# Hair Regrowth with Cannabidiol (CBD)-rich Hemp Extract – A Case Series

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## ABSTRACT

Androgenetic alopecia (AGA) is the most common cause of hair loss. Several FDA approved medications are available but offer limited results. Studies have shown that the endocannabinoid system (ECS) is a key player in hair follicle cell growth. The ECS cannabinoid type one (CB1) receptors are well expressed in the hair follicle cells. Cannabidiol CBD is a negative allosteric modulator of the CB1 receptor and has been shown to result in hair shaft elongation. In addition, the hair follicle cycle phases are controlled by the ECS vanilloid receptor-1 (TRPV1). CBD has also been shown to increase Wnt signaling pathways that are involved in the differentiation of dermal progenitor cells into new hair follicles and maintaining the anagen phase of the hair cycle. The effects of CBD on hair growth are dose dependent and higher doses may result in premature entry into the catagen phase via a receptor known as vanilloid receptor-4 (TRPV4). Topical application of CBD reaches hair follicles where it is a CB1 negative modulator, and TRPV1, and TRPV4 agonist. A study was done of 35 subjects with AGA using a once daily topical hemp oil formulation, averaging about 3-4 mg per day of CBD and minimal amounts of other cannabinoids for six months. A hair count of the greatest area of alopecia was carried out before treatment and again after six months. The results revealed that men did slightly better than women, and the vertex area did better than the temporal areas. On average there was statistically significant 93.5% increase in hair after 6 months. All subjects had some regrowth. There were no reported adverse effects. Since the CBD works through novel mechanisms different from finasteride and minoxidil it can be used in conjunction with these current drugs and would be expected to have synergistic effects.

**Key words**: = cannabidiol (CBD). cannabinoid one receptor (CB1), vanilloid receptor-1 (TRPV1), androgenetic alopecia (ACA)

Androgenetic Alopecia (AGA) is a very common condition, that occurs in both men and women, and increases in prevalence with age. It is by far the most common cause of baldness and hair thinning. It generally starts in the third and fourth decades of life and significantly increases in prevalence in women after menopause. Is it estimated that 50% of Caucasian men and 19% of Caucasian women are affected by age 50 (Shankar et al., 2009). There is a lower prevalence and severity of the condition in Asian and black men. AGA may adversely impact a person both psychologically and socially, especially in women (Levy & Emer, 2013). The condition is characterized by follicular miniaturization in a specific pattern due to the effects of systemic androgens and genetic factors (Salman et al., 2017).

In the male pattern phenotype, the hairline regresses at the bitemporal regions and at the vertex. In the female pattern then is a diffuse thinning with preservation of the frontal hairline. However, the pathogenesis is the same (Levy & Emer, 2013). AGA develops due to a disturbance in the cyclic transformation of hair follicles from active hair shaft growth and pigment production (anagen) to apoptosis-driven (cell death) hair follicle involution (catagen).

### *Current Treatment*

Two medications, minoxidil topical and oral finasteride are FDA approved for the treatment of AGA. Unfortunately, these medications offer limited results (Gupta & Charrette, 2015; Shapiro & Kaufman, 2003). The new combination of

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topical minoxidil and topical finasteride has shown more promising results (Suchonwanit et al., 2018). Hair transplantation is the only current successful permanent option, and it requires surgical procedures. Several other medical options, such as antiandrogens such as spironolactone, oral contraceptives, cyproterone, flutamide, dutasteride, prostaglandin analogs and ketoconazole are reported to be beneficial (Levy & Emer, 2013). However, they can be associated with significant adverse effects, such as depression and elevated liver enzymes. Laser and light therapies have also become popular despite the lack of documented profound benefit.(Levy & Emer, 2013).

Minoxidil was first evaluated for treatment of hair loss in 1984 as a 1% topical solution (Olsen & Weiner, 1987). It became clear that higher concentrations were needed. A 12-month double-blind trial was done on 60 subjects with AGA. The use of twice-daily topical 2% and 3% Minoxidil revealed that at month 4 the average total nonvellus hair counts had increased from a baseline mean of 158.2 to 270.2 (71% increase) in the 2% minoxidil group, from 156.6 to 287.0 (83% increase) in the 3% minoxidil group (Roberts., 1987). At month 12 the means were 415.6 (163% increase) and 448.5 (186% increase) for 2% minoxidil, 3% minoxidil, respectively. The increases from month 4 to month 12 were highly significant for each group ($p = 0.0001$). More recently, a 5% once-a-day foam has been shown to be equally effective to twice-daily application of lower concentration topical minoxidil (Blume-Peytavi et al., 2011).

Finasteride, a type 2-selective 5α-reductase inhibitor, was approved in 1997 as the first oral pharmacologic therapy for the treatment of men with AGA. It was originally developed for the treatment of men with benign prostatic hyperplasia (BPH) at a dose of 5 mg/day. Subsequent studies demonstrated that finasteride was an effective treatment for men with AGA at an optimal dose of 1 mg/day. The net improvement in hair count (finasteride vs. placebo) was 14% at 1 year and 16% at 2 years (Shapiro & Kaufman, 2003).

A 48-week-long clinical trial of men with AGA was started in November 2018. (https://www.clinicaltrials.gov/ct2/show/NCT03742518). The study used an investigational new topical drug called SM04554. Phase III trials were completed in January 2021; however, no results are published at this time. It has shown some promising results in early Phase I and II trials and works by modulating the Wnt pathway that is postulated to initiate and maintain the anagen phase of the hair cycle. Wnt signaling also causes dermal progenitor cells to differentiate into new hair follicles. It is interesting to note that CBD has also been shown to increase Wnt signaling (Vallée et al., 2017).. However, to date there is little basic science or clinical research on CBD and Wnt signaling.

Recently, with the increasing acceptance of *cannabis sativa*-based therapies, cannabidiol (CBD) has come under consideration as a possible, effective, safe, inexpensive non-prescription, topical AGA therapy (Expert Committee on Drug Dependence, 2018). CBD works through the endocannabinoid system (ECS) in the body and has novel effects on hair follicle elongation and hair matrix keratinocytes activated through ECS receptors in the hair follicle cells (Bíró et al., 2009). As such, the therapeutic effects of CBD would complement the physiologic effects of minoxidil, finasteride and antiandrogen therapies.

### *ECS and Hair Follicles*

The ECS was only discovered in the 1990s. In essence, it is a system involved with maintaining cellular homoeostasis in response to excess oxidative stress. It down-regulates the damaging inflammatory response, and up-regulates regenerative processes. It is comprised of two receptors, cannabinoid receptor 1 and 2 (CB1 and CB2) and has two messenger molecules known as the endocannabinoids, anandamide (AEA) and 2-arachidonylglycerol (2-AG). One of the many systems that the ECS is involved with is thermoregulation within the skin. There are a substantial number of CB1 and CB2 receptors on various cell lines within the skin (Tóth et al., 2019). CB1 receptors are well expressed in the hair follicle cells. Stimulation of the CB1 receptor with the endocannabinoids leads to decreased hair shaft elongation (Telek et al., 2007).

Studies have shown that the ECS is a key player in hair follicle cell growth control. (Bíró et al., 2006; Telek et al., 2007; Tóth et al., 2019). The hair follicle cycle (anagen, catagen, telogen phases) is controlled by the vanilloid receptor-1

(TRPV1; Bíró et al., 2006).TRPV1 receptors are found on the hair matrix keratinocytes. Mouse studies have shown that activation promotes hair follicle regression (catagen) and hair matrix keratinocyte apoptosis (cell death) thru retarding hair shaft elongation. (Bíró et al., 2006). Endocannabinoids, and cannabis-derived phytocannabinoids, such as THC and CBD message TRPV1 receptors. It is postulated that CBD has therapeutic effects via TRPV1 receptors by excessive activation of the receptor that they become desensitized. (Muller et al., 2019).

Tetrahydrocannabinol (THC) is a CB1 receptor partial agonist, and it has been shown to dose-dependently inhibit hair shaft elongation, decrease proliferation of hair matrix keratinocytes and induce intraepithelial apoptosis and premature hair follicle regression (catagen). These effects which occur with our innate endocannabinoid anandamide and with plant-based THC were inhibited by a selective CB1 antagonist. Furthermore the studies revealed that CB1 receptors were expressed in a hair cycle-dependent manner on the hair follicle. (Bíró et al., 2006; Telek et al., 2007).

The available research suggests that THC and other CB1 agonists can be used to manage unwanted hair growth, and likewise, CB1 antagonists, such as CBD and tetrahydrocannabivarin (THCV) and cannabidivarin (CBDV) can be used to promote hair growth (Telek et al., 2007). CBD is a CB1 antagonist that likely has its effects via negative allosteric modulation of the CB1 receptor (Chung et al., 2019; Laprairie et al., 2015). THCV and CBDV have more potent direct antagonistic effects on the CB1 Receptor.

A more recent study of human hair follicle cultured cells (Szabó et al., 2017) revealed that use of lower doses of CBD resulted in hair shaft elongation, likely via CB1 antagonism. However, much higher doses resulted in premature entry into the catagen phase, probably via a different receptor, the vanilloid receptor-4 (TRPV4). Therefore, the dosing of the topical CBD needs to be evaluated in order to obtain positive hair regrowth.

*CBD*

Over the past decade CBD has been extensively researched for a myriad of therapeutic benefits (Expert Committee on Drug Dependence, 2018). CBD does not cause euphoria or addiction. It has a wide therapeutic window and few adverse effects. Topical application of CBD has not been associated with any significant adverse effects (Bíró et al., 2009; Tóth et al., 2019). CBD in an oral form has been FDA approved for treatment of recalcitrant epilepsy and is now an over-the-counter drug (www.Epidoloex.com). CBD in sublingual, oral, inhaled and topical versions are relatively inexpensive and widely available as nutraceuticals. It is estimated that as many as 14% of the United States population has tried CBD products. (Corroon & Phillips, 2018).

CBD is fat-soluble and poorly absorbed past the epidermis, but topical application of CBD easily reaches hair follicles where it is a CB1 antagonist, and TRPV1, and TRPV4 agonist (Szabó et al., 2017).

*The Present Study*

The study was conducted to evaluate the efficacy of daily topical application of a CBD-rich hemp oil formation on AGA. Secondary goals of the study were to look for adverse effects associated with the daily topical application. Based on the pre-clinical evidence of the hair regrowth benefits of antagonizing the CB1 receptors, and from over stimulating TRPV1 receptors we would expect a significant increase in hair follicles in the treated areas.

## METHODS

The study is a case series of adults presenting to a 'Hair and Scalp' center in Clearwater Florida. Adult subjects, not currently using minoxidil or finasteride were offered the opportunity to receive the hemp oil extract free of charge through Facebook advertising. The first thirty-five subjects who responded were selected (28 males, 7 females). All were Caucasian and were diagnosed with AGA based on the presence of gradually progressing bitemporal and/or vertex alopecia. Clinical diagnosis of AGA with Norwood-Hamilton Classification score of 3V or 4.

The Norwood-Hamilton Classification is used to score stages of male pattern baldness, from 1-7. Stage 3V vertex: There is slight recession of the hairline around the temples, but there is significant hair loss on the top of the scalp (the vertex). Stage 4: The hairline recession is more than slight recession of the hairline around the

temples, and there is sparse hair or no hair on the vertex. The two areas of hair loss are separated by a band of hair that connects to the hair remaining on the sides of the scalp.

The predefined endpoints were hair counts obtained in a defined, representative area of scalp hair loss, and investigator clinical assessment of hair growth. The females were ages 46-76 (average age 61) and the males 28-72 (average age 43). The subjects gave their written informed consent for this six-month trial. The study adhered to the Helsinki guidelines and was institutionally approved. Each participant was provided with an informed consent form that they signed. None of the subjects were currently using minoxidil or finasteride. No other hair loss treatments were used during the six months of the research.

The subjects were given a topical extract in a 2 oz jar once a month and advised to apply a thin layer once each morning to the areas of baldness. The subjects were advised that she could use blow dryers, conditioners and other hair preparations. The 2 oz topical was replaced as needed at monthly visits at throughout the six-month trial. The amount used varied significantly based on the area of the scalp to be treated. None of the subjects used more than 2 oz in any one-month period.

The topical extract was made of high CBD *cannabis sativa* (hemp) flower that had been ultrapulverized into a fine powder. This chalk-like green powder was independently analyzed by Cannalysis Labs in Santa Ana, CA. It was found to contain 10.78% CBD, and 0.21% THC, and there was no detectable THCV or CBDV. This powder was infused into a lanolin base paste and natural Emu oil carrier. Each 2 oz jar contained 1000 mg of the power, or 108 mg of CBD. The subjects were advised to apply thin layer of the paste over all bald or balding areas once each morning. The 2 oz jar lasted approximately one month, which is an average daily dose of 3-4mg of topically applied CBD.

A hair count of the greatest area of alopecia was carried out before treatment was started and again after six months of treatment. To facilitate consistent hair count analysis, a clear acrylic mold was made of each subject's head. The front of the mold was positioned at the hair line, with additional measurements from the tip of the nose to the front of the mold. A one-centimeter square was removed from the mold in the area of greatest alopecia, which was either in the temporal or vertex region. The hair count was done within the 1 cm area. The nonvellus hairs within the one square centimeter were pulled through the opening with a surgical skin hook. A Bodelin ProScope with fifty times magnification was used to perform hair counts.

## RESULTS

The specific data and hair count for each subject is demonstrated in Table 1.

*Temporal Area.* This table reveals that hair counts in the temporal area increased an average of 74.1% in men, and 55.2% in women. In men the number of hairs increased from baseline of 20.6 to 33.7 (paired t-test $p < 0.01$) in the temporal area, and in women from 20.3 to 30.5 (paired t-test $p < 0.01$)

*Vertex Area.* In the vertex area the hair counts increased an average of 120.1% for men, and 64.9% for women. In men, the number of hairs increased from baseline of 16.8 to 32.9 (paired t-test $p < 0.01$) in the temporal area, and in women from 18.7 to 30.7 (paired t-test $p < 0.01$).

For all males, the baseline hair count was 18.28 (95% Confidence Interval +/- 3.02) and at six months it was 33.21 (95% Confidence Interval +/- 4.86). For all females, the baseline hair count was 19.57 (95% Confidence Interval +/- 4.83) and at six months it was 30.57 (95% Confidence Interval +/- 7.51). The paired samples t-value for men before and after difference was 7.38 ($p < 0.00001$). The paired samples t-value for women before and after difference was 5.56 ($p = 0.0014$).

The hair count increased 93.5%, from 18.5 to 32.7 ($p < 0.001$) when temporal and vertex areas were combined. In general males and the vertex area did the best. All subjects had some increase in hair count. No self-reported survey of cosmetic appearance was done.

One-third of the patients reported some slightly increased hair shedding during the first month of treatment, this was no longer was noted at the two-month visit. Otherwise, there was no reported adverse effects from use of the extract.

Table 1. *Subject Change in Hair Count Over Six Months*

| Patient | Age | Sex | Area | Baseline | 6 Months After | Difference | Change(%) |
|---|---|---|---|---|---|---|---|
| 1 | 47 | M | T | 23 | 45 | 22 | 95.7 |
| 2 | 34 | M | T | 33 | 51 | 18 | 54.5 |
| 3 | 28 | M | T | 22 | 31 | 9 | 40.9 |
| 4 | 56 | M | T | 6 | 11 | 5 | 83.3 |
| 5 | 35 | M | T | 16 | 28 | 12 | 75 |
| 6 | 29 | M | T | 38 | 56 | 18 | 47.4 |
| 7 | 34 | M | T | 12 | 46 | 34 | 283.3 |
| 8 | 51 | M | T | 18 | 27 | 9 | 50 |
| 9 | 63 | M | T | 16 | 16 | 0 | 0 |
| 10 | 29 | M | T | 15 | 23 | 8 | 53.3 |
| 11 | 36 | M | T | 28 | 37 | 9 | 32.1 |
| 12 | 55 | M | V | 8 | 22 | 14 | 175 |
| 13 | 37 | M | V | 36 | 41 | 5 | 13.9 |
| 14 | 29 | M | V | 22 | 61 | 39 | 177.3 |
| 15 | 34 | M | V | 19 | 36 | 17 | 89.5 |
| 16 | 51 | M | V | 18 | 27 | 9 | 50 |
| 17 | 48 | M | V | 14 | 64 | 50 | 357.1 |
| 18 | 59 | M | V | 12 | 23 | 11 | 91.7 |
| 19 | 29 | M | V | 18 | 26 | 8 | 44.4 |
| 20 | 38 | M | V | 22 | 28 | 6 | 27.3 |
| 21 | 56 | M | V | 18 | 31 | 13 | 72.2 |
| 22 | 35 | M | V | 22 | 39 | 17 | 77.3 |
| 23 | 46 | M | V | 12 | 23 | 11 | 91.7 |
| 24 | 72 | M | V | 12 | 33 | 21 | 175 |
| 25 | 42 | M | V | 12 | 23 | 11 | 91.7 |
| 26 | 60 | M | V | 12 | 27 | 15 | 125 |
| 27 | 42 | M | V | 24 | 38 | 14 | 58.3 |
| 28 | 30 | M | V | 4 | 17 | 13 | 325 |
| 29 | 56 | F | T | 32 | 51 | 19 | 59.4 |
| 30 | 66 | F | T | 19 | 27 | 8 | 42.1 |
| 31 | 71 | F | T | 22 | 29 | 7 | 31.8 |
| 32 | 46 | F | T | 8 | 15 | 7 | 87.5 |
| 33 | 64 | F | V | 19 | 29 | 10 | 52.6 |
| 34 | 76 | F | V | 18 | 36 | 18 | 100 |
| 35 | 49 | F | V | 19 | 27 | 8 | 42.1 |

*Note*. T = Temporal; V = Vertex.

## DISCUSSION

This case study supports significant hair regrowth benefits in both men and women with AGA. In general men did slightly better than women, and the vertex area did better than the temporal areas. On average there was 93.5% increase in nonvellus hair after six months of once-daily use. All subjects had some regrowth.

The exact mechanism of therapeutic effects is not entirely clear, and furthermore, definitive research is planned. CBD may be functioning as a CB1 receptor antagonist, via negative allosteric effects, excessive TRPV1 agonism and potentially also via Wnt messaging. The dosing of the CBD needs to be further evaluated as preclinical research suggests that much higher doses of CBD may cause agonistic effects at TRPV4 receptors which can cause premature entry of the hair follicle into the catagen phase, thereby, inhibiting hair growth. (Boudaka et al., 2020)

The safety of topically applied CBD has been previously well-documented (Bíró et al., 2009; Expert Committee on Drug Dependence, 2018). Once again there is no reported significant adverse effects for six-month application of this CBD topical.

Since the CBD works through novel mechanisms entirely different from both finasteride and minoxidil it can be used in conjunction with these current drugs and would be expected to have synergistic effects. Just as finasteride and minoxidil have been shown to have synergism (Suchonwanit et al., 2018).

Further research is planned with a hemp extract that is high in CBD, THCV and CBDV. In addition, comparative, cross-over studies with minoxidil should be considered.

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