



Research article

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Skin Anti-Aging Effect of a Melatonin-based In & Out Strategy in Comparison with Topical Treatment Alone: A Randomized, Assessor-Blinded, Prospective Trial with VISIA evaluation

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Abstract

Aim: Topical use of Mel has demonstrated beneficial effects in skin aging treatment. So far, no clinical data are available regarding the anti-skin aging effect of an "In & Out" regimen consisting of a Mel-based cream and a Mel-based (0.5 mg) dietary supplementation containing also hyaluronic acid and apigenin.

Methods: In a 12-week multicenter, randomized, assessor-blind trial, fifty subjects, with mild to moderate face skin aging were randomized to cream treatment (Group A; n=25) or to cream treatment plus a Mel-based oral supplementation (Group B; n=25). The main outcome was the evolution of the Skin Ageing Global Score (SAGS) evaluated at baseline, week 6, and week 12. VISIA analysis was performed in a subgroup of 20 subjects.

Results: At baseline, the SAGS score was 13 ± 3 and 14 ± 4 in Group A and Group B, respectively. In both groups, the SAGS significantly decreased after 6 (-10%) and 12 weeks (-23% and -27% for Group A and B, respectively), confirming the efficacy of the topical treatment and suggesting a greater clinical improvement for the combination treatments compared to the topical treatment alone. These results were supported by the VISIA analysis.

Conclusion: In conclusion, this "In&Out" regimen has demonstrated a greater clinical improvement of skin ageing signs in comparison with the topical treatment alone.

Keywords: Melatonin; In & Out strategy; Anti-aging; VISIA

Introduction

Melatonin (Mel) is an endogenous substance, involved in different physiological functions including skin functions, inflammatory response, and protection against oxidative stress [1,2]. Mel is considered a multitasking molecule able to retard ageing processes. Biological aging is a complex phenomenon characterized by a progressive alteration of physiological cell integrity [3]. At skin level aging is influenced by internal (chrono ageing) and external factors (sun exposure, pollution etc.; the

so called photoaging). Skin is a complete and independent melatonineric system and expresses Mel receptors MT1 and MT2 [4]. Mel acts as a relevant antioxidant at the skin level and exerts DNA and mitochondrial protective action and anti-senescence activity [5]. The proprieties of Mel are in part related to its receptor-mediated action: Mel exerts many effects on cell growth regulation and skin tissue homeostasis via Mel receptors MT1 and MT2 [6]. Mel exerts antioxidant proprieties directly, through its

radical scavenging activity, and indirectly through its antioxidative enzyme-stimulating actions [2,7] and could also protect DNA from oxidative damage [8] and mitochondrial membrane potential [9,10]. Several data support the role of Mel at the skin level against physicochemical stressors, supporting its possible role as a cytoprotective and antiaging molecule. Mel synthesis, both systemically and at the skin level, is reduced over time [11]. Therefore, from a theoretical point of view, supplementation of exogenous Mel could be considered an interesting and promising anti-aging strategy. Mel increases the production of a relevant aging suppressor like Sirtuin 1 [3]. A key factor in the aging process seems related to cumulative mitochondrial dysfunctions [12]. Preserving mitochondrial functions is now considered a relevant aspect to counteract skin changing in both chrono and photoaging [13]. It is known that intercellular transfer of “activated” functionally active mitochondria between mesenchymal stem cells and fibroblasts has been detected as a repair mechanism to regenerate skin cells [14]. Mitochondria provide the energy level necessary to maintain skin capacity for elevated turnover. Mel is involved in the regulation of mitochondrial respiratory protein production [3]. For efficient mitochondrial activity, a normal intracellular level of Mel is therefore important. Reiter et al. have demonstrated that Mel is also synthesized inside mitochondria [15], and this production is reduced during aging. Pineal secretion of Mel peaks before 20 years of age and declines after that. Serum Mel levels at the age of 50 years are less than 10% of the value during childhood.

Several experimental data support the evidence that Mel exerts relevant anti-aging properties on aged human epidermal and dermal cells. For example, Mel can down-regulate the mTORC1 activity [16]. This molecule can promote cell and tissue aging. Mel is able to modulate the expression of degradation enzymes like Matrix Metallo Proteinase 1 (MMP-1) [16]. Mel stimulates the intraepidermal production of VEGF, considered a key factor for skin rejuvenation [16]. In addition, Mel could increase the expression and also the activity of DNA repair and ROS scavenging enzymes. In fact, Mel is a potent antioxidant molecule. From a chemical point of view, Mel is amphiphilic, and this characteristic favors the penetration of biological membranes thereby improving the protection of relevant structures like DNA, proteins, lipids, and mitochondria [16]. Mel counteracts UV radiation-induced skin damage, one of the crucial mechanisms of photoaging. Recent data regarding aging research point out the relevance of the accumulation of senescent cells during aging [17]. These cells are characterized by an elevation of ROS production and a set of enzymes with pro-inflammatory action. Senescent cells accumulate during their lifetime and these kinds of cells are characterized by a cell arrest state. Senescence cells are difficult to eliminate, probably due to a defect in the apoptosis mechanism [18]. The senescence process may induce extensive change in gene

expression and there is a specific and characteristic senescence-associated secretory phenotype called SASP which is able to stimulate a continuous inflammatory state (inflammome). Mel is able to positively modulate the SASP expression [19]. All these data point out that Mel could be considered an attractive anti-aging molecule due to its pleiotropic mechanism of action. Some authors have defined Mel as a “senolytic” or “geroprotector” molecule. Table 1 resumes the demonstrated anti-aging activity of Mel. The use of topical Mel as an anti-aging and photoprotective substance has been evaluated in different studies thanks to its ability to easily penetrate the stratum corneum [20]. In the cream used in this study, Mel is incorporated into a mixture of two natural oils: *Opuntia ficus indica* seed oil and *Persea gratissima* (Melatonsphere™), representing a new delivery system able to improve stability and skin penetration of Mel when used in topical formulations. Two recent clinical trials have shown that topical Mel carried in Melatonsphere™ improves signs of skin aging, evaluated both clinically and instrumentally [4,5]. Few studies have evaluated the efficacy of an oral supplementation of Mel. In this study, the efficacy of an “In&Out” regimen consisting of a Mel-based cream and a Mel-based (0.5 mg) dietary supplementation containing also hyaluronic acid (150 mg; HA) and apigenin (0.9 mg) was evaluated. Different clinical studies have demonstrated the efficacy of oral hyaluronic acid in improving skin hydration, and elasticity reducing the trans epidermal water loss and facial wrinkles [21]. Apigenin, a natural flavone, exerts antioxidant and anti-inflammatory properties [22], in addition, it decreases the activity of MMP-1, an endopeptidase that destroys the collagen matrix [23].

Methods

Population and Study Design

Between October 2023 and April 2024, a total of 50 participants (46 women and 4 men, median age 59.7 ± 8.1 years), were enrolled and randomized in a 1:1 allocation ratio and instructed to apply the 0.1% Mel-based cream twice a day (Group A) or to apply the cream twice a day and orally consume one tablet daily of a food supplement containing melatonin (0.5 mg/tablet), hyaluronic acid (150 mg/tablet) and apigenin (0.9 mg/tablet) (Group B). A dedicated computer program was used to generate the randomization list. Both products were commercially available (Cantabria Labs Difa Cooper, Caronno Pertusella, Italy). The main inclusion criteria were men and women with age > 50 years, with moderate-severe skin aging (Glogau Score > 2). The main exclusion criteria were pregnancy or breastfeeding, allergies to components present in the products, and acute skin diseases. The study was conducted over 12 weeks, and participants were evaluated at the baseline and after 6 and 12 weeks. The trial took place in four different dermatology clinics in Italy. The trial was conducted according to Good Clinical Practice Guidelines and

Helsinki Declaration and consistent with the Good Clinical Practice (GCP) regulatory requirements. All subjects provided a signed informed consent. The clinical study was registered on ISRCTN registry with the following reference number: ISRCTN58661770.

Study Outcomes

The primary efficacy outcome was the evaluation of the Skin Aging Global Score (SAGS), a subjective score that assesses six parameters (elasticity, wrinkle, roughness, pigmentation, erythema, and skin pores) with a 5-point score for each item (from 0 to 4; maximum score that indicated the highest skin-aging condition: 24). The SAGS was evaluated in an assessor-blinded fashion by a panel of dermatologists at the baseline and after 6 and 12 weeks. The secondary efficacy outcomes were the evolution of the Glogau score and of the single parameters of SAGS. In addition, a VISIA® objective face sculptor analysis was performed in a subgroup of 20 subjects. The VISIA Complexion Analysis Camera (Canfield Scientific, Parsippany, New Jersey, United States) is a camera system that captures multi-spectral photos of the face. It uses specific lighting (standardized and cross-polarized lighting) to evaluate different skin surface characteristics:

(1) spots on the skin surface (they occur when melanin coagulates below the skin surface as a result of sun damage and are generally invisible under light conditions);

(2) wrinkles;

(3) skin texture;

(4) pores;

(5) brown spots (occur from an excess of melanin, they are lesions on the skin such as hyper-pigmentation, freckles, lentigines, and melasma);

(6) red areas (blood vessels and hemoglobin). The results are expressed as percentile scores using, as a comparison, a database of skin features of a group of people of the same age and skin type. The 50% percentile represents the average of the reference group, and higher scores are associated with an improvement in terms of skin condition [34].

Statistical Analysis

A total of 50 participants were enrolled and randomized in a 1:1 allocation ratio. The sample size calculation was performed by hypothesizing a reduction of at least -20% of SAGS. With an effect size (Cohen's d value) of 0.69, an alpha value of 0.05, and a power of 90%, a total of at least 20 subjects should be enrolled in each group. The sample size was calculated using G*Power statistical software version 3.1.9.4 (G*Power, Heinrich Heine University, Kiel, Germany). Statistical analyses were conducted using GraphPad statistical software version 5.0 (GraphPad Software Inc., La Jolla, CA, USA). A non-parametric paired test was used to compare data

at baseline and after 6 and 12 weeks, while a non-parametric unpaired test was used to compare the different groups. Data are expressed as mean $\pm$ standard deviation (SD), and a p-value < 0.05 was considered significant.

Results

This was a four-center randomized prospective assessor-blind trial. The study was conducted according to the Declaration of Helsinki and GCP directive. The study protocol was approved by each Investigation Review Board of participating centers. The trial was carried out between October 2023 and April 2024. A total of 50 participants were enrolled in all the subjects but two (4%) completed the treatment period. Subjects were randomized into two groups: Group A (n=25, mean age 58.3 ± 8.2 years, mean SAGS at baseline 13.0 ± 3.6) and Group B (n=25, mean age 61.1 ± 8.0 years, mean SAGS at baseline 14.2 ± 4.1). Demographic and baseline characteristics are reported in Table 2 and were similar between groups ($p > 0.05$). The SAGS at baseline directly correlates with the age of all participants (Figure 1), confirming the reliability of this parameter. The flow diagram of the study is illustrated in Figure 2. The Skin Aging Global Score (SAGS), based on the sum of six different parameters (elasticity, wrinkle, roughness, pigmentation, erythema, and skin pores) significantly decreased in both groups ($p < 0.001$): -10% and -23% at 6 and 12 weeks respectively in Group A; -10% and -27% at 6 and 12 weeks respectively in Group B (Table 3). After 6 weeks (T1), more subjects in Group B showed a reduction in GASG score (20 out of 25, 80%) than subjects in Group A (16 out of 25, 64%); in addition, at T1, subjects with at least 10% reduction of SAGS were 11 out of 25 in Group A (44%) compared with 16 out of 25 in Group B (64%) ($p = 0.04$, Chi-square test). The score of the single parameters considered in SAGS generally decreased in both groups (Table 3), confirming the improvement of skin aging. However, the pigmentation statistically improved after 12 weeks only in Group B ($p < 0.05$). In addition, although the skin pores statistically improved in both groups after 6 and 12 weeks, in Group B the reduction of this parameter after 12 weeks compared to the baseline was significantly higher than that observed in Group A ($p < 0.05$). A higher reduction in Glogau score was observed after 12 weeks in Group B (11 out of 23, 48%) than subjects in Group A (5 out of 25, 20%) ($p = 0.04$). A VISIA® face sculptor analysis was performed in a subgroup of 20 subjects. No statistical differences were observed between T0 (baseline) and T2 (12 weeks) for all the parameters considered. However, a positive trend was observed in both Groups for different parameters: wrinkles, texture, and pores (Figure 3). Regarding the pores, a positive result in terms of percentile was observed in 80% of subjects in Group B compared to 60% of subjects in Group A at T1 and 63% of subjects in Group B compared to 50% of subjects in Group A at T2, supporting the data observed with the clinical score SAGS.

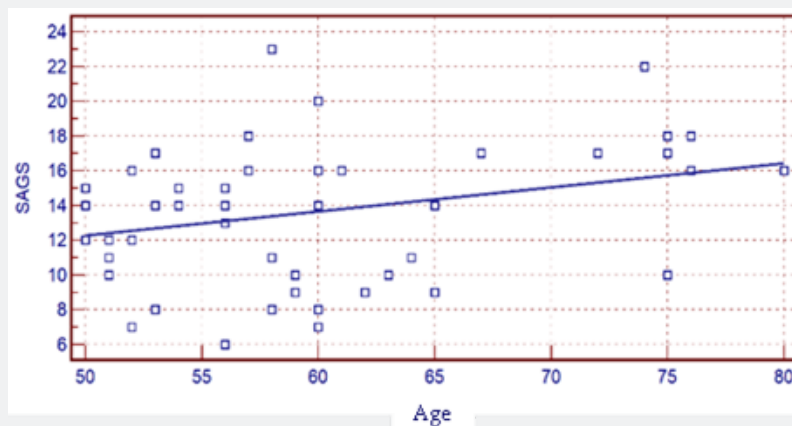


Figure 1: Correlation between SAGS at baseline and age in the whole population (n=50).

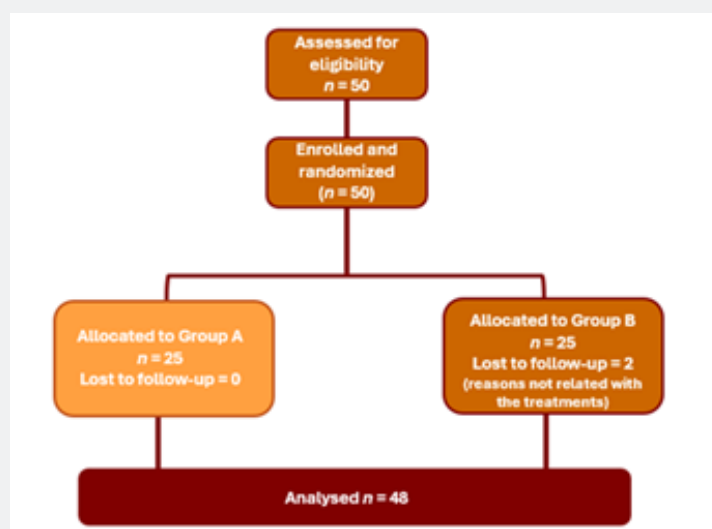


Figure 2: Flow diagram of the study.

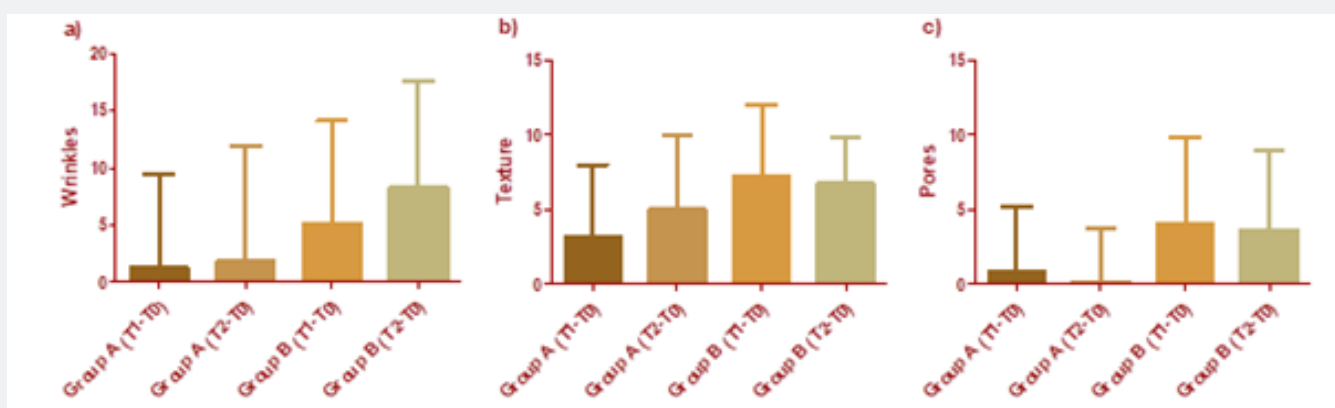


Figure 3: VISIA® results of different skin surface characteristics (a – wrinkles) (b – texture) (c - pores): improvement of per-centile scores from baseline (T0) to week 6 (T1) and 12 (T2).



Figure 4: VISIA® results of different skin parameters (wrinkles, texture, and pores) evaluated on baseline (a, c, e) and 12 weeks (b, d, f) in a subject of Group B (Mel-based cream + Mel-based oral supplement).

Table 1: Demonstrated anti-aging activity of Mel.

1.	Direct antioxidant activity
2.	Indirect antioxidant activity
3.	Mitochondrial protection
4.	DNA protective action
5.	Anti UV-induce damage
6.	Anti senescenze activity
7.	Stimulation of Sirtuin 1
8.	Inibition of MMP production
9.	Downregulation of mTORC and Claveolin expression
10.	Promotion of VEGF production
11.	Simulation of dermal fibrillin and collagen production

Table 2: Demographic and baseline characteristics.

	Group A (Mel-based cream) n=25	Group B (Mel-based cream + Mel-based oral supplement) n=25
Age, years (mean±SD)	58.3±8.2	61.1±8.0
Female	23 (92%)	23 (92%)
Glogau Score		
I	1 (4%)	0 (0%)
II	3 (12%)	1 (4%)
III	20 (80%)	19 (76%)
IV	1 (4%)	5 (20%)
SAGS (mean±SD)	13.0±3.6	14.2±4.1

Table 3: Evaluation of elasticity, wrinkle, roughness, pigmentation, erythema, and skin pores parameters and Skin Aging Global Score (SAGS) in Group A (Mel-based cream) and Group B (Mel-based cream + Mel-based oral supplement). A reduction in parameters reflects a clinical improvement of the skin aging.

	Group A Mean±SD			Group B Mean±SD		
	T0 – baseline	T1 – 6 weeks	T2 – 12 weeks	T0 – baseline	T1 – 6 weeks	T2 – 12 weeks
Elasticity	2.2±1.0	1.9±0.1**	1.6±0.7***	2.5±1.0	2.3±0.8*	1.8±0.7***
Wrinkle	2.4±0.8	2.4±0.9	2.2±0.7*	2.8±0.7	2.7±0.7	2.3±0.7*
Roughness	2.1±0.7	1.8±0.8**	1.3±0.8***	2.0±0.9	1.8±1.0*	1.3±0.8**
Pigmentation	2.4±0.8	2.3±0.8	2.2±0.8	2.7±0.8	2.6±0.9	2.4±1.0*
Erythema	1.9±1.0	1.5±1.0**	1.2±0.9***	1.8±1.1	1.5±1.0*	1.2±0.8***
Skin pores	2.0±1.1	1.7±1.1*	1.5±1.0**	2.4±1.2	2.0±1.2**	1.4±0.9***
SAGS	13.0±3.6	11.6±4.0***	10.0±3.5***	14.2±4.1	12.8±3.9***	10.4±3.5***

Significant differences compared to baseline: *p<0.05; **p<0.01; ***p<0.001

A higher reduction in Glogau score was observed after 12 weeks in Group B (11 out of 23, 48%) than subjects in Group A (5 out of 25, 20%) (p=0.04)

Discussion

Melatonin (Mel) is considered a potent senolytic molecule. It is produced by the pineal gland in a circadian rhythm fashion but also by extra-pineal tissues such as skin. Human skin presents an efficient melatonineric system and it is characterized by a significant level of Mel [24,25]. Mel has potent antioxidant activity, DNA and mitochondrial protective action, and anti-senescence activity. Different studies demonstrated the penetration, the antioxidant and mitochondrial effect of topical melatonin [10,11,26]. The use of topical Mel for anti-aging purposes has been evaluated in some clinical studies. The rationale for the use of topical formulations of Mel could be based on the consideration that Mel can penetrate the stratum corneum thanks to its low molecular weight and lipophilicity [27]. In the present study, the cream contains Mel molecules incorporated in lipospheres

(Melatosphere) with the aim to further increase the skin penetration of the molecule [4]. The efficacy of this topical formulation was previously demonstrated by Milani and Sparavigna: the use of 0.1% Mel-based creams improved significantly skin tonicity and skin hydration with a significant reduction in skin roughness [4]. These data were confirmed in other two clinical trials involving more than 50 subjects [5,28]. Few studies have evaluated the anti-aging efficacy of oral Mel supplementation. Sagan et al., observed that oral Mel (2.5 mg before bedtime) in the group of former smokers was effective in reducing the serum lipid peroxidation, improving the sebum, moisture, and elasticity [29]. In the present study, the efficacy of an “In&Out” regimen consisting of a Mel-based cream and a Mel-based (0.5 mg) dietary supplementation containing also hyaluronic acid (150 mg; HA) and apigenin (0.9 mg) was evaluated.

In both groups, the SAGS significantly decreased after 6 (-10% for both groups) and 12 weeks (-23% and -27% for Group A and B, respectively), confirming the efficacy of the topical treatment and suggesting a greater clinical improvement for the combination treatments compared to the topical treatment alone. In particular, the pigmentation parameter in SAGS statistically improved after 12 weeks only in Group B ($p < 0.05$). This could be explained by the action of Mel: current evidence suggests that Mel and some of its metabolites inhibit both melanogenesis (via reducing tyrosinase activity) and melanocyte proliferation by stimulating Mel membrane receptors (MT1, MT2) [30]. In addition, although the skin pores statistically improved in both groups after 6 and 12 weeks, in Group B the reduction of this parameter compared with baseline after 12 weeks was statistically higher than that observed in Group A. This could be explained by the contribution of hyaluronic acid (HA) present in the oral supplement. In fact, HA can have a plumping effect improving skin texture [31]. This action makes the pores to look less prominent. Different clinical studies have demonstrated the efficacy of oral HA in improving skin hydration, and elasticity reducing the trans epidermal water loss and facial wrinkles [21]. HA helps to stimulate collagen synthesis in the dermis, which also influences pore dilation. Although no clinical data are available on the role of the oral or topical application of HA on this parameter a study conducted by Qian et al. [32] concluded that intradermal injection of LMW-HA, among other parameters, can significantly reduce pore size. The data on pigmentation and pore parameters support the consideration that the oral supplement can give additional benefits to the topical treatment. The efficacy of the in & Out strategy was also confirmed by the Glogau score, a significantly higher reduction of the score was observed after 12 weeks in Group B (48%) than in Group A 20%. In a recent review, Ahmed et al. [33] state that an effective dermo-cosmetic therapy should strength skin barrier function, provide antioxidant proprieties, stimulate epidermal rejuvenation, counteract age-related pigmentation, and boost connective tissue production. We believe that this "In&Out" approach can work on all these aspects. The VISIA analysis also supported the potentiality of the combination treatment.

The oral supplement used in this study contained, apart from melatonin, different active molecules that could contribute to the anti-aging effects of the "In&Out" approach: apigenin exerts antioxidant and anti-inflammatory properties [22], in addition, it decreases the activity of MMP-1 [23] while hyaluronic acid in is able to improve skin hydration, elasticity reducing the trans epidermal water loss and facial wrinkles [21]. Although it is difficult to identify the action and the role of the single actives contained in the oral supplementation, it has demonstrated an additional clinical benefit in improving skin ageing signs in comparison with the topical treatment alone. Some limitations should be considered in evaluating our study results. The main limitation was that this study is an open trial, however, to increase the internal validity of our results, we adopted an assessor-blinded evaluation. Another limitation is the lack of control group, however different in vivo studies demonstrated the topical efficacy

of the 0.1% Mel-based cream used in this trial [4,5,28], and the aim of this study was to evaluate the additional effect of the In & Out strategy compared to the topical treatment alone. Our study was a comparative assessor blinded two-arm trial. This study design in our opinion increases the internal validity of the results and could be considered sounding in term of trial design. A control group added no additional values in term of evaluation of the antiaging effect of the proposed strategy. Another limitation is the lack of an oral placebo in Group A. It is well known that placebo is able to increase the internal validity of a study. However, considering the complexity of designing a well-conducted placebo control trial, studies with cosmetics generally do not adopt this strategy.

Conclusions

Topical Mel-based cream improves skin aging evaluated both clinically and instrumentally. These data are in agreement with previous clinical studies. An "In&Out" regimen using Mel cream and melatonin-based oral supplementation has demonstrated an additional clinical benefit in improving skin ageing signs in comparison with the topical treatment alone.

Aknowledgements

Authors' Contributions

M.B, A.G, E.R, F.S. participate to the investigation. M.M. and F.C. participated in the study design and drafting of the manuscript. All authors contributed to the review and final approval of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

F.C., S.A. and M.M. are employees of Difa Cooper Cantabria Labs which commercialized the products used in the trial. All other authors declare no conflict of interest.

Ethical approval and consent to participate

No ethical approval was required since our study was based on the application of cosmetics and the consumption of an oral supplement. The study was registered on ISRCTN registry with the following reference number: ISRCTN58661770.

Consent for publication

All participants provided written informed consent and a photo consent statement before starting the study. Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not

publicly available due to privacy or ethical restrictions.

References

- Tudjman S, Chokron S, Delorme R, Charrier A, Bellissant E, et al. (2017) Melatonin: Pharmacology, Functions and Therapeutic Benefits. *Curr Neuroparmacol* 15(3): 434-443.
- Greco G, Di Lorenzo R, Ricci L, Di Serio T, Vardaro E, et al. (2024) Clinical Studies Using Topical Melatonin. *Int J Mol Sci* 25(10): 5167.
- Majidinia M, Reiter RJ, Shakouri SK, Yousefi B (2018) The Role of Melatonin, a Multitasking Molecule, in Retarding the Processes of Ageing. *Ageing Res Rev* 47: 198-213.
- Milani M, Sparavigna A (2018) Antiaging Efficacy of Melatonin-Based Day and Night Creams: A Randomized, Split-Face, Assessor-Blinded Proof-of-Concept Trial. *Clin Cosmet Investig Dermatol* 11: 51-57.
- Milani M, Puviani M (2018) Anti-Aging Efficacy of Melatonin-Based Cream: Clinical and Instrumental Skin Evaluation. *Cosmetics* 5: 60.
- Slominski A, Pisarchik A, Semak I, Sweatman T, Wortsman J, et al. (2002) Serotonergic and Melatonergic Systems Are Fully Expressed in Human Skin. *The FASEB Journal* 16(8): 896-898.
- Tan D, Manchester LC, Reiter RJ, Qi W, Zhang M, et al. (1999) Identification of Highly Elevated Levels of Melatonin in Bone Marrow: Its Origin and Significance. *Biochimica et Biophysica Acta (BBA) - General Subjects* 1472(1-2): 206-214.
- Sliwinski T, Rozej W, Morawiec-Bajda A, Morawiec Z, Reiter R, et al. (2007) Protective Action of Melatonin against Oxidative DNA Damage-Chemical Inactivation versus Base-Excision Repair. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* 634(1-2): 220-227.
- Fischer TW, Zmijewski MA, Wortsman J, Slominski A (2008) Melatonin Maintains Mitochondrial Membrane Potential and Attenuates Activation of Initiator (Casp-9) and Effector Caspases (Casp-3/Casp-7) and PARP in UVR-exposed HaCaT Keratinocytes. *J Pineal Res* 44(4): 397-407.
- Slominski AT, Zmijewski MA, Semak I, Kim TK, Janjetovic Z, et al. (2017) Mitochondria, and the Skin. *Cellular and Molecular Life Sciences* 74(21): 3913-3925.
- Rusanova I, Martínez-Ruiz L, Florido J, Rodríguez-Santana C, Guerra-Librero A, et al. (2019) Protective Effects of Melatonin on the Skin: Future Perspectives. *Int J Mol Sci* 20(19): 4948.
- Trifunovic A, Larsson NG (2008) Mitochondrial Dysfunction as a Cause of Ageing. *J Intern Med* 263(2): 167-178.
- López-Lluch G, Hernández-Camacho JD, Fernández-Ayala DJM, Navas P (2018) Mitochondrial Dysfunction in Metabolism and Ageing: Shared Mechanisms and Outcomes? *Biogerontology* 19(6): 461-480.
- Martic I, Papaccio F, Bellei B, Cavinato M (2023) Mitochondrial Dynamics and Metabolism across Skin Cells: Implications for Skin Homeostasis and Aging. *Front Physiol* 14: 1284410.
- Reiter R, Tan D, Rosales-Corral S, Galano A, Zhou X, et al. (2018) Mitochondria: Central Organelles for Melatonin's Antioxidant and Anti-Aging Actions. *Molecules* 23: 509.
- Samra T, Gomez-Gomez T, Linowiecka K, Akhundlu A, Lopez de Mendoza G, et al. (2023) Melatonin Exerts Prominent, Differential Epidermal and Dermal Anti-Aging Properties in Aged Human Eyelid Skin Ex Vivo. *Int J Mol Sci* 24(21): 15963.
- Ogrodnik M, Salmonowicz H, Gladyshev VN (2019) Integrating Cellular Senescence with the Concept of Damage Accumulation in Aging: Relevance for Clearance of Senescent Cells. *Aging Cell* 18(1): e12841.
- Childs BG, Baker DJ, Kirkland JL, Campisi J, van Deursen JM (2014) Senescence and Apoptosis: Dueling or Complementary Cell Fates? *EMBO Rep* 15(11): 1139-1153.
- Piekarska K, Bonowicz K, Grzanka A, Jaworski LM, Reiter RJ, et al. (2023) Melatonin and TGF- β -Mediated Release of Extracellular Vesicles. *Metabolites* 13(4): 575.
- Dubey V, Mishra D, Asthana A, Jain NK (2006) Transdermal Delivery of a Pineal Hormone: Melatonin via Elastic Liposomes. *Biomaterials* 27(18): 3491-3496.
- Morgado-Carrasco D, Gil-Lianes J, Jourdain E, Piquero-Casals J (2003) [Translated Article] Oral Supplementation and Systemic Drugs for Skin Aging: A Narrative Review. *Actas Dermosifiliogr* 114(2): 114-124.
- V Elayne Arterbery, Sanjay Gupta (2018) Apigenin as an Anti-Aging Skin Treatment. *Journal of Clinical and Cosmetic Dermatology* 2(2).
- Das S, Das J, Paul A, Samadder A, Khuda-Bukhsh AR (2013) Apigenin, a Bioactive Flavonoid from *Lycopodium Clavatum*, Stimulates Nucleotide Excision Repair Genes to Protect Skin Keratinocytes from Ultraviolet B-Induced Reactive Oxygen Species and DNA Damage. *J Acupunct Meridian Stud* 6(5): 252-262.
- Slominski A, Wortsman J, Tobin DJ (2005) The Cutaneous Serotonergic/Melatonergic System: Securing a Place under the Sun. *The FASEB Journal* 19(2): 176-194.
- Slominski A, Pisarchik A, Johansson O, Jing C, Semak I, et al. (2003) Tryptophan Hydroxylase Expression in Human Skin Cells. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* 1639(2): 80-86.
- Fischer TW, Greif C, Fluhr JW, Wigger-Alberti W, Elsner P (2004) Percutaneous Penetration of Topically Applied Melatonin in a Cream and an Alcoholic Solution. *Skin Pharmacol Physiol* 17(4): 190-194.
- Yu H, Dickson EJ, Jung SR, Ko DS, Hille B (2016) High Membrane Permeability for Melatonin. *Journal of General Physiology* 147(1): 63-76.
- Puviani M, Eisendle K (2020) Anti-Wrinkle Efficacy of a Melatonin-Based Eye Contour Balm: An Antera 3D Prospective 2-Month Pilot Trial. *Article in Journal of Clinical & Experimental Dermatology Research* 11(6).
- Sagan D, Stepniak J, Gesing A, Lewinski A, Karbownik-Lewinska M (2017) Melatonin Reverses the Enhanced Oxidative Damage to Membrane Lipids and Improves Skin Biophysical Characteristics in Former-Smokers – A Study in Postmenopausal Women. *Annals of Agricultural and Environmental Medicine* 24(4): 659-666.
- Sevilla A, Chéret J, Slominski RM, Slominski AT, Paus R (2022) Revisiting the Role of Melatonin in Human Melanocyte Physiology: A Skin Context Perspective. *J Pineal Res* 72(3): e12790.
- Draeos ZD, Dia I, Namkoong J, Wu J, Boyd T (2021) Efficacy Evaluation of a Topical Hyaluronic Acid Serum in Facial Photoaging. *Dermatol Ther (Heidelb)* 11(4): 1385-1394.
- Qian W, Zhang Y, Hou Y, Lyu W, Cao Q, et al. (2018) Effect Analysis of Intradermal Hyaluronic Acid Injection to Treat Enlarged Facial Pores. *J Cosmet Dermatol* 17(4): 596-599.
- Ahmed IA, Mikail MA, Zamakshshari N, Abdullah ASH (2020) Natural Anti-Aging Skincare: Role and Potential. *Biogerontology* 21(3): 293-310.
- Investigation of the Precision of the Visia® Complexion Analysis Camera System in the Assessment of Skin Surface Features Untersuchung Der Genauigkeit Des Visia® Kamerasystems Zur Hautanalyse Bei Der Untersuchung von Aspekten Der Hautoberfläche.



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