

Review

Topical Use of *Cannabis sativa* L. Biochemicals

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Abstract: *Cannabis sativa* L. plant is currently attracting increasing interest in cosmetics and dermatology. In this review, the biologically active compounds of hemp are discussed. Particularly the complex interactions of cannabinoids with the endocannabinoid system of the skin to treat various conditions (such as acne, allergic contact dermatitis, melanoma, and psoriasis) with clinical data. Moreover, the properties of some cannabinoids make them candidates as cosmetic actives for certain skin types. Hemp seed oil and its minor bioactive compounds such as terpenes, flavonoids, carotenoids, and phytosterols are also discussed for their added value in cosmetic formulation.

Keywords: *Cannabis sativa*; cannabinoid; endocannabinoid topical; hemp seed oil

1. Introduction

It has already been 6000 years that humans use Cannabis as food, fiber, and medicine [1]. Nowadays, Cannabis has widely spread through the world [1]. It is a predominantly dioecious species, with only male flowers or female flowers [2]. This particularity opened the path to hybridization of the plant, and lead to thousands of cultivars [1]. There is a long taxonomic problem with the classification of the different strains [1]. It is generally accepted to divide the *Cannabis sativa* L. species into 3 subspecies: “Sativa” refers to strains with a limited amount of THC, “Indica” refers to strains producing principally THC, and “Ruderalis” refers to wild hemp strains [1].

The *Cannabis sativa* L. plant contains a diversity of bio-active compounds which are promising for topical application in dermatology [3] or as cosmetic ingredients [4,5]. Firstly, because of the high content of cannabinoids, which can modulate diverse inflammatory conditions and immune response via the endocannabinoid system [6]. Secondly, because of the Hemp Seed Oil, which has beneficial properties for the skin [7,8]. And thirdly, because of the diversity of minor bioactive active compounds such as terpenes, flavonoids, carotenoids, phytosterols [9–11].

Firstly, this review aims to gather knowledge about the various cannabinoids and their biological actions within and outside the endocannabinoid system. Secondly, to determine the added value of Hemp Seed Oil and its minor constituents compared to other oils for cosmetic formulations or dermatological use.

2. *Cannabis sativa* L. Botany

Cannabis sativa L. belongs to the Cannabaceae family. It is an annual herb [1]. The plant can reach a height higher than 5 m in the outdoor 6 months growing season, as shown in Figure 1a [12]. The leaves grow on opposite sides of the stem [13]. The leaves, stems, and bracts of the plants are covered by epidermal protuberances called trichomes [1]. There are two types of trichomes: glandular and non-glandular. The non-glandular trichomes are in the bracts, petioles, stipules, leaves, and stems and serve as a defense mechanism against abiotic and biotic stress. The glandular trichomes are responsible for the synthesis of cannabinoids, secondary metabolites, and terpenes in a viscous resin, as shown in Figure 1b [14]. When the days start to shorten, the inflorescence is triggered and buds of



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flowers develop. Male plants die after the inflorescence while the females remain until winter [1].

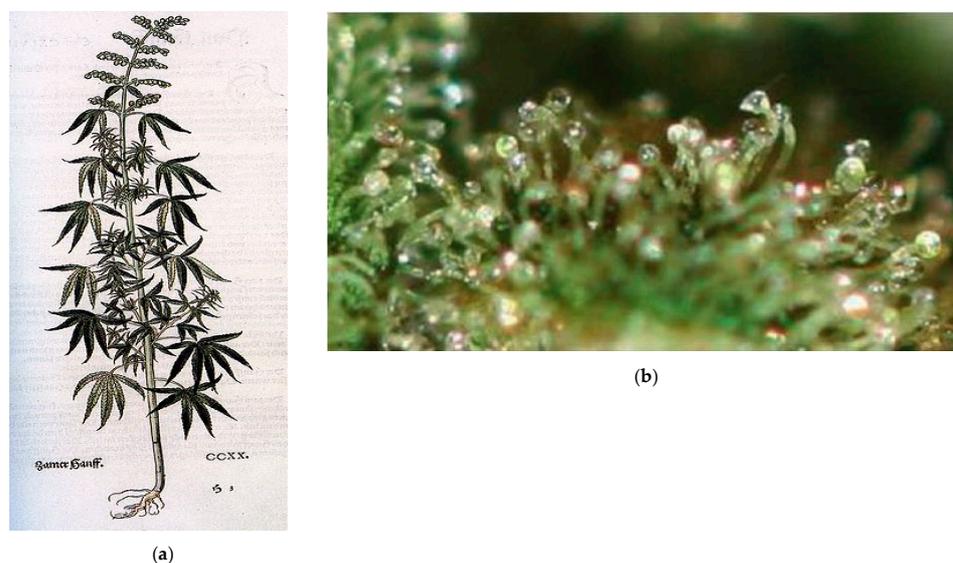


Figure 1. (a) Illustration of *Cannabis sativa* L. from Heinrich Füllmaurer, 1543 (b) *Cannabis sativa* L. glandular trichomes, photography by Ethan Budd Russo, reproduced by permission of Wiley-VHCA AG, Zurich, Switzerland [15].

3. The Endocannabinoid System

The endocannabinoid system (ECS), in the skin, is implied in cutaneous function such as cell differentiation modulation, growth and survival, inflammatory and immune responses, nociception, and hair growth. Indeed, dysregulation of the ECS seems to be involved in various skin disease conditions [16]. Two G protein-coupled receptors are involved in the ECS's regulation: cannabinoid type 1 receptor (CB1) and cannabinoid type 2 receptor (CB2) [17]. In the skin, CB1 is expressed in hair follicular cells, sensory neurons, immune cells, sebaceous glands, and keratinocytes while CB2 is expressed in sensory neurons, immune cells, sebaceous glands, and keratinocytes [18]. The CB1 main activity is the regulation of pain, of excessive neural activity and the extinction of evasive memories in the central nervous system [19]. It has been recently shown that CB1 regulate inflammatory response in various peripheral organs [20–22]. As for the skin, activation of CB1 downregulate the production of pro-inflammatory cytokine in keratinocytes, and protects the skin barrier [19]. Activation of CB2 has anti-inflammatory effects in skin; by inhibiting the macrophage 1 polarizations they downregulate pro-inflammatory cytokines [23]. The orphans G-coupled proteins receptors GPR55 and GPR18 can also be activated by some cannabinoids ligands [24–27]. Further studies are warranted to determine if GPR55 can be officially considered as a CB3 receptor or not. Depending on the target cell, GPR55 can have a pro-inflammatory or anti-inflammatory effects [27]. Nevertheless, its activation promotes human skin tumors and other squamous cell carcinomas [28]. GPR18 was revealed to have anti-inflammatory and anti-nociceptive activity in case of intestinal inflammation [29]. GPR18 is an active inhibitor of apoptosis in melanoma cells [30].

Two endogenous cannabinoids have been studied as the main natural ligands of the ECS, N-arachidonylethanolamine (AEA), and 2-arachidonoylglycerol (2-AG [31]. AEA is synthesized by phospholipase D, 2-AG is synthesized by diacylglycerol lipase (DAGL), their degradation is mainly controlled by fatty acid amide hydrolase (FAAH), and monoacylglycerol lipase (MAGL) [32]. Palmitoylethanolamide (PEA) is also an endogenous ligand that binds with GPR55 but not with CB1 nor CB2, it has synergistic activity with AEA. PEA is synthesized by *N*-acyl-phosphatidyl-ethanolamine-selective phospholipase D and its degradation is mainly controlled by FAAH and *N*-acylethanolamine-hydrolyzing

acid amidase (NAAA) [33]. The MAGL, FAAH, and NAAA inhibition has an antipruritic effect [34–36].

4. Secondary Cannabinoid Target

Some of the cannabinoids ligands modulate greatly the response of the ECS by the activation of various transient receptor potential ion channels (TRPV1, TRPV2, TRPV3, TRPV4, TRPA1, and TRPM8) [18], of peroxisome proliferator-activated receptor alpha and gamma (PPAR α ; PPAR γ) transcription factors [16], and of serotonin receptors (particularly 5-HT1A, 5-HT2A, and 5-HT3 receptors) [37]. TRP ion channels permit the transit of various cations in the cells when activated by specific ligands [38]. PPAR enables, upon activation by specific ligands, the proliferation of peroxisomes which regulate inflammatory response and lipid metabolism [39].

The sum of these factors may result in synergistic or antagonistic biological effects. Therefore, it is important to take them into account to predict the pharmacological or cosmetic activity of a cannabinoid ligand. The biodynamic effect of these secondary cannabinoid targets and their location in the skin are detailed in Table 1 and illustrated in Figure 2.

Table 1. Location and biodynamic effects of main secondary targets of cannabinoid ligands.

Type of Target	Name of Target	Cell	Biodynamic Effect upon Activation
Transient potential ion channel	TRPV1 [18,40–42]	Sweat glands, Sebaceous glands, Hair follicle, Keratinocytes, Nerve ending, Fibroblasts, Langerhans Cells	Pro-inflammatory activity in cases of psoriasis, atopic dermatitis [42], fungal infection, burn wound, and UVB wound Anti-inflammatory activity in case of allergic contact dermatitis, barrier tissue infection, and corneal wound
	TRPV2 [18,41,43]	Keratinocytes, Nerve ending, Fibroblasts, Langerhans Cells	Anti-inflammatory activity Reduces chronic pain Slows wound healing [43] Promotes epidermal differentiation and hair growth [18].
	TRPV3 [18,41,44–46]	Hair follicle, Keratinocytes, Nerve ending, Fibroblasts, Langerhans Cells	Pro-inflammatory activity in sebaceous glands and epidermal keratinocytes [44]. Pro-inflammatory activity in case of atopic dermatitis [46]. Repairs damaged skin
	TRPV4 [18,41,47,48]	Keratinocytes, Nerve ending, Fibroblasts, Langerhans Cells	Downregulates lipid synthesis Involved in the pathogenesis of scleroderma [48]
	TRPA1 [18,41,49]	Keratinocytes, Nerve ending, Fibroblasts, Langerhans Cells	Contributes to the pathogenesis of atopic dermatitis and allergic contact dermatitis itch Protective role against psoriasis
	TRPM8 [18,41,50]	Keratinocytes, Nerve ending, Fibroblasts, Langerhans Cells	Anti-inflammatory activity
Peroxisome proliferator-activated receptor transcription faction	PPAR α [51]	Keratinocytes, Langerhans Cells	Anti-inflammatory activity via NF κ -B ¹ pathway
	PPAR γ [52–55]	Hair follicle, Keratinocytes, Fibroblasts, Melanocytes	Anti-inflammatory activity via NF κ -B ¹ pathway [52] Modulates potential of fibrotic skin disease [53–55]
Serotonin receptor	5-HT1A [56–60]	Keratinocytes, Fibroblasts, Melanocytes	Promotes wound healing [59] Anti-inflammatory activity in psoriatic skin [56–58,60]
	5-HT2A [56,57,60]	Keratinocytes, Fibroblasts, Nerve ending, Melanocytes	Pro-inflammatory activity in psoriatic skin
	5-HT3 [57]	Basal keratinocytes	Mediates the pruritus reaction

¹ Nuclear factor kappa-B.

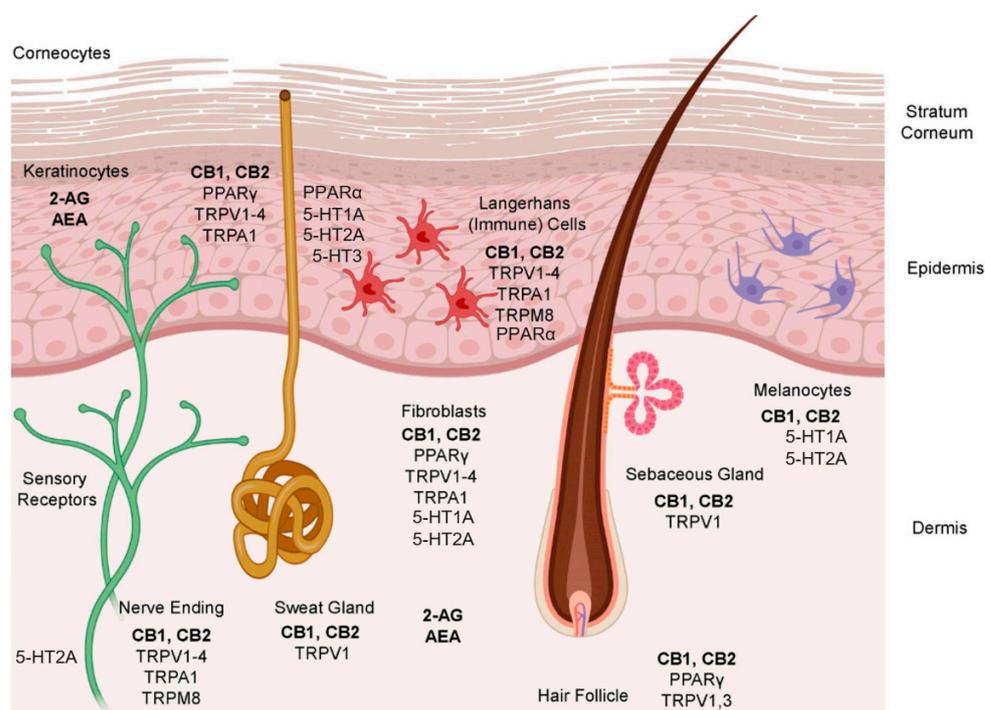


Figure 2. The repartition of CB1 and CB2, the TRPV1-4 channels, the TRPM8 channel, the PPARs transcription factors, and serotonin 5-HT1A, 5-HT2A, 5-HT3 receptors in skin cells, modified with the permission of Dove Medical Press, Macclesfield, United Kingdom [61].

5. Cannabinoids

The cannabinoids, which are synthesized in the glandular trichomes [2] of *Cannabis sativa* L. are exogenous ligands of the ECS [62]. Therefore, they can interact with endocannabinoid receptors and some of the channels and receptors described below [62].

To date, almost 200 cannabinoids have been identified, and a vast majority of them are from *Cannabis sativa* L. [63]. They are divided into 11 classes: Delta-9 Tetrahydrocannabinol (Δ^9 -THC) type, Cannabigerol (CBG) type, Cannabinol (CBN) type, Cannabichromene (CBC) type, Cannabitrinol (CBT) type, Cannabidiol (CBD) type, Delta-8 Tetrahydrocannabinol (Δ^8 -THC) type, Cannabielsoin (CBE) type, Cannabicyclol (CBL) type, Cannabinodiol (CBND) type, and miscellaneous type.

The biosynthesis of all these cannabinoids (see Figure 3) originates from Cannabigerolic Acid (CBGA) products by Geranyl Pyrophosphate (GPP) and Olivetolic Acid (OA) or Divarinic Acid (DA), catalyzed by the Cannabigerolic Acid Synthase (CBGAS) enzyme.

Delta-9 Tetrahydrocannabinol (Δ^9 -THC) is the principal cannabinoid from *Cannabis sativa* L. Cannabidiol (CBD) is the most abundant non-psychoactive cannabinoid derived from *Cannabis sativa* L. [1]. Δ^9 -THC, Δ^9 -THCA, Δ^9 -THCV, Δ^9 -THCVA, CBD, CBDA, CBDV, CBG, CBGA, CBGV, CBC, and CBN have been studied regarding their interaction with the ECS and the secondary cannabinoid targets. The data regarding these interactions is available in Table 2.

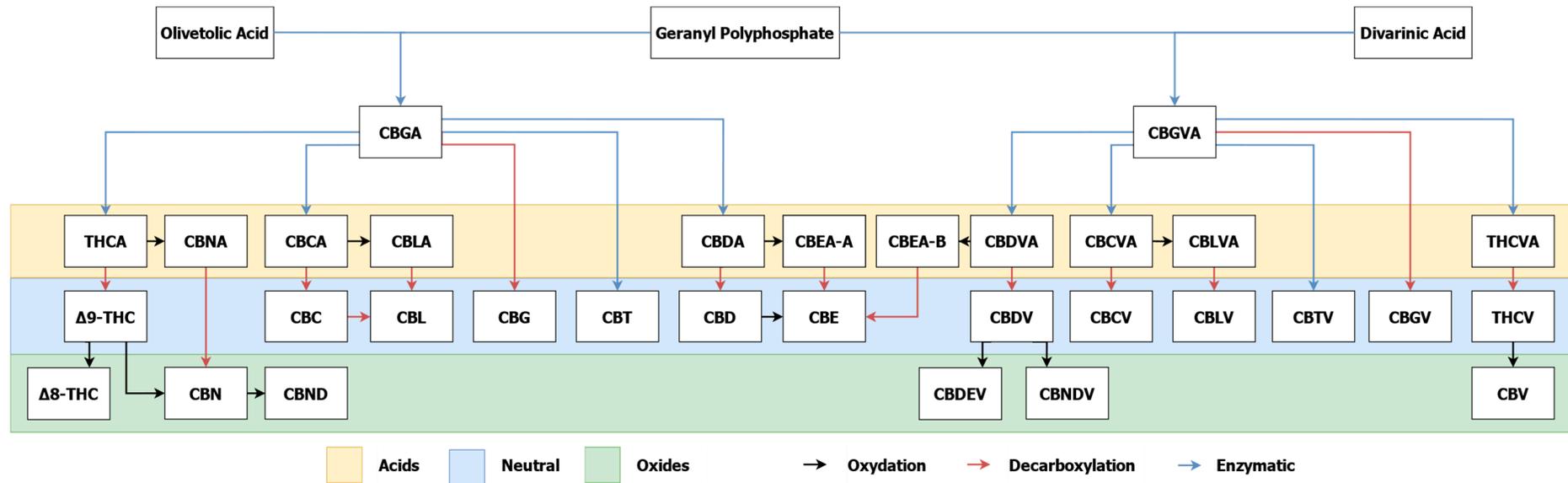


Figure 3. The Biosynthesis of most known cannabinoids [64–66], CBGA: cannabigerolic acid; CBGVA: cannabigerovarinic acid; THCA: tetrahydrocannabinolic acid; Δ 9-THC: delta-9 tetrahydrocannabinol; Δ 8-THC: delta-8 tetrahydrocannabinol; CBNA: cannabinolic acid; CBN: cannabinol; CBND: cannabiniol; CBCA: cannabichromenic acid; CBC: cannabichromene; CBLA: cannabicyclolic acid; CBL: cannabicyclol; CBG: cannabigerol; CBT: cannabitol; CBDA: cannabidiolic acid; CBD: cannabidiol; CBEA-A: cannabielsoin acid A; CBEA-B: cannabielsoin acid B; CBE: cannabielsoin; CBDVA: cannabidivarinic acid; CBDV: cannabidivarin; CBDEV: cannabidielsoinvarin; CBNDV: cannabivarinodiol; CBCVA: cannabichromevarinic acid; CBCV: cannabichromevarin; CBLVA: cannabicyclolvarinic acid; CBLV: cannabicyclolvarin; CBTV: cannabitolvarin; CBGV: cannabigerovarin; THCVA: tetrahydrocannabivarinic acid; THCv: tetrahydrocannabivarin; CBV: cannabivarin.

Table 2. Biodynamic effects of 12 cannabinoids.

Cannabinoid	Δ^9 -THC	Δ^9 -THCV	Δ^9 -THCA	Δ^9 -THCVA	CBD	CBDA	CBDV	CBG	CBGA	CBGV	CBC	CBN
CB1	PAG ¹ [67]	AN ³ [68]	AG ² [69]		NCAG ⁴ [70,71]	wAG ^{2,6} [72]	/ ⁹ [72]	wAG ^{2,6} [73]	/ ⁹ [74]	IAG ⁵ [74]	/ ⁹ [75]	PAG ¹ [76]
CB2	PAG ¹ [67]	PAG ¹ [68]	IAG ⁵ [69]		IAG ⁵ [70,71]	wAG ^{2,6} [68]	AG ² [68,74]	wPAG ^{1,6} [72,73]	/ ⁹ [74]	IAG ⁵ [74]	AG ² [75]	PAG ¹ [76]
GPR18	AG ² [77]				AN ³ [77]							AG ² [78]
GPR55 [79,80]	AN ³ [28]	wAG ^{2,6} [79]	wAG ^{2,6} [79]		wAN ^{3,6} [79,80]	wAN ^{3,6} [79]	PoAN ^{3,7} [79]	AN ³ [79]	PoAN ^{3,7} [79]	PoAN ^{3,7} [79]		AN ³ [78]
TRPV1 [81]	wAG ^{2,6}	PoAG ^{2,7}	wAG ^{2,6}	wAG ^{2,6}	PoAG ^{2,7}	wAG ^{2,6}	wAG ^{2,6}	AG ²	PoAG ^{2,7}	PoAG ^{2,7}	wAG ^{2,6}	wAG ^{2,6}
TRPV2 [81]	PoAG ^{2,7}	PoAG ^{2,7}	PoAG ^{2,7}	wAG ^{2,6}	AG ²	wAG ^{2,6}	AG ²	PoAG ^{2,7}	wAG ^{2,6}	PoAG ^{2,7}	wAG ^{2,6}	AG ²
TRPV3 [82]	wAG ^{2,6}	PoAG ^{2,7}	wAG ^{2,6}	wAG ^{2,6}	AG ²	wAG ^{2,6}	wAG ^{2,6}	wAG ^{2,6}	wAG ^{2,6}	wAG ^{2,6}	wAG ^{2,6}	wAG ^{2,6}
TRPV4 [82]	wAG ^{2,6}	PoAG ^{2,7}	wAG ^{2,6}	wAG ^{2,6}	wAG ^{2,6}	wAG ^{2,6}	AG ²	wAG ^{2,6}	AG ²	wAG ^{2,6}	wAG ^{2,6}	wAG ^{2,6}
TRPA1 [81]	AG ²	wAG ^{2,6}	wAG ^{2,6}	wAG ^{2,6}	PoAG ^{2,7}	AG ²	AG ²	AG ²	wAG ^{2,6}	AG ²	PoAG ^{2,7}	PoAG ^{2,7}
TRPM8 [81]	PoAN ^{3,7}	AN ³	PoAN ^{3,7}	AN ³	PoAN ^{3,7}	AN ³	AN ³	AN ³	AN ³	AN ³	AG ²	PoAN ^{3,7}
PPAR α	AG ² [83]		/ ⁹ [84]		/ ⁹ [85]	PAG ¹ [85]		PAG ¹ [85]	AG ² [85]			
PPAR γ [83,85]	AG ² [83,86]	/ ⁹ [83]	PAG ¹ [69,83]		AG ² [86,87]	PAG ¹ [85,88]		PAG ¹ [73,85]	PAG ¹ [85]		wAG ^{2,6} [86]	
5-HT1A	/ ⁹ [89]	AG ² [90]			AG ² [76]	AG ² [91–93]		PoAN ^{3,7} [73]				
5-HT2A	/ ⁹ [94]				PAG ¹ [76]							
5HT3	AN ³ [76,95]				AN ³ [76]							
MAGL [81]		IN ⁸	PoIN ^{7,8}	IN ⁸	/ ⁹	IN ⁸	/ ⁹	PoIN ^{7,8}	IN ⁸	wIN ^{6,8}	PoIN ⁸	PoIN ⁸
NAAA [81]		wIN ^{6,8}	IN ⁸	wIN ^{6,8}	IN ⁸	PoIN ^{7,8}	IN ⁸	wIN ^{6,8}	PoIN ^{7,8}	PoIN ^{7,8}	IN ⁸	IN ⁸
FAAH [81]		wIN ^{6,8}	PoIN ^{7,8}	wIN ^{6,8}	PoIN ^{7,8}	PoIN ^{7,8}	IN ⁸	IN ⁸	PoIN ^{7,8}	PoIN ^{7,8}	IN ⁸	IN ⁸

¹ Partial agonist; ² Agonist; ³ Antagonist; ⁴ Non-competitive agonist; ⁵ Inverse agonist; ⁶ weak; ⁷ Potent; ⁸ Inhibitor; ⁹ No activation.

Moreover, some cannabinoids have specific particularities regarding their biodynamic activity regarding the skin.

CBD and CBG are transcriptional repressors that can control cell differentiation and proliferation in the skin [96]. CBD induces nuclear export and degradation of BACH1, reducing stress oxidation and skin aging [61,97]. CBG is an agonist of α 2-adrenoceptor [73,98], it inhibits the endocannabinoid membrane transporter [50,79,82]. CBC is the most potent agonist of the TRPA1 channel [81,82,99]. CBDV is a partial agonist of dopamine D2-like receptors [100]. It has been shown recently that D2-like receptor agonism in the skin, promotes the recovery of the skin barrier and wound healing [101–103].

Some of these phytocannabinoids (mainly THC and CBD) have been tested as a treatment against various skin conditions (see Table 3).

Table 3. Clinical evidence of the therapeutical potential of various cannabinoids.

Disease	Phytocannabinoid	Model	Outcome	Reference
Acne	THC and CBD	In vivo (mouse)	Inhibition of cyclooxygenase and lipoxygenase	[104]
	CBD	In vitro (human sebocytes)	Inhibition of pro-inflammatory p65 NF- κ B ¹ pathway	[70]
	THCV CBC, CBDV CBG, CBGV	In vitro (human sebocytes)	THCV suppresses sebocytes proliferation, arachidonic acid-induced seborrhoea lipogenesis, and has a strong anti-inflammatory action. CBC, CBDV suppresses arachidonic acid-induced seborrhoea lipogenesis. CBG and CBGV increase the sebaceous lipid production (pro-lipogenic and pro-acne effect).	[105]
	BTX 1503 (CBD)	Phase 2 successfully ended (5 dose groups, 368 subjects)	40% reduction of lesions after 12 weeks	[106]
Allergic Contact Dermatitis	CBD	In vitro (HaCaT cells)	Suppresses inflammatory reaction by the inhibition of MCP2 ² , IL-6 ³ , IL-8 ³ , and TNF- α ⁴	[107]
	CBD	In vitro (Splenocytes)	Suppresses inflammatory reaction by the inhibition of IL-6 ³ , IL-8 ³ , IL-17 ³ , TNF- α ⁴ , and IFN- γ ⁵ . Inhibition of T-cells and B-cells mediated response	[108]
	THC	In vivo (CBR-deficient mouse)	Suppresses inflammatory reaction by the inhibition of IFN- γ ⁵ , MCP1 ² , MCP2 ² , and IP-10 ⁶ .	[109]
Kaposi Sarcoma	CBD	In vitro (infected endothelial cells)	Induction of apoptosis by the reduction of GRO- α ⁷ , the inhibition of vGPCR ⁸ , and by the reduction of VEGF-C ⁹ and VEGFR-3 ¹⁰	[110]
Melanoma	THC THC and CBD (Sativex)	In vitro (melanoma cells) and in vivo (mouse)	Reduction in tumor size with THC+CBD more effective than THC alone	[111]
	THC	In vivo (mouse)	Inhibition of melanoma growth	[112]
	CBD	In vivo (mouse)	Reduction in tumor size	[113]
Psoriasis	THC and CBD	In vitro (human-skin keratinocytes)	Inhibition of keratinocytes proliferation	[114]
	CBD and CBG	Human trial (2 subjects)	16–33% reduction of lesions after 6 weeks	[115]

¹ Nuclear factor kappa-B; ² Monocyte chemotactic protein; ³ Interleukin; ⁴ Tumor necrosis factor alpha; ⁵ Interferon gamma; ⁶ interferon gamma-induced protein 10; ⁷ Growth-regulated oncogene alpha; ⁸ v G-protein coupled receptor; ⁹ Vascular endothelial growth factor C; ¹⁰ Vascular endothelial growth receptor 3.

Cannabinoids exhibit frequently antioxidant, antimicrobial activity, and less frequently a photoprotectant (see Table 4).

Table 4. Antioxidant, antibacterial and photoprotectant activity of various phytocannabinoids.

Cannabinoid	Δ^9 -THC	Δ^9 -THCV	Δ^9 -THCA	Δ^9 -THCVA	CBD	CBDA	CBDV	CBG	CBGA	CBGV	CBC	CBN
Antioxidant activity	+ [62]	+ [116]	+ [62]	+ [116]	+ [62,117]	+ [62,118]	+ [116]	+ [62]	+ [62]			+ [62]
Antibacterial gram-positive activity	+ [61,119,120]	+ [116,120]	+ [121]	+ [116]	+ [61,119,120]	+ [121]	+ [116,120]	+ [61,119,120]	+ [122]	+ [120]	+ [119–121]	+ [61,119]
Photoprotectant activity	– [123]				+ (UVA) [123]			+ (UVA) [123]			+ (UVB) [123]	+ (UVB) [123]

Because of its wide range of effects, formulation technologies are being developed to ensure better topical delivery of CBD for medical and cosmetic use [124–128].

6. Hemp Seed Oil

6.1. Generalities

Hemp Seed Oil is extracted from the seeds by cold-pressed extraction or supercritical CO₂ for better stability [129]. It represents about 30% of the raw material [130]. The cultivars employed and the growth condition of the plant directly impact the composition of the oil. The oil contains linoleic acid (55.41–59.64%), α -linoleic acid (16.51–20.40%), oleic acid (11.40–15.88%), palmitic acid (6.08–6.82%), and stearic acid (2.34–2.67%) [8]. Furthermore 25–35% of the oil weight are proteins, 10–15% are fibers, and 20–30% are carbohydrates [131]. Certain strains also contain up to 4% of γ -linoleic acid [129]. Sometimes, Hemp Seed Oil can also be classified by saturated, monounsaturated, and poly-unsaturated acids or by omega-3, omega-6, omega-9 acids composition:

- 80.0% poly-unsaturated acids, 10.8% monounsaturated acids, and 9.2% saturated acids [132].
- 59.6% omega-6 acids, 29.7% of omega-3 acids, and 10.8% omega-9 acids [132].

Hemp Seed Oil, as an oil rich in essential fatty acids (ELA), has an action on atopic dermatitis, psoriasis, and particularly acne. Many studies find conflicting results, which indicates that the actions of ELA are dose-dependant and length-dependant [133]. Both α -linolenic acid and linoleic acids reduce UV damage and hyperpigmentation [134]. Clinical evidence highlights the positive hydrating and anti-aging effect of essential fatty acids on the skin for oral use [135]. A favorable portion of fatty acids in Hemp Seed Oil improves the gliding of a skin care cream and the smoothness of the skin [4,136]. Moreover, Hemp Seed Oil is a non-comedogenic [137] dry oil that does not leave a greasy and sticky layer on the skin [137]. As a result, formulations have been developed with Hemp Seed Oil as long-term moisturizing patches [138] and stable emulsions in sunscreen cosmetics [5,136]. Hemp Seed Oil's global antioxidant activity can be measured by 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) test [130]. DPPH leads to 60–65% scavenging activity and ABTS leads to 40–88% scavenging activity [130,132].

Hemp Seed Oil extraction leads to byproducts of seed paste which can be recycled as a dermo-cosmetic agent by use of eco-friendly processes: Ultrasound-Assisted Extraction or Supercritical Fluid Extraction. These pastes contain 14 bioactive metabolites: seven cannabinoid acid derivatives, four lignamides, two amides, and a phenolic acid. The paste showed more than 80% of inhibition for the collagenase enzyme. The global antioxidant activity was measured by DPPH; it is up to 50% of radical scavenging [9].

6.2. Biological Value of the Minor Compounds of Hemp Seed Oil

6.2.1. Essential Fatty Acids

Linoleic acid, α -linoleic acid and γ -linoleic acid are considered ELA. These compounds are required for the wealth being but not synthesized by our body [139]. Because of the competition of omega-6 and omega-3 family acids for the Δ -6 desaturase enzyme, the ratio of their consumption is important. Hemp Seed Oil fits perfectly in the (ω -6/ ω -3) ideal ratio which is between 2:1 to 3:1 this ratio [140].

Linoleic acid is involved in the biosynthesis of leukotrienes, endocannabinoids, and arachidonic acid which is the main precursor of prostaglandins. Linoleic acid is also engaged in β -oxidation in the sebaceous gland to synthesize squalene and wax esters. When skin's linoleic acid levels are low, epidermal barrier function is impaired, the comedone wall becomes permeable to inflammatory substances, resulting in a comedogenic effect [134,141].

α -linoleic acid is a compound in cell and mitochondrial membranes that modifies cell transport and signaling through the lipid layers. The α -linolenic acid metabolites permit the synthesis of the anti-inflammatory prostaglandin and leukotriene [134]. Therefore, α -linoleic acid is involved in barrier function maintenance, the stratum corneum maturation and differentiation, lamellar body formation, lipoxygenase, and pro-inflammatory eicosanoid inhibition, cytokine suppression, inhibition of mast cell degranulation, and modulation of other immune cells [133].

The γ -linoleic acid decreases the production of pro-inflammatory leukotriene B4 by increasing the concentration of dihomogamma-linoleic acid in the skin [142].

6.2.2. Carotenoids

Hemp Seed Oil contains carotenoids, particularly β -carotene, lutein, and zeaxanthin [7,143]. These carotenoids exhibit antioxidant and UV-filtering properties because of their high solubility in the lipid bilayer membrane [144]. Therefore, β -carotene inhibits the UVB-induced upregulation of pro-inflammatory cytokines, resulting in an anti-inflammatory action [145,146]. Carotenoids improve skin hydration, promote skin regeneration, and stimulate fibroblasts to produce collagen and elastin [137].

6.2.3. Tocopherols

Hemp Seed Oil contains α -tocopherol, β -tocopherol, δ -tocopherol, γ tocopherol [130,147]. γ -tocopherol is the principal isomer with 85-91% of the tocopherols [143]. It is the main antioxidant of the Hemp Seed Oil and is responsible for most of the global antioxidant and anti-aging activities [7].

6.2.4. Phytosterols

Hemp Seed Oil contains phytosterols that inhibit the matrix metalloproteinases. The matrix metalloproteinase action inhibits COL1A1 and COL1A2 genes responsible for collagen synthesis. Therefore phytosterols permit better collagen synthesis and prevent skin aging [148].

6.2.5. Chlorophyll

Chlorophyll is surprisingly high in Hemp Seed Oil, it varies between 100 μ g/g to 230 μ g/g, depending on the extraction method, which is 11 times higher than in Flax Seed Oil and 88 times higher than in Canola Oil [143]. This component is responsible for the green color of the Hemp Seed Oil. The chlorophyll has beneficial action for wound-healing by promoting tissue growth, and by its antibacterial activity [149]. Therefore, it is an interesting ingredient in topical application against acne [150,151], eczema, and ulcers [152].

6.2.6. Flavonoids

There are 26 flavonoids in Hemp. Orientin, vitexin, luteolin-7-O-glucoside, and apigenin-7-O-glucoside are the main flavonoids in Hemp [153]. It also contains Quercetin

which exerts a strong antioxidant effect [154]. There are 3 new flavonoids exclusive to Cannabis called Cannflavins (Cannflavin A, Cannflavin B, and Cannflavin C). Cannflavins are present in the leaves and the flower of Hemp [11]. Cannflavin A's anti-inflammatory activity is 30 times stronger than Aspirin [155]. This anti-inflammatory effect is explained by the inhibition of the molecular targets microsomal prostaglandin E synthase-1 (mPGES-1) and 5-lipoxygenase (5-LO) [156].

6.2.7. Terpenes

More than 200 terpenes have been identified in *Cannabis sativa* L. [10]. Terpenes are responsible for the aromatic properties of the plant [157]. Terpenes are secreted and stored inside the glandular trichomes with cannabinoids [158]. The most concentrated terpenes in Cannabis are α -pinene, β -pinene, α -humulene, β -caryophyllene, β -myrcene, limonene, and linalool. Each strain conducts to different chemotypes of terpenes, a strain rarely contains more than 50 terpenes [10,157–160]. All these compounds have a biodynamic effect [161] (see Table 5.), but β -caryophyllene has the particularity to bind specifically with the CB2.

Table 5. Biodynamic effect of the main terpenes found in *Cannabis sativa* L.

Terpene	Biodynamic Effect
β -caryophyllene	Anti-viral, antioxidant, anti-inflammatory, anticancerogenic, analgesic, anxiolytic, antibacterial, antifungal, antiproliferation, antidepressant, neuroprotective and gastroprotective [161]
β -myrcene	Antioxidant, anti-inflammatory, anticancerogenic, analgesic, sedative, muscle relaxant and antipsychotic [161]
α -pinene	Anti-inflammatory, antibacterial, bronchodilator, antiseptic and gastroprotective [161]
β -pinene	Antiseptic [161]
α -humulene	Anti-inflammatory, anticancerogenic, antifungal and analgesic [161]
limonene	Antibacterial, antifungal, antimicrobial, antiproliferative, anxiolytic, antidepressant, antispasmodic and gastroprotective [161]
linalool	Antineoplastic, antiepileptic, anticonvulsant, sedative, anxiolytic, antipsychotic, analgesic, antidepressant and anesthetic [161]

6.3. The Entourage Effect

The term «entourage effect» refers to the capacity of two or more cannabinoids or non-cannabinoids to have a better combined synergistic effect than when taken separately [162]. The concept was introduced in 1998 by Mechoulam [163].

Studies consider 4 types of synergies: multi-target effects (each component affects multiple targets), pharmacokinetic effects (components can increase the solubility or the re-sorption rate of an active), agent interactions affecting bacterial resistance, and modulation of adverse effects and toxicity [164].

The THC and CBD 1:1 combination is the most known case of entourage effect: it alleviates the adverse effects of pure THC [162].

Currently, evidence in favor of an entourage effect of Terpenes or Flavonoids combined with THC is contradictory, further studies are warranted to determine to which extent this concept is relevant [165,166].

7. Conclusions

The cannabinoids contained in *Cannabis sativa* L. are of dermatological interest for treating most inflammatory skin conditions as well as skin cancer. We now have a better understanding of the endocannabinoid system of the skin and the possible mode of action of cannabinoids. However, the focus of research remains on CBD and THC, which

have demonstrated therapeutic value, but at the expense of studying the action of other cannabinoids.

As for their use in cosmetics, CBD, CBC, THCV and CBDV have potential for formulations for acne-prone skin, while CBG and CBGV are promising for regulating sebum production in dry skin. CBN and CBD also appear to be of interest for sunscreens. Almost all cannabinoids have an antibacterial and antioxidant action which is a good added value. Moreover, the immunoregulatory effects of cannabinoids seem interesting for sensitive skin. It should be noted, however, that their safety for regular use has not yet been demonstrated, apart from CBD. Further studies are warranted in this regard.

Hemp Seed Oil is interesting because of its content of flavonoids, terpenes, carotenoids and phytosterols which ensure its anti-inflammatory and anti-aging action. In addition, its ω -6/ ω -3 content is ideal for the skin. It is a rapidly absorbed and non-comedogenic oil. It naturally contains tocopherol and chlorophyll. This oil is therefore of interest for formulations for all skin types, especially sensitive skin, and as a sun cream. It has potential for anti-ageing formulations.

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