CBD Oil and the Skin

WRITTEN BY:
CAMILLE CHARLIER

THE SCHOOL FOR
AROMATIC STUDIES

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WELCOME

Our CBD Oil and the Skin E-book was exquisitely written by our lead researcher and writer at the School for Aromatic Studies, Camille Charlier..

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Skin Deep:
The Role of the Endocannabinoid System in Cutaneous Homeostasis

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The secret to well-being, inside the body and out, is balance. In physiology it's referred to as homeostasis -- the tendency towards a relatively stable equilibrium between interdependent elements.

Homeostasis is an active process, one that takes work. Any biological system is tightly regulated and requires constant adjustment to maintain. It's a precarious tightrope act: When things wobble too far one way or another they topple and we're faced with dysfunction and disease.

Skin health is no exception. The skin is regulated by an elaborate homeostatic complex responsible for: coordinating inflammation, tissue proliferation, sebum production, and more: **the endocannabinoid system (ECS).** Indeed, this network is known to act globally to modulate such parameters as pain sensation, memory, and fertility, but only recently have researchers identified the existence of a functional cutaneous ECS.

The skin's role of protecting the internal milieu from the outside world presents a remarkable challenge in balance. Take a look at any common cutaneous disorder and evidence of dysregulation arises. Immune dysfunction, for example, plays a major role in pathologies of the skin such as acne vulgaris, allergic contact dermatitis, eczema, psoriasis, and rosacea (Dainichi et al., 2014).

It's a sophisticated dance, and sometimes things get knocked off kilter. In light of our new understanding of the cutaneous ECS, however, treatments with cannabinoids, endogenous and otherwise, provide a novel approach to optimizing our hides. To understand what Cannabis and cutaneous salubrity have in common, we'll take a whirlwind tour of the anatomy of the skin, physiology of the endocannabinoid system, and methodology of the modern Cannabisindustry. The age-old adage "it's only skin deep" belies the stunning complexity of our soft human coverings. Perhaps it's time to reconsider our idioms.

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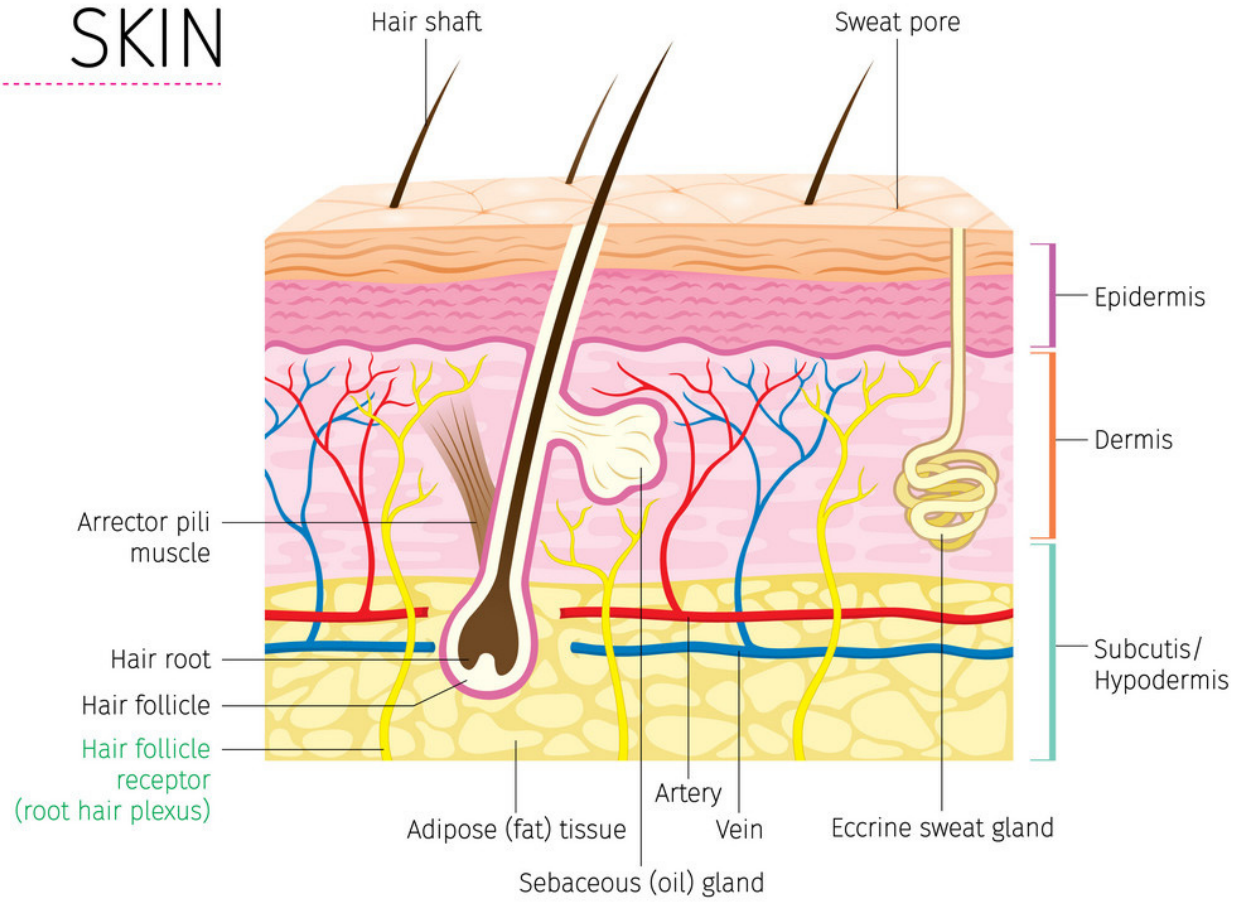
SKIN



Skin: An Exposé

The skin is the largest organ in the human body, comprising as much as 15% of the total adult body weight. It is the principal barrier between the internal body and the external world; a deeply sensitive organ that protects against biological, chemical, mechanical, and ultraviolet threats. It serves an essential role in systemic thermoregulation and the prevention of excess water loss and is an important mediator of the interrelationship between the immune, neurologic, and endocrine systems.

Skin consists of three major layers:

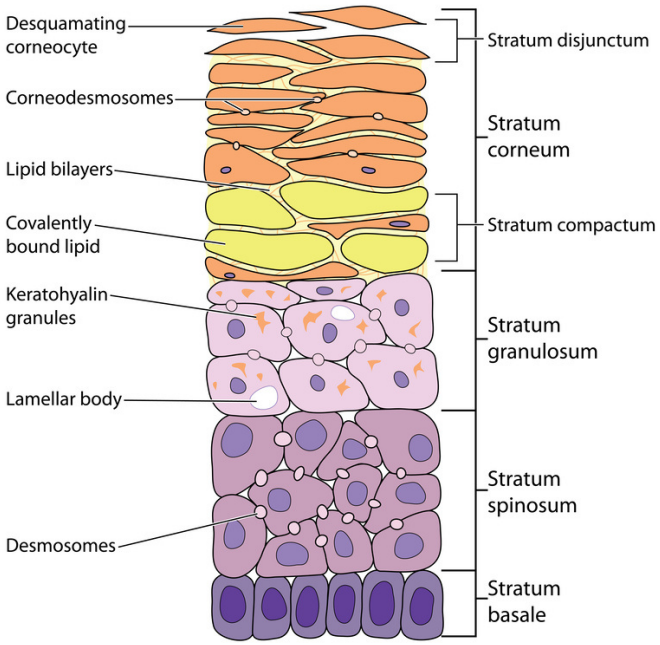
1. the epidermis,
2. the dermis,
3. and the subcutaneous tissue.

The epidermis, the outermost layer, is characterized by a constellation of cells known as keratinocytes. These cells synthesize the protective protein keratin, a fibrous intermediate alpha-helical filament and component of the cell's cytoskeleton.

Below the epidermis lies the **dermis**, a layer composed of the fibrillar structural protein collagen. Adjacent to this we find the lipocyte-containing **subcutaneous tissue**.

The epidermis is a remarkable structure, perpetually renewing itself and giving rise to hair follicles and sweat glands.

SKIN: AN EXPOSÉ



It is itself composed of five layers, the deepest of which is called the **basal layer**.

This is a hotspot of mitotic action, from whence cells arise to repopulate the outer layers. Basal cells engage in dynamic cycles of proliferation and migration, sending cells towards the surface of the skin to continually reconstitute the outer epidermis.

Epidermal stem cells are clonogenic in nature, which means that they are capable of proliferating interminably to give rise to a colony of cells. Under normal conditions the cells progress through their life cycle at a leisurely rate. In the case of a wound, however, the basal cells kick into high gear and increase the number of cycling epidermal cells via stimulation of stem cell division. Mechanical damage isn't the only mechanism by which the rate of cell division can be altered -- DNA damage caused by carcinogenic agents can also ramp up the cell proliferation machinery, resulting in hyperproliferation (Kolarsick, et al., 2011).

Embedded in the epidermis we find sebaceous glands, crucial regulators of human skin homeostasis, often associated with hair follicles in a structure known as the pilosebaceous unit. Sebaceous glands produce sebum, an oily secretion composed of triglycerides, cholesterol esters, squalene, free fatty acids, and wax esters. These lipids play an essential role in promoting integrity of the skin, from the mediation of inflammatory processes, to antioxidant delivery, to management of microbial populations.

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THE CUTANEOUS MICROBIOTA

The cutaneous microbiota, an oft unappreciated microcosm, plays a critical role in skin fitness or distress. Sebum composition is a major factor in regulating the growth of the cutaneous commensal organisms -- restricting undesired microbes while promoting the preferred populations. This behavior renders the sebaceous glands key instigators of cutaneous microbiota cross-talk essential for healthy skin homeostasis.

Sebaceous glands participate in the cutaneous endocrine and immune system, and serve as stem cell reservoirs. Dysfunction of the sebaceous gland contributes to myriad pathologies such as the ubiquitous acne and dry skin. Overproduction of sebum and pathological alterations of its chemical composition are key steps in the etiology of acne. On the flip side of the same coin, insufficient sebum production in adults may lead to dry skin, xerosis, skin aging, and atopic dermatitis (reviewed in Zákány et al., 2018).

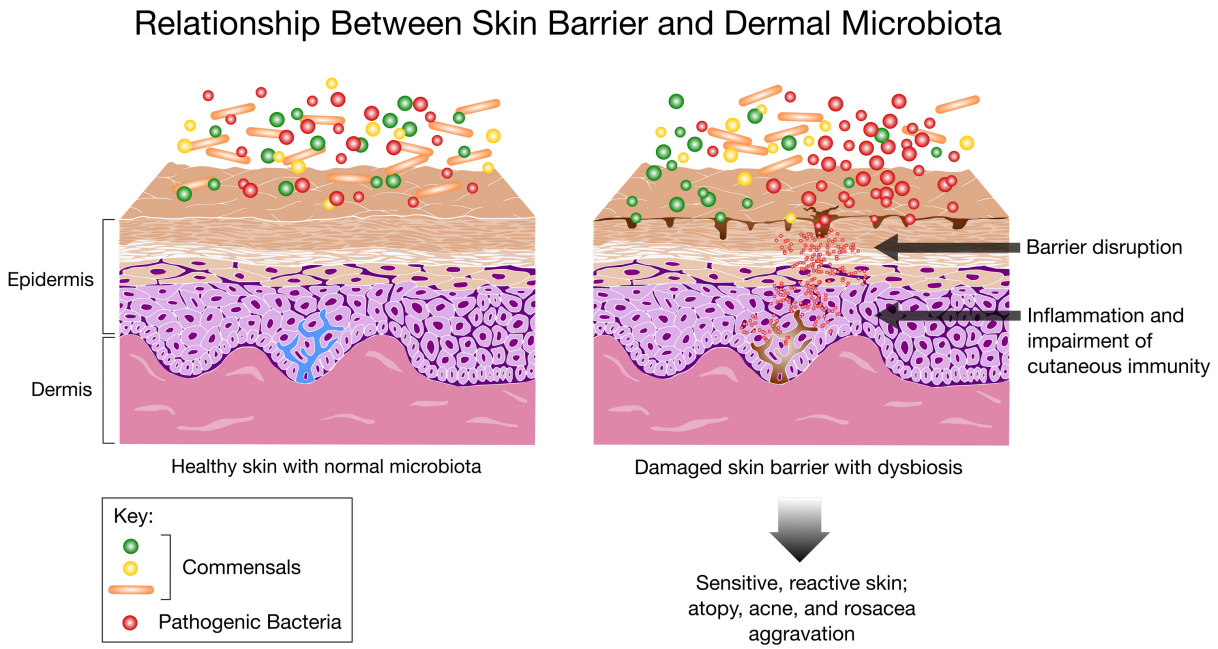

Image by: Camille Charlier

The Endocannabinoid System -

A CRITICAL CUTANEOUS REGULATOR

Everything from embryological development, neural plasticity, neuroprotection, immunity and inflammation, apoptosis and carcinogenesis, pain and emotional memory, hunger, and metabolism falls under the purview of the Endocannabinoid System(ECS).

THE ENDOCANNABINOID SYSTEM - A CRITICAL CUTANEOUS REGULATOR

The endocannabinoid system is a psychoneuroimmunological network responsible for promoting the activities ‘‘relax, eat, sleep, forget, and protect” (Di Marzo, 1998). Cannabis has been used medicinally and recreationally since time immemorial. Its effects are well recognized, but only as recently as 1992 did scientists establish conclusive experimental evidence for the existence of endogenous cannabinoids with the isolation of anandamide -- named for the Sanskrit word meaning “bliss,” ananda. Due to this whimsical dub, anandamide is sometimes referred to as the “bliss molecule,” an endogenous fatty acid neurotransmitter that binds to the same receptors as Δ9-tetrahydrocannabinol (THC), the principal psychoactive constituent of Cannabis.

The ‘‘classic’’ endocannabinoid system is comprised of the G protein-coupled cannabinoid receptors CB1 and CB2, arachidonic acid-derived ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and their metabolic enzymes. CB1 receptors are predominantly expressed in the central nervous system, and in some peripheral organs and tissues such as the spleen, skeletal muscle, liver, pancreas, and adipose tissue. CB2 receptors are also expressed in the brain, though not as densely as CB1, as well as the peripheral nervous system, gastrointestinal system, and immune tissues of the spleen, tonsils, thymus gland, monocytes, macrophages, mast cells, B cells, and T cells.

Mammals are far from unique in their possession of such a system. Indeed, cannabimimetic metabolites and cannabinoid receptors are popular across the animal kingdom, and have endured over 500 million years of evolutionary emprise in organisms as ancient as the leech, sea urchin, and marine mollusc (reviewed in Di Marzo, 1998).

Everything from embryological development, neural plasticity, neuroprotection, immunity and inflammation, apoptosis and carcinogenesis, pain and emotional memory, hunger, and metabolism falls under the purview of the ECS. Importantly, this system can be acted upon not only by endogenous and phytocannabinoids, but also by pharmaceuticals, complementary/alternative clinical interventions, lifestyle modifications, and other ingested substances.

In 2014 McPartland et al. published an article entitled “The Care and Feeding of the Endocannabinoid System,” a literature review of clinical interventions that upregulate the ECS. They noted that pharmaceuticals including analgesics (acetaminophen, non-steroidal anti-inflammatory drugs, opioids, glucocorticoids), antidepressants, antipsychotics, anxiolytics, and anticonvulsants have all been found to influence the ECS, along with non-pharmaceutical clinical interventions such as massage and physical manipulation, acupuncture, dietary supplements, and herbal medicines. Lifestyle modifications (diet, weight control, exercise), and the use ofpsychoactive substances (alcohol, tobacco, coffee, Cannabis) have been found to modulate the eCB system as well (McPartland et al., 2014).

The clinical relevance of these types of interventions becomes increasingly significant as our understanding of the endocannabinoid system deepens.

Certainly, the ECS's critical role in promoting a state of balance and vitality cannot be overstated. Dr. Ethan Russo, neurologist and medical researcher, writes in his article 2016 "Beyond Cannabis: Plants and the Endocannabinoid System" published in Trends in Pharmacological Sciences, "The ECS performs major regulatory homeostatic functions in the brain, skin, digestive tract, liver, cardiovascular system, genitourinary function, and even bone." Russo has even proposed the existence of an "endocannabinoid deficiency syndrome," which he theorizes may be the cause of such disorders as migraine, fibromyalgia, irritable bowel syndrome, and depression. Interestingly, the integrity of the system, or 'endocannabinoid tone,' is contingent upon a multitude of determinants. He explains:

Various lifestyle factors including diet and aerobic activity affect the overall ECS function or 'endocannabinoid tone', a function of the density of cannabinoid receptors, their functional status (upregulated or downregulated) and relative abundance or dearth of endocannabinoids

Cannabis is not the only plant to act on the endocannabinoid system; other common plants and foods likewise contain phytocannabinoids that bind to CB1 and CB2 receptors. Just a few examples: Carrots, which contain falcarinol, a pesticide and fungicide that covalently binds CB1 and acts as an inverse agonist, kava kava (as Russo charmingly writes, "the 'mystic pepper', a convivial beverage of the South Pacific Islands"), and some liverworts which, according to our man, "spurred a spate of Internet 'trip reports' from amateur psychonauts variably documenting prominent psychoactive versus no effects after smoking these agents."

It should be noted, however, that not all cannabinoids act via binding to CB1 and CB2 receptors. Non-intoxicating phytocannabinoid cannabidiol (CBD) acts on transient receptor potential vanilloid-1 (TRPV1), potentially "turning down the heat and pain" of sensation. Russo suggests that, due to its desensitizing properties at the receptor level, possible therapeutic targets for CBD and similar agents (capsaicin from chili peppers, black pepper, and ginger) would include neuropathic pain (causalgia, complex regional pain syndrome, migraine), burns, irritable bladder, interstitial cystitis, prostatitis, chronic pelvic pain, fibromyalgia, inflammatory bowel disease, irritable bowel syndrome, pancreatic pain, and numerous dermatological pruritic conditions (Russo, 2016).

For our current purposes, we'll zero in on the role that the endocannabinoid system plays in skin health. As previously stated, the skin is an active physio-chemical barrier against constant environmental challenges including microbial threat, allergens, UV exposure, and chemical irritation, and cutaneous integrity arises via an elegantly orchestrated neuroimmunoendocrine homeostasis. Healthy skin requires the life-long regeneration and rejuvenation of cutaneous tissues and its associated mini-organs such as hair follicles and sebaceous glands. This process is contingent upon the exquisite balance of cell growth and proliferation, survival and programmed death (apoptosis), which is regulated by a host of growth and trophic factors, cytokines, and chemokines discharged from the skin cells.

The mismanagement of cutaneous growth and immunoendocrine functions can result inpathological conditions such as hyperproliferative skin diseases (e.g. psoriasis and tumors), hair growth disorders

(e.g. alopecia, effluvium, and hirsutism), acne vulgaris, and atopic dermatitis.

The endocannabinoid system is thought to manage skin cell proliferation, differentiation, and survival, the proper regulation of which is essential for functional cutaneous homeostasis. The ECS influences skin health in myriad ways, from modulating allergic response to mediating skin-derived sensory phenomena. When it comes to allergic inflammation of the skin, the ECS exerts a protective action. Studies found that mice lacking CB1 and CB2 receptors, or treated with antagonists for these receptors, demonstrated an exaggerated allergic inflammatory response.

The ECS also mediates central and peripheral processing of skin-derived sensory phenomena such as pain and itch. Endocannabinoids and synthetic cannabinoid receptor agonists have been found to exert potent analgesic effects in humans and other animals via the activation of CB1 and CB2, and possibly by stimulating receptors such as TRPV1 at sensory nerve terminals and inflammatory cells (reviewed in Bíró, et al, 2009).

Various human skin cell compartments (epidermal keratinocytes, hair follicles, sebaceous and sweat glands) synthesize the endocannabinoids anandamide and 2-AG, along with enzymes that participate in their synthesis and metabolism. The potent role that these lipid mediators play in growth control of the human pilosebaceous unit renders them a topic of significant interest in cutaneous neuropharmacology. Indeed, CB1 and CB2 receptors, along with the ionotropic cannabinoid receptor TRPV1 were identified in situ and in vitro on manifold skin cells populations, from epidermal and hair follicle keratinocytes to sebaceous gland-derived sebocytes.

Anandamide was found to inhibit proliferation and induce cell death in cultured human epidermal keratinocytes and in situ.

In other words, locally synthesized endocannabinoids prevent skin growth from spiraling out of control. A cutaneous ECS gone awry can therefore trigger and/or aggravating chronic hyperproliferative, pruritic, and pro-inflammatory skin diseases. In light of this, targeted manipulation of the endocannabinoid system offers a promising treatment approach for hyperproliferative dermatoses such as psoriasis and keratinocyte-derived skin tumors (Tóth, et al., 2011).

Human sebaceous glands are also capable of synthesizing the endocannabinoids anandamide and 2-AG, and express both CB1 receptors (primarily in differentiated cells) and CB2 receptors (mostly in proliferating basal layer sebocytes). Studies have shown that exogenous administration of anandamide and 2-AG dramatically increased lipid production via sebocytes, an intervention of particular interest in dry skin conditions (Zákány et al., 2018).

The Skinny According to Science

"Despite its seeming ubiquity, and obvious importance as a homeostatic regulator of human physiology, the ECS topic receives short shrift in contemporary medical education, if mentioned at all."

THE SKINNY ACCORDING TO SCIENCE

At this current juncture scientific knowledge of ECS signalling has far outstripped the development of ESC-based therapies. The eloquent Dr. Ethan Russo remarks:

Despite its seeming ubiquity, and obvious importance as a homeostatic regulator of human physiology, the ECS topic receives short shrift in contemporary medical education, if mentioned at all. This educational deficit, born perhaps of lingering prejudice towards a plant called cannabis, must surely end soon, as it is contrary and detrimental to potential significant contributions to public health.

Barriers aside, this research on plants affecting the ECS portends to lead to important advances in endocannabinoid tone, as well as a better understanding of the complex stance of the ecological roles of phytochemicals and their interactions with our own biochemistry and pathophysiological mechanisms (Russo, 2016).

We still don't know much about how ESC-related treatments operate in whole living systems. In their article "Endocannabinoid signaling at the periphery: 50 years after THC" published in Trends in Pharmacological Science, Maccarrone and colleagues also recognize the need to fill this gap in the research. They firmly prod, "Clinical trials are therefore urgently required to assess the putative in vivo efficiency of ECS-oriented treatments in e.g. hyperproliferative skin conditions (tumors, psoriasis), as well as in allergic and inflammatory skin diseases (acne vulgaris, atopic dermatitis)" (reviewed in Maccarrone et al., 2015).

We'll take a look at the case studies and clinical evidence available.

A 2018 case study published in Pediatric Dermatology observed three individuals with epidermolysis bullosa who self-initiated use of topical cannabidiol. Epidermolysis bullosa is a rare blistering skin disorder that's difficult manage due to skin fragility and repeated wound healing which causes itching, pain, limited mobility, and recurrent infections. With cannabidiol use, one patient was able to completely cease their oral opioid analgesics, while all three reported faster wound healing, less blistering, and pain relief (Chelliah et al., 2018).

> *"We still don't know much about how ESC-related treatments operate in whole living systems."*

Trusler et al. reviewed the relationship between the ECS and skin pathology in their 2017 article "The Endocannabinoid System and Its Role in Eczematous Dermatoses," published in the official journal of the American Contact Dermatitis Society. In healthy conditions, the cutaneous endocannabinoid system responds to xerotic tissue (xero from the Greek, meaning "dry") by increasing lipid synthesis in the stratum granulosum.

Researchers have noted an association between abnormally low levels of endocannabinoids and dry skin, and theorize that symptoms of asteatotic eczema and xerotic dermatitis are caused, in part, by impaired skin barrier repair. In one 4-week clinical trial a cannabinoid-containing cream was tested topically on xerotic skin. 60 patients with asteatotic eczema (AE) were randomized to receive treatment with an emollient containing palmitoylethanolamide (PEA) and anandamide (AEA), or a standard emollient sans cannabinoids. Subjects who used the PEA/AEA cream demonstrated significant improvement in itching and skin hydration, along with a reduction in erythema, scaling, and dryness.

PEA, an endogenous fatty acid amide, is not strictly classified as an endocannabinoid because it doesn't bind to CB1 or CB2 receptors, but it does increase anandamide activity via an "entourage effect." The authors theorize that, as endogenous cannabinoids in the skin augment skin barrier function by increasing epidermal lipid production, a topical cannabinoid application will thus mimic the natural process and stimulate skin repair.

PEA has been similarly helpful in atopic dermatitis. In one study of adults and children researchers found that the cohort using a PEA-containing cream in combination with a class IV topical steroid cream (0.1% clocortolone pivalate) experienced a prolonged time to before their subsequent atopic dermatitis flare as compared to a cohort treated solely with steroid cream.

Another study of 2000 atopic dermatitis patients found that subjects treated with a PEA-containing cream enjoyed a statistically significant improvement in itch and reduced their weekly topical steroid use by 62%. Finally, a pilot study of 20 pediatric patients with mild atopic dermatitis found that subjects who used a product containing a PEA analogue, 2% adelmidrol, experienced a 80% resolution of symptoms, as measured by the Investigator Global Assessment score of the physician. Researchers propose that pruritus relief in response to ECS simulation occurs via the down-regulation of mast cell degranulation, inhibition of inflammatory cytokines, and reduction of proinflammatory cytokine TNF-α during inflammation, or possibly by inducing analgesia (reviewed in Trusler et al., 2017).

Furthermore, PEA has been found to associate with CB2 receptors on mast cells, and is thought to modify the immune reaction to triggers through mast cell stabilization and downregulation of the Th2 cytokine response that correlates with atopic disease. In one experimental model, PEA downregulated interleukin 4, a cytokine that is overactive in atopic dermatitis (reviewed by Del Rosso, 2007).

A 2015 study published in the Pakistan Journal of Pharmaceutical Sciences found that topical application of a cream made with 3% Cannabis seed extract reduced sebum production and erythema on the cheeks of 11 healthy male volunteers between the ages of 20 and 35. In this experiment volunteers were given two products, one with a base of paraffin oil and "fragrance," with added 3% Cannabis seed extract, and one with base alone. The subjects were instructed to apply 500 mg of the cannabis cream to the right cheek and the control cream to the left cheek with their fingertips twice a day (mornings, 7:00-9:00; Evenings, 19:00-21:00). Skin assessment was performed every other week for three months. Sebum levels were measured via Sebumeter, while erythema was evaluated by reflectance spectrophotometer. Cannabis extract was found to significantly reduce sebum production and erythema compared to base cream alone. No irritant or allergic reactions were observed during the test period. Antioxidant activity was assessed by measuring the free radical scavenging capability of the extract.

The researchers attribute reduced sebum production to the inhibition of 5-alpha reductase, the enzyme primarily responsible for converting testosterone to dihydrotestosterone (DHT), DHT is known to be a potent stimulator of sebum secretion. The cannabis seed extract was also observed to have significant antioxidant activity. The authors note that the inflammatory activity associated with acute UV exposure and the degenerative processes resulting from chronic UV radiation are predominantly mediated via the overproduction of reactive oxygen species (ROS). The observed reduction in erythema suggests the calming of inflammatory processes, which is thought by the authors to be protective against dermal photo-damage (Ali and Akhtar, 2015).

A 2010 study published in Biochemical Pharmacology found that CB1 receptor antagonist falcarinol, a skin irritant found in carrots, parsley, celery, and Panax ginseng, had an allergy-promoting effect on the skin. Falcarinol was found to exacerbate histamine-induced edema in skin prick tests. The authors report that falcarinol non-selectively binds to both CB receptors, but selectively alkylates the CB1 receptor. Evidence points to an upregulation of pro-inflammatory chemokines at the CB1 receptor level in keratinocytes via the inhibition of anandamide signaling.

In vitro experiments implicate the involvement of specific chemokine mediators notorious for promoting inflammation. C-C Motif Chemokine Ligand-2 (CCL2), also known as Monocyte Chemoattractant Protein-1 (MCP-1), is one of the key regulators of the migration and infiltration of macrophages and monocytes. Interleukin-8 (IL-8) is a chemokine with potent neutrophil activating and chemotactic attributes that fire up in inflammatory conditions, and is known to synergize with histamine. CCL2/MCP-1 and IL-8 have been implicated in contact dermatitis, while IL-8 is the likely recruiter of neutrophils from the circulation in many human inflammatory skin conditions. The peripheral endocannabinoid system operates predominantly through the keratinocytes, which have been shown to express both CB1 and CB2 receptors. The pro-allergic effects CB1 antagonist effects via falcarinol in the keratinocytes indicate the significance of the endocannabinoid system in modulating inflammation of the skin (Leonti, et al., 2010).

The available research is promising, but the field requires more well-controlled randomized clinical trials to establish safety and efficacy for mainstream medical purposes. Let's leave the world of scientific validation behind us for now, and take a look at the actual plant that set all these discoveries in motion.

Cannabis: Plant, Industry, and Ideology

Cannabis entered the United States Pharmacopoeia in 1850 and was widely employed as a patent medicine until it was stymied by the federal restrictions of the 1937 Marihuana Tax Act.

CANNABIS: PLANT, INDUSTRY, AND IDEOLOGY

Cannabis, from the latin *Cannabis sativa* L., is a member of the Cannabaceae, a small family of flowering plants containing hemp, hops, and hackberries. Cannabis means "*cane-like*," while the genus name sativa refers to that which is "*planted or sown*," meaning that the plant is propagated from seed as opposed to perennial roots. The 170 species in the Cannabaceae family are grouped into 10 genera -- trees (Celtis), erect herbs (Cannabis), and twining herbs (Humulus) are all represented.

Cannabaceae tend to be dioecious, meaning that the plants are distinctly male and female. The flowers are actinomorphic (characterized by radial symmetry) and wind-pollinated.

Cannabis sativa is an annual dioecious flowering plant which is believed to originate in central Asia circa 5000 BC. It's been used for thousands of years in the production of fibers and oils, and for medicinal purposes. Medicinally active constituents include cannabinoids, terpenoids, flavonoids, and alkaloids. Cannabinoids are a class of terpenophenolic compounds found exclusively in Cannabis plants which accumulate in the cavity of the trichomes. Upwards of 80 cannabinoids have been identified in C. sativa; the dominant psychoactive compound is Δ9-tetrahydrocannabinol (THC) (Farag and Kayser, 2017).

As a consequence of social and legal stigma, Cannabis and its 'sticky' lipophilic phytocannabinoids have only recently been legitimized. The respectable institution of scientific research has managed to validate medicinal actions of the plant that have been recognized and documented for millennia. The earliest known records of Cannabis' medicinal use are found in the 16th century BC Egyptian Ebers papyrus. Later the plant makes an appearance as a medicament in Assyrian texts. Evidence of Cannabis used as an obstetric aid in the 4th century AD was unearthed in the ashes of a tomb near Jerusalem. The Israel Police Forensic Lab analyzed a grey, carbonized material found near the abdomen of a skeleton and confirmed the presence of Δ6-tetrahydrocannabinol, a minor but highly stable constituent of Cannabis sativa. The remains were thought to be that of a young girl who died in childbirth. As the story goes, Cannabis was administered by a midwife to a 14 year old girl as an inhalant to support a difficult labor. Modern research corroborates traditional usage -- medical publications confirm that the plant effectively increases the force of uterine contractions and significantly reduces labor pain (Zlas, et al., 1993).

Cannabis entered the United States Pharmacopoeia in 1850 and was widely employed as a patent medicine until it was stymied by the federal restrictions of the 1937 Marihuana Tax Act. Cannabis was subsequently dropped from the Pharmacopoeia in 1942, with legal penalties for possession escalating in 1951 in response to the Boggs Act, and in 1956 with the Narcotic Control Act. Federal prohibition struck with the 1970 Controlled Substances Act, legislation that simultaneously criminalized Cannabis possession and suffocated research by restricting acquisition for academic purposes.

With the passage of the 1996 Compassionate Use Act, California was the first US state to legalize cannabis for medical use under the supervision of a physician. Over half the states have since followed suit. As of January 1st, 2017, 28 states, as well as the District of Columbia, Puerto Rico, and Guam, have enacted legislation regarding the sale and distribution of medicinal cannabis.

The transition to legalization has been fraught. Controversy stems from concerns over the psychoactive and impairing effects of the plant, stigma of Cannabis as a “gateway drug,” a dearth of randomized, controlled clinical trials to establish efficacy and potential for harm, lack of standardization of potency and quantity of pharmacologically recognized constituents in products, and the potential for dependence, addiction, and abuse. Despite anxieties over “reefer madness,” however, we’ve seen that cannabinoids present an impressive potential for therapeutic use (Bridgeman and Abazia, 2017).

"The modern industry’s objective has evolved to encompass strict regulation of plant propagation and constituent extraction, scientific validation of the efficacy of standardized extracts for specific pathologies, and ultimately technical domination and pharmaceuticalization of the plant."

The recent transition towards mainstream medicalization of Cannabis has sparked major shifts in the industry -- standardization practices and sophisticated extraction technologies are the new default. It’s an interesting balance to strike for businesses, capitalizing on authoritative Science cred while preserving the vibe of countercultural cool that has historically defined Cannabis use.

Consider the copy on the webpage of US company HempMeds, “This Is How CBD Oil Is Made:”

We test like crazy for accurate cannabinoid content and purity. We don’t mess around. And it all starts with quality hemp sources and a superior CO2 extraction process. Why CO2 extraction you ask? Well, because it’s awesome, that’s why. Carbon dioxide is a non-toxic, non-flammable gas used extensively in a variety of industries, including the food industry... CO2 extraction processes don’t contribute to carbon emission increases in the atmosphere, and this process doesn’t bring any flammable petroleum based solvents (like butane) into contact with your product. Extraction using supercritical CO2 is the state-of-the-art way to utilize this inexpensive and safe industrial solvent for creating high quality hemp oil (HempMeds, 2017).

The language is telling — a slurry of casual banter and technical terms. Companies marketing Cannabis tiptoe a fine line between the Hip and the Institutionally Legitimate. Indeed, the aim of achieving mainstream credibility has led to perhaps an overcompensation for the rougeish reputation of Cannabis.

The modern industry's objective has evolved to encompass strict regulation of plant propagation and constituent extraction, scientific validation of the efficacy of standardized extracts for specific pathologies, and ultimately technical domination and pharmaceuticalization of the plant. Let's take a look at the strategies of a handful of major Cannabis-producing companies across the globe.

Modern Methods of Cannabis Manufacture

The complexity of the whole Cannabis plant presents a challenge to modern medicinal methodologies. The current game is to prescribe standardized, targeted drugs containing the barebones "active" constituents. Cannabis, on the other hand, contains a surfeit of constituents mingled in highly variable and unpredictable concentrations depending on such factors as plant strain, climate, nutrient availability, photoperiod, and other growing conditions.

With the medicalization of Cannabis and the entanglements of legalization, the industry has shifted from using the whole plant to producing extracts that contain only the "medicinal" cannabinoids without the cognitive effects of THC.

International companies, though geographically and culturally disparate, share many of the prevailing ideologies currently imbuing Cannabis product manufacture:

aspirations of standardization, quality control, industrial efficiency, ecological stewardship, and harnessing the medicinal virtues of Cannabis while eliminating psychoactive properties to accommodate legal mandates are common.

So how does a major company extract CBDs from Cannabis on a commercial scale with any degree of consistency? Several strategies are at play. We'll begin with the aforementioned California-based company HempMeds, established in 2012 by parent company MYM Nutraceuticals. HempMeds employs supercritical CO2 (sCO2) extraction, perhaps the most well-known extraction technology to date. Large-scale commercial plants utilizing sCO2 are most common in the food industries, and are particularly popular for the decaffeination of coffee and tea and the extraction of hops.

To understand how sCO2 works as a solvent we need to dive into a little chemistry. Supercritical CO2 is essentially carbon dioxide in a fluid state. In daily life we find CO2 behaving as a gas (at standard temperature and pressure (STP)), and when frozen it solidifies to form the ever-famous dry ice. If, however, temperature and pressure are brought to CO2's critical point or above, the substance assumes properties somewhere between a gas and a liquid. Once a compound surpasses its critical values, the boundary of the liquid-vapor phase ceases to exist. A compound in its supercritical state thus possesses a fluid-like density, while adopting the diffusivity, surface tension, and viscosity of a gas.

Due to this liquid-esque density, the solvent strength of a supercritical fluid is comparable to that of a liquid, which renders it distinctly favorable for industrial applications (Chemical Engineering, 2010).

This technique took on an important role as a commercial and industrial solvent for its chemical extraction capabilities, with the added bonus of low toxicity and minimal environmental impact. Due to the relatively low temperature and the stability of sCO2, compounds can be extracted with little damage or denaturing. Interestingly, the solubility of extracted compounds varies contingent upon pressure, which allows for a degree of selectivity in extraction. For this reason, sCO2 is known as a "tunable" solvent. In the case of Cannabis, varying pressure settings of the equipment allows for the collections of distinct extracts containing waxes, heavy oils and resins, and light oils.

There are distinct advantages to using supercritical CO2 as a solvent. Traditionally, organic solvents -- integral to the chemical process industries -- have posed several challenges: Many are carcinogenic and neurotoxic, highly flammable, and hazardous to the environment. Consequently, conventional solvents are regulated as volatile organic compounds (VOC), and some have been banned due to their potential for ozone depletion.

CO2 is not considered a VOC, and results in no net increase of atmospheric CO2 as it is initially drawn from the environment into which is it subsequently released.

Furthermore, in contrast to many organic solvents, sCO2 is non-flammable. It is inert and non-toxic, inexpensive, and requires relatively lower temperatures and pressure to achieve supercritical status. sCO2 is considered a "green" alternative to hydrocarbon solvents, which are notoriously toxic and persistent in nature. Hydrocarbon solvents demand significant effort to purge from products, whereas sCO2 requires minimal post-processing, and any residual solvent is non-toxic (Eden Labs, 2018).

Supercritical CO2 has been around since the '80s, but as the Cannabis industry evolves, so does the technology. Precision Extraction Solutions, headquartered in Troy, Michigan, manufactures closed loop light hydrocarbon extraction equipment which utilizes hydrocarbon solvents to commercially extract constituents from Cannabis. In a closed loop system botanical material is contained in a column and flooded with a solvent, in this case butane and propane, which draws out the desired oils. The mixture is collected and the solvent evaporated off, leaving a botanical extract. In an open system propane and butane, gases at standard temperature and pressure, would evaporate off and be lost. The closed loop retains the solvent which is more efficient, not to mention safe.

Precision claims closed loop hydrocarbon extraction is the most efficient method: "Seven times the throughput of comparable CO2 supercritical extraction equipment at a fraction of the cost." Their industrial-scale equipment is graced with edgy names like "the Judge," "the Predator," and "the Executioner."

As their vision statement declares, "We work with many large scale producers and are experts in both local and state level code compliance. Our expertise covers a wide range of competencies including ASME Section VIII code, UL, International Fire Code, and 3A food processing compliance. We help our clients succeed through safety, innovation, service, and meticulous quality control." Again, the copy recapitulates the industry ethos: cutting edge cool (Precision, 2018).

Canadian company Abattis Bioceuticals, founded in 1997, recently developed a Cannabis extraction technology using column chromatography. According to president and CEO Rob Abenante in their December 12, 2017 press release:

The extraction method using proprietary polymers has very distinct competitive advantages over traditional methods. The technology is capable of extraction on an industrial scale, which delivers significant cost advantages. It is also capable of separating cannabinoids on a molecular level which allows for the extraction of pure isolates such as CBD and THCA and even the separation pesticides from the biomass.

Column chromatography isolates individual chemical compounds from a mixture based on the differential adsorption of compounds to the adsorbent. Compounds move through the column at divergent rates, which allows them to be separated into distinct fractions. The developer of the technology performed a quantitative recovery measurement which demonstrated 99% recovery of all cannabinoids from the biomass material. These yields are compared to "conventional methods," which yield less than 80%.

The press release enthusiastically heralds the advantages of the innovation, claiming, "The technology successfully removes all traces of any pesticides or harmful residues from the cultivation and transportation process," and concludes that "The cost of capital equipment and overall cost of operation is less than half of conventional CO2." With the advent of 'proprietary polymers,' novel technology rises to meet consumer demand (Abattis, 2017).

Perhaps the most fastidious of all, Netherlands-based company Bedrocan proclaims "Consistency through standardisation" as their procedural motto. On their webpage "Our Method" they delve into the relevance of standardization. "Why should you care?" they inquire, then answer:

For one, it's not just about stable THC and CBD content from one batch to another. It is also about balancing over one hundred potential active components, from cannabinoids to terpenes. Standardisation is the only method of ensuring that prescribers and patients can achieve a consistent therapeutic effect over time. Standardisation helps assure dosage composition, the repeatability of dose, and greater ability for patients and prescribers to adjust dose by titration. This allows for proper monitoring of the product's efficacy, safety and potential side effects. Standardisation enables the comparison of findings from different clinical trials and studies across time. It is a critical factor for building the evidence-base of for the efficacy medicinal cannabis.

Interestingly, the standardization aims of the industry seem to be predominantly driven by the the manner in which contemporary scientific research is conducted. In vitro assays, animal studies, and clinical trials are currently the only valid means of assessing medical efficacy in mainstream culture.

Thus, plants must be converted to products that interpretable within this reductionist paradigm. Certainly, scientific research is a useful tool, but with this model much is lost. The healing power of a plant often emerges through the synergy of its constituents; the whole is abundantly greater than the sum of its parts.

Bedrocan's strict commitment to their discipline is remarkable. They've quashed every imaginable quirk of capricious nature; "control" is the mantra. Behold: *Our indoor growing rooms use state-of-the-art environmental control technologies to control all variables, including light, temperature, nutrients, and water. Each of these rooms is sealed with special doors to prevent contact with airborne contaminants.*

Our production process has been specifically refined to grow standardised cannabis flos without the use of any pesticides. In addition, our international quality assurance measures are proudly achieved with very high hygiene standards, relevant testing requirements, and strict pesticide and fungicide restrictions. Every week a fresh batch can be harvested, 52 weeks per year, to a schedule we can predict years in advance. Each cultivar originates from one single seed. Our plants are grown by multiplying the original plant material. Bedrocan uses proprietary vegetative propagation techniques to give our products remarkable genetic stability. This method prevents 'genetic drift', a problem resulting from repeated vegetative propagation of the mother plants, which can cause major changes and weakness in the plant over time (Bedrocan, 2017).

The technical mastery that makes such standardization possible is impressive, certainly, but does this process produce the best medicine?

Diversity, Synergy, and the Old Ways of Knowing

Identifying “active” constituents and standardizing them in an extract may satisfy the compulsion for order, but it does so at the expense of other ways of knowing and encountering the natural world.

DIVERSITY, SYNERGY, AND THE OLD WAYS OF KNOWING

The implicit supposition that "control" is the superior way to relate to Nature is nothing new. English philosopher, statesman, and scientist Francis Bacon wrote in his 1620 publication The Great Instauration, "The nature of things betrays itself more readily under the vexations of art than in its natural freedom." By "art" Bacon means the manipulations of technology; the constraints applied to phenomena through the establishment of meticulous experimental conditions (Bacon, et al., 1937).

This attitude prefigures the ethos of the Enlightenment -- the belief that everything can be rationally known, and once known, controlled. As Greek mathematician Archimedes famously said, "Give me a fulcrum and I shall move the world." With the right leverage, in this case scientific data, we can manage the material realm and remodel it to our liking. 21st century technology has at last caught up with our metaphysical ambitions, and we are finally in position to execute the age-old Western objective of manipulating nature through intellectual and technological mastery. The belief in the preeminence of control, however, is an authoritarian doctrine; in politics we call it "fascism."

Identifying "active" constituents and standardizing them in an extract may satisfy the compulsion for order, but it does so at the expense of other ways of knowing and encountering the natural world. So what are the alternatives? The natural variability of plants may be precisely what makes medicines derived from them so powerful. Nature is infinitely complex, synergistic; emergent properties abound. A whole plant tends to be more vibrant and medicinally viable than single-constituent extracts, a phenomenon even observed in the lab with the discovery of the "entourage effect." Consider the case of palmitoylethanolamide (PEA), a cannabinoid that lacks an affinity for the CB1 and CB2 receptors, and yet has been found to augment anandamide activity (Ho, et al., 2008).

In contrast to the reductionism of modern science, we have the traditional healer's method of "Simpling," one which acknowledges the participation of the whole plant in medicine. Appalachian folk herbalist Phyllis Light describes the practice of Simpling, which asserts that one herb can be used in "umpteen thousand ways." She tells the story of her grandmother and father, saying, "*They didn't need complex formulas because they really, really knew their plants.*

“Nature is infinitely complex, synergistic; emergent properties abound. A whole plant tends to be more vibrant and medicinally viable than single-constituent extracts, a phenomenon even observed in the lab with the discovery of the “entourage effect.”"

DIVERSITY, SYNERGY, AND THE OLD WAYS OF KNOWING

My father used Ginseng for most ailments and knew exactly how much to decoct for how long or whether it should be taken raw" (Hardin, 2014). I was told a story by word of mouth that when Light had someone to heal, she would go out and talk to the ginseng. She'd ask the ginseng which plant should be harvested for her purposes, which part, and what preparation. The ginseng answered her. The remedies worked.

This might sound absurd, and yet many professional healers communicate with plants in this manner to inform their clinical practice. Perhaps it's not so unbelievable that plants might communicate with us considering that they communicate with each other using an "internet" of fungus (Fleming, 2014). We might not think about it much, but plants are highly skilled at capturing the attention of potential symbiotic partners. Just think of the vibrant hues and lush aroma of mouthwateringly ripe fruit.

Our senses provide us with sophisticated information about the natural world. There's a name for this -- **organoleptics**. We engage this system every time we sniff milk to see if it's gone off, when we choose attractively colored vegetables for the dinner table, or identify the subtle notes in wine.

It's powerful stuff. Consider the anecdote presented in the 1952 article "Organoleptic Panel Testing as a Research Tool" published in Analytical Chemistry: Consumers complained that their cigarettes were plagued by an "objectionable odor" that experts guessed might be caused by a specific insecticide. An organoleptic panel was convened to verify the hypothesis, and after tasting dilutions of that insecticide and samples from the cigarette packaging, the panel confirmed that the suspected insecticide was the culprit. It was present in the cardboard container at 1/10th of a pound of insecticide per ton of packaging material; 0.005% contaminant by mass. At the time, the authors concluded that this was the sole means of identifying the contaminant. Technological advancements may have since rendered this problem irrelevant, but it is still an illustration of the human sensorium as a potent analytical tool (Cartwright, et al., 1952).

These days, it seems like everyone is hanging on by the skin of their teeth. Chronic diseases, skin pathologies included, are on the rise in the industrialized world. Outbreaks of acne are associated with increased air pollution (Krutmann, et al., 2017), while psychological stress is known to exacerbate psoriasis, urticaria, eczematous dermatitis, and herpes simplex (Kimyai-Asadi et al., 2001). In our hectic modern lives we must use all the tools available to us, whether technological or traditional, to bring ourselves back to health, back to balance.

The skin, hardly superficial, offers a clue.

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