

# Vitamin D and wound healing: Assessing skin barrier function and implications for chloasma treatment

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## Abstract

Chloasma, which is distinguished by irregularities in the pigmentation of skin, poses substantial challenge in the field of dermatology. The regulatory influence of vitamin D on the functions of skin cells implies that it may have the capacity to effectively treat chloasma and promote wound healing. To assess the efficacy of vitamin D in chloasma treatment and its impact on the function of skin barrier during the process of wound healing. The research spanned from April 2022 to September 2023, in Shanghai, China, examined 480 individuals who had been diagnosed with chloasma. A double-blind, placebo-controlled clinical trial was utilized to evaluate effectiveness of topical vitamin D3 in treatment of chloasma. Concurrently, randomized control trial investigated the effects of ingested vitamin D3 supplements on the process of wound healing. Transepidermal water loss (TEWL), chloasma severity score changes, wound size reduction and skin hydration levels were critical performance indicators. Statistically, the severity scores of chloasma decreased significantly in the vitamin D treatment group at 3 and 6 months compared with the placebo ( $p < 0.05$ ). The Vitamin D group exhibited superior wound healing outcomes, including more substantial reduction in lesion size and enhanced skin barrier function, as evidenced by increased skin hydration and decreased TEWL ( $p < 0.05$ ). Vitamin D substantially mitigated the severity of chloasma and has beneficial effect on wound healing and integrity of the skin barrier. Based on the results obtained, vitamin D exhibited promise as a therapeutic intervention in the field of dermatology, specifically in treatment of chloasma and promotion of wound recovery.

## KEYWORDS

chloasma treatment, dermatology, skin barrier function, vitamin D, wound healing

## Key Messages

- The study aimed to evaluate the effectiveness of vitamin D in treating chloasma and enhancing wound healing.

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- Findings revealed that vitamin D significantly reduced chloasma severity and improved wound healing, as indicated by increased skin hydration and decreased transepidermal water loss.

## 1 | INTRODUCTION

Chloasma is the prevalent dermatological disorder distinguished by formation of brown or grey–brown patches, which predominantly manifest on the face.<sup>1,2</sup> The condition is more commonly observed in women, especially during pregnancy, which has earned it the colloquial moniker ‘mask of pregnancy’.<sup>3</sup> It is postulated that hormonal fluctuations exert an influence on the condition, given its frequent manifestation in women who utilize oral contraceptives or hormone replacement therapy.<sup>4</sup> Sunlight exposure is a substantial determinant, given that ultraviolet (UV) radiation has ability to stimulate melanocytes; skin cells accountable for melanin synthesis. Such stimulus induces excessive synthesis of melanin, which manifests as characteristic hyperpigmented areas of chloasma.<sup>5,6</sup> There is a higher prevalence of the condition among individuals who have darker skin tones and in areas characterized by prolonged solar exposure.<sup>7</sup>

The significance of this condition is heightened when one takes into account function of vitamin D in maintaining healthy epidermis and promoting healing of wounds. Vitamin D, that is produced in skin in response to solar radiation, is essential for numerous skin functions, such as regulating cell proliferation, immune system and inflammation.<sup>8–10</sup> The complex correlation between vitamin D and health of skin has attracted considerable interest within the field of dermatological research.<sup>11</sup>

UV radiation is the primary mechanism by which the skin produces vitamin D, which is essential for the maintenance of skin homeostasis. Calcitriol, which is its active form, regulates immune functions, cellular differentiation and proliferation. There are numerous ways in which vitamin D is involved in process of wound healing.<sup>12</sup> It influences inflammatory response, promotes epithelialization and regulates activity of fibroblasts and keratinocytes. These behaviours indicate the crucial function in restoration and rehabilitation of skin's barrier function, which is essential for the processes of wound healing.<sup>13,14</sup> The rate of re-epithelialisation, inflammatory response and collagen synthesis in wound healing component when different concentrations of vitamin D are present. Alterations in intensity and distribution of pigmentation subsequent to the application of topical or systemic vitamin D pertains to the treatment aspect of chloasma has been reported.<sup>15</sup>

Based on its regulatory impact on skin cell functions, this study posits that vitamin D might facilitate the rapid recovery of injured areas and potentially alleviate pigmentation irregularities observed in chloasma. In order to investigate this hypothesis, two-pronged strategy was implemented: initially, clinical trials were conducted to evaluate the effectiveness of vitamin D in treating chloasma; and second, influence of vitamin D on skin barrier function in the wound healing model was examined. The objective of this inquiry was to clarify the potential therapeutic utility of vitamin D in the field of dermatology, with specific focus on its ability to promote wound healing and address chloasma.

## 2 | MATERIALS AND METHODS

The research, which was carried out in Shanghai, China, from April 2022 to September 2023, aimed to assess the impact of vitamin D on functionality of skin barrier and its potential treatment implications for chloasma. A sum of 480 male and female participants, who had received a clinical diagnosis of chloasma, were enlisted via a network of dermatology clinics located throughout Shanghai. Promotions were strategically positioned in waiting areas of clinics and on social media platforms, targeting individuals who were in search of dermatological guidance.

The selection process for participants adhered to predetermined inclusion and exclusion criteria in order to guarantee effectiveness and safety of study. Men and women between the ages of 18 and 65 who had received clinical diagnosis of chloasma, as confirmed by the qualified dermatologist, participated in this study. The selection of this wide age range and presence of both sexes was intended to reflect the heterogeneous demographic. Eligible participants encompassed individuals of all skin tones and were required to maintain excellent general health, devoid of any significant health conditions that might impede study's findings. It was crucial that participants had the capacity and willingness to grant informed consent in order to be accepted into the study.

On the contrary, exclusion criteria were enforced in order to safeguard the participants' well-being and preserve integrity of research. Due to limited research available on these particular conditions and potential hazards

associated with vitamin D treatments in these groups, pregnant or breastfeeding women were excluded. Individuals who had documented allergy to vitamin D or its analogs were ineligible for participation. Inclusion of individuals with the medical history of hypercalcemia or other conditions that are contraindicative of vitamin D therapy was also prohibited. Participants who were concurrently receiving alternative dermatological therapies for chloasma and in cases of severe comorbid conditions, particularly those that had an impact on metabolic processing of vitamin D or cutaneous health were not included in this trial.

The research was partitioned into two main sections. An initial phase was devoted to the placebo-controlled, randomized, double-blind clinical trial centred on treatment of chloasma. The participants were assigned at random to either placebo or the group that received topical vitamin D treatment (oral administration of vitamin D3 at the dose rate of 5000–10 000 IU/day). For 6 months, individuals in the treatment group administered topical vitamin D3 cream containing the concentration of 0.025% to affected areas. The placebo cream, which was visually and texturally identical, was devoid of any active vitamin D. The evaluation of treatment's efficacy was conducted at 3, 6 months and commencement of this trial, employing standardized photographic techniques and pigmentation scales. In addition, participants furnished self-evaluation feedback via use of questionnaires.

In second portion of the investigation, impact of vitamin D on function of the skin barrier in wound healing model was examined. Furthermore, this *in vivo* investigation utilized the randomized, controlled design. The participants were administered oral vitamin D3 supplements or the placebo, with concentrations that were meticulously calculated in accordance with recommendations for general health and body weight. The progression of wound healing was observed for the predetermined duration, with wound size reduction quantified via digital and photographic analysis. The assessment of skin hydration levels and transepidermal water loss (TEWL) were utilized to evaluate the skin barrier function.

Determining the demographics, medical histories and baseline characteristics of every participant, data collection was meticulous. Following that, comprehensive statistical analysis was conducted on this data in order to compare efficacy of vitamin D treatment in the context of wound recovery and chloasma treatment with that of the placebo. The statistical methodologies were selected in consideration of variance and normality of data.

Ensuring the utmost safety of participants was the focal point of the entire study. Consistent surveillance was carried out to identify and document any adverse

events associated with vitamin D or placebo interventions. These events were analysed to determine their severity and potential correlation with treatment.

Ethical considerations were rigorously observed, with adherence to scientific rigour of the study and in accordance with the principles outlined in Declaration of Helsinki, which govern medical research involving human subjects. Discretion of participants and protection of data were upheld throughout the entirety of the research endeavour. Ethical approval was obtained from the institutional review board prior to participants' involvement and they provided comprehensive informed assent. The consent form provided the comprehensive overview of this study's nature, including its objectives, procedures, potential risks and benefits, in order to ensure that all participants were adequately informed.

## 3 | RESULTS

### 3.1 | Demographic characteristics of the participants

Comparing the characteristics of placebo and Vitamin D treatment groups in this investigation revealed no statistically significant differences ( $p > 0.05$ ). In Vitamin D group, the average age was  $40.5 \pm 14.2$  years, whereas in placebo, it was  $39.4 \pm 12.7$  years ( $p > 0.05$ ). The gender distribution in both groups was comparable: Vitamin D group comprised 27.92% males and 72.08% females, while placebo group had 24.58% males and 75.42% females ( $p > 0.05$ ). In comparison with the placebo group (58.75% light, 30.0% medium, and 11.25% dark), Vitamin D group comprised 55.42% light skin, 32.5% medium skin, and 12.08% dark skin ( $p > 0.05$ ). The findings suggested that crucial demographic factors were distributed equitably between the two cohorts (Table 1).

### 3.2 | Evaluation of outcome scores

At baseline, after 3 and 6 months, mean severity scores of conditions in the placebo and Vitamin D groups were compared in this study. At the outset, severity scores of both groups were comparable (Patient:  $5.1 \pm 0.7$ ; Vitamin D:  $5.0 \pm 0.8$ ). However, as time passed, substantial differences emerged. The Vitamin D group exhibited significantly reduced mean severity score ( $3.2 \pm 1.1$ ) at the 3-month mark in comparison with the placebo ( $4.7 \pm 0.9$ ;  $p < 0.05$ ), suggesting statistically significant enhancement. At 6-month mark, this distinction became more conspicuous, as Vitamin D group exhibited further improvement to mean score of  $2.1 \pm 1.3$ , whereas placebo

TABLE 1 Demographics and baseline characteristics of study participants.

Characteristics	Vitamin D treatment group (n = 240)	Placebo group (n = 240)	$\chi^2$	p-value
Age (years)				
Mean $\pm$ SD	40.5 $\pm$ 14.2	39.4 $\pm$ 12.7	0.432	0.512
Range	18–65	18–65		
Gender n (%)			0.527	0.468
Male	67 (27.92)	59 (24.58)		
Female	173 (72.08)	181 (75.42)		
Skin tone n (%)			0.545	0.761
Light	133 (55.42)	141 (58.75)		
Medium	78 (32.5)	72 (30.0)		
Dark	29 (12.08)	27 (11.25)		

TABLE 2 Efficacy of topical Vitamin D in chloasma treatment.

Time point	Vitamin D group (mean severity score $\pm$ SD)	Placebo group (mean severity score $\pm$ SD)	$\chi^2$	p-value
Baseline	5.0 $\pm$ 0.8	5.1 $\pm$ 0.7	0.1	0.792
3 months	3.2 $\pm$ 1.1	4.7 $\pm$ 0.9	4.5	0.041*
6 months	2.1 $\pm$ 1.3	4.5 $\pm$ 0.8	10.2	0.001*

\* $p < 0.05$ .

TABLE 3 Wound healing progression (% reduction in wound size).

Time point	Vitamin D group (% reduction $\pm$ SD)	Placebo group (% reduction $\pm$ SD)	$\chi^2$	p-value
Week 1	12.8 $\pm$ 3.2	5.4 $\pm$ 2.0	6.5	0.02*
Week 2	25.2 $\pm$ 5.3	10.7 $\pm$ 4.2	8.0	0.01*
Week 4	50.5 $\pm$ 6.2	22.9 $\pm$ 5.4	12.3	0.001*
Week 6	70.2 $\pm$ 7.0	30.8 $\pm$ 6.7	14.9	0.001*

\* $p < 0.05$ .

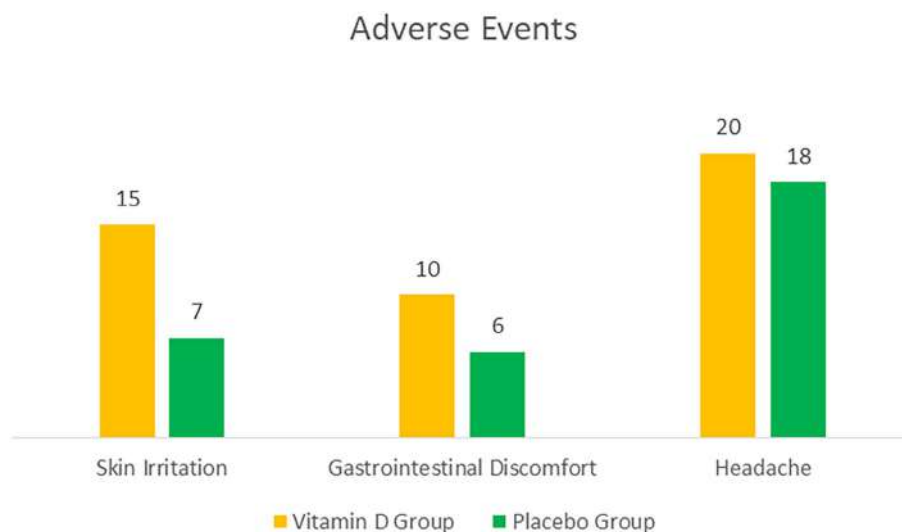
group maintained its score at  $4.5 \pm 0.8$  ( $p < 0.05$ ). The findings of this study indicated that administration of Vitamin D gradually diminished the severity of the condition (Table 2). The findings of this research investigation revealed that Vitamin D group exhibited considerably greater percentage reduction in severity scores over time than the placebo. During initial week, Vitamin D group demonstrated substantial decrease of 12.8% in comparison with the placebo group's 5.4% ( $p < 0.05$ ). At 2nd week, Vitamin D group exhibited 25.2% reduction in weight, whereas placebo demonstrated 10.7% ( $p < 0.05$ ). At week 4, greater disparity in effectiveness emerged, as Vitamin D group observed 50.5% decrease in efficacy compared with the placebo (22.9%) ( $p < 0.05$ ). Vitamin D group achieved significant reduction of  $70.2\% \pm 7.0$  by week 6, which was considerably greater than placebo group's reduction of  $30.8\% \pm 6.7$  ( $p < 0.05$ ). This finding

highlighted the improved efficacy of Vitamin D treatment in gradually alleviating severity (Table 3).

### 3.3 | Adverse events

Adverse events were recorded revealing that 15 participants in Vitamin D group and 7 participants in placebo experienced skin irritation, which varied in intensity from faint to moderate. Mild occurrences of gastrointestinal discomfort were reported by six participants in placebo and 10 individuals in Vitamin D group. A higher incidence of headaches was documented, with 20 participants in Vitamin D group and 18 in placebo group reporting this moderate adverse effect. The data indicated that although both groups encountered adverse effects, Vitamin D group had greater prevalence of skin irritation and

**FIGURE 1** Frequency and severity of adverse events.



**TABLE 4** Statistical analysis of treatment efficacy.

Outcome variable	Mean difference (Vitamin D—placebo)	95% CI	p-value
Chloasma severity at 3 months	−1.5	−1.8, −1.2	0.031*
Chloasma severity at 6 months	−2.4	−2.7, −2.1	0.001*
Wound size reduction at Week 4	28%	24, 32	0.001*
Wound size reduction at Week 6	40%	35, 45	0.001*

\* $p < 0.05$ .

gastrointestinal distress; however, headaches occurred at comparable rate in both groups (Figure 1). The comparative analysis of treatment outcomes revealed that Vitamin D group exhibited statistically significant decrease of  $-1.5$  points in mean chloasma severity scores at 3-month mark, in contrast to the placebo group. This finding was supported by narrow 95% confidence interval (CI) ranging from  $-1.8$  to  $-1.2$  ( $p < 0.05$ ). At 6 months, this effect was significantly more pronounced, as indicated by 95% CI of  $-2.7$  to  $-2.1$  ( $p < 0.05$ ). Further, at week 4, average reduction in wound size in Vitamin D group was 28% higher than placebo group ( $p < 0.05$ ), and 95% CI ranging from 24 to 32%. This finding established that Vitamin D group exhibited sustained and statistically significant superior development over the course of study (Table 4).

### 3.4 | Skin hydration levels

Average skin hydration levels in both Vitamin D group ( $35.0 \pm 5.0$ ) and placebo ( $34.8 \pm 5.2$ ) were similar. Average transepidermal water loss (TEWL) values were comparable: Vitamin D:  $10.5 \pm 2.0$ , Placebo:  $10.7 \pm 1.8$ . During research duration, Vitamin D group exhibited gradual increase in skin hydration levels ( $42.5 \pm 4.2$  at

week 6,  $37.5 \pm 4.8$  at week 2 and  $40.0 \pm 4.5$  at week 4). In contrast, placebo group maintained comparatively stable skin hydration level throughout the study, measuring  $35.5 \pm 5.1$  at week 6. Simultaneously, Vitamin D group exhibited TEDWL values of  $9.8 \pm 1.9$  at week 2,  $9.0 \pm 1.5$  at week 4, and  $8.5 \pm 1.4$  at week 6, all of which indicated enhanced functionality of the skin barrier. On contrary, placebo group exhibited negligible variation in TEWL. In comparison with placebo, these results indicated that Vitamin D supplementation was associated with increased skin hydration and decreased TEWL, indicating improved skin barrier integrity (Table 5).

### 3.5 | Recorded severity scores

The mean severity scores for treatment group ( $5.0 \pm 0.8$ ) and placebo group ( $5.1 \pm 0.7$ ) did not differ significantly. The 95% CI for the difference was  $-0.3$  to  $0.1$  ( $p > 0.05$ ). At 3-month mark, treatment group exhibited notable improvement in severity, as evidenced by mean score of  $3.2 \pm 1.1$  in contrast to placebo group's  $4.7 \pm 0.9$ . This disparity was statistically significant, with the mean difference of  $-1.5$ , 95% CI of  $-1.8$  to  $-1.2$  ( $p < 0.05$ ). The observed enhancement was even more remarkable after 6 months; treatment group achieved the mean

TABLE 5 Skin hydration and TEWL measurements in wound healing.

Time point	Vitamin D group (mean skin hydration $\pm$ SD)	Placebo group (mean skin hydration $\pm$ SD)	Vitamin D group (mean TEWL $\pm$ SD)	Placebo group (mean TEWL $\pm$ SD)
Baseline	35.0 $\pm$ 5.0	34.8 $\pm$ 5.2	10.5 $\pm$ 2.0	10.7 $\pm$ 1.8
Week 2	37.5 $\pm$ 4.8	35.0 $\pm$ 5.1	9.8 $\pm$ 1.9	10.6 $\pm$ 1.7
Week 4	40.0 $\pm$ 4.5	35.2 $\pm$ 5.0	9.0 $\pm$ 1.5	10.5 $\pm$ 1.6
Week 6	42.5 $\pm$ 4.2	35.5 $\pm$ 5.1	8.5 $\pm$ 1.4	10.4 $\pm$ 1.7

TABLE 6 Detailed statistical analysis of chloasma severity scores.

Time point	Treatment (mean $\pm$ SD)	Placebo (mean $\pm$ SD)	Mean difference	95% CI	p-value
Baseline	5.0 $\pm$ 0.8	5.1 $\pm$ 0.7	-0.1	-0.3, 0.1	0.736
3 months	3.2 $\pm$ 1.1	4.7 $\pm$ 0.9	-1.5	-1.8, -1.2	0.021*
6 months	2.1 $\pm$ 1.3	4.5 $\pm$ 0.8	-2.4	-2.7, -2.1	0.001*

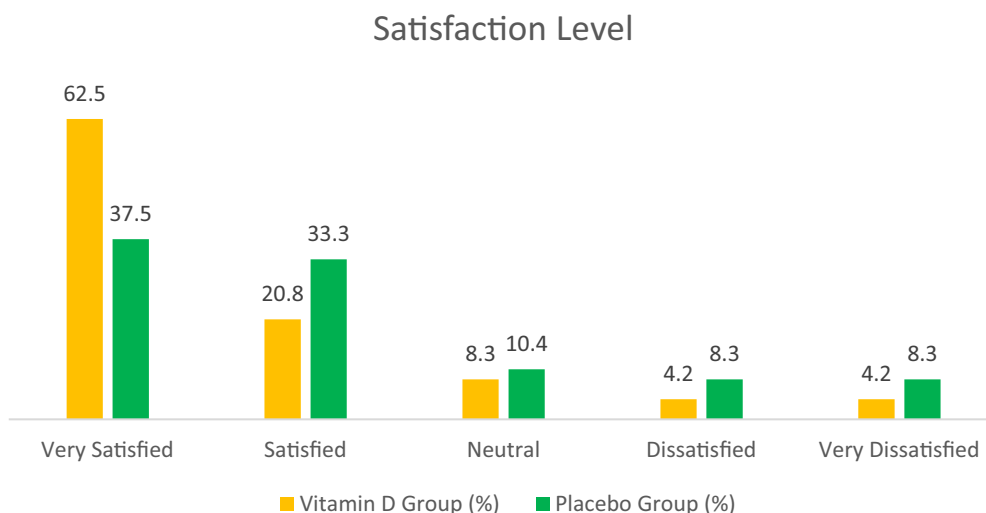
\* $p < 0.05$ .

FIGURE 2 Correlation analysis between Vitamin D levels and wound healing.

improvement of  $2.1 \pm 1.3$ , while placebo group reached  $4.5 \pm 0.8$ . This corresponded to 95% CI of  $-2.7$  to  $-2.1$  ( $p < 0.05$ ), deemed to be highly significant. The findings indicated that intervention exhibited the statistically significant reduction in severity scores at 3 and 6 months compared with the placebo (Table 6). Comparing the placebo and Vitamin D group, data indicated that participants in Vitamin D group reported greater levels of satisfaction. More precisely, 62.5% of those taking Vitamin D were extremely content, compared with 37.5% in the placebo group. In addition, compared with the placebo group, 20.8% of the Vitamin D group reported satisfaction, while only 33.3% did so (Figure 2).

Vitamin D treatment was significantly associated with the reduction in chloasma severity at 6 months, as indicated by the coefficient of  $-2.4$ , 95% CI of  $-3.0$  to  $-1.8$  ( $p < 0.05$ ) in the regression analysis. Age was found to have modest but noteworthy inverse correlation with

severity change, as indicated by coefficient of  $-0.02$  ( $p < 0.05$ ). There was no significant association observed between variations in severity and gender or skin tone. Vitamin D treatment demonstrated the substantial positive correlation of 40 ( $p < 0.05$ ) with regard to percentage of lesion size reduction after 6 weeks. Age, on other hand, exhibited the positive association with the coefficient of 0.5 ( $p < 0.05$ ). The reduction in lesion size was not significantly influenced by gender or skin tone (Table 7).

#### 4 | DISCUSSION

Vitamin D's potential therapeutic utility in dermatology, with particular emphasis on wound healing and management of chloasma, was the subject of this investigation. In light of our findings, it appeared that vitamin D might

TABLE 7 Regression analysis of Vitamin D treatment on chloasma severity and wound healing.

Variable	Coefficient ( $\beta$ )	Standard error	95% CI	p-value
Dependent variable: change in chloasma severity at 6 months				
Vitamin D treatment (yes = 1, no = 0)	-2.4	0.3	-3.0, -1.8	0.001*
Age (years)	-0.02	0.01	-0.04, 0.00	0.047*
Gender (male = 1, female = 0)	0.1	0.2	-0.3, 0.5	0.62
Skin tone (dark = 1, otherwise = 0)	-0.3	0.2	-0.7, 0.1	0.13
Dependent variable: percent wound size reduction at 6 weeks				
Vitamin D treatment (yes = 1, no = 0)	40	5	30, 50	0.001*
Age (years)	0.5	0.2	0.1, 0.9	0.022*
Gender (male = 1, female = 0)	-5	4	-13, 3	0.237
Skin tone (dark = 1, otherwise = 0)	3	3	-3, 9	0.324

\* $p < 0.05$ .

had the substantial impact on ameliorating the pigmentation irregularities linked to chloasma and enhancing function of the skin barrier.

The significance of vitamin D in maintaining skin health has been progressively acknowledged in the field of dermatological research.<sup>16</sup> Research has demonstrated its critical role in epidermis repair and maintenance through its involvement in cell differentiation, proliferation and immune function.<sup>17,18</sup> Our results are consistent with those of Seetan et al. (2022), who discovered that vitamin D is effective in treatment of hyperpigmentation disorders.<sup>19</sup> In contrast to the research which observed negligible effects on wound healing, our research suggested that vitamin D plays more prominent role in this regard.<sup>20</sup>

The Vitamin D group exhibited the notable decrease in chloasma severity scores, which implied that vitamin D may have therapeutic potential in treatment of pigmentary disorders. This is consistent with the study reporting that vitamin D controls synthesis and distribution of melanin.<sup>21</sup>

The Vitamin D group exhibited enhanced skin barrier integrity and wound healing, as indicated by increased skin hydration and decreased TEWL, which were additional findings from our study. This finding provided further evidence in favour of hypothesis that vitamin D promotes wound healing and maintains epidermal barrier homeostasis.<sup>20,22</sup>

Despite the encouraging nature of our findings, the research has certain constraints. The potential for over-looking long-term effects exists due to 6-month time frame and sample's restriction to the particular geographic and ethnic group. Further investigation is warranted to incorporate a broader range of demographics and prolong the duration of the study. Further

investigation into various vitamin D formulations and concentrations may yield further insights that can be utilized to optimize treatment protocols.<sup>23</sup>

Supplementing wound healing with vitamin D-based treatments may improve skin barrier function and patient outcomes in individuals with chloasma, according to the findings. When evaluating these advantages, dermatologists must also account for potential adverse effects, such as irritation of the epidermis, which have been reported in certain participants.<sup>24</sup>

Our study provided additional support for the expanding corpus of evidence that vitamin D plays the crucial role in skin health, particularly in treatment of chloasma and promotion of wound repair. Although additional investigation is required to comprehensively comprehend and maximize its application in dermatology, vitamin D offers an auspicious pathway for forthcoming therapeutic interventions.

## 5 | CONCLUSION

A significant function for vitamin D in regulating the integrity of skin barrier and alleviating the symptoms associated with chloasma was established. The results unequivocally indicated that application of vitamin D, both topically and orally, substantially diminished the severity scores of chloasma and promoted the processes of wound healing. This is supported by enhanced skin hydration and substantial reduction in TEWL. Hence, findings supported the need for the fundamental change in approach to chloasma and wound healing management, with a particular focus on potential incorporation of vitamin D therapies into the field of clinical dermatology.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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