Original Contribution

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The assessment of the effect of a cosmetic product brightening the skin of people with discolorations of different etiology

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Summary

Background Hyperpigmentations are disorders displayed with a change in the color of the skin, its strange shape, the lack of symmetry, and irregular placement. They appear no matter on the age, gender, and often as a congenital defect. Disorder connected with overproduction of melanin by pigmentary cells. The change of color is due to endogenous and exogenous cause.
Objectives The aim of this thesis was to conduct a research *in vivo*. This will allow to judge the effectiveness of the cosmetic product which brightens the skin with hyperpigmentation problems. The characteristics of dermocosmetics were tested on people with various etiology of hyperpigmentation. The aim of the research was to assess the effect of the active substances used daily on skin hyperpigmentation.
Methods The tests were carried out on groups of patients with hyperpigmentations. The application of the pharmaceutical and the use of specific apparatus measurements were taken on every medical checkup. A survey was conducted to assess the changes in the face, neck, and neckline skin. The research was based on the apparatus analysis of the skin condition (MPA®, VISIA®).
Results Regular application of the pharmaceutical caused brightening of hyperpigmentations ($P < 0.05$). General improvement in skin condition was also observed – the increase in skin elasticity, smoothness, and the enhancement of hydration levels.
Conclusions Dermocosmetics for people with hyperpigmentation are an essential part of their medical treatment. In case of epidermal hyperpigmentation, the recipe of individually chosen and tested combination of ingredients enables us to reach satisfactory results.

Keywords: cosmetic formulation, hyperpigmentation, melanin, niacinamide, pigmentation

Introduction

Dermocosmetics was intended for the care of facial skin with discoloration of various etiologies. A study of the cream for the day was to specify in a qualitative as well as quantitative effectiveness of ingredients to lighten discolored skin changes color.

Melanin is a high molecular weight hydrophobic pigment, the amount of which determines skin color. The pigment is concentrated within neuroectodermal dendritic cells known as melanocytes, which synthesize melanin from the endogenous amino acid tyrosine. The number of melanocytes is fixed and does not directly

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influence the skin color. The cells themselves are located in the epidermis, vascular membrane, iris and retina of the eye, as well as the basal layer of the roots of the hair. They are the most plentiful in the skin between the living cells of the basal layer of the epidermis.

Melanin can be synthesized endogenously within nucleated keratinocyte cells or acquired through the diet as phenylalanine. Keratinocytes pass the produced melanin to their neighboring pigment cells. Melanophores on the endocytosis pathway accumulate melanin in the form of granules.[1,2] Melanin production is organized into melanin units, with a single unit comprising 36 keratinocytes connected to one pigment cell. Melanin itself is formed by the conversion of L-phenylalanine, exogenous amino acid, and L-tyrosine amino acid, followed by further conversion into L-DOPA (L-3,4-dihydroxyphenylalanine), which is then oxidized into to L-Dopaquinone. Polymerization into pheomelanin, a bright pigment with a reddish yellow color, then takes place, following initiation by amino acids with a sulphur group, that is. glutathione or cysteine.

The conversion of pheomelanin into eumelanin, a dark brownish-red pigment, then occurs in two stages. It is first converted to labile dopachrome, which then undergoes decarboxylation to 5,6-dihydroxyindole (DHI) or by tautomerization to 5,6-dihydroxyindole-2-carboxylic acid (DHICA). The emergence of DHI and DHICA initiates a polymerization process resulting in the production of black-brown eumelanin.[3] The melanin accumulates within the cytosol, where it serves to protect the DNA from the destructive effects of ultraviolet radiation. The melanosome can rupture and release the dye into the cell in response to internal factors, such as hormonal, endocrine, genetic, and systemic diseases, or external factors, such as ultraviolet radiation, mechanical trauma, and chemical damage to the dermis or epidermis.

Skin hyperpigmentation is defined as heterogeneous constitutional changes in skin color. It occurs due to overproduction of melanin by the physiological cell number, or simply the presence of an excessive number of pigmented melanocytes in the skin.[4]

From a clinical point of view, the distribution of the stain is accepted as the depth at which the dye is positioned. When making a diagnosis using a Wood's lamp, a distinction can be made on the basis of discoloration: that is, whether the skin is epidermal or dermal-mixed. The dye which has accumulated in the skin during exposure enhances the contrast between the unchanged skin and the focus of hyperpigmentation.[5]

The discoloration could have many causes. Genetic and metabolic factors can affect skin pigmentation, as can drugs or cosmetics administered in response to disturbances in the secretion of pituitary hormones (adrenocorticotropic hormone and melanocyte-stimulating hormones) such as active photo-sensitizers or photo-allergic substances. In addition, hormone therapy, or any history of skin dermatoses accompanied by inflammation can influence skin coloration.[6]

The alignment of skin tone requires multifaceted action. Externally applied products should include biologically active substances with a bleaching effect in their composition. Cream intended for skin care during the day (1473) incorporates a triactive complex with three modes of action: niacin blocks the transport of melanin to skin cells (keratinocytes), a biomimetic peptide-receptor blocks MC1R, thus reducing the production of melanin in the melanocytes, and *Rumex* spp. extract inhibits the activity of tyrosinase: the major enzyme of melanogenesis. In addition, the formulation contains substances such as vitamin C, E, shea butter, and Sunscreen SPF 50 + 7.

Aim

The aim of the study was to evaluate the effectiveness of cosmetic products for use during the day.

Materials and methods

The study was conducted in a group of 26 healthy women, mean age 48 years, selected in accordance with the guidelines of the Helsinki Declaration. Consent for the study was given by the Medical University of Lodz Ethics Commission (RNN/58/15/KE/M). The patients used the day cream for a period of 6 weeks. The condition of the skin was measured at the start of the test, and after 3 and 6 weeks of using the product (1473). These three sets of tests were designated as D0, D21, and D42, respectively. In addition, the participants completed a survey concerning their perception of the effect.

A detailed examination of symptoms was performed to verify the existing hyperpigmentation and their etiology. The participants were interviewed to determine the prevailing changes in pigmentation. In addition, skin tone was analyzed using images acquired with the VISIA® apparatus. In addition, each participant completed an initial questionnaire about skin sensitivity. The inclusion criterion for testing the cream (1473) was the presence of discoloration on the skin of the face. The exclusion criteria comprised the use of other brightening therapies, the use of a solarium, the presence of lesions and inflammatory skin conditions, as

well as the participant being pregnant or breastfeeding. All study participants gave their voluntarily consent to participate.

The impact of the systematic application of cream per day was determined by measuring the level of melanin pigment in the discolored places of the skin. Skin tone measurements were taken on the cheeks and forehead using Multi Probe Adapter (Courage-Khazaka Electronic GmbH, Cologne, Germany) the Mexameter® MX 18 and VISIA® Complexion Analysis system (Canfield Company, Parsippany, NJ, USA). Measurements D0, D21, and D42 were taken in the measuring room with controlled humidity (H = 30–50%) and temperature (T = 19–21 °C).

In all patients, photographic documentation of the VISIA® skin texture analysis allowed the progress of the bleaching treatment to be followed. Readings were taken using an MX18 Mexameter® in a selected spot, which was used for all subsequent measurements. The VISIA® allowed measurements to be made of the left and right side of the profile and the entire surface of the face. All participants within the study were qualified and registered. Study with the use of Mexameter® MX18 probe was conducted in the area of selected skin changes and the measurement was repeated on the same pigmented area.

The results were defined as the mean values of the individual partial measurements. The data were recorded in the form of each characteristic (the quantity of the measured characteristics, regardless of the intensity of these changes and their size) and result (including total size, intensity, and area). Photographic and numeric analysis of the skin was performed under UV light, also white light or cross-polarized light the RBX® technology using the VISIA® system.

The study included a control group of 12 people to confirm whether the amount of melanin changed over time in response to standard daily care without the use of specialized cosmetics. Measurements using the MX18 Mexameter® were performed three times in 3 months (January, February, and March). In a subjective evaluation, participants described the efficiency with the use of a questionnaire after 3 and 6 weeks of applying the cream.

Statistical analysis was performed using Statistica (StatSoft 12.0 Poland, Krakow, Poland). The ANOVA Friedman test was used to identify the relationships between the tested groups. The normality of the data distribution was examined using the Shapiro–Wilk test. A P-value <0.05 was considered as significant for all tests.

The cream consisted of niacin, *Rumex* spp., a biomimetic peptide (αMSH antagonist, Nonapeptide-1; Lucas Meyer, Champlan, France), UVB/UVA filters, shea butter and vitamin E. This publication presents selected results from the study.

Results

Thirteen participants were identified with postsun hyperpigmentation. Results are presented in Figure 1. The participants were also diagnosed with freckles, old spots, postacne spots, lentigines, and hormonal spots, including melasma, as well as the side effects of drug application.

Questionnaire results

Preliminary survey results showed that 31% of respondents noticed an instance of skin irritation or conjunctivitis after applying other cosmetics.

Of the participants, 8% indicated watery eyes and 4% lumps and/or spots following the initial application of the cream or during the course of its use (Table 1). None of the participants who indicated these changes discontinued the application of the cream. Traits describing the skin condition after the first application are presented in Table 1.

In addition, after the 6-week course, 88% of participants did not indicate any adverse effects as a result of applying the day cream (1473). Regular application of the product for 6 weeks resulted in the alignment of skin color in 92% of participants, with the same percentage reporting a noticeable lightening of the skin. Features of determining the condition of the skin after first application of the day the cream, it means improvement of moisturized, smoothed, regenerated, nourished, fine, fresh and radiant, are summarized in Figure 2.

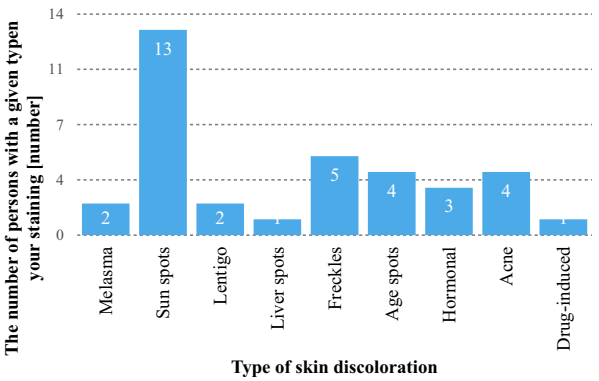


Figure 1 Types of hyperpigmentation diagnosed in people taking part in the study day cream (1473).

Table 1 A detailed description of the adverse reaction cases found on three patients, taking into account their duration

Cases of advert reaction	After 6 weeks		
	Patient 1	Patient 2	Patient 3
Symptoms	Spots/clumbs	Watery eyes	Watery eyes
How long the symptoms persisted advisable?	Few days	10–15 min	Momently
Whether the test was discontinued?	No	No	No

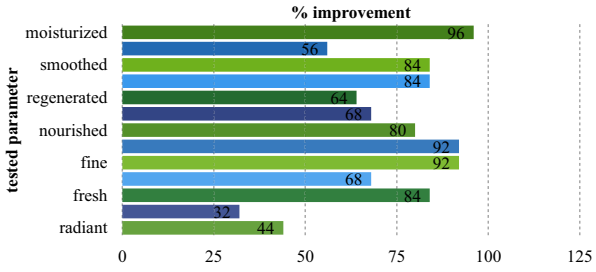


Figure 2 Chart showing the condition of the skin after 6-week day cream application (1473), $n = 26$.

Results of application

The Mexameter® MX18 examination of the intensity and redness of the pigmented spots found the amount of melanin was reduced by 13% in 88% of patients after 3 weeks, and by 20% in 96% of patients after 6 weeks ($P < 0.0001$). VISIA® examination of discoloration sunspots revealed age spots, wrinkles, skin photodamage and alterations in skin texture, and blood vessels (write results respectively after 3 and 6 weeks) in patients demonstrating actual improvement (Table 2, Figs 3–5).

- Reduction of spots (brown or red skin lesions) by 5% and 20 % ($P = 0.00001$).
- Reducing the spot UV (sun damage score) by 5% and 6% ($P = 0.00059$).
- Reduction of brown spots by 3% and 8% ($P = 0.00032$).
- Reducing the ruggedness by 6% and 27 % ($P < 0.0001$).
- Reduction in redness (i.e. erythema and telangiectasia) by 2% and 13% ($P = 0.01193$).

All of the aforementioned differences were statistically significant, with the results demonstrating a reduction in their total intensity and the size. The changes in the number of feature spots, brown, and UV spots after 3- and 6-week applications of day cream (1473) are presented in Figure 6.

Table 2 The results of measurements using VISIA, taking into consideration their level of significance

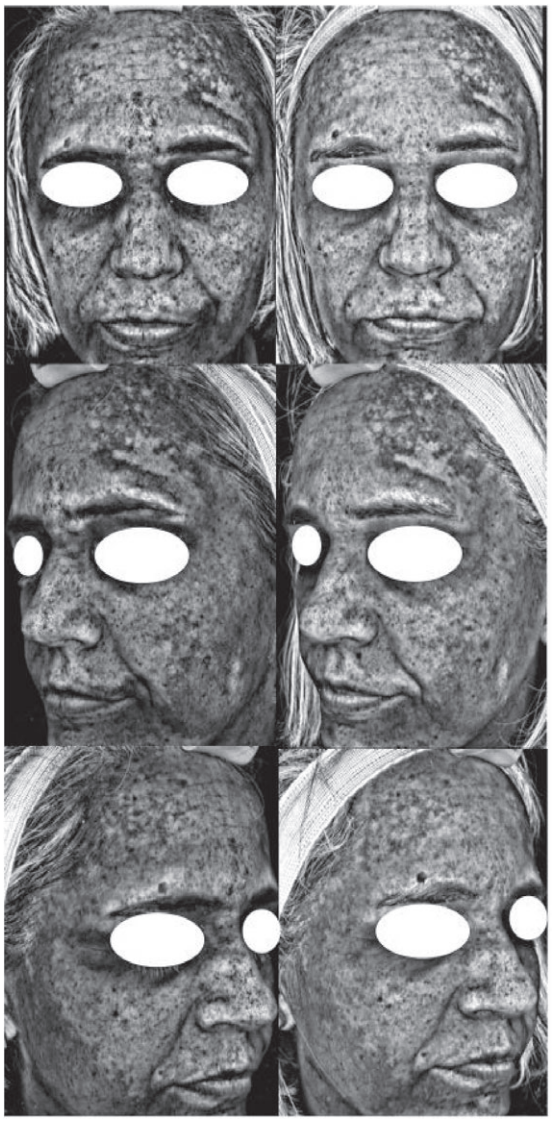
Features	Reducing changes after 3 weeks, %	Reducing changes after 6 weeks, %	Significance level ($P < 0.05$), P
Spots (brown or red skin lesions)	5	20	0.00001
UV spots (sun damage score)	5	6	0.00059
Brown spots	3	8	0.00032
Ruggedness	6	27	<0.0001
Redness (erythema and telangiectasia)	2	13	0.01193

In addition to lightening face discoloration, application of the cream was found to affect the overall condition of the skin. After 3 weeks, a 17% improvement in skin moisture was observed in 65% of patients, 8% greater elasticity in 69%, and a 12% reduction of redness in 62% ($P < 0.05$). Positive changes were observed over the following 3 weeks: 21% greater hydration in 68% of participants, 12% greater flexibility in 64%, and a 16% reduction of erythema in 76%. Mean melanin scores for the 12 people in the control group were 99 in January, 99 in February, and 100 in March.

Discussion

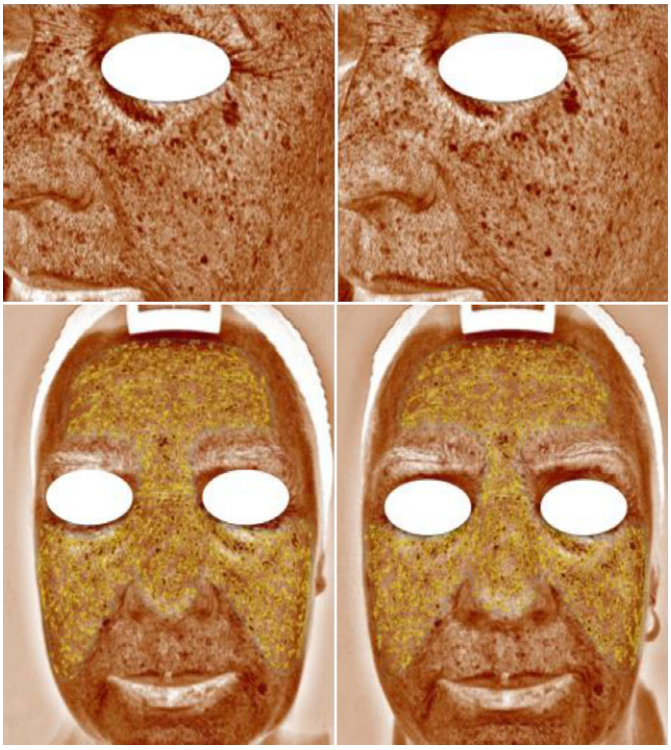
The study examines the activity of a ternary lightening complex on various hyperpigmentation changes. Hyperpigmentation is manifested as a primary efflorescence of spots present in the level of the skin. The spots are imperceptible to the touch but differ from the surrounding skin color. These changes are characterized by uneven shape and are clearly delimited. Formulations containing biologically active substances can be applied to reduce the quantity and size of skin hyperpigmentation, with the aim of efficiently and safely lightening discolored areas of the skin, returning it to its previous condition.[7]

The present *in vivo* analysis of skin condition confirmed that the administered complex, day cream (1473), possesses brightening properties. The formulation was administered for 6 weeks, with measurements taken prior to the treatment D(0), during its course D (21), and at the end D(42) of the study. The results of



number - uv spots (patient MZ)	measure before the application(D0)	Measurement after 6- weeks (D42)	difference after 6-weeks (D42)
Left profile	258	223	**-35**
Right profile	215	194	**-21**
En face	417	385	**-32**

Figure 3 Patient MZ (42 l.) before and after-6 weeks of using the cream for the day. Reduce the amount of UV spots view from the left profile, the right profile, and en face. Images under UV light.

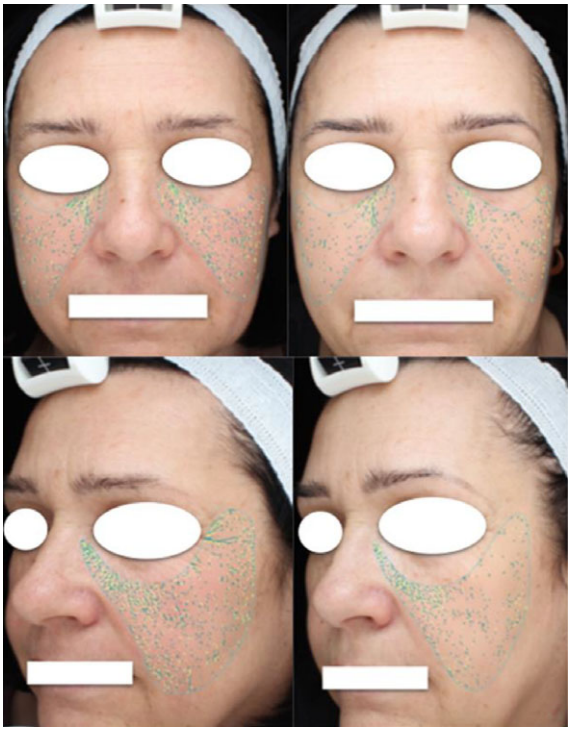


number - brown spots (patient BK)	measure before the application (D0)	Measurement after 6-weeks (D42)	difference after 6-weeks (D42)
Left profile	325	282	**-43**
Right profile	324	287	**-37**
En face	527	495	**-32**

Figure 4 Patient BK (57l) before and after 6 weeks of using the cream for the day. Reducing the amount of brown spots view from the left profile and en face. Images in the light of the cross-polarization in RBX®. Photo without founded the mask.

the three measurement points were subjected to appropriate mathematical and statistical analyses and the participants were surveyed for their subjective opinion of the results.

The active components of day cream (1473) include niacin, *Rumex* spp., αMSH antagonist, shea butter, and vitamin E. Niacin is a water-soluble vitamin also known as niacin (vitamin B3): a nicotinic acid whose amide, niacinamide, is present in foods and human cells as the nucleotides nicotinamide adinine dinucleotide phosphorous and nicotinamide adenine dinucleotide. Niacinamide is a natural antioxidant which exerts a protective influence against the harmful effects of UVB radiation on the skin by inhibiting the formation of free radicals in the body. Due to its hydrophilic character and high solubility in polar solvents, niacin effectively passes through the deeper layers of the epidermis. Niacin lightens skin by blocking the transfer of melanin to the cells of the epidermis. It also suppresses the transport of melanosomes, organelles



number - ruggedness (patient BK)	measure before the application(D0)	Measurement after 6- weeks (D42)	difference after 6-weeks (D42)
Left profile	1074	578	**-496**
Right profile	739	496	**-243**
En face	749	468	**-281**

Figure 5 Patient BK (57l) Before and after 6 weeks of cream a day. Reducing the amount of ruggedness view from the left profile and en face. Images in daylight.

that contain melanin, from the melanocytes to the keratinocytes of the epidermis, thus reducing the accumulation of pigment in keratinocytes. Niacin does not directly affect the activity of tyrosinase, the enzyme which facilitates melanogenesis. In addition, niacin stimulates ceramides and intensifies the amount of intracellular NADP. It supports the healing processes and prevents inflammation and has been shown to avoid clogging of the sebaceous glands, which enables more effective treatment of acne lesions. Clinical trials have demonstrated the effectiveness of niacinamide in lightening skin hyperpigmentation. Niacin is most commonly at concentrations from 2% to 5%. Also used in combination therapy with *N*-acetyl-glucosamine.[8–10]

The αMSH antagonist is a biomimetic peptide that is active during the induction of melanin synthesis, where it is responsible for blocking the MC1R receptor by competing with αMSH hormone, which is induced by UV radiation. The result of this is the inhibition of further activation of tyrosinase, thus preventing the

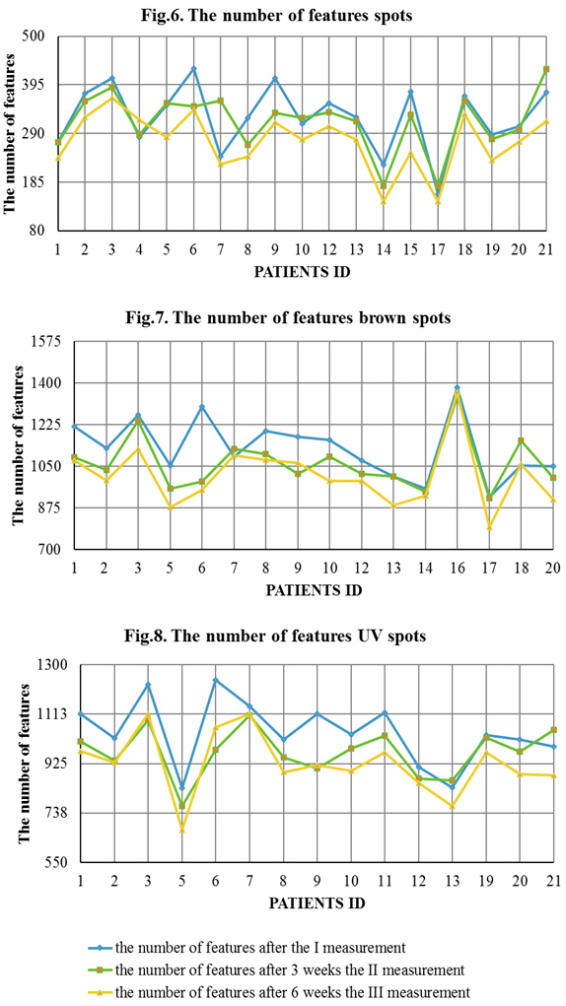


Figure 6 Graphs (Figures 6–8) show a reduction in the number of features in the form of spots in selected test persons. Posted ID assigned to each participant a study shows people who have noticed a real improvement in the brightening discoloration indicated. The improvement occurred after 3 and 6 weeks after preparation, and compared with the measurement chart was obtained prior to application of the cream.

synthesis of melanin. *In vitro* studies have shown that this is facilitated by the inhibition of cAMP synthesis. The αMSH antagonist has been demonstrated to hamper tyrosinase production, slow the hyperpigmentation process in melanocytes and keratinocytes and prevent the synthesis of melanin.[11]

Rumex spp., the knotweeds, are species of the Polygonaceae, which act as natural skin lighteners by slowing the activity of tyrosinase. The knotweeds contain a number of active components including polyphenols, tannins, anthraquinones, flavonoids, organic compounds of iron, or vitamin C. *Rumex* has been demonstrated to have brightening effects were proved in the studies conducted by the manufacturer. It is known to inhibit tyrosinase activity, resulting in the reduction of hyperpigmentation and erythema, as well as the reduction of age spots. Furthermore, extract of *Rumex* spp. has shown greater inhibition of tyrosinase than hydroquinone, Indian saffron or arbutin.[11,12]

A randomized study by Mendoza *et al.* performed on 45 Philippine citizens compared the effects of 3% *Rumex occidentalis* (sorrel extract) with 4% hydroquinone for treating melasma. The formulation was applied twice a day for a period of 8 weeks, with examinations every 2 weeks using a Mexameter® system. The results indicate that while similar declines in skin pigmentation were observed for both 3% sorrel extract and 4% hydroquinone, sorrel extract proved to be a safe and effective means of lightening discoloration in melasma.[13]

A cream containing 4% niacinamide +2% NAG was tested by Kimball *et al.* as part of a 10-week, double-blind, vehicle-controlled, full-face clinical study on women aged 40–60 years. The results showed that the cream was significantly ($P < 0.05$) more effective than the vehicle control formulation in reducing facial spots and the appearance of pigmentation on the skin.[14] Hakozaki *et al.* and Bissett *et al.* note that 2–5% niacinamide is effective when used alone or in combination with *N*-acetyl glucosamine for the treatment of melasma and UV-induced hyperpigmentation in fair-skinned and Asian patients. Niacinamide reduced cutaneous pigmentation in the PREP model, indicating that melanosome transfer is inhibited to a greater degree than in the coculture model.[15,16]

A further study of the brightening properties of biomimetic peptide and *R. occidentalis* extract was conducted on 50 women of Asian origin. Complementary and coherent path of action biomimetic peptide and sorrel extract, causing a reduction in the intensity of discolored skin conditions such as sunspots, freckles, or uneven pigmentation of the skin. The survey showed a lightening of discolored skin after 4 weeks of use in 80% of patients. The results show that 88% of participants reported alignment of skin color, 90% improved skin firmness and smoothness, and 78% reported reduced intensity of the stain, that is age spots. The concentrations of biologically active substances tested were 2% for the sorrel extract and 4% for biomimetic peptide.[11]

Bazela *et al.* examined the effectiveness of a product containing niacin, extract of *Rumex* spp. and a biomimetic peptide (αMSH antagonist). The examination comprised clinical measurements and surveys of a group of 10 people. Regular use of the cream for a period of

4 weeks resulted in the skin pigment lightening by 18.2%. In addition, after a 3-week application, more than half of those surveyed noted improved hydration and skin elasticity. The results of the survey confirm the positive results obtained during the clinical study.[17]

When comparing the results of the present study analyzing the effect of day cream (1473) with those given above, it appears that the triple whitening formula is effective in the treatment of hyperpigmentation. Both the physical examination and the results of the questionnaire confirm that a gradual brightening of darker spots occurs while using the day cream (1473), which can be attributed to the active component contained in the cream. No such improvement was found in the control group, with the skin color being found to be similar during the three successive months of measurements.

The above mentioned test results confirm the effectiveness of the tested products based on the following composition: 4% of niacin, 0.1% extract of *Rumex* spp. (*R. occidentalis*), and 7% biomimetic peptide. The tested cream incorporates a triply active complex. The excipients are naturally occurring antioxidants which offer protection of the skin against adverse external influences. The fragrance contained in the cream has a low potential for irritation and does not contain potentially allergenic substances. Hence it is safe for use and can be used for daily care of sensitive skin.

Presented research had some limitation that requires discussion. The control group (individuals classified as having no hyperpigmentation changes) has not been tested with all devices used to assess changes in the study of cream per day. However, it should be emphasized that the measurements were performed in each case by the main contractor of the study. In addition, it must be assumed that the application of the product by the patient were not verify by the main contractor. To sum up, results received by the authors suggest that a daily application of a cream for the day (1474), during 6 weeks of treatment, results in optimum brightening-stimulatory effects. However, the use of many tools to measure changes and the introduction of three points of measurement, to assess changes over time, reduced the risk of going wrong in analysis.

Conclusions

The cosmetics market has many new products intended for lightening discoloration. Cosmetologists, in collaboration with chemists and pharmacologists, work on obtaining effective preparations to eliminate excessive pigmentation of the skin. Appropriately selected treatment, regular use, and high quality products are needed to eliminate hyperpigmentation in facial skin. The results of the present study confirm the effectiveness of the use of dermocosmetics in lightening epidermal localized discoloration. The results of *in vivo* examination confirm the activity of the ingredients in the daily cream (1473) in the treatment of facial hyperpigmentation.

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