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Research Article

Melasma

A prospective, observational study of Cosmelite NextTM therapy to evaluate the efficacy and safety of a novel plant-derived combination in the treatment of Melasma at dermatological centres in Hyderabad

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Background and objectives: Melasma, an acquired condition of skin hyperpigmentation, is a difficult condition to treat. This study was conducted to evaluate the efficacy and safety of a novel plant-derived combination for Melasma, Cosmelite NextTM, containing a combination of silymarin (0.7%), soy Isoflavones (0.25%), pTerowhite (0.10%), kojic acid (2%), ascorbic acid (1%), niacinamide (4%) and mandelic acid (3%). **Material and Methods:** This was an open-label, single-arm, prospective, multi-centre observational study at dermatological centres in Hyderabad, India. Patients diagnosed with Melasma of either gender and skin type consistent with Fitzpatrick phototypes I-IV categories were enrolled across Hyderabad, India. Outcomes included melasma area and severity index (MASI) score, lesion score, physician's global assessment (PGA) and patient's global assessment score. **Results:** In terms of the primary variable, the change from baseline score to 12 weeks in MASI was statistically significant (mean difference 1.46 (95% CI 1.39–1.52); p=0.001), and the decreasing trend was observed from week four onwards. Lesion scores also decreased from the baseline to week 12, with a mean difference of 1.46 (95% CI 1.39–1.52; p=0.001). At the end of the study period, 91% of the patients showed some improvement in the PGA, whereas 93% showed improvement in the patients' global assessment score. **Conclusion:** Cosmelite NextTM was safe and efficacious, and the improvements in assessment scores were seen as early as four weeks. The novel combination could be an effective alternative to conventional treatments such as hydroxyquinone, retinoids and steroid preparations.

Keywords: Melasma, Silymarin, Soy Isoflavones, Kojic acid, Ascorbic acid, Mandelic acid

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Introduction

Melasma, an acquired condition of skin hyperpigmentation, has a causal relation to sun exposure [1]. In India, 20-30% of women aged 40-65 years present with facial Melasma [2]. Pathophysiologically, both epidermis and dermis are affected with up-regulation in melanocytes and other pigment-associated cells [3]. Melasma is a difficult condition to manage, and the treatment modalities include topical, oral and procedural techniques [4]. As per clinical practice guidelines, sun exposure avoidance is the cornerstone for effective disease management [5]. In terms of pharmacological agents, hydroxyquinone, usually in combination with other agents, is considered the gold standard treatment [5]. However, hydroxyquinone use is associated with skin irritation, contact dermatitis and exogenous ochronosis, especially in dark-skinned individuals [6].

Apart from hydroxyquinone, another depigmenting agent, azelaic acid, is known to cause skin irritation side effects [7]. Topical steroids improve outcomes; however, they have been associated with local and systemic side effects, especially with long-term usage [8]. Topical retinoids increase melanocyte turnover and reduce melanocyte activity. They are to be used with caution, as they have reported teratogenic side effects [9]. Other side effects with retinoid derivatives include mild skin irritation, reversible photosensitivity and less commonly paradoxical hyperpigmentation. Alternatively, plant-based extracts have been developed with the hope of providing a better safety profile. Although several studies have demonstrated that the addition of polypodium leucotomos extract (PLE) to sun protection creams has resulted in improvement of melasma area and severity index (MASI) and quality of life scores, well-controlled randomized studies have failed to show a significant benefit [10].

As researchers started exploring natural plant derivatives, silymarin, a flavonoid, showed encouraging results in this regard. Nofal et al. demonstrated that the use of silymarin resulted in a similar reduction in the MASI score compared to hydroxyquinone; however, side effects were fewer [11]. Silymarin has been used in different dermatological conditions

For its antioxidant, anti-inflammatory, immunomodulatory and photoprotective properties. Other plant-based active compounds include soy isoflavones, kojic acid, pterostilbene, Ascorbic Acid, niacinamide and mandelic acid. Soy isoflavones are protease inhibitors, while kojic scavenges free radicals, inhibits tyrosinase and has antioxidant properties [12]. Pterostilbene has demonstrable anti-ageing and skin-brightening properties [13]. Studies have suggested that they improve outcomes in Melasma compared to hydroxyquinone, at times having a faster response time [14]. As combination therapies have come to the forefront in the management of Melasma, it is prudent to explore various combinations of natural remedies for their efficacy and safety in melasma patients. In this regard, Oaknet Healthcare Pvt Ltd has formulated a novel skincare cream, Cosmelite Next™, containing a combination of silymarin (0.7%), soy isoflavones (0.25%), p-terowhite (0.10%), kojic acid dipalmitate (2%), 3-o-ethyl ascorbic acid (1%), niacinamide (4%) and mandelic acid (3%) for the treatment of Melasma in Indian patients. Given the novelty of this combination, we decided to conduct this study to generate evidence on the efficacy and safety of this product.

Materials and Methods

An open-label, single-arm, prospective, multi-centre, observational study was planned to evaluate the efficacy and safety of Cosmelite Next™ in patients suffering from Melasma. The dermatological centres for the study were selected exclusively from Hyderabad, India. The combination drug was administered in real-world settings for 12 weeks. Ethics committee approval was obtained from individual centres. The study was conducted in accordance with the good clinical practice guidelines laid down by the 'International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Eligibility: Patients of either gender and skin type consistent with Fitzpatrick phototypes I-IV categories diagnosed with Melasma were enrolled into the study. The entry criterion for the study was an age cut-off of 18 years. Only patients willing to provide informed consent for a photographic release were eligible to participate. Patients were instructed to stop all facial treatments such as topical, systemic, laser or surgical treatment,

Otherwise interfering with the efficacy assessment. Investigators had the option of excluding a subject if any associated skin condition would interfere with study evaluation. Patients were not allowed any new facial make-up products during the treatment period. If they were taking any product before the study entry, they should have done so for the preceding two weeks without any issue.

Pregnant or nursing women, patients using concomitant skincare products, patients whose primary occupation involved outdoor activities and patients who had a history of non-compliance to the prescribed dosage schedule were excluded from the study. Further, patients with a history of photosensitivity, skin conditions such as psoriasis, rosacea, acne, eczema and known allergy to similar components of the test drug were also excluded.

Study procedure and schedule of assessments: Patients were briefed on the procedures by the study personnel. Following the briefing, if they agreed to participate, informed consent was taken, and they were assigned a patient enrollment identification number and assessed for eligibility, including concomitant medication usage. These checks were part of the screening visit. On 'Day 0' corresponding to the baseline visit Cosmelite Next™, the study medication was prescribed, and outcome assessments were carried out, including facial photographs. Instructions for applying the study cream were imparted, and patients were strictly advised to avoid sun exposure, especially from 10 AM to 2 PM. Patients were also provided sunscreen for sun protection. After the baseline visit, patients were asked to visit the clinic every four week, corresponding to week 4 (1st follow-up visit), week 8 (2nd follow-up visit) and end of the study visit, i.e., week 12. At each follow-up visit, facial photographs were taken for outcome assessments, adverse events were noted, and patients were verbally enquired regarding the compliance to the medication.

Study medications: Cosmelite Next™ was prescribed as per the instructions mentioned in the package insert. The recommended schedule of the drug is a twice-daily application in and around the affected lesions. Before application, patients are advised to wash their face gently with a face wash.

Outcome assessment: Four efficacy outcomes were evaluated for each patient. First, the MASI score [33] from baseline and at every follow-up Visit. This scoring system comprises a pigment score weighted by area and homogeneity across different areas of the face. The score was calculated as follows:

MASI= 0.4 ($a \times p^2$) l+ 0.4 ($a \times p^2$) r+ 0.2 ($a \times p^2$) n. In the formula, 'a' stands for the 'area of involvement', 'p' for the 'severity of pigmentation', 'l' for the left face, 'r' for the right face and 'n' for the nose. The area involved, as well as the severity of pigmentation, was scored from 0 to 4, wherein score 0 represented no visible pigmentation; score 1: rarely visible pigmentation; score 2: mild pigmentation; score 3: moderate pigmentation and score 4: severe pigmentation.

Second, the area lesion score was assessed and rated as follows: score 1: area of involvement less than or equal to 10%; score 2: area involvement of 11-30%; score 3: area involvement of 31-60% and score 4: area involvement of > 60%.

Third, patients were also rated by the investigator based on the physician's global assessment (PGA) scale and, fourth, the patients themselves assessed improvements based on the patient's global assessment. A 7 points grade rating system was used, where '0' represented 'clear lesion' except for residual discolouration; '1' represented 'almost clear, with 90% clearance of the lesion; '2' represented marked improvement (~75%); '3' represented moderate improvement (~50%); '4' represented moderate improvement (~20%), '5' represented no improvement (condition unchanged) and '6' represented worse, indicating condition deterioration compared to baseline.

Adverse events were noted during the follow-up visits and were graded as mild, moderate and severe. Additionally, the causal nature of the adverse event was also ascertained. If in the investigator's opinion, the study medication caused unacceptable adverse side effects, then the investigator could exercise discretion to stop the treatment.

Statistical analysis

All variables that followed normal distribution were represented as mean and reported along with their standard deviation (SD). Categorical variables were defined using frequencies and percentages. For the outcome variables– MASI, and area lesion score, a paired t-test was applied

For comparison from baseline to the follow-up visits. Clinical scales such as PGA and patients' global assessments were analyzed using the Mc Nemar test. To compute the sample size based on the primary variable, MASI score**,** we assumed an effect size of 0.2 for change from baseline to 12 weeks with 80% power and an alpha error of 5%. Given these assumptions, we arrived at a sample size of 200.

Results

A total of 180 patients were recruited for this study across Hyderabad, India. Females constituted 62% (112 out of 180) of the cohort. There were 20 dropouts in the study due to the COVID-19 pandemic. The mean age of the patients was 45 (12 SD). They were ethnically Indians (100%) with a mean body mass of 24.96 (4.34) kg/m2. In the entire study population, 53 (29.4%) were housewives, and 65 (36.1%) worked in the service industry. History of pregnancy was noted in 79 (69.2%) of the female cohort, and 8 (7.1%) had a history of oral contraceptive usage. Facial Melasma was diagnosed in 157 (87.22%) patients, whereas Melasma restricted to the cheeks was diagnosed in 23 (12.77%) patients of the study population. Relevant medical history is enumerated in Table 1.

In terms of the outcome variables, the MASI score at baseline was 20.62 (6.29 SD). There was a statistically significant decrease in the MASI score from week four onwards, and the trend continued till the end of week 12 (Table 2). The primary variable, i.e., change from baseline in the MASI score to week 12, was statistically significant (mean difference 1.46 (95% CI 1.39–1.52); p=0.001). The analysis of the lesion score showed a similar trend of decrease from week four onwards. The lesion score decreased from a baseline value of 6.42 (1.14 SD), and at the end of week 12, the value was 4.96 (1.23 SD), representing a mean difference of 1.46 (95% CI 1.39–1.52; p=0.001).

Subjective assessments in PGA and the patient's global assessment showed a statistically significant decrease from week four onwards (P=0.001). At the end of the study period (week 12), 91% of the patients showed improvement as per the PGA, and 93% showed improvements according to patients' global assessment (Figures 1 and 2).

There were no dropouts in the study due to adverse Events. Safety findings included 2 (1.11%) patients reporting itching and 1 (0.55%) patient reporting burning sensation. No serious adverse events were noted.

Table 1: Baseline characteristics of the study population

Baseline characteristics	N=180
Age, mean ± SD	45 ± 12
Female gender, n (%)	112 (62.22)
Height in cms, mean ± SD	161.28 ± 19.46
Weight in kgs, mean ± SD	63.23 ± 11.88
Body mass index kg/m2, mean ± SD	24.96 ± 4.34
Ethnicity, n (%)	180 (100)
Occupation, n (%)	
Business	23 (12.77)
Professional	12 (6.66)
Housewife	53 (29.44)
Retired life	17 (9.44)
Service industry	65 (36.11)
Student	10 (5.55)
History of pregnancy, n (% of females)	79 (69.29)
Diagnosis, n (%)	
Facial Melasma	157 (87.22)
Melasma cheeks	23 (12.77)
Medication history, n (%)	
Oral contraceptive use, n (% of females)	8 (7.14)
Golite/T.Tresma/Photostable	3 (1.66)
Hypothyciel, 75mg/day	2 (1.11)
Vit C/Sun Ban/Cute E tab	13 (7.22)
Past medical history, n (%)	
Diabetes Mellitus	25 (13.88)
Hypothyroidism	10 (5.55)
Hypertension	1 (0.55)
Hemorrhoids	1 (0.55)
Hysterectomy, n (% of females)	2 (1.75)
Tubectomy, n (% of females)	1 (0.87)
LSCS, n (% of females)	1 (0.87)

LSCS, lower segment caesarean section

Table 2: MASI throughout the study period

	MASI score (mean ± SD)	Mean difference (95% CI)	P-value*
Baseline	20.62 (6.29)		
Week 4	16.27 (4.71)	4.35 (3.25–5.45)	0.001
Week 8	14.31 (4.84)	6.31 (5.13-7.50)	0.001
Week 12	10.31 (4.16)	10.32 (9.17-11.46)	0.001

*Paired t-test

CI, confidence interval

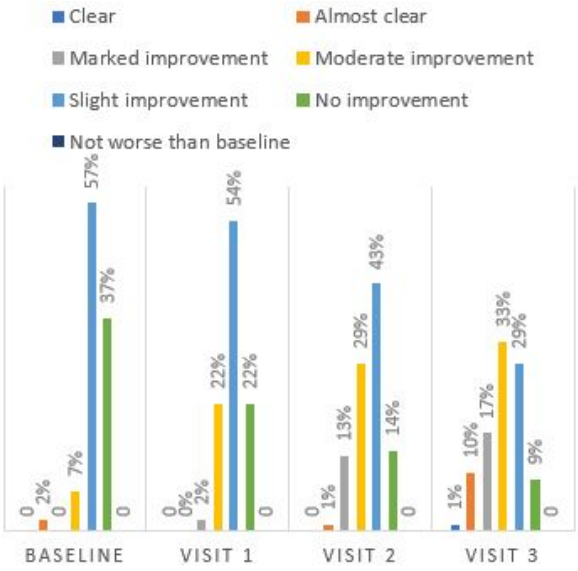
Table 3: Lesion score throughout the study period

	Lesion score (mean ± SD)	Mean difference (95% CI)	P-value*
Baseline	6.42 (1.14)		
Week 4	5.94 (1.16)	0.48 (0.44–0.51)	0.001
Wek 8	5.48 (1.16)	0.94 (0.89–0.99)	0.001
Week 12	4.96 (1.23)	1.46 (1.39–1.52)	0.001

*Paired t-test

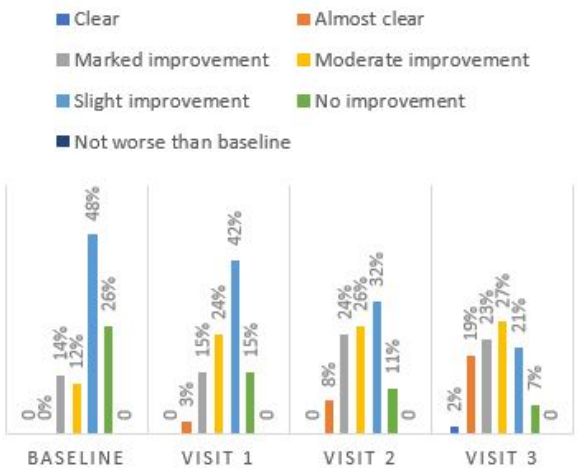
CI, confidence interval

Figure 1: Physicians global assessment



*P=0.001 for improvement from baseline to week four onwards, calculated by Mc Nemar chi-square test

Figure 2: Patient's global assessment



*P=0.001 for improvement from baseline to week four onwards, calculated by Mc Nemar chi-square test

Discussion

As no treatment for Melasma has shown to be fully effective, the focus has shifted from achieving good efficacy to a better safety profile. In this study, Cosmelite NextTM was used in real-world settings as per the investigators' discretion across India. The main findings of the study were 1) there was a significant reduction in MASI over 12 weeks with efficacy seen as early as week four onwards; 2) similarly, the size of the lesion reduced significantly from week four onwards, and the decreasing trend continued till week 12; 3) subjective improvements assessed by PGA and patient's global assessment showed significant improvements starting from week 4, and the improvements continued till the end of week 12 and 4) adverse events were mild and reported only in 3 (1.6%) patients. Due to multiple ingredients in the formulation and the challenges because of having no comparators in our study, we intend to discuss silymarin as it is a unique ingredient in the formulation.

The MASI score decreased approximately 50% from the baseline value of 20.62 (6.29 SD) to 10.31 (4.16 SD) at the end of week 12. The improvements were observed as early as week 4 onwards, with a mean difference of 4.35 (95% CI 3.25–5.45) of the baseline values. In Nofal et al.'s study (11), silymarin (0.7%) showed a 36.11% decrease in the MASI score at the end of week 12, a comparatively lesser reduction to our study findings. A mean difference of 4.62 was observed after four weeks, similar to a mean difference of 4.35 in our study. The comparator arm containing hydroxyquinone also showed similar results [11]. A lower percentage decrease in Nofal et al.'s (19) could be because our study had additional active biological molecules that could independently decrease pigment scores. Therefore, although our study had no comparator arm, the decrease in the MASI score was slightly more, which could be attributed to the additional active ingredients in the Cosmelite NextTM formulation.

The lesion score in our study improved from a baseline value of 6.42 (1.14 SD) to 4.96 (1.23 SD), indicating a mean difference of 1.46 (95% CI 1.39–1.52) at the end of week 12. Moreover,

A statistically significant mean difference of 0.48 (95% CI 0.44–0.51) was observed at the beginning of week 4. As the MASI score is an area-weighted pigment score, the arguments relevant to MASI apply to the lesion score as well. Therefore, we do not intend to discuss the implications of this score separately.

PGA and patients' global assessments are necessary outcome measures in dermatological studies. Our study showed that PGA decreased from week four onwards, and 91% of patients showed improvement at the end of week 12. On the other hand, 93% of patients reported improvements in their appearance as adjudicated by the patient's global assessment. In Nofal et al.'s study, 35.7% of patients had 'medium' to 'good' responses at the end of 4 weeks and only

78.6% showed improvement at the end of 12 weeks [19]. These lower response rates can be explained by the fact that our study used other biologically active substances in addition to silymarin. In contrast, Nofal et al.'s study used silymarin as a monotherapy. Since Melasma can have psychological effects, impacting the quality of life, a promising new treatment must be perceived from the patient's perspective to be effective. Given the results of our study, patients perceived Cosmelite NextTM to be highly efficacious, and this could be an indirect measure of the impact on the quality of life. The small percentage of the patients, i.e., 7% who did not respond to the treatment, were likely melasma-resistant cases. Non-responders to the treatment in our study were similar to the previously reported results [11]. For resistant patients, there are other modalities of treatment, such as chemical peels and lasers, that can be explored [5].

In terms of safety, findings were uneventful, with only 2 (1.11%) patients reporting adverse events and no dropouts in the study. It is noteworthy that previous studies with silymarin reported no adverse events compared to 71.4% in the hydroxyquinone arm [11]. The adverse events reported in our study were, moreover, of mild grade. These findings were expected as most naturally occurring remedies have decreased adverse events compared to conventional treatments such as hydroxyquinone, retinoids and steroids [15].

Biologically, it is difficult to pinpoint the precise mechanism for improved efficacy as Cosmelite NextTM Combines multiple pharmacologically active substances. Undoubtedly, the effects of silymarin scavenging free radicals and the antioxidant property are well known and would have likely contributed to the higher responses seen [16]. Besides, some studies have suggested that silymarin inhibits interleukin-1b, prostaglandin E2, and tumour necrosis factor-alpha collectively constitute an anti-inflammatory effect, which also may have a role in the overall response [16]. Kojic Acid and niacinamide affect the melanin synthesis pathway [16], acting at different levels and turnover of melanocytes at different stages. Ascorbic acid and mandelic acid's anti-blemishing properties could have also equally contributed to the overall appearance [17]. Skin irritation and erythema that accompany most topical preparation would be mitigated by the post-inflammatory hyperpigmentation effect of mandelic acid [17]. Additionally, pterostilbene's skin brightening properties would reinforce the beneficial effects of other ingredients. Taken together, with multiple biological mechanisms involved, Cosmelite NextTM could be an effective alternative to hydroxyquinone and steroids, as the formulation is not only efficacious but has superior safety because it is devoid of commonly occurring adverse events with conventional agents [15].

Our study had several limitations. First, there was no comparator arm, which otherwise would have helped us in reasonably concluding the efficacy of a particular ingredient. Second, long-term effectiveness and safety were not ascertained in our study. Third, objective assessments in terms of wood-lamp examination were not carried out. Fourth, subjective assessments have an inherent bias, which cannot be discounted. Nevertheless, capturing real-world experience gives an essential perspective on how a drug is perceived in clinical settings rather than strictly controlled-experimental scenarios. Future randomized-controlled trials would shed more light on the possible mechanisms and the individual contributory aspect of each ingredient towards the efficacy of the formulation.

Conclusion

Cosmelite NextTM was efficacious, and the improvements in assessment scores were seen as early as four weeks. There were no tolerability and safety concerns with the study

Medication. The formulation could prove to be an effective alternative to conventional treatments such as hydroxyquinone, retinoids and steroid preparations.

What this study adds to the existing knowledge?

The study cream, Cosmelite NextTM is often prescribed in the management of melasma, however, there are no clinical studies on this product. Therefore, this study was conducted to document the efficacy and safety of Cosmelite NextTM. The results of this study would be helpful to dermatologist in planning management of melasma. This is the first report on the use of Cosmelite NextTM in the management of melasma.

Authors Contribution

Conception, design, collection, assembly of data, data analysis and interpretation, manuscript writing: All authors

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