

Skin Anti-Aging Benefits of a 2% Resveratrol Emulsion

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Abstract

Background: Young and intact skin is highly responsive. As skin ages, its responsiveness decreases. Production of structural components of the skin slows down and signs of skin aging appear. External influences like UV radiation and pollution contribute to signs of skin aging. They lead to an increased formation of so-called free radicals. Bioactive antioxidant compounds, such as polyphenols, have beneficial effects on skin health by free radical scavenging. The purpose of this study was to evaluate the topical effects of new and highly concentrated resveratrol containing emulsion (Medskin Solutions Dr. Suwelack AG, 2% trans-resveratrol) on age-related alterations to the skin. **Methods:** A clinical observation study was performed on 20 subjects to observe the effects of a 2% resveratrol emulsion on typical signs of skin aging. Product was applied once daily for a period of 8 weeks in combination with a standardized treatment. Tested parameters were skin elasticity, skin barrier function, skin smoothness, skin thickness and density. **Results:** After 8 weeks of treatment, skin pH value is significantly lowered and skin barrier function improved. The value of skin elasticity (+5.3%), and skin density (+ 10.7%) had increased, while skin roughness (−6.4%) and skin dispensability (−45.9%) had diminished. Intensity of skin redness had decreased. Furthermore, expert and participant evaluations show satisfaction, especially with regard to skin smoothness and skin moisture. **Conclusion:** The resveratrol emulsion shows positive outcomes by supporting reduction of skin wrinkling and increasing skin firmness, as well as reducing skin redness, and is therefore an all-round anti-aging treatment.

Keywords

Resveratrol, Emulsion, Skin Care, Skin Aging

1. Introduction

Attractiveness and beauty play an important role in modern human society. Facial attractiveness is mainly characterized by youth and even and smooth skin texture and pigmentation [1] [2]. These parameters are strongly affected by aging. External influences like UV radiation and pollution contribute to signs of skin aging. They lead to an increased formation of so-called free radicals. These highly aggressive oxygen particles are poison for all living cells. Normally, the skin responds to these external influences with its own defense system, which includes multiple pathways via enzymes and vitamins to fight oxidative stress. But constant pollution can cause this protective system to fail.

This in turn results in the degradation of skin's structural components like collagen and elastic fibers. Skin naturally becomes less elastic and drier, lines and wrinkles may begin to appear, and makes skin look and feel older [3] [4]. Furthermore, the skin responds to oxidative stress by showing signs of irritation and inflammation. This is induced even more when the skin is dry and the skin barrier is compromised. Over time skin becomes more sensitive with increased skin redness. All these processes are mediated by reactive oxygen species (ROS). ROS are generated constantly in the skin, and are rapidly neutralized both by nonenzymatic and by antioxidant enzymatic activity. The combined functioning of these systems and substances maintains a good antioxidant balance.

Evidence shows that depletion of natural antioxidants is a major cause for skin aging that serves as a defense mechanism against free radical damage [5].

Antioxidants are divided into two classes: chemicals that are added to products to prevent oxidation, and naturally occurring compounds that are present in foods and intrinsically produced by human tissue itself.

In recent years increased attention is given to various polyphenols serving as antioxidants that occur naturally in plant foods, including fruits, vegetables, nuts, seeds, flowers and bark [6].

Resveratrol, a polyphenol, is found in many plant species such as grapes, peanuts and the Japanese knotweed. It has been described to have health-promoting effects, including antioxidant, anti-inflammatory and anti-tumor activities [7]. Resveratrol can be found in the cis or trans configuration, with the trans form being biologically active. In cosmetic products, resveratrol is used as an active ingredient having antioxidant and anti-inflammatory activity [8]. Resveratrol has been shown to be active in neutralizing and inhibiting the formation of ROS and is an effective neutralizer for synthetic radicals [9] under in vitro conditions. The antioxidant activity of resveratrol (95%) is higher than vitamin E (65%) and C (37%), respectively and has been shown to counteract lipid peroxidation and protein oxidation [10]. Several other signs of aging have been described to be improved by resveratrol, by increasing epidermal hydration, skin elasticity and skin thickness. Furthermore, it has been shown to reduce skin wrinkles and augmenting the content and quality of collagen and the level of vascularization [8] [11] [12] [13].

As resveratrol itself is very difficult to incorporate in soluble form (soluble in water only by 30 mg/L), most water-based creams available for cosmetic care contain low concentrations of solubilized resveratrol. As far as we are aware of currently no water-based cream with a concentration as high as 2% of solubilized, bioavailable trans-resveratrol is available on the market.

The aim of this prospective observational study was to evaluate the efficacy and tolerability of emulsion containing 2% resveratrol during an 8-week topical application to the face and to determine whether this topical treatment with resveratrol can reduce anti-aging effects by improving skin barrier, elasticity, and skin roughness.

2. Material and Methods

Participants for this study were recruited as volunteers from the University of Hamburg and asked to participate, and were informed about the study and signed a consent form. 20 subjects with healthy skin but visible signs of skin aging who met the inclusion and exclusion criteria were enrolled in this prospective study. Main inclusion criteria were visible sign of skin aging, age between 35 - 30 years old and women who were pre-menopausal. Exclusion criteria were: injections of hyaluronic acid or botulinum toxin A in the last 6 months, treatments with other absorbable filling materials in the last 12 months, known hypersensitivity to the contained ingredients, cosmetic treatments (chemical peelings, microdermabrasion, etc.) in the period of 4 weeks before the study, use of skin care products with the active ingredients: Vitamin A (retinol), Vitamin C (ascorbic acid), resveratrol or other polyphenols.

The total duration of the study was 9 weeks and a total of 5 appointments (V1 project inclusion and start of the wash-out phase, V2 baseline, V3 after 1 week, V4 after 4 weeks and V5 after 8 weeks to the study site (Department of Cosmetic Sciences, University of Hamburg) were scheduled for objective and subjective skin assessments. Subjects were instructed not to wash their face at least 6 hours before the first appointment and should not apply any skin care product at least 12 hours prior to the study visit. In addition, no make-up, powder or rouge was allowed to be used. At V1 subjects were informed about the study and instructions were given. After a wash-out phase of one week, where standardized skin care products were used, a dermatological assessment of the skin was performed as baseline measurement (V2). After this, the test product 2% resveratrol emulsion (Resveratrol Concentrate, reveal by Medskin Solutions Dr. Suwelack AG, genova GmbH.) was used once per day for 8 weeks. After 1 week (V3), after 4 weeks (V4) and after 8 weeks (V5) a dermatological assessment was done. Following an acclimatization period of 30 minutes, all measurements were done under standardized room conditions (20°C and 50% relative humidity) of 12 hours after the last application of the test product.

2.1. Measurements and Assessments

The following measurements and skin assessments were performed: The pH-value

of the skin was measured with a pH-Meter (Courage and Khazaka Electronic GmbH, Cologne, Germany); skin barrier function was evaluated by measurement of the transepidermal water loss (TEWL) on the face using the Tewameter (Courage + Khazaka Electronic GmbH, Cologne, Germany) and expressed as $\text{g/h}\cdot\text{m}^2$. Skin roughness was assessed using PRIMOS (GF Messtechnik GmbH, Berlin, Germany) and expressed as Rz. The Cutometer MPA 589 (Courage and Khazaka Electronic GmbH, Cologne, Germany), equipped with a 2 mm measuring probe, was used to measure skin elasticity. Measurements were repeated three times. The mechanical properties were expressed as skin dispensability ($U_f = [R_0]$) and skin elasticity ($U_a/U_f = [R_2]$). Photo documentation and skin redness measurements were taken before (V2) and after the application period of 8 weeks with the resveratrol emulsion (V5) with the VISIA-System (Canfield Scientific Inc., Parsippany, New Jersey, USA). A 20 MHz ultrasound device DUB-system (Taberna pro medicum, Luneburg, Germany) was used to obtain measurements of skin density through digitalized two-dimensional pictures in which the difference in reflections in pixel brightness represent skin density.

2.2. Skin Expert Analysis and Subject Questionnaire

Skin condition was assessed by a dermatologist using a 5-point scoring scale (1—very good, 2—good, 3—satisfactory, 4—sufficient, 5—inadequate).

Subjects were asked to rate their skin and product use with a standardized questionnaire using a 5-point scoring scale (1—very good, 2—good, 3—satisfactory, 4—sufficient, 5—inadequate).

2.3. Data Analysis

As a summary and overview of quantitative aspects, descriptive statistics were evaluated, which included the standard deviation and mean values. For this study, a subsequent statistical evaluation with the program IBM® SPSS® Statistics 20 for Windows was carried out for the overall result. The statistical evaluation of the biophysical data was carried out by means of a non-parametric T-test with connected samples in order to compare mean values and to prove possible significances. A conventional significance level determination of $(*)p < 0.05$ was used as a basis for the overall evaluation.

3. Results

Of the 20 female subjects enrolled in this study, 18 subjects (average age: 44.6 years \pm 4.31) completed the study according to protocol and used the resveratrol emulsion for 8 weeks. Two subjects were excluded from the final analysis because of an incomplete dataset. No side effects were reported with the use of the resveratrol emulsion, except for one subject reporting pimples at the 4 week visit.

3.1. pH and TEWL

After a 8-week application of the test product the mean TEWL units indicate a

reduction of the TEWL of 8.3%, from V2 (11.73 ± 4.00 g/h/m²) to V5 (10.76 ± 3.28 g/h/m²) (**Figure 1(a)**).

A significant reduction of the pH value was observed (V2: 5.60 ± 0.44 to V5: 5.13 ± 0.32 , $p = 0.001$), which represents a reduction by 8.3% (**Figure 1(b)**).

3.2. PRIMOS

Skin roughness (Rz) diminished significantly between baseline and final examination (V2: 109.77 ± 28.66 vs. V5: 102.79 ± 25.76 , $p = 0.048$) by -6.4% (**Figure 2**).

3.3. Cutometry

The dispensability of the skin was significantly reduced after 8 weeks of application of the test product compared to baseline (V2: 0.26 ± 0.07 vs. V5: 0.14 ± 0.02 , $p = 0.001$). Additionally, skin elasticity improved during the 8 weeks by 5.3% compared to baseline (V2: 0.64 ± 0.01 vs. V5: 0.67 ± 0.07) (**Figure 3**).

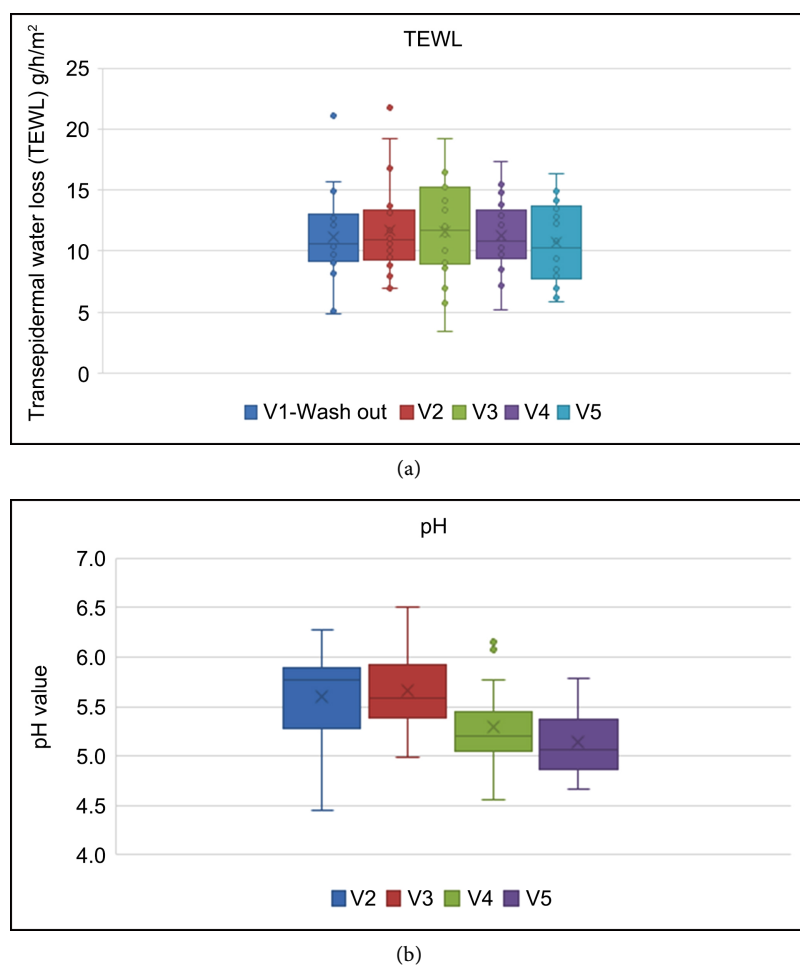


Figure 1. (a): TEWL measurements expressed as g/h/m² at V1 Wash-out Phase, V2 Baseline, V3 after 1 week, V4 after 4 weeks and V5 after 8 weeks; (b): pH-meter measurements of the skin at the cheek at V2 Baseline, V3 after 1 week, V4 after 4 weeks and V5 after 8 weeks of resveratrol emulsion treatment, (V2 vs. V5: $p = 0.001$). The red diamond represents the mean value.

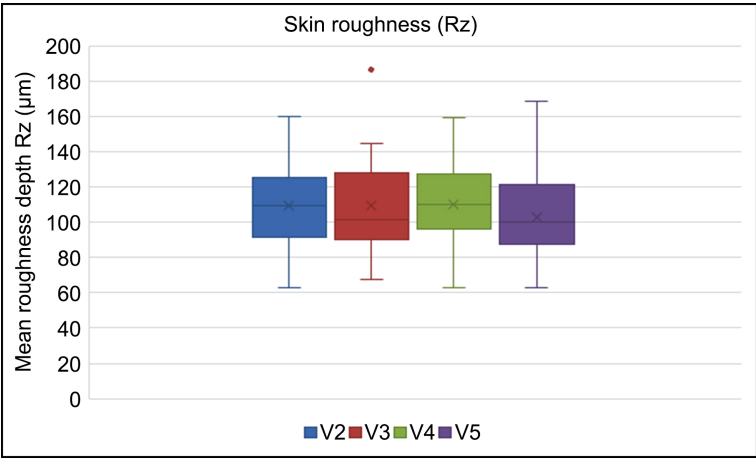
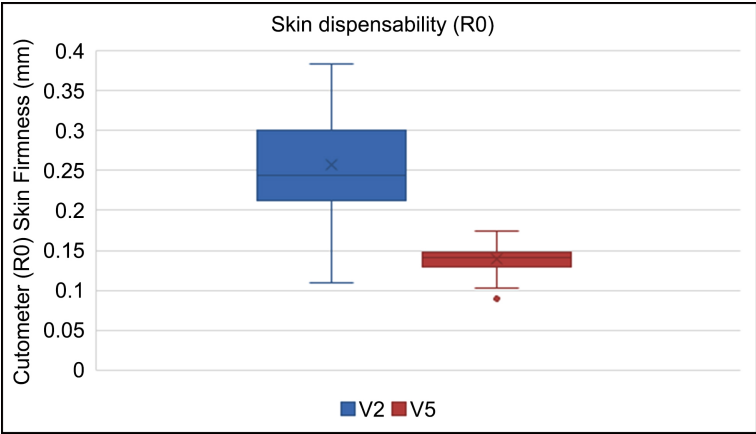
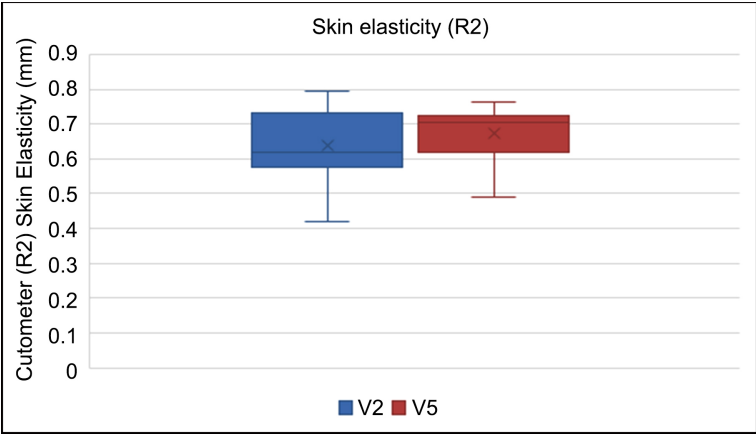


Figure 2. PRIMOS measurement (Rz, in μm) of the skin before at V2 Baseline, V3 after 1 week, V4 after 4 weeks and V5 after 8 weeks of resveratrol emulsion treatment to determine skin roughness (Rz). The red diamond represents the mean value. (V2 vs. V5, $p = 0.048$).



(a)



(b)

Figure 3. Cutometer measurements to determine the parameter (a) skin dispensability (R0) before at V2 Baseline and V5 after 8 weeks (V2 vs. V5, $p < 0.001$) and (b) skin elasticity (R2) before at V2 Baseline and V5 after 8 weeks (of resveratrol emulsion treatment. $p = 0.017$). The red diamond represents the mean value.

3.4. Ultrasound

Measurement of dermal density using skin ultrasound was performed. One ultrasound image was taken at baseline (V2) and the other was taken 8 weeks after (V5). **Figure 4** is an example of one subject before (a) and after 8 weeks (b) of resveratrol emulsion treatment. The quantitative evaluation of the skin density is increased from baseline V2 at the final examination V5 (after 8 weeks) (V2: 17.67 vs. V5: 19.56, $p = 0.064$).

3.5. Expert Skin Analysis

The expert skin analysis showed a highly significant increase in skin glow between baseline and final examination (V2 vs. V5, $p = 0.002$). The skin analysis documented a highly significant increase in skin hydration between baseline and final examination (V2 vs. V5, $p = 0.001$). The parameter “smoothness of the skin” increased significantly between baseline and final examination (V2 vs. V5, $p < 0.001$) (**Figure 5**).

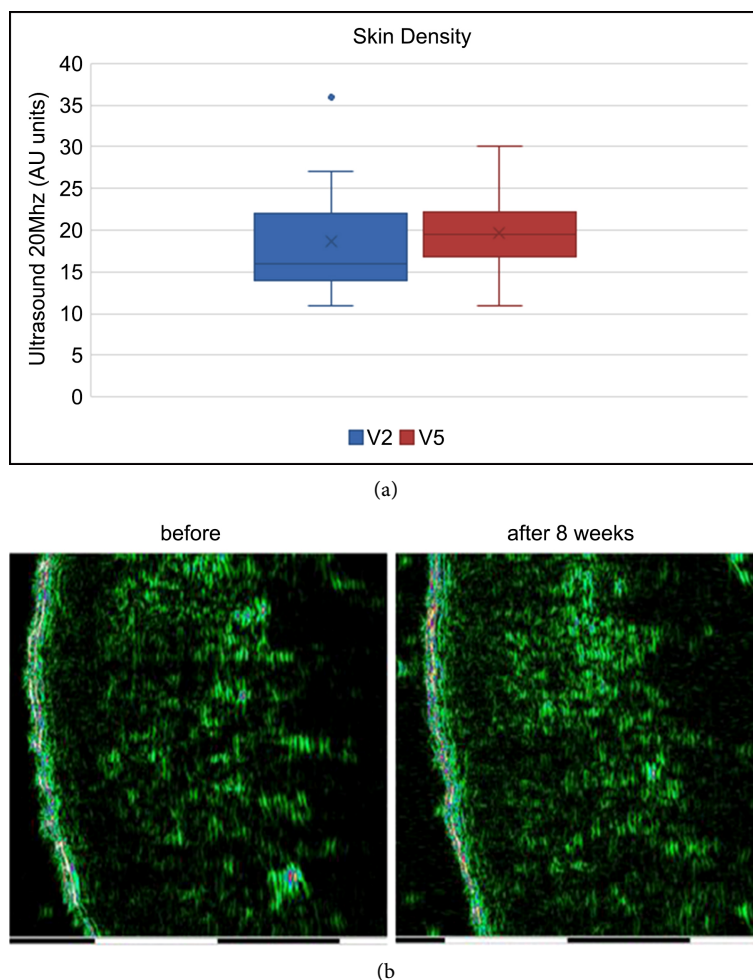


Figure 4. Quantitative results of skin density measurements (ultrasound 20 MHZ), (V2 vs. V5, $p = 0.064$) (a); Representative sonographic measurement at baseline V2 and after 8 weeks V5 (b). Bright pixels represent strong reflections indicative of skin density.

3.6. VISIA

Analysis of skin redness via VISIA demonstrates an individual reduction of skin redness; however results for all subjects could not be processed due to technical reasons. **Figure 6** is an example of an examination before (left) and after 8 weeks (right) demonstrating the reduction of skin redness especially in the area of the nose and cheek.

4. Discussion

The increasing demand of a youthful appearance and reducing signs of aging is reflected an increasing demand in anti-aging therapies.

In this study a 2% resveratrol emulsion was assess in a prospective study to analyze the anti-aging efficacy. Overall results showed a marked improvement in all skin parameters over a period of 8 weeks.

Skin barrier functions, such as skin barrier regeneration and antimicrobial response, are related to the acidic nature of the skin surface pH [13]. When the natural skin barrier protective function of the skin is impaired, the risk of bacterial infections and skin irritations increases [14].

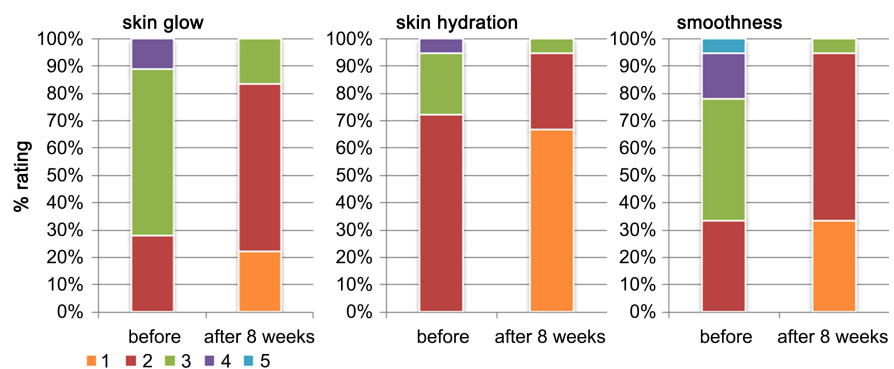


Figure 5. Expert skin analysis of skin glow, skin hydration and skin smoothness in percentage of scores. (1 = very good, 5 = inadequate) before (V2, baseline) and after 8 weeks (V5) of resveratrol emulsion treatment.

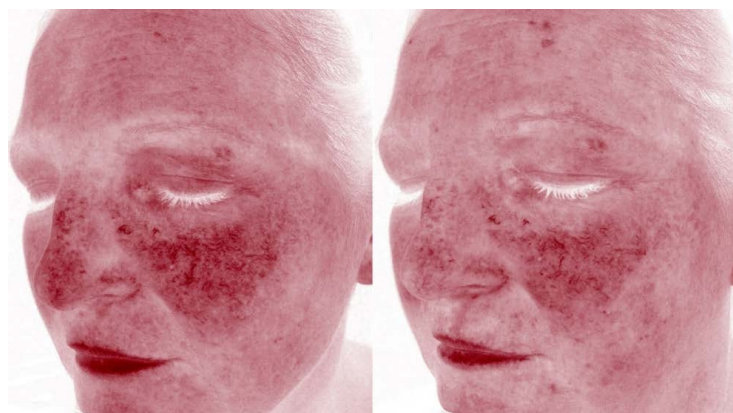


Figure 6. Exemplary Visia Scan before (V2, baseline) and after 8 weeks (V5) of resveratrol emulsion treatment to determine skin redness.

The resveratrol emulsion used in this study leads to a highly significant skin surface pH-value reduction ($p = 0.001$) and a stable barrier function parameter that is in the physiological range. Furthermore, the expert skin analysis demonstrated a highly significant increase in skin moisture during the 8-week application ($p = 0.001$).

In addition to the stabilization of the epidermal barrier, a highly significant increase in skin firmness ($p = 0.001$) was observed after 8 weeks demonstrated by a 45.9% decrease in skin dispensability compared to the baseline. The significant increase in firmness and elasticity was confirmed in the expert skin analysis as well as by the participant questionnaire. Luebberding *et al.* [15] analyzed the mechanical properties of human skin during aging via Cutometer and demonstrated that all assessed parameters progressively decrease with increasing age. Skin elasticity parameters decreased by 9%/decade with age, while the skin dispensability parameter decreased by 22.9%/decade, showing a more or less linear decrease in skin elasticity with age. The 5.3% improvement in skin elasticity and 45.9% improvement in skin dispensability observed in this study is a major improvement compared to the decrease in these parameters due to age as determined by Luebberding *et al.* The results in this study indicate that signs of skin aging with respect to skin elasticity and firmness can be reduced and represent a 5 and 20 years younger age, respectively.

Furthermore, it was demonstrated, that the effectiveness of the test product after 8 weeks of application improved skin roughness. Subjective impressions were supported by objective measurement. For example, a significant reduction of the mean roughness depth (R_z $p = 0.048$) was documented between baseline and final examination, which underlines the results of the expert skin analysis and the participant questionnaire. According to the expert skin analysis, the suppleness/softness of the skin increased significantly between baseline and final examination ($p = 0.001$) and the skin smoothness also increased significantly (reduction of static wrinkles V2 vs. V5, $p = 0.014$).

Collagen provides the structural framework of the dermal layer, which plays essential roles in maintaining good skin health [12] [16] [17] [18] [19] [20]. Sun-exposed aged skin is characterized by the solar elastosis (thickening, wrinkling). The sparse distribution and decrease of the collagen content in the photoaged skin may be due to increased collagen degradation by various matrix metalloproteinases, serine and other proteases [21] [22] [23] [24] [25]. In aged skin, collagen looks irregular and disorganized [26]. The total collagen content of the skin surface decreases by about 1%/year [27].

In this study sonographic examinations, showed a tendency for an improvement in skin density of good quality collagen fibers. This could indicate that the resveratrol emulsion may be able to induce collagen synthesis in vivo.

Although the molecular mechanism of this resveratrol emulsion is not clearly established, several studies have generally shown that resveratrol has antioxidative properties and exerts its effect through these properties. The mechanism of

protective activity is related to the ability to counteract the formation of free radicals and reactive oxygen species, prevent lipid oxidation processes and protect antioxidant cellular enzymes [28] [29]. In addition, resveratrol reduces the expression of AP-1 and NF- κ B transcription factors, limiting the degradation process of collagen and elastin, and inflammation of the skin. In an in vitro study by Gopaul *et al.* [29], it was demonstrated that resveratrol is able to stimulate collagen type I and III gene expression.

The anti-aging effect of resveratrol demonstrated in this study was also observed in other clinical studies and the current study results are in line with the following described effects. In a 12-week clinical trial with 55 women between 40 - 60 years, it was demonstrated that the use of a night cream containing 1% resveratrol, 1% vitamin E and 0.5% baicalin could improve the appearance of aged skin by improving skin firmness and elasticity and smoothing fine wrinkles [30]. The effect of the preparation containing resveratrol, baicalin and vitamin E is primarily related to the rich antioxidant activity of the ingredients as well as their effect on gene expression such as vascular endothelial growth factor (VEGF) A and collagen III alpha 1. After 12 weeks, it was observed that the decrease of VEGF expression directly affected the reduction of vascular permeability and therefore the decrease in skin's redness and the reduction of inflammation. In addition, an increase in collagen type III production was observed. Goncalves *et al.* evaluated the effects of topical trans-resveratrol on the recovery and rejuvenation of rat skin after chemical peeling demonstrating that epidermal and dermal thickness was increased through the impact on greater collagen production, which may lead to increased skin elasticity and wrinkle reduction [31]. The anti-redness effect of a topical product containing resveratrol was demonstrated by Ferzli *et al.* [32] in 16 subjects, whereby in most cases facial redness was reduced after 6 weeks of daily use.

Altogether, resveratrol can be used in anti-aging cosmetics to protect the skin from (photo) aging (19, 31 - 34).

Developing formulations with resveratrol can be challenging however. Different studies have been focused on the development of new formulations for resveratrol delivery, in order to overcome its poor solubility, chemical instability and low bioavailability [33] [34] [35] [36] [37]. It has been demonstrated that the biological activity of resveratrol only depends on its concentration in soluble trans form [38] [39]. Most creams available for cosmetic care only contain low concentrations of solubilized, bioavailable resveratrol. A recent work by Alonso *et al.* has assessed in both in vitro and in vivo the permeation of topical application of resveratrol, showing that the topically applied resveratrol penetrates into the skin in a gradient fashion and that resveratrol after its penetration was able to maintain its antioxidant efficiency [40]. Nevertheless, it was demonstrated that resveratrol must be used at relatively high concentration for topical in vivo application in order for it to be effective [41].

In this context, we aimed to develop a resveratrol emulsion with a high con-

centration of bioavailable stable trans-resveratrol. As far as we are aware of currently no cream with a concentration as high as 2% of solubilized, bioavailable resveratrol is available on the market. We were able to demonstrate that the tested resveratrol emulsion has anti-aging effects on human skin especially in terms of increased skin elasticity and skin firmness.

5. Conclusion

We investigated an emulsion with a high concentration of 2% bioavailable, solubilized resveratrol. In this clinical and biophysical investigation, we have shown that the test product is well tolerated and has a strong skin rejuvenating effect in vivo. Further research is needed to reveal the underlying molecular mechanism of the findings in this study.

Conflicts of Interest

A. S., C. J. are employees of MedSkin Solutions Dr. Suwelack AG. The study was funded by Medskin Solutions Dr. Suwelack AG, Germany. The authors declare no conflicts of interest regarding the publication of this paper.

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