Contribution to the discussion on CBD

Cannabidiol (CBD) has been a subject of research and investigation in the medicinal field and other sectors for several years and products with medicinal use such has the treatment of epilepsy and seizure have reached the market. Nowadays the possibilities have reached the food supplements and cosmetic products.

Summary

The view will show that CBD can be topically administered and, with adequate formulations, reach the blood flow and have potential therapeutic effects.

Regulatory perspective

The use of any substance extracted from Cannabis sativa is banned with the Regulation 1223/2009 Annex II number 306. CANNABINOIDS, as such, are not listed in the Schedules of the 1961 Single Convention on Narcotic Drugs. However, these shall be prohibited from use in cosmetic products (II/306), if prepared from a substance controlled in Schedule I of the 1961 Single Convention on Narcotic Drugs[i].

The schedule I, published in 1961, explicit refers in entry 14 *"Cannabis and cannabis resin and extracts and tinctures of cannabis"* .

From a regulatory perspective, in the frame of the Cosmetics European Regulation nº1223/2019 (CPR), there is no doubt that any extract from Cannabis and cannabis resin or tinctures are substances banned from the use in cosmetics.

If the classification is questioned, products that due to their presentation mode of action or properties may fall into the Medicines or Medical Device regulations, should be classified under the regulation that has stricter rules for the risk evaluation and product authorization.

Regulatory uncertainty

The 1961 convention deals with cannabis extracts tinctures but if these molecules were obtained by organic chemistry, chemical synthesis, they would not be banned per se but they must endure the safety assessment.

There are substances that are listed in COSING / European Glossary of ingredients that are extracted from cannabis sativa and do not have a link to annex II.

There are products manufactured in other regions where the CPR does not apply that seek to reach the European market.

Administration of CBD. Studies performed in the skin

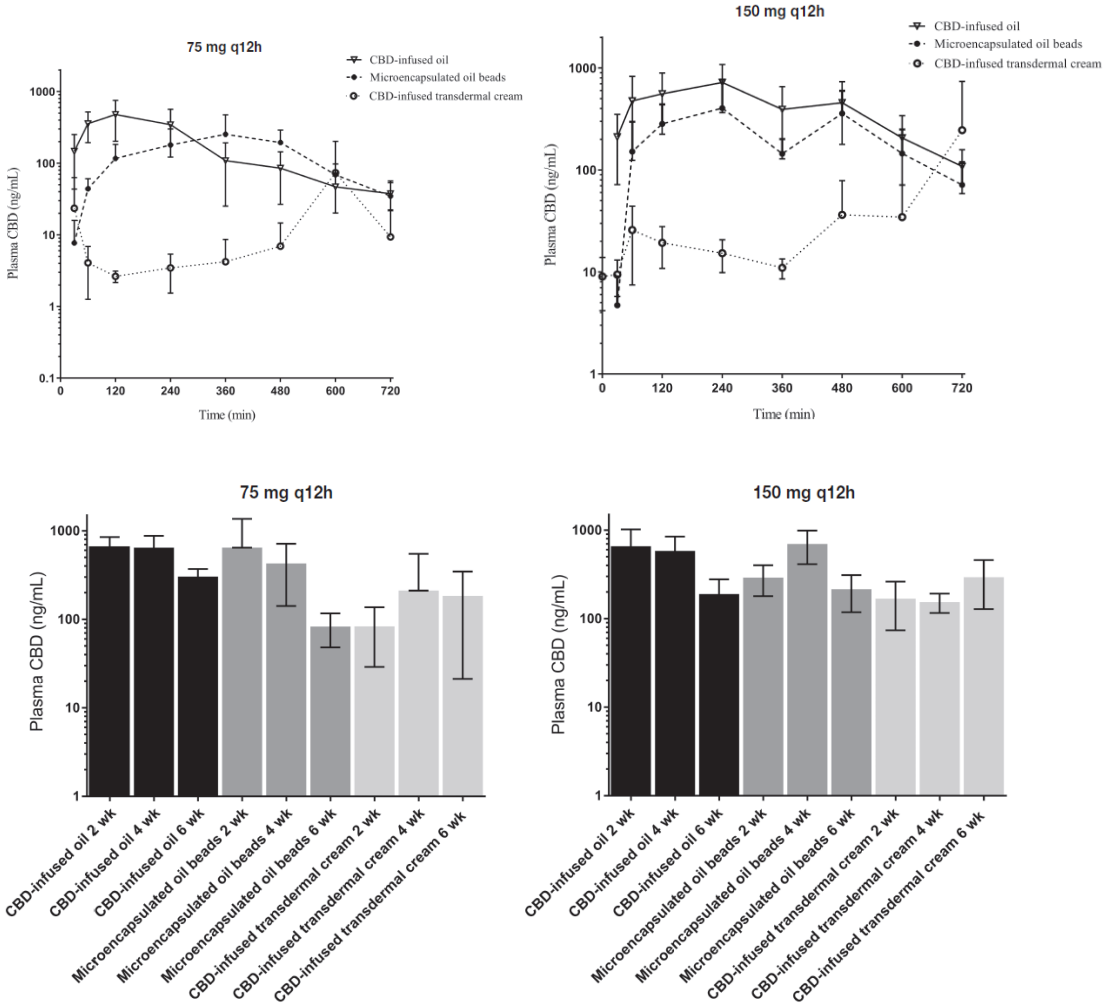
Since CBD is highly lipophilic, it accumulates within the stratum corneum of human and rodent skin and does not easily penetrate deeper skin layers.

The absorption of CBD was studied using beagle dogs. Authors compared the administration of: i) a single dose of CBD result in measurable blood levels within 12 h; ii) daily administration of CBD and topical formulations for CBD delivery may have higher blood levels because of the elimination of the hepatic first-pass effect.

Table I. Dosing regimen for CBD administered to healthy beagle dogs.

Group (5 dogs/group)	Delivery method	Approximate dose (mg/kg body weight per day)	Dose (mg q12h)
1a	CBD-infused transdermal cream	10	75
1b	CBD-infused transdermal cream	20	150
2a	Microencapsulated oil beads	10	75
2b	Microencapsulated oil beads	20	150
3a	CBD-infused oil	10	75
3b	CBD-infused oil	20	150

The plasma concentration found were:



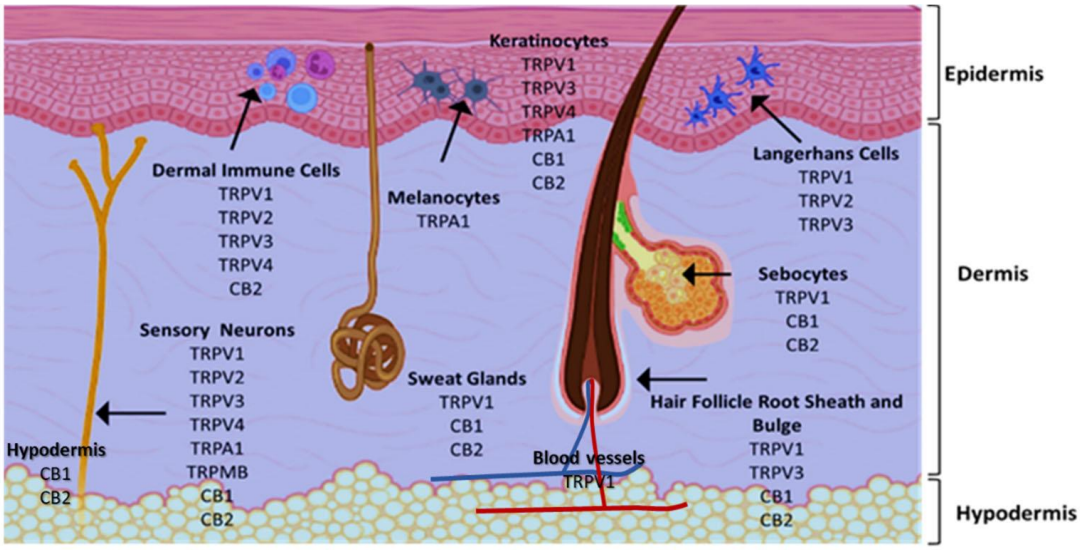
Although bioavailability could not be determined in this cohort of dogs, authors demonstrated that the CBD-infused transdermal cream did not reach similar plasma concentrations as the other 2 formulations. In general, transdermal absorption may be incomplete because of

diffusion barriers, such as thickness of the skin of the pinnae or absorptivity of the CBD-infused transdermal cream. Since CBD is highly lipophilic, it accumulates within the stratum corneum of human and rodent skin and does not penetrate deeper skin layers

The administration of cannabinoids through the skin has been reviewed[ii]. the authors show that the topical and transdermal products usually have a higher bioavailability rate with a prolonged steady-state plasma concentration. Additionally, these administrations have the potential to eliminate the psychotropic impacts of the drug by its diffusion into a nonreactive, dead stratum corneum.
This modality avoids oral administration and, thus, the first-pass metabolism, leading to constant cannabinoid plasma levels.

Several solutions have been developed for oral, nasal-inhalation, intranasal, mucosal (sublingual and buccal), transcutaneous (transdermal), local (topical), and parenteral routes of drug delivery. The interest of topical administered CBD is due to the anti-inflammatory and immunosuppressive (psoriasis, atopic dermatitis, and abrasions).
Another review published by Yeroushalmi to investigate the willingness of dermatologists to recommend medical cannabis, and 75% of dermatologists recommended topical formulations [iii]. This route is likely preferred due to its convenience, without the concerns of the psychoactive impacts of systemic absorption, as well as the high safety profile of topical administration routes.

Cannabinoid's Receptors and effects
The medicinal and psychoactive effects of phytocannabinoids are mediated via the endocannabinoid system (ECS) present in all tissues.
In health and disease, the ECS involves several regulatory mechanisms via G protein-linked receptor-mediated signalling pathways. The two famous subtypes of G protein-coupled receptors (GPCRs) are CB1, which is mainly expressed in the nervous and immunological systems, and CB2, which is incorporated in cytokine release in immune cells.Most investigations show that D9-THC has an affinity to cannabinoid receptor (CBR)-dependent pathways (CB1 and CB2 receptors); on the other hand, non-psychoactive cannabinoids, such as CBD, regulate the activity of other deorphan and orphan G protein receptors (GPCRs) and non-GPCRs.
Cannabinoids are lipophilic agents that bind to previously mentioned endocannabinoid receptors that regulate numerous signalling pathways in many tissues and organs, including skin, blood vessels, immune cells, lungs, liver, and the brain for the re-establishment of homeostasis following multiple disorders [25,39], for instance, pain and inflammatory management, Alzheimer's disease, and cancer.



The endocannabinoid system of the skin

The expression of all the receptors makes the skin a tremendous potential target to deliver phytocannabinoids to treat a multitude of dermatological diseases affecting human health, e.g., eczematous eruptions, acne and seborrhoea, fibrotic skin disease, psoriasis, and skin cancer. In terms of skin cancer, several key signalling pathways and cellular processes crucial to tumour development are targeted by endogenous cannabinoids and phytocannabinoids. The presence of cannabinoid receptors in various skin cells show the value of the multiple efforts made to formulate cannabinoids to take advantage of this high potential route of delivery, due to its large surface area (nearly 20 square feet) to manage some dermatological conditions.
Moreover, by improving cannabinoid permeability through the skin into deeper layers and into blood circulation may result in the sustained delivery of Phyto cannabinoids to targeted organs and tissues.

Studies on cutaneous delivery of cannabinoids.

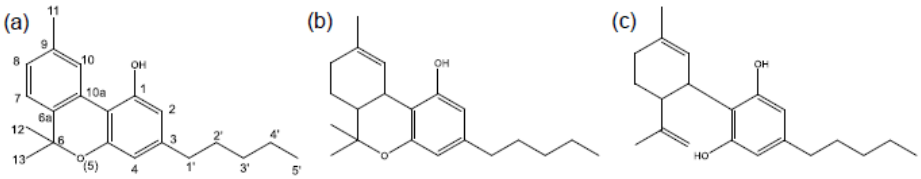
Active substance	Formulation	Concentrate	Applications	Result	
Cannabidiol (CBD)	Ointment		Inflammatory skin Diseases and cutaneous scars (psoriasis, atopic dermatitis, scars)	Improved skin parameters as: hydration, transepidermal water loss, and elasticity in humans	[iv]
Cannabidiol (CBD)	Hydroalcoholic proprietary gel	2.5g CBD/100 g gel permeation enhancer Transcutol HP	The prevention of relapse to drug use (alcohol or cocaine)	CBD has potential in relapse prevention in the rat model	[v]
Cannabidiol (CBD)	Gel	6.2 and 62 mg/day	Inflammation and pain	Reduction of proinflammatory markers, joint swelling, and immune infiltration in rat model of arthritis	[vi]
Cannabidiol (CBD)	Gel	The 1%, 2.5%, and 5% (w/w) CBD gels	Alcohol-induced neurodegeneration	Neuroprotection and reduction of alcohol-induced neurodegeneration in rodent models	[vii]

Cannabidiol (CBD)	Topical CBD (oil, cream, spray)		Epidermolysis bullosa	Decrease in pain and blistering; fast wound healing; no effects reported	viii
Cannabidiol (CBD)	Emulsions stabilized with chitosan/collagen peptides nanoparticles	0.6 g CBD in olive oil and liquid paraffin mixture to make 6 mg/mL	Cosmetic purposes	Effective penetration of nanoparticles through deeper skinlayers	ix
Cannabidiol (CBD)	Microemulgel	1% w/w CBD Solutol HS 15 (20%, surfactant), Transcutol P (9%, cosolvent), isopropyl myristate (5%, oil phase), water (66%)	Skin diseases	Highly stable formulation, controlled drug release, retention in the skin layers	x
Cannabidiol (CBD)	Topical CBD (oil, cream, and spray)		Epidermolysis bullosa	Decrease in pain and blistering; fast wound healing; no effects reported	xi
Cannabidiol (CBD)	Cream	CBD-infused oil (75 mg/mL or 150 mg/mL)	Pharmacokinetics	Probable incomplete Transdermal absorption in healthy dogs	xii

Action of cannabinoids

The pharmacology of cannabidiol is complex. A review published recently by Hustis[xiii], refers that, despite the non-intoxicating profile of cannabidiol, CBD is not risk free and there are topical administration and permeation.

If CBD is transdermal administered, it may enter the circulation and might endure a conversion process described. The conversion of Conversion of Cannabidiol (CBD) into Psychotropic Cannabinoids including Tetrahydrocannabinol (THC) has been reviewed by Patricial Golombek[xiv]



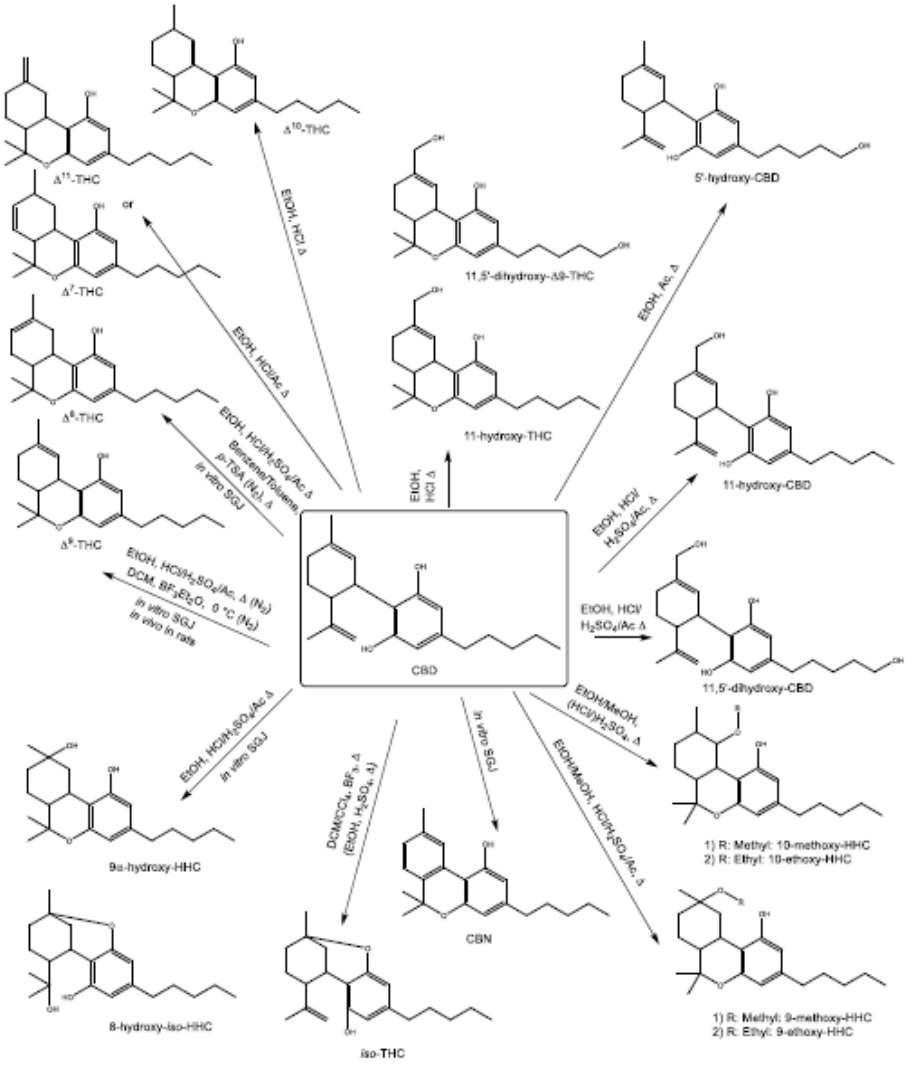
Chemical structures of (**a**) cannabinol (CBN) including the numbering system, (**b**) D9-tetrahydrocannabinol (D9-THC) and (**c**) cannabidiol (CBD).

Regarding the consumer safety of these OTC products, the question whether or not CBD might be degraded into psychotropic cannabinoids, most prominently tetrahydrocannabinol (THC), under in vivo conditions initiated an ongoing scientific debate.

Besides $\triangle^9$-THC, the non-psychotropic cannabidiol (CBD, figure c) gained increasing popularity due to a broad spectrum of health-promoting effects ascribed to it with the publication of several reviews on safety and efficacy. In recent years, this culminated in extensive consumer interest with heavily increasing numbers starting in 2018. Since then, so-called CBD extracts

used as a food constituent, in cosmetic products or in the liquids for electronic cigarettes are found with a large variety in drug stores or in online shops.
Controversial is installed around these molecules and the cosmetics industry has replaced several molecules due to a potential CMR effect of the substances via the oral route.

CBD is a molecule with a potential pharmacological effect and this molecule, if administered topically without a prescription of surveillance might diffuse across the blood brain barrier and be converted into a potentially and eventually dangerous derivative.



Overview of various chemical conversions of cannabidiol (CBD) to different conversion products and the respective conditions, which are reported in the literature

Reflections on the topical administration of CBD

In the medicinal perspective, there are several advantages of cannabinoids topical/transdermal administration: It is preferred administration route for dermatologists and patients; Despite the evidence that aqueous layers of the skin's tissue beneath the stratum corneum present a rate-limiting step for hydrophobic cannabinoid diffusion there are also nano-systems for topical delivery including micellar, liposomal, microemulgel and nano-emulsions; these administration

strategies enhance the permeation improving the delivery of cannabinoids despite their high lipophilicity and low bioavailability features.
This conclusion shows a promising potential in the transdermal delivery of cannabinoids to enhance their bioavailability, safety, stability, efficacy, and also to avoid the fluctuation of plasma cannabinoid concentrations during the treatment period.

On the other hand, these formulations potentiate the problems and drawbacks in the administration of CBD in the cosmetic field, making these molecules pharmacologically more effective but potentially much more dangerous.

In addition to the regulatory restriction already mentioned, the use of these substances should be discussed and the SCCS consulted.

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[i] https://www.unodc.org/unodc/en/treaties/single-convention.html

[ii] Mahmoudinoodezh, H. et al., The Transdermal Delivery of Therapeutic Cannabinoids. Pharmaceutics 2022, 14, 438. https://doi.org/10.3390/pharmaceutics14020438

[iii] Yeroushalmi, S.; Perceptions and recommendation behaviors of dermatologists for medical cannabis: A pilot survey, Complement. Ther. Med. 2020, 55. https://doi.org/10.1016/j.ctim.2020.102552

[iv] Palmieri, B.; Laurino, C.; Vadalà, M. A therapeutic effect of cbd-enriched ointment in inflammatory skin diseases and cutaneous scars. Clin. Ter. 2019, 170, e93–e99.

[v] Gonzalez-Cuevas, G.; Martin-Fardon, R.; Kerr, T.M.; Stouffer, D.G.; Parsons, L.H.; Hammell, D.C.; Banks, S.L.; Stinchcomb, A.L.; Weiss, F. Unique treatment potential of cannabidiol for the prevention of relapse to drug use: Preclinical proof of principle. Neuropsychopharmacology 2018, 43, 2036–2045.

[vi] Hammell, D.; Zhang, L.; Ma, F.; Abshire, S.; McIlwrath, S.; Stinchcomb, A.; Westlund, K. Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis. Eur. J. Pain 2016, 20, 936–948.

[vii] Liput, D.J.; Hammell, D.C.; Stinchcomb, A.L.; Nixon, K. Transdermal delivery of cannabidiol attenuates binge alcohol-induced neurodegeneration in a rodent model of an alcohol use disorder. Pharmacol. Biochem. Behav. 2013, 111, 120–127.

[viii] Chelliah, M.P.; Zinn, Z.; Khuu, P.; Teng, J.M. Self-initiated use of topical cannabidiol oil for epidermolysis bullosa. Pediatr. Dermatol. 2018, 35, e224–e227.

[ix] Sharkawy, A.; Silva, A.M.; Rodrigues, F.; Barreiro, F.; Rodrigues, A. Pickering emulsions stabilized with chitosan/collagen peptides nanoparticles as green topical delivery vehicles for cannabidiol (CBD). Colloids Surf. A Physicochem. Eng. Asp. 2021, 631, 127677.

[x] Vanti, G.; Grifoni, L.; Bergonzi, M.C.; Antiga, E.; Montefusco, F.; Caproni, M.; Bilia, A.R. Development and optimisation of biopharmaceutical properties of a new microemulgel of cannabidiol for locally acting dermatological delivery. Int. J. Pharm. 2021, 607, 121036.

[xi] Chelliah, M.P.; Zinn, Z.; Khuu, P.; Teng, J.M. Self-initiated use of topical cannabidiol oil for epidermolysis bullosa. Pediatr. Dermatol. 2018, 35, e224–e227.

[xii] Bartner, L.R.; McGrath, S.; Rao, S.; Hyatt, L.K.; Wittenburg, L.A. Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. Can. J. Vet. Res. 2018, 82, 178–183.

[xiii] Huestis, Marilyn A., et al, Cannabidiol Adverse Effects and Toxicity, Current Neuropharmacology, 2019, 17, 974-989 *DOI:10.2174/1570159X17666190603171901*

[xiv] Golombek, Patrici, et al., Conversion of Cannabidiol (CBD) into Psychotropic Cannabinoids Including Tetrahydrocannabinol (THC): A Controversy in the Scientific Literature, Toxics 2020, 8, 41; doi:10.3390/toxics8020041