifactorial nature of the disease [1,2].

Melasma predominantly affects women and individuals with darker skin phototypes, particularly Fitzpatrick skin types III-V, and is more common in populations exposed to high levels of ultraviolet (UV) radiation [3,4,5]. Several risk factors have been implicated in its pathogenesis, including genetic predisposition, hormonal influences such as pregnancy and oral contraceptive use, UV exposure, and certain medications [6,5]. Clinically, melasma is classified into centrofacial, malar, and mandibular patterns, with centrofacial involvement being the most frequently observed [7]. The disease often exhibits chronicity, with prolonged duration and frequent recurrence contributing to therapeutic challenges.

The pathogenesis of melasma is complex and involves multiple interrelated mechanisms, including increased melanogenesis, enhanced melanosome transfer, oxidative stress, dermal inflammation, and vascular proliferation. UV radiation plays a central role by inducing melanocyte activation and stimulating the release of inflammatory mediators, which further promote pigmentation [1,2]. Additionally, emerging evidence suggests the involvement of dermal fibroblasts, increased vascular endothelial growth factor (VEGF), and disruption of the basement membrane, reinforcing the need for therapies targeting multiple pathogenic pathways.

Management of melasma remains challenging due to its recalcitrant nature and variable response to treatment. A variety of therapeutic modalities have been employed, including topical depigmenting agents, chemical peels, laser therapies, and systemic treatments. Among these, topical therapies remain the first-line approach owing to their safety, accessibility, and ease of use. Conventional agents such as hydroquinone, retinoids, and corticosteroids have demonstrated efficacy; however, their long-term use is often limited by adverse effects such as irritation, exogenous ochronosis, and rebound hyperpigmentation [8].

In recent years, combination topical therapies have gained increasing attention due to their ability to target multiple steps in the melanogenesis pathway. A formulation comprising 3% kojic acid, 10% liposomal azelaic acid, 1% tranexamic acid, 3% glycolic acid, and 1.5% 4-n-butyl resorcinol represents a rational multi-mechanistic approach to melasma treatment. Kojic acid acts as a tyrosinase inhibitor, reducing melanin synthesis, while azelaic acid exerts anti-inflammatory and anti-proliferative effects on melanocytes. Tranexamic acid has been shown to inhibit plasmin-mediated melanocyte activation, thereby reducing pigmentation. Glycolic acid promotes epidermal turnover and enhances penetration of active agents, facilitating the removal of pigmented keratinocytes. Additionally, 4-n-butylresorcinol is a potent inhibitor of tyrosinase and related enzymes, contributing to significant depigmenting effects.

An important advancement in this formulation is the incorporation of liposomal azelaic acid, which may offer advantages in the delivery and local availability of azelaic acid compared with conventional formulations. Azelaic acid is a naturally occurring dicarboxylic acid with established anti-tyrosinase, anti-inflammatory, and anti-proliferative effects on abnormal melanocytes, supporting its use in the management of hyperpigmentary disorders including melasma [9,10]. Conventional topical formulations may be limited by local tolerability and variable delivery of the active ingredient. Liposomal delivery systems encapsulate active compounds within phospholipid vesicles and may enhance their stability, skin deposition, and local availability, providing a rationale for their use in topical depigmenting therapies. In particular, studies of liposomal azelaic acid formulations have demonstrated enhanced accumulation of azelaic acid in the stratum corneum and improved pharmaceutical bioavailability, supporting the potential advantages of this delivery approach [11]. Improved local availability may facilitate the pharmacological effects of azelaic acid while potentially improving formulation tolerability. These properties provide a rationale for incorporating liposomal azelaic acid into a multi-mechanistic combination formulation for melasma.

Despite the theoretical advantages and emerging clinical use of such combination therapies, robust large-scale evidence evaluating their effectiveness and tolerability in real-world clinical settings remains limited. Most available studies are small, controlled trials or case series, which may not fully reflect treatment outcomes in routine practice, where factors such as adherence, disease chronicity, environmental exposure, and patient heterogeneity play critical roles.

Real-world evidence has increasingly been recognized as an essential complement to randomized controlled trials, providing insights into treatment effectiveness, safety, and patient satisfaction in diverse populations. Such data are particularly valuable in chronic relapsing dermatological conditions such as melasma, where long-term management and patient adherence significantly influence outcomes.

In this context, the present multicenter retrospective study was conducted to evaluate the effectiveness and tolerability of a combination cream containing 3% kojic acid, 10% liposomal azelaic acid, 1% tranexamic acid, 3% glycolic acid, and 1.5% 4-n-butyl resorcinol in patients with melasma in routine clinical practice. The study aims to assess changes in melasma severity, identify factors influencing treatment response, evaluate safety and tolerability, and analyze patient-reported outcomes. By leveraging a large real-world dataset, this study seeks to provide clinically relevant evidence to support optimized and individualized treatment strategies for melasma.

Materials And Methods

Study design

This retrospective, multicenter, questionnaire-based observational study was conducted to evaluate the effectiveness and tolerability of a topical combination cream containing 3% kojic acid, 10% liposomal azelaic acid, 1% tranexamic acid, 3% glycolic acid, and 1.5% 4-n-butyl resorcinol in patients with melasma in real-world clinical practice. The study involved a systematic review of electronic medical records (EMRs) along with structured physician-reported data collected across participating dermatology centers in India. The study was conducted in accordance with the principles of the International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines, ensuring adherence to ethical standards, data integrity, and patient confidentiality. Prior to initiation, the study protocol was reviewed and approved by an Independent Ethics Committee (IEC) at Lifepoint Multispeciality Hospital, Pune (Approval Date: 25/Apr/2024). Data were collected for the period between May 2024 and November 2025.

The analysis was performed over a defined study period during which patients underwent routine dermatological evaluation, including assessment of the Melasma Severity Scale [12] and documentation of treatment regimens. The study was designed to assess both cross-sectional associations and longitudinal changes in melasma severity following treatment, while also exploring potential modifiers such as demographic characteristics, skin type, disease duration, lesion distribution, and treatment adherence.

Study population

The study included a total of 3,090 patients diagnosed with melasma who received treatment with the combination cream as part of routine clinical care.

Patients were eligible for inclusion if they had a documented diagnosis of melasma based on clinical evaluation by a dermatologist, along with complete medical records capturing baseline characteristics, treatment details, and follow-up outcomes. Only patients with available data on baseline and follow-up Melasma Severity Scale [12] were included to ensure robust analysis.

Exclusion criteria included patients with other facial pigmentary disorders (e.g., post-inflammatory hyperpigmentation, vitiligo), concomitant dermatological conditions affecting the face, incomplete or missing medical records, and lack of documented treatment details. These criteria ensured the inclusion of a well-defined and homogeneous cohort suitable for evaluating treatment effectiveness.

Data collection

Data were extracted retrospectively from EMRs using standardized data collection procedures to ensure consistency and reliability. In addition, structured questionnaires were used to capture physician-reported outcomes and patient-reported satisfaction.

Appendix A presents the data collection form used for retrospective abstraction of study-related information from the available medical records and clinical documentation. The form includes the demographic, clinical, treatment, efficacy, patient- and physician-reported outcomes, and safety variables evaluated in the present study.

Extracted variables included demographic characteristics (age, gender), Fitzpatrick skin type, duration of melasma, and clinical distribution of lesions (centrofacial, malar, mandibular). Baseline severity of melasma was assessed using a standardized severity scoring system, categorized as mild, moderate, or severe (Table *1*).

Disease Activity	Melasma Severity Score
Melasma lesions almost equivalent to surrounding normal skin or with minimal residual pigmentation	0
Mild, slightly darker than surrounding normal skin	1
Moderate, moderately darker than surrounding normal skin	2
Severe, markedly darker than surrounding normal skin	3

TABLE 1: Melasma Severity Scale

[12]

Treatment-related data included details of the topical combination cream, duration of therapy, and treatment continuation or modification during follow-up. Outcome data included changes in the Melasma Severity Scale at follow-up visits (one month and two months), physician global assessment, patient satisfaction, improvement in appearance, and willingness to continue treatment. Safety data included the incidence, type, and severity of adverse reactions such as skin irritation, erythema, burning sensation, and allergic reactions. Adverse events were categorized as mild, moderate, or severe, and corresponding management strategies (continuation, dose adjustment, or discontinuation) were documented.

All data were subjected to validation checks, and identifiable patient information was anonymized to ensure confidentiality.

Objectives and outcome measures

The primary objective of the study was to evaluate the effectiveness of the combination cream in reducing melasma severity in patients treated in routine clinical practice. The secondary objectives were to assess changes in melasma severity over time, evaluate the association between demographic and clinical factors (age, gender, skin type, duration, and distribution) and treatment response, assess physician and patient-reported outcomes, evaluate safety and tolerability of the treatment, and explore the impact of treatment duration on clinical outcomes.

Outcome measures

The study evaluated clinical effectiveness, patient- and physician-reported outcomes, and safety of the combination topical therapy in patients with melasma. Effectiveness was assessed through changes in the Melasma Severity Scale [12] from baseline to follow-up visits, along with categorical improvement status (mild, moderate, marked improvement, no change, or worsening). Additional assessments included the Physician Global Assessment of disease severity, physician satisfaction, patient-reported satisfaction, perceived improvement in appearance, willingness to continue treatment, and the incidence, severity, and management of adverse reactions. Associations between demographic and clinical characteristics and treatment response were also explored.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Version 27.0 (IBM Corp., Armonk, NY). Continuous variables were summarized using means and standard deviations (SD), whereas categorical variables were presented as frequencies and percentages.

The primary longitudinal outcome was a physician-rated ordinal Melasma Severity Score ranging from 0 to 3, with higher scores indicating greater disease severity. Because this outcome was ordinal and measured repeatedly in the same patients at baseline, one month, and two months, longitudinal changes were analyzed using generalized estimating equations (GEE) with an ordinal multinomial distribution and cumulative logit link function. Patient ID was specified as the subject variable, time point was specified as the within-subject variable, and an exchangeable working correlation structure was used to account for within-patient correlation. The overall effect of time was assessed using type III Wald χ^2 statistics.

Although the Melasma Severity Scale (0-3) is an ordinal variable, it is presented as mean ± standard deviation for descriptive purposes only. All inferential analyses involving repeated severity measurements treated the score as an ordinal outcome, and longitudinal changes were analyzed using a GEE with an ordinal multinomial distribution and cumulative logit link.

Associations between categorical variables, including gender, Fitzpatrick skin type, melasma subtype, lesion distribution, and treatment response, were evaluated using the chi-square test. Cramér's V was reported as a

measure of association strength. Prespecified subgroup analyses examined treatment response according to relevant demographic and clinical characteristics.

All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

Ethical considerations

The study protocol was reviewed and approved by the Independent Ethics Committee. Due to the retrospective nature of the study and the use of anonymized data, the requirement for informed consent was waived.

All patient data were anonymized prior to analysis to ensure confidentiality. Strict data management protocols were followed to maintain data integrity and compliance with institutional and regulatory standards. Access to study data was restricted to authorized personnel only, ensuring adherence to ethical guidelines and protection of patient privacy.

Results

Baseline demographic and clinical characteristics

This multicenter retrospective study included 3,090 patients contributed from 383 dermatology clinics and centers across India. There was a clear female predominance (64.1%), consistent with the known hormonal and environmental influences associated with melasma. The mean age was 34.38 ± 7.20 years, with over half of the patients (54.5%) in the age group of 30-39 years, highlighting that melasma predominantly affects individuals during their most socially and economically active years, potentially amplifying its psychosocial burden.

Skin phototype distribution revealed that the majority of patients belonged to Fitzpatrick types V-VI (68.3%), reinforcing the higher susceptibility of darker phototypes to pigmentary disorders. Clinically, the centrofacial pattern was the most common (63.0%), followed by malar (24.2%) and mandibular (12.8%) distributions, aligning with classical clinical presentations of melasma.

The mean disease duration of 17.56 ± 14.53 months indicates a chronic and persistent condition. Importantly, baseline severity assessment showed that 72.4% of patients had moderate-to-severe disease, emphasizing the need for effective therapeutic strategies capable of delivering sustained improvement (Table *2*).

Variable	Category	n (%) / Mean ± SD
Age (years)	Mean ± SD	34.38 ± 7.20
Age group (years)	13–19	31 (1.0%)
	20–29	713 (23.1%)
	30–39	1,685 (54.5%)
	40–49	559 (18.1%)
	50–65	102 (3.3%)
	Total	3,090 (100%)
Gender	Female	1,981 (64.1%)
	Male	1,109 (35.9%)
	Total	3,090 (100%)
Fitzpatrick skin type [1]	I–II	18 (0.6%)
	III–IV	960 (31.1%)
	V–VI	2,112 (68.3%)
	Total	3,090 (100%)
Duration of melasma (months)	Mean ± SD	17.56 ± 14.53
Melasma characteristics [1,2]	Dermal	409 (13.2%)
	Epidermal	2,681 (86.8 %)
	Total	3,090 (100%)
Distribution [3,7]	Centrofacial	1,948 (63.0%)
	Malar	747 (24.2%)
	Mandibular	395 (12.8%)
	Total	3,090 (100%)
Melasma Severity Scale [12]	Mean ± SD	1.79 ± 0.94
Severity category	Mild (0–1)	854 (27.6%)
	Moderate (2)	1,579 (51.1%)
	Severe (3)	657 (21.3%)
	Total	3,090 (100%)

TABLE 2: Baseline demographic and clinical characteristics (N = 3,090)

Note: data are presented as n (%) unless otherwise indicated. Melasma subtype and distribution patterns were classified according to established clinical and histopathological descriptions [1-3,7,12].

Effectiveness outcomes

A clear trend toward progressive clinical improvement was observed over time. At one month, the mean reduction in the Melasma Severity Scale was modest (-0.42 ± 0.76), with 46.7% of patients demonstrating improvement, primarily in the mild category. A substantial proportion (53.3%) showed no change at this early stage, suggesting that short-term response may be limited.

By two months, the therapeutic effect became more pronounced, with a greater mean reduction in the Melasma Severity Scale (-1.01 ± 1.23). The proportion of patients demonstrating improvement increased to 67.5%, accompanied by a notable shift toward moderate (34.7%) and marked improvement (7.1%). Simultaneously, the proportion of patients with no change decreased significantly from 53.3% to 32.5%,

indicating a greater treatment response with longer treatment duration (Tables 3, 4 and Figures 1-3).

Parameter	Mean ± SD
Baseline Melasma Severity Scale	1.79 ± 0.94
Change at 1 month	-0.42 ± 0.76
Change at 2 months	-1.01 ± 1.23

TABLE 3: Effectiveness Outcomes

Category	1 Month, n (%)	2 Months, n (%)
Marked improvement	4 (0.1%)	220 (7.1%)
Moderate improvement	138 (4.5%)	1,071 (34.7%)
Mild improvement	1,301 (42.1%)	795 (25.7%)
No change	1,647 (53.3%)	1,004 (32.5%)
Total	3,090 (100%)	3,090 (100%)

TABLE 4: Improvement at follow-up

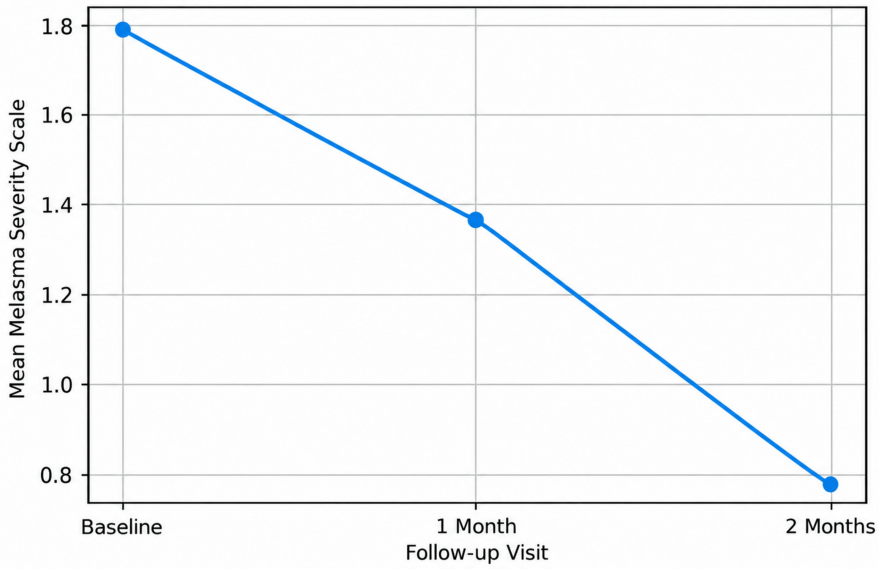


FIGURE 1: Mean Melasma Severity Scale over time

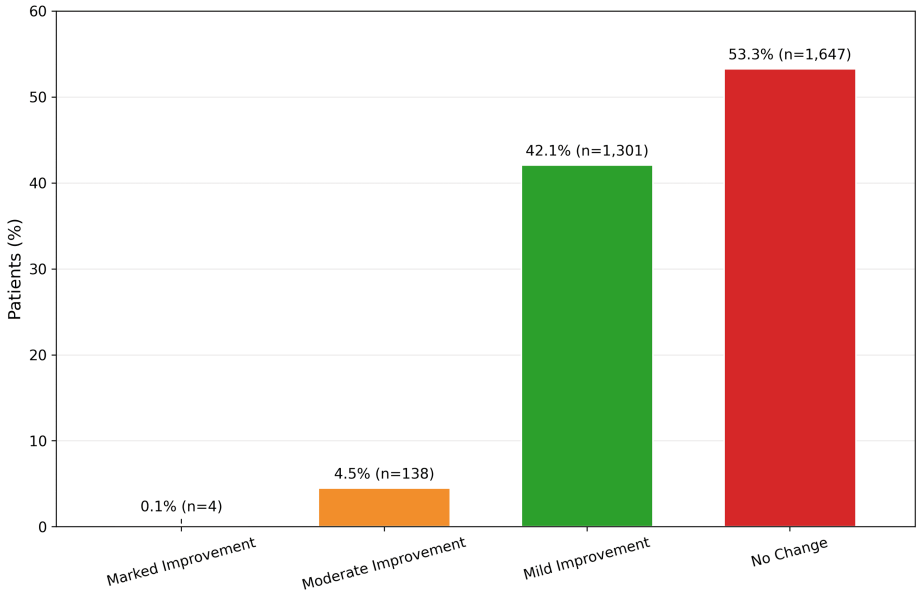


FIGURE 2: Improvement in melasma at the one-month follow-up (n = 3,090)

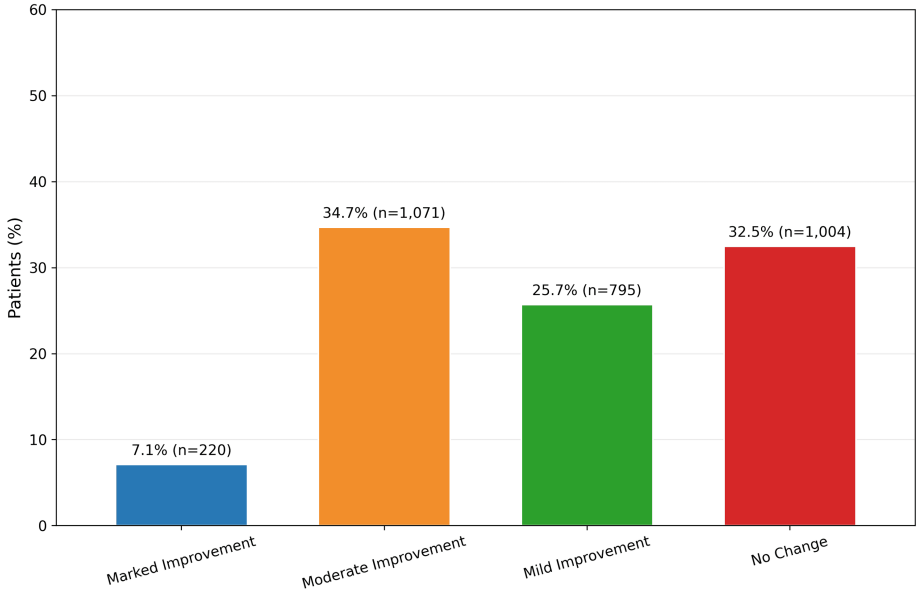


FIGURE 3: Improvement in melasma at the two-month follow-up (n = 3,090)

Physician and patient-reported outcomes

Physician assessments indicated substantial clinical improvement, with 43.5% of patients achieving minimal residual disease and only 5.8% remaining in the severe category. The majority of patients were categorized as having minimal-to-moderate disease at follow-up, reflecting effective disease control.

Physician satisfaction was notably high, with 93.6% reporting satisfaction, including more than half (54.7%) who were very satisfied. Patient-reported outcomes were even more striking, with over 99% of patients expressing satisfaction and perceiving improvement in their appearance. Additionally, 99.6% expressed willingness to continue treatment, indicating strong acceptance, perceived efficacy, and adherence (Table *5*).

Variable	Category	n (%)
Physician Global Assessment	Minimal (0–1)	1,343 (43.5%)
	Moderate (2–3)	1,567 (50.7%)
	Severe (≥4)	180 (5.8%)
Physician satisfaction	Very satisfied	1,691 (54.7%)
	Satisfied	1,201 (38.9%)
	Others	198 (6.4%)
Overall patient satisfaction	Satisfied	3,076 (99.5%)
	Not satisfied	14 (0.5%)
Improvement in appearance	Yes	3,078 (99.6%)
	No	12 (0.4%)
Willingness to continue	Yes	3,078 (99.6%)
	No	12 (0.4%)

TABLE 5: Physician and patient-reported outcomes

Safety and tolerability

Although local irritation was common with this topical depigmenting therapy, the vast majority of adverse reactions were mild and did not require treatment discontinuation. The most frequently reported reactions were skin irritation (52.4%) and burning sensation (19.0%), followed by erythema (13.1%) and allergic reactions (5.9%). Because patients could experience more than one adverse reaction, the percentages for individual reaction types were not mutually exclusive and therefore may not sum to the overall proportion of patients experiencing adverse reactions. Among the 2,919 patients who experienced adverse reactions, 87.5% had mild reactions, while 11.5% and 1.0% had moderate and severe reactions, respectively. Most patients continued treatment (78.5%), whereas 20.9% required dose adjustment and only 0.7% discontinued therapy. Overall, 2,919 (94.5%) of the 3,090 patients experienced at least one adverse reaction, while 171 (5.5%) reported no adverse reactions (Table *6*). Importantly, most patients (78.5%) continued treatment without modification, and only a small proportion required dose adjustment (20.9%). Treatment discontinuation was extremely low (0.7%), indicating excellent tolerability.

Variable	Category	n (%)
Type of reaction	Skin irritation	1,620 (52.4%)
	Burning sensation	588 (19.0%)
	Erythema	406 (13.1%)
	Allergic reaction	181 (5.9%)
	Others	124 (4.0%)
	No reaction	171 (5.5%)
Severity (N = 2,919)	Mild	2,554 (87.5%)
	Moderate	337 (11.5%)
	Severe	28 (1.0%)
Action taken (N = 2,919)	Continued	2,290 (78.5%)
	Dose adjusted	610 (20.9%)
	Discontinued	19 (0.7%)

TABLE 6: Adverse reactions

Subgroup and association analysis

At one month, no statistically significant association was observed between gender and treatment response ($\chi^2 = 1.911$, $p = 0.167$). The corresponding Cramér's V of 0.025 indicated a negligible association, suggesting comparable early treatment response between female and male patients.

At two months, a statistically significant association was observed between gender and treatment response ($\chi^2 = 10.11$, $p = 0.0015$); however, the magnitude of association remained very small (Cramér's V = 0.057). Although females demonstrated a higher improvement rate than males (69.5% vs. 63.9%), the small effect size suggests that gender accounted for only a limited proportion of the variability in treatment response (Tables *7*, *8*).

Gender	Improvement (%)	No Improvement (%)	Total
Female	944 (47.7%)	1,037 (52.3%)	1,981
Male	499 (45.0%)	610 (55.0%)	1,109
Total	1,443 (46.7%)	1,647 (53.3%)	3,090

TABLE 7: Association between gender and treatment response at one month

Chi-square = 1.911, df = 1, p = 0.167 Cramér's V = 0.025

Gender	Improvement (%)	No Improvement (%)	Total
Female	1,377 (69.5%)	604 (30.5%)	1,981
Male	709 (63.9%)	400 (36.1%)	1,109
Total	2,086 (67.5%)	1,004 (32.5%)	3,090

TABLE 8: Association between gender and treatment response at two months

Chi-square = 10.11, df = 1, p = 0.0015 Cramér's V = 0.057

Note: data are presented as n (%). Comparisons between gender and treatment response were performed using the chi-square test. Effect size was assessed using Cramér's V. A p-value of <0.05 was considered statistically significant.

A statistically significant association was observed between Fitzpatrick skin type and treatment response at both one month and two months ($p < 0.001$). The strength of association was small at one month (Cramér's V = 0.142) and increased to a small-to-moderate association at two months (Cramér's V = 0.196).

Patients with Fitzpatrick skin types V-VI demonstrated the highest improvement rates at both one month (51.4%) and two months (73.7%), compared with patients with skin types III-IV (36.9% and 54.6%, respectively). The limited number of patients with skin types I-II (n = 18) warrants cautious interpretation of this subgroup (Tables *9*, *10*). These findings suggest that Fitzpatrick skin type may be a clinically relevant modifier of treatment response in this cohort, although the observed effect sizes indicate that skin phototype alone does not fully explain the variability in clinical improvement.

Fitzpatrick Type	Improvement	No Improvement	Total
I–II	3 (16.7%)	15 (83.3%)	18
III–IV	354 (36.9%)	606 (63.1%)	960
V–VI	1,086 (51.4%)	1,026 (48.6%)	2,112
Total	1,443 (46.7%)	1,647 (53.3%)	3,090

TABLE 9: Association between Fitzpatrick skin type and treatment response at one month

Chi-square = 62.660, df = 2, p < 0.001 Cramér's V = 0.142

Fitzpatrick Type	Improvement	No Improvement	Total
I–II	6 (33.3%)	12 (66.7%)	18
III–IV	524 (54.6%)	436 (45.4%)	960
V–VI	1,556 (73.7%)	556 (26.3%)	2,112
Total	2,086 (67.5%)	1,004 (32.5%)	3,090

TABLE 10: Association between Fitzpatrick skin type and treatment response at two months

Chi-square = 119.305, df = 2, p < 0.001 Cramér's V = 0.196

Note: data are presented as n (%). Comparisons between gender and treatment response were performed using the chi-square test. Effect size was assessed using Cramér's V. A p-value of <0.05 was considered statistically significant.

Improvement was observed in both dermal and epidermal melasma, with response rates increasing from 39.1% and 47.9% at one month to 64.3% and 68.0% at two months. Although epidermal melasma showed numerically higher improvement rates, the difference between melasma types was modest (Table *11*).

Melasma Type	1 Month, n (%), Improved	2 Months, n (%), Improved
Dermal	160 (39.1%)	263 (64.3%)
Epidermal	1,283 (47.9%)	1,823 (68.0%)
Overall	1,443 (46.7%)	2,086 (67.5%)

TABLE 11: Association between melasma type and treatment response

Note: data are presented as n (%). Comparisons between gender and treatment response were performed using the Chi-square test. Effect size was assessed using Cramér's V. A p-value of <0.05 was considered statistically significant.

Patients with centrofacial melasma demonstrated the highest improvement rate (72.5%), followed by malar (60.2%) and mandibular distribution (56.7%). Although the statistically significant association indicates that response varied according to lesion distribution, the small effect size suggests that anatomical distribution explained only a limited proportion of the variability in treatment response (Table *12*).

Distribution	Improvement	No Improvement	Total
Centrofacial	1,412 (72.5%)	536 (27.5%)	1,948
Malar	450 (60.2%)	297 (39.8%)	747
Mandibular	224 (56.7%)	171 (43.3%)	395
Total	2,086 (67.5%)	1,004 (32.5%)	3,090

TABLE 12: Association between lesion distribution and treatment response (two months)

Chi-square = 45.31, df = 2, $p < 0.001$ Cramér's V = 0.121

Note: data are presented as n (%). Comparisons between gender and treatment response were performed using the Pearson chi-square test. Effect size was assessed using Cramér's V. A p-value of <0.05 was considered statistically significant.

The observed differences may reflect the influence of anatomical, biological, and environmental factors; however, these potential mechanisms should be interpreted cautiously because this retrospective observational study was not designed to establish causality.

Longitudinal change in melasma severity

The longitudinal distribution of the Melasma Severity Scale demonstrated a progressive shift toward lower severity categories during treatment (Table *6*). At baseline, scores of 0, 1, 2, and 3 were recorded in 458 (14.8%), 396 (12.8%), 1,579 (51.1%), and 657 (21.3%) patients, respectively. At one month, the distribution shifted toward lower severity scores, with scores of 0, 1, 2, and 3 observed in 483 (15.6%), 1,173 (38.0%), 1,238 (40.1%), and 196 (6.3%) patients, respectively. By two months, a further shift toward lower severity categories was observed: 1,300 (42.1%) patients had a score of 0, 1,250 (40.5%) had a score of 1, 451 (14.6%) had a score of 2, and 89 (2.9%) had a score of 3.

A GEE model with a cumulative logit link and multinomial probability distribution demonstrated a statistically significant overall effect of time on the Melasma Severity Scale (Wald $\chi^2 = 1007.283$, df = 2, $p < 0.001$). Patient ID was specified as the subject variable, time as the within-subject variable, and an exchangeable working correlation structure was used to account for within-patient correlation. These findings indicate a significant longitudinal change in the distribution of Melasma Scale scores across baseline, one month, and two months, with a progressive shift toward lower severity categories during treatment.

Overall, these findings provide robust statistical evidence supporting the effectiveness of the combination therapy, demonstrating not only significant reductions in melasma severity but also a progressive, time-dependent treatment response (Table *13*).

Melasma Severity Scale	Baseline, n (%)	1 Month, n (%)	2 Months, n (%)
0	458 (14.8)	483 (15.6)	1,300 (42.1)
1	396 (12.8)	1,173 (38.0)	1,250 (40.5)
2	1,579 (51.1)	1,238 (40.1)	451 (14.6)
3	657 (21.3)	196 (6.3)	89 (2.9)
Total	3,090 (100.0)	3,090 (100.0)	3,090 (100.0)

TABLE 13: Longitudinal distribution of melasma severity scale and GEE analysis

Overall longitudinal effect of time: Wald $\chi^2 = 1007.283$; df = 2; $p < 0.001$

Note: data are presented as n (%). Longitudinal changes in the Melasma Severity Scale scores were analyzed using a generalized estimating equation model. A p-value of <0.05 was considered statistically significant.

Statistical model: GEE with cumulative logit link and multinomial probability distribution; Patient ID was specified as the subject variable, time as the within-subject variable, and an exchangeable working correlation structure was used.

GEE, generalized estimating equation

Discussion

In this retrospective, multicenter observational study, the evaluated combination topical therapy was associated with progressive improvement in melasma severity over the two-month follow-up period, with greater improvement observed at two months than at one month. This finding is consistent with previous evidence supporting the effectiveness of topical interventions for melasma. Systematic reviews have reported beneficial effects with several topical agents, including azelaic acid, kojic acid, tranexamic acid, and combination therapies, although considerable heterogeneity exists across treatment regimens, patient populations, and outcome measures [8,9,13,14]. The present study complements this evidence by providing treatment-response data from a large, multicenter population managed under routine clinical practice.

The rationale for combination topical therapy is supported by the multifactorial pathogenesis of melasma, involving melanogenesis as well as alterations in keratinocytes, the basement membrane, dermal components, and inflammatory pathways [1,2]. Combining agents with complementary mechanisms may therefore provide a broader therapeutic approach than targeting a single pathway. Recent literature increasingly supports individualized and multimodal management of melasma, with treatment selected according to clinical phenotype, severity, skin type, and patient response [10,15]. The present formulation incorporates several agents with established or emerging evidence in melasma, including azelaic acid, kojic acid, tranexamic acid, glycolic acid, and 4-n-butylresorcinol [8,9,14,16-17]. However, because the study evaluated the combination formulation as a whole, the independent contribution of individual components cannot be determined.

The progressive improvement observed between the first and second months is clinically relevant and suggests that continued treatment may provide additional benefit during the early treatment period. Previous systematic reviews of topical interventions have similarly demonstrated variability in response according to treatment modality and duration [9,12,14]. Tranexamic acid, in particular, has been increasingly investigated for melasma, with recent meta-analytic evidence supporting its efficacy while also highlighting heterogeneity across treatment approaches [16]. The liposomal formulation of azelaic acid may offer formulation-related advantages in topical delivery, as previous research has demonstrated enhanced pharmaceutical bioavailability with liposomal azelaic acid preparations [11]. Nevertheless, formulation performance was not directly assessed in the present study.

The safety findings were favorable, with most adverse reactions being mild, localized, and transient, primarily consisting of application-site irritation, erythema, and burning sensation. This is broadly consistent with the safety profile reported for topical treatments for melasma, in which local irritation is among the most frequently reported adverse effects [8,9,14]. The low discontinuation rate and high patient and physician satisfaction observed in the present study further suggest good short-term treatment acceptance. However, satisfaction and discontinuation should not be considered direct measures of adherence, as adherence was not independently assessed using a validated instrument.

Variability in treatment response is expected in melasma because of its heterogeneous clinical presentation and the influence of factors such as skin phototype, disease duration, lesion distribution, UV exposure, hormonal influences, and skincare practices [3-7]. The differences in response observed according to skin

type, melasma subtype, disease duration, and lesion distribution in the present study further support the importance of individualized management. Photoprotection remains an essential component of melasma treatment, and recent consensus recommendations emphasize continued photoprotection together with individualized topical and multimodal approaches [10].

An important strength of the present study is its large sample size and multicenter real-world design, providing complementary evidence to randomized clinical trials and systematic reviews. The study also provides information on treatment tolerability and patient and physician acceptance in routine clinical settings. However, the retrospective design may have introduced selection bias and variability in clinical assessment. The absence of a comparator arm limits direct assessment of comparative efficacy and prevents attribution of the observed improvement to any individual component of the formulation. The lack of routine Wood's lamp or dermoscopic assessment precluded evaluation according to the depth of melasma. In addition, sunscreen use and concomitant skincare or treatments were not standardized and may have influenced outcomes. Finally, the short follow-up period of one to two months limits conclusions regarding long-term efficacy, recurrence, maintenance of response, and long-term safety.

Conclusions

This large real-world retrospective study demonstrates that the combination topical therapy was associated with progressive improvement in melasma severity over the two-month observation period, with improvement observed in more than two-thirds of patients at two months. Treatment response varied across selected patient and disease characteristics, including Fitzpatrick skin type, melasma subtype, disease duration, and treatment duration.

The treatment was well tolerated, with predominantly mild local adverse reactions, low discontinuation rates, and high patient and physician satisfaction. These findings support the use of the combination regimen as a treatment option for melasma in routine clinical practice over the observed follow-up period. Prospective studies with longer follow-up are warranted to evaluate long-term efficacy, safety, maintenance of response, and relapse.

Appendices

Appendix A

Protocol Number: IND/MEL/01

Sponsor: Indchemie Health Specialities Pvt. Ltd.

Patient No.:

Patient Initials:

Date of Enrollment:

Patient Information:

- Date of Birth:
- Gender:
- Ethnicity:
- Fitzpatrick Skin Type:
- Melasma Characteristics: Epidermal | Dermal
- Date of Melasma Diagnosis:
- Duration of Melasma (months/years):
- Distribution of Pigmented Lesions (e.g., centrofacial, malar, mandibular):
- Baseline Melasma Severity Score (e.g., MSS score):

Disease activity	Melasma Severity Score
Melasma lesions almost equivalent to surrounding normal skin or with minimal residual pigmentation	0
Mild, slightly darker than surrounding normal skin	1
Moderate, moderately darker than surrounding normal skin	2
Severe, markedly darker than surrounding normal skin	3

TABLE 14: Baseline Melasma Severity Score

- Start Date of Cream Treatment (3% kojic acid, 10% liposomal azelaic acid, 1% tranexamic acid, 3% glycolic acid, and 1.5% 4-n-butylresorcinol):
- Duration of Cream Use:
- Frequency of Application (times per day/week):
- Melasma Severity Score (e.g., MSS): Visit: one month

Disease activity	Melasma Severity Score
Melasma lesions almost equivalent to surrounding normal skin or with minimal residual pigmentation	0
Mild, slightly darker than surrounding normal skin	1
Moderate, moderately darker than surrounding normal skin	2
Severe, markedly darker than surrounding normal skin	3

TABLE 15: Melasma Severity Score at one month

- Melasma Severity Score (e.g., MSS): Visit: two months

Disease activity	Melasma Severity Score
Melasma lesions almost equivalent to surrounding normal skin or with minimal residual pigmentation	0
Mild, slightly darker than surrounding normal skin	1
Moderate, moderately darker than surrounding normal skin	2
Severe, markedly darker than surrounding normal skin	3

TABLE 16: Melasma Severity Score at two months

- Physician global assessment: The physician global assessment is quantitated using a 0- to 6-point scale according to the residual area of Melasma after treatment:

Score	Description
0	Completely or almost completely cleared
1	≥90% clearance
2	75%–90% clearance
3	50%–74% clearance
4	25%–49% clearance
5	<25% clearance
6	Worsening

TABLE 17: Physician Global Assessment

Physicians Satisfaction:

- Very satisfied (⩾75% improvement)
- Satisfied (50%-75% improvement)
- Average (25%-50% improvement)
- Dissatisfied (⩽25% improvement)

Adverse Reactions:

- Skin irritation
- Erythema
- Burning sensation
- Allergic reaction

Severity of Adverse Reaction

- Mild
- Moderate
- Severe

Action Taken

- Continuation Of Treatment
- Dose Adjustment
- Discontinuation
- Additional Comments on Treatment Response:

Patient Satisfaction:

- Overall Satisfaction with Treatment (satisfied/not satisfied):
- Improvement in Melasma Appearance (yes/no):
- Willingness to Continue Treatment (yes/no):

Investigator's Comments:

Additional Notes or Observations:

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Rahul Pathak, Bikash Kar, R. D. Kharkar, Sharmistha Basu, Shruti Pal

Acquisition, analysis, or interpretation of data: Rahul Pathak, Bikash Kar, R. D. Kharkar, Sharmistha Basu, Shruti Pal

Drafting of the manuscript: Rahul Pathak, Bikash Kar, R. D. Kharkar, Sharmistha Basu, Shruti Pal

Critical review of the manuscript for important intellectual content: Rahul Pathak, Bikash Kar, R. D. Kharkar, Sharmistha Basu, Shruti Pal

Supervision: Rahul Pathak, Bikash Kar, R. D. Kharkar, Sharmistha Basu, Shruti Pal

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Lifepoint Research Ethics Committee issued approval IND/MEL/01. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** Statistical analysis for this study was conducted by an independent third party, HREE Research Pvt. Ltd., Pune, India. This study was sponsored by Indchemie Health Specialities Pvt. Ltd. **Financial relationships:** Dr. Rahul Pathak and Shruti Pal declare(s) employment from Indchemie Health Specialities Pvt Ltd. Mumbai, Maharashtra, India. Rahul Pathak and Shruti Pal declare(s) employment from Indchemie Health Specialities Pvt Ltd, Mumbai, India. Rahul Pathak and Shruti Pal are full-time employees of Indchemie Health Specialities Pvt Ltd, Mumbai, India. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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References

1. Sanchez NP, Pathak MA, Sato S, Fitzpatrick TB, Sanchez JL, Mihm MC Jr: Melasma: a clinical, light microscopic, ultrastructural, and immunofluorescence study. J Am Acad Dermatol. 1981, 4:698-710. 10.1016/s0190-9622(81)70071-9
2. Grimes PE, Yamada N, Bhawan J: Light microscopic, immunohistochemical, and ultrastructural alterations in patients with melasma. Am J Dermatopathol. 2005, 27:96-101. 10.1097/01.dad.0000154419.18653.2e
3. Tamega Ade A, Miot LD, Bonfietti C, Gige TC, Marques ME, Miot HA: Clinical patterns and epidemiological characteristics of facial melasma in Brazilian women. J Eur Acad Dermatol Venereol. 2013, 27:151-6. 10.1111/j.1468-3083.2011.04430.x
4. Hexsel D, Lacerda DA, Cavalcante AS, et al.: Epidemiology of melasma in Brazilian patients: a multicenter study. Int J Dermatol. 2014, 53:440-4. 10.1111/j.1365-4632.2012.05748.x
5. Achar A, Rathi SK: Melasma: a clinico-epidemiological study of 312 cases . Indian J Dermatol. 2011, 56:380-2. 10.4103/0019-5154.84722
6. Guinot C, Cheffai S, Latreille J, et al.: Aggravating factors for melasma: a prospective study in 197 Tunisian patients. J Eur Acad Dermatol Venereol. 2010, 24:1060-9. 10.1111/j.1468-3083.2010.03592.x
7. Mandry Pagán R, Sánchez JL: Mandibular melasma. P R Health Sci J. 2000, 19:231-4.
8. González-Molina V, Martí-Pineda A, González N: Topical treatments for melasma and their mechanism of action. J Clin Aesthet Dermatol. 2022, 15:19-28.
9. Chang YF, Lee TL, Oyerinde O, et al.: Efficacy and safety of topical agents in the treatment of melasma: What's evidence? A systematic review and meta-analysis. J Cosmet Dermatol. 2023, 22:1168-76. 10.1111/jocd.15566
10. Passeron T, Desai SR, Abdallah M, et al.: Global consensus on the management of melanin hyperpigmentation disorders. J Eur Acad Dermatol Venereol. 2026, 40:760-72. 10.1111/jdv.70185
11. Burchacka E, Potaczek P, Paduszyński P, Karłowicz-Bodalska K, Han T, Han S: New effective azelaic acid

liposomal gel formulation of enhanced pharmaceutical bioavailability. Biomed Pharmacother. 2016, 83:771-5. 10.1016/j.biopha.2016.07.014

12. Heidemeyer K, Cazzaniga S, Feldmeyer L, et al.: Skin hyperpigmentation index in melasma: a complementary method to classic scoring systems. J Cosmet Dermatol. 2023, 22:3405-12. 10.1111/jocd.15866
13. Pennitz A, Kinberger M, Avila Valle G, Passeron T, Nast A, Werner RN: Self-applied topical interventions for melasma: a systematic review and meta-analysis of data from randomized, investigator-blinded clinical trials. Br J Dermatol. 2022, 187:309-17. 10.1111/bjd.21244
14. Sarkar R, Handog EB, Das A, et al.: Topical and systemic therapies in melasma: a systematic review . Indian Dermatol Online J. 2023, 14:769-81. 10.4103/idoj.idoj_490_22
15. Philipp-Dormston WG: Melasma: a step-by-step approach towards a multimodal combination therapy . Clin Cosmet Investig Dermatol. 2024, 17:1203-16. 10.2147/CCID.S372456
16. Calacattawi R, Alshahrani M, Aleid M, et al.: Tranexamic acid as a therapeutic option for melasma management: meta-analysis and systematic review of randomized controlled trials. J Dermatolog Treat. 2024, 35:2361106. 10.1080/09546634.2024.2361106
17. Madan Mohan NT, Gowda A, Jaiswal AK, Sharath Kumar BC, Shilpashree P, Gangaboraiah B, Shamanna M: Assessment of efficacy, safety, and tolerability of 4-n-butylresorcinol 0.3% cream: an Indian multicentric study on melasma. Clin Cosmet Investig Dermatol. 2016, 9:21-7. 10.2147/CCID.S89451