Clinical Study MELINE® Dark Circles

2019

ME®
LINE

A STUDY OF THE EFFICACY AND SAFETY OF "MELINE® DARK CIRCLES" THERAPEUTIC PLAN FOR TREATING PERIORBITAL HYPERPIGMENTATION.

AUTHORS:
Zambrano Rafael MD, García Guevara Víctor MD and Bouffard Fernando PhD.

INTRODUCTION

Periorbital hyperpigmentation, also known as periocular hyperpigmentation, periorbital melanosis, dark circles, infraorbital darkening, infraorbital discolouration, or idiopathic cutaneous hyperchromia, is a common condition encountered in aesthetic medicine practice, and can affect an individual's emotional well-being and influence their quality of life (1). This type of periocular skin change affects individuals of many different ages, both genders, and every race. Additionally, it worsens with the ageing process whereby skin flaccidity and changes to the subcutaneous fat distribution play an important role.

There is a scarcity of scientific data available about the clinical profile and pathogenesis, with several exogenic and endogenic factors potentially involved. The causative factors include genetic or heredity (2), excessive pigmentation (3), postinflammatory hyperpigmentation secondary to atopic and allergic contact dermatitis (4), periorbital oedema, excessive vascularity (5), and shadowing due to skin laxity and tear trough associated with ageing (6).

Excessive pigmentation is also present with conditions such as dermal melanocytosis. In some cases, pigmentation can be exacerbated by the swelling of the lower eyelids due to the pseudo-afference of orbital fat (7). Swollen lower eyelids add a shadowing effect and worsen appearance. Environmental causes of dermal melanocytosis include excessive solar exposure and drug ingestion. Infraorbital dark circles in patients with atopic or allergic contact dermatitis present as postinflammatory hyperpigmentation through rubbing or scratching the periorbital area.

Dark circles can also derive from thin and translucent lower eyelid skin covering the orbicularis oculi muscle of the eyes, making the subcutaneous venous plexus or vasculature inside the muscle visible. This condition generally involves the entire lower eyelid, appearing a violet colour.

Huang el al (8) carried out a clinical analysis and proposed a classification based on the clinical pattern of pigmentation and vasculature. Periorbital hyperpigmentation is classified as pigmented (brown colour), vascular (blue / pink / purple colour), structural (skin colour), and a mixed type, based on the doctor's evaluation of its clinical appearance. The mixed type included the following four subtypes: vascular pigmented (VP), structural pigmented (SP), structural vascular (SV), and a combination of the three.

The pigmented (P) type appears as a infraorbital brown tone. The vascular (V) type appears as infraorbital blue, pink, or purple colour, with or without a periorbital oedema. The structural (S) type appears as a structural shadowing formed by surface anatomical facial contours, and can involve infraorbital palpebral dark circles, blepharoptosis, and a loss of fat with bone prominence. The mixed (M) type combines two or three of the previous types. This classification can help to introduce the therapeutic modes based on the diagnosed type, given that they respond to different treatment types.

In general, different approaches to treating this change have been proposed, one of which involves using products with a topical action and chemical microexfoliations. Topical use products are designed with depigmenting agents with modes of action that inhibit tyrosinase activity, inhibit DNA synthesis of hyperactive melanocytes, reduce melanin content in the epidermis, and thicken the epidermis.

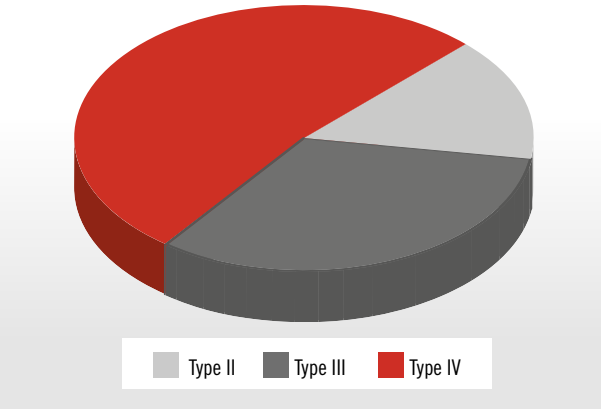
Retinoids are another key active ingredient in those treatments, which reduce pigmentation by inhibiting tyrosinase gene transcription, also deriving in significant thickening of the granular layer and the epidermis. Other compounds used as depigmenting agents include azelaic acid, kojic acid, tranexamic acid, ascorbic acid, which aim to increase the efficacy and limit the side effects when treating a range of hyperpigmentation disorders.

This study evaluates the efficacy and safety of a new treatment involving controlled chemical microexfoliation and topical product application (MELINE® Dark Circle, Laboratorio Innoaesthetics SL, Barcelona, Spain). This exfoliation combination improves the potency of the action without having to use high active ingredient concentrations, meaning that they do not cause any potential adverse effects when healing and permanent depigmentation.

MATERIAL AND METHODS

The study included 30 female and 10 male patients ranging in age from 25 to 45 years old (average age, 35 years old) with infraorbital hyperpigmentation. The patients were classified as Fitzpatrick skin phototypes II to IV. Figure 1 shows the distribution. Twenty two patients reported a family history of dark circles (55%). Each patient gave consent after being informed about the procedure. A detailed history was taken, and in some cases, clinical and blood tests were undertaken.

FIGURE 1. Distribution of the study population based on Fitzpatrick Skin Phototype



Inclusion criteria:

- Voluntary nature.
- Adults aged 25 to 45 years old with a diagnosis of dark circles.
- Not treated for dark circles in the last 6 months.
- Not using any topical or cosmetic treatment on the periocular area.
- No signs of anatomical changes through ageing, such as dark circles through accumulated fat or a deep tear trough.

Exclusion criteria:

- Congenital anomalies of the eyelids or any other relevant anatomical involvement.
- Corneal diseases.
- A history of exuberant scarring and allergic processes.
- Mental disorders that impede the procedure.
- Any involuntary eyelid movements.
- Dermatological diseases.
- Pregnancy or breastfeeding.
- Hypersensitivity to any of the components of the products used during the treatment.

Digital photos were taken of each patient both before and after the treatment. Each patient was scored on the severity index prior to treatment. According to the classification provided by Huang et al, 45% of patients have a pigmented type and 55% have a mixed vascular - pigmented type. As indicated in the exclusion criteria, patients with structural dark circles that agreed to participate in the study were excluded. The periorbital hyperpigmentation intensity was evaluated as mild, moderate, or severe, based on the colour of the orbital region compared to the patient's natural colour using Fitzpatrick's scale. Table 1 shows the diagnostic values.The data in table 1 therefore indicates that 52.5% of patients were diagnosed with mild dark circles, 32.5% with moderate dark circles, and 15% with severe dark circles.

The microexfoliation procedure (01 MELINE® Dark Circles, Laboratorio Innoaesthetics, Barcelona – Spain) involved 2 steps. The step 1 components are acetic acid derivatives and lactic acid, and the step 2 components are vitamin A, ascorbic acid, and phytic acid. Both products are in the form of a solution. The application procedure was as follows:

1. Mark out the treatment area.
2. Clean and remove any greasiness from the area.
3. Apply three layers (3) using cotton buds, waiting 30 seconds between each application for step 1. The patients were also instructed to keep their eyes closed during the application.
4. Then apply two layers of solution 2 using cotton buds and leave each layer to act for 15 minutes.

DARK CIRCLE SEVERITY DIAGNOSIS BY SKIN PHOTOTYPE

		Mild	Moderate	Severe
Number of patients	SKIN PHOTOTYPE II	4	2	0
	SKIN PHOTOTYPE III	9	7	5
	SKIN PHOTOTYPE IV	8	4	1
%	SKIN PHOTOTYPE II	10	5	0
	SKIN PHOTOTYPE III	22,5	17,5	12,5
	SKIN PHOTOTYPE IV	20	10	2,5

Table 1. Distribution of patients by dark circle severity based on Fitzpatrick Skin Phototype.

5. Then clean the area with fresh water and apply sunscreen.
6. The patients received the procedure every two weeks, with a total of four treatments.

Every patient was instructed to avoid direct sunlight, to apply a sunscreen (SPF 50+) before going out into sunlight, and to use sunglasses. Home treatment (02 MELINE® Dark Circles, Laboratorio Innoaesthetics, Barcelona – Spain) was also indicated. This consisted of a gel containing active ingredients to improve the circulatory condition, such as ruscus aesculeatus, meliloti, flavonoids, and procyanidins, and depigmenting active ingredients like alpha arbutin, tranexamic acid, and kojic acid. This product is applied to the treatment area at night two days after the procedure in the office and then stopped 24 hours before returning for the next procedure in the office.

An improvement scale was created to observe the patients being studied, as shown in Table 2.

Evaluation	Description
Worse	Stronger colour, post-inflammatory hyperpigmentation.
No change	No apparent improvement
Deficient	Up to 25 % improvement.
Fair	26 to 50 % improvement.
Good	51 to 75 % improvement.
Excellent	76 % improvement or above.

Table 2. Improvement evaluation scale after treatment for dark circles.

Patients participating in the study also created their own evaluation scale as shown in Table 3:

Evaluation	Description
Very satisfied	Highly pleased with the treatment.
Mildly satisfied	Satisfied, but expected a more significant outcome.
Dissatisfied	Did not note any change with the treatment.

Table 3. Patient satisfaction scale relating to treatment with the MELINE® Dark Circles plan.

RESULTS

The skin was observed to lighten in most patients, improving as the weeks of treatment completed. Patient observation and photographic evaluation was able to show that none of them could be classified as "worse" after the treatment.

Evaluation of the results

DARK CIRCLE SEVERITY DIAGNOSIS BY SKIN PHOTOTYPE

Evaluation at	Worse	No change	Deficient	Fair	Good	Excellent
SKIN PHOTOTYPE II						
30 days	0	2 (05.00%)	1 (02.50%)	3 (07.50%)	0	0
60 days	0	0	0	3 (07.50%)	1 (02.50%)	2 (05.00%)
90 days	0	0	0	1 (02.50%)	3 (07.50%)	2 (05.00%)
120 days	0	0	0	1 (02.50%)	3 (07.50%)	2 (05.00%)
SKIN PHOTOTYPE III						
30 days	0	4 (10.00%)	9 (22.50%)	8 (20.00%)	0	0
60 days	0	0	6 (15.00%)	7 (17.50%)	6 (15.00%)	2 (05.00%)
90 days	0	0	2 (05.00%)	7 (17.50%)	9 (22.50%)	3 (07.50%)
120 days	0	0	2 (05.00%)	7 (17.50%)	9 (22.50%)	3 (07.50%)
SKIN PHOTOTYPE IV						
30 days	0	4 (10.00%)	7 (17.50%)	2 (05.00%)	0	0
60 days	0	2 (05.00%)	6 (15.00%)	3 (07.50%)	2 (05.00%)	0
90 days	0	1 (02.50%)	3 (07.50%)	5 (12.50%)	4 (10.00%)	0
120 days	0	1 (02.50%)	0	0	4 (10.00%)	0

Table 4. Evaluation of the results of applying the MELINE® Dark Circles plan to patients with dark circles.

The evaluation of the treatment program during the first 30 days provided values for the first three skin phototypes that improved from deficient (42.5% of all patients in the study) to fair (32.5% of all patients in the study). However, on completion of the treatment cycle and evaluation at 90 days, 42.5% of patients showed a great improvement, with 40% of all patients in the study showing a good improvement, and 12.5% of all patients in the study showing an excellent improvement. This is in addition to 32.5% of patients showing a fair improvement with only one treatment cycle. During the final evaluation, only 1 patient (2.5%) with phototype IV remained unchanged.

Most patients (77.5%) were very satisfied with the outcome. They were interviewed about their level of satisfaction with the clinical results after the treatment. Patients were requested to assess the clinical results and select one of the three categories, with the results shown in Diagram 2.

The safety was evaluated by assessing the tolerability and adverse events. Most patients described good to excellent tolerability, with only some mild discomforts, such as a prickly feeling or mild itching during treatment. They did not present significant erythema, rashes, or swelling. They reported that the itchy feeling occurred temporarily while applying the product, but that it notably subsided after a few minutes. The exfoliation was more pronounced 24-48 hours after treatment when it presented.

Figure 2. Results from applying the patient satisfaction scale relating to treatment using the MELINE® Dark Circles plan.

DISCUSSION

There is no ideal treatment for hyperpigmentation in the periocular zone at present. Very little has been published in medical literature and the most mentioned treatment types specifically target tissue replenishment and not pigmentation treatment. In this study, 40 healthy individuals with periorbital hyperpigmentation (dark circles) under the eyes were treated using a therapeutic plan consisting of controlled microexfoliation using low concentration active ingredients and home use topical treatment. The study results show an effective improvement in pigmentation reduction and the general appearance of the treated skin.

Chemical peels have been a key tool in the therapeutic armamentarium of aesthetic medicine doctors over the last twenty years, given that they can be used to treat some skin disorders and provide a very good cosmetic benefit. This study presents a treatment that combines controlled microexfoliation, whereby the use of its active ingredients was conceived to be gentle on the treatment area and obtain better results with periocular hyperpigmentation. Thoroughly understanding the active ingredients and their modes of action is important in order to be able to apply the necessary care and to avoid possible undesirable effects.

The carboxylic acids include acetic acid derivatives and it is possible to obtain different formulations to replace some of the methyl group hydrogen atoms with chlorine atoms. Many acetic acid derivatives have been used in medicine for exfoliation purposes, like trichloroacetic acid, a versatile and safe component, dichloroacetic acid, and other acetic acid derivatives in order to produce aesthetic treatments (9), and chloroacetic (monochloroacetic) acid that has been used more as a component for treating warts.

The chemical effect of chlorinated carboxylic acids is protein denaturation. Chlorinated carboxylic acids applied to the skin produce changes in the epidermis and melanin dispersion, improving hyperpigmentations. Similarly, they derive in epidermis and dermis regeneration through new collagen deposition. Acetic acid derivatives have also been used to treat epidermal and mixed melasma without any significant side effects occurring, with the benefit of increasing the efficacy of other topical active ingredients when used in combination, such as alpha-hydroxy acids, promoting skin regeneration (10, 11).

One alpha-hydroxyacid, lactic acid, produces very superficial exfoliation and forms part of the natural moisturising factor, meaning it helps to replenish and maintain the skin barrier and rehydrate (10). Lactic acid reduces cohesion between corneocytes, deriving in dead cell elimination and stimulation of the growth of new cells in the basal layer (12).

Retinoids are vitamin A derivatives that affect multiple pathways to reduce the appearance of dark circles in the infraorbital region. Firstly, they promote collagen synthesis and collagen bundle reorganisation to improve the skin's turgor and quality. They also reduce melanin content and the size of the Golgi apparatus and the endoplasmic reticulum in melanocytes. Vitamin A derivatives can increase type I procollagen gene expression mediated by inhibited ultraviolet induction of c-Jun protein (13), leading to the inhibition of dermal collagen degradation, inhibiting metalloproteinase transcription factor activation (14, 15). Retinoids also improve dyschromia on inhibiting tyrosinase activity. This derives in reduced melanin synthesis, less melanosome transfer, and increased keratinocyte elimination (16, 17).

Topical use vitamin C (ascorbic acid) has been shown to reduce erythema induced by ultraviolet radiations and the appearance of wrinkles (18, 19). Vitamin C plays an important role in producing collagen and has been shown to stimulate its production when it is added to human skin fibroblast cultures (20). Vitamin C also restores the antioxidant capacity of vitamin E (21, 22), a much more potent inhibitor of lipid peroxidation.

The active ingredients contained in the home use product are very important and essentially look to improve the factors that lead to melanin pigmentation and to benefit the vasculature.

We mentioned the compound aimed at controlling melanin production earlier. Topical use niacinamide, the biologically active form of vitamin B3, both presents antioxidant and anti-inflammatory properties (23) and can improve hyperpigmentation on reducing melanosome transfer to keratinocytes. The effects of topical use niacinamide include improved skin texture and tone, along with a reduction in fine lines and hyperpigmentation (24).

Kojic acid is derived from fungi of natural origin produced by the species, Aspergillus and Penicillium. It acts by inhibiting tyrosinase in limiting steps (25). In a study undertaken by Lim et al. (26), adding kojic acid to a gel containing 10% glycolic acid and 2% hydroquinone was found to further improve melasma pigmentation. Despite the absence of studies, kojic acid has been tested anecdotally to treat periorbital hyperpigmentation and found to be effective.

When it comes to arbutin, we can say that it inhibits tyrosinase activity, while also inhibiting melanosome maturation. A randomised open trial undertaken by Ertam et al (27) found that a gel containing topical use arbutin was effective in reducing pigmentation in patients with melasma.

Lastly, tranexamic acid, a synthetic derivative of the amino acid, lysine, acts by inhibiting ultraviolet radiation-induced plasmin activity in keratinocytes, through a process that stops plasminogen from binding to keratinocytes, as such reducing arachidonic acid and prostaglandin production, with latter known to be stimulators of tyrosinase activity (28). Additionally, plasmin is believed to convert ECM-bound vascular endothelial growth factor (VEGF) into freely diffusible forms, deriving in angiogenesis. Kim et al. (29) discovered an increase in the gauge and count of dermal vasculature in melasma lesions along with an increase in VEGF expression compared to non-involved areas in the same patients. Therefore, when

treating pigmentations, tranexamic acid can have a dual effect, reducing promelanogenic factor production and reducing erythema and vasculature.

The ingredients chosen to act on the vasculature, Ruscus Aculeatus, Ginkgo Biloba, Troxerutin, and Melilotus Officinalis, combine to act to improve lymphatic circulation, strengthening capillaries through improving vascular integrity and reducing capillary permeability. Furthermore, other studies have shown additional activities from these ingredients that contribute to the treated periorbital change. Of those, Melilotus Officinalis, which has been shown to have anti-inflammatory effects, reducing the activation of circulating phagocytes and reducing citrulline production (30), and Ginko Biloba, which may have directly protective effects on mitochondria, contribute to its antioxidant effects because the mitochondrial respiratory chain is the main target and the source of oxygen reactive species (31, 32).

We can therefore assume that the skin lightening process observed during the studied treatment plan is due to the activity against melanin pigmentation, vascular effects, and the changes that occurred in the skin due to its restructuring. No significant complications were observed, meaning the products provide good safety when used. The treatment's effects lasted at least 4-6 months in most patients in combination with the use of suitable sunscreen.

When it comes to arbutin, we can say that it inhibits tyrosinase activity, while also inhibiting melanosome maturation. A randomised open trial undertaken by Ertam et al (27) found that a gel containing topical use arbutin was effective in reducing pigmentation in patients with melasma. Lastly, tranexamic acid, a synthetic derivative of the amino acid, lysine, acts by inhibiting ultraviolet radiation-induced plasmin activity in keratinocytes, through a process that stops plasminogen from binding to keratinocytes, as such reducing arachidonic acid and prostaglandin production, with latter known to be stimulators of tyrosinase activity (28). Additionally, plasmin is believed to convert ECM-bound vascular endothelial growth factor (VEGF) into freely diffusible forms, deriving in angiogenesis. Kim et al. (29) discovered an increase in the gauge and count of dermal vasculature in melasma lesions along with an increase in VEGF expression compared to non-involved areas in the same patients. Therefore, when treating pigmentations, tranexamic acid can have a dual effect, reducing promelanogenic factor production and reducing erythema and vasculature.

The ingredients chosen to act on the vasculature, Ruscus Aculeatus, Ginkgo Biloba, Troxerutin, and Melilotus Officinalis, combine to act to improve lymphatic circulation, strengthening capillaries through improving vascular integrity and reducing capillary permeability. Furthermore, other studies have shown additional activities from these ingredients that contribute to the treated periorbital change. Of those, Melilotus Officinalis, which has been shown to have anti-inflammatory effects, reducing the activation of circulating phagocytes and reducing citrulline production (30), and Ginko Biloba, which may have directly protective effects on mitochondria, contribute to its antioxidant effects because the mitochondrial respiratory chain is the main target and the source of oxygen reactive species (31, 32).

We can therefore assume that the skin lightening process observed during the studied treatment plan is due to the activity against melanin pigmentation, vascular effects, and the changes that occurred in the skin due to its restructuring. No significant complications were observed, meaning the products provide good safety when used. The treatment's effects lasted at least 4-6 months in most patients in combination with the use of suitable sunscreen.

Bibliography

1. Rashmi Sarkar, Rashmi Ranjan, Shilpa Garg, Vijay K. Garg, Sidharth Sonthalia, Shivani Bansal. Periorbital Hyperpigmentation: A Comprehensive ReviewJ Clin Aesthet Dermatol.2016;9(1):49–55.
2. Goodman RM, Belcher RW. Periorbital hyperpigmentation. An overlooked genetic disorder of pigmentation. Arch Dermatol. 1969;100(2):169–174.
3. Watanabe S, Nakai K, Ohnishi T. Condition known as "Dark Rings under the Eyes" in the Japanese population is a kind of dermal melanocytosis which can be successfully treated by Q-switched ruby laser. Dermatol Surg. 2006;32:785–789.
4. Sardana K, Rajpal M, Garg V, Mishra D. Periorbital hyperpigmentation mimicking fixed drug eruption: a rare presentation of erythema dyschromicum perstans in a paediatric patient. J Eur Acad Dermatol Venereol. 2006;20(10):1381–1383.
5. Freitag FM, Cestari TF. What causes dark circles under the eyes? J Cosmet Dermatol. 2007;6(3):211–215.
6. Roh MR, Chung KY. Infraorbital dark circles: definition, causes, and treatment options. Dermatol Surg. 2009;35:1163–1171.
7. Sheth PB, Shah HA, Dave JN. Periorbital hyperpigmentation: a study of its prevalence, common causative factors and its association with personal habits and other disorders.Indian J Dermatol. 2014;59(2):151–157.
8. Huang YL, Chang SL, Ma L, et al. Clinical analysis and classification of dark eye circle. Int J Dermatol. 2014;53(2):164–170.
9. Haynes, Willam M., ed. (2011). CRC Handbook of Chemestry and Physics (92 ne ed.). Boca ratón, FL.
10. Kumari R, Thappa DM. Comparative study of trichloroacetic acid versus glycolic acid chemical peels in the treatment of melasma. Indian J Dermatol Venereol Leprol. 2010 Jul-Aug;76(4):447.
11. Soliman MM, Ramadan SA, Bassiouny DA, Abdelmalek M. Combined trichloroacetic acid peel and topical ascorbic acid versus trichloroacetic acid peel alone in the treatment of melasma: a comparative study. J Cosmet Dermatol. 2007 Jun;6(2):89-94.
12. Surabhi Dayal, MD, Priyadarshini Sahu, MD, Vijay Kumar Jain, MD, & Sneh Khetri, MD. Clinical efficacy and safety of 20% glycolic peel, 15% lactic peel, and topical 20% vitamin C in constitutional type of periorbital melanosis: a comparative study. 2016. Journal of Cosmetic Dermatology, 0, 1-7.
13. Griffiths CE, Russman AN, Majmudar G, et al. Restoration of collagen formation in photodamaged human skin by tretinoin (retinoic acid). N Engl J Med 1993;329:530–5.
14. Fisher GJ, Datta SC, Talwar HS, et al. Molecular basis of sun-induced premature skin aging and retinoid antagonism. Nature 1996;379:335–9.
15. Fisher GJ, Wang ZQ, Datta SC, et al. Pathophysiology of premature skin aging induced by ultraviolet light. N Engl J Med 1997;337:1419–28.
16. Kang S. Photoaging and tretinoin. Dermatol Clin 1998;16:357–64.
17. Orlow SJ, Chakraborty AK, Pawelek JM. Retinoic acid is a potent inhibitor of inducible pigmentation in murine and hamster melanoma cell lines. J Invest Dermato.l 1990;16:357–64.
18. Humbert PG, Haftek M, Creidi P, et al. Topical ascorbic acid in photoaged skin. Clinical topographical and ultrastructural evaluation: double-blind study vs. placebo. Exp Dermatol 2003;12(3):237–44.
19. Traikovich SS. Use of topical ascorbic acid and its effects on photodamaged skin topography. Arch Otolaryngol Head Neck Surg 1999;125(10):1091–8.
20. Geesin JC, Darr D, Kaufman R, et al. Ascorbic acid specifically increases type I and type III procollagen messenger RNA levels in human skin fibroblast. J Invest Dermatol 1988;90(4):420–4.
21. McCay PB. Vitamin E: interaction with free radicals and ascorbate. Annu Rev Nutr 1985;5:323–40.
22. Chan AC. Partners in defense, vitamin E and vitamin C. Can J Physiol Pharmacol 1993;71:725–31.
23. Gehring W. Nicotinic acid/niacinamide and the skin. J Cosmet Dermatol 2004;3:88–93.
24.Bissett DL, Oblong JE, Berge CA. Niacinamide: a B vitamin that improves aging facial skin appearance. Dermatol Surg 2005;31(7 Pt 2):860–5.
25. Garcia A, Fulton JE Jr. The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. Dermatol Surg. 1996;22(5):443–447.
26. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. Dermatol Surg. 1999;25(4):282–284.
27. Ertam I, Mutlu B, Unal I, et al. Efficiency of ellagic acid and arbutin in melasma: a randomized, prospective, open-label study. J Dermatol. 2008;35(9):570–574.
28. Li D, Shi Y, Li M, Liu J, Feng X. Tranexamic acid can treat ultraviolet radiation-induced pigmentation in guinea pigs. Eur J Dermatol. 2010;20(3):289–92.
29. Kim EH, Kim YC, Lee E-S, Kang HY. The vascular characteristics of melasma. J Dermatol Sci. 2007;46(2):111–6.
30. Luminita Plesça-Manea, Alina Elena Parvu, M.Parvu, M. Taamas¸ R. Buia, M. Puia. Effects of Melilotus officinalis on Acute Inflammation. Phytother. Res. 2002. 16, 316–319.
31. Shi C, Liu J, Wu F, et al. Ginkgo biloba extract in Alzheimer's disease: from action mechanisms to medical practice. Int J Mol Sci 2010;11:107–23.
32. Diamond BJ, Bailey MR. Ginkgo biloba Indications, Mechanisms, and Safety. Psychiatr Clin N Am 36 (2013) 73–83.

ME®
LINE

www.melineskin.com

Version 1. 2019 ING