

How to Cite:

Mieze, L., Salijuma, E., Brunina, L., & Kokina, M. (2022). Rosacea symptoms significantly decrease after skin barrier improvement. *International Journal of Health Sciences*, 6(S2), 4218–4231. <https://doi.org/10.53730/ijhs.v6nS2.5946>

Rosacea symptoms significantly decrease after skin barrier improvement

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Abstract---Rosacea is a common chronic inflammatory skin disease, characterised by wavy course – exacerbation alternates with remission. Currently rosacea is not completely curable, but using appropriate pharmacological treatment, medical devices, appropriate daily skin care routine and educating patients, is possible to control a rosacea activity. This study aims on testing whether there is skin barrier improvement leads to associated rosacea symptoms decrease after the application of the products developed on natural emollient emulsion base with active ingredients of natural origin without the use of traditional preservatives and preservatives of natural origin with irritating potential. This was a prospective, single-centre, placebo-controlled, double-blind randomised pilot study. The enrolled participants were randomised to receive one of four interventions. The testing was performed by clinical grading, assessment of facial skin condition and determination of qualitative parameters with skin diagnostic device. The results show reduction in redness and red spots, which indicates the blood vessel-strengthening and anti-inflammatory properties of the product ingredients. The decrease of porphyrins was observed in all participant groups. The decrease of porphyrins was observed in all participant groups of the study, which is explained by the high quality of the product emollient base developed with plant oils. Improvement results show that rosacea symptoms are not reduced efficiently enough by anti-inflammatory substances only, it is essential to restore the protective skin barrier

and immunity by boosting natural regulatory processes and diminish the adverse effects of irritants on the skin.

Keywords---rosacea, clinical grading, perspective pilot study.

Introduction

Rosacea is a common chronic inflammatory skin disease, characterised by wavy course – exacerbation alternates with remission. Complaints are mainly seen in the central part of the face – diamond-shaped on the chin, cheeks, nose and forehead. The main clinical signs are facial redness, telangiectasia and inflammatory lesions like papules and pustules. In addition, there may be subjective complaints such as burning, tingling or itching of different intensities. In severe cases patients complain about skin dryness as well. Four different subtypes of rosacea have been identified and although the exact pathogenesis is unknown. It is associated with cutaneous vascular abnormalities and dysregulation of the inflammatory response of the innate and possibly the acquired immune system [1-4].

This study is of particular significance taking into account that rosacea is associated with significant psychological distress, decreased quality of life and increased feelings of stigmatisation, as well as higher risk of mood, anxiety, impulse control and personality disorders in patients suffering from this skin condition [5, 6]. Although there are no exact and verified data about the prevalence of rosacea by countries and studies researching this topic have not observed latitude-dependent gradient in rosacea prevalence [7], there are genetic and racial differences, and it is commonly acknowledged that this skin condition more frequently affects individuals with lighter skin types, which generally represent the population of northern countries, and that the external conditions are the ones that significantly influence the development of rosacea, which is also applicable to the climatic conditions of northern latitudes. There has been no research conducted in Latvia on incidence, as well as prevention and reduction of the symptoms of rosacea, moreover in connection with the consequent effects of skin ageing.

Objectives

This study aims on testing whether there is skin barrier improvement using the natural cosmetics and whether associated rosacea symptoms decrease after the application of the products developed on natural emollient emulsion base with active ingredients of natural origin with anti-age and/or anti-rosacea or anti-acne activity, without the use of traditional preservatives and preservatives of natural origin with irritating potential.

The objectives of study testing were:

- to assess the allergenic potential of the products.
- to evaluate the effect of products on redness of the skin.
- to evaluate the effect of products on the skin microrelief (wrinkles, lines).

- to evaluate the effect of the products on the skin's macro-relief (general skin surface smoothness, texture).
- to evaluate the effect of products on porphyrins (end products of bacterial P. acne biosynthesis).
- to evaluate the effect of products on pores.

Materials and methods

Study participants

The participants of the approbation were selected on a voluntary basis, after signing informed consent forms. The study was completed by 72 participants aged 24 to 67 years (71 females, 1 male) with erythematotelangiectatic rosacea, papulopustular rosacea and signs of skin aging.

Inclusion criteria

In the rosacea test group, patients over the age of 18 (patients under the age of 18 parental permission require) who experience the following skin problems: permanent redness of the skin, redness of the skin caused by various external factors, clearly visible small blood vessels, papulopustular rash on a background of erythema, previously diagnosed rosacea. In the anti-age group, patients over the age of 35 who experience the following skin problems: uneven skin relief (static visible small, shallow and/or deep lines), wrinkles created by facial expressions, dull and thin skin, skin that has lost elasticity, firmness, easily slipped.

Exclusion criteria:

1. Pregnancy.
2. Scars, open lesions and wounds at the product application site.
3. Allergy to any of the components of the study drug.
4. The study protocol is not followed.

The participants are randomly divided into four groups. Three test groups using the product with the test active substances and the control group using placebo products without the test active substances:

- rosacea/anti-age group
- rosacea/acne group
- anti-age group
- placebo group

Study design

This prospective, single-centre, placebo-controlled, grader-blinded, double-blind randomised pilot study was carried out between January 2020 and March 2020. The division of the participants into intervention and control groups was based on randomisation and the graders were totally blinded to intervention which each subject received. The blinded graders assessed the skin condition and changes of

each participant during the testing process by images and measurements obtained by skin analysis performed at baseline and at week 4 and 8 visits (56 days). Subjects were also asked to perform a self-assessment before and after the conduction of the study, as well as to report any adverse effects throughout the study. Subjects were seen at a screening visit followed by a baseline visit for initial facial skin analysis (visit 1), at week 4 for interim facial skin analysis (visit 2) and at week 8 for final facial skin analysis and response evaluations (visit 3). The entire study was performed at the Dermatological Clinics of the Health Center 4 (Riga, Latvia). The primary endpoint was VISIA skin analysis based on measurements of skin pigmentation, areas of redness, pore size, and porphyrins (evidence of bacteria lodged in pores), as well as UV spots, sun damage, skin texture, and wrinkles. For each group selected parameters were analysed: Rosacea/Anti-age group – redness, Rosacea/Acne group – redness, porphyrines, pores, Anti-age group – micro- and macro relief, Placebo group – redness, porphyrines, pores, micro- and macro relief. Data processing was performed using the statistical data processing program – SPSS (Statistical Package for the Social Sciences), performing descriptive and inferential data analysis.

Patients were randomised and pre-allocated by using an online made by research study assistant prior to study subject recruitment and kept off-site by a separate member of personnel not involved in the study. Study personnel were blinded to the allocation. After recruitment and assignment of subject numbers in sequential order of study visits, the research team member dispensed the package of skincare products to be used labelled with the corresponding subject number. The codes were not revealed to the evaluators until the study was complete. Participants were to report any discomfort, skin irritation if occurred during testing, in which case the testing should be terminated.

Study products

The products tested in the conducted study were developed, patented and clinically tested. The composition of the study products is unique in respect of combining properties of anti-age and reduction of symptoms of rosacea and acne. The set of products applied was comprised of a facial cream and serum. All the products are developed on natural emollient emulsion base with active ingredients of natural origin with anti-age and/or anti-rosacea or anti-acne activity, without use of synthetic and irritant preservatives. The natural oil emollient ingredients were selected to have the following properties: anti-inflammatory, anti-microbial, barrier repairing and low potential for irritation or allergy. The placebo group used a natural emollient base without active ingredients. The set of products applied was comprised of a facial cream and serum. All the products are developed on natural emollient emulsion base with active ingredients of natural origin with anti-age and/or anti-rosacea or anti-acne activity, without the use of traditional preservatives and preservatives of natural origin with irritating potential like benzyl alcohol [8,9], benzoic acid [10,11] and its sodium salts, glyceryl caprylate [12,13], caprylyl glycol [14,15], cinnamic acid and derivatives [16,17], salicylic acid and its salts [18,19]. The use of glycols (propylene, butylene glycol) is also excluded (except pentylene glycol at 2% wt which is used for the formula protection purposes). The natural oil emollient ingredients were selected to have the following properties: anti-inflammatory,

anti-microbial, barrier repairing and low potential for irritation or allergy. The placebo group used a natural emollient base without active ingredients.

- Rosacea and acne cream and Rosacea cream main active ingredients: rosmarinic acid, caffeic acid, gallic acid derivatives, Laminaria Ochroleuca Extract
- Anti-age face cream main active ingredients: Ceramide NP, Olea Europaea Callus Culture Lysate, Sodium Mannose Phosphate
- Acne serum main active ingredients: Juniperus communis callus culture extract (and) Usnea barbata extract
- Rosacea serum main active ingredients: Helichrysum Italicum extract, Juniperus communis callus culture extract, Arctium Lappa Root Extract

Use

At the baseline visit all subjects were given a set of skincare products and instructed on their application, as well as advised to avoid using any other skincare products during the trial period. During the study, participants were instructed to use only the facial wash provided within the study (product No. 9) 1-2x/day and/or micellar water (product No 10). After cleansing the face in the morning or overnight (product No 9 and/or No 10), the serum issued in the study (product No. 1, 3, 5 or 7) is applied, after which the face cream (product No 2, 4, 6 or 8) is used at the discretion of the participants.

Results

In total 80 participants enrolled in and were randomised into four groups (Placebo, Rosacea/Anti-age, Rosacea/Acne and Anti-age), 20 participants per group. Eight participants dropped out of the study due to the reasons related to the COVID-19 situation and the study was completed by 72 participants (Placebo group – 20, Rosacea/Anti-age – 18, Rosacea/Acne- 15 and Anti-age – 19 participants). There were no adverse events reported. There are other factors such as subject diets and medication taken during the time period of conduction of the study that could potentially influence results; however, these data were not collected. Assessment of the skin condition of the participants with VISIA Skin Analysis® skin diagnostic equipment was performed at day 0, 28 and 56 of use of the study products for detection of changes in superficial and deepest skin structures in regard of redness, microrelief (wrinkles, lines), macro-relief (general skin surface smoothness, texture) (Figure No 1), porphyrins (end products of bacterial *P. acne* biosynthesis), pores. In tables No 1 to No 3 the value of each parameter shows the position compared to the 100 other people of the same age, gender and skin type available in the database of the VISIA Skin Analysis® (the higher the value, the better the result). For the participants that used placebo products redness and red spots on face intensified (Table No 1).

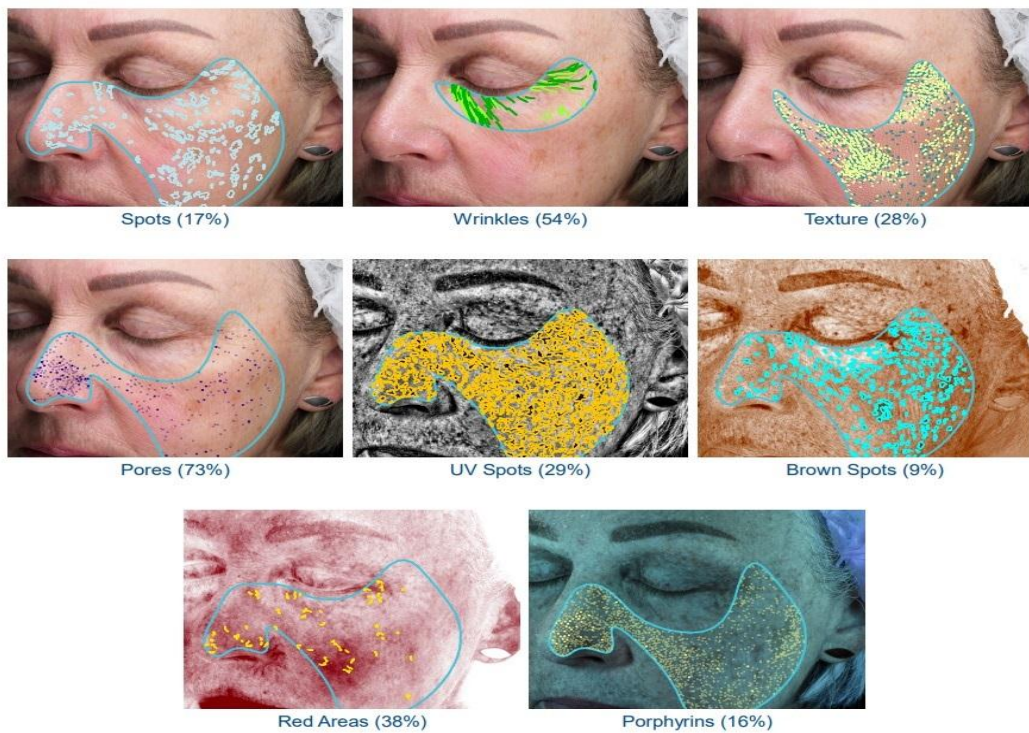


Figure No. 1: Various dimensions of the skin analysis

Table No 1: Results of application of Rosacea/Anti-age vs Placebo study product

		Rosacea/Anti-age		PLACEBO	
		2 scan	3 scan	2 scan	3 scan
Texture	Left side	0	0,1	0	0,0715
	Right side	-0,1	-0,05	0	0,2143
Wrinkles	Left side	-0,35	-0,15	0,5	0,2857
	Right side	-0,3	-0,2	0,2143	0,1428
Pores	Left side	-0,15	-0,2	0	-0,0714
	Right side	-0,1	-0,1	0,0714	-0,1429
Porphyrins	Left side	-0,45	-0,25	0,0715	0,0715
	Right side	-0,4	-0,2	-0,1429	0
Red spots	Left side	-0,15	0,05	0	0,1428
	Right side	0,2	0,05	0,0715	0,1429

Rosacea/Anti-age group test results demonstrate statistically significant positive differences between measurements 1 and 2 – porphyrins right side ($P=0.022$) and left side ($P=0.049$), as well as between measurements 1 and 3 – porphyrins right side ($P=0.046$) and left side ($P=0.025$). In regard of redness of the skin, positive dynamics is observed on both sides – redness of the skin is decreased after product use within this participant group (Figure No 2 before and Figure No 3 after the application).



Figure No. 2: Patient photo before the study product application in Rosacea/Anti-age group



Figure No. 3: Patient photo after the study product application in Rosacea/Anti-age group

There are also statistically significant differences for the indicator “red spots” (right side) in both stages between 1st and 2nd measurement ($p = 0.014$) and 1st and 3rd measurement ($p = 0.046$). Comparing the results of Rosacea/Acne group against the results of skin analysis of the participants of Placebo group (Table No 2), the 2nd facial analysis session demonstrates worsening in the condition of skin texture and wrinkles, as well as in porphyrins and red spots, and only for texture and wrinkles there are improvements detected at the 3rd facial analysis session.

Table No 2: Results of application of Rosacea/Acne vs Placebo study product

		Rosacea/Acne		PLACEBO	
		2 scan	3 scan	2 scan	3 scan
Texture	Left side	0,2222	0,1111	0	0,0715
	Right side	0,2222	0,1111	0	0,2143
Wrinkles	Left side	0,4445	0,1111	0,5	0,2857
	Right side	0,5556	0,4445	0,2143	0,1428
Pores	Left side	0	0,1111	0	-0,0714
	Right side	-0,1112	0	0,0714	-0,1429
Porphyrins	Left side	0	0	0,0715	0,0715
	Right side	0,1111	0,2222	-0,1429	0
Red spots	Left side	0,1111	0,2223	0	0,1428

	Right side	0	0,1111	0,0715	0,1429
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Only indicator which is improved in this group is for pores on the right side of the face at the 2nd session (Figure No 4 before and Figure No 5 after the application). In this comparison, the participants from Placebo group demonstrated better results.



Figure No. 4: Patient photo before the study product application in Rosacea/Acne group



Figure No. 5: Patient photo after the study product application in Rosacea/Acne group

Similarly, the results for participants of Anti-age group show deterioration in the skin condition for measurements regarding the skin texture, wrinkles, pores, as well as red spots right side of the face (Figure No 6 before and Figure No 7 after the application), with only difference from the Rosacea/Acne group being that these indicators tend to downgrade further on as is evidenced by the results of the 3rd analysis session results. Only indicator that shows unambiguous improvement is for porphyrins.



Figure No. 6: Patient photo before the study product application in Anti-age group



Figure No. 7: Patient photo after the study product application in Anti-age group

The comparative analysis of the results for participants of Anti-age group versus Placebo group demonstrate that overall, there are similar tendencies in detected changes in skin condition (Table No 3).

Table No 3: Results of application of Anti-age vs Placebo study product

		ANTI-AGE		PLACEBO	
		2 scan	3 scan	2 scan	3 scan
Texture	Left side	0,077	0,1539	0	0,0715
	Right side	0,1539	0,2308	0	0,2143
Wrinkles	Left side	0	0,0769	0,5	0,2857
	Right side	0,2308	0,4615	0,2143	0,1428
Pores	Left side	0,1539	-0,0769	0	-0,0714
	Right side	0,1538	0,1538	0,0714	-0,1429
Porphyrins	Left side	-0,1538	-0,2308	0,0715	0,0715
	Right side	-0,2307	-0,3077	-0,1429	0
Red spots	Left side	-0,077	-0,1539	0	0,1428
	Right side	0,3077	0,1538	0,0715	0,1429

Discussion

The most improvements after the product use were observed for those participants who used Rosacea/Anti-age skincare products with statistically significant differences in number of porphyrins, as well as showed reduction of the redness of the skin, some improvement regarding the depth and length of wrinkles and overall skin texture. Positive dynamics was observed regarding the redness of the skin on both sides – it is decreased after product use within this participant group, which indicates the strengthening and anti-inflammatory properties of the substances in the product. The skin of rosacea patients is characterised by severe dryness and low epidermal hydration levels and at the same time it may be highly sebaceous [20]. The results show that the concentration of porphyrins had decreased, indicating that the tested products contain the properties reducing the activity of sebaceous glands and balancing of skin microbiota. The decrease of porphyrins was observed in all participant groups of the study, which is explained by the high quality of the product emollient base developed with plant-based oils. Results of a comparative study report suggest that sebum-modifying nonantibiotic treatments may have beneficial therapeutic effects for patients with rosacea [21]. The emollient cream base for the study products has been adapted so that their plant-based oil compounds would provide sufficient moisturisation of the skin while not being too heavy to cause the sebaceous glands to be trapped by lodged pores and result in formation of bacteria and inflammation. Another beneficial feature of the study products is due to exclusion of synthetic preservatives, which are irritant to the skin, especially in cases of rosacea. The mechanism of action of preservatives, depending on the specific chemical compound, is based on the reduction of the membrane activity of microorganisms affecting the membrane potential, enzyme activity or membrane permeability, and other impacts. Parabens, 1,2-hexanediol and phenoxyethanol have been proven to inhibit not only the growth of pathogens but also the viability of skin-friendly microorganisms such as *Staphylococcus epidermidis*, *Shigella flexneri*, *Enterobacter aerogenes*, etc., thus upsetting the natural balance and exposing the skin to external irritation [22]. The study products were developed by using an alternative green preservative produced from non-edible elements of corn and sugarcane, as well as natural chelating agents as biodegradable replacements for EDTA, which significantly limit the irritation and causing possible allergic or otherwise adverse reactions on the skin. The exact mechanisms underlying occurrence of rosacea and facial redness have yet to be determined, and likely vary among individuals. The study results demonstrate that, apart from the Rosacea/Anti-age group, other participant groups of the study exhibited worsening in most of the measured aspects of the skin condition, the results being even slightly better for the participants who used placebo study products. The results of facial analysis show one peculiarity – inconsistency between the measured condition of skin texture on the right and the left side of the face for the Rosacea/Anti-age group and inconsistency between the measured condition of red spots on the right and the left side of the face for Rosacea/Anti-age group and Anti-age group. One far-fetched but plausible explanation could be that such was caused by mechanic covering the left side of the face with hand by the participants who are mainly right-handed, while sitting. As both these groups used products with anti-age properties, that might explain the key role of skin barrier restoration in order to prevent reddening. On the other hand, the

diminished condition of the skin texture on the left side might be directly related to mechanical damage caused to skin by physical friction and pressure induced.

However, the results of the conducted study can be interpreted as indicating the beneficial effects of the use of nature-based skincare products in case of rosacea. As it is evidenced also in study reports, use of products of natural origin show clinical improvements in overall skin appearance in minimal, mild, and moderate rosacea severity, the observed performance of natural regimen versus synthetic products being superior in all severities of the disease. Therefore, it can be acknowledged that nature-based skin care products can be effective adjunct to prescription medication in the management of all rosacea severities [23]. Moreover, the dermatological tests conducted within this study demonstrate that use of the products addressing rosacea symptoms in combination with anti-age properties have the most capability to achieve improvements in skin condition. This is of particular importance considering that rosacea patients often are limited in possibilities to use anti-age skincare [20].

The study has several limitations. One is the relatively small number of respondents, which is a constraint to generalise the conclusions. The sensitive issue of the subject matter of the study itself is a significant limitation as it makes it difficult for get enough respondents to involve forming a representative sample. Studies have shown that people who are affected by rosacea are prone to experience depression, anxiety, embarrassment, decreased self-esteem and increased social phobia and stress [5, 24], and, consequently, are more introverted and tend to hide the problem, thus are less likely to actively take part in activities that emphasise and publicise the problematic skin condition. The withdrawal of study participants can be explained also by the limitations of COVID-19 pandemic situation.

Conclusion

Improvement results are shown in the Rosacea/Anti-age group that implicate the efficacy of the nature-based rosacea treatment in combination with compounds of restorative activity. Reduction of the porphyrins after the product use of this study group indicates that the tested products contain the properties reducing the activity of fat and sebaceous glands and balancing of skin microbiota. The results obtained from this study group show also reduction in redness and red spots, which indicates the blood vessel-strengthening and anti-inflammatory properties of the product ingredients. The decrease of porphyrins was observed in all participant groups of the study, which is explained by the high quality of the product emollient base developed with plant oils. Higher improvement results in the Rosacea/Anti-age group show that rosacea symptoms are not reduced efficiently enough by anti-inflammatory substances only, it is essential to restore the protective skin barrier and immunity by boosting natural regulatory processes and diminish the adverse effects of irritants on the skin.

Acknowledgment

BaltlineGlobe project “Development of innovative face cosmetics with controlled release of active ingredients by use of Metal Organic Frameworks or Cocrystals” Nr. 1.1.1.1/18/A/176

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