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## **Efficacy of use of combined skincare routine on reduction of dermatitis symptoms**

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**Abstract---**Atopic dermatitis is a chronic inflammatory skin disorder. However, careful skin care can help to control and alleviate everyday symptoms, such as very dry, irritated and red skin. The majority of the even natural skincare products aiming at the relief of the dermatitis symptoms are developed using traditional and typically irritating preservative systems being effective systems for maintaining the product often become a problem or harm to the user - causing loss of microbial diversity, causing the user to experience discomfort due to irritation. The study aims at checking the efficiency of the combined skincare routine of two formulations having been developed using a delicate preservation and lipid regeneration layer system to promote balanced skin-cell interactions and reduce homeostasis disorders in the form of skin barrier dysfunction or inflammation. Results show the overall decrease of all sensitive and visual symptoms. The most significant symptom reduction in the dimension of skin sensations was noted in burning/heat sensation and in the dimension of visible skin changes in extended vascular networking reduction. 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 atopic dermatitis.

**Keywords---**dermatitis, atopic skin condition, clinical grading, pilot study.

## Introduction

Atopic dermatitis is a chronic inflammatory skin disorder and there is no simple cure to heal it. However, careful skin care can help to control and alleviate everyday symptoms, such as very dry, rough, irritated and red skin. A common characteristic for atopic dermatitis is an impaired skin barrier that results in an increased transepidermal water loss that leaves the skin dry and itchy. Microorganisms and allergens can easily penetrate through the broken skin barrier and cause further irritation [1,2]. Studies have suggested that a thinner Stratum corneum with smaller corneocytes and reduced levels of Stratum corneum ceramides lead to impaired barrier function in sensitive skin [3]. It is believed that both transepidermal water loss and Stratum corneum hydration levels can serve as indicators of the severity of pruritus and quality of life in patients with atopic dermatitis [4]. In the skincare routine it is advised to use products containing both emollients and humectants, while emollients provide an occlusive barrier for skin with atopic dermatitis, retain moisture and protect it from irritants. Specially formulated emollient products may claim to have antimicrobial, anti-itch and anti-inflammatory actions [5]. The same time humectants attract water vapor to moisturize the skin. They are similar to the natural moisturizing factors in the corneocytes. Consequently, emollients fill the cracks between desquamating corneocytes and smoothen the skin. Occlusive agents work by forming a thin hydrophobic film on the surface of the skin to retard transepidermal loss of moisture while being similar to the intercellular lipid bilayers of ceramide, cholesterol and free fatty acids [6].

The study of the skincare routine and its possible efficiency in the reduction of the atopic dermatitis symptoms is a substantive topic nowadays while studies show the atopic dermatitis symptoms are present in 2.4% of the population around the globe with the specific prevalence in some countries, especially of the Eastern and Northern Europe [7]. Atopic dermatitis significantly impact the quality of life of the patients, while the vast majority of the patients experience permanent itching that is consequently leading to the continuous mental distress as well as the decrease of the self-esteem and overall negative impact on the quality of life [8].

However, majority of the even natural skincare products aiming at the relief of the atopic dermatitis symptoms are developed using traditional and typically irritating preservative systems or antibacterial agents like benzyl alcohol [9,10], benzoic acid [11,12] and its sodium salts, glyceryl caprylate [13,14], caprylyl glycol [15,16], cinnamic acid and derivatives [17,18], salicylic acid and its salts [19,20] while being effective systems for maintaining the product, but often become a problem or harm to the user - causing loss of microbial diversity, causing the user to experience discomfort due to irritation. The study aims at checking the efficiency of the combined skincare routine of two formulations having been developed using a delicate preservation and lipid regeneration layer system to promote balanced skin-cell interactions and reduce homeostasis disorders in the form of skin barrier dysfunction or inflammation. The results of the study serve as the basis for the future research and the development of the product of natural origin without using the traditional preservation system therefore reducing the potential irritating factor to the patients with atopic dermatitis symptoms. There

has been no natural cosmetics research conducted in Latvia on incidence, as well as prevention and reduction of the symptoms of atopic dermatitis. Considering the above, this study contributes to the issue of possible treatment and maintenance of this skin disorder in relation to improvement and restoration of the overall health and condition of the skin based on nature-originated skincare product use.

## Methods

The participants of the approbation were selected on a voluntary basis, after signing informed consent forms accepting participants of both genders. 52 subjects showing the clinical signs of dry skin, mild-to-moderate dermatitis symptoms and/or diagnosed atopic dermatitis in the facial and neck zones are enrolled, while 43 have completed the study being considered as participants that formed the study sample. The age of the participants was from 19 to 51 (mean age = 35.51 years old). All participants having completed the approbation are females. The study did not involve ethic committee while studies on cosmetic products are usually carried out without any approval from an ethics committee. In Europe, all cosmetic products are safe for human use according to the Cosmetic Regulation EC 1223/2009. The techniques employed in cosmetic testing, and in this study, are non-invasive to minimally invasive. The study is carried out according to the declaration of Helsinki to take into account the research ethics related to studies involving humans.

Participant inclusion criteria were as follows:

- Patients over the age of 18 years
- Diagnosed atopic dermatitis and/or mild-to-moderate dermatitis symptoms in the facial and neck zones
- Has not been recently involved in any other similar study
- Willingness to use during all the study period only the product to be tested in the facial and neck zones
- Willingness to not vary the normal daily routine

Participant exclusion criteria

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

The study is registered in the ISRCTN registry as per the requirements set out by the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and the International Committee of Medical Journal Editors (ICMJE) guidelines: ISRCTN52512550. The study is single-centre double-blinded randomized trial was conducted in Latvia from November 2021 to the January 2022. The primary study design is interventional study, when the secondary study design is a randomised parallel trial.

The division of the participants into two groups was based on randomisation and the graders were totally blinded to intervention which each subject received. Subjects were randomised and pre-allocated by using an online software service using a list of randomly generated numbers 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 would dispense the package of skincare products to be used by a participant during the study labelled with the corresponding subject number. The codes were not revealed to the evaluators until the study was complete.

The blinded graders assessed (dermatologist, MD) the skin condition and changes of each participant during obtained by skin analysis performed at baseline and at week 4 visits. 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 are asked to attend dermatologist visits at baseline and after 28 days of product combination use. The participants were asked not to use other cosmetics and other make-up on dermatitis/dry skin during the study. The first group of participants are asked to apply the washing gel oil (product 1) to the dermatitis/dry face/neck skin in the morning and evening for 28 days. The product is washed off with water for not more than 1 minute. Afterwards participants are requested to apply the product nourishing daily cream (product 2) for restoring and preserving the lipid layer of natural origin on dermatitis/dry face/neck skin. The second group of participants are asked to apply the washing gel oil (product 1) to the dermatitis/dry face/neck skin in the morning and evening for 28 days. The product is washed off with micellar water of natural origin (without water). Afterwards participants are requested to apply the product nourishing daily cream (product 2) for restoring and preserving the lipid layer of natural origin on dermatitis/dry face/neck skin. At each visit, skin dermatological conditions and dermatitis symptoms are evaluated by the dermatologist. All the check-ups and evaluations are carried out using minimally non-invasive procedures. The total duration of each visit is 15 minutes. The study duration is 28 days. Participants were to report any discomfort, skin irritation if occurred during testing, in which case the testing should be terminated.

The primary outcome measures were as follows: 1. Severity of skin condition in the dimension of skin sensations, measured by a Likert scale from 0 - no feeling to 5 - acute or severe in four dimensions (sting sensation/tingling; burning/heat sensation; heat wave; skin irritation/discomfort/sensitivity) at baseline and 28 days; 2. Severity of skin condition in the dimension of visible skin changes, measured by a Likert scale from 0 - no symptoms to 5 - acute or severe in four dimensions (diffuse redness/flushing; extended vascular networking; rash; edema/swelling) at baseline and 28 days. The secondary outcome measures are visual appeal and overall participant quality of life changes associated with the symptoms of dermatitis assessed during the discussion and observations of a dermatologist at baseline and 28 days.

Data processing was performed using the statistical data processing program – SPSS (Statistical Package for the Social Sciences), performing descriptive and inferential data analysis. Within the descriptive statistics, the arithmetic mean, median, mode and standard deviation were analysed. Within the framework of the inferential statistics, a non-parametric method was used for the analysis of differences – the Wilcoxon Signed Ranks Test, which allows to conclude whether there are statistically significant differences before and after the use of the product, as well as the Kruskal-Wallis H test was performed to assess whether there are statistically significant changes in the measurement across various groups of skin type and phototype.

Product 1: The composition of gentle facial oil to milk cleanser has been created with oil phase grated than 90% to gently clean the face and remove all impurities (make-up, pollution particles), without negatively affecting skin natural pH system and skin defensive barrier. The product is formulated only with naturally derived ingredients. All the components of the product are carefully assessed and hypoallergenic potential evaluated. The oil phase of the product consists of caprylic/capric triglyceride, coco caprylate/caprate, Plukenetia Volubilis seed oil, Olea Europaea fruit oil, Vaccinium Macrocarpon seed oil and Helianthus Annuus seed oil. When in contact with water, the oil gel acts as O/W emulsion and the structure turns into milk, which allows impurities to be easily rinsed off.

The product is free from any irritating preservatives, perfumes (and fragrance allergens). The antimicrobial properties are ensured with the addition of Lactobacillus ferment - probiotic-based ingredient created by the fermentation of Lactobacillus. The concentration of surfactants in final composition is less than 1.5 % (wt%). The oil to milk cleanser was specifically developed for the everyday cleansing routine for the skin conditions associated with the AD. The active ingredient composition consists of betaine, ceramide NP, Laminaria Ochroleuca extract and Curcuma Longa root extract. The ceramide NP and betaine are selected in order to help skin retain moisture. Curcuma Longa root extract (the distilled fraction of turmeric oil extracted from the roots of curcuma longa by supercritical carbon dioxide) contains at least 65% of turmerones is selected for the anti-oxidant activity of the product in combination with tocopherol.

Product 2: The composition of O/W cream base prepared for dermatitis affected skin consists of ingredients from natural origin in accordance with Regulation (EC) No. 1223/2009 of the European Parliament and of the Council on cosmetic products. The allergenic potential of the substances included in the composition of the cosmetic product has been carefully assessed, in order to minimise potential allergic skin reactions. The oil phase consists of Butyrospermum parkii (Shea) butter, Butyrospermum Parkii (Shea) butter extract, canola oil, coco-caprylate/caprate and C15-19 akane. The cream does not contain any traditional (and typically irritating) preservatives (as of ones listed under Annex II of the Regulation (EC) No. 1223/2009 of the European Parliament and of the Council on cosmetic products) used in natural product development (like benzyl alcohol, benzoic acid and its sodium salts, glyceryl caprylate, caprylyl glycol, cinnamic acid and derivatives, salicylic acid and its salts). The mild antimicrobial system of the product is established and consists of combination from Lactobacillus ferment, sodium levulinate, sodium anisate and methylheptylglycerin in order to

maintain healthy skin microbiome. As previously reported the role of the skin microbiome in maintaining normal skin immune function, and addressing the detrimental consequences of microbial dysbiosis in driving inflammation, is a promising direction for development of new treatments [21]. The emulsion base is also free from perfume (which usually are loaded with allergens) that can be harmful to individuals with sensitive and atopic skin. The cream was specifically developed for the relief of symptoms associated with AD. The active ingredients composition of cream consisting of ceramide NP, magnesium carboxymethyl beta-glucan, hydrolyzed jojoba esters, Betaine and Avena sativa (Oat) kernel extract have been found to have protective and healing effects on skin (improve skin barrier, maintain a moist skin environment, reduce transepidermal water loss), the effectiveness of which has been tested by manufacturers of ingredients.

## Results

Demographic data of the participants show that 60.5% of the respondents present the skin phototype 1 and 30.2% of the participants show the skin phototype 2 that prove the diversification of the sample across the most often presented skin phototype in the region. Regarding the type of the skin then 27.9% of the participants report the normal skin type, 14% the oily skin type, 37.2% dry skin type and 20.9 % report the combined skin type that serves to the possibility to compare the use of the product across the various skin types. All the gathered data were checked using the reliability test with the Cronbach's Alpha to be acceptable from the 0.7 value. Table 1 reports comparison of the means of the overall results before and after application of the products across the whole sample. The difference is statistically significant with the p-value <0.05.

Table 1: Trend of skin condition changes in both dimensions of the primary measurement

	Baseline	28 days	Deviation
Severity of skin condition in the dimension of skin sensations			
sting sensation/tingling	1.5116	1.2791	-0.2325
burning/heat sensation	1.7674	1.2326	-0.5348
heat wave	1.5581	1.1628	-0.3953
skin irritation/discomfort/sensitivity	1.7209	1.4419	-0.2790
Severity of skin condition in the dimension of visible skin changes			
diffuse redness/flushing	1.8837	1.5349	-0.3488
extended vascular networking	1.8372	1.3256	-0.5116
rash	1.8140	1.4651	-0.3489
edema/swelling	1.4186	1.1628	-0.2558

Results show the overall decrease of the symptoms in both dimensions of the primary assessment measures. As soon as the sample was randomly divided into two groups then the authors assessed also the impact across the groups of

respectively use and no use of water during the intervention. Table 2 reports the results across the both groups.

Table 2: Cross-sectional trend of skin condition changes in both dimensions of the primary measurement

	Group 1 (ordinary water)			Group 2 (micellar water)		
	Baseline	28 days	Deviation	Baseline	28 days	Deviation
Severity of skin condition in the dimension of skin sensations						
sting sensation/tingling	1.6818	1.4545	-0.2273	1.3333	1.0952	-0.2381
burning/heat sensation	1.9091	1.3636	-0.5455	1.6190	1.0952	-0.5238
heat wave	1.7727	1.4545	-0.3182	1.3333	.8571	-0.4762
skin irritation/discomfort/sensitivity	1.6364	1.5000	-0.1364	1.8095	1.3810	-0.4286
Severity of skin condition in the dimension of visible skin changes						
diffuse redness/flushing	2.0455	1.7727	-0.2727	1.7143	1.2857	-0.4286
extended vascular networking	2.0455	1.5455	-0.5000	1.6190	1.0952	-0.5238
rash	1.8636	1.4545	-0.4091	1.7619	1.4762	-0.2857
edema/swelling	1.4545	1.2727	-0.1818	1.3810	1.0476	-0.3333

As the results present then the group not using ordinary water in the intervention areas reported larger positive change in all aspects except for the burning or heat sensation out of the dimension of skin sensation as well as rash on the skin. The analysis of the sample across the different skin types and phototype presented there is no statistically significant differences among the subjects of different skin types, however the results presented statistical significance in relation to the phototype of the subject in the following dimensions: sting sensation/tingling; skin irritation/discomfort/sensitivity; extended vascular networking that is mostly strongly noticed in the subjects with the first skin phototype.

## Discussion

The results of application have presented positive outcome in the effective reduction of the dermatitis symptoms in subjects. The results were reached thanks to the combination of the ingredients as well as 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. Some preservatives inhibit electron transfer and inhibit the activity of aerobic bacteria. Benzoic acid and parabens inhibit folic acid synthesis, while ethyl alcohol and phenols denature proteins. The study products were developed by using an alternative preservative system which significantly limit the irritation and causing possible allergic or otherwise adverse reactions on the skin. Cleansing cosmetics, due to their ability to cause skin irritations and disturb the hydrolipidic barrier, can increase

problems with atopic skin. New solutions to reduce the effects of these products on the skin are crucial. Basic requirements in managing eczema and sensitive skin include effective cleansers that do not compromise skin barrier integrity, alleviation of skin dryness, and restoration of skin barrier function through the use of therapeutic moisturizers. The selection of a skin cleanser is therefore an important part of managing these conditions [22]. Regarding the ingredients used, then carboxymethyl beta-glucan have shown various effects on atopic skin conditions both in vitro and in vivo. The effect of magnesium carboxymethyl beta-glucan was analyzed using 3 in vitro assays related to atopic dermatitis: Immunglobuline E (IgE) release by anti-CD40/IL-4 stimulated CD19+ B lymphocyte, Staphylococcus aureus adhesion onto (RHE) and reconstructed human epidermis (RHE) gene expression profile analysis in an atopic dermatitis chronic phase model. Magnesium carboxymethyl beta-glucan tested at 0.1 and 0.5 mg/mL, showed a strong and concentration dependent inhibitory effect on S. aureus adhesion onto reconstructed human epidermis (48 and 84 % of inhibition). Active substance tested at 0.5 mg/mL showed an inhibitory effect on IL8 expression (53 % decrease) and 0.8 mg/mL tested concentration showed an inhibitory effect on IgE release by anti-CD40 + IL-4-stimulated CD19+ cells (26 % inhibition) [23]. Study on 0.1% carboxymethyl beta-glucan containing cream on eczema (number of individuals 20, age 27-61) confirmed that after 28 days of treatment the skin showed a significant decrease of TEWL versus untreated. The hydration significantly increased by 31 % and smoothness by 16 % versus untreated and placebo [24]. The unique lipid profile of Avena sativa (Oat) kernel extract helps to replenish skin lipids lost through environmental factors and ageing. The lipid composition mimics that of the natural skin, containing a lipid barrier identical complex of ceramides, polyunsaturated fatty acids, sterols, tocopherols, tocotrienols, triacylglycerols and phospholipids which are known for their ability to maintain skin health and slow down skin ageing. The phospholipids mainly fuse with the outer layer of the stratum corneum, potentially acting as permeability enhancers for skin actives. They also been shown to enhance the skin barrier and display an anti-inflammatory effect by regulating the covalently bound hydroxy ceramides in the epidermis and decreasing the gene expression of both thymus activation-regulated chemokine and thymic stromal lymphopoietin. Fatty acid deficiency contributes to a disrupted skin barrier as it is a key component of lamella structure. In dry skin conditions, long chain fatty acids like palmitic (C16) and stearic acids (C18) are known to be deficient [25,26]. It has been previously reported that the use of a 1% colloidal oat eczema cream improves microbiome composition and significantly repairs skin barrier defects [27]. It has been previously reported, that the ceramides containing emulsions are able to improve the skin barrier function. The study resulted in a significant increase in skin hydration over time. skin hydration measured for ceramide cream was significantly greater ( $P<0.05$ ) than that measured for all three of the reference moisturizers tested. Ceramide cream was also found to significantly decrease TEWL ( $P<0.001$ ) over 24 hours, and was shown to be non-sensitizing to the skin of both adults and children and non-irritating to the skin, eyes and related eye area [28]. Hydrolysed jojoba esters is a jojoba-derived emollient with long lasting moisturizing and protective film forming properties. Studies were undertaken to evaluate the role of hydrolysed jojoba esters as unique technologies for development of long-acting barrier function activity. A combination of transepidermal water loss (TEWL) measurements,



impedance measurements for skin moisturization, expert grading of dry skin, dermatologist grading of the signs and symptoms of hand dermatitis, as well as clinical photography were used to investigate the effects of hydrolysed jojoba esters. It was confirmed that hydrolysed jojoba esters potentiate the effect of glycerine in increasing skin moisturization, may potentiate the effect of glycerine in reducing dry, flaky skin, can statistically reduce TEWL, erythema, and scaling over 7-14 days of use, may have an inhibitory effect on the expression of IL-6 and filaggrin in dermatitis skin [29]. Summing up, choosing an appropriate emollient for atopic dermatitis patients would improve acceptability and adherence for emollient treatment. Deeper appreciation of the active role that the skin barrier plays in the initiation and maintenance of skin inflammation. The epidermis forms a physical, chemical, immunological, neurosensory, and microbial barrier between the internal and external environment. Not only lesional, but also non-lesional areas of atopic dermatitis skin displays many morphological, biochemical and functional differences compared with healthy skin [2].

The study has several limitations: relatively small number of respondents, which is a constraint to generalise the conclusions. The withdrawal of study participants can be explained also by the limitations of COVID-19 pandemic situation. The outbreak of COVID-19 pandemic was a major limitation of the study that has to be highlighted, as it had a significant influence on all aspects of life of the study participants and society in general, the exact impacts and their extent remaining unknown. Another limitation of the study is related external factors that can be neither influenced nor specifically identified and recorded. One of such major factors is seasonal changes, which significantly affect the skin's response, as well as particular foods and drinks consumed, diets followed, medications taken, other products used by the participants, etc. similarly, other habits, such as preferred sleeping position, etc., living conditions and emotional environment of the participants and other factors potentially influencing manifestation or augmentation of symptoms. To obtain more profound results, the observations should be made over longer periods of time and registering the data on cumulative intrinsic and extrinsic environmental factors that constitute an impact pattern and would help to interpret the results better.

## **Conclusion**

Results show the overall decrease of all sensitive and visual symptoms in both dimensions of the primary assessment measures. The most significant symptom reduction of severity of skin condition in the dimension of skin sensations was noted in burning/heat sensation and in the dimension of visible skin changes in extended vascular networking reduction. The group not using ordinary water in the intervention areas reported greater positive change in all symptoms except for the burning or heat sensation out of the dimension of skin sensation as well as rash on the skin. The results may be associated with the physical impact of the water in terms of skin dryness. 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 atopic dermatitis. As it is evidenced also in study reports, use of products of natural origin shows clinical improvements in overall skin appearance in dermatitis symptoms, the observed performance of natural regimen versus synthetic products being superior in all severities of the disease.

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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