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## Overnight Skin Regeneration: Melatonin-Like Effects of Rose Hip Extract

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K. Kappler\*, F. Wandrey, F. Zilli

Melatonin is a key regulator of circadian rhythm and sleep, with additional direct effects on skin health. It is produced not only in the brain but also in skin cells, where it acts as a potent antioxidant and supports skin regeneration. Age and environmental factors can disrupt melatonin synthesis and signaling, contributing to skin aging. A bioactive rose hip extract from organic roses (*Rosa rugosa*) was shown to mimic melatonin-like effects in keratinocytes by upregulating melatonin receptor expression and changing the expression of circadian clock genes in keratinocytes in a melatonin-like manner. It enhances antioxidant defense, strengthens the skin barrier, and improves mitochondrial function. Clinical studies demonstrated that the extract improves skin radiance and hydration, while reducing redness, dark eye circles, and wrinkles, especially in sleep-deprived individuals, resulting in visibly regenerated and rejuvenated skin.

## Introduction

Sleep is essential for life and optimal health, yet many people today experience reduced sleep duration. Sleep deficiency can impair cognitive performance, cause mood swings, and increase the risk of chronic diseases [1]. It also affects the skin, making it dry, pale, and rough, with dark circles and more wrinkles. While the link between sleep deprivation and inflammatory skin conditions is well known, how exactly does sleep influence skin health?

The circadian rhythm is our internal 24-hour clock, regulated by sunlight and the molecules cortisol and melatonin. Melatonin is crucial for sleep quality and supports skin regeneration during the night. Interestingly, melatonin is produced not only in the brain but also in the skin [2], where it acts as a powerful antioxidant. It protects skin cells from UV damage, reduces oxidative stress and inflammation, supports mitochondrial function, and helps maintain the skin barrier [2].

Therefore, our skin benefits both indirectly and directly from melatonin.

Melatonin works by neutralizing free radicals and by binding to receptors like melatonin receptor 1A in the skin and influencing genes involved in circadian rhythm, antioxidant defense, and inflammation. However, melatonin production declines with age and can be disrupted by factors like shift work or blue light exposure. A disturbed systemic melatonin production does not only lead to disturbed circadian rhythm and sleep problems but can also contribute to age-related diseases and, specifically, skin aging. In addition, melatonin receptor expression is reduced in aged skin [3]. Therefore, the negative effects of insufficient melatonin on the skin may have two causes: a disturbed day-night cycle and a lack of sleep with the skin's inability to regenerate during the night and the loss of the direct functions of melatonin in the skin.

This study investigates a rose hip extract for its potential to counteract the effects of melatonin deficiency on the skin. The extract is derived from a specific variety of organic *Rosa rugosa* hybrids grown in Finland, which adapted to the region's cold climate and unique day-night cycles. The edible fruits, called hips, of *Rosa rugosa* are known for their antioxidant, anti-inflammatory, and antimicrobial properties and therapeutic potential [4].

## Materials & methods

### Materials

The water-based rose hip extract was produced by extracting 5% dried rose (*Rosa rugosa*) hips. For the rose hip active used in the clinical studies, the resulting plant extract was spray granulated on maltodextrin (product name: LunaRose™, INCI: Rosa Rugosa Fruit Extract (and) Maltodextrin (and) Aqua/Water).

## Gene expression analysis

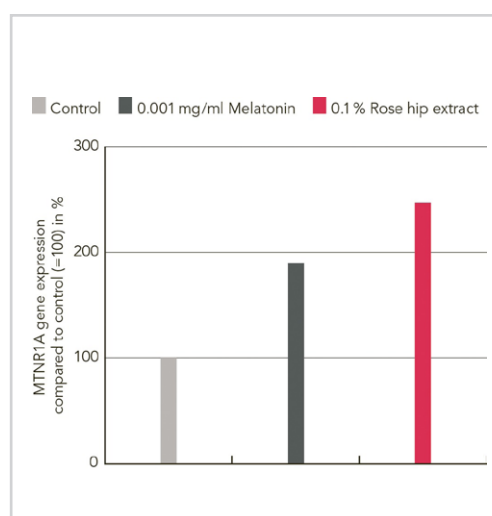
To assess melatonin-like effects, normal human epidermal keratinocytes (NHEK) were treated with 0.1% rose hip extract or 0.001 mg/ml melatonin for 8, 16, or 24 hours in triplicates and gene expression of melatonin receptor (MTNR1A) and genes involved in the circadian clock was assessed. To evaluate effects on skin physiology-relevant genes, NHEK were treated with 0.2% rose hip extract for 24 hours in triplicates. For all treatments, replicates were pooled, RNA was extracted (TriPure™, Merck, Germany), reverse transcribed, and analyzed by qRT-PCR (LightCycler®, Roche Molecular System Inc., Switzerland) in duplicates. Gene expression was normalized to housekeeping genes and compared to untreated controls.

## Analysis of mitochondrial respiration

NHEK were seeded in 96-well plates and cultured for 48 hours before incubation with assay medium containing 0.2% rose hip extract for 24 hours (n=3). Mitochondrial respiration was assessed using the Seahorse XF assay (Agilent Technologies, CA, USA), measuring real-time oxygen consumption rate (OCR). Assay validation was based on the OCR profile of untreated cells.

## Clinical study on sleep-deprived subjects

To investigate the effects of rose hip active on the skin, a placebo-controlled clinical study was conducted in South Korea with 43 sleep-deprived female volunteers aged 20–48 years (mean age: 39.5 years) showing facial redness and sleeping only 5–7 hours per night. Participants were split into two groups and applied either a cream with 2% rose hip active or a corresponding placebo cream twice daily for 28 days. Parameters were measured at baseline and after 28 days. Dark circles were assessed via melanin index (Mexameter® MX 18, Courage+Khazaka, Germany), skin hydration and TEWL via Corneometer® CM 825 and Tewameter® TM300 (Courage+Khazaka, Germany), and radiance via Skin Glossmeter® (Delfin, Finland). Skin texture was evaluated using PRIMOS® CR (GF Messtechnik GmbH, Germany), redness via hemoglobin-mode images and ANTERA 3D® CS (Miravex Limited, Ireland), and facial images were captured with VISIA® CR (Canfield, USA).



**Fig. 1** Bar graph representing the gene expression of MTNR1A (melatonin receptor 1A) in keratinocytes treated with either 0.001 mg/ml melatonin or 0.1% rose hip extract for 16 hours or in untreated cells as a control.

## Clinical study on nasolabial fold reduction

A placebo-controlled study with 42 female Caucasian volunteers aged 50–70 years (mean age: 64.5 years) assessed the effect of rose hip active on the nasolabial fold. Participants applied either 2% rose hip active or a placebo cream twice daily for 28 days. Wrinkle depth was measured at day 0 and day 28 using AEVA®3D-HE2 (Eotech, USA).

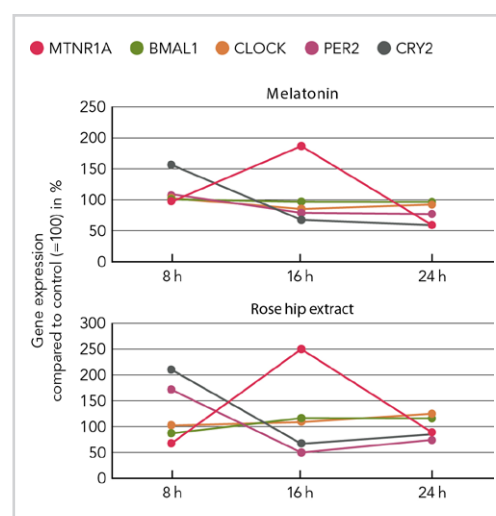
## Clinical study on the décolleté

In a placebo-controlled study, 38 female Caucasian volunteers aged 45–55 years (mean age: 50 years) applied either 2% rose hip active formulated in a cream or corresponding placebo cream once daily in the evening to the décolleté. Wrinkle depth (ANTERA 3D®, Miravex Limited, Ireland) and skin surface volume (Visioscan® VC 20plus, Courage + Khazaka, Germany) were measured in the mornings on day 0, after one night, and after 7 nights. Skin surface volume reflects the virtual volume needed to flatten the skin. Its reduction therefore indicates skin filling.

## Results

### Melatonin-like effect of rose hip extract

To assess the melatonin-like effect of rose hip extract, human epidermal keratinocytes were treated with either rose hip extract or melatonin and gene expression was analyzed. Both treatments resulted in an upregulation of MTNR1A, the gene encoding melatonin receptor 1A, after 16 hours of treatment (Fig. 1). In addition, several genes involved in the circadian clock, including BMAL1, CLOCK, PER2, and CRY2 showed a similar time-dependent expression profile after the treatment with either melatonin or the rose hip extract (Fig. 2).



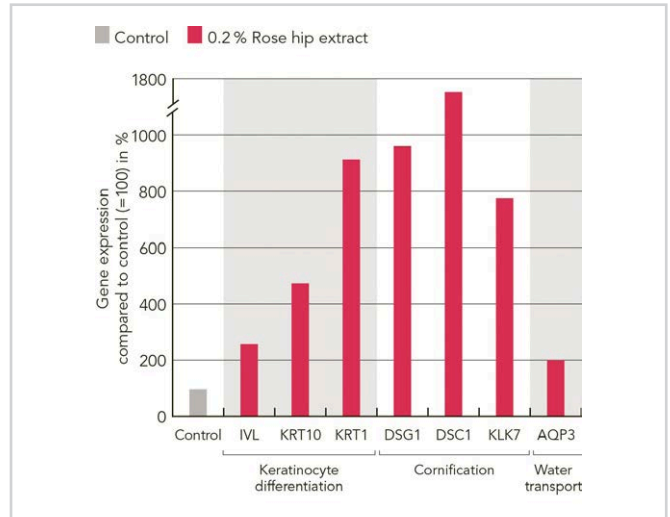
**Fig. 2** Graphs representing the expression of genes involved in the circadian clock (MTNR1A, BMAL1, CLOCK, PER2, CRY2) in keratinocytes treated with either 0.001 mg/ml melatonin or 0.1% rose hip extract for 8, 16 or 24 hours.

In another study on the effect of rose hip extract on gene expression, the treatment of keratinocytes with rose hip extract increased the expression of IVL, KRT10, and KRT1, all markers of keratinocyte differentiation. In addition, genes that are important for corneodesmosome formation, including DSG1 and DSC1, as well as KLK7, involved in desquamation and the water transporter AQP3, were upregulated by the treatment (Fig. 3). The results indicated an improved skin barrier function. Moreover, the treatment increased the expression of genes involved in detoxification and the antioxidant response, including GSTA4 (+119%), HMOX1 (+119%), HSPA1A (+258%) and SOD1 (+84%), and it resulted in a strong downregulation (−80%) of the collagen-degrading enzyme MMP1.

In the same gene expression study, many genes involved in mitochondrial function and in the degradation of defective mitochondria, a process called mitophagy, namely NMNAT3 (+101%), UCP3 (+132%), ULK1 (+113%), BNIP3L (+139%), ATP5L (+243%), and SIRT4 (+161%), were upregulated by the treatment with rose hip extract. Additional genes involved in mitochondrial function, such as MNF2, RHOT2, MIEF2, ALDH2, FDRX, UCP2, MPZL3 and SIRT3, showed a slight up-regulation (+50-100%). As this data suggested a beneficial effect of rose hip extract on mitochondrial function, its effect on mitochondrial respiration was measured using a seahorse assay. Treatment of cells with 0.2% rose hip extract for 24 hours increased mitochondrial basal respiration, maximal respiration, and ATP synthesis, indicating an improved functionality of mitochondria.

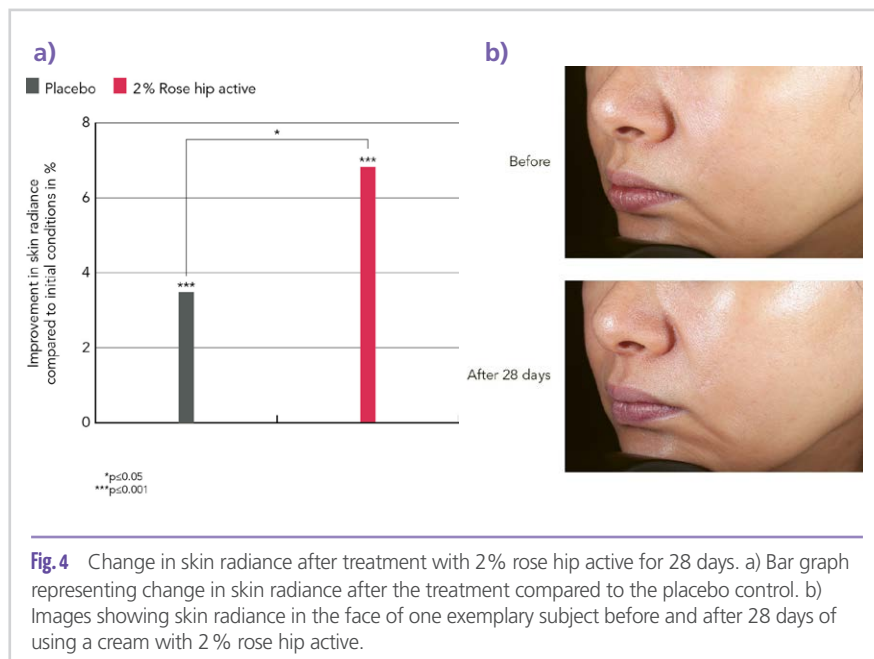
**Benefits for sleep-deprived skin**

To evaluate the effects of rose hip active on sleep-deprived skin, a placebo-controlled clinical study was conducted with

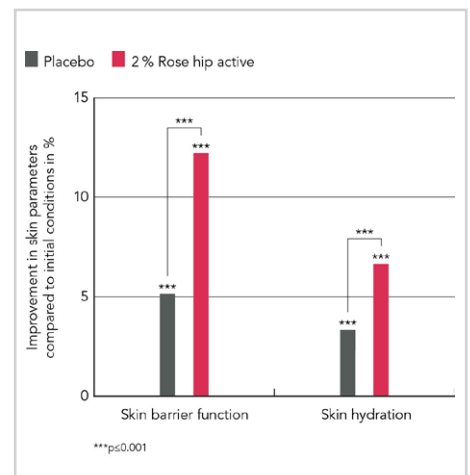


**Fig. 3** Bar graph representing the expression of different genes involved in the skin barrier function in keratinocytes treated with 0.2% rose hip extract for 24 hours or in untreated cells as a control.

43 sleep-deprived Asian women (aged 20-48 years) showing facial redness. Parameters commonly affected by a lack of sleep – radiance, dark circles, TEWL, hydration, redness, and roughness – were assessed at baseline and after 28 days of treatment with 2% rose hip active or placebo. Treatment with rose hip active significantly improved skin appearance. Radiance increased by 6.7%, which was confirmed by visual documentation (Fig. 4). Dark circles were reduced, indicated by a significant decrease in the melanin index versus baseline and placebo. TEWL dropped by 12.4%, reflecting enhanced skin barrier function, while hydration rose by 6.6% (Fig. 5). Skin texture improved, with roughness parameters Rmax and Rp reduced by 6.3% and 4.4%, respectively. Additionally, facial redness visibly decreased, as shown in hemoglobin-mode images and confirmed by quantitative analysis (data not shown).



**Fig. 4** Change in skin radiance after treatment with 2% rose hip active for 28 days. a) Bar graph representing change in skin radiance after the treatment compared to the placebo control. b) Images showing skin radiance in the face of one exemplary subject before and after 28 days of using a cream with 2% rose hip active.



**Fig. 5** Bar graph representing the changes in skin barrier function assessed by TEWL measurement and skin hydration assessed with corneometry after treatment with 2% rose hip active for 28 days compared to placebo treatment.

## Reduction of wrinkles in the face and on the décolleté

Facial wrinkles can be the result of sleep deprivation, but some types of wrinkles can also be aggravated by restful sleep depending on one's sleeping position. To evaluate the effect of rose hip active on facial wrinkles, specifically the nasolabial fold, a second placebo-controlled clinical study was conducted in a panel of 42 female Caucasian volunteers aged 50 to 70 years. After 28 days of treatment with 2% rose hip active, a significant reduction in the nasolabial fold was observed. Maximum wrinkle depth decreased by 9.1%, and average depth by 5.3% compared to baseline (Fig. 6a). No significant changes were seen in the placebo group. These improvements were also visible in topographic images (Fig. 6b).

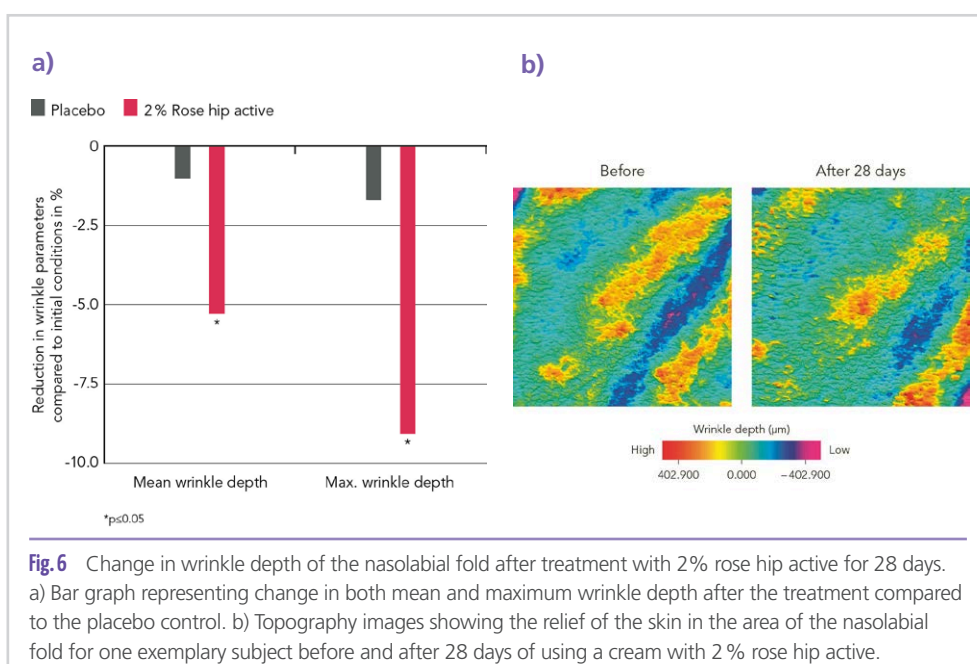
Wrinkles on the chest are a common type of sleep wrinkles, often caused or worsened by side sleeping. To assess the efficacy of rose hip active on décolleté wrinkles, a third placebo-controlled study was conducted with 38 female volunteers who applied either a cream with 2% rose hip active or a placebo once daily in the evening. Measurements were taken the following mornings. After just 7 nights, wrinkle depth in the décolleté was reduced by 8.6%, with 90% of participants showing improvement. A single application of the active cream also significantly reduced skin surface volume by 5.6%, enhancing the skin's filling effect overnight – an effect not observed with the placebo (Fig. 7a). The smoothing effect was seen in 100% of volunteers using the active cream and was clearly visible in before-and-after images (Fig. 7b).

## Discussion

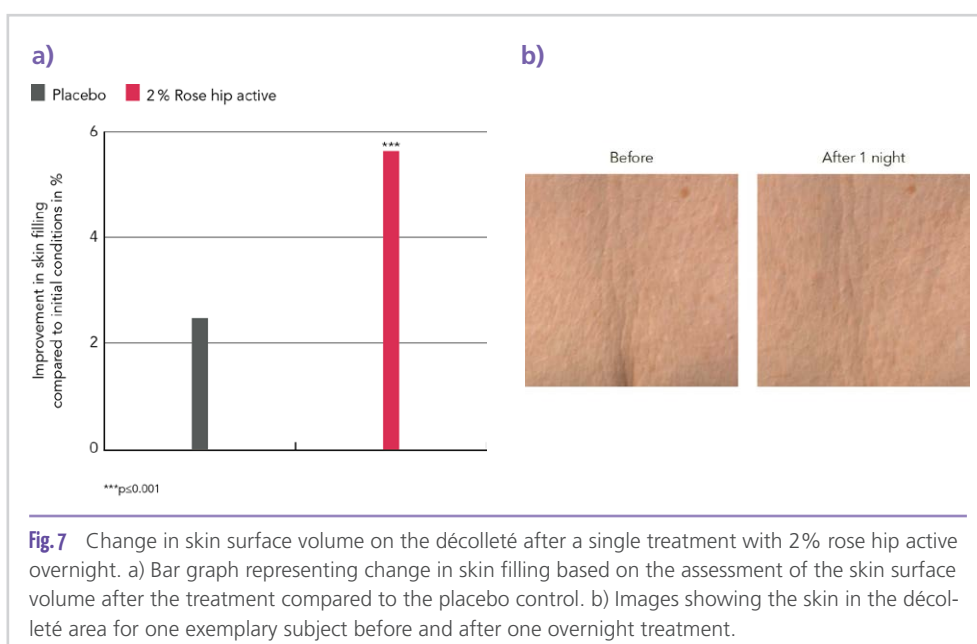
This study demonstrated a melatonin-like effect of rose hip extract, as it increased melatonin receptor expression and regulated key circadian clock genes in a manner similar to

melatonin. Additionally, gene expression analysis revealed that the extract supports the skin barrier and protects against oxidative stress. *In vitro* data also indicated a positive impact on mitochondrial function, which is vital for cellular metabolism. These effects are consistent with known actions of melatonin, which protects mitochondria not only through its antioxidant properties but also by regulating genes involved in mitochondrial dynamics, function, and degradation [5]. These findings further support the melatonin-like activity of rose hip extract, potentially driven by enhanced melatonin receptor expression, amplifying the effects of endogenous melatonin.

Based on these *in vitro* results, a clinical study was conducted in sleep-deprived subjects. Treatment with rose hip active led to visibly rested skin, with increased radiance, improved texture,



**Fig. 6** Change in wrinkle depth of the nasolabial fold after treatment with 2% rose hip active for 28 days. a) Bar graph representing change in both mean and maximum wrinkle depth after the treatment compared to the placebo control. b) Topography images showing the relief of the skin in the area of the nasolabial fold for one exemplary subject before and after 28 days of using a cream with 2% rose hip active.



**Fig. 7** Change in skin surface volume on the décolleté after a single treatment with 2% rose hip active overnight. a) Bar graph representing change in skin filling based on the assessment of the skin surface volume after the treatment compared to the placebo control. b) Images showing the skin in the décolleté area for one exemplary subject before and after one overnight treatment.

reduced redness, and diminished dark circles. Furthermore, skin barrier function and hydration, both negatively affected by sleep deprivation, were significantly improved, aligning with the observed upregulation of skin barrier-related genes. While restful sleep is essential for healthy skin, it can also contribute to sleep wrinkles depending on sleeping position. Clinical studies with rose hip active specifically targeted wrinkles on the décolleté and nasolabial fold, which may be caused or worsened by unfavorable sleep positions and pillow materials. Results showed that rose hip active effectively smooths the skin and reduces sleep wrinkles, even after a single application.

## Conclusions

With its melatonin-like properties, including antioxidant activity, skin barrier support, and mitochondrial benefits, rose hip active offers regenerating and rejuvenating effects overnight.

## References

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