International Journal of Research in Dermatology
Vedamurthy M et al. Int J Res Dermatol. 2018 Nov;4(4):471-478
http://www.ijord.com

DOI: http://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20184453

Original Research Article

A randomized, open label, comparative, five-arm, controlled study evaluating the benefit and tolerability of oral superoxide dismutase combined with gliadin as add-on neutraceutical therapy with standard therapy in Indian patients with melasma

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Received: 04 June 2017
Revised: 27 September 2017
Accepted: 29 September 2017

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ABSTRACT

Background: Melasma management is often difficult and unsatisfactory, and there is need to explore newer modalities for melasma treatment. Disruption in antioxidant balance occurs in melasma. Superoxide dismutase (SOD) is a cellular antioxidant and restores this balance. Our hypothesis is that the oral SOD-Gliadin can replenish the SOD stores in body and quench the 'reactive oxygen species'-induced damage in melasma.
Methods: A randomized, open label, single centre, comparative, five arm study was conducted in 90 patients with facial mixed melasma, for 12 weeks to evaluate the efficacy, safety and tolerability of two regimens (BD & OD) of oral SOD as add-on treatment with triple combination cream in melasma patients compared with two regimens (BD & OD) of beta-carotene (BC) and placebo. Primary outcome measure was improvement in Melasma Area and Severity Index (MASI) score, and secondary outcome measures were quality of life score, patient satisfaction score, global assessment by investigator and patients. Pair-wise comparisons were performed on adjusted mean using SAS v9.1.3.
Results: There was significant reduction in MASI score with add-on treatment with SOD BD (67.97%) as compared to BC BD (43.04%), BC OD (33.68%) and placebo (22.60%). There was significant reduction in MASI score with SOD OD (51.93%) as compared to placebo (22.60%). The subjective assessments reported by patient and evaluator also ranked SOD BD as a superior regimen.
Conclusions: By inhibiting oxidative stress, nutraceutical SOD-Gliadin Combination offers significantly better efficacy and higher treatment satisfaction as add-on treatment compared to beta-carotene in Indian patients.

Keywords: Melasma, Superoxide dismutase, MASI, Quality of life, Hyper-pigmentation

INTRODUCTION

Melasma is a common dyschromia characterized by symmetrical and confluent grey-brown patches mostly on the areas of the face exposed to the sun, such as the cheek, forehead, and chin.[1] Its prevalence varies according to ethnic composition, skin phototype, and intensity of sun exposure. It accounts for 0.25 to 4% of the patients seen in Dermatology Clinics in South East Asia, and is the most common pigment disorder among Indians.[2,3] Women are more commonly affected with a 90% predisposition. It is more commonly seen in darker skin types, particularly fitzpatrick skin types III, IV, V & VI.[4]

Melasma results from hyperactivity of epidermal melanocytes. The reported risk factors include genetic predisposition, exposure to ultraviolet light, pregnancy, exogenous hormones, consumption of certain food items, ovarian tumors, intestinal parasitoses, hepatopathies, use of cosmetics and photosensitizing drugs, procedures and inflammatory processes of the skin, and stressful events.It also causes great psychological concern.[5,6] Monteiro et al had reported that social interactions and emotional well-being were impacted in melasma.[7] Treatment of melasma is challenging because it is often recalcitrant to therapy, especially in the dermal type, and tends to recur. The range of treatments investigated for melasma covers systemic, procedural, and topical modalities. Various treatments have been trialled, including topical hypo-pigmentation agents, laser or light therapies, systemic tranexamic acid (TXA), and chemical peels. Yet according to the most recent Cochrane review, there is insufficient robust guidance for practice in the field of melasma treatment, and more randomized clinical trials are needed.[8] Furthermore, to explore synergistic combinations with standard treatment, drug combinations must be evaluated.

Research by Seckin et al showed balance between oxidant and anti-oxidants (superoxide dismutase and glutathione peroxidase) is disrupted and the oxidative stress increased in melasma with correlation of MASI value.[9,10] Superoxide dismutase (SOD) is an important enzyme that functions as a cellular antioxidant, catalyses the dismutation of superoxide anion, reduces both the oxidative stress and the activation of mediators of inflammatory response.[11] Reactive oxygen species causes melanocyte damage in melasma, and therefore a powerful ROS quencher like SOD is a logical therapeutic agent.

Orally administered drugs have advantage over topical therapies, in terms of better systemic bioavailability and target tissue concentration. However, oral delivery of the pure enzyme superoxide dismutase to boost the body's natural antioxidant defences is limited by the gastric pH. Superoxide dismutase (SOD) combined with the wheat gliadin biopolymer can significantly and progressively increase SOD stability and delivery during gastric passage, as shown by results from in vitro, in vivo and human studies. Present study is to evaluate the benefits of oral capsule SOD-gliadin in Indian patients of melasma.

SOD has been studied earlier for treatment of acne, psoriasis, vitiligo, wound healing and multiple other skin disorders and its efficacy is well established.[12-15] The dermatological effects of SOD on these skin conditions has been implicated to be enzymatic radical scavenging, anti-inflammatory effects, and restoring the skin's natural anti-oxidant balance. However, no previous study investigated oral SOD as add-on to standard treatment of melasma. The aim of this study was to investigate efficacy, safety and tolerability of oral SOD-Gliadin as an add-on neutraceutical therapy with topical triple combination cream in Indian melasma patients. Beta carotene was used as comparative arm since it's a well-researched and commonly prescribed add-on neutraceutical agent for melasma in India.[16] Also, since melasma has significant psychological effect and can reduce the quality of life therefore we included a robust approach for qualitative assessment in our study as reported by patient, doctor and others.

METHODS

Study design

A randomized, open label, comparative, five arm, controlled study was done in 90 patients with facial melasma, for a period of 12 weeks. The recruitment period was April, 2015 to January, 2016 and the study was conducted at single centre in Chennai. Approval of institutional review board (IRB) was taken and written informed consent was obtained before beginning therapy for every patient.

Patient recruitment and study groups

Healthy female subjects with age between 18 to 50 years with facial mixed melasma were enrolled in the study. All study participants had Fitzpatrick skin types III, IV or V and had not used any topical treatments for melasma for 2 weeks prior to enrollment. Enrolled patients had a 2 week washout period if they had prior treatment for melasma. Strict avoidance of UV light exposure 2 weeks before and for the duration of the study was advised.

Subjects under treatment for other dermatologic condition like eczema, dermal melasma, psoriasis, or any other acute or chronic pathology that could interfere with the studied parameters as per investigator's judgment, were excluded from the study. Other exclusion criteria were pregnant or lactating females, hypersensitivity to any ingredients of study drugs, hormonal therapies less than or equal to 4 weeks prior to study, or patients on photo-sensitizing medications. At the first visit, the patients were divided randomly into following five groups, using a table of random numbers. The study groups were as follows -

- Group A - SOD BD (20 patients): Triple combination cream + Sunscreen (SPF 50+) + Cap SOD 250 IU BD
- Group B - SOD OD (20 patients): Triple combination cream + Sunscreen (SPF 50+) + Cap SOD 250 IU OD
- Group C - BC BD (20 patients): Triple combination cream + Sunscreen (SPF 50+) + Cap BC HC
- Group D - BC OD (20 patients): Triple combination cream + Sunscreen (SPF 50+) + Cap BC HC
- Group E - Control Group (10 patients) Triple combination cream + Sunscreen (SPF 50+)

All the patients were followed for the duration of three months which includes 4 visit viz. visit 0(Screening 15 days before baseline), Visit 1 (Baseline), Visit 2 (end of 6 weeks treatment) Visit 3 (end of 12 weeks treatment).

After screening patients were given 15 days washout period. All the patients were assessed objectively on the basis of melasma area and severity index (MASI) scoring and subjectively by using quality of life questionnaire and patient satisfaction questionnaires.

Patients were instructed on use of triple combination Lumaglo cream (Hydroquinone 2%, Tretinoin 0.05%, Flucinoloneacetonide 0.01%), to be applied once daily at night for the study duration of 3 months, and sunscreen 50 aqua lotion (Octinoxate 7.5%, Avobenzone 2%, Oxybenzone 3%, Octocrylene 3% and Zinc oxide 2%), to be applied daily at 9 am, 12 noon and 3 pm for the study duration of 3 months. In addition to using a sunscreen, reduced exposure to the sun during afternoons was advised. Patients were instructed to wear protective clothing and Sunglasses and to avoid swimming. This standard treatment was constant for all the five arms.

Study outcomes measures

Primary outcome measure for the study was improvement in melasma area and severity index (MASI) score, while secondary outcome measures were quality of life questionnaire and patient satisfaction questionnaire, global assessment by investigator and patients.

Qualitative assessment

All patients were interviewed on quality of life parameters by the evaluator. It included patients own evaluation about self, patient reporting how others feel about the patients response to treatment, and evaluators own assessment about response. Specific questions were framed and graded response was obtained.

The first quality of Life questionnaire included the parameters of 'improvement in complexion', 'superior luminance than before' and 'feedback of Family/Friends/People at work'. A graded response was generated where Grade 0 means No Change, grade 1 means 0-25% Improvement, grade 2 means 25-50% Improvement, Grade 3 means 50-75% Improvement and grade 4 means 75-100% Improvement.

Secondly, patients' feedback on 'Continuation of Treatment' and whether the patient would 'Recommend the treatment to others' was assessed at Visit 2 and Visit 3. Percentage of patients responding 'yes' was recorded.

Third qualitative analysis consisted of patient reported graded outcome of 'overall satisfaction', 'improvement in dark spots', 'improvement in luminance' and 'improvement in skin firmness'.

Lastly, a graded score of investigator's global assessment and patient's global assessment was recorded. The grading reporting system remained the same.

Records for 'missed dose' and any adverse event reported were maintained.

Statistical analysis

Descriptive statistics was provided for each parameter (i.e. number of observations, mean, SD, SEM, minimum, maximum, median, quartiles). A study of the distribution of the parameters at inclusion was carried out with the Shapiro-Wilk test. Statistical comparisons of basal values, of evolutions between assessments at different time and for the 3 groups (Student or Wilcoxon depending of the normality of the distribution) and of the delta was carried out with the ANOVA or Friedman test (depending of the normality of the distribution). Statistical significance set at 5% (double sided) and at 5% to 10% for trends. Pair-wise comparisons were performed on adjusted mean (Least square means) at two-sided 5% level of significance using SAS v9.1.3. Baseline value (Visit1) has been considered covariate in the model. Analysis of covariance (ANCOVA) was performed at Visit 2 and 3, separately.

RESULTS

Of the proposed 90 patients that were to be screened for the study, 22 did not fulfil inclusion criteria. 68 patients were enrolled in the study, of which 47 patients completed 12 weeks of treatment. 21 patients were lost to follow up.

Table 1: Baseline characteristics.

GROUP		Age	SGOT	SGPT	BUN	S Creat
Group A	Mean	42.60	29.20	25.90	11.50	0.74
	Std. Deviation	6.62	6.32	15.29	6.26	0.16
Group B	Mean	45.55	25.55	19.64	10.73	0.74
	Std. Deviation	5.79	5.39	12.18	4.03	0.14
Group C	Mean	44.70	21.20	13.40	13.10	0.74
	Std. Deviation	8.51	8.59	3.50	5.43	0.14
Group D	Mean	44.10	20.70	29.90	12.10	0.69
	Std. Deviation	5.00	9.14	15.43	5.80	0.14
Group E	Mean	45.33	26.17	23.33	12.00	0.67
	Std. Deviation	6.35	9.56	16.59	4.82	0.05
	p Value	0.868	0.099	0.074	0.892	0.761
	Significance	Not Significant	Not Significant	Not Significant	Not Significant	Not Significant

The comparison of baseline characteristics of all 5 groups is shown in table 1. All 5 groups were statistically similar. Standard ANOVA test was applied.

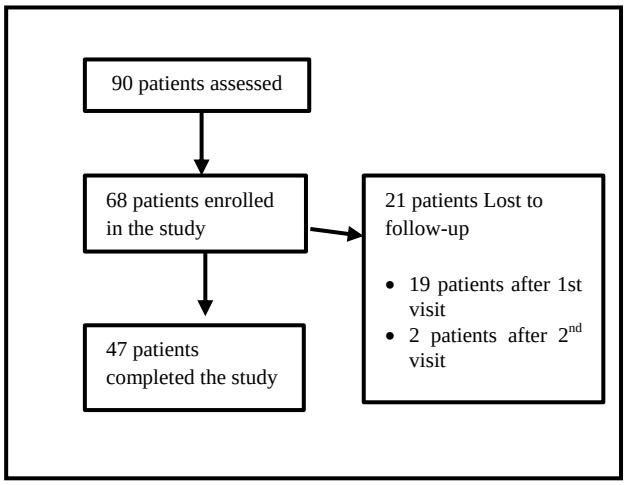

Figure 1: CONSORT flow diagram.

Primary outcome measures

1. *Improvement in melasma area and severity index (MASI)*

Evaluation done at Visit 1(Baseline); Visit 2 (At end of 6 weeks); Visit 3 (At end of 12 weeks)

The baseline MASI score at Visit 1 in all the groups were comparable. The mean MASI Score in all the treatment groups represented in Table 2 and Figure 1. In all the groups a reduction in the MASI score at the end of study was observed.

Table 2: MASI score (mean) in treatment groups.

Group (Number of patients completed 12 weeks treatment)	MASI Score Visit 1	MASI Score Visit 2	MASI Score Visit 3
Group A - SOD BD (10)	7.16	4.36	2.29
Group B - SOD OD (11)	6.83	4.73	3.28
Group C - BC BD (10)	6.97	4.90	3.97
Group D - BC OD (10)	6.80	5.17	4.51
Group E – Placebo (6)	6.93	5.63	5.37

2. *Percentage reduction of MASI Score*

Percentage reduction of mean MASI score at end of 6 and 12 weeks of treatment compared to Baseline (Visit 1) in Group A, B, C, D and E is shown in Table 3. At the end of treatment, there was significant reduction in MASI score in Group A (SOD BD) of 67.97% as compared to Group C (BC BD) of 43.04%, Group D (BC OD) of 33.68% and Group E (placebo) of 22.60%. There was significant reduction in MASI score in Group B (SOD OD) of 51.93% as compared to Group E (placebo) of 22.60%.

Table 3: MASI score: percentage reduction in MASI score compared to baseline.

Group (Number of patients completed 12 weeks treatment)	% Reduction in MASI, Compared to Baseline	
	Visit 2	Visit 3
Group A - SOD BD (10)	39.11	67.97*
Group B - SOD OD (11)	30.76	51.93**, #
Group C - BC BD (10)	29.70	43.04
Group D - BC OD (10)	23.97	33.68
Group E – Placebo (6)	18.75	22.60

*p<0.05, vs Visit 3 MASI Score of Group C, Group D and Group E; **p<0.05, vs Visit 3 MASI Score Group E; #p=0.05, vs Visit 3 MASI Score Group D; 002 A p<0.05, vs Group C (BC BD), Group D (BC OD) and Group E (placebo); **p<0.05, vs Group E (placebo)

Following comparisons were noted significant (p<0.05) at visit 3: A vs C p-value =0.0086, A vs D p-value =0.0006, A vs E p-value =0.0001 and B vs E p-value =0.0086. Other comparisons - A vs B, B vs D and C vs E were noted to be borderline significant.

Secondary outcome measures

1. *Quality of life (qol) questionnaire*

The data represented in Table 4 is the mean grade score as reported by the patient for individual questions. There was improvement in the 'Grades' in all the groups in Visit 2 and Visit 3, but numerically the improvement was maximum for SOD BD regimen.

2. *Assessment of continuation of treatment and recommendation to others*

Patients' feedback on 'Continuation of Treatment' and whether the patient would 'Recommend the treatment to others' was assessed at Visit 2 and Visit 3. The data represented in Table 5 depicts the percentage of patients who has responded 'positively' to the questions.

3. *Patient satisfaction questionnaire*

Patient satisfaction questionnaire for skin lightening effect was used for assessment of patient satisfaction at Visit 2 and Visit 3.

The data represented in Table 6, is the mean 'Grade' score for individual parameters that was assessed by the Investigator. There has been an improvement in 'Grades' in all the groups in Visit 2 and Visit 3.

4. *Global assessment*

The data represented here in Table 7, is the mean Grade score for individual parameters that was assessed by the Investigator and by the patient. There has been an improvement in the grades in all the groups in Visit 2 and Visit 3.

Table 4: QoL questionnaire: mean grade score for individual questions.

Group (Number of patients completed 12 weeks treatment)	Improvement in complexion		Superior luminance		Feedback from family/friends/people at work	
	Visit 2	Visit 3	Visit 2	Visit 3	Visit 2	Visit 3
Group A - SOD BD (10)	2.30	2.90	2.00	3.10	2.30	3.00
Group B - SOD OD (11)	1.73	2.36	1.18	1.73	2.09	2.00
Group C - BC BD (10)	1.00	1.60	1.20	1.50	1.40	1.50
Group D - BC OD (10)	0.90	1.10	1.10	1.60	1.30	1.20
Group E – Placebo (6)	0.67	0.83	0.67	1.33	1.00	0.83

Table 5: Percentage of patients who has responded positively to continue or recommend treatment.

Group (Number of patients completed 12 weeks treatment)	Will continue treatment (% responded Yes)		Recommend treatment to others (% responded Yes)	
	Visit 2	Visit 3	Visit 2	Visit 3
Group A - SOD BD (10)	100	90	100	90
Group B - SOD OD (11)	72.73	90.91	81.82	81.82
Group C - BC BD (10)	70.00	70.00	80.00	70.00
Group D - BC OD (10)	70.00	80.00	90.00	70.00
Group E – Placebo (6)	66.67	50.00	66.67	66.67

Table 6: Mean grade score for individual parameters of patient satisfaction questionnaire.

Group (Number of patients completed 12 weeks treatment)	Overall satisfaction		Improvement in dark spots		Improvement in luminance		Improvement in skin firmness	
	Visit 2	Visit 3	Visit 2	Visit 3	Visit 2	Visit 3	Visit 2	Visit 3
Group A –SOD BD (10)	2.90	2.70	2.30	2.90	2.10	2.80	1.30	1.20
Group B –SOD OD (11)	2.27	2.36	1.91	1.82	1.09	1.73	1.00	1.36
Group C - BC BD (10)	1.90	2.50	1.50	1.90	0.80	1.70	0.80	0.90
Group D - BC OD (10)	1.50	1.80	1.10	1.20	0.90	1.30	0.70	1.10
Group E – Placebo (6)	1.33	1.50	1.33	1.00	0.33	0.83	0.33	0.50

Table 7: Mean grade score of investigators and patients global assessment.

Group (Number of patients completed 12 weeks treatment)	Investigator's global assessment		Patient's global assessment	
	Visit 2	Visit 3	Visit 2	Visit 3
Group A - SOD BD (10)	1.90	3.10	2.60	2.60
Group B - SOD OD (11)	1.64	2.09	2.27	2.36
Group C - BC BD (10)	1.70	1.50	2.10	1.90
Group D - BC OD (10)	1.44	1.40	1.80	1.60
Group E – Placebo (6)	1.17	1.33	0.83	0.67

5. Missed doses and adverse events

The average number of missed doses was 1.3 for SOD BD and 1 for BC BD; the values for OD regimens were smaller. There was not statistically significant difference. There were no adverse events reported in any of the groups.

DISCUSSION

The present study was undertaken to test the hypothesis that the neutraceutical SOD (chemically combined with wheat gliadin) was effective, safe and tolerable in Indian melasma patients as an add-on to standard treatment. To the best of our knowledge this is the first study or orally administered SOD in melasma reported in literature. The results of this study confirmed that both the regimens SOD twice a day and once a day were more effective in treating melasma as add-on therapy compared to beta-carotene OD/BD regimen or to placebo. However, SOD twice a day appeared to have higher efficacy with regards to the patient satisfaction score and MASI score.

The process of melanogenesis takes place inside the melanocytes. Melanin production is a chain of oxidizing reaction. Thus melanocytes are constantly exposed to

oxidative stress by the intermediary oxidative species like IL6, IL1a, IL 1b, PGD2, PGE2, and PGF2. The superoxide ion is the starting point of the cascade of reactions of free radical (reactive oxygen species ROS) production. Oral delivery of the pure enzyme to replenish natural antioxidant stores is limited by low pH of stomach. However, combination of SOD extracted from cantaloupe melon (*Cucumis melo* LC) with the wheat gliadin biopolymer can increase SOD stability in gastric passage, as shown by results from *in vitro*, *in vivo* and human studies. Gliadin is a bio-adhesive, and adheres to the walls of small intestine, progressively releasing SOD, countering its intestinal inactivation and increasing the permeability of the intestinal wall by promoting the release of a zonulin, thereby allowing the transport of SOD across the intestinal barrier into the blood circulation.[17] For example, Muth et al and Mac-Mary et al evaluated protection in DNA damage due to exposure to hyperbaric oxygen using the comet assay in vivo, and found significantly better results for SOD-supplemented group.[18,19]

Efficacy of melasma treatments can be assessed objectively, like by using the semi-quantitative scale - MASI, or subjectively using qualitative parameters. MASI has been the most common endpoint for evaluation of the treatment effect in randomized clinical trials on melasma. Melasma is a disorder of great psychosocial concern that lowers individuals self esteem and poses significant negative impact on health-related quality of life, as reported by previous studies.[20,21] Thus evaluation of response based on subjective evaluation was imperative. Soft subjective endpoints such as patient satisfaction, although criticized in earlier decades to be used in clinical trials, have gained more attention in recent years. The more the patients are satisfied with the treatment, the more likely they are to comply with medical treatment ensuring to have a better outcome.[22,23] As cosmetic outcome is a major demand in the field of dermatology, and especially with respect to pigmentation disorders, it is critical to include 'patient satisfaction' among the evaluation outcomes of melasma improvement.

For the MASI score, the difference in mean reduction in the five regimes was statistically significant. At the end of treatment, there was significant reduction in MASI score in Group A (SOD BD) of 67.97% as compared to Group C (BC BD) of 43.04%, Group D (BC OD) of 33.68% and Group E (Placebo) of 22.60%. Also, there was significant reduction in MASI score in Group B (SOD OD) of 51.93% as compared to Group E (Placebo) of 22.60%. Thus it was established that SOD BD was statistically significantly better than BC BD, BC OD and placebo. SOD OD was significantly better than placebo. This shows that SOD has the efficacy to treat melasma in a dose dependent manner and is superior to BC as add-on to standard treatment for melasma.

The mean grade score reported by the patient for quality of life variables like improvement in complexion, superior luminance and feedback from family/friends/people at work was highest for SOD BD regimen at treatment completion. The next highest values observed were for SOD OD regimen. Second type of subjective analysis conducted was patient's response on 'continuation of treatment' and if the patient would 'recommend the treatment to others'. It was highest for SOD BD - 100% at Visit 2 and 90% at Visit 3. This was complemented by our third subjective assessment – 'Patient satisfaction questionnaire for skin lightening effect' at Visit 2 and Visit 3. The specific parameters studied were overall satisfaction, improvement in dark spots, improvement in luminance and improvement in skin firmness. At study completion, the values were highest for SOD BD regimen for first 3 parameters, whilst for the fourth parameter 'improvement in skin firmness' highest value was observed in SOD OD regimen. The patient and investigator global assessment of therapy was undertaken at visit 2 and visit 3. Once again the highest scores were recorded for SOD BD. Hence, the findings of objective assessment matched those of subjective assessments i.e., SOD BD regimen was the most superior treatment modality.

Our results are in line with the in vivo results of Muth et al and Mac-Mary et al which showed that SOD-Gliadin Combination supplementation reduced skin-reddening when healthy fair-skinned volunteers were exposed to UV radiation.[18,19] The results showed that supplementation with SOD-Gliadin Combination resulted in an increase in the minimum exposure to UV rays necessary to produce skin burn for fair-skinned people (phenotype II & III), compared to placebo. Another study by Laverdet et al in 150 patients of sensitive skin by 40 dermatologists in France, reported higher quality of life on administration and 75% patients felt that skin was well prepared for exposure to the sun after 8 weeks of SOD-Gliadin treatment.[24]

No adverse effects to the either regimes were seen in any of the patients.

We recognize that there are some limitations in this study. Neither the evaluators nor the subjects were blinded to treatment, which could have affected the subjective assessments. A larger cohort group size evaluated over a longer duration encompassing at least 4 courses (2 months each) of SOD would have provided more statistical power for more robust conclusions. These limitations notwithstanding, these preliminary promising results of the present study, from both objective and subjective assessments, provided consistent results and showed that the SOD BD regimen significantly improved the efficacy of standard treatment of melasma and larger clinical trials could now be planned in order to better depict the potential applicability of the study data.

CONCLUSION

Melasma treatment outcome improves significantly by adding an antioxidant to standard line of therapy, specifically superoxide dismutase. By inhibiting oxidative stress, nutraceutical SOD-Gliadin Combination offers significantly better efficacy and higher treatment satisfaction as add-on treatment compared to beta-carotene in Indian patients. The best response was to the super-oxide dismutase BD regimen followed by super-oxide dismutase OD regimen. This was followed by beta-carotene BD lastly beta-carotene OD. Further controlled, blinded, multicenter studies are required to support these results.

ACKNOWLEDGEMENTS

Medical writing support was provided by Dr. Pratishtha Banga.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Vedamurthy M, Humbert P. A randomized, open label, comparative, five-arm, controlled study evaluating the benefit and tolerability of oral superoxide dismutase combined with gliadin as add-on neutraceutical therapy with standard therapy in Indian patients with melasma. Int J Res Dermatol 2018;4:471-8.