Cosmeceuticals – The Emerging Role of Cannabis

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Introduction

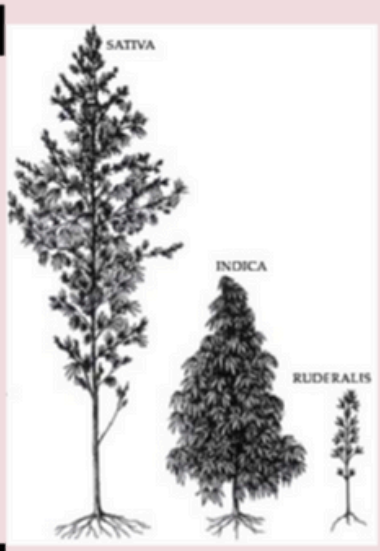
Cannabis sativa is a plant with a rich yet highly controversial history. It has been used medicinally and recreationally for over 6000 years in various cultures across the globe (1,2). In the 19th century, the investigation into the pharmacokinetics of the active constituents of Cannabis, the cannabinoids, began to shed light on their potential application in modern medicine. First-pass hepatic metabolism of cannabinoids through the oral route of drug administration and the abundance of the endocannabinoid system (ECS) in skin unlocked multiple research avenues. In recent years, there has been an increase in both pre-clinical and clinical studies exploring the utility of cannabinoids to treat dermatologic conditions. The combined global sales of cannabidiol medical and adult-use recreational cannabis topped USD 27.4 billion in 2021 and are postulated to rise to USD 102 billion by 2026 (3). This article introduces the reader to the world of Cannabis, endocannabinoid systems, and the essential compounds dominating the multi-billion cosmeceutical and beauty industry.

Cannabis vs Hemp

Cannabis and hemp are terms for the plants in the Cannabaceae family, but there are significant differences between them. In most countries (such as the United States of America and the European Union), the level of THC (tetrahydrocannabinol) is a legal defining line between hemp and Cannabis. Hemp is generally defined as Cannabis Sativa L. plants that contain no more than 0.3% w/w THC (Tetrahydrocannabinol)(4,5). Plants exceeding the 0.3% w/w THC limit are considered Cannabis.

Cannabis historically was divided into three species, Cannabis sativa, Cannabis Indica and Cannabis ruderalis (6). The United States Pharmacopeia (USP) Cannabis Expert Panel, concerned with the disparity and chaos surrounding proper classification, has recommended Cannabis be categorized, based on its cannabinoid content: Type I - THC predominant, Type II – cannabis that contains both THC and CBD (Cannabidiol), and Type III - CBD predominant (figure 1) (4,6).

A



B

Sativa	Indica
10-16 weeks to harvest	8-12 weeks to harvest
3-16 oz yield per plant	1.5-3oz yield per plant
Long, Thin, Light Green, Fluffy Buds	Short, Wide, Dark Green, Dense Buds
THC dominant	CBD dominant
e.g. Super Lemon Haze	e.g. Afghan Kush

C

THC-dominant chemotype	CBD – dominant chemotype	THC/CBD intermediate chemotype
Contains NLT 80% and NMT 120% labelled amount (mg/g) of total THC	Contains NLT 80% and NMT 120% labelled amount (mg/g) of total CBD	Contains NLT 80% and NMT 120% labelled amount (mg/g) of total THC and total CBD
Ratio of total THC content to total CBD content is NLT 5:1 NMT 10mg/g of total CBD and NLT 10mg/g of total THC	Ratio of total THC content to total CBD content is NLT 1:5 NMT 10mg/g of total CBD and NLT 10mg/g of total THC	Ratio of total THC content to total CBD content is NLT 0.2:1 NMT 10mg/g of total CBD and NLT 10mg/g of total THC
Contains NLT 80% and NMT 20% of labelled amount of all other cannabinoids (measured in mg/g)	Contains NLT 80% and NMT 20% of labelled amount of all other cannabinoids (measured in mg/g)	Contains NLT 80% and NMT 20% of labelled amount of all other cannabinoids (measured in mg/g)
Cannabis inflorescence must be labeled with the name and amount of any cannabinoid present in an amount of 10mg/g or more	Cannabis inflorescence must be labeled with the name and amount of any cannabinoid present in an amount of 10mg/g or more	Cannabis inflorescence must be labeled with the name and amount of any cannabinoid present in an amount of 10mg/g or more
CBN Content is NMT 2% of content of total THC	N/A	CBN Content is NMT 2% of content of total THC

Figure 1: Over the past century, Cannabis has been classified based on its geographical origin and growth characteristics (A) as Sativa, Indica or Ruderalis. However, more recently, a widely accepted classification has been based on its harvest cycle and bud characteristics (B). Recognizing the disparity in classification and nomenclature, United States Pharmacopoeia's Cannabis Expert Panel has recommended categorization based on the plant's chemotype or chemical constitution(C) (4).

Cannabinoids and the endocannabinoid system

Cannabinoids are a class of compounds like those derived from Cannabis. Cannabinoids can be grouped as endocannabinoids (produced endogenously), phytocannabinoids (derived from plants), and synthetic cannabinoids (chemically or biosynthetically manufactured). The most clinically relevant endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Phytocannabinoids include over 100 compounds; the most notable of these are delta-9-THC (THC), CBD (cannabidiol), CBG (cannabigerol), CBN (cannabinol), and CBC (cannabichromene). Nabilone and Ajulemic acid are synthetic molecules with a structure similar to cannabinoids.

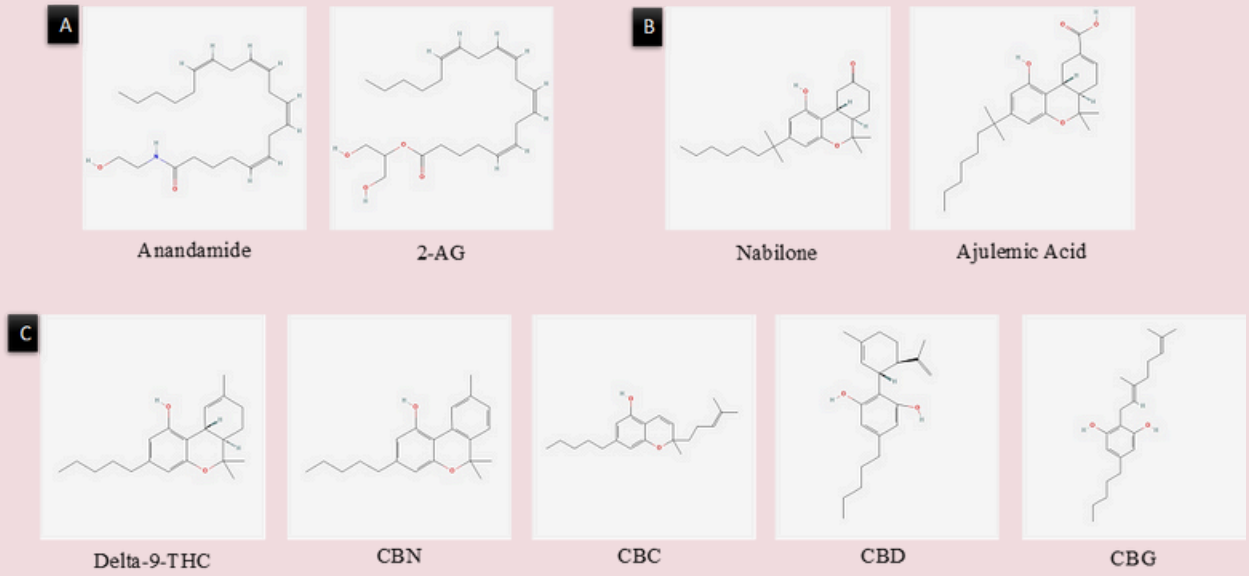


Figure 2: Chemical structures of endocannabinoids (A), synthetic cannabinoids (B), and phytocannabinoids (C).

The ECS is a widespread neuromodulatory system that plays a vital role in central nervous system (CNS) development, synaptic plasticity, and the response to endogenous and environmental insults. The ECS comprises cannabinoid receptors, endocannabinoids, and the enzymes responsible for the synthesis and degradation of the endocannabinoids.

The physiologic effects of cannabinoids are mediated through cannabinoid receptors (CB1 and CB2), which are members of the large family of rhodopsin-like G protein-coupled receptors. In general, the CB1 receptor is highly expressed in the central nervous system and is primarily responsible for memory, mood, and modulation of pain sensation through the release of neurotransmitters(7). The CB2 receptor is expressed mainly in the immune cells and the periphery and is primarily responsible for the anti-inflammatory and immunomodulatory effects of cannabinoids (7). Transient receptor potential (TRP) channels, especially TRPV1, and peroxisome proliferator-activated receptors (PPARs) such as PPAR alpha and PPAR gamma -are also engaged by some cannabinoids (8,9). An overview of the primary receptors, ligands and their interactions in the skin is provided in Table 1. Several review articles have discussed the promise of Cannabis in dermatology as anti-inflammatory, antiproliferative, antibacterial, and antioxidant agents (7,9–12).

Table 1: Cannabinoids and their interactions with the ECS (13)

	Type of Receptor	Name	Main Ligands (ECBs and pCNBs)	Interaction
Main receptors	G-protein-coupled receptor	CB1R	AEA	Weak partial agonist
			CBD	Negative allosteric modulator
			THC	Partial agonist
			THCV	Antagonist
		CB2R	AEA	Weak partial agonist
			CBD	Inverse agonist
			THC, THCV	Partial agonist
Secondary receptors	Transient potential ion channels	TRPV-1	AEA, THC	Weak agonist
			CBD, CBGA, CBGV, THCV	Strong agonists
			CBG	Agonist
		TRPV-2	CBD, CBG, CBGV, THC, THCA, THCV	Strong agonists
		TRPV-3	CBD	Agonist (action similar to the typical agonist carvacrol)
			THCV	Strong agonist
			THC	Weak agonist
		TRPV-4	AEA, 2-AG	Agonists (indirect activation)
			CBDV, THCV	Strong agonists
			THC	Weak agonist
		TRPA1	AEA, THC	Agonist
			CBD, CBC, CBN	Strong agonists
		TRPM8	AEA, THC, THCA, CBD, CBN	Strong antagonists
	Peroxisome proliferator-activated receptors	PPAR-α	THC, CBGA	Agonists
			CBDA, CBG	Partial agonists
		PPAR-γ	THC, CBD	Agonists
	Serotonin receptors	5-HT1A	CBG	Strong antagonist
			CBD, THCV, CBDA	Agonists
		5-HT2A	CBD	Partial agonist
		5-HT3	CBD, THC	Antagonists

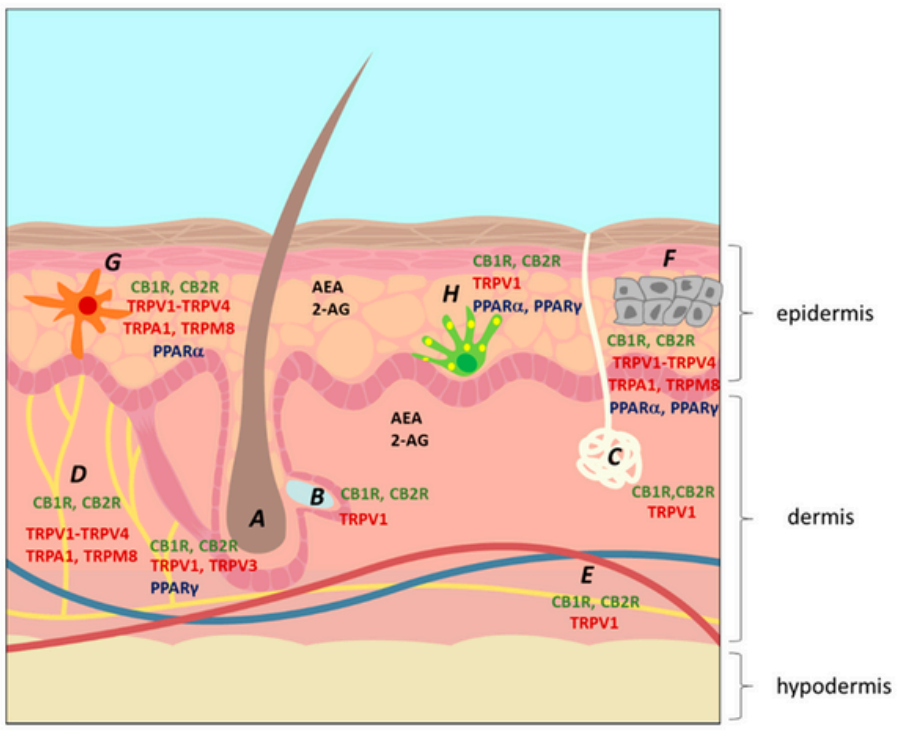


Figure 3: The location of the endocannabinoid system on the skin. A hair follicle; B, sebaceous gland; C, sweat gland; D, nerve; E, blood vessels; F, keratinocytes; G, Langerhans cell (immunocyte); H, melanocytes. The figure shows the location of the two main endocannabinoids, 2-arachidoynylarachidonicarachidonic-glycerol (2-AG) and anandamide (AEA), and of several endocannabinoid receptors, including the primary cannabinoid receptors CB1R and CB2R, several transient potential ion channel receptors (TRPs) and peroxisome proliferator-activated receptors (PPARs) (13)

Cosmeceuticals

The term cosmeceutical was coined in 1984 by Dr. Albert Kligman, describing a hybrid category of products mid-way on the spectrum of 'cosmetics and pharmaceuticals. While cosmeceuticals have indisputably taken over the personal care industry across the globe, they are still not formally recognized by the US FDA, the European Union, Japan, Health Canada or the CDSCO (India). In Europe and Japan, cosmeceuticals are a subclass of cosmetics; however, they can only be considered a subclass of drugs in the US. This, of course, has complex regulatory implications that only get more convoluted when cannabis and cannabis-based ingredients enter the picture. Regardless of the controversy around its nomenclature, cosmeceuticals or functional cosmetics or wellness products are gaining popularity across the globe. Demand for natural, organic, cruelty-free, effective and environmentally friendly products has constantly risen.

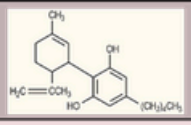
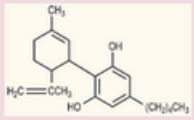
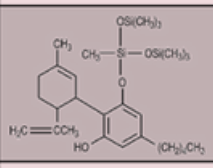
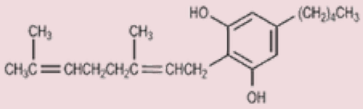
Hero Ingredients- Cannabis Cosmeceuticals CBG, CBD and Hemp seed oil

The most well-known and studied of all the cannabinoids is cannabidiol – CBD, partly because it has no known psychoactive effects and therefore has a sense of being less harmful. In vivo and in vitro studies have demonstrated its antioxidant, antibacterial, anti-acne, and anti-aging properties, which led to a surge of CBD based cosmetics where it has been marketed as an analgesic, anti-wrinkle, skin brightener, and moisturizer with claims to alleviate pruritus, psoriasis, acne, and eczema (14–16).

Cannabigerol (CBG), a direct precursor to CBD and THC, is generally found in meagre quantities in cannabis extracts and, therefore, is often categorized as a minor cannabinoid. From receptor binding data, it appears CBG is more like THC at the CB1/CB2 receptors than CBD. Still, with a lower affinity (by a factor of between 5-fold and 27-fold) (17), CBG has been reported to increase been reported to possess anti-inflammatory, antioxidant properties and modulate differentiation in keratinocytes. Additionally, it has also been reported to increase lipogenesis in sebocytes. A 0.1% CBG serum applied topically reduces inflammation redness and significantly improves the skin barrier function compared to a placebo (18).

Therefore, it is not surprising that both CBD and CBG are accepted in the CosIng database. As of February 2021, CBD derived from extract or tincture or resing of Cannabis, synthetically produced, and cannabidiol trisiloxane is considered cosmetic ingredients. Table 2 provides a summary of the CosIng database (19).

Table 2: Cannabis Sativa L derived ingredients accepted in the CosIng Database (19)

Sr. No	INCI name	Description	CAS#	Functions
1	Cannabidiol-derived from extract or tincture or resin of cannabis		13956-29-1	Anti-sebum Antioxidant Skin Conditioning Skin Protecting
2	Cannabidiol – synthetically produced		13956-29-1	Anti-sebum Antioxidant Skin Conditioning Skin Protecting
3	Cannabidiol trisiloxane		2414491-99-7	Dispersing Non-Surfactant Film Forming
4	Cannabigerol		25654-31-3	Skin Conditioning
5	Hydrogenated Hemp Seed Oil	Hydrogenated hemp seed oil is the end-product of the controlled hydrogenation of Cannabis Sativa Seed Oil	-	Skin Conditioning Skin Conditioning – Emollient

Industrial hemp is mainly grown for fibre, and for this, harvesting is done at the flowering stage. Due to the growing knowledge of macronutrients and phytochemicals in hemp seed, hemp production for seed sources has recently gained much interest. The central hemp seed and hemp seed oil constituents are characterized in Table 3 below. Hemp seed oil is rich in tocopherols, which help repair the skin barrier and are potent emollients. Callaway et al. studied the benefits of hemp seed oil in patients with atopic dermatitis. They found that dietary hemp seed oil, compared to olive oil, significantly improved the symptoms in atopic patients (20).

Table 3: Important nutritional components of hemp seed and hemp seed oil (21)

Product	Compound	Content
Hemp seed	Carbohydrate	20–30 †
	Crude fat	25–35 †
	Crude protein	20–25 †
	Neutral detergent fiber	30-40 †
	Acid detergent fiber	23-29 †
	Ash	4.5-6†
Hemp seed oil	Cannabidiol (CBD)	10 ‡
	Linoleic acid (omega-6 PUFA)	52–62 §
	Alpha-linolenic acid (omega-3 PUFA)	12–23 §
	Beta-tocopherol	6 ‡
	Gamma-tocopherol	200-733 ‡
	Alpha-tocopherol	34 ‡
	Delta-tocopherol	12-25 ‡

†, % Hemp seed fresh weight; ‡, mg/kg Hemp seed oil; §, % Total fatty acids; ¶, % Hemp seed oil. PUFA, polyunsaturated fatty acid.

Conclusion

The cannabis market is emerging rapidly across the globe, and disruption in the nutraceutical, personal care, and wellness industry has been very organic. As a plant, cannabis and industrial have much more to offer than the hero ingredients identified today. Hemp is a sustainable resource for fibre, nutrients, and active ingredients such as tocopherols. Canada legalized the production and commercialization of medical and adult-use cannabis at a federal level in 2018. Since then, the Canadian Chamber of Commerce estimates it has “contributed over $17 billion to the Canadian economy annually, created thousands of direct jobs and tens of thousands of ancillary jobs” (22). We can genuinely influence regulatory agencies and contribute to the global economy's growth through scientific rigour and systematic studies.

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