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Original Research Article

Management of epidermal hyperpigmentation with a novel depigmenting formulation: a research survey

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ABSTRACT

Background: Epidermal hyperpigmentation is an important dermatological concern with a high prevalence in the Indian population. Kojic acid-based depigmenting formulations have proven to be effective in the management of epidermal hyperpigmentation. A questionnaire-based survey was conducted to assess physicians' knowledge about epidermal hyperpigmentation and practice patterns about a novel depigmenting formulation containing a combination of kojic acid dipalmitate 4%, azelaic acid 12%, glycolic acid 3%, niacinamide 4%, arbutin 2%, glycogen liquid 2%, sodium hyaluronate solution 2%, and shea butter 1% for epidermal hyperpigmentation treatment in India.
Methods: The survey was conducted among 235 dermatologists across different geographical regions of India over 3 months. The questionnaire evaluated prevalence and choice and duration of therapies for epidermal hyperpigmentation in Indian clinical practice, and dermatologists' real-life experience with efficacy of the novel formulation. Descriptive statistics were used to summarize survey results.
Results: All 235 dermatologists completed the questionnaire and responded to questions based on experience in treating patients with epidermal hyperpigmentation. In all, 58% dermatologists preferred kojic acid-based combinations. Furthermore, 57% of dermatologists agreed that glycolic acid can enhance the penetration of kojic acid and azelaic acid, 47.45% strongly agreed that a kojic acid-based formulation could be a safe alternative to steroid and hydroquinone-based formulations. Overall, 67% of dermatologists agreed that the kojic acid-based formulations with additional moisturizers helped in faster resolution of epidermal hyperpigmentation compared to other depigmenting formulations.
Conclusions: The survey findings indicate that the novel kojic acid-based formulation with additional moisturizers could be a preferred choice for epidermal hyperpigmentation management.

Keywords: Depigmenting formulation, Epidermal hyperpigmentation, Kojic acid

INTRODUCTION

Hyperpigmentary disorders such as melasma and post-inflammatory hyperpigmentation (PIH) are important dermatological concerns for individuals with pigmented skin phototypes, and these disorders present with a high prevalence in the Indian population.[1] Melasma is the most common cause of hyperpigmentation with a prevalence of 33.6%, followed by PIH at 12.5% and ephelids or freckles at 6.9%.[2]

PIH is a type of epidermal hyperpigmentation with hypermelanosis, that can be triggered by various stimuli, including dermatoses, trauma, cutaneous procedures, ultraviolet radiation or drugs.[3] On the other hand, exposure to UV radiation, increased estrogen levels, genetic predisposition, and phototoxic drugs may play a crucial role in the development of melasma. The role of UV exposure has been observed to be important in development and mainly in exacerbation of melasma.[1]

Numerous topical depigmenting agents, including both pharmacological agents and cosmetic agents have been used clinically, with variable degrees of success.[4] First-line therapy of PIH involves the use of topical depigmenting agents along with photoprotection. Topical tyrosinase inhibitors, like azelaic acid, kojic acid, hydroquinone, arbutin, and certain licorice extracts have been effective in lightening the areas of hypermelanosis. Additionally, depigmenting agents like retinoids, mequinol, ascorbic acid, niacinamide, N-acetyl glucosamine, and soy have also been effectively used.[5]

Kojic acid is a potent inhibitor of tyrosinase, and acts by chelating copper at the active site of the enzyme.[6] It is available in concentrations of 1% to 4%, and can be formulated with other lightening agents like glycolic acid to improve efficacy.[5] Kojic acid may be useful in patients not responding to hydroquinone therapy.[7] Several studies have confirmed the efficacy of formulations containing a combination of kojic acid and glycolic acid for the treatment of melasma.[6] The depigmenting agent azelaic acid has demonstrated effectiveness in the treatment of PIH. It acts via tyrosinase inhibition and selective cytotoxic and antiproliferative effects toward abnormal melanocytes to depigment skin.[5] Niacinamide, which is the physiologically active derivative of vitamin B_3, is stable and not affected by light, moisture, acids, alkalis, or oxidizers. Topical 2% to 5% niacinamide has exhibited efficacy when used alone or in combination with N-acetyl glucosamine for the treatment of melasma and UV-induced hyperpigmentation in fair-skinned patients and Asians.[5] Furthermore, clinical trials using 2% niacinamide have reported that it significantly reduces the total area of hyperpigmentation and further lightens the skin after 4 weeks of therapy.[8]

Arbutin, the b-D-glucopyranoside derivative of hydroquinone, is one of the most commonly prescribed skin-lightening and depigmenting agents globally.[8] It enables depigmentation by inhibiting tyrosinase activity and melanosome maturation.[5] It has shown sustained improvement and general skin-lightening and a safety profile comparable to that of hydroquinone.[8] Glycolic acid, which elicits its response by inducing epidermolysis, dispersing basal layer melanin, and increasing dermal collagen synthesis, enables significant clinical improvement in PIH when combined with other lightening agents.[6] Hydroquinone is a key component of topical pharmacological agents, but it is associated with a higher rate of adverse events than other agents. In contrast, cosmetic agents such as kojic acid, azelaic acid, glycolic acid, niacinamide, and arbutin are safer and exhibit fewer adverse reactions.[4] Lastly, hyaluronic acid and sodium hyaluronate are vital cosmetic ingredients in moisturizing products and provide excellent skin hydration and exhibit a good tolerability profile.[9,10]

An open-label, non-comparative study by Nayak et al involving 114 participants confirmed the effectiveness and tolerability of a kojic acid-based formulation following 90 days of treatment for PIH.[6] Another 12-week, open-label, non-comparative study by Chandrashekar et al. with 60 patients reported that kojic acid-based formulations had a good safety profile and were effective in the treatment of epidermal pigmentation. The cream formulation enabled overall improvement in the percentage of melanin and erythema, which could be attributed to the tyrosinase inhibition as well as anti-inflammatory and peeling properties of the botanical components in the cream.[11] Melaglow Prime is a novel depigmenting cosmetic formulation containing a combination of kojic acid dipalmitate 4%, azelaic acid 12%, glycolic acid 3%, niacinamide 4%, arbutin 2%, glycogen liquid 2%, sodium hyaluronate solution 2%, and shea butter 1%.

Objective

The current survey was conducted with an aim to assess nationwide knowledge among dermatologists about the prevalence of and choice and duration of therapies for epidermal hyperpigmentation in Indian clinical practice, and real-life experience of dermatologists with Melaglow Prime.

METHODS

Survey design

This was a cross-sectional, questionnaire-based survey conducted among 235 dermatologists practicing across different geographical regions of India from April to July 2021. Dermatologists who provided written informed consent and had experience with prescribing Melaglow Prime (Abbott Healthcare Pvt. Ltd.) to patients presenting with epidermal hyperpigmentation were included in the survey. Physician confidentiality and anonymity were maintained throughout the survey conduct and data analysis. As this survey did not involve any direct intervention to patients, ethical approval by an independent ethics review board was not obtained.

Survey questionnaire

The survey questionnaire consisted of 4 sections comprising 32 questions: section 1) patient profiling of epidermal hyperpigmentation; section 2) management of epidermal hyperpigmentation; section 3) physicians' perspective on Melaglow Prime; and section 4) patients' perspective on Melaglow Prime (Supplementary Table 1 in Appendix).

Data analysis

The data was collected from 235 dermatologists who took part in the survey from all over India. Responses gathered from all respondents were analyzed by question and reported as descriptive statistics. Data were represented as n and percentages.

RESULTS

Profiling of patients with epidermal hyperpigmentation

Majority of the dermatologists (65.0%) were of the opinion that epidermal hyperpigmentation is common in the age group of 30-40 years, whereas 30.0% opined that the 20-30 years age group is commonly affected, and the remaining 5.0% agreed that epidermal hyperpigmentation is common in individuals aged ≥50 years. A majority of the dermatologists (97.0%) stated that epidermal hyperpigmentation is more commonly seen in females as compared to males. In clinical practice, mixed hyperpigmentation (65.3%) was the most common type of hyperpigmentation observed, followed by epidermal hyperpigmentation (32.6%), and dermal hyperpigmentation (2.1%). It was found that in clinical practice, the most frequent cause of epidermal hyperpigmentation was melasma (31.8%), or PIH (16.1%) or freckles (0.4%). Moreover, majority of dermatologists (59.7%) strongly agreed that pigmentary disorders could cause psychosocial impairment in individuals. Furthermore, 55.5% dermatologists agreed and 27.5% dermatologists strongly agreed that exposure to visible light (blue light) from electronic devices like laptops and cellphones could cause epidermal hyperpigmentation.

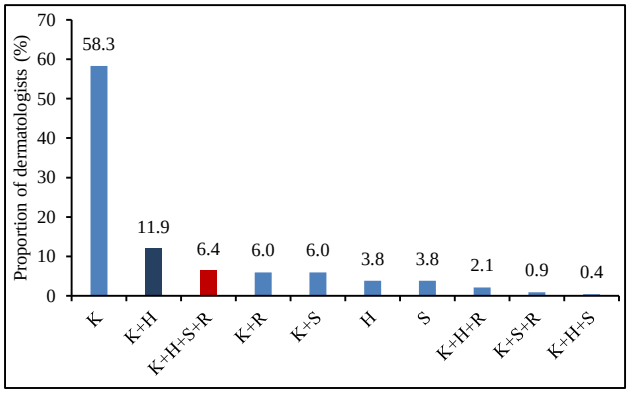

Figure 1: Preferred choice of treatment in epidermal hyperpigmentation.

K, kojic acid-based cosmeceutical combinations, H, hydroquinone monotherapy; S, steroid-based triple combination; R, retinoid monotherapy.

Management of epidermal hyperpigmentation

In all, 58.3% dermatologists preferred kojic acid-based cosmeceutical combinations for treatment of epidermal hyperpigmentation. Furthermore, 11.9% dermatologists preferred kojic acid-based cosmeceutical combinations with hydroquinone (Figure 1). With regard to preferred concentration of kojic acid, 25.4% dermatologists strongly agreed and 62.7% agreed that a formulation containing higher concentration of 4% kojic acid was thought to be more effective than 2% in treating patients with epidermal hyperpigmentation (Figure 2). Out of all the dermatologists, 59.5% agreed and 30.2% strongly agreed that topical depigmenting agents like azelaic acid at a strength of 12.0% can be efficacious and safe in the management of epidermal hyperpigmentation. Furthermore, a proportion of 53.4% dermatologists agreed and 33.5% dermatologists strongly agreed that an exfoliating agent like glycolic acid at a strength of 3% can be efficacious and safe in the management of epidermal hyperpigmentation.

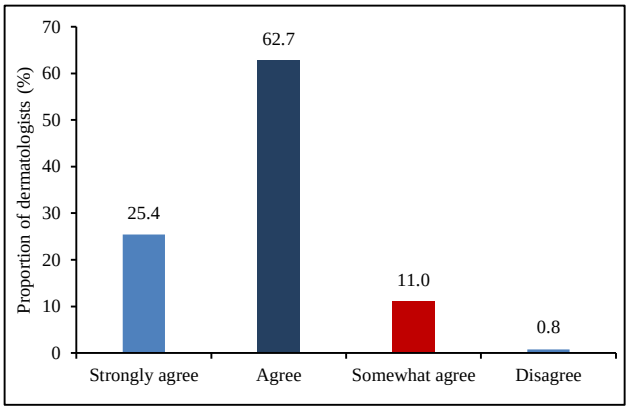

Figure 2: Preference for use of higher concentration of 4% kojic acid versus 2% in treating epidermal hyperpigmentation.

Out of all the dermatologists, 57.4% agreed and 39.0% strongly agreed that combining an exfoliating agent like glycolic acid could enhance the penetration of kojic acid and azelaic acid and further improve the effectiveness of a depigmentary formulation (Figure 3). A proportion of 59.3% dermatologists agreed and 28.4% strongly agreed that an anti-inflammatory agent like niacinamide at a concentration of 4% in combination with depigmenting agents could be beneficial in treating epidermal hyperpigmentation. Furthermore, a proportion of 57.6% dermatologists agreed and 33.5% strongly agreed that a formulation with antioxidants like niacinamide and kojic acid in addition to depigmenting agents could be beneficial in the management of epidermal hyperpigmentation.

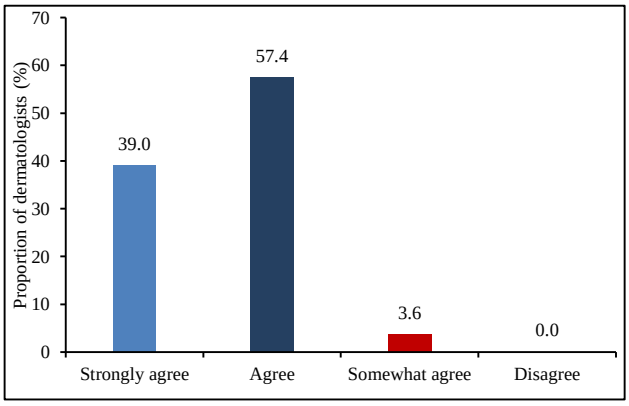

Figure 3: Preference for use of a combination of exfoliating agents like glycolic acid for enhancing penetration of kojic acid and azelaic acid.

According to the dermatologists, various factors like the burden of multiple medications (13.1%), discontinuing application of medication once patients feel better (12.3%), forgetting to apply the agent regularly (10.2%), and adverse events due to the formulation (3.0%) can affect the compliance of a patient with epidermal hyperpigmentation on treatment with depigmenting agents. In many instances, a combination of two or more of the above-mentioned factors can result in poor patient compliance. Majority of the dermatologists (72.5%) were of the opinion that 0%-25% patients commonly complained of irritation while on topical depigmenting agents. Additionally, 23.7% dermatologists opined that 26%-50% patients commonly complained of irritation while on topical depigmenting agents. A proportion of 42.4% dermatologists frequently prescribed a moisturizer with a depigmenting cream, whereas 30.5% dermatologists prescribed it occasionally to reduce irritation.

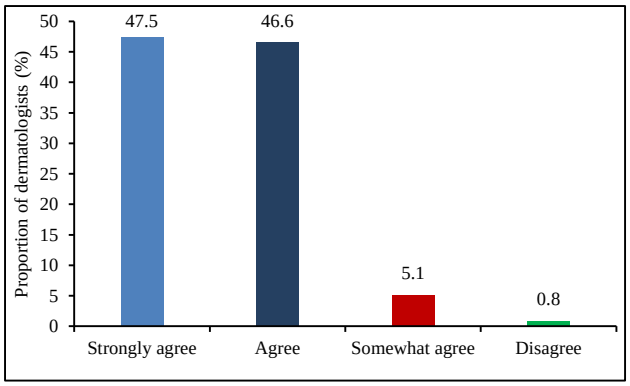

Figure 4: Dermatologists' opinion on safety of kojic acid-based cosmeceutical formulations as an alternative to steroid and hydroquinone-based formulations in the management of epidermal hyperpigmentation.

A total of 83.1% dermatologists believed that a depigmentary agent in combination with a moisturizer was more beneficial than a stand-alone depigmentary agent in treating epidermal hyperpigmentation. According to 47.5% dermatologists, a kojic acid-based formulation should be continued for 3-6 months in the management of epidermal hyperpigmentation. On the other hand, 26.7% dermatologists opined that it should be continued for 2-3 months while 22.9% dermatologists were of the opinion that it must be continued for more than 6 months. Out of all the dermatologists, 47.5% strongly agreed and 46.6% agreed that a kojic acid-based cosmeceutical formulation could be a safe alternative to steroid- or hydroquinone-based formulations in the management of epidermal hyperpigmentation (Figure 4).

Majority of the dermatologists (95.8%) preferred using a paraben-free formulation in the management of epidermal hyperpigmentation. Similarly, 96.0% dermatologists preferred using a steroid-free and fragrance-free formulation in the management of epidermal hyperpigmentation.

Physicians' perspectives on the novel depigmenting kojic acid-based formulation in the management of epidermal hyperpigmentation

Based on clinical experience, majority of the dermatologists (66.8%) opined that visible results of the novel depigmenting kojic acid-based formulation could be seen in 2-4 weeks. A total of 52.0% dermatologists preferred using it as spot application, whereas the remaining 48.0% dermatologists preferred using it as a face application. Based on clinical experience, 66.8% dermatologists agreed and 22.1% dermatologists strongly agreed that the novel depigmenting kojic acid-based formulation can help in faster resolution of epidermal hyperpigmentation in comparison with other depigmenting formulations (Figure 5).

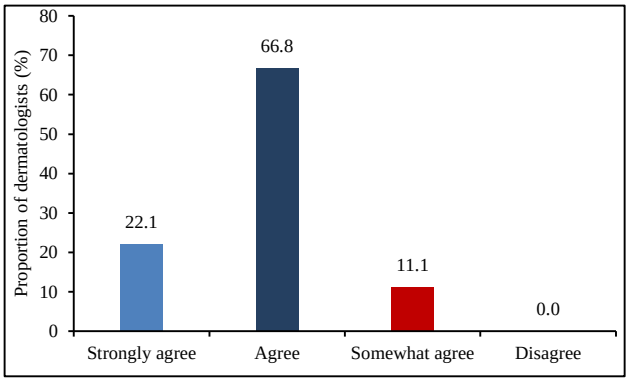

Figure 5: Dermatologists' opinion regarding faster resolution of epidermal hyperpigmentation with the novel depigmenting kojic acid-based formulation compared to other depigmentation formulations.

Based on clinical practice, 64.3% and 34.9% dermatologists rated the effectiveness of novel depigmenting kojic acid-based formulation as 'good' and 'excellent', respectively. Furthermore, 61.7% and 37.9% dermatologists rated that patient adherence of novel depigmenting kojic acid-based formulation was 'good' and 'excellent', respectively.

Patients' perspectives on the novel depigmenting kojic acid-based formulation in the management of epidermal hyperpigmentation

A total of 60% and 39% dermatologists opined that their patients rated the spreadability of the novel depigmenting kojic acid-based formulation as 'good' and 'excellent,' respectively. A total of 46.6% dermatologists opined that based on feedback, 56-75% patients preferred the fragrance-free formulation of the cream. A total of 64.4% and 35.2% dermatologists opined that their patients rated the consistency of the formulation as 'good' and 'excellent,' respectively. Furthermore, 62.7% and 35.2% dermatologists stated that patients rated the texture of the

formulation as 'good' and 'excellent,' respectively. Majority of the dermatologists (61.0%) were of the opinion that 56-75% patients were satisfied with the results of this formulation (Figure 6).

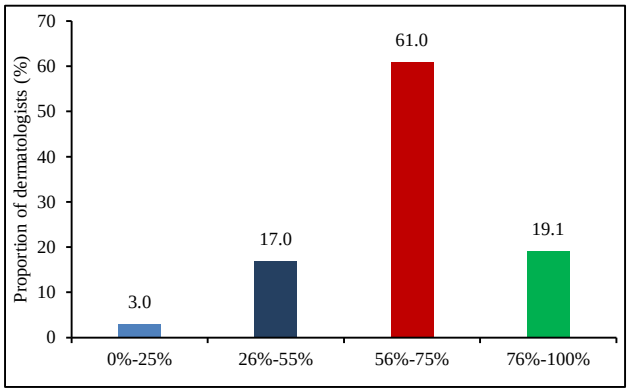

Figure 6: Responses of dermatologists regarding the percentage of patients' satisfaction with the results of the novel depigmenting kojic acid-based formulation.

DISCUSSION

Hyperpigmentary problems occur commonly and therefore their management is of broad interest.[12] Indian skin is more prone to pigmentation disorders compared to other ethnicities. As discussed previously, melasma followed by PIH are the leading causes of hyperpigmentation in the Indian population.[2] PIH is a commonly seen chronic acquired disorder that occurs after skin inflammation or injury. It is more frequent and severe in darker-skinned individuals (Fitzpatrick skin types III-VI).[13] Cosmeceuticals like kojic acid, azelaic acid, arbutin, and niacinamide have been effectively used for managing hyperpigmentation. These agents selectively target hyperplastic melanocytes and inhibit important regulatory steps in melanin synthesis.[8]

Kojic acid used at concentrations 1-4% decreases hyperpigmentation by inhibiting the production of free tyrosinase and is also a potent antioxidant.[8] Azelaic acid interferes with deoxyribonucleic acid synthesis, inhibits mitochondrial oxidoreductase, competitively inhibits tyrosinase, and reduces free radical formation. It preferentially targets abnormal and highly active melanocytes with negligible effect on uninvolved skin. Clinical evidence suggests that azelaic acid enables a reduction in PIH.[14] Glycolic acid, a peeling agent, also enables significant clinical improvement in PIH when combined with other lightening agents.[6] Arbutin is a naturally occurring plant derived-compound that inhibits tyrosinase activity competitively, but at non-cytotoxic concentrations in a dose-dependent manner in cultured melanocytes. Additionally, it inhibits melanosome maturation and is less cytotoxic to melanocytes compared to hydroquinone.[8] Niacinamide interferes with the interaction between keratinocytes and melanocytes, thus inhibiting melanogenesis and subsequently reducing hyperpigmentation.[8] A skin-brightening compound including niacinamide improved hyperpigmentation with statistical significance compared to baseline following 4 weeks of treatment.[14]

Apart from skin lightening agents, the depigmenting formulation used in the current survey also contained moisturizing agents like sodium hyaluronate and shea butter. Hyaluronic acid and its sodium and potassium salts are imperative cosmetic ingredients that are incorporated in moisturizing products.[9] Hyaluronic acid is very effective for moisture retention of the skin.[15] On the other hand, shea butter is composed of triglycerides with oleic, stearic, linoleic, and palmitic fatty acids, as well as unsaponifiable compounds. It exhibits potent anti-inflammatory and antioxidant properties.[16]

The current survey findings suggested that in the opinion of dermatologists the depigmenting formulation containing kojic acid helped in the treatment of epidermal hyperpigmentation. Moreover, sodium hyaluronate provided additional moisturizing benefits. The survey findings concurred with previous evidence on efficacy of kojic acid-based depigmenting combinations. Furthermore, the novel depigmenting kojic acid-based formulation was found to be a suitable choice by dermatologists that could help in faster resolution of epidermal hyperpigmentation.

The survey had a few limitations, such as cross-sectional design, absence of internal validity of the questionnaire, and risk of recall bias by survey participants. Studies involving patients with epidermal hyperpigmentation and prospective evaluation of treatment outcomes will be needed to address these concerns.

CONCLUSION

The prevalence of epidermal hyperpigmentation is on the rise in the Indian population. Several factors contributing to its occurrence include dermatoses, trauma, cutaneous procedures, ultraviolet radiation, or drugs. The current survey with dermatologists assessed the real-world practice and established clinical opinion on the efficacy and safety of a novel depigmenting kojic acid-based formulation used in epidermal hyperpigmentation. The survey findings indicated that the novel kojic acid-based depigmenting formulation could be a preferred therapeutic option for the management of epidermal hyperpigmentation

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APPENDIX

Supplementary Table 1: Survey questionnaire.

Section 1: profile of patients with epidermal hyperpigmentation				
1)	In your clinical practice in which age group is epidermal hyperpigmentation common?			
	A) 12-20 years	B) 20-30 years	C) 30-40 years	D) 50 years and above
2)	In your clinical practice in which gender is epidermal hyperpigmentation more common?			
	A) Males		B) Females	
3)	In your clinical practice which is the most common type of hyperpigmentation?			
	A) Dermal hyperpigmentation	B) Epidermal hyperpigmentation		C) Mixed hyperpigmentation
4)	In your clinical practice what are the common causes of epidermal hyperpigmentation? (one or more options can be selected)			
	A) Melasma	B) PIH		C) Freckles
5)	Do you agree that pigmentary disorders can cause psychosocial impairment?			
	A) Strongly agree	B) Agree	C) Somewhat agree	D) Disagree
6)	Do you agree that exposure to visible light (blue light) from electronic devices like laptop and mobile can cause epidermal hyperpigmentation?			
	A) Strongly agree	B) Agree	C) Somewhat agree	D) Disagree
Section 2: management of epidermal hyperpigmentation				
1)	What is your preferred choice of treatment in epidermal hyperpigmentation? (one or more options can be selected)			
	A) Kojic acid based cosmeceutical combinations		B) Hydroquinone as monotherapy	
	C) Steroid based triple combination		D) Retinoids as monotherapy	
2)	Do you agree that higher concentration of 4% kojic acid can be more effective than 2% kojic acid in treating patients of epidermal hyperpigmentation?			
	A) Strongly agree	B) Agree	C) Somewhat agree	D) Disagree
3)	Do you agree a topical depigmenting agent like azelaic acid at a strength of 12% can be efficacious and safe in the management of epidermal hyperpigmentation?			
	A) Strongly agree	B) Agree	C) Somewhat agree	D) Disagree
4)	Do you agree that an exfoliating agent like glycolic acid at a strength of 3% can be efficacious and safe in the management of epidermal hyperpigmentation?			
	A) Strongly agree	B) Agree	C) Somewhat agree	D) Disagree
5)	Do you agree that a combination of exfoliating agent like glycolic acid can enhance the penetration of kojic acid and azelaic acid, and can further improve the effect of a depigmentary formulation?			
	A) Strongly agree	B) Agree	C) Somewhat agree	D) Disagree
6)	Do you agree that an anti-inflammatory agent like niacinamide at a concentration of 4% in combination with depigmenting agents can be beneficial in treating epidermal			
	A) Strongly agree	B) Agree	C) Somewhat agree	D) Disagree
7)	Do you agree that a formulation with antioxidants like niacinamide and kojic acid in addition to depigmenting agents can be beneficial in the management of epidermal hyperpigmentation?			
	A) Strongly agree	B) Agree	C) Somewhat agree	D) Disagree
8)	Among the reasons mentioned below, which are the ones that can affect the compliance of a patient of epidermal hyperpigmentation on treatment with depigmenting agents? (one or more options can be selected)			
	A) Forgetting to apply regularly	B) Burden of multiple medications	C) Stop applying medication once they feel better	D) Adverse event/s due to formulation
9)	What percentage of patients commonly complain of irritation while on topical depigmenting agents?			
	A) 0-25%	B) 26-50%	C) 51-75%	D) 75-100%
10)	How often do you prescribe a moisturizer with a depigmenting cream to reduce the irritation?			
	A) Very frequently	B) Frequently	C) Occasionally	D) Rarely
11)	Do you believe that a depigmentary agent in combination with a moisturizer is more beneficial than stand-alone depigmentary agent in treating epidermal hyperpigmentation?			
	A) Yes		B) No	
12)	For how long should kojic acid-based formulations be continued in the management of epidermal hyperpigmentation?			
	A) 1 - 2 months	B) 2 - 3 months	C) 3 - 6 months	D) >6 months
13)	Do you agree that a kojic acid based cosmeceutical formulation can be a safe alternative to steroid and hydroquinone-based formulation in the management of epidermal hyperpigmentation?			
	A) Strongly agree	B) Agree	C) Somewhat agree	D) Disagree
14)	Do you prefer using a paraben free formulation in the management of epidermal hyperpigmentation?			
	A) Yes		B) No	
15)	Do you prefer using a steroid free formulation in the management of epidermal hyperpigmentation?			
	A) Yes		B) No	
16)	Do you prefer using a fragrance-free formulation in the management of epidermal hyperpigmentation?			
	A) Yes		B) No	

Section 3: physicians' perspectives on Melaglow Prime				
1)	Based on your clinical experience, how early were the visible results of melaglow prime seen in patients with epidermal hyperpigmentation?			
	A) 1-2 weeks	B) 2-4 weeks	C) 4-6 weeks	
2)	Do you prefer using Melaglow Prime as:			
	A) Spot application	B) Entire face application		
3)	Based on your clinical experience, do you feel that Melaglow Prime can help in faster resolution of epidermal hyperpigmentation in comparison with other depigmentary formulations?			
	A) Strongly agree	B) Agree	C) Somewhat agree	D) Disagree
4)	Based on clinical practice, how do you rate the effectiveness of Melaglow Prime in patients with epidermal hyperpigmentation?			
	A) Excellent	B) Good	C) Poor	
5)	Based on clinical practice, how will you rate the adherence of Melaglow Prime in your patients?			
	A) Excellent	B) Good	C) Poor	
Section 4: patients' perspectives on Melaglow Prime				
1)	How did the patients rate the spreadability of melaglow prime formulation?			
	A) Excellent	B) Good	C) Poor	
2)	Based on the feedback, what percentage of patients preferred the fragrance-free formulation of Melaglow Prime?			
	A) 0-25%	B) 26-55%	C) 56-75%	D) 76-100%
3)	How did the patients rate the consistency of melaglow prime formulation?			
	A) Excellent	B) Good	C) Poor	
4)	How did the patients rate the texture of Melaglow Prime formulation?			
	A) Excellent	B) Good	C) Poor	
5)	What percentage of patients were overall satisfied with the results of Melaglow Prime?			
	A) 0-25%	B) 26-55%	C) 56-75%	D) 76-100%