A Single-center Study Evaluating the Effects of a Novel Retinol and Cannabidiol Combination Topical on Facial Skin

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ABSTRACT

**Background.** While retinol is known to reduce the appearance of fine lines and wrinkles, it is associated with irritating effects. When combined with water-soluble cannabidiol (CBD; CR-Topical) however, CBD acts to reduce oxidative stress and inflammation, mitigating irritation from retinol and further improving the skin’s appearance through independent anti-aging mechanisms.

**Objective.** To assess efficacy and tolerability of CR-Topical for improving facial skin.

**Methods.** In this prospective, single-center pilot study, 10 female subjects and one male subject aged 20-53 years who presented with facial skin imperfections (visible pores, dehydration, roughness, and/or static/dynamic wrinkles), applied CR-Topical to the entire face once daily for 42 days. Outcomes were measured at days 1, 21, and 42 using the Global Ranking Scale (GRS) with Comprehensive Skin Analysis by the subject and senior investigator, as well as by a blinded reviewer (board certified plastic surgeon). Dynamic videos and static imagery were taken before and after treatment and subject satisfaction surveys were completed.

**Results.** Global improvement across all 13 domains was observed, with the greatest mean differences for visible pores (2.0; 95% CI, 1.5-2.5), dehydration (2.0; 95% CI, 1.4-2.6), surface roughness (1.8; 95% CI, 1.2-2.4), static wrinkles (1.8; 95% CI, 1.1-2.5), and dynamic wrinkles (1.6; 95% CI, 0.8-2.3). Subject satisfaction (100%) and willingness to recommend the product to others (90%) was high and tolerability of CR-Topical was excellent.

**Conclusions.** CR-Topical is effective at improving global skin quality, including static and dynamic wrinkles. This study also used 4D analysis in the evaluation, a novel and developing method.
Skin aging is influenced by a number of factors, including extrinsic factors like exposure to ultraviolet (UV) light, poor diet, or pollutants, and intrinsic factors such as collagen and elastin loss over time.\(^1\) Within the skin, intrinsic aging is due, in part, to the decreased capacity of keratinocytes, fibroblasts, and melanocytes to proliferate and the degeneration of the fibrous extracellular matrix, while 80\% of extrinsic aging can be attributed to UV radiation.\(^2\)-\(^4\) Interestingly, for both intrinsic and extrinsic aging, reactive oxygen species (ROS) and associated oxidative stress can accelerate these processes in the skin through multiple mechanisms and contribute to dyspigmentation, reduced barrier function, laxity, and uneven texture.\(^1\),\(^5\) In addition, ROS are associated with inflammation, which can further negatively impact the skin’s appearance.\(^5\),\(^6\)

In clinical practice, one of the few topical treatments for which there is strong clinical evidence of efficacy for reducing the signs of aging is retinol.\(^7\) The anti-aging effects of retinol are manifested by promoting proliferation of keratinocytes, strengthening the epidermis, and increasing collagen; however, retinol may indirectly decrease the antioxidative effects of the skin, leaving it prone to damage from ROS.\(^8\)-\(^10\) Furthermore, skin reactions such as redness, drying, peeling, or burning associated with retinol treatment can lead to inconsistent use or discontinuation by patients. In the current study, purified, water-soluble cannabidiol (CBD) was evaluated with 0.2\% retinol as a combination product (CR-Topical, Aforé, Chicago, IL). By combining these agents, CR-Topical face cream was designed to combat both the intrinsic and extrinsic factors involved in skin aging by increasing skin turnover while protecting the skin through antioxidative and anti-inflammatory mechanisms, such that both efficacy and tolerability is improved.

In the current pilot study, due to the novelty of the combination and the need to characterize the impact of these treatments on the skin, a more granular approach was taken to measuring outcomes. Typically, aesthetic conditions are measured using validated and non-validated scales (eg, FACE-Q, GAIS) using static photos taken from multiple angles.\(^11\),\(^12\) Subject satisfaction questionnaires may also be used to gauge perceptions of efficacy, satisfaction, and overall impressions. However, these scales are limited in their ability to detect specific changes to features such as skin quality. Therefore, the nine-domain Global Ranking Scale (GRS) and four-domain Skin Quality assessment was applied.\(^13\) The GRS is unique in that it is used as a collaborative tool by the physician with the patient, and therefore additional methods, described below, were used to confirm observations, including blinded review and ordering of before and after images by a board-certified plastic surgeon and inclusion of patient survey questions, which were completed independently, that overlap with GRS skin quality domains to confirm outcomes.

In addition to the capture of static images, this study evaluated patients using video of a series of facial expressions as an exploratory endpoint. Even the best before and after static images represent an incomplete picture of treatment efficacy. Moreover, optimal static correction can result in unnatural mimetic movement, overfilling, and/or inadequate or imbalanced correction. Compared with static images, dynamic videos are better able to capture global improvement across four dimensions, encompassing glide plane movement and multiple facial expressions (Table 1). The use
of videos in this study was exploratory in nature and represents the first time that this four-dimensional beauty (4D Beauty, Afore, LLC, Chicago IL) assessment has been used in a clinical study. So much of how patients perceive themselves and are perceived by others is embedded in expressions and even qualities like facial positioning and openness can be appreciated with video. This type of assessment is in its infancy, and development will likely involve extensive multidisciplinary research and development of novel measures, as well as protocols for video capture, however its inclusion here paves the way for further development. In this pilot study, the use of 4D Beauty assessment is detailed, but is not part of the formal evaluation of efficacy. However, this work paves the way for use in clinical practice and study.\textsuperscript{13,14}

**METHODS**

This single-center pilot study evaluated the efficacy, safety, and tolerability of CR-Topical (300 mg of purified, medical grade, water-soluble CBD; 0.2% retinol; proprietary botanicals; and stabilizing agents) applied once daily to the facial skin. The study enrolled 10 healthy female subjects between 20 and 53 years of age who presented with any combination of the following on the facial skin: visible pores, dehydration, roughness, static or dynamic wrinkles, skin laxity, and/or facial fine lines. Subjects were informed of the potential for exposure to CBD, and were blinded as to whether they were receiving active treatment or placebo. Each subject was provided with a tube of CR-Topical labeled “A” by the manufacturer and instructed to apply 2 pumps (0.3ml) of CR-Topical to their entire facial skin in the evening before bed after using a mild facial cleanser. After enrollment, subjects immediately began treatment and continued the regimen for 42 days (6 weeks) until study completion. For the duration of the study, subjects were asked to fill out a daily log detailing any changes to their skin appearance and any side effects they experienced. Subjects served as their own control.

Subjects who had botulinum toxin or filler within 3 months of study enrollment were excluded. Additionally, subjects who used topical, inhaled, or ingested cannabis and/or hemp-derived products including CBD or tetrahydrocannabinol within 30 days of the study start date or during the study period were excluded. Further key exclusionary characteristics included facial rejuvenation procedures (eg, chemical peels, microneedling, microdermabrasion, etc); pregnancy; advanced or poorly controlled diabetes; current smoker or history of heavy smoking; the use of anti-inflammatory topical products during the study period; or regular continuous use of systemic or topical corticosteroids on the area to be treated.

The primary efficacy endpoint consisted of clinical evaluations of the face based on comparison of GRS scores at each time point, compared to baseline, as well as qualitative comparison of standardized before and after photographs on days 1, 21, and 42. During visits on day 1 (baseline), 21, and 42, standardized photographs of the treatment areas were taken and global skin appearance was assessed using the GRS with Comprehensive Skin Analysis by joint evaluation of severity by the
lead investigator and the subject (Figure 1). Note, the investigator and subject were blinded to
their original assessment scores at the time of evaluation. Each of the scale’s 13 domains, including
loss of elasticity, surface roughness, dehydration, static and dynamic wrinkles, volume loss, sagging,
asymmetry, imbalance, scar presence, visible pores, pigmentation, and vasculature were graded
from 0-3 (0, none; 1, mild; 2, moderate; 3, severe), and mean scores at baseline and at 42 days were
calculated for each domain and compared. Paired mean difference with each subject used as their
own control, and lower and upper 95% confidence intervals for each domain was calculated. Due
to the small number of subjects and the use of a 4-point scale across numerous domains, paired t-tests
with p-values are less informative (p-values calculated using a paired two-tailed t-test were
significant for all measures assessed), and are not presented here.

Because the GRS is intended to be used as a collaborative tool by the physician with the patient, it is
not conducive to blinded review. Instead, a blinded reviewer was asked to order the static baseline
and 42-day images as before and after, and percent agreement with whether the actual photograph
was taken at baseline or day 42 was calculated. In addition, questions overlapping with GRS skin
quality domains were included in the subject questionnaire to confirm outcomes. These
questionnaires were completed by subjects independently, following completion of the GRS.

Secondary efficacy endpoints included subject observations from satisfaction questionnaires
regarding major cutaneous changes such as smoothness, irritation, pruritus, burning, and erythema.
Exploratory endpoints included the use of 4D assessment as an assessment tool for qualitative
measure of dynamic and animation-related patient features. On days 21 and 42, daily subject diaries
were reviewed for compliance and tolerability, and subjects completed an 8-question satisfaction
survey. Filmed video evaluations occurred on days 1 and 42 for 4D assessment.

Safety was monitored by the investigator through application site assessment during each follow-up
visit (days 1, 21, and 42). Because of the established propensity for retinol to cause irritation, an
additional, virtual safety assessment of the application site occurred on day 3. At each follow-up
visit, study medication tubes were weighed for compliance. This study was approved by an
institutional review board (Advarra IRB, Columbia, MD) and adhered to the Good Clinical Practice
and standards set forth in the World Medical Association’s Declaration of Helsinki. Written consent
was provided, by which the patients agreed to the use and analysis of their data.

RESULTS

Ten subjects were enrolled in this pilot study, with a median age of 42.5 (Table 2). A greater
proportion of subjects had either white (30%) or white to light brown (30%) skin compared with
other skin types, as determined using the GRS scale. All 10 subjects reported using CR-Topical once
daily at night before bed for 42 days and product weight was consistent with the high level of
compliance reported. No subjects were lost to follow up.
At 42 days, GRS with Comprehensive Skin Analysis score improvement was observed from baseline to day 42 across all 13 domains, including domains for which improvement was unexpected (e.g., sagging). While improvement was consistent, some areas improved more than others, generally those most consistent with a topical treatment (Figure 2). Among subjects, the highest mean scores at baseline were visible pores (2.6), dynamic wrinkles (2.5), surface roughness (2.4), pigmentation (2.3), and static wrinkles (2; Higher mean scores correlate to worse skin quality [0, none; 1, mild; 2, moderate; 3, severe]).

When assessing the relative degree of improvement for each domain, those with ≥ 1-point improvement from day 0 to day 42 were found to be consistent with topical treatments (Figure 3, black dotted line). While statistically significant changes were observed for each domain including both the GRS and skin quality measures, the areas of greatest change were visible pores (2.0-point change; 95% CI, 1.5-2.5), dehydration (2.0-point change; 95% CI, 1.4-2.6), surface roughness (1.8-point change; 95% CI, 1.2-2.4) static wrinkles (1.8-point change; 95% CI, 1.1-2.5), and dynamic wrinkles (1.6-point change; 95% CI, 0.8-2.3). Notably, while the greatest possible score change is 3, not all subjects began with “severe” skin quality, making a 3-point change impossible. However, a two-point change represents a change from “severe” to “mild” or “moderate” to “none,” both of which represent very impactful improvements. Each subject who reported severe static wrinkles, dynamic wrinkles, surface roughness, scars, visible pores, or vasculature at baseline reported at least “mild” severity for these domains at study completion. Moreover, all subjects with “severe” dehydration reported “none” at the end of the study. The blinded reviewer correctly ordered before and after images for 80% of the subjects.

Satisfaction and functional outcomes assessed using subject questionnaires completed on days 21 and 42 revealed that at day 42, 90% of subjects either agreed (50%) or strongly agreed (40%) that they experienced visible reduction of facial fine lines and wrinkles (Figure 4). Overall, 100% of subjects felt that CR-Topical made them more confident in the physical appearance of their face. In agreement with GRS outcomes, subjects strongly agreed that the use of CR-Topical significantly improved the texture/smoothness (90%) and pore size (70%) of the skin, outcomes consistent with those measured with the GRS. Subjects either agreed or strongly agreed (30% vs 70%, respectively) with the statement that they experienced minimal irritation for the duration of the study, demonstrating the excellent tolerability of CR-Topical. Furthermore, 90% of subjects strongly agreed that they were very satisfied with the product, with 90% expressing both their willingness to use CR-Topical again and recommend the cream to family and friends.

Representative patient images (Figures 5 and 6), illustrate improvement across a range of GRS domains. Changes in skin quality are apparent in before and after images, and Figure 7 shows a close-up view of each patient so that changes in skin quality can be appreciated.
DISCUSSION

This pilot study demonstrated that CR-Topical, a novel formulation of retinol, peptides, and antioxidants combined with water-soluble CBD, increases global skin quality and leads to positive subject functional outcomes. While retinol is correlated to a decrease in the depth of fine lines and wrinkles, it is known to have irritating effects on the skin that can lead to erythema, pruritus, peeling, and redness with long-term use. Here, these negative effects appear to be counteracted by CBD, improving the tolerability of the product. It will be important to characterize relative tolerability in a split-face study in the future.

Although research on CBD oil as a topical agent is still emerging, supplementary use has been shown to decrease inflammation and improve therapeutic outcomes for severe inflammatory skin diseases, supporting this potential role. Anecdotally, the improvements observed for the combination of retinol and water-soluble CBD are better than for either product alone, suggesting an additive, or potentially synergistic benefit. Larger controlled studies will need to be carried out in order to understand the relative effects of CR-Topical and retinol, and to define any synergistic activity for the two ingredients. Importantly in these studies, a larger number of patients should be followed for an extended period of time to best understand the impact of treatment.

When considering the potential for synergistic activity, the mechanism of action for broth retinol and CBD is informative. Through the combined effects of promoting cell proliferation and reducing oxidative stress, these agents may work synergistically to combat both the extrinsic and intrinsic causes of aging. While the mechanism of action of CBD in the skin has yet to be fully elucidated, its antioxidant and anti-inflammatory activities are well recognized, and can be partially attributed to its activation of Nrf2-target activation genes, including HMOX1, which plays crucial roles in modulating inflammation, apoptosis, and oxidative stress. Importantly, CBD-induced activation of HMOX1 expression occurs through a Nrf2-independent mechanism. Because retinol suppresses expression of Nrf2-target antioxidative genes, the addition of CBD oil can potentially restore antioxidative effects inhibited by retinol while allowing for retention of skin strengthening properties. This activity of CBD is in addition to independent mechanisms, including modulation of the human endocannabinoid system (ECS), which is linked to anti-aging effects through its role in maintaining skin homeostasis and barrier function, antioxidant and anti-inflammatory activity, as well optimal sebum production. For Retinol, independent effects are manifested through promoting keratinocyte proliferation, strengthening of the epidermis, and increasing collagen (through protection of existing collagen and stimulation of neocollagenesis) in the skin. Importantly, the combination of CBD and retinol appears to reduce skin irritation often observed with retinol alone. Notably, 100% of subjects who reported “severe” dehydration at baseline reported “none” at the conclusion of the study, indicating that CBD may combat the irritation characteristic of retinol topicals, providing considerable benefit to subject tolerability and indirect improvement in efficacy due to increasing the likelihood of adherence. Importantly, the CBD used in this study is water soluble. Most often, CBD is administered dissolved in oil, commonly coconut oil or medium-chain
triglyceride (MCT) oil. The absence of oils in this formulation that could potentially clog pores or otherwise irritate skin is also an important contributor.

While improvement across all 13 domains for all subjects suggests a global effect of CR-Topical, improvements in areas such as sagging or asymmetry may signal some variability in day-to-day perceptions, some level of bias that stems from the investigator and the subject completing the assessment together, or incomplete ability of the subject to differentiate entirely between the contributions of individual domains to overall global improvement. In future studies, placebo control and blinding both the subject and evaluating investigator will shed light on this topic. Additionally, when interpreting results, it is important to consider that the rating scale ranged from 0 to 3. Therefore, seemingly modest changes (eg, “severe” at 3 to “mild” at 1) do indeed reflect a significant improvement. Because of the granular nature of the GRS scale, it is possible that future studies could also evaluate combination treatment with other products or modalities versus monotherapy, further characterizing the effects of distinct interventions on global outcome when used together.

As skin treatments continue to emerge and become increasingly multi-modal in nature, it is essential to better understand the specific effects that different treatments have on the skin. While historical measurements for skin treatment efficacy have relied on static imagery, this methodology cannot capture the movement of glide planes and facial expressions, and it is how our faces move during communication that most informs perceptions of beauty. Capturing movements of the face with short videos more accurately reflects what is observed in day-to-day life as opposed to static imagery, and provides a real-world context for evaluating the most relevant effects of treatment. This novel and dynamic 4D assessment may prevent overcorrection or unnatural looking results by encouraging consideration of youthful dynamics in expression as well as facial proportion. Further, 4D assessment can be used in conjunction with new or existing scales and opens the door for incorporation of new measures rating naturalness of outcomes, projection or correction across multiple facial expressions, apparent confidence, openness, or other characteristics that are not traditionally thought of as study outcomes. Moreover, subjects can use the videos to better evaluate their overall satisfaction and experience by observing their facial movements before and after treatment. Like the GRS, 4D assessment can be used as a tool for patient education, treatment planning, and encouraging pursuit of natural-looking results. The exploratory assessment using 4D dynamic imagery in this study revealed that video documentation and 4D beauty is an important element of a comprehensive efficacy profile for any product or device and paved the way for video and dynamic assessments as measures of treatment effect.

Shortcomings of this study include the small sample size and short duration of follow-up time. A larger cohort and increased length of the study could lead to more robust results, especially if the design includes a control group or is a split-face study. Future studies will compare the efficacy of CR-Topical with retinol alone.
CONCLUSION

When used in combination, water-soluble CBD and retinol offer significant improvements in skin quality, as well as in static and dynamic lines, with minimal irritation. Synergistic activity of CBD and retinol may explain this high level of efficacy. Additionally, a more granular assessment of aesthetic outcomes is long overdue and should be incorporated into future clinical studies evaluating topical skin treatments. Dynamic, 4D beauty assessment is a newly emerging mode of evaluation that could be fully developed and applied to better capture the effects of treatment.

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Figures legends

Figure 1. Global Ranking Scale and Comprehensive Skin Analysis. Scale adapted from Jain et al. J Cosmet Dermatol. 2017;16(1):132-143.

Figure 2. Facial skin appearance across domains at baseline (blue) and day 42 (teal).

Figure 3. Mean change among domains from baseline for the GRS (teal circles) and Skin Quality domains (blue circles) with 95% confidence intervals (navy blue bars).

Figure 4. Subject satisfaction and functional outcomes measured using the subject survey.

Figure 5. A 20-year-old male (A-E) at baseline with facial skin characterized by active acne blemishes, acne scarring, and hyperpigmentation; and (F-J) after 42 days of nightly application of CR-Topical. Note the significant decrease in the intensity of acne-related hyperpigmentation and appearance of inflammation. Additionally, the facial skin is more hydrated indicated by the more even distribution of light.

Figure 6. A 53-year-old female (A-E) at baseline with facial skin characterized by excessive global fine lines and lentigines; and (F-J) after 42 days of nightly application of CR-Topical. Note the shallow depths of the fine wrinkles in the running vertically on the cheek and horizontally in the crow’s feet region. Additionally, the highly pigmented lentigines brought on by excessive sun or age have lightened significantly.

Figure 7. Representative close-up images of patients shown in (A) Figure 5 and (C) Figure 6 at baseline; and (B) Figure 5 and (D) Figure 6 after 42 days of nightly application of CR-Topical.
**Table 1. 4-Dimensional vs Static Measurement of Facial Skin Improvement.**

| Four Dimensions                                                                 | Static Dimensions                                                                 |
|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| • Natural-looking facial expressions and transitions between facial expressions (glide planes) | • Single-expression                                                              |
| • Changes apparent during communication                                           | • Non-communicative changes in appearance                                         |
| • Consistent age-appropriate correction across the face                          | • Limited measure of “rejuvenation”                                               |
|                                                                                 | • Can miss imbalances or overcorrection and/or give the impression of suboptimal correction |
Table 2. Subject characteristics.

| Characteristic                          | Value          |
|----------------------------------------|----------------|
| Mean age, years (range)                | 42.5 (20-53)   |
| GRS skin type, n (%)                   |                |
| I: pale white or freckled              | 1 (10)         |
| II: white                              | 3 (30)         |
| III: white to light brown              | 3 (30)         |
| IV: moderate brown                     | 1 (10)         |
| V: dark brown                          | 2 (20)         |
| VI: very dark brown to black           | 0 (0)          |

GRS, global ranking scale
Global Ranking Scale

For the four categories below please:

- Grade the severity of each feature using the “Severity Evaluation Scale”.
- Link the dots to better visualize your patient’s treatment needs.

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Comprehensive Skin Analysis

Skin Quality
Please grade the severity of each feature:

- Scars
  - 0
  - 1
  - 2
  - 3

- Visible Pores
  - 0
  - 1
  - 2
  - 3

- Pigmentation
  - 0
  - 1
  - 2
  - 3

- Vasculature
  - 0
  - 1
  - 2
  - 3

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Skin Type
Please select the appropriate skin type of your patient

- TYPE I: Pale white or freckled
- TYPE II: White
- TYPE III: White to light brown
- TYPE IV: Moderate brown
- TYPE V: Dark brown
- TYPE VI: Very dark brown to black
Figure 2

A line graph showing the mean scores of various skin conditions over time. The conditions include:
- Baseline
- Day 42

The conditions are categorized as:
- Severe
- Moderate
- Mild
- None

Conditions measured include:
- Dehiscence
- Skin and wrinkles
- Volume loss
- Sagging
- Asymmetry
- Imbalance
- Loss of elasticity
- Skin roughness
- Scars
- Visible pores
- Pigmentation
- Vasculature

The graph shows changes in scores over time for each condition.
Figure 3

Mean Change Among Domains From Baseline

Circles indicate paired mean difference, with bars representing 95% confidence intervals.
Figure 4

Satisfaction and Functional Outcomes

- I felt that there was a visible reduction in the fine lines and wrinkles on my face
- The CR Topical made me feel more confident in the physical appearance of my face
- I felt there was a significant improvement in the texture/smoothness of the skin treated with CR Topical
- I felt there was a significant improvement in the pore size of the skin treated with the CR Topical
- I experienced minimal irritation while applying CR topical
- Overall I am very satisfied with the results from CR Topical
- I would use the CR Topical again
- I would recommend the CR Topical to family and friends

Positive functional outcomes
Measures correlating to global scale
Excellent tolerability
High satisfaction

Percentage of Subjects (%)

Agree
Strongly Agree
Figure 5J
Figure 6F
Figure 6H
