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A Summary of Pre-Clinical and Clinical Evidence for Cannabinoid Hair Follicle Effects

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Abstract

The endocannabinoid system (ECS), discovered in the 1990s, is a system involved with maintaining cellular homoeostasis by down-regulating the damaging inflammatory responses and upregulating regenerative processes. Tetrahydrocannabinol (THC), Cannabidiol (CBD), tetrahydrocannabivarin (THCV) and cannabidivarin (CBDV) are all phytocannabinoids that have novel therapeutic effects on hair growth through the ECS receptors on hair follicles. These cannabinoids are fat-soluble and poorly absorbed past the epidermis, but topical application easily reaches hair follicles where CBDV, THCV and CBD act as partial or full CB1 antagonists and agonists of vanilloid receptor-1 (TRPV1) and vanilloid receptor-4 (TRPV4). All these ECS receptors relate to hair follicle function. THC on the other hand has the opposite effects decreasing hair shaft elongation and matrix production.

A summary of the pre-clinical and clinical cannabinoid research is reviewed. The studies confirm that for androgenetic alopecia (AGA) the method of action is different from and synergistic with current hair regrowth therapies. Blocking the CB1 receptor on the hair follicle has been shown to result in hair shaft elongation and matrix production via keratinocytes, in addition, the hair follicle cycle (anagen, catagen, and telogen phases) is controlled by TRPV1. The effects of CBD on hair growth are dose dependent and higher doses may result in premature entry into the catagen phase via a different receptor known as TRPV4. CBD has also been shown to increase Wnt signaling, which causes dermal progenitor cells to differentiate into new hair follicles and maintains anagen phase of the hair cycle.

Two recent six-month duration clinical trials of adults with androgenetic alopecia (AGA) have revealed an average 93.5% increased hair count with CBD alone, and 164% increased hair count with hemp extract high in CBD, THCV, CBDV and menthol. A current study is underway to look at punch biopsies of the areas of hair regrowth in patients treated with a combination of CBD, THCV isolate, menthol and caffeine. Another study is underway looking at using hexahydrocannabinol (HHC) a hydrogenated version of THC to decrease facial hair growth as a cosmetic effect.

Keywords: Cannabinoid; Hair; Hair growth; Alopecia

Abbreviations: THCV: Tetrahydrocannabivarin; CBDV: Cannabidivarin; CBD: Cannabidiol; THC: Tetrahydrocannabinol; AGA: Androgenetic Alopecia; HF: Hair Follicle; ECS: Endocannabinoid System; CB1: Cannabinoid One Receptor.

Introduction

The ECS was discovered in the 1990s. In essence, it is a system involved with maintaining cellular homeostasis in response to excess oxidative stress. It down regulates the damaging inflammatory response, and it upregulates 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) [1]. 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 types within the skin including hair follicles (HF) [2].

Over the past decade, CBD has been extensively researched for a myriad of therapeutic benefits [3]. CBD does not cause euphoria or addiction. It is safe, with a wide therapeutic window and few adverse effects. Topical application of CBD has not been associated with any significant adverse effects [3,4]. CBD in an oral form has been FDA approved for treatment of recalcitrant epilepsy. CBD in sublingual, oral, inhaled, and topical versions are relatively inexpensive and widely available as nutraceuticals. It is estimated that 14% of the U.S. population has tried CBD products [5].

THCV and CBDV, known together as the 'varins,' have not been as extensively researched because of the dearth of available hemp extract containing any significant amounts of these two cannabinoids. There has been considerable research of ingested varins derived from marijuana (high-THC *Cannabis sativa*) for the treatment of obesity and diabetes mellitus [6,7].

In the past three years, hemp extract high in 'varins' has become readily available, as well as THCV and CBDV isolates synthesized from CBD. For the first time, commercial quantities of the 'varins' are now available to do research.

The following is a review of the available pre-clinical and recent clinical research findings and discussion of current research.

Mini-review

Pre-clinical studies in rodents and humans have revealed that CB1 receptors are well expressed in HF cells. Stimulation of the CB1 receptor with endocannabinoids leads to decreased hair shaft elongation and decreased matrix production [8].

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 from THC were inhibited by a selective CB1 antagonist [4,8].

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, THCV and CBDV, can be used to promote hair growth [4,9]. CBD is a CB1 partial antagonist that probably produces its effects via negative allosteric modulation of the CB1 receptor [9,10]. Whereas, THCV and CBDV are novel neutral CB1 receptor full antagonists [4,7].

The HF cycle (anagen, catagen, and telogen phases) is controlled by the vanilloid receptor-1 (TRPV1) [11,12]. TRPV1 receptors are found on hair matrix keratinocytes. Mouse studies have shown that activation promotes HF regression (catagen) and hair matrix keratinocyte apoptosis (cell death) through retarding hair shaft elongation [12]. Endocannabinoids, and cannabis-derived phytocannabinoids, such as THC and CBD, message TRPV1 receptors. It is postulated that CBD has therapeutic effects on hair growth via TRPV1 receptors by such excessive activation of the receptor that they become desensitized [13].

A recent study of human HF cultured cells revealed that use of lower doses of CBD resulted in hair shaft elongation, probably via CB1 antagonism [14]. 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 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 [14].

A 2021 case series [9] of adults, thirty-five subjects, 28 males, 7 females with AGA (Norwood-Hamilton Classification score of 3V or 4) were in the study. The predefined endpoints were hair counts obtained in a defined, representative area of worst scalp hair loss, and investigator clinical assessment of hair growth.

Ages ranged from 46-76 for the females and 28-72 for the males. The subjects gave their written informed consent

for this six-month trial. 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 applied a thin layer once each morning to the areas of alopecia. The paste was made of high CBD *cannabis sativa* (hemp) flower that had been ultrapulverized into a fine powder. This hemp extract 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 2oz jar contained 108mg of CBD. Each 2oz 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 using a Bodelin ProScope with 50× magnification. In the temporal area, hair counts 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; in women, it increased from 20.3 to 30.5 (paired t-test $p< 0.01$). In the vertex area, 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; in women, it increased 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 pair t-value for men before and after difference was 7.38, $p <0.00001$). The pair 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. In general, the increased hair counts were associated with a cosmetically pleasing result.

One-third of the patients reported some slightly increased hair shedding during the first month of treatment, which was no longer noted at the two-month visit. There was no reported significant adverse effects for six-month application of this CBD topical.

The topical CBD formulation has superior results to oral finasteride given at a dose of 1mg per day [15]. The study revealed only 11% increase in hair count with finasteride. The topical CBD had comparable results to topical minoxidil twice daily application with 71% to 83% increase in hair counts after 4 months [16]**.** Since the CBD works through novel mechanisms entirely different from finasteride and minoxidil, it can be used in conjunction with these current drugs and would be expected to have synergistic effects.

A recently published study [17] is a case series of adults 31 subjects 15 males, 16 females. Ages ranged from 31 to 65 for the females and 39 to 64 for the males. None of the subjects were currently using minoxidil or finasteride. No other hair loss treatments were used during the six months of the research. They were treated with once daily hemp extract (CBD 60.00%, CBDV 12.63%, THCV 3.71%, delta 9 THC 0.18%, cannabigerol (CBG) 0.86% and cannabinol (CBN) 0.05%). This hemp extract was independently analyzed by ACS Laboratory, Sun City Center, Florida.

Each ounce of the formulation contained active ingredients of one gram of this hemp extract, five grams of menthol, six hundred grams of peppermint oil infused into a vehicle of five grams of ethanol, six hundred grams of Emu oil and 14.9 grams of HFA 134A (1,1,1,2-tetrafluoroethane) propellant, and nine hundred milligrams of dimethicone. The one-ounce foam spray or tincture lasted approximately one month on average. This is an average daily dose of 33 mg of topically applied hemp extract. The subjects were advised that they could use blow dryers, conditioners, and shampoos. The formulation was replaced as needed throughout the six-month trial.

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 permanent black tattoo dot was placed at the point of maximum hair loss on the scalp. The nonvellus hairs within the 1 cm^2 around the tattoo were pulled through the opening of a one-centimeter mold with a surgical skin hook and a hair count taken using a Bodelin ProScope with 50x magnification.

For all males, the baseline hair count was 6.13/cm^2 and at six months, it was 21.20/cm^2 (one-tailed paired t-test $p<.00001$). This represented an average increase of 246% or 15.50 additional hairs in the one square centimeter mold. For all females, the baseline hair count was 12.69/cm^2 and at six months, it was 28.75/cm^2 (one-tailed paired t-test $p<.00001$). This represented an average increase of 127% or 15.50 additional hairs in the one square centimeter mold. For all adults the baseline hair count was 9.50/cm2 and it increased after six months to 25.00 (one-tailed paired t-test $p<.00001$). This represented an average increase of 164% or 15.50 additional hairs in the one square centimeter mold. All

subjects had some increase in hair count. The increase ranged from 31.25% in a female (16 to 21 hairs/cm^2) to 2000% in a male (1 to 21 hairs/cm^2). In general, the increased hair counts were associated with a cosmetically pleasing result.

All subjects rated their psychosocial perception of the effects of the hair loss, as 'happy' (17 out of 31, 55%), or 'very happy' (14 out of 31, 45%).

This case study suggests that topical hemp extract high in THCV, CBDV, CBD, menthol and peppermint oil is associated with significant hair regrowth in both men and women with AGA. This topical was superior to high-CBD hemp extract alone [17], minoxidil and oral finasteride. In general, men did better than women. On average, there was a 164% (p <.00001) increase in nonvellus hair after six months of once-daily use. All subjects had some regrowth and cosmetic benefits.

Although the exact mechanism of therapeutic effects is not entirely clear, CBD is most likely functioning as a CB1 receptor antagonist, via negative allosteric effects, and potentially also via Wnt messaging. THCV and CBDV are acting as full CB1 neutral antagonists and via TRPV1 agonism. The menthol and peppermint (40% menthol) are probably acting by promoting the rapid onset of anagen phase [1].

The safety of topically applied hemp extract has been previously well documented. Once again, there is no reported significant adverse effects for six-month application of this hemp extract topical.

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