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Cannabidiol—A friend or a foe?

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ABSTRACT

Cannabidiol (CBD), one of the main actives from *Cannabis sativa* has been perpetually explored lately for its therapeutic effects. Its main attributes, such as anti-inflammatory and antioxidant effects, snowball into pain management, epilepsy and seizure alleviation, anxiety relief, as well as numerous other implications through the entire metabolism. However, conventional administration routes challenge its therapeutic potential, with reported poor water solubility, hepatic degradation, gastric instability and erratic bioavailability observed in oral administration. As a result, the transdermal delivery systems have emerged as a promising alternative to oral or inhaled routes, offering improved bioavailability and targeted effects. The medical use of CBD throughout Europe, UK, USA or Australia is extensive and usually represented by pharmaceutical preparations recommended after conventional treatment routs fail. The non-medical use is limited by each country's own legislation, a wider range of products being available, but the irregular regulatory landscape coupled with the growing market of cannabinoid-infused products, emphasizes the need for standardized formulations and further clinical research. The present work critically examines the transdermal administration of cannabidiol, explores the skin's potential as a route and the strategies involved in using it for systemic targeting. We highlighted key challenges and provided insights into CBD`s variable bioavailability based on different administration routes and methods, thus compiling a literature-based absorption, distribution, metabolism, and excretion (ADME) study. We also explore the role of the endocannabinoid system, its function in various medical conditions, and the therapeutic effects associated with CBD, particularly in light of the varying legislation across countries. While the breadth of potential benefits is compelling, it is essential to emphasize the ongoing nature of CBD research as individual responses to it can vary significantly.

1. Introduction

Cannabis (*Cannabis sativa* L.) has a long history of medicinal use, dating back over 4000 years and recent research has attributed its therapeutic potential to the bioactive compounds known as cannabinoids, which are found primarily in the resinous trichomes of the plant's flowers and leaves (Brand and Zhao, 2017). Among the more than 100 identified cannabinoids, tetrahydrocannabinol (THC) is well-known for its psychoactive effects, thus cultivation of *Cannabis sativa* L. varieties in Europe is allowed only if the seeds are registered in the European Union (EU)'s 'Common Catalogue of Varieties of Agricultural Plant Species' and their THC content does not exceed 0.2 % (w/w). Another bioactive compound is cannabidiol (CBD), that is devoid of psychotomimetic effects, thus gaining significant attention for broad applications, reflected in the infusion of either cosmeceuticals, alternative-medicine remedies, supplements, foods, or beverages on the European market (Andre et al., 2016). Plant-derived and synthetic CBD are not controlled under the Single Convention on Narcotic Drugs and may therefore be used in finished cosmetic products (Couteau and Coiffard, 2010; Shelley and Metz, 2013).

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CBD has been explored for its anxiolytic, anti-inflammatory, neuroprotective, and antiepileptic properties, an in-depth understanding regarding its bioavailability in correlation with intake forms is not yet clearly formed and due to gaps in available data regarding NOAEL (No Observed Adverse Effect Level), safety concerns have been raised (Hanuš et al., 2016; Turck et al., 2022). In addition, its therapeutic use has been limited by its poor water solubility and low oral bioavailability, which can fluctuate between 6–20 % due to extensive first-pass metabolism, requiring appropriate delivery methods. Among them, transdermal drug delivery offers several advantages, including bypassing the digestive system, with bioavailability rates higher than oral – gastric ones and allowing for controlled, sustained release of the active compound, leading to improved therapeutic outcomes, while alleviating localized and systemic conditions associated with pain and inflammation (Lodzki et al., 2003; Varadi et al., 2023). Following the ban on animal testing of cosmetic products in the EU, (as part of Reg. 1223/2009), there is little *in vivo* testing data available for cosmetic products, therefore risks arising from dermal exposure to CBD need further exploration and data gathering to help regulatory parties make informed decisions and provide safe recommendations for proper usage.

Here we report on CBD's therapeutic properties and challenges associated with its various administration routes. This review examines current findings on the transdermal delivery of CBD, a non-invasive approach that addresses issues of bioavailability, efficacy and safety. An overview of the available legislation, medical cannabis policies and accessibility, the lack of standardized regulation for non-prescription CBD products, as well as a lack of balance between accessibility and rigorous scientific validation to ensure safety, efficacy, and equitable access is included. Ultimately, it invites us to consider: is CBD a friend or a foe?

2. The path of cannabidiol in the body: absorption, distribution, metabolism & excretion insights for systemic delivery

CBD and Δ^9-THC are both 21-carbon terpenophenolic compounds, found in the plant, Δ^9-THC in acid forms (THCA and CBDA) that decompose slowly during storage to the corresponding chemically neutral but pharmacologically potent THC and CBD (Andre et al., 2016; Atakan, 2012). These compounds easily undergo decarboxylation during the drying of the plant material, its combustion or its analysis (Wang et al., 2016). CBD consists of a pale-yellow resin or crystals with the molecular formula $C_{21}H_{30}O_2$ and a molecular weight of 314.46 g/mol. CBD is almost insoluble in water (0.0122 mg/L at 25 °C), but has good solubility in organic solvents, such as methanol, ethanol, diethyl ether, benzene and chloroform. The octanol/water partition coefficient log Ko/w is 8.01 (Cannabidiol, 2021). Animal studies indicate that CBD's oral bioavailability is low, and there is insufficient data from human studies to fully understand its efficacy. To achieve systemic delivery, cannabinoids need to be administered in a manner that allows distribution throughout the entire body, influencing various physiological processes. This contrasts with localized or topical methods, which target specific areas like skin or muscles without widespread distribution.

Each of the delivery methods has its advantages and disadvantages, and the choice of the method may depend on individual preferences, the medical condition being treated, and the desired onset and duration of effects. It is important to note that the pharmacokinetics of cannabinoids can vary depending on the delivery method, that influence its bioavailability, rate of absorption, and overall efficiency. Additionally, the legality and availability of these delivery methods may vary depending on the region and the specific cannabinoid products being used.

2.1. Low bioavailability of CBD and the influence of administration routes for systemic delivery

The bioavailability of CBD varies greatly with route and mode of administration. In clinical trials and research studies, CBD is generally administered orally as either a capsule or dissolved in oil solutions. It can also be administered through sublingual or intranasal routes.

A wide range of oral doses have been reported in the literature, with most dosages ranging from 10 mg/day to 800 mg/day (in high dosages cases) (Millar et al., 2020; Huestis, 2007; Fasinu et al., 2016). It is generally accepted that CBD is less active on the endocannabinoid brain receptors than THC. This has been used to explain the lack of psychoactive effects of CBD even at high dose (Nelson et al., 2020).

Oral delivery of an oil-based capsule formulation of CBD has been assessed in humans. Probably due to its poor aqueous solubility, the absorption of CBD from the gastrointestinal tract is erratic, and the resulting pharmacokinetic profile is variable. Bioavailability from oral delivery was estimated to be 6 % due to significant first-pass metabolism (Fasinu et al., 2016; Ujváry and Hanuš, 2016).

In healthy male volunteers, the 12 mean ± SD whole blood levels of CBD at 1, 2 and 3 h after administration of 600 mg oral CBD were reported to be 0.36 (0.64) ng/mL, 1.62 (2.98) ng/mL and 3.4 (6.42) ng/mL, respectively (Brown and Winterstein, 2019). Aerosolized CBD has been reported to yield rapid peak plasma concentrations in 5–10 mins and higher bioavailability than oral administration. CBD is rapidly distributed into the lung tissues with a high volume of distribution of ~32 L/kg (Fasinu et al., 2016). In rats, analysis of blood and brain 21.5 h after intra-gastric administration of 23.4 mg/kg of CBD in olive oil solution showed respective tissue concentrations of unchanged CBD of 20.2 ng/mL and 6.4 ng/g; the hepatic concentration was higher throughout the experiment and 20.8 ng/g was recorded even 84 h after administration. In other tests with rats, analysis of brain parts 5 mins after administration of CBD (1 mg/kg intravenous) revealed an even distribution of the radiolabel (CBD+ its unspecified metabolites) at about 1 ng/mg as initial peak concentrations throughout all brain regions examined.

After oral administration of chocolate cookies containing 40 mg of CBD in healthy human subjects, mean plasma CBD levels ranged between 1.1 and 11 ng/mL (mean: 5.5 ng/mL) after one hour and the course of CBD in the plasma over six hours was in the same range as the course after 20 mg of THC (Agurell et al., 1981). Oral intake of 5.4 mg of CBD resulted in plasma CBD concentrations ranging between 0.2 and 2.6 ng/mL (mean: 0.95 ng/mL) after one hour (Nadulski et al., 2005). Bioavailability through the oral route was estimated at 6 % (Agurell et al., 1981; Zhornitsky and Potvin, 2012).

Differences in CBD bioavailability when administered orally may be influenced by non-standardized CBD formulation, and/or the body size and composition of the recipient. With regards to the former, differences in formulation might include water vs. lipid solubility, administration as a food vs. a beverage, co-administration with additional ingredients, and/or preparation as a ready-made product vs. a powder to be mixed with liquid by the consumer before ingestion. Once ingested, the resultant circulating CBD concentration will be influenced by rates of absorption from the gut, breakdown during first pass metabolism, and potentially by the body size and composition of the consumer. For example, lean mass is positively associated with total blood volume. Adults with a higher lean mass may demonstrate lower circulating CBD concentrations on account of a larger blood volume to dilute the CBD. Fat mass may influence CBD absorption as CBD is lipid soluble and can therefore potentially accumulate in adipose tissue in a manner similar to Δ^9-THC, a psychoactive component of *Cannabis sativa* L (Williams et al., 2021).

In general, the plasma concentration of CBD is dose-dependent, although this can be nonlinear, especially at high doses, CBD has low fasting bioavailability (<10 %), kinetic parameters were noted to be similar to those of Δ^9-THC. The maximum concentration (C_{max}) of CBD can range between 0.9 ng/mL following a low dose and 192 ng/mL following a high dose (Huestis, 2007).

In a study involving CBD oral administration in mice, 120 mg/kg resulted in a range of maximum brain tissue concentrations of 4−21 μM.

Another study looked at the concentration of CBD in the brain of mice after subcutaneous administration at 10 mg/kg and reported a C_{max} of 1−2 μM (Nelson et al., 2020). The concentration of CBD in brain tissue is always measured as being lower than the correlating plasma concentration. Therefore, CBD levels in human brain tissue are likely to be lower than the reported plasma concentrations in humans (as presented in the table below, human studies, <50 nM); however there appears to be no significant barrier to brain penetration of CBD (Nelson et al., 2020).

A recent study examined gastric and plasma concentrations of cannabinoids in mini pigs after repeated CBD administration (15 mg/kg/day for 5 d). The results indicated no THC or THC metabolites in plasma or gastric fluid matrices after CBD administration. There is no evidence that this transformation occurs in humans after oral CBD administration. One human study administered 600 mg of CBD to healthy participants and detected no THC and trace concentrations of THC metabolites (11-OH-THC, THC-COOH). In general, clinical studies have reported that even high doses of oral CBD do not cause THC-like effects (e.g., impairment, increased heart rate/tachycardia, dry mouth). There is no evidence that oral administration of CBD in humans results in clinically relevant, subjective or physiological effects similar to those of THC, or appreciable plasma concentrations of THC or its metabolites (WHO 2018).

2.2. Metabolism and cytochrome P450 interaction

CBD is absorbed in the body similarly to THC. It has been claimed that CBD can be transformed to THC and other cannabinoids under acidic conditions (Adams et al., 1940). The experimental conversion of CBD to THC and delta8-THC in simulated gastric fluid (SGF) studied by Merrick et al. (2016) based on the pioneering work done by Adams *et. al.* suggests that soluble CBD converts *in vitro* to THC at 1.5:1 ratio in 120 min. Fortunately these results may remain valid only *in vitro* conditions, as in the over 40 years of CBD research, in humans the conversion to THD does not occur after oral administration of CBD, even at doses exceeding 800 mg/mL (Nahler et al., 2017; Sholler et al., 2021). However, low levels of THC metabolites have been detected for more than five weeks in the urine and faeces of cannabis users. CBD is rapidly distributed into the tissues with a high volume of distribution of ~32 L/kg.

Like THC, CBD may preferentially accumulate in adipose tissues due to its high lipophilicity (Fasinu et al., 2016; Fasinu et al., 2016; Jiang et al., 2013). While cannabinoids are lipophilic and dissolve better in fats and oils, the influence of various fats on cannabinoid absorption *in vivo* has been poorly studied.

A pre-clinical study examined the effect of dietary fats on THC and CBD absorption in rats with a dose of 12 mg/kg of THC or CBD in either lipid-free formulation or lipid long-chain triglycerides (LCT)-based formulation (sesame oil) that was administered to rats by oral gavage showed the absolute bioavailability of THC of 2.5 times higher in the lipid-based (C_{max} = 172 ng/mL; AUC = 1050 h.ng/mL) versus lipid-free formulation (C_{max} = 65 ng/mL; AUC = 414 h.ng/mL). The absolute bioavailability of CBD was three times higher in the lipid-based (C_{max} = 308 ng/mL; AUC = 932 h.ng/mL) versus lipid-free formulation (C_{max} = 87 ng/mL; AUC = 327 h.ng/mL). Furthermore, an *in vitro* lipolysis model was used to assess the mechanism by which lipids could enhance the bioavailability of THC and CBD. Results showed that 30 % of THC and CBD was solubilized in the micellar layer and therefore was readily available. Incubation studies suggested that cannabinoids have a 70 to 80 % association range with natural chylomicrons from rat and human. Chylomicrons act as carriers in the intestine and potentially transfer THC and CBD to the systemic circulation via the intestinal lymphatic system and therefore avoid hepatic first-pass metabolism, which would explain the increased bioavailability with the lipid-based formulation (Hanan Abramovici et al., 2018).

Most cannabinoid metabolism occurs in the liver, and different metabolites predominate depending on the route of administration. CBD has the ability to interact with CYPs (Cytochrome P450 enzymes). The primary route is hydroxylation to 7-OH-CBD which is then metabolized further in the liver, resulting in a number of metabolites that are excreted in faeces and urine (Jiang et al., 2011).

A study in human liver microsomes (HLMs) demonstrated that CBD was metabolized to eight monohydroxylated metabolites. Among these metabolites, 6α-OH-, 6β-OH-, 7-OH-, and 4″-OH-CBDs were the major ones. Seven recombinant human CYP enzymes were identified as capable of metabolizing CBD: CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5, the two most active being the isoforms CYP3A4 and CYP2C19 (Jiang et al., 2011). In other studies CBD has been shown to inhibit CYP isozymes *in vitro*, but it is not clear that this occurs at concentrations achieved with clinical doses (Nasrin et al., 2021; Jiang et al., 2013; Yamaori et al., 2010).

The first CBD metabolites to be identified were isolated from rat liver homogenate and their structures were determined as a primary alcohol derived from the oxidation at the allylic C-7 methyl group on the cyclohexene moiety (7-OH-CBD) and a secondary alcohol resulting from the oxidation of the central (C-3″) methylene group of the pentyl side chain (3″-OH-CBD). Biotransformation studies in mammals, including humans, using various types of CBD administration have indicated considerable species variability.

The major safety concern associated with CBD is drug interaction (Vázquez et al., 2021). Potential for adverse drug events (ADEs) and drug–drug interactions (DDIs) is based on pharmacologic targets of CBD, pharmacodynamic effects, and interactions between CBD and other medications related to metabolism, absorption, and elimination.The metabolism of CBD involves cytochromes, and UGT (uridine diphosphoglucuronosyltransferases) enzymes. Moreover, CBD can inhibit various CYP and UGT enzymes, leading to potentially significant drug interaction, notably with antiepileptic drugs (Brown and Winterstein, 2019; Landmark and Brandl, 2020) and antiseizure medications (Gilmartin et al., 2021). CBD may notably inhibit CYP2C9, CYP1A1/2 and CYP1B1, but also CYP2D6, CYP2C19, CYP2B6, CYP2J2 (Bornheim et al., 1981; Jiang et al., 2013; Bornheim et al., 1993; Qian et al., 2019; Yamaori et al., 2010, 2012, 2015, Zendulka et al., 2016). CBD also inhibit UGT1A9 and UGT2B7 (Qian et al., 2020). On the other side, a 2013 report (Stott et al., 2013) on a clinical trial using GW Pharmaceutical's Sativex, a whole plant CBD-rich sublingual spray, found no interactions with CYP enzymes when approximately 10 mg of CBD were administered. A subsequent clinical trial, however, found that 25 mg of orally administered CBD significantly blocked the metabolism of an anti-epileptic drug (Geffrey et al., 2015).

It should be kept in mind that CBD is also administered in patients with serious medical conditions that are treated with medications that have their own side effect profiles. Co-administration increases the potential of experiencing overlapping profiles even with direct DDIs via metabolic or transport pathways (Brown and Winterstein, 2019).

The available data demonstrates the possible drug-interaction between CBD and several medications such as: Methadone (Madden et al., 2020), Lithium (Singh et al., 2020), Carmazepine (Darweesh et al., 2020), Anticonvulsant drugs such as Clobazam (Anderson et al., 2019; Devinsky et al., 2020; Geffrey et al., 2015; Gunning et al., 2021; Van-Landingham et al., 2020), Stiripentol (Ben-Menachem et al., 2020; Morrison et al., 2019) or Brivaracetam (Klotz et al., 2019). However, CBD has no effect on Valproate pharmacokinetics (Ben-Menachem et al., 2020; Morrison et al., 2019), Warfarin (Grayson et al., 2017), Anaesthetic and sedative agents such as Hexobarbital (Bornheim et al., 1981; Benowitz et al., 1980), Barbiturate (Karler et al., 1979), Hexobarbitone (BORYS et al., 1979), or Pentobarbitone (Frizza et al., 1977), but has no effect on Secobarbital pharmacokinetic parameters (Dalton et al., 1976). CBD is also not associated with any side effect in case of Fentanyl intravenous administration (Manini et al., 2015), Levothyroxine (Guido et al., 2021).

2.3. Excretion and half-life of CBD

In a controlled study involving 18 participants, 100 mg of CBD in four types of formulations were administered orally or by vaporization. After 58 h, from collected samples the urinary CBD concentrations (ng/mL) were higher after oral (mean Cmax: 734; mean Tmax: 4.7 h, n = 18) versus vaporized CBD (mean Cmax: 240; mean Tmax: 1.3 h, n = 18), and oral dose formulation significantly impacted mean Cmax (Epidiolex = 1274 ng/mL, capsule = 776 ng/mL, syrup = 151 ng/mL, n = 6/group) with little difference in Tmax. Overnight fasting had limited impact on CBD excretion in urine, and there was no evidence of CBD conversion to Δ8- or Δ9-THC in any route or formulation in which pure CBD was administered (Sholler et al., 2021).

In another study focusing on administering medical cannabis and pharmaceutical preparations, 13 healthy volunteers were administered 100 mL of cannabis decoction first and, after 15 d, 0.45 mL of oil. Urine samples were collected at different time points. The most excreted CBD metabolite was 7-OH-CBD (242.9 ± 141.35 μg in the case of decoction and 239.1 ± 143.1 μg in the case of oil). The second most prevalent metabolite, 7-COOH-CBD was about four time less concentrated than 7-OH-CBD (65.9 ± 46.2 μg and 42.7 ± 20.3 μg after decoction and oil consumption, respectively). Additionally, 6-β-OH-CBD was detected in urine samples at a concentration 30 times lower than that of the hydroxy metabolite (8.7 ± 4.9 μg for decoction vs. 7.6 ± 5.0 μg for oil), and finally, 6-α-OH-CBD was excreted in urine with concentrations two orders of magnitude less (2.5 ± 2.0 μg after decoction intake and 0.7 ± 0.6 μg after oil intake) (Pérez-Acevedo et al., 2020).

Smoking one light cannabis cigarette containing 58 mg CBD and 1.6 mg THC (by 6 participants) lead to detection in urine of 7.9 ± 2.1 ng/mL CBD at 3 h, increasing to 18.6 ± 4.0 ng/mL at 8 h post administration, and then decreasing to 12.6 ± 2.1 (12.4) ng/mL at 24 h; 0.2 ng/mL of THC were also detected (Pacifici et al., 2020).

Plasma clearance of CBD is similar to that of THC, ranging from 58 to 94 L/h (i.e. 960 – 1560 mL/min). In a study (WALL and PEREZ-REYES, 1981) including healthy volunteers who were given 20 mg of CBD by intravenous injection, 7-COOH-CBD was the most abundant metabolite in the plasma, while 7-OH-CBD was only a minor biotransformation product. In the urine, unchanged CBD and, to a lesser extent, conjugated CBD were the main excretion products and about 16 % of the total radioactivity was eliminated in 72 h by this route of excretion. It was also observed that 33 % of the total radioactivity, again mostly unchanged CBD accompanied by several metabolites.

A recent study reported that CBD, when given at doses of 5, 10 and 20 mg/kg/d to children ages 4–10 with Dravet syndrome, produced dose-proportional increases in area-under-the curve plasma concentrations for CBD and its metabolites, 6-OH-CBD, 7- OH-CBD, and 7-COOH-CBD (Yamaori et al., 2012).

A significant portion of administered CBD is excreted either intact or as its glucuronide conjugate. Within 72 h, 16 % of the administered CBD dose was recovered in the urine as either intact or conjugated CBD, while 33 % was recovered in the feces, predominantly unchanged, along with several mono- and di-hydroxylated metabolites and monocarboxylic derivatives. The decline of CBD levels is also multi-phasic, and the half-life of CBD in humans has been estimated at 2 – 5 days after oral administration (Hanan Abramovici et al., 2018).

The half-life of elimination ($t_{1/2}$) of CBD is variable and depends especially on its route of administration. Generally, oral administration (e.g. via oil) leads to a $t_{1/2}$ of about 2 h. The families of oxidized and glucuronidased metabolites are largely excreted by the kidneys and can be identified in the urine (Nelson et al., 2020).

2.4. Toxicological insights for systemic delivery

In January 2019, the World Health Organization (WHO) changed position after 60 years and proposed rescheduling of cannabis and cannabinoids for therapeutic purposes (Mayor, 2019; Forty-first meeting of the Expert Committee on Drug Dependence 2021). Three months after FDA Epidiolex® approval, the U.S. Drug Enforcement Administration (DEA) removed Epidiolex® from the most restricted Schedule 1 (no approved medical use and high abuse liability) to Schedule V with low abuse potential (D. of J. Drug Enforcement Administration 2018).

Assessment of *in vitro* genotoxicity of hemp extracts with high CBD content by bacterial reverse mutation test (AMES) resulted in no substantial increases in revertant colony numbers (Huestis et al., 2019; de Faria et al., 2020). Synthetic cannabinoid also did not induce gene mutations (Russo et al., 2019; Zimmerman and Raj, 1980; Schleicher et al., 2019).

Assessment using the chromosomal aberration test on a product containing 25 % cannabinoids, including 96 % CBD and less than 1 % THC did not induce an increase in the number of cells with aberrations or rates of polyploidy or endoreduplicated metaphases at concentrations ranging from 10 to 90 μg/mL (Huestis et al., 2019). There were no statistically significant differences between treatment and the solvent control groups, and no dose-response relationships were noted.

Despite positive genotoxicity results, CBD was found to induce DNA damage in single cell gel electrophoresis (SCGE) experiments in a human liver cell line (HepG2) and in buccal-derived cells (TR146) at low levels (≥ 0.2 μM). Results of micronucleus (MN) cytome assays showed that the damage leads to formation of micronuclei (MNi) which reflect chromosomal aberrations and leads to nuclear buds and bridges which are a consequence of gene amplifications and dicentric chromosomes. Additional experiments indicate that these effects are caused by oxidative base damage and that liver enzymes (S9) increase the genotoxic activity (Marx et al., 2018).

There are a number of mouse and rat studies using the intravenous (i.v) and intraperitoneal (i.p) route of CBD exposure which showed no significant effects on the following: weight gain, locomotor activity, blood glucose levels, catalepsy, antinociception, hypothermia, motor changes, gastrointestinal motility, blood pH, rectal temperature, blood pressure, cardiovascular parameters, respiratory parameters (Ewing et al., 2019; Dziwenka et al., 2020; Bhattacharyya et al., 2010; Oberbarnscheidt and Miller, 2020). The doses used ranged from 1–100 mg/kg/b.w.

The repeated oral dose studies on CBD extract in animals revealed dose-related toxicity, including changes in organ weights (liver, thymus, spleen, adrenal glands) and histopathological alterations (e.g., hepatocellular hypertrophy, adrenal vacuolation, and thymus involution) (Huestis et al., 2019). Acute studies highlighted central nervous system effects (sedation, tremors, convulsions), and significant impacts on reproductive and metabolic parameters at higher doses, with lethality observed in extreme cases (Ferk et al., 2016).

The 90-day repeated dose oral toxicity studies revealed dose-related decreases in body weight and changes in organ weights, notably liver hypertrophy, which were generally reversible after a recovery period. The no-observed-adverse-effect level (NOAEL) varied by species and sex: 100 mg/kg/day for male rats and 360 mg/kg/day for females, while in monkeys, significant impacts on organ weights and testicular size were observed at higher doses, with inhibition of spermatogenesis persisting post-recovery (Huestis et al., 2019; Ferk et al., 2016).

Chronic toxicity studies found liver effects (hepatocellular hypertrophy and increased liver enzymes) at all CBD doses in rats and dogs. Reproductive and developmental studies showed fertility impacts, fetal growth reduction, and delayed sexual maturation, with a NOAEL of 150 mg/kg/day. No carcinogenic effects were observed in a 104-week rat study (Koller et al., 2015).

Human acute studies show that CBD is generally safe and well-tolerated across a wide range of doses (20–1500 mg), with no evidence of tolerance or significant adverse effects on psychomotor, physiological, or psychological functions. Clinical trials, including those in patients with type 2 diabetes, found no major effects on metabolic, cardiovascular, or inflammatory markers, and adverse events were mild to moderate (National Toxicology Program 1996; Russo, 2019; Riedel

et al., 2009; El-Remessy et al., 2006; Resstel et al., 2009; Zanelati et al., 2010). Chronic oral CBD administration has demonstrated safety across multiple studies. Neurological, clinical, and psychiatric assessments of doses ranging from 10 mg/day to 1500 mg/day showed no significant adverse effects (Rosenkrantz et al., 1981; Lu and Mackie, 2021; Howlett et al., 2002; Basu and Dittel, 2011). In epilepsy studies, including severe cases like Dravet syndrome, CBD reduced seizures effectively, though side effects like somnolence, diarrhea, and transaminase elevation (noted primarily with valproate co-administration) were reported (Cabral et al., 2015; Mecha et al., 2016). Studies in children and adults with treatment-resistant epilepsy found CBD generally well-tolerated, with common adverse events being mild to moderate and reversible through dose adjustments (Atwood and MacKie, 2010; Irving et al., 2017; Di Marzo, 2008; Health Effects, 2022). In patients with Parkinson's psychosis and schizophrenia, CBD improved symptoms without serious side effects . However, its immune-modulatory effects suggest potential risks in certain contexts, such as HIV-1 progression (National Toxicology Program 1996).

Among the 100 orphan G-protein coupled receptors (GPCRs), three have been linked to the cannabinoid system. GPR18, GPR55, and GPR119 exhibit limited sequence homology with the established CB1 and CB2 cannabinoid receptors. However, the pharmacology of these orphan receptors displays overlap with CB1 and CB2 receptors, particularly for GPR18 and GPR55. The linking of GPR119 to the cannabinoid receptors is less convincing and emanates from structural similarities of endogenous ligands active at these GPCRs, but which do not cross-react (P et al., 1986).

It is now well established that endocannabinoids are synthesized and released "on demand" and that this process can be regulated both physiologically and under pathological conditions. Therefore, the endocannabinoid signaling implications concerning pharmacological mechanisms involve an intricate path from synthesis, to release, interaction with receptors, followed by cellular uptake and metabolism, which may trigger critical therapeutic effects.

Studies that explored the endocannabinoid biology as new leads for drug development and specific correlation with various conditions/ diseases have used several tools – or families of tools, in order to group in a functional way the interactions (Divac et al., 2016). Therefore, there are (i) "indirect" cannabinoid receptor agonists (i.e. inhibitors of endocannabinoid inactivation), (ii) "direct" cannabinoid receptor agonists, (iii) "indirect" antagonists of cannabinoid receptors (i.e. inhibitors of endocannabinoid biosynthesis), (iv) cannabinoid receptor inverse agonists and antagonists, and (v) cannabinoid receptor allosteric modulators. Each of these super-families can be divided into various families of compounds, for twelve such families.

Section Highlights

CBD's poor water solubility and first-pass metabolism result in low oral bioavailability (~6 %). Lipid-based formulations enhance bioavailability by bypassing first-pass metabolism. Routes like sublingual, aerosolized, and intranasal offer higher and faster absorption than oral forms.

CBD is metabolized by liver enzymes (CYP450 family) into hydroxylated and gluco- forms. CBD inhibits some CYP enzymes, potentially affecting other drugs, especially antiepileptics, though it remains unclear whether this occurs at physiological concentrations.

CBD is eliminated in feces and urine as metabolites, with a half-life of 2–5 days. Similar to THC, with detectable levels in urine for days post-administration.

Long half-life and extensive tissue distribution make CBD suitable for systemic applications, but variability remains a challenge for consistent therapeutic outcomes.

CBD is widely considered safe and well-tolerated across various doses and conditions, with mild and reversible side effects such as somnolence and gastrointestinal issues; however, its immunomodulatory effects may pose risks in certain contexts, such as HIV-1 progression.

3. The endocannabinoid system – an overview of its functions implication in various conditions with medicinal effects

The endocannabinoid system (ECS) is a widespread neuromodulatory network involved in both the developing of the central nervous system (CNS) as well as playing a major role in tuning many cognitive and physiological processes. The ECS is composed of endogenous cannabinoids, cannabinoid receptors and the enzymes responsible for the synthesis and degradation of endocannabinoids. In addition to its endogenous roles, cannabinoid receptors are the primary target of THC, the intoxicating component of cannabis (Hampson et al., 1998). ECS is far from being a discrete system, its presence and response being influenced by a number of signaling pathways. The vastly well characterized G-protein coupled receptors - CB1 and CB2 are considered primary switches of the system, being able to inhibit adenylyl cyclase and certain voltage-sensitive calcium channels, stimulate mitogen-activated proteins kinases (MAP kinases) and inwardly rectifying potassium channels (GIRKs), and recruit beta-arrestins, among other actions (Cheng et al., 2014). The diversity of CB1 signaling is enhanced by their propensity to heterodimerize with other GPCRs, including D2 dopamine, hypocretin/ orexin, and opioid receptors. CB1 receptors are particularly enriched in the nervous system, but are also present in diverse organs including liver, adipose tissue, or skin. While are primarily expressed in cells of immune origin (Effects of 2022) including microglia (Xiong and Lim, 2021), though they may also be expressed in neurons (I et al., 2014), particularly in pathological states (Hammell et al., 2016).

Regarding the medical cannabis, the current scientific literature provides conclusive and substantial evidence that both cannabis and cannabinoids have therapeutic effects: they are used to treat chronic pain in adults, work as an antiemetic when treating nausea and vomiting induced by chemotherapy and improve symptoms of muscle spasticity in multiple sclerosis.

A 2017 meta-analysis on the benefits and side effects of cannabis (performed by the National Academy of Sciences, Engineering, and Medicine, USA, which analyzed more than 10,000 scientific abstracts) showed that marijuana (or cannabinoid-containing products) is effective in relieving chronic pain. Marijuana is not suitable for severe pain, such as postoperative pain or a fracture, but can be used successfully in neuralgia, fibromyalgia, endometriosis, interstitial cysts and any other disease that is characterized by chronic pain (Holloman et al., 2021).

Most scientific studies have focused in the last 40 years on the potential toxicity of THC, dealing less with other cannabinoids, which has ironically led to the discovery that THC and other cannabinoids are active lipophilic antioxidant compounds, which explains the therapeutic potential traditionally associated with *Cannabis* species (Elliott et al., 2018).

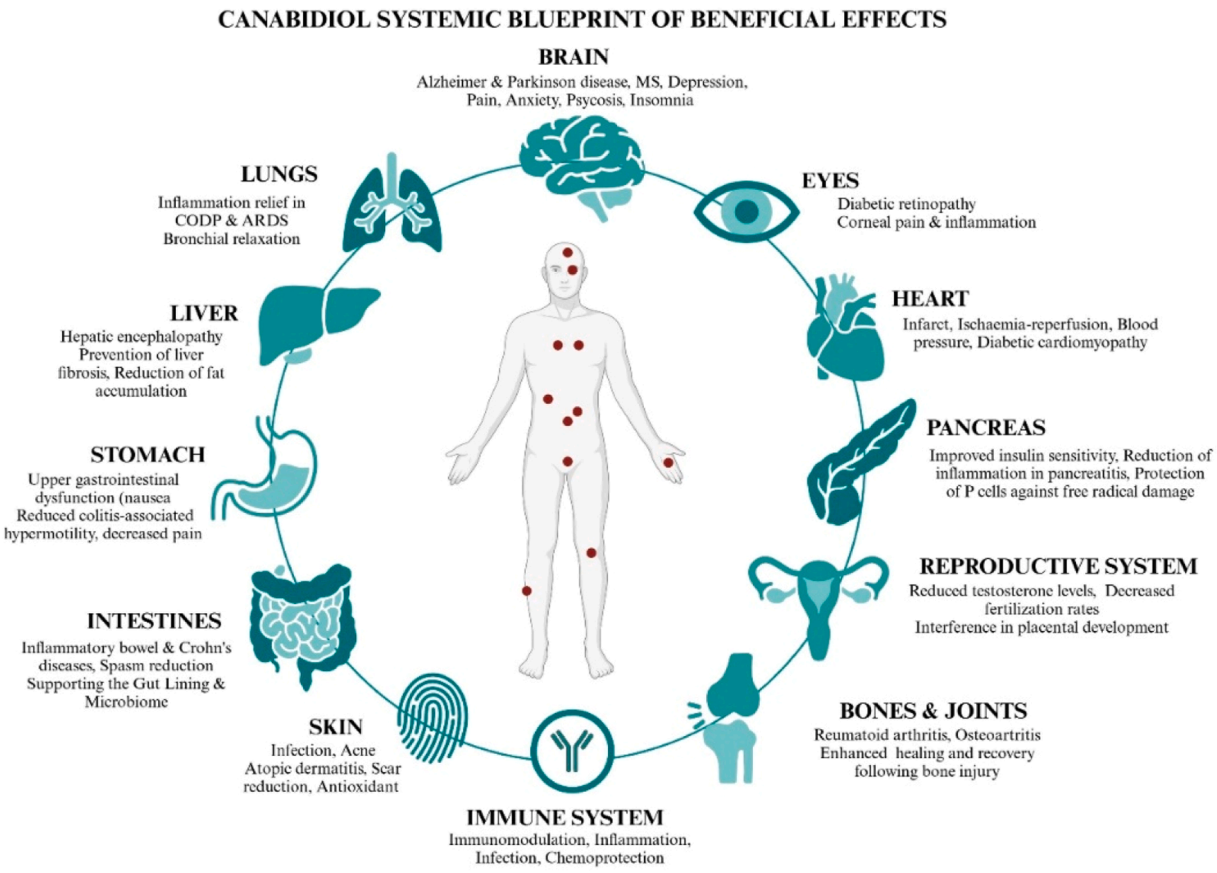

Fig. 1. Blueprint of CBD`s therapeutic benefits across the human body. This figure illustrates CBD's therapeutic potential across major body systems. It highlights neuroprotective effects (e.g., Alzheimer's, Parkinson's, anxiety), anti-inflammatory actions in the lungs, cardiovascular, and immune systems, and its role in improving liver, gut, and pancreatic health. Additionally, it shows benefits for skin conditions, bone and joint recovery, and reproductive health, underscoring CBD's systemic impact on inflammation, pain, and cellular protection. Original figure created using Biorender.

Table 1
Overview of therapeutic beneficial effects of CBD in association with various diseases.

Nr. Crt.	Disease	Effects	References
1	**Alzheimer's disease**	Anti-inflammatory, antioxidant, anti-apoptotic *in vitro* and *in vivo* models of Aβ-evoked neuro-inflammatory and neurodegenerative responses.	(Moreno-Martet et al., 2015; Nichols and Kaplan, 2020; Furgiuele et al., 2021)
2	**Parkinson's disease**	Attenuation of the dopaminergic impairment *in vivo*; neuroprotection; improvement of psychiatric rating and reduction of agitation, nightmare and aggressive behaviour in patients.	(Giacoppo et al., 2014; Coles et al., 2020; Fernández-Ruiz et al., 2013; Prakash and Carter, 2021)
3	**Multiple sclerosis**	Improved signs of EAE in mice, anti-inflammatory and immunomodulatory properties.	(Valdeolivas et al., 2015; Valdeolivas et al., 2017; Mohsenpour et al., 2021; Kossatz De Mello et al., Lafuente et al., 2016)
4	**Huntington's disease**	Neuroprotective and antioxidant in mice transgenic models; no significant clinically important differences in patients.	(Garberg et al., 2016; Pazos et al., 2012; Mlost et al., 2020; Xiong et al., 2012; Campos et al., 2021; Bennici et al., 2021)
5	**Hypoxia-ischemia injury**	Short-term neuroprotective effects; inhibition of cytotoxicity, oxidative stress and inflammation *in vitro* and in rodent models.	(Davies and Bhattacharyya, 2019; Rodrigues da Silva et al., 2020; Gomes et al., May 2015; Blessing et al., 2015; Masataka, 2019)
6	**Pain**	Analgesic effect in patients with neuropathic pain resistant to other treatments.	(Bergamaschi et al., 2011; Linares et al., 2019; Gallego-Landin et al., 2021; Silote et al., 2021)
7	**Psychosis**	Attenuation of the behavioral and glial changes in animal models of schizophrenia; anti-psychotic properties on ketamine-induced symptoms.	(García-Gutiérrez et al., 2020; Zanelati et al., 2010; Solinas et al., 2015)
8	**Anxiety**	Reduction of muscular tension, restlessness, fatigue, problems in concentration, improvement of social interactions in rodent models of anxiety and stress; reduced social anxiety in patients.	(Gross et al., 2021; Ladin et al., 2016; Zhelyazkova et al., 2020; Tomko et al., 2020; Seltzer et al., 2020)
9	**Depression**	Anti-depressant effect in genetic rodent model of depression.	(Massi et al., 2013; Parker et al., 2011; Rock and Parker, 2013; Bolognini et al., 2013)
10	**Cancer**	Antiproliferative and anti-invasive actions in a large range of cancer types; induction of autophagy-mediated cancer cell death; chemopreventive effects.	(Rock and Parker, 2013; Rock et al., 2013; Rock and Parker, 2016; Lowin et al., 2020; Kozela et al., 2009; Suryavanshi et al., 2021; Atalay et al., 2020)
11	**Nausea**	Suppression of nausea and conditioned gaping in rats	(Nagarkatti et al., 2009; Mechoulam et al., 2007; Mechoulam et al., 2002; Lowin et al., 2020, Peyravian et al., 2020; Klahn, 2020)

(*continued on next page*)

Table 1 (*continued*)

Nr. Crt.	Disease	Effects	References
12	**Inflammatory diseases**	Anti-inflammatory properties in several in vitro and in vivo models; inhibition of inflammatory cytokines and pathways.	(Blaskovich et al., 2021; Wassmann et al., 2020; Martinenghi et al., 2020; Antimicrobial Studies of Cannabidiol 2022; Krohn et al., 2016)
13	**Rheumatoid arthritis**	Inhibition of TNF-α in an animal model.	(Anil et al., 2022; Ambrose and Simmons, 2019; Hryhorowicz et al., 2021; Kicman and Toczek, 2020)
14	**Infection**	Activity against methicillin-resistant *Staphylococcus aureus*.	(Cassano et al., 2020; Walsh et al., 2010; Stanley et al., 2013; El-Azab et al., 2022; Rajesh et al., 2010)
15	**Inflammatory bowel and Crohn's diseases**	Inhibition of macrophage recruitment and TNF-α secretion *in vivo* and *ex vivo*; reduction in disease activity index in Crohn's patients.	(Horvth et al., 2012; Stella et al., 2021; Bolzinger et al., 2012; Moser et al., 2001)
16	**Cardiovascular diseases**	Reduction of infarct size through antioxidant and anti-inflammatory properties demonstrated *in vitro* and *in vivo*.	(Alkilani et al., 2015; Goyal et al., 2016; Soethoudt et al., 2018; Stasiulewicz et al., 2022)
17	**Diabetic complications**	Attenuation of fibrosis and myocardial dysfunction.	(Robinson et al., 2017; Vincenzi and Tosti, 2020; Palmieri et al., 2019)

The following Fig. 1 and Table 1 include the main therapeutical effects of CBD and a high number of references which refer to this subject.

Section Highlights

The **endocannabinoid system (ECS)** plays a crucial role in modulating cognitive and physiological processes via endogenous cannabinoids and receptors (CB1, CB2).

Cannabinoid receptors, especially **CB1**, interact with multiple signalling pathways, including dopamine and opioid systems, influencing CNS function.

CBD and **THC** have distinct therapeutic profiles, with CBD offering non-psychoactive benefits and potential in treating conditions like **chronic pain, anxiety, and epilepsy**.

4. Transdermal delivery of CBD- bioavailability and formulation challenges

4.1. Understanding skin involvement as a route for transdermal delivery of CBD

The transdermal delivery of cannabidiol has garnered attention due to its potential to provide steady, systemic release while bypassing first-pass metabolism. However, achieving therapeutic levels through the skin presents notable challenges in bioavailability and formulation. CBD's low bioavailability through transdermal delivery arises from several factors such as the general skin structure (*stratum corneum* limitations), the absorption variability and dose limitations. However, other factors as well are likely to decrease absorption such as the possibility of local irritation and the low skin penetration of strongly lipophilic CBD, which is estimated to have a log Kow/log P value of approximately 6 (Maghfour et al., 2020). Whereas in formulation, challenges such as solubility and stability are encountered alongside selection of suitable enhancers and delivery systems capable of sustained release and generation of peak plasma concentration. Whilst scalability and consistency still remain to be considered.

The skin's unique characteristics make it permeable to the surrounding environment, allowing the diffusion of air, heat, fluids, and low molecular weight molecules (Samanta et al., 2018). Skin diffusion can occur through three main pathways: (a) intracellularly, via gaps between corneocytes; (b) transcellularly, through corneocytes and the surrounding lipid matrix; or (c) through appendages, such as sweat glands and hair follicles (Watanabe et al., 2003). These properties offer an alternative method for drug delivery, particularly via transdermal application into the bloodstream, which is often more convenient for patients comfort and accessibility compared to oral or parenteral administration (Baswan et al., 2020). Transdermal administration primarily targets local effects, reducing the need for systemic drug therapies, lowering the overall dosage required to treat specific sites, and minimizing side effects (Sangiovanni et al., 2019) (Fig. 2).

In recent years, several discoveries have revealed how cannabinoids, such as CBD, can benefit the skin and serve as an improved route of administration for systemic conditions. In this realm, dermal formulations can be categorized into two types: transdermal (for systemic effects) and topical (for localized effects on the skin). To advance the development of cutaneous pharmaceutical delivery technologies for cannabinoids, it is crucial to have a thorough understanding of the skin's intricate organization and the principles governing drug permeation through it.

The affinity of endocannabinoids and exogenous cannabinoids for cannabinoid receptors influences their potential therapeutic applications. Understanding the receptor affinity of cannabinoids helps in tailoring transdermal formulations for specific therapeutic applications. High receptor affinity ensures effectiveness at lower doses, while selective targeting of CB1 or CB2 receptors enables precision in addressing particular conditions such as pain, inflammation, or skin disorders (Gupta and Talukder, 2021; Oláh et al., 2014) (Fig. 3). For example, localized CB2 activation helps in treating psoriasis, dermatitis, and eczema (Wójcik et al., 2020; Maghfour et al., 2020; Perez et al., 2022; Casares et al., 2020).

A series of studies (Baswan et al., 2020; Sangiovanni et al., 2019; Gupta and Talukder, 2021) have shown that influencing the endocannabinoid system through CBD gives the skin a bright and rejuvenated appearance. The studies of Bíró *et al* demonstrated the anti-inflammatory effects of CBD, thus making it a very useful substance in the treatment of acne, psoriasis and eczema (Oláh et al., 2014). Their *in vitro* studies (on cellular models) demonstrated the inhibitory effect of

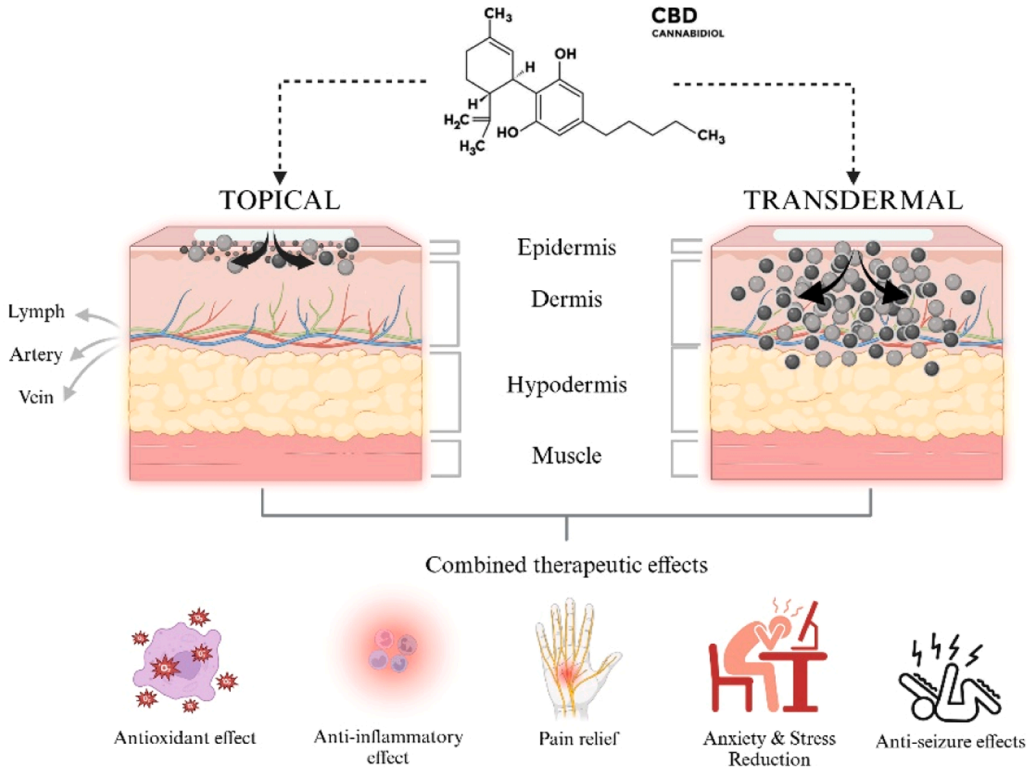

Fig. 2. Topical vs. transdermal CBD - distinct mechanisms of action and therapeutic effects. Original figure created using Biorender.

CBD on sebum production and the normalization of hyperactive sebaceous glands. Studies on human subjects also highlighted a number of beneficial effects of CBD on various skin diseases or conditions, at cellular or molecular level (Wójcik et al., 2020; Maghfour et al., 2020; Perez et al., 2022; Casares et al., 2020; Maghfour et al., 2021; Martins et al., 2022; Gao et al., 2022).

Designing a topical and transdermal drug delivery system (TDDS) requires careful consideration of the physicochemical properties of the compounds involved. While cannabinoids (CBs) fall within the desired molecular weight range (300–350 Da) and exhibit a suitable melting point (66–67 °C), their highly lipophilic nature (logP 6–7) poses significant challenges. They present poor aqueous solubility (2–10 μg/mL) and are susceptible to degradation from light and heat, undergoing autooxidation in solution (Tijani et al., 2021). One major challenge with lipophilic compounds like cannabinoids is their tendency to preferentially accumulate in the stratum corneum rather than penetrate deeper skin layers or enter systemic circulation, limiting passive drug diffusion and complicating formulation development. Researchers are addressing this issue by using penetration enhancers, volatile oils, alcohols, and solubilizers to improve topical delivery of cannabinoids. Various

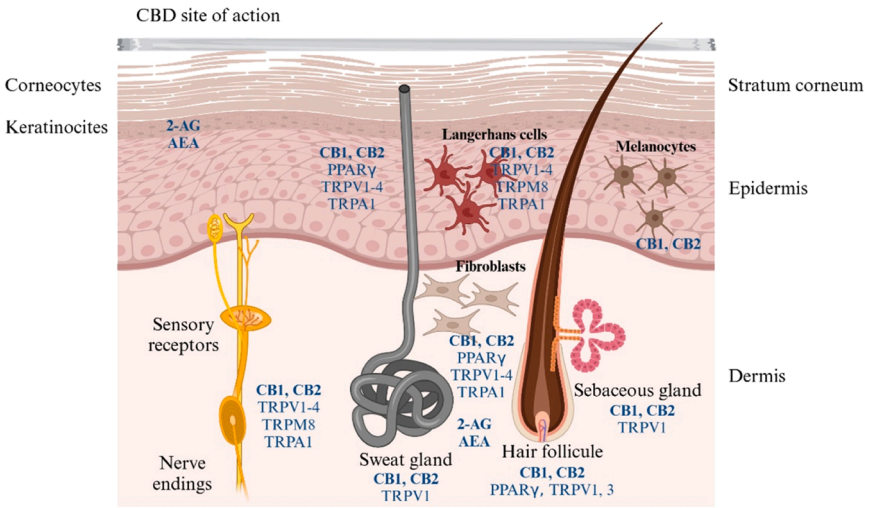

Fig. 3. Illustration of ECS components in skin layers: exploring CBD's topical and transdermal therapeutic effects through its cannabinoid receptors (CB1 and CB2). Transient receptor potential (TRP) channels are trans-membrane ion channels involved in transduction in response to CBD. From the TRP vanilloid (TRPV), TRP ankyrin (TRPA), and TRP melastatin (TRPM) subfamilies, six TRP channels have been reported to mediate cannabinoid activity: TRPV1, TRPV2, TRPV3, TRPV4, TRPA1 (Samanta et al., 2018). The first endogenous agonist of TRPV1 to be discovered was the endocannabinoid, anandamide (AEA). Endogenous ligands such as AEA, 2-arachidonoylglycerol (2-AG) are able to activate TRPV4 (Watanabe et al., 2003).

formulations may include essential oils, argan oil, non-genetically modified sunflower oil, mineral oil, monohydric alcohol solutions, aldehydes, ketones, carboxylic acids, hydroxyl acids, and non-ionic surfactants.

The absorption rates through cosmetics are summarized in the table below: Table 2

This indicates a wide range of doses, from as low as 0.6 mg/day to as high as 62.3 mg/day, highlighting the adaptability of CBD formulations for various use cases. Dogs (pinnae application) showed low bioavailability (8.6 %-9.9 %) relative to oral administration. This suggests that the application site or species-specific absorption dynamics could play a role in limited CBD uptake. While rodents (rats and mice) displayed higher plasma concentrations, especially at higher doses. This could imply that their thinner skin or metabolic differences facilitate absorption.

In an endeavor to unravel the therapeutic possibilities inherent by this delivery pathway, in 2021 the first human open-label pharmacokinetic study conducted by Varadi *et al* (Hammell et al., 2016) aimed to delve into the absorption dynamics and bioavailability of CBD and THC as they're introduced through the skin via transdermal means. In their exploratory study, results obtained from 18 patients demonstrate that CBD and THC successfully permeate through the skin and enter the systemic circulation. These results are significant as several benefits can be obtained for patients suffering from chronic conditions that require treatment over longer periods of time.

Hammell *et al* evaluated the topical application of CBD as a therapeutic approach for inflammation and pain reduction in rat models of arthritis. Their findings indicate that transdermal application of CBD gel significantly reduced joint swelling, limb posture scores as a rating of spontaneous pain, immune cell infiltration and thickening of the synovial membrane in a dose-dependent manner. Paw withdrawal latency (PWL) recovered to near baseline level. Immunohistochemical analysis of spinal cord (CGRP, OX42) and dorsal root ganglia (TNFα) revealed dose-dependent reductions of pro-inflammatory biomarkers. Results showed 6.2 and 62 mg/day were effective doses. Exploratory behavior was not altered by CBD indicating limited effect on higher brain function (Hammell et al., 2016).

Paudel *et al* determined the cannabidiol transdermal bioavailability in the presence of enhancers. Their results indicated that the steady-state CBD concentration increased by 3.7-fold in the presence of enhancer. The plasma concentration of CBD in guinea pigs after transdermal gel application was 6.3 ± 2.1 ng/mL, which was attained at 15.5 ± 11.7 h. The achievement of a significant steady-state plasma concentration indicates that CBD is useful for chronic pain treatment through this route of administration. Authors concluded that a good *in vitro* and *in vivo* correlation existed for transdermal studies (Hammell et al., 2016).

Table 2
Absorption rate through cosmetic use of CBD.

CBD content/ dose	Cream/gel co- formulants	Species (application site)	AUC	Cmax	Other	Bioavailability	Study
10 mg/kg/ bw 20 mg/ kg/bw	N/A	Dog (pinnae)	11.7 ± 18.9 min*µg/ mL 29.7 ± 29.6 min* µg/ mL	74.3 ± 127 ng/mL 277.6 ± 476 ng/mL	N/A	8.6 % 9.9 % (Relative bioavailability compared with -oral administration)	(Bartner et al., 2018)
0.6 mg/day 3.1 mg/ day 6.2 mg/ day 62.3 mg/ day	Ethanol, nanopure water, isopropyl myristate, sodium hydroxide.	Rat (back)	N/A	N/A	Plasma concentrations: 4.3 ± 2.6 ng/mL 18.8 ± 2.6 ng/mL 34.6 ± 11.0 ng/mL 1470.1 ± 260.7 ng/mL	N/A	(Hammell et al., 2016)
6 mg/day	CBD ethosome delivery system used in this study contained 3 % w/w CBD and 40 % w/w ethosome in a carbomer gel	Mouse (abdomen)	N/A	N/A	Plasma concentrations After 12 h: 1.37± 0.72 mg (22.83 ± 12 % of the initial dose) After 72 h: 2.60 ± 0.79 mg (43.33 ± 13.16 % of the initial dose)	N/A	(Lodzki et al., 2003)
1 % CBD Cream	Pure CBD solubilized in propylene glycol and basic dense cream O/A to a concentration of 1 % of CBD.	Mouse (both hind legs)	N/A	8.3 ± 2.1 ng/mL	Steady State plasma concentration: 6.1 ± 1.9 ng/mL attained at 14.9 ± 12.0 h (Tlag)(	N/A	(Giacoppo et al., 2014)
1 % CBD gel 2.5 % CBD gel 5.0 % CBD gel	CBD formulated with ethanol, propylene glycol, sterile water, Transcutol®, preservatives and a crosslinked polyacrylate polymer.	Rats (Dorsal)	N/A	N/A	Plasma concentration: ~10 ng/mL ~45 ng/mL ~100 ng/mL	N/A	(Liput et al., 2013)
18 mg/mL CBD solution	CBD formulated in a solution of 80:20 propylene glycol: nanopure water, with Transcutol HP then added to 6 % v/v.	Guinea Pigs (Dorsal)	AUC0–48 CBD only =276 ± 93 ng/mL/h CBD + Transcutol = 888 ± 419 ng/mL/h	CBD only = 8.6 ± 2.5 ng/mL CBD + Transcutol = 35.6 ± 11.6 ng/mL	Tmax: CBD only = 38.4 ± 19.2 hours CBD + Transcutol = 31.2 ± 29.4 h	N/A	(Paudel et al., 2010)

Table 3
Completed or undergoing clinical studies of cosmetic products with CBD.

NCT Number	Study Title	Study Status	Conditions	Interventions
NCT05651607	Evaluation of the Efficacy of CANNABIDIOL on the Pruritus in Children With Hereditary Epidermolysis Bullosa	RECRUITING	Hereditary Epidermolysis Bullosa	DRUG: Cannabidiol
NCT04045314	Effect of an Emollient Cream Containing 0.5 % Cannabidiol and 1 % Hemp Oil in the Hydration and Erythema of the Skin	COMPLETED	Cosmetics; Eczema	OTHER: Topical moisturizer
NCT05121506	A Study to Investigate the Bioavailability and Skin Absorption of CBD and THC From GT4 Technology in Healthy Adults	COMPLETED	Biological Availability| Skin Absorption| CBD| THC	COMBINATION_PRODUCT: CBD and THC with GT4 technology
NCT02976779	A Phase I, Double Blind, Randomized, Placebo Controlled, Maximal Dose Study to Determine the Safety, Tolerability of Topical Cream Containing MGC (Medical Grade Cannabis) in Healthy Volunteers	COMPLETED	Safety Study for Future Treatment of Psoriasis	DRUG: OWC MGC cream| DRUG: OWC Control Cream
NCT03824405	Study of the Safety, Tolerability and Efficacy of BTX 1204 in Patients With Moderate Atopic Dermatitis	COMPLETED	Atopic Dermatitis	DRUG: BTX 1204|DRUG: Vehicle
NCT05279495	Double-Blind Study Determining the Efficacy of CannaXR in Decreasing UVA Premutagenic and Photoaging Markers	COMPLETED	Photoaging	DEVICE: In a double-blinded fashion, 250 mg CANNAXR cream| DEVICE: Topical VEHICLE cream
NCT04045119	Effect of a Facial Cream Containing Cannabidiol and Hemp Oil on Skin Hydration and Acne-prone Skin	COMPLETED	Cosmetic Acne	OTHER: Topical Moisturizer
NCT03573518	Evaluation of BTX 1503 in Patients With Moderate to Severe Acne Vulgaris	COMPLETED	Acne Vulgaris	DRUG: BTX 1503|DRUG: Vehicle
NCT01663935	Vision Response to Dopamine Replacement	TERMINATED	Albinism| Oculocutaneous Albinism	DRUG: Levodopa/carbidopa
NCT06022874	The Therapeutic Effects of Topical Cannabidiol (CBD) Products for Atopic Dermatitis	RECRUITING	Atopic Dermatitis	OTHER: Phoilex Releaf Gel

Oláh *et al* findings suggested that due to the combined lipostatic, antiproliferative, and anti-inflammatory effects, CBD has potential as a promising therapeutic agent for the treatment of acne vulgaris. It was observed the downregulation of nuclear receptor interacting protein-1 (NRIP1) and A2a adenosine receptor-dependent upregulation of tribbles homolog 3 (TRIB3) and inhibition of the NF-κB signaling, which correlates with sebostatic and anti-inflammatory effects of CBD (Tijani et al., 2021).

Liput *et al* showed that transdermal administration of 5 % CBD gel decreased Fluoro-Jade B (FJB+) cells in the entorhinal cortex by 56.1 % ($p < 0.05$), while intraperitoneal injection of CBD resulted in a 50.6 % ($p < 0.05$) reduction in FJB+ cells. These results demonstrate the feasibility of using CBD transdermal delivery systems for the treatment of alcohol-induced neurodegeneration (Liput et al., 2013).

Current research suggests that CBD could play a part in enhancing wound healing and reducing scar formation, as well as reducing inflammation (Palmieri et al., 2019; Tóth et al., 2019; Zurier and Burstein, 2016), among other skin and wound related applications (Filipiuc et al., 2023; Makhakhe, 2022; Ferreira et al., 2023; Baswan et al., 2020), potentially being a noninvasive alternative for improving the quality of life for patients with an inflammatory background.

According to the US National Library of Medicine – ClinicalTrials.gov, several clinical trials are either completed or currently recruiting for studying the effect of CBD on various skin conditions, from atopic dermatitis to acne and psoriasis (Table 3).

4.2. Treatment strategies via transdermal delivery of CBD

4.2.1. CBD in skin therapy

The success of transdermal CBD treatment strategies depends on a thorough understanding of its physicochemical properties. While significant progress has been made in CBD research, particularly in Europe where the European Medicines Agency (EMA) has authorized 75 clinical trials, none focus specifically on skin applications. These trials instead target conditions such as chronic migraines, neurological disorders, muscular spasticity, epilepsy, and anxiety (Clinical Trials register 2023).

Transdermal CBD delivery has shown promise in addressing various skin conditions (Millar et al., 2018; Millar et al., 2020). Its potential to modulate inflammatory responses makes it suitable for treating dermatological conditions such as psoriasis, atopic dermatitis, and acne (Millar et al., 2020; Bruni et al., 2018; Sheriff et al., 2020). Additionally, it has been proposed for scar and wound management (Krohn et al., 2016; Casares et al., 2020; Parikh et al., 2024; Sangiovanni et al., 2019), offering benefits such as localized delivery, reduced first-pass metabolism, and enhanced adherence. However, limitations such as skin irritation, dryness, and failure to regenerate tissue can hinder its efficacy. Among topical treatments currently available for scars caused by injuries, acne, or surgery, non-CBD products such as Aldara® (Imiquimod 5 %) and Mederma® (onion extract and allantoin) are commonly used. However, transdermal CBD-based therapies could offer a viable alternative, particularly given its advantages in pharmacokinetics compared to oral routes (Table 4).

Table 4
Key differences in topical vs transdermal applications of CBD.

Aspect	CBD Topicals	CBD Transdermals
Action Area	Localized to the application site	Systemic (enters bloodstream)
Skin Penetration	Stays in surface layers	Designed to penetrate deeply
Onset/Duration	Quick onset, shorter effects	Slower onset, longer-lasting effects
Best For	Local pain, inflammation, skincare	Chronic pain, anxiety, systemic issues
Delivery Methods	Creams, balms, lotions	Patches, specialized gels

4.2.2. Pharmacokinetic advantages of transdermal delivery of CBD

Since EMA approved in 2019 the first CBD-based orphan medicine Epidyolex® (GW Pharma International B.V., Amersfoort, the Netherlands) as an oral solution (100 mg/mL) indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut and Dravet syndromes (European Medicines Agency (EMA) 2019), low bioavailability of CBD (13–19 %) was observed due to its very-limited water solubility in gastrointestinal fluids, other intake routs being now studied (Bulbake et al., 2017). It has been observed that the (trans) dermal administration of CBD is advantageous in terms of pharmacokinetics in comparison to the gastroenteric one (Bruni et al., 2018). Several studies evidenced that topical route of CBD administration represents a significant therapeutic tool; plasma concentrations of CBD were observed in animal models after the transdermal gel application. According to FDA, to date, no CBD-containing drug has met applicable

FDA requirements to be legally marketed for nonprescription use (U.S. Food and Drug). In order to bridge the gap between science and clinical treatment there is an unmet clinical need for effective treatments for skin conditions, in particular to address inflammation, pruritus, dryness and redness, commonly cited by patients as the factors which affect them most (Sidgwick et al., 2015).

4.3. Novel approaches to transdermal delivery of CBD

The peculiar organisation of *stratum corneum* that creates the protective barrier with its overlapping layers of corneocytes embedded into the lipid matrix ensures no molecules can passively diffuse. Although this level of imperviousness is beneficial for homeostasis, thermoregulation, and immunity shielding, it limits greatly the administration of transdermal actives unless specific physico-chemical properties are met (i.e. molecular weight, log Kow/log P value, daily dose vs. therapeutic dose). CBD presents the desired molecular weight range (300–350 Da) and exhibits a suitable melting point (66–67 °C), but it's highly lipophilic nature (logP 6–7) poses significant challenges. Literature reports several strategies for breaching the stratum corneum, among the most sought-after being nano-based technologies. From various penetration enhancers (Kováčik et al., 2020) either chemical of physical, to nanocarriers (Partalis, 2022; Grifoni et al., 2022; Hasan et al., 2023; Morakul et al., 2023), micro-nanoemulsions (Demisli et al., 2023; Nakano et al., 2019; Muresan et al., 2023), patches and microneedles (Thota, 2019; Shi et al., 2023; Bagde et al., 2024; Amato et al., 2024; Salau et al., 2022; Yu et al., 2022), seems like every variant has been explored, and yet challenges still arise.

Novel strategies such as micelles-in-liposome systems proposed by Franzè *et.al* (Franzè et al., 2023) provide enclosure of hydrophobics into the inner core of the vesicles, resulting in an enhanced TDDS, namely a drug-in-micelles-in-liposome system (DiMiL). The CBD permeation was significantly improved in comparison to deformable liposomes DS (3–5 times increased permeation), thus justifying the DiMiL systems rationale and utility. An interesting insight from these findings is the use of pro-liposomes as starters or midway builders for preparation of other deformable liposome-based cutaneous dosage systems, thus improving their stability without compromising the overall performances.

Others explored nanosuspension-loaded dissolving microneedle patches (Cheng et al., 2024) targeting intradermal delivery of high doses of CBD and enhancing its solubility. According to authors, their approach in using nanosuspensions aims to offer a high drug-loading capacity with minimal use of surfactants (Aparicio-Blanco et al., 2019; Kok et al., 2022; Rao et al., 2022). Although not being a novel strategy, implementing it alongside dissolving microneedles (DMNs – improved dissolution and mechanical strength by including hyaluronic acid (HA), PVP, and trehalose) provides unwavering particle distribution and flow, sustained concentration gradient and enhanced passive diffusion, especially for highly lipophilic drugs. The skin permeation obtained using this system peaked at 44.14 ± 3.55 % (61.36 ± 67.44 μg CBD) after 8 h and remained at the site for at least 48 h. 80 % of CBD was delivered under 24h, efficacy higher the similar TDDS (Shi et al., 2024).

In the first pharmacokinetic study in humans that demonstrated systemic circulation entering of CBD (and THC) via transdermal administration (Varadi et al., 2023), a novel Gefion GT4 technology (Canada, 2020) comprised of an emulsion technology containing penetrating agents, basement membrane disruptors, and vasodilators was utilized for transporting CBD into the dermis layer. After administering 100 mg of CBD emulsion topically a C_{max} of 576.52 ± 1016.18 pg/mL at aprox. 8 h was obtained; with CBD being absorbed at a faster rate compared with THC (123.36 ± 530.97 versus 71.5 ± 1142.19 h-1). The study concluded that C_{max} of cannabinoids delivered transdermal appear to be lower than that of inhaled or oral routes of administration, despite a higher delivered dose. But, considering the low number on participants (n = 18), as well as the variability between individuals, structure and integrity of the skin, metabolisms, age, etc., the results must be considered in the context of these limitations. It's important to underline that the majority of CBD transdermal applications target conditions related to pain management (chronic) and inflammation (e.g. arthritis) (Urits et al., 2020; Botea et al., 2024; Ferreira et al., 2023; Trial et al., Maida and Corban, 2017).

Section Highlights

Skin as a Route for Delivery: The skin's unique properties enable the transdermal delivery of CBD, facilitating diffusion through three main pathways: intercellular, transcellular, and appendageal. This method offers a convenient alternative to oral administration, primarily targeting localized effects while minimizing systemic side effects.

Benefits of Cannabinoids: CBD demonstrates potential benefits for skin health, including anti-inflammatory effects and improved skin conditions such as acne, psoriasis, and eczema. Recent studies have shown that CBD can normalize sebum production and rejuvenate the skin's appearance.

Challenges in Delivery: The lipophilic nature of CBD (logP ~6) poses significant formulation challenges, including low aqueous solubility and poor skin penetration. Effective penetration enhancers and innovative formulation techniques are crucial to improve CBD's bioavailability and stability.

Research Insights: Ongoing clinical trials are investigating CBD's effects on various skin conditions, revealing promising therapeutic applications. Recent pharmacokinetic studies suggest that transdermal delivery systems may enhance CBD's efficacy for chronic conditions.

5. Global overview of medical cannabis policies

5.1. Industrial Hemp vs. Marijuana

The global landscape of medical cannabis policies reflects diverse approaches to regulation, access, and applications of cannabis-derived products for therapeutic purposes. While some countries have embraced widespread medical use, others maintain more restrictive frameworks.

The difference between industrial hemp and marijuana lies in the amount of THC they contain: in marijuana THC is the main active compound and it is found in a proportion of over 20 %, while in hemp it does not exceed 0.3 %, the dominant active being cannabidiol. From a medical point of view, THC and CBD have many similar effects, but CBD does not produce euphoria, that "high" associated with the drug, which actually comes from THC (Controversatul Cannabis 2022). That is why THC is considered a psychoactive molecular compound, while CBD is classified as a phytocannabinoid devoid of psychotomimetic effects (Martin-Santos et al., 2012) which could even be used as an anti-psychoactive substance, because it seems to be able to modify the effects of Δ9–THC by decreasing anxiety and antagonizing other THC-effects (Nadulski et al., 2005).

In addition, it should be mentioned the WHO Expert Committee on Drug Dependence recommendation (a footnote to be added to Schedule I of the 1961 Single Convention on Narcotic Drugs) mentions that "Preparations containing predominantly cannabidiol and not more than 0.2 percent of delta-9-tetrahydrocannabinol are not under international control." The motivation was that cannabidiol is used to treat childhood epilepsy. It is not intoxicating, not psychoactive and there is no evidence of dependence or abuse, on the contrary, it is generally well tolerated with no evidence of problematic use or associated public health concerns (Drugs (psychoactive) 2022; UN Commission on Narcotic 2022).

5.2. Regional policies and access to medical cannabis

5.2.1. Europe

In Germany the access to non-psychotropic CBD for medical purposes is extensive. Since 2017 *Cannabis* formulations were allowed to be prescribed for any life-threatening illness and for improvement of the quality of life of patients with severe diseases (Stöver et al., 2019), namely patients which have a serious medical conditions and where the conventional means of treatments have been exhausted (The Germany Cannabis Report 2022).

The cannabis policy is associated in Italy with the application of pharmacologically active plant-origin compounds based on doctor prescriptions for medical use, pain or cachexia due to cancer or HIV.

Croatia provide greater access to medical cannabinoids than Czechia, but lesser than Germany or the Netherlands (Kirilov et al., 2020). All drugs that contain any amount of THC used to be accepted as narcotics since 2019 in Norway, when the common use of CBD oils with less than 0,3 % THC became available.

In Ireland was introduced a Medicinal Cannabis Access Scheme in June 2019 that allows patients with specific conditions (MS spasticity, chemotherapy-induced nausea and vomiting) to obtain as treatment of last resort the medicinal cannabis. In the meantime, the prescription CBD-containing products (Epidiolex™ and Sativex™) are not currently marketed in Ireland, despite both having EU marketing approval. The non-medical use of *Cannabis* remains illegal (Medical Cannabis Access Programme 2023).

The recent survey research of Zobel *et al* (2019) indicates CBD use by a range of people, with flower-based, light cannabis products used by young groups (were often also consuming illegal cannabis), while the major segment of users are older group, who use CBD oil for medical purpose or well-being (Cannabidiol (CBD) 2023).

In Austria, the use of CBD was introduced in 2019 as an investigational new drug (IND) and its consumption has been considered reasonable on the basis of extensive scientific data, while Finland and Slovenia have limited CBD formulations - magistral preparations. Other countries, such as Slovakia and Portugal have restricted CBD use.

In Bulgaria, magistral preparations of Cannabis are not allowed, and a clear strategy do not exist for the use of medicinal cannabis or for the use of CBD as an IND for medical conditions. Kirilov *et al* (2020) showed that medical CBD is commonly used in Bulgaria for pain, cancer an anxiety, as well as for sleep disorders, for relaxation and epilepsy and more rarely for anorexia or prevention of unwanted effects related to another therapy (Kirilov et al., 2020).

In Romania a law project regarding the regulation of medical cannabis (which is currently regulated as narcotic) was submitted to the Parliament in 2019 and is still under debate in the Chamber of Deputies (Plx 631/2019 - Law project of the legal status/regime of Cannabis plants, substances and preparations derived from Cannabis used for medical purpose) (PL-x nr 2022).

5.2.2. North America

There is currently legal access in USA to medicinal cannabis products (including THC and CBD-containing products) in 33 states and the District of Columbia, while 15 states have medical programs permitting access to CBD products only (Warning Letters and Test Results 2022). Non-prescription products are already available in drug stores in many USA states and online purchases with home delivery are also widely available. A well-known pharmacy chain – Walgreens, has CBD patches, sprays and creams available in more than 1500 stores in 9 states across the USA (Walgreens to sell CBD products 2023). Online products include capsules, edibles, oils, CBD crystal, vaping oils and pet products. The highest strength orally administered products tended to involve daily CBD doses of less than 100 mg.

5.2.3. Latin America and Caribbean region

As of 2021, Mexico and Uruguay were the only two countries in Latin America that had approved legislation related to the use of recreational cannabis. Another nine Latin American countries, including Argentina, Chile, and Colombia, had approved legislation related to the medicinal use of cannabis. As of 2023, an estimated three million people were considered users of medical cannabis in the region (Ransing et al., 2022). Cultivation in this region is generally restricted to licensed or medical purposes, with Uruguay and Jamaica allowing personal cultivation.

In the Dominican Republic, cannabis is illegal for all type of uses, with strict penalties for possession. Law 50–88, enacted in 1988, categorizes offenses based on the amount possessed, with penalties ranging from six months to 20 years in prison (No, 1988). Here cannabis remains classified as a dangerous drug. Alongside Dominican Republic, Venezuela and Cuba also have a strict prohibition position for recreational and medical use of cannabis. As for the Cayman Islands, in October 2024, plans were announced for holding a referendum to decide whether possession of small amounts of marijuana should be treated as a minor offense, similar to a traffic ticket (Cayman Islands 2025). Here medical marijuana was legalized in May 2017, but recreational use remains illegal pending the referendum's outcome. Medical use is allowed under license in Argentina, Colombia, Mexico, Brazil, Chile, Peru and Ecuador, and its being decriminalized in Costa Rica and Jamaica. This reflects the region's progressive yet uneven approach to cannabis reform.

5.2.4. United Kingdom

In UK, the legislative changes from November 2018 defined a new category of "cannabis based products for medicinal use" allowing these products to be prescribed by specialist doctors in cases of exceptional needs (Home Office 2018). Recent analyses demonstrated that many non-prescription CBD products, both OTC and via online purchase contain concentration of THC higher than those legally permitted in UK (Gibbs et al., 2019), making their sale and possession illegal (home office 2018).

5.2.5. Australia and New Zeeland

Australia introduced in 2016 the legal medicinal cannabis availability and allowed the cultivation and the manufacture of cannabis-based medical products according to strict security and quality requirements. A range of more than 100 unregistered products (oils, capsules, cannabis flower and buccal sprays) with varying CBD/THC content are available in Australia for prescription, preferentially accessed by patients suffering from epilepsy, while other illegally sold are used to self-medicate conditions such as chronic pain and anxiety (Lintzeris et al., 2020).

Similar, in New Zeeland since 2018 the medical cannabis and cannabis- based medicines are available, but sometimes their prescription is requiring a written approval from the Ministry of Health. A new Medicinal Cannabis Agency (MCA) became operational in April 2020, aiming to improve the access to quality cannabis medicines for patients, through a new Medicinal Cannabis Scheme. Remarkable health outcomes were reported by the first 400 patients that have obtained CBD on prescription, which have noted significant improvement in anxiety, pain and quality of their life (Gulbransen et al., 2020).

5.2.6. Asia and Pacific region

Excepting Australia, New Zealand, and Thailand where medical use has been approved, in South Korea and Singapore it is still limited and even illegal in other countries from this region. Except for Australia, none of the Asia-Pacific region countries allow recreational use. China and Japan are expected to approve medical use, whereas Australia and New Zealand are working on decriminalization. Most cultivation is limited and allowed under strictly regulated medical use. Cannabis seizures have changed following these policies (Areesantichai et al., 2020). Survey data from Australia, New Zealand, Japan, and Thailand conducted in different years show that the use of cannabis among the general population has increased.

In June 2022 cannabis was legalized in Thailand, making it the first Southeast Asian country to do so (Yimsaard et al., 2023). India prohibits the cultivation (large and home-based), possession, trafficking, and consumption of all cannabis preparations except bhang (Balhara et al., 2020) (with a maximum threshold of THC set between 0.2 - 0.5 %). Cannabis is not being decriminalized, nor permitted for use other than medicinal or research purposes. Nepal and Malaysia, on the other hand do not even allow medicinal or research use. Turkey and Iran ban all cannabis use with the exception of dronabinol capsules and Sativex® sprays for some limited research projects (in Iran) and medical conditions (in Turkey). The punishment methods that are being instated for not obeying drug legislation are extremely high, including the death penalty. China, Singapore, Malaysia, Vietnam, Indonesia, North Korea, Iran, and Kuwait practice a high application of the death penalty for drug offenses (The Death Penalty for Drug Offences 2025). Ninety-eight percent of all the confirmed drug-related executions in 2023 took place in Iran.

5.2.7. Africa and the Middle West

In 2018, the Constitutional Court of South Africa decriminalized the private use and cultivation of cannabis for personal purposes by adults. However, public consumption and commercial activities remain prohibited (Cannabis law 2025). Lesotho was the first African country to legalize the cultivation of cannabis for medical and scientific purposes in 2017 (Thetsane, 2024). The goal of this action was to boost economic growth and draw in foreign investment. In 2018, Zimbabwe legalized the cultivation of cannabis for medical and scientific use, issuing licenses to both individuals and companies, followed by Zambia in 2019, Malawi, Rwanda and Ghana in 2020. Recreational use remains illegal in this region. In 2021, Morocco legalized the cultivation of cannabis for medical and industrial uses in certain regions, aiming to improve farmers' incomes and curb illegal production (Morocco pardons 2025).

As for the Middle East, Israel has a well-established medical cannabis program (since 1992 medical use being approved), with the Israeli Agency on Medical Cannabis (IMCA) overseeing licensing for cultivation, extraction, packaging, and distribution (Aguilar et al., 2018). Recreational use remains illegal, though enforcement is relatively lenient. The United Arab Emirates (UAE) enforces stringent anti-drug legislation, including harsh penalties for cannabis possession and consumption. However, the law allows for the use of cannabis for medical purposes, provided it is prescribed by a licensed physician in the UAE (Aguilar et al., 2018).

These examples highlight how cannabis laws in Africa and the Middle East are dynamic and diverse, with some nations adopting reform for industrial and medical uses while others uphold stringent bans, particularly with regard to recreational use.

5.3. Cannabis based medication – prescription only

The prescription-only CBD medication - Epidiolex™, has received marketing approval by regulatory agencies worldwide including Food and Drug Administration (FDA) and European Medicines Agency (EMA), in response to the urgent need expressed by parents of children with intractable epilepsy. This is an oil containing 100 mg/ml CBD recommended for patients over 2 years of age in the treatment of certain intractable epilepsies, namely rare forms of pediatric epilepsy (such as Dravet and Lennox-Gastaut Syndrome) (Dos Santos et al., 2015). Through the mutual recognition procedure, Epidiolex™ is already marketed in 17 EU Member States. This medicine/drug is typically administered at doses of 20 mg/kg/day (800 mg total daily dose of CBD for a 40 kg child) (Thiele et al., 2018; Health Effects 2022).

There are also many countries that have on the market the buccal spray Nabiximols - Sativex™ containing both THC and CBD in a 1:1 ratio (27 mg/mL THC, respectively 25 mg/mL CBD) (Kirilov et al., 2020) which is administered for moderate to severe spasticity treatment in multiple sclerosis, using a dose of 8–16 spray per day, delivering around 20–40 mg CBD in total (Rice and Cameron, 2018) and as an adjunctive analgesic treatment in cancer patients. As of September 2016, Nabiximols has been launched in 15 countries, including Canada, Germany, Italy, Spain, the United Kingdom, and has been approved in a further 12, but not in the United States. In some countries, such as Czech Republic, Ireland, Netherlands, Slovakia and Slovenia there is the possibility for it to be available for an individual patient through s special permit.

The U.S. Food and Drug Administration has licensed three drugs based on cannabinoids, some are from natural derived compounds, while others are synthetic. For example, Dronabinol, the generic name for synthetic Δ^9-THC, marketed under the trade name of Marinol® is clinically indicated to counteract the nausea and vomiting associated with chemotherapy and to stimulate appetite in AIDS patients affected by wasting syndrome. Another substance, a synthetic analog of Δ^9-THC, nabilone (Cesamet®), is prescribed for similar indications. Both Dronabinol and nabilone are given orally and have a slow onset of action. In July 2016 the FDA approved Syndros®, a liquid formulation of Dronabinol, for the treatment of patients experiencing chemotherapy-induced nausea and vomiting who have not responded to conventional antiemetic therapies. The agent is also indicated for treating anorexia associated with weight loss in patients with AIDS.

According to an extensive report emitted by of the Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda Board on Population Health and Public Health Practice Health and Medicine Division Washington, DC, 2017, there is conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of chronic pain in adults (especially cannabis), that is an effective antiemetic in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids), and helps in improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids).

There is moderate evidence that cannabis or cannabinoids are effective for improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols). There is limited evidence that cannabis or cannabinoids are effective for increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids), improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol), improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial). There is currently insufficient evidence to conclusively support or refute the use of cannabis or cannabinoids as an effective treatment for several conditions. These include cancers such as glioma, cancer-associated anorexia-cachexia syndrome, and anorexia nervosa. Similarly, evidence is lacking for the efficacy of cannabinoids in treating symptoms of irritable bowel syndrome (via dronabinol), spasticity in patients with spinal cord injuries, and symptoms associated with amyotrophic lateral sclerosis. Additionally, cannabinoids have shown limited evidence in addressing motor symptoms in Parkinson's disease, levodopa-induced dyskinesia, dystonia (via nabilone and dronabinol), achieving abstinence from addictive substances, and mental health outcomes in individuals with schizophrenia or psychosis (via cannabidiol). As the extensive report concluded, there is limited evidence of a statistical association between cannabinoids and better outcomes (i.e., mortality,

disability) (E and M National Academies of Sciences 2017).

5.4. Cannabis based medication – non-prescription

Non-prescription CBD products involve relatively low daily doses of CBD, namely capsules containing 10–50 mg CBD or oils of 50–100 mg/ml concentration, which are dosed at a few drops per day. Millar *et al* (Millar et al., 2019) suggested that such doses are below those identified as effective in clinical trials. Many countries now permit over-the-counter (OTC) or online access to a variety of CBD products, which are often extracts of the flowering heads of industrial hemp cultivars that are grown for seeds and fibre. There are multiple forms of presentation, such as CBD oils and tinctures, gel capsules, purified CBD crystals as well as balms and lotions for topical applications (McGregor et al., 2020). Accessible CBD products include also chewing gum, lozenges, gummy bears and sports drinks. High concentration of CBD vapes oils (to be used in e-cigarettes devices) are available in some European countries (such as Germany, Ireland, UK, Switzerland) or no-EU (such as USA, Canada and Japan) and third countries.

Currently, CBD-based products are not subject to any mandatory testing or regulatory framework to determine the indication of origin, daily dosage, route of administration, maximum permitted dose, packaging or product stability. There is an exception, namely magistral CBD formulation prepared by pharmacists. In Germany, for example, the German Drug Codex (DAC) suggests that the preparation of 5 % CBD in medium chain triglyceride-containing oils requires detailed analytical control (DAC/NRF 2022). In Italy, galenic pharmacies are allowed to prepare precise doses of cannabis for inhalation (vaping), herbal teas, resins, micronized capsules and oils. The preparation of the oil requires considerable attention since it is easy to adjust the individual recommended doses and the duration of treatment, knowing that the bioavailability of the active compounds significantly influence the efficacy of the product. There are Dutch varieties of hemp (e.g. Bedrolite) with a CBD content of 9 % and a THC below 1 % which are commonly used in the preparation of CBD-based oil. It should be also emphasized that in Italy pharmacists are allowed to distribute CBD oils obtained from hemp, but they are declared as additives or aromatic preparations (if they are produced in Italy) or as food supplements (if they are imported from other EU countries) (Pavlovic et al., 2018).

The European Commission has updated the EU's Cosmetic ingredient database to include an entry for CBD derived from extracts, tinctures or resin of *Cannabis sativa* L. The change means naturally derived CBD may now be used in cosmetics in the EU. It follows a ruling in a French case that went before the EU Court of Justice in late 2022 in which the high court ruled that CBD cannot be regarded as a narcotic, and that CBD products should enjoy the same free movement of goods between and among member states as other legal products (CJEU landmark ruling confirms 2024). That case eventually led the Commission to reset its position, and establish that CBD should not be considered a drug (International groups 2022) (Fig. 4).

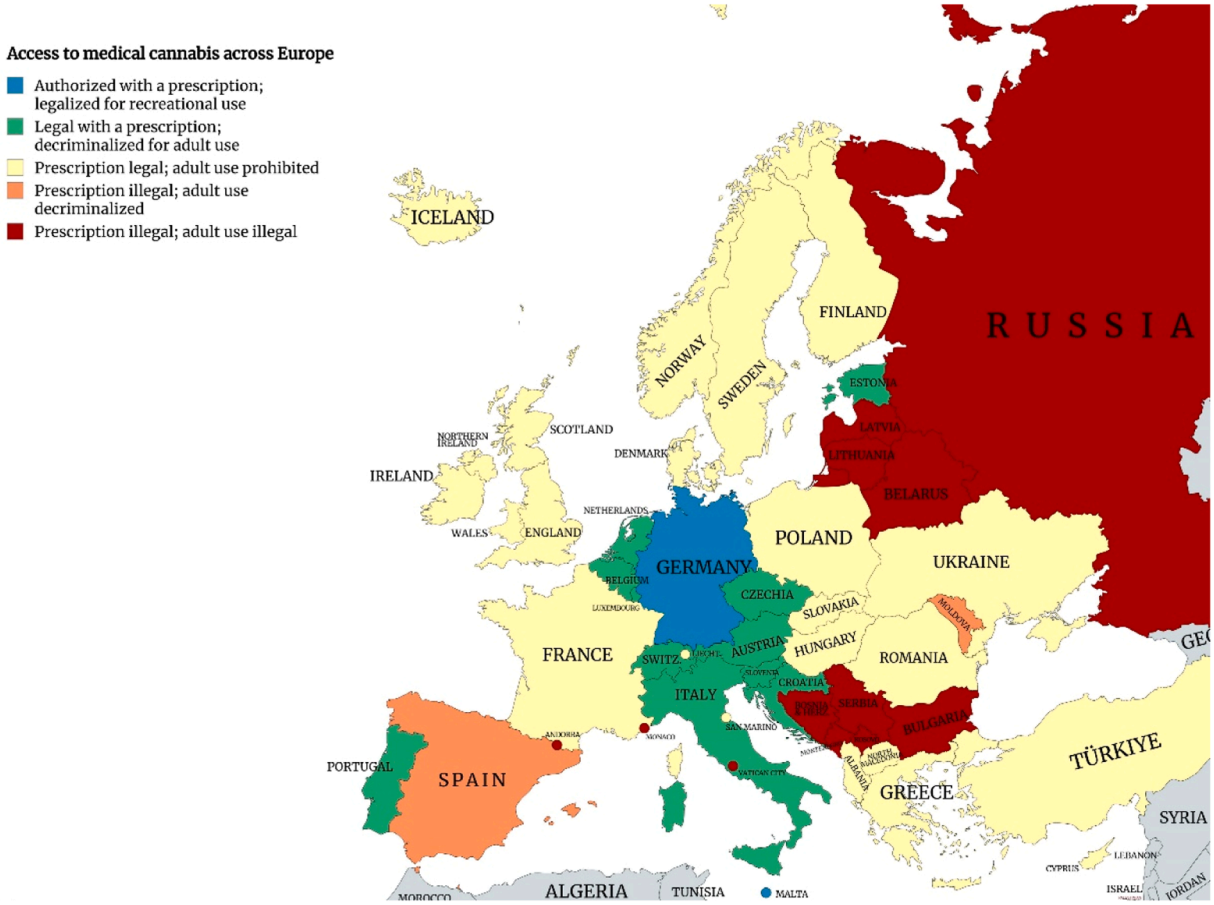

Fig. 4. Access to medical cannabis across Europe varies widely due to differing national policies, but progress is evident in most countries. The landscape is dynamic, with increasing public acceptance driving changes in both medical and recreational cannabis policies. Each country's approach depends on cultural, legal, and healthcare priorities, resulting in a diverse but evolving environment across the continent. Germany and Malta (blue) are the only EU countries that allow prescription and recreational use of cannabis. Original figure created with mapchart.net.

5.5. Cosmetic applications and market dynamics

For cosmetic products containing CBD, the European Commission has updated the EU's Cosmetic Ingredient Database to include CBD derived from extracts, tinctures, or resin of *Cannabis sativa* L. This change permits the use of naturally derived CBD in cosmetics across the EU. Additionally, transdermal delivery targets conditions such as chronic pain, epilepsy, and spasticity.

Dosing is a critical factor in the efficacy of CBD cosmetic products and should not be constrained by economic considerations. Most skin-care vendors advertise products in the 200 mg to 400 mg range, but, a quick survey of common over-the-counter CBD products finds a tenfold concentration range variance in the effective dose i.e., from 0.3 mg to more than 10 mg of CBD per mL of the base product, especially since cosmetic products are not regulated by FDA. Among commercially available cosmetic products we enumerate: Herbivore Botanicals Emerald CBD + Adaptogens Deep Moisture Glow Oil, Saint Jane Luxury Beauty Serum, Cannuka Nourishing Body Cream, Kiehl's Cannabis Sativa Seed Oil Herbal Concentrate, Josie Maran Skin Dope CBD Argan Oil, Cannuka CBD Cleansing Body Bar, Lord Jones High CBD Formula Body Lotion, The CBD Skincare Co. Exfoliating Cleanser, CBD For Life Pure CBD Eye Serum, etc.

There are several CBD products on the market in the cosmetic sector for topical use all around the world. These include but are not limited to serums, creams, washes/rinse-off products (cleansers, shampoos, conditioners, body washes, masks), bath products (capsules, oils, tablets and salts), deodorants, balms and toothpastes.

5.5.1. Market growth and opportunities

The innovative positioning of CBD infused skin care products coupled with effective distribution strategies are expected to boost the CBD skin-care market growth during the forecast period (CBD Skin Care Market Size 2022).

The global CBD skin-care market size was valued at $633.6 million in 2018 and is anticipated to reach $3484.00 million by 2026, with a CAGR of 24.80 % during the forecast period. The CBD skin care market exhibits an incremental revenue opportunity of $2747.4 million from 2019 to 2026 (CBD Skin Care Market Size 2022).

The North America and Europe regions have offer lucrative growth opportunity for new entrants as well as established manufacturers owing to increased spending on personal care and cosmetic products and rise in incidences of skin diseases. The liberalization of hemp and marijuana cultivation in Canada is expected to play an important role in the growth of CBD based personal care products. In addition, the continuous efforts in terms of R&D from leading cosmetic companies are expected to boost the growth of product innovations in the CBD skin-care market analysis (CBD Skin Care Market Size 2022).

The list of the key players operating in the global CBD skin-care industry includes, but is not limited to, famous companies such as: Kiehl's LLC, Cannuka LLC, Leef Organics, Medical Marijuana Inc., Lord Jones, Elixinol Global Ltd, Fab CBD Company, and Endoca LLC. Other CBD Skin Care market players identified in the value chain are L'Oréal, Apothecanna, Kana Skincare, Josie Maran Cosmetics, Cronos Group, CBD Biotech, and Estee Lauder. Among commercially available cosmetic products could be mentioned: Herbivore Botanicals Emerald CBD + Adaptogens Deep Moisture Glow Oil; Saint Jane Luxury Beauty Serum; Cannuka Nourishing Body Cream; Kiehl's Cannabis Sativa Seed Oil Herbal Concentrate; Josie Maran Skin Dope CBD Argan Oil; Cannuka CBD Cleansing Body Bar; Lord Jones High CBD Formula Body Lotion; The CBD Skincare Co. Exfoliating Cleanser; CBD For Life Pure CBD Eye Serum, etc.

Section Highlights

Global access to CBD-based products for medical purposes is expanding, with regulatory approvals in regions across **EU, USA, Australia**, and **New Zealand**.

Prescription-only CBD medications (e.g., **Epidiolex®, Sativex®**) have been approved for treating rare epileptic conditions and multiple sclerosis-related spasticity.

Studies show **mixed evidence** on CBD's impact on the immune system and hormonal changes, while non-prescription CBD products are widely available, though some regulatory challenges remain.

Market Trends: The global CBD skincare market is projected to grow significantly, with increasing demand for CBD-infused products for skin health. However, the regulatory landscape for CBD cosmetics varies by region, with no FDA-approved non-prescription CBD drugs currently available.

Product Variability: A wide range of CBD products is available on the market, including serums, creams, and cleansers, with significant variability in CBD concentrations. Effective dosing remains critical for therapeutic outcomes, particularly in the cosmetic sector.

6. Challenges and perspectives

Several points challenges were identified due to inherent limitations and variances in research findings, and due to the nature of the compound.

- ☐ ***Bioavailability and absorption limitations***: Although transdermal CBD delivery has the advantage of bypassing first-pass metabolism, which may enhance bioavailability compared to oral routes, CBD's high lipophilicity and limited skin penetration present significant challenges. Readers should note that bioavailability benefits may not be universally applicable and are dependent on specific formulation strategies, such as the use of penetration enhancers, which require further clinical validation.
- ☐ ***Therapeutic vs. cosmetic efficacy***: While CBD shows potential for anti-inflammatory and analgesic effects, the therapeutic efficacy observed in medical-grade formulations may not translate directly to cosmetic-grade products, which often lack standardized dosages and formulation guidelines. This distinction is important, as the potency, stability, and bioavailability of CBD differ markedly between therapeutic and cosmetic applications, especially given the absence of comprehensive regulatory oversight in some markets.
- ☐ ***Immune system interactions***: Research indicates that CBD may have dual effects on the immune system, potentially suppressing immune responses at high doses while stimulating it at lower concentrations. However, these findings are predominantly derived from preliminary *in vitro* and animal studies, and their relevance to human

application remains uncertain. Readers are advised to interpret these results with caution until more robust clinical data are available.

- ***Regulatory variability and market***: The legal status and quality standards for CBD products vary widely by region. While some jurisdictions have approved medical-grade products, many over-the-counter CBD products lack regulatory consistency in potency, purity, and labeling accuracy. This disparity raises concerns about the safety and efficacy of non-prescription CBD products, particularly for consumers seeking therapeutic benefits.

Further research is essential to standardize formulations, optimize bioavailability, and clarify the scope of transdermal CBD's effects, ensuring both efficacy and safety across applications.

7. Conclusions

The medicinal applications of CBD encompass a wide range of therapeutic benefits, making it a compound of significant interest in healthcare. Notably, CBD has demonstrated efficacy in pain management, showcasing its analgesic properties and potential utility in addressing chronic pain conditions. Its anti-inflammatory effects further enhance its versatility, particularly for conditions like arthritis, where inflammation plays a central role.

Beyond pain relief, CBD has shown promise as an anxiolytic, effectively alleviating anxiety and stress-related disorders. This potential extends to sleep disorders, as CBD's calming effects may improve sleep quality for individuals struggling with insomnia or related issues. In the realm of neurological health, CBD has attracted attention for its neuroprotective properties, suggesting potential applications in treating neurodegenerative disorders such as Alzheimer's disease. Additionally, its established role in managing certain forms of epilepsy—highlighted by FDA-approved medications like Epidiolex™ underscores its efficacy in reducing seizure frequency.

CBD's influence is not limited to neurological and psychological domains; it also extends to dermatological concerns. Its anti-inflammatory attributes may aid in acne management by reducing inflammation and regulating sebum production. Furthermore, preliminary research is exploring the cardiovascular benefits of CBD, with indications that it may help lower blood pressure and promote heart health. Additionally, some studies suggest a role for CBD in substance abuse treatment, potentially reducing cravings and alleviating withdrawal symptoms.

While the breadth of potential benefits is compelling, it is essential to emphasize the ongoing nature of CBD research. Individual responses to CBD can vary significantly, so consulting with healthcare professionals is advisable to ensure informed and safe use for specific medical concerns.

Transdermal CBD delivery methods, such as patches, creams or nano-based solutions, offer targeted and sustained relief for conditions like joint pain and muscle soreness. These methods bypass the liver's first-pass metabolism, enhancing CBD's bioavailability and ensuring a more consistent therapeutic effect. The convenience of direct application to the skin, coupled with a potential reduction in systemic side effects, makes transdermal CBD delivery an accessible and patient-friendly option. This approach provides both localized efficacy and ease of use for individuals seeking reliable and long-lasting solutions.

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Declaration of competing interest

Authors declare no competing interests.

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Data availability

Data will be made available on request.

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