Association of emblica, licorice and belides as an alternative to hydroquinone in the clinical treatment of melasma *

Associação de emblica, licorice e belides como alternativa à hidroquinona no tratamento clínico do melasma

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Abstract: BACKGROUND: Melasma is a common skin pigment disorder with a difficult clinical response to treatment. Objectives: To evaluate the clinical efficacy and safety of the association of Belides, Emblica and Licorice 7%, compared to Hydroquinone 2%, in the treatment of melasma. METHODS: After 60 days of exclusive use of an SPF35 sunscreen, 56 women, 18 to 60 years of age, phototypes I to IV, with epidermal or mixed melasma, were divided into two different groups in a mono-blind clinical study: A) cream with Belides, Emblica and Licorice, applied twice a day; B) cream with Hydroquinone 2%, used at night. They were observed in a 60-day study; every 15 days, they were submitted to medical evaluation, self-evaluation, and photographic registration (Visia®). RESULTS: 50 volunteers (89%), 23 in Group A and 27 in Group B, concluded the study. Two volunteers in Group A and 7 in Group B had mild skin adverse events. Depigmentation was observed through medical evaluation (Group A: 78.3%; Group B: 88.9%) and volunteers' self-evaluation (Group A: 91.3%; Group B: 92.6%); these results were statistically significant ($p<0.001$), with no differences between groups ($p>0.05$). This pattern of results was observed by Visia® in the number ($p = 0.001$) and size and tone ($p<0.001$) of the UV stains, for both groups, with no differences between them ($p>0.05$). CONCLUSION: There were no statistic differences between groups in the improvement of melasma. Group A showed less skin adverse events. Therefore, the association of Emblica, Licorice and Belides is a safe and efficient alternative for the treatment of melasma.
Keywords: Hydroquinones; Melanosis; Phyllanthus emblica

Resumo: FUNDAMENTOS: Melasma é uma melanodermia comum, cuja terapêutica representa um desafio clínico. OBJETIVOS: Avaliar a eficácia e segurança clínicas do complexo despigmentante emblica, licorice e belides, em comparação à hidroquinona 2%, na abordagem do melasma.
MÉTODOS: Após 60 dias de uso exclusivo de fotoprotetor FPS35, 56 mulheres com idades entre 18 e 60 anos, fotótipos I a IV, com melasma epidérmico ou misto, foram divididas em dois grupos de um estudo clínico monocego: A) creme contendo complexo despigmentante emblica, licorice e belides 7%, usado duas vezes ao dia; B) creme de hidroquinona 2%, usado à noite. O estudo durou 60 dias consecutivos e avaliações médica, das voluntárias (auto-avaliação) e fotográfica (Visia®) foram realizadas quinzenalmente.
RESULTADOS: 89% das voluntárias (50/56), 23 do Grupo A e 27 do Grupo B, concluíram o estudo. Duas voluntárias do Grupo A contra sete do Grupo B apresentaram eventos adversos leves transitórios. Houve despigmentação do melasma pelas avaliações médica (Grupo A: 78,3%; Grupo B: 88,9%) e auto-avaliação (Grupo A: 91,3%; Grupo B: 92,6%), todos estatisticamente significantes ($p<0,001$), sem diferenças entre os grupos ($p>0,05$). O mesmo padrão foi observado pelo Visia®, tanto no número ($p = 0,001$) quanto no tamanho e no tom ($p<0,001$), para ambos os grupos, e sem diferenças entre eles ($p>0,05$) nas manchas UV.
CONCLUSÕES: Não houve diferença estatística na melhora do melasma nos dois grupos; o Grupo A apresentou menor incidência de eventos adversos. Logo, o complexo despigmentante emblica, licorice e belides é uma alternativa segura e eficaz na abordagem do melasma.
Palavras-chave: Hidroquinona; Melanose; Phyllanthus emblica

Received on 19.08.2009.
Approved by the Advisory Board and accepted for publication on 30.04.2010.
* Work conducted at KOLderma Clinical Research Institute Ltda. Campinas (SP), Brazil.
Conflict of interest: None / *Conflito de interesse: Nenhum*
Financial funding / *Suporte financeiro*: The products Clariderm Clear®, Clariderm® and SpectraBAN T® FPS35 and food and transportation expenses for the volunteers were provided and paid by Laboratórios Stiefel Ltda., Guarulhos/SP, Brazil, for the completion of this study, of interest to the researcher.

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INTRODUCTION

Melasma is a common melanodermia, characterized by irregular light to dark brown macules in photoexposed areas, usually affecting women in fertile age. [1] It shows greater incidence in inhabitants of tropical and equatorial regions and in individuals with light brown to brown skin. It is estimated that the disease affects 5 to 6 million people in the United States. [1]

Its etiopathogeny is not completely understood, but various factors are implicated in the exacerbation or development of melasma. Periods of partial remission are observed during the winter and periods of exacerbation, during the summer. Lesions may appear suddenly, due to intense sun exposure, or gradually, by constant exposure. One of the most accepted theories is that ultraviolet radiation leads to lipid peroxidation of the cell membrane with consequent formation of free radicals, which stimulate the melanocytes to excessively produce melanin, thus promoting skin hyperpigmentation. [1,2]

Hormonal influence in the etiopathogeny of melasma is supported by the increased frequency of the disease in pregnant women, in those who use birth control pills, and those who undergo hormone therapy. [2,3]

Other factors that contribute to the development of melasma include petroleum-derived cosmetics, psoralens and other photosensitizing drugs, [2,4] as well as hereditary predisposition, since most patients affected by melasma have family members with the disease. [5]

Three patterns of distribution are observed in clinical examination: central-facial (63%), malar (21%), and mandibular (16%). Wood's light examination allows the classification of the melasma into four types: epidermal, dermal, mixed and unapparent. [6]

Hydroquinone has been the most used therapeutic option to treat melasma for over 50 years. [7-9] It inhibits tyrosinase, reducing the conversion of DOPA to melanin. Other possible mechanisms of action of the drug are melanocyte destruction, melanosome degradation, and DNA and RNA synthesis inhibition. When combined with tretinoin and corticoid, it has its potency increased and irritation reduced. However, the diversity of adverse effects resulting from its use such as irritative and allergic contact dermatitis, post-inflammatory hyperpigmentation, cataract, and ochronosis, among others, stimulated the search for new skin lightening products. [10,11]

Many vegetable extracts have lightening properties. Belides is a new botanical ingredient, obtained from *Bellis perennis* flowers, which acts on nearly all the stages of the melanin synthesis process. [12]

When there is skin exposure to UV rays, keratinocytes release proinflammatory mediators, such as Endothelin-1 (ET-1), which in high levels stimulate the synthesis of tyronase and the proliferation, migration and formation of melanocyte dendrites. Belides is the only active ingredient that is proven to inhibit ET-1; [12] Moreover, it promotes the reduction of ·-MSH (alpha-melanotropin hormone)-receptor binding, with consequent reduction of eumelanin production. [12] Studies show that, during melanogenesis, Belides reduces the formation of free radicals (ROS); after the formation of melanin, it acts directly on skin lightening by decreasing the transfer of melanosomes formed in the melanocyte to epidermal cells, reducing skin pigmentation. [12]

Another vegetable extract with an important depigmenting property is Licorice, obtained from *Glycyrrhiza glabra.* Known as "alcaçus", it contains many compounds, of which saponins and flavonoids have the greatest antiphlogistic action. [13]

In mouse cell culture, it was observed that Licorice has glabridine, the main component of the hydrophobic fraction of the extract, with the ability to inhibit tyrosinase without affecting DNA synthesis. The *in vivo* results were compatible with those *in vitro,* and immunohistochemical analysis showed a reduction of DOPA-positive melanocytes. [14] Moreover, Licorice has antiinflammatory action by inhibiting some enzymes of the arachidonic acid cascade, especially cyclooxigenase, released after exposure to UV rays. [13,15] Due to these properties, glabridine is an important depigmenting component of the extract. Nonetheless, Licorice has other components with depigmenting effects, such as liquiritin, which disperses melanin. [11]

Emblica is an active ingredient derived from the fruit of *Phyllanthus emblica*, known in Indian ayuverdic medicine for thousand of years and currently used in the manufacturing of anti-aging and skin lightening products. [16] Its cosmiatric properties are attributed to its wide spectrum of antioxidant activity. [17,18]

Ultraviolet radiation in the skin leads to the formation of peroxydes that induce the development of free radicals. [19] Emblica has polyphenols in its composition and moderately inhibits peroxidase and strongly prevents the reaction of Fe^{+} with peroxide, blocking the formation of free radicals and protecting fibroblasts. In addition, it increases collagen production and reduces MMP-1. Such enzyme, responsible for the degradation of collagen, is zinc-dependent and inhibited by Emblica, since it quells this ion. [20] Associated with these functions, it has the capacity to inhibit tyrosinase, promoting skin lightening. The efficacy and safety of this depigmenting agent make it an excellent choice for cosmetic formulations. [17]

MATERIAL AND METHODS

This was a monocentric clinical study, phase IV, prospective, comparative, randomized, mono-blind (volunteers knew the name of the product to be tested, but the researcher did not, as products were provided by a member of the team that did not participate in the clinical and photographic analysis of the volunteers), of interest to the researcher, approved by the Ethics Committee for Research with Human Beings of the Pontifical Catholic University of Campinas – PUC-CAMPINAS. [56] Women aged from 18 to 60 years, phototypes I to IV, with epidermal or mixed melasma, were recruited from the volunteer database of KOLderma Institute of Clinical Research Ltda., Campinas-SP. Participants were included in the study after having read, agreed to (including the publication of photos in scientific media) and signed the Term of Voluntary and Informed Consent.

Sixty days before the study, the volunteers used only photoprotector (SpectraBAN T ® FPS 35, Stiefel Laboratories, Inc. – Guarulhos, SP, Brazil), reapplied every 2 hours. The volunteers did not show before and/or during the study any dermatosis, systemic disease or the need to use medication and/or products that interfered with the clinical evaluation of the treatment, such as hormonal contraceptives or hormonal replacement therapy.

After triage, 56 volunteers were divided into two treatment groups: Group A, cream with Emblica, Licorice and Belides 7% (Clariderm Clear®, Stiefel Laboratories Inc. – Guarulhos, SP, Brazil), used twice a day; Group B, Hydroquinone cream 2% (Clariderm Clear®, Stiefel Laboratories Inc.), used at night. Participants used both products according to their habitual prescriptive routine and to minimize the risks of phototoxicity or photoirritation of hydroquinone. They used the products for 60 consecutive days without eliminating or changing the daily photoprotective routine that had been established 60 days prior to the beginning of treatment.

Every 15 days, medical and self-evaluations were conducted to follow the evolution of the treatment. The clinical response patterns for both groups were: 0) worsened; 1) stable 2) improved; 3) improved considerably. On D0, D30 and D60 visits the face of the volunteer was photographed using a digital image analysis system with polarized light (Visia®, Canfield Imaging System - Fairfield, EUA). Intent on capturing brownish skin spots (melanocytic pigmentation), the objective of this study, we used the photographic image obtained with the ultraviolet lamp of the machine; these spots, by convention, are called "UV spots". Volunteers could miss only one visit, with the exception of D0 and D60.

Photographs were taken with the patient facing forward, 45^0 to the right and 45^0 to the left, combining all the facial regions analyzed for the presentation of results. The variables studied were count (number) and score (size and tone) of the UV spots (characterized by the accumulation of melanin below the skin surface caused by sun exposure), as determined by the machine.

During the study, the volunteers could miss one visit other than D0 or D60. Those that complied with this criterion had their data analyzed by physicians (medical evaluation) and by themselves (self-evaluation). For the photographic analysis, only those that did not miss D0, D30 and D60 had their images analyzed by this digital-photographic method without having their data excluded from the medical and voluntary evaluations.

RESULTS

Non-parametric statistical tests were used in the study since variables did not have a standard normal distribution (Gaussian distribution), based on the Anderson-Darling test. The level of significance established was 0.05 and the reliability rate, 95%.

Of the 56 patients with melasma (28 in each group, A and B), 89% concluded the study – 23 patients in Group A and 26 in Group B. The 7 excluded volunteers left the study due to non-adhesion to the protocol (personal reasons) and not for a disabling adverse event. In the period between visits, some volunteers reported skin manifestations with the use of both products: two in Group A (burning and increase of the number of previous acne lesions); seven in Group B (erythema, burning, and erythematous papules in the perioral region). However, manifestations receded spontaneously, even before doctor's visits, and did not require suspension of treatment.

Based on the medical evaluation, the patients did not report "worsening" at any time in the study in both groups (Table 1; Graphs 1 and 2). Using McNemar's test, it was observed that both products showed an improvement in lesion depigmentation by D60 (Group A: 78.3%; Group B: 88.9%), statistically significant in relation to D0 ($p<0.001$). There were no statistical differences between Groups A and B ($p>0.05$), as verified by the equality of proportions test. It was noticed that, within the first days of use of both products, there was significant improvement.

In the self-evaluation, a significant improvement in the depigmentation of lesions by D60 ($p<0.001$) was perceived for Groups A and B (91.3% and 92.6%, respectively), based on McNemar's test (Table 2; Graphs 3 and 4). This improvement was also observed within the first days of use of both products, without statistical differences between groups ($p>0.05$),

according to the Equality of Proportions Test. A volunteer in Group B was the only one whose clinical condition worsened at a particular time in the study.

The 48 volunteers that were submitted to photographic evaluation (22 volunteers from Group A and 26 from group B), that is, those that did not miss D0, D30 and D60, showed satisfactory clinical depigmenting evolution (UV spots) in the photography, as compared with D0.

Based on Friedman and Wilcoxon statistical tests, it was observed that both in Group A and Group B there was a statistically significant decrease in the number ($p=0.001$) (Tables 3), size and tone ($p<0.001$) of the UV spots (Tables 4) of the volunteers. However, it is worth noting that this clinical benefit was not only obtained by the volunteers with lighter phototypes (Figure 1), but also by more melanodermic patients (Figure 2) treated with the combination of active vegetable ingredients (Emblica, Licorice and Belides 7% depigmenting complex).

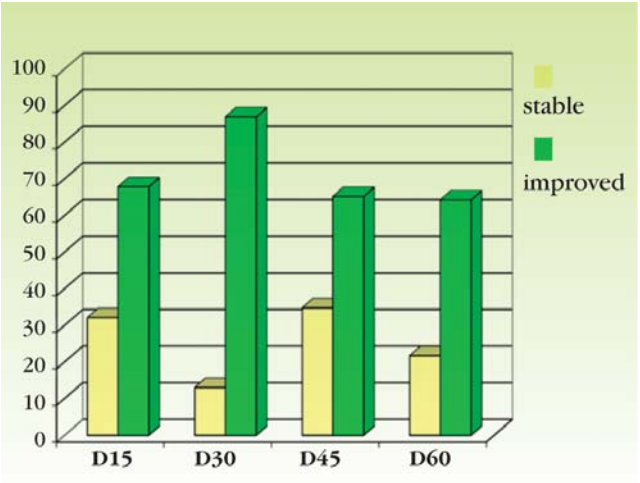
The clinical differences obtained through digital-photographical analysis for both groups were not statistically significant when both groups were compared ($p<0.001$), according to Mann-Whitney test.

DISCUSSION

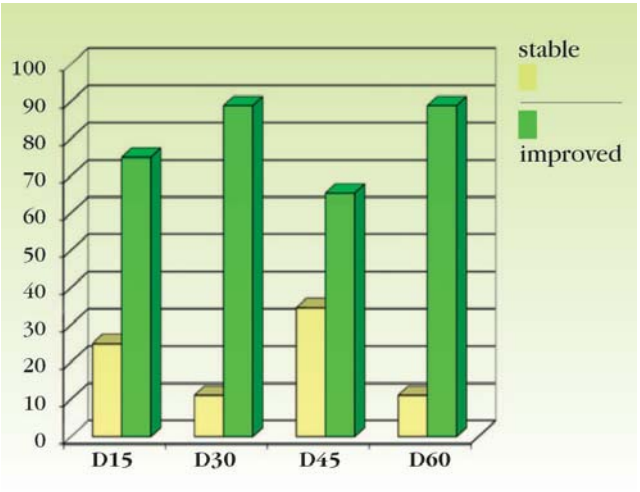
Before clinically investigating the melasma, knowledge about the localization of the melanin deposit allows prediction of the response to treatment. A good diagnostic tool to make this evaluation is Wood's lamp, since epidermal melasmas are more responsive to topical treatments, while dermal melasmas need more treatment time for a similar result because treatment depends on the elimination of melanin by macrophages. [6]

Table 1: Percentage comparison of the medical evaluation of Groups A and B

		Group A		Group B		P-value
		N	%	N	%	
D10	Stable	28	100,0	28	100,0	- x -
	Improved	0	0,0	0	0,0	- x -
D15	Stable	9	32,1	7	25,0	0,554
	Improved	19	67,9	21	75,0	0,554
D30	Stable	3	13,0	3	11,1	0,834
	Improved	20	87,0	24	88,9	0,834
D45	Stable	8	34,8	9	34,6	0,990
	Improved	15	65,2	17	65,4	0,990
D60	Stable	5	21,7	3	11,1	0,307
	Improved	18	78,3	24	88,9	0,307



Graph 1: Evolution of the clinical profile of Group A based on the medical evaluation



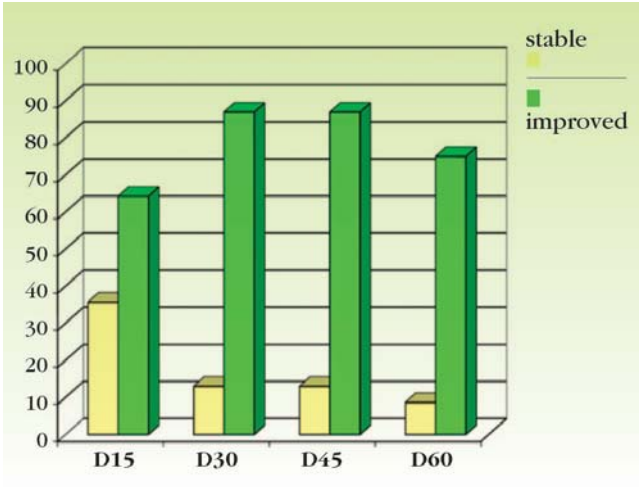
Graph 2: Evolution of the clinical profile of Group B based on the medical evaluation

Treatment does not depend on the type of melasma. It should include the daily use of a wide-spectrum sunscreen that contains opaque physical agents, such as titanium dioxide or zinc oxide, as well as chemical agents. [21] Superficial and medium peelings, dermoabrasion, and laser treatments are therapeutic alternatives, but they carry some risk of postinflammatory hyper- or hypopigmentation, scarring, and even keloid formation. [22,23]

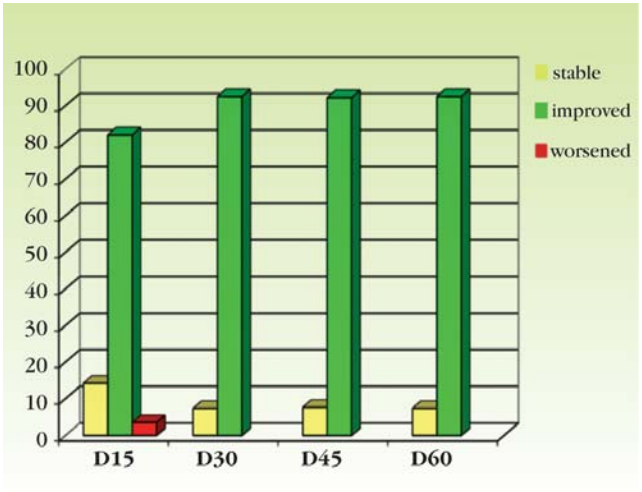
Traditionally, the use of depigmenting topical substances is without a doubt the best therapeutic option for the clinical treatment of melasma. Hydroquinone, although having some disadvantages, is the most used therapeutic alternative. [8-11] Nonetheless, many other substances, mostly of vegetable origin, have become more popular in dermatologic treatment. [11]

Table 2: Percentage analysis based on the self-evaluation of groups A and B

		Group A		Group B		P-value
		N	%	N	%	
D0	Stable	28	100,0	28	100,0	- x -
	Improved	0	0,0	0	0,0	- x -
D15	Worsened	0	0,0	1	3,6	0,313
	Stable	10	35,7	4	14,3	0,064
	Improved	18	64,3	23	82,1	0,131
D30	Stable	3	13,0	2	7,4	0,508
	Improved	20	87,0	25	92,6	0,508
D45	Stable	3	13,0	2	7,7	0,537
	Improved	20	87,0	24	92,3	0,537
D60	Stable	2	8,7	2	7,4	0,867
	Improved	21	91,3	25	92,6	0,867



Graph 3: Evolution of the clinical profile of Group A based on self-evalution



Graph 4: Evolution of the clinical profile of Group B based on self-evaluation

In this study we evaluated the combination of a depigmenting complex constituted by the association of three vegetable agents (Emblica, Licorice and Belides depigmenting complex 7%) compared to Hydroquinone 2%, for 60 days, in the treatment of epidermal and mixed melasmas. Because melasma is a dermatosis highly reactive to the action of UV radiation, the use of a photoprotective cream (FPS 35) was instituted 60 days prior to the beginning of and throughout the study.

Hydroquinone has a depigmenting pattern that is often superior to that of other substances used for the same purpose. [24] In this work, however, the association of Emblica, Licorice and Belides 7% showed a depigmenting capacity (Figures 1 and 2) with no significant statistical differences when compared to hydroquinone 2%.

Based on the medical evaluation at the end of the study, 78.3% of the volunteers in Group A (Emblica, Licorice and Belides 7% depigmenting complex) and 88.9% of those in group B (Hydroquinone 2%) (Table 1; graphs 1 and 2) showed a significant clinical improvement and there was no aggravation of lesions in both groups. According to the self-evaluation of the volunteers, 91.3% of the patients in Group A and 92.6% of those in Group B showed clinical improvement (Table 2; Graphs 3 and 4). These results are statistically similar ($p>0.05$). This proved that the association of Emblica, Licorice and Belice 7% is as efficient as hydroquinone 2% in melasma depigmentation.

It is possible to verify that, for both groups, in the interval between D30 and D45, there was a decrease in the perception of improvement according to the medical evaluation. This, however, was not a sign of aggravation, but of treatment stability for both products in relation to the depigmenting evolution achieved up to D30. From D45, we could see clinical improvement and reduction of stability, which has already been described as a characteristic of both products.

The finding of higher clinical stability for both groups in the middle of the treatment makes us consider the following hypotheses: 1) perhaps, until D30, patients with only epidermal melasma showed a sharp clinical improvement, whereas those with dermal melasma also presented such epidermal pigmentary *clearance*, but a great dermal component to be lightened remained, increasing the number of stable volunteers, as compared with those who improved; or 2) it was a period of higher incidence of UV radiation in the region and, even with the use of lightening products

Table 3: Evolution of Groups A and B in relation to the number (count) of spots (Visia® UV spots)

Count (Group A)		Mean	Median	Standard deviation	Q1	N	IC	p-value
UV Spots	D0	216,1	203	141,6	111	22	59,2	0,001
	D30	220,5	191	160,1	103	22	66,9	
	D60	150,9	163	132,9	14	22	55,5	
Count (Group B)		**Mean**	**Median**	**Standard deviation**	**Q1**	**N**	**IC**	**p-value**
UV Spots	D0	215,3	170	135,9	115	26	52,2	0,001
	D30	203,3	138	140,2	106	26	53,9	
	D60	161,2	109	122,3	80	26	47,0	

Table 4: Evolution of Groups A and B in relation to score (size and tone) of Visia® UV spots

Score (Group A)		Mean	Median	Standard deviation	Q1	Q3	N	IC	p-value
Manchas UV	D0	7,187	5,63	6,98	2,62	7,40	22	2,916	<0,001
	D30	7,755	4,75	7,36	2,21	9,80	22	3,077	
	D60	4,334	4,03	4,37	0,32	6,86	22	1,827	
Score (Group B)		**Mean**	**Median**	**Standard deviation**	**Q1**	**Q3**	**N**	**IC**	**p-value**
Manchas UV	D0	6,829	4,99	5,91	2,93	7,25	26	2,271	<0,001
	D30	5,924	4,15	5,41	2,35	7,94	26	2,081	
	D60	4,454	2,74	4,52	1,35	6,09	26	1,736	

and photoprotectors, volunteers of both groups had the speed of their skin lightening treatment stabilized.

A surprising occurrence was the perception of a volunteer in Group B who reported that between D0 and D15 there was an aggravation of the melasma. Even though this finding is not statistically significant, Group A did not show a similar result. We believe that this was perceived by the volunteer: 1) perhaps due to a transitory hyperchromic capacity of hydroquinone, as it may have this characteristic; [10,11] or 2) due to an attempt of the melanocyte to respond to the aggressive cytotoxic action of hydroquinone as rebound melanogenesis, [10, 11] or 3) due to a subjective perception caused by the clinical signs and symptoms of adverse effects, since the patient was one of the 7 volunteers who reported them in this group.

As known, the lack of objective criteria to understand the clinical response to the various treatments of many dermatoses is a great challenge in Dermatology. Oftentimes, this limits the accurate registration of the evaluated clinical pattern, secondary to a particular therapy. [25]

Visia® is a multi-spectral imaging system used in study methodologies about aesthetical dermatology because it allows an in-depth analysis of the skin. [26-28] With a polarized light technology called *RBX® Technology*, useful in the dermatologic investigation of epidermal and dermal alterations, [29] it produces digital images taken with various lamps, one of which is an ultraviolet light lamp. [30] With this lamp, it is possible to visualize spots that are invisible to the naked eye, caused by UV radiation (reactive melanocytic pigmentation), making them clearer; the spots revealed by this lamp are called UV spots. Therefore, the evolution of a particular lightening treatment can be monitored in relation to the number (count) and size and tone (score). [30]

Based on the similar clinical involution of UV spots presented by both groups in the study, we conclude that both products were equally efficient in the treatment of melasma.

The clinical and instrumental findings in Group A corroborate the technical information that the association of Emblica, Licorice and Belides 7% has similar depigmenting functions to hydroquinone 2%. This study strengthens the clinical benefits of these substances in the literature due to their melanin-dependent action (inhibiting tyrosinase, depleting or preventing the migration of melanosomes) and/or free radical-dependent action (melanogenic inhibition by preventing radicalar action on the melanocyte).

Both Group A (Association of Emblica, Licorice and Belides at 7%) and Group B (Hydroquinone at 2%) showed a reduction in the absolute number of

Figure 1: Volunteer patient, phototype III, with epidermal melasma

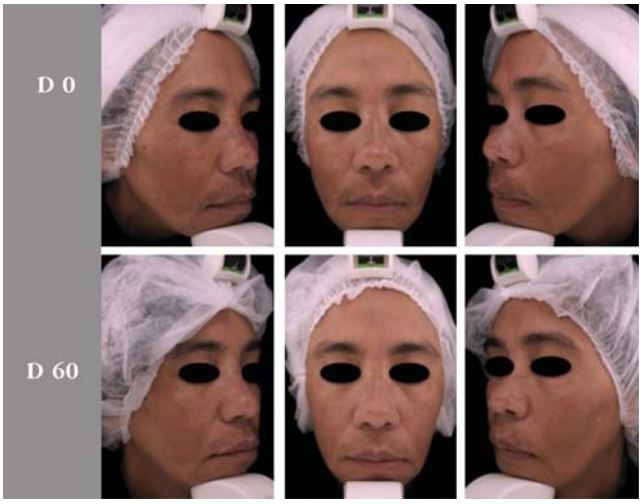


Figure 2: Volunteer patient, phototype IV, with dermal melasma

lesions, according to the results obtained by digital photographic imaging, without significant statistical differences between the groups ($p>0.05$).

The adverse effects observed in both groups were well tolerated, spontaneously regressing with the use of the products. We observed, however, that these effects were less noticed in Group A (association of Emblica, Licorice and Belides 7%), in which two events were reported (burning and increase of the number of previous acne lesions). Group B (hydroquinone 2%) described seven adverse reactions (erythema, burning, erythematous papules on the perioral region). Such data suggest the higher safety of the product used by Group A as compared with hydroquinone, whose degree of tolerance has already been questioned in the literature. [10,11]

The superiority of this greater depigmenting tendency could be better assessed in a prospective clinical study with a higher number of volunteers.

CONCLUSION

By analyzing the data obtained for the two groups, we conclude that the perceptive, medical and self-evaluation about the improvement of melasma was higher than 50% throughout the study (D15, D30, D45, D60) for both products (association of Emblica, Licorice and Belides 7% and hydroquinone 2%), without significant statistical differences between them.

The instrumental results of the count and score of the UV spots (melanogenesis secondary to UV radiation) obtained with Visia® revealed a reduction of these parameters with the use of both products. This indicates that, depending on the concentrations used, vegetable extracts can be as efficient as hydroquinone in the treatment of melasma. This confirms the viability of future competitive clinical studies to accurately elucidate a possible clinical superiority and ratify a tendency of higher tolerability of this new depigmenting alternative. ❑

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How to cite this article/*Como citar este artigo*: Costa A, Moisés TA, Cordero T, Alves CRT, Marmirori J. Association of emblica, licorice and belides as an alternative to hydroquinone in the clinical treatment of melasma. An Bras Dermatol. 2010;85(5):613-20.