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REVIEW



Palmitoylethanolamide: A Potential Alternative to Cannabidiol

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ABSTRACT

The endocannabinoid system (ECS) is a widespread cell signaling network that maintains homeostasis in response to endogenous and exogenous stressors. This has made the ECS an attractive therapeutic target for various disease states. The ECS is a well-known target of exogenous phytocannabinoids derived from cannabis plants, the most well characterized being Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD). However, the therapeutic efficacy of cannabis products comes with a risk of toxicity and high abuse potential due to the psychoactivity of THC. CBD, on the other hand, is reported to have beneficial medicinal properties including analgesic, neuroprotective, anxiolytic, anticonvulsant, and antipsychotic activities, while apparently lacking the toxicity of THC. Nevertheless, not only is the currently available scientific data concerning CBD's efficacy insufficient, there is also ambiguity surrounding its regulatory status and safety in humans that brings inherent risks to manufacturers. There is a demand for alternative compounds combining similar effects with a robust safety profile and regulatory approval. Palmitoylethanolamide (PEA) is an endocannabinoid-like lipid mediator, primarily known for its anti-inflammatory, analgesic and neuroprotective properties. It appears to have a multi-modal mechanism of action, by primarily activating the nuclear receptor PPAR- α while also potentially working through the ECS, thus targeting similar pathways as CBD. With proven efficacy in several therapeutic areas, its safety and tolerability profile and the development of formulations that maximize its bioavailability, PEA is a promising alternative to CBD.

KEYWORDS

cannabidiol;
efficacy;
endocannabinoid;
endocannabinoid
modulators;
endocannabinoid system;
palmitoylethanolamide;
pharmacology;
safety;
Side effects

Abbreviations: PEA: Palmitoylethanolamide; CBD: Cannabidiol; EC: Endocannabinoid; ECS: Endocannabinoid System; NAE: N-acyl-ethanolamine; PPAR- α : Peroxisome proliferator-activated receptor- α ; PPAR- γ : Peroxisome proliferator-activated receptor- γ ; GPCR: G protein-coupled receptor; GPR55: G protein-coupled receptor 55; GPR119: G protein-coupled receptor 119; CB1: Cannabinoid receptor 1; CB2: Cannabinoid receptor 2; AEA: Anandamide; 2-AG: 2-Arachidonoylglycerol; TRPV1: Transient receptor potential vanilloid 1; MC: Mast cells; ALIA: Autacoid Local Inflammation Antagonism; TNF- α : Tumour necrosis factor *alpha*; IL: Interleukin; ICAM-1:

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Intercellular Adhesion Molecule 1; NF- κ B: Nuclear factor kappa B; CNS: Central nervous system; FABP: Fatty acid amide binding protein; FAAH: Fatty acid amide hydrolase; NAAA: N-acylethanolamine acid amidase; 2,4-DNFB: 2,4-dinitrofluorobenzene; CAD: Contact allergic dermatitis; AD: Alzheimer's disease; PD: Parkinson's Disease; AE: Adverse Effects; NOAEL: No observed adverse effect level; GI: Gastrointestinal; THC: Δ^9 -tetrahydrocannabinol; FSMP: Food for Special Medical Purposes; DSS: Dextran Sodium Sulfate

Introduction

Found throughout the animal kingdom, the endocannabinoid system (ECS) is a regulatory signaling network that has evolved for over 600 million years to help maintain and restore bodily homeostasis in the face of cellular stressors (1). The ECS modulates numerous bodily functions in both health and disease states, including sleep, appetite, exercise, pain, mood, memory and reward (2–5). Briefly, this system is comprised of two primary G protein-coupled receptors (GPCRs), namely Cannabinoid receptors 1 and 2 (CB1 and CB2) and two primary endogenous cannabinoid (EC) neurotransmitters: arachidonoyl ethanolamide, also known as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (6–8). It also includes transmembrane and intracellular transport systems (9, 10) and the EC degrading enzymes, fatty acid amide hydrolase (FAAH) (11) and N-acylethanolamine acid amidase (NAAA) (12).

CB1 is widely expressed in mammalian cells, including nociceptive areas of the central nervous system and spinal cord (13). In contrast, CB2 is prominent in lymphatic and immune tissues where it contributes to the modulation of pain and inflammatory processes (14, 15). The endocannabinoids 2-AG and AEA are agonists to both cannabinoid receptors and act as anti-inflammatory, neuroprotective, anxiolytic and analgesic agents (16). However, at non-physiological concentrations, the ECs can also interact with non-EC receptors such as the Transient Receptor Potential Vanilloid Channel 1 (TRPV1) (17). These are found ubiquitously in the body including the aforementioned immune cells and nociceptive centers as well as in the cardiovascular tissue, muscles, skin, bones, adipose tissue, kidney, GI tract and liver (18). Modulation of the ECS may therefore have therapeutic potential in multiple pathological states (16).

Apart from ECs, phytocannabinoids present in the cannabis plant (*Cannabis sativa* L.) targets cannabinoid receptors which lend the plant its medicinal properties and conversely its high abuse potential. The two most abundant phytocannabinoids found in cannabis are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD), together with over a hundred chemically related compounds (19). Although CBD lacks the intoxicating effects of THC it comes with ambiguity in efficacy, safety and regulatory status. As a result, identifying alternative ECS modulators is significant in the scientific community (20). Endogenous endocannabinoid-like compounds such as palmitoylethanolamide (PEA) target similar pathways to cannabinoids, but without the abuse risk and legal ambiguity surrounding phytocannabinoid usage (21).

CBD is a major constituent of *Cannabis* that does not cause a euphoric high (22, 23). It is one of the most extensively studied phytocannabinoids and has been shown

to have significant anti-inflammatory and antioxidant effects (24). Additionally, it attenuates the memory-impairing effects produced by congener psychotropic compounds in *Cannabis* (24, 25). Clinical and pre-clinical studies have reported its analgesic, neuroprotective, anticonvulsive, anxiolytic, anti-depressant, antiemetic, anti-tumoral and antipsychotic properties (23, 26–31). It has been most successfully medicalized as an adjuvant treatment for refractory epilepsy in children under the brand name Epidiolex® (32). A handful of studies have explored the role of CBD in other disease conditions such as Parkinson's disease (PD) (24), Alzheimer's disease (AD) (24), Schizophrenia (33) and Tuberous Sclerosis (34).

However, there are non-unanimous laws regarding the regulations (35, 36) of commercially available CBD products due to its close affiliation with THC (22). Moreover, adverse effects of CBD have been documented in animals (37) and humans alike (38). There is also a paucity of information on its mechanisms of action through the ECS and its long-term safety profile, specifically changes that may occur in the CNS with long-term exposure (24, 31–33). No study to date has elucidated CBD as an ECS modulator in a healthy state.

PEA is an endocannabinoid-like lipid mediator belonging to the family of N-acyl ethanolamine (NAE) phospholipids (39). It is present in all cells, tissues and fluids of the human body, including the brain, and acts locally (40). PEA levels are altered in pathological states, suggesting its protective role (41). First isolated from soybean lecithin and egg yolk in 1957, PEA was initially identified to have anti-inflammatory and antiallergic effects (42).

PEA exerts its analgesic and anti-inflammatory effects primarily through activation of the ligand-operated transcription factor PPAR- α (43–45). During chronic inflammation, tissue levels of endogenous PEA decrease due to reduced production and increased degradation (12), and are therefore inadequate to restore homeostasis. Several exogenous PEA formulations have therefore been developed. PEA containing products and supplements have been marketed under brand names such as Levagen®, Levagen⁺, Normast®, Glialia®, Adolene®, Visimast®, and Pelvilin® in different countries either as a Food for Special Medical Purposes (FSMP), nutraceuticals or food supplements, usually at a dose of 1200 mg/day (46). The efficacy of exogenous PEA is impaired by poor oral bioavailability, due to its highly lipophilic nature (39). Bioavailability is improved by micronizing (0.1 to 100 microns), ultra-micronizing (90% of particles < 6 microns), and water-dispersion systems such as LipiSpense®, which acts by preventing agglomeration of lipophilic particles (21, 47).

This paper compares the mechanisms of action, pharmacology, safety profile and regulatory status of CBD and PEA in order to determine whether PEA could be a suitable alternative to CBD.

Molecular mechanisms

CBD

While CBD is currently only approved for use in two rare pediatric conditions (Dravet and Lennox-Gaustaut syndromes), it has been used experimentally to treat a range of mental and physical ailments (48). It recruits various mechanistic

pathways to exert its effect on the human body, including regulation of the ECS system. A few studies using inflammatory stimuli report that CBD's action is attributed to CB1 and CB2 receptors such as in a bacterial liposaccharide induced sepsis model and CB1 receptor antagonist AM251 reversed CBD-induced gastric emptying (49). In another report using an asthma like disease murine model, CBD-induced Interleukin-5 (IL-5) suppression was inverted by a CB2 receptor antagonist (50). However, the same study identified no clear receptor dependence suppression of IL-4, IL-13 and Eotaxin. Nichols and Kaplan (2020) also showed cytokines were suppressed by CBD administration in mouse splenocytes in both wild-type and CB1 and CB2 receptor knockout mice (22). Previous studies have also demonstrated that in a corneal inflammation mouse model, ophthalmic administration of CBD reduced neutrophils in both wild-type and CB2 receptor knockout mice (51). The overall body of evidence therefore indicates that CBD may have other pathways of action other than direct interaction with the ECS, which can be only achieved at supraphysiological levels *in vitro* (52).

It has also been suggested that CBD may modulate cannabinoid receptor activation *via* an allosteric mechanism (16). At nanomolar range it antagonizes the pharmacological effects of THC and AEA, presumably by binding to a negative allosteric site (49–55). CBD as an allosteric modulator of cannabinoid receptors can subtly yet powerfully influence agonist signaling (16). Furthermore, CBD may be considered as a negative allosteric modulator of 2-AG (54). This may also explain why CBD can attenuate the psychotropic effects of THC such as anxiety and short-term memory loss (56). However, the actual presence of these allosteric sites has not yet been directly demonstrated (57).

In terms of CBD's anxiolytic effect, Fogaca et al., 2018 suggested that CBD prevents the neuroplasticity and behavioral changes induced by chronic stress *via* CB1 and CB2 receptor activation. They showed that repeated injections of 30 mg/kg body weight CBD for 14 days exerted anxiolytic effects in chronic unpredictable stress-induced mice and prevented stress induced-decrease in neurogenesis, dendritic remodeling and the expression of synaptic proteins in the hippocampus (23). Selective antagonists of CB1 and CB2 receptors abolished the CBD-induced behavioral response. Furthermore, the pro-neurogenic effect of CBD was dependent to a greater extent on CB2 receptors. The study concluded that CBD's anti-stress effect is differentially and complementarily mediated by cannabinoid receptors. In single dose studies, CBD was demonstrated to be anxiolytic through simulated public speaking tests at doses of 300–600 mg (58–60).

A few studies suggest that lower doses of 10 mg/kg may have greater anxiolytic effects than 100 mg/kg in rats (61). The anxiolytic effect may contribute to CBD's role in sleep modulation. For example, a crossover study compared nitrazepam with CBD and reported that a high dose of 160 mg/kg CBD increased the duration of sleep for patients with insomnia (62). Previously, CBD (600 mg) was shown to induce sedative effects in healthy volunteers with six hours of sleep (58). Conversely more recent studies have reported that injecting CBD directly into the lateral hypothalamus and brain ventricles increased waking and decreased REM sleep (63, 64). Notably, along with the contradictory dose ranges and efficacy outcomes of CBD on anxiety and sleep, these studies failed to elucidate CBD's direct mechanism of action through cannabinoid receptors.

Many of the aforementioned studies hint at the entourage effect of CBD on AEA in a cannabinoid receptor-independent mechanism. The study conducted by Fogaca et al., in 2018 also demonstrated that CBD administration decreased expression of FAAH enzyme, and over-expression of FAAH prevented the neurogenic effect of CBD (23). FAAH is responsible for the degradation of AEA (2). CBD was shown to moderately inhibit AEA hydrolysis by FAAH in both pre-clinical and clinical studies (2, 49, 65, 66). Moreover, studies have demonstrated that CBD competes with AEA and 2-AG for binding sites on the putative EC transporter, which in turn inhibits the cellular uptake and catabolism of AEA (67). Therefore, CBD may indirectly regulate the EC tone by augmenting ECB signaling, and increased circulating levels of FAAH substrates have been reported upon ingestion of CBD (65). Overall, CBD exerts both direct and indirect actions on cannabinoid receptors and endocannabinoid levels.

Since the ECS has a broad spectrum of physiological importance during neuronal development, CBD's ECS modulation is assumed to contribute to its effectiveness in treating epilepsy and other neurological disorders (52). Epidiolex®, a US Food and Drug Administration (FDA) approved drug with purified CBD, has been used since 2018 in children with Dravet Syndrome and Lennox-Gastaut Syndrome (68, 69). A recent controlled study with pediatric epilepsy documented the beneficial effect of CBD in reducing seizure frequency by almost 50%. Six patients from the CBD group withdrew from the trial due to adverse events compared to one patient from the placebo group. Moreover, 9% of the CBD treated patients demonstrated elevated liver aminotransferase levels (70).

The numbers of adequately powered, placebo-controlled randomized studies on the safety and efficacy of CBD-based therapy in children are very limited (69). Additionally, most of these therapies reported higher rates of adverse events associated with the administration of a wide dose range of CBD (70). In epileptic adult volunteers CBD was associated with fewer adverse events, although its effectiveness was not always confirmed (68–71). In neurodegenerative disorders such as Parkinson's and Alzheimer's disease, no studies have been identified which demonstrate protection against progression. No studies have been conducted on these patients evaluating the safety of long-term CBD use (24).

Apart from ECS regulation, CBD's mechanistic pathways include activation of non-cannabinoid receptors such as non-GPCR PPAR- γ and ligand-gated ion channels TRPV1 (72, 73). It is also reported to interact with opioid, serotonin, adenosine and GABA receptors (72). Interactions through TRPV1, opioid-sparing effect and regulating the EC tones have been associated with CBD's anti-inflammatory, analgesic and temperature modulating effect (73, 74). Direct and/or indirect agonist action at HT1A receptors is considered to account for CBD's anxiolytic and antiemetic effects (75, 76).

The contribution of each of the above actions to CBD's various therapeutic effects is not entirely clear. The effects of chronic CBD-based therapies with long-term follow up periods for the above conditions have yet to be researched (48, 68, 70, 71). Furthermore, the current science of CBD is limited to disease states. There remain, therefore, serious questions on the safety and efficacy of CBD as an ECS modulator in lifestyle management. There is a need for further research on the long-term safety

and efficacy of CBD, with regulatory changes if these prove to be necessary, and proven safer alternatives for ECS in the interim.

PEA

PEA is said to have several molecular targets which can be activated directly or indirectly (39). This may allow it to confer protection through synergistic mechanisms of action. Initial research into the mechanisms of action of PEA came from the work of Professor Rita Levi-Montalcini, who discovered that PEA prevented the activation of mast cells (MCs). This mechanism was termed the “Autacoid Local Injury Antagonism” (ALIA) (77).

PEA's primary mechanism of action is its direct activation of the nuclear receptor PPAR- α (43). Activation of the PPAR- α receptor initiates a cascade of events that causes the suppression of pain and inflammatory signals, including inhibiting the release of pro-inflammatory cytokines such as IL-1 β and 6, and TNF- α (78). Preclinical studies have demonstrated PEA's function through the PPAR- α receptor, also evidenced by the abolition of its efficacy in PPAR- α knockout models or when blocked by selective PPAR- α antagonists (39, 43, 45). Lo Verme and colleagues reported that in mouse models of carrageenan-induced paw edema and phorbol ester-induced ear edema, PEA treatment caused an amelioration of inflammation in wild type, but not in PPAR- α null mice (43). In a Chronic Constriction Injury (CCI) model of neuropathic pain, repeated PEA treatment (30 mg/kg) not only reduced edema and macrophage infiltrates, but also reduced the decrease in axon diameter and myelin thickness. These effects were not present in PPAR- α null mice (79). Another study showed that in a mouse model of dextran sodium sulfate (DSS)-induced colitis, PEA's dose-dependent amelioration of symptoms was abolished by the selective PPAR- α antagonist MK866 (80). Whilst not considered part of the endocannabinoid system, PPAR receptors have been suggested to be an extension of the endocannabinoid system due to their association with endocannabinoids (81). Interestingly, recent evidence has shown that PEA, through binding to PPAR- α , resulted in an increased expression of CB2 receptors and TRPV1 activation, providing another mode of action in which PEA interacts with the endocannabinoid and endovanilloid systems (82, 83).

There is also evidence that PEA activates the orphan receptors GPR55 and GPR119, which have been putatively identified as novel cannabinoid receptors (84, 85). Ryberg and colleagues reported that PEA stimulated GTP γ S binding with an EC₅₀ value of 4 nM (84). Some animal studies have also suggested the involvement of the GPR55 receptor in PEA mediated actions. In mice sensitized with ovalbumin there was a significant increase of CB2 and GPR55 receptors. In the same study, 10 mg/kg PEA pretreatment caused significant inhibition of MC recruitment and degranulation, and pulmonary inflammation, indicating an action mediated by these receptors (86). Another study reported that intra-ventral hippocampal PEA micro-infusion in rats led to behavioral changes which were blocked by the selective GPR55 antagonist CID 160 (87). In an experimental colitis model, PEA administration (1 mg/kg) reduced inflammation and intestinal permeability and stimulated colonic cell proliferation. These effects were attenuated by GPR55, CB2 receptor or PPAR- α antagonists (88).

It has been hypothesized that PEA may also function indirectly through the endocannabinoid and endovanilloid systems. 5 mg/kg PEA administration to mice with 2,4-dinitrofluorobenzene (DNFB)-induced contact allergic dermatitis (CAD) resulted in restoration of levels of 2-AG. Additionally, PEA inhibited MC activation and neo-angiogenesis which were blocked by a CB2 receptor antagonist, suggesting the involvement of the CB2 receptor (89). In male Wistar rats induced with seizures, pretreatment with CB1 and CB2 antagonists altered the effects of PEA (90). Another study showed that in mice with accelerated gastrointestinal transit following induced intestinal inflammation, PEA administered in doses ranging from 1–10 mg/kg significantly attenuated motility beginning from the 2.5 mg/kg dose. This effect was blocked by the CB1 receptor antagonist rimonabant (91). Another possible molecular target of PEA is the TRPV1 receptor. PEA itself has little direct effect on the TRPV1 receptor, and activates it only at very high concentrations (92). Petrosino and colleagues reported that the administration of PEA increased levels of 2-AG 3-fold in human keratinocytes and 2-fold and 20-fold in human plasma and canine plasma respectively, and slightly enhanced the activity of 2-AG at TRPV1 channels (93). In another study, PEA treatment (5–10 mg/kg) in mice induced with CAD prevented ear inflammation, an effect which was inhibited by a TRPV1 antagonist. These authors also reported that PEA inhibited poly-(I:C)-induced MCP-2 expression and release in HaCaT cells, which was attenuated by a TRPV1 selective receptor antagonist (94).

Extensive research has been conducted on PEA in preclinical models, and the reported efficacy of PEA in preclinical studies has been replicated in clinical studies. A large proportion of these have pertained to various pain states such as neuropathic pain (95), joint pain (96, 97), endometriosis (98–100), migraine (101, 102), post-operative pain (103) and fibromyalgia (104). Clinical studies have also shown some efficacy of PEA in eczema (105), exercise recovery (106) and influenza and common cold (107). In neurodegenerative disorders such as PD and Amyotrophic Lateral Sclerosis, PEA as an add-on treatment may slow down disease progression (108, 109).

Pharmacokinetics

CBD

In studies assessing CBD's pharmacokinetic parameters, high intra- and inter-subject variability make it difficult to definitively characterize its pharmacokinetics in both humans and animals (110, 111). Such processes are affected by differing drug formulations, routes of administration and extent of drug exposure in subjects (110). Challenges are also posed by rapid metabolism, reduced drug recovery due to adsorption of compounds to multiple surfaces, low analyte concentration and reduced separation of compounds (110). CBD has a low oral bioavailability (13–19%) (111, 112) due to high first-pass metabolism by the liver and extrahepatic tissue (110, 111). While being primarily metabolized by cytochrome P450 (CYP) enzymes, it may also be glucuronidated by several UDP-glucuronosyltransferase (UGT) isoforms (113). Its metabolites are mainly excreted by the kidneys (111) and eliminated in the feces, urine, sweat, oral fluid and hair (110). A large proportion of CBD is excreted unchanged in the feces (110).

Studies using diverse CBD formulations and routes of administrations have shown different plasma concentrations and half-lives ranging from 0–5 days (111, 112). For instance, plasma concentrations are increased and reached faster after smoking, inhalation or intravenous administration (111). Moreover, human studies show that peak plasma concentration (C_{max}) and area under the curve (AUC) of CBD are dose-dependent, while T_{max} (0–5 h) is not affected by dose (111). However, there may be a saturation effect at higher dosages (111, 114). A dose of 10 mg CBD given orally was shown to produce a mean C_{max} of 2.47 ng/mL at 1.27 h (115). This value increased by approximately 50–100-fold when 400 and 800 mg CBD was administered (111, 116). CBD half-life also substantially increases after chronic oral administration (111, 117), though minimal plasma accumulation is reported (111, 118, 119). Animal studies display a similar trend with dose-dependent increases in both plasma and brain CBD concentrations (111, 120–122). Plasma concentrations have been shown to increase in a fed state (111, 119), or with specific drug encapsulation systems such as pro-nano liposphere (PNL) formulations (111, 123, 124). As CBD is lipophilic, its solubility may be increased after dissolution in the fat component of food (111).

There is limited data on tissue distribution, clearance and elimination rate of CBD in humans (111). One study investigating the pharmacokinetics of GW Pharmaceutical's highly purified CBD (Epidiolex®) reported their CBD to have a high oral clearance and large volume of distribution. Additionally, its elimination was found to be multiphasic with terminal elimination half-life being approximately 60 h and effective half-life estimated to be 10–17 h after 750 mg and 1500 mg CBD administration twice daily (113). In this study CBD reached steady state at around 2 days with moderate accumulation after repeated dosing (113). After single ascending doses (1500, 3000, 4500 or 6000 mg), C_{max} and area under the plasma concentration-time curve from time zero to time t (AUC $_t$) increased in a less than dose-proportional manner (113).

There are potential limitations to the efficacy of CBD due to its unique pharmacokinetics. Several studies reported a bell-shaped dose-response curve after oral administration of purified CBD, such that therapeutic efficacy is only achieved within a limited dose range (74). Gallily et al. sought to overcome this by using standardized plant extracts from the Cannabis clone 202, which is highly enriched in CBD and contains only traces of THC. The clone 202 extract provided a clear dose-dependent therapeutic effect in contrast to purified CBD (74). Some studies report that CBD may modify the effects of THC by inhibiting CYP450-mediated conversion of THC to 11-OH-THC (110, 125), while others report that this is not the case, or that CBD's influence on THC metabolite formation is slight (110, 126). Furthermore, there are limitations to accurately gauging the pharmacokinetics of CBD due to methodological issues with many of the randomized controlled trials including publication bias, selective reporting, inadequate designs and heterogeneity of subjects, doses, schemes and formulations (111, 112).

The absolute oral bioavailability of CBD in humans remains obscure due to a lack of dose-ranging studies and non-standardization of formulations (111, 127), causing ambiguity on minimum effective doses and therapeutic dose ranges (127). There may be variability of data among different populations (healthy vs. patient populations, males vs. females, cannabis naive vs. frequent users, obese vs non-obese), who are

generally grouped together rather than studied separately (111). This is a concern as different populations may have varying pharmacokinetic profiles in response to cannabinoids (111, 128). For example, as CBD accumulates in lipid compartments (111, 129), cannabinoid pharmacokinetics are likely affected by BMI (111). Clarification of these issues will require further human studies with stringent methodological controls to investigate a variety of CBD doses and formulations in distinct populations.

PEA

PEA's pharmacokinetics pose a similar challenge to CBD, in that it has a low oral absorption in aqueous solvents (21, 41, 130). Thus, its dissolution rate is most often the rate limiting step for its poor oral bioavailability (21, 130), coupled with its metabolism in the intestine and liver (39). PEA reportedly reaches peak plasma concentration within 2 h, after which its levels return to baseline, suggesting a short-lived action (93). Its bioavailability and volume of distribution have not yet been definitively characterized (131), but the literature is growing.

Researchers from Umeå University provided estimates of PEA plasma concentration, volume of distribution and half-life using data from an *in vitro* study investigating plasma concentrations of PEA after oral treatment of male Wistar rats (body weight 150–250 g) with 100 mg/kg PEA in a corn oil suspension (131, 132). They determined that even at a low bioavailability (1%) PEA's volume of distribution was greater than its plasma volume, indicating that most of the PEA was outside the blood following oral administration (131, 132). Moreover, the AUC was estimated to be $37 \pm 10 \times 10^{-6}$ of given dose/h, while the plasma elimination half-time in the rat was calculated as 12 min (131, 132). In the same study, a half-life of about 25 min was found after incubating rat liver homogenates with 50 nM PEA (132). Studies of the tissue distribution of PEA show that PEA is widely distributed around the body appearing in the adrenal glands, diaphragm, spleen, kidney, testis, lung, liver, heart, plasma, erythrocytes, retina and heart (41, 131, 133, 134). It penetrates the blood brain barrier, primarily accumulating in the hypothalamus and pituitary and presenting also in the white matter, brain stem, cerebellum and brain cortex (41, 131, 135).

PEA is primarily metabolized to form palmitic acid and ethanolamine by two enzymes, endoplasmic reticulum localized fatty acid amide hydrolase (FAAH) and lysosomal N-acyl ethanolamine acid amidase (NAAA) (39, 41, 136, 137). The relative actions of these enzymes are dependent on their expression in different tissues (39). For instance, FAAH expression may be higher in the brain and liver (138–140), while NAAA expression may be greater in the gut and macrophages (140, 141). However, FAAH potentially plays a greater role in the catabolism of exogenous PEA, which is delivered to FAAH by intracellular fatty acid binding proteins upon cellular uptake (39, 142). While the metabolism of palmitic acid, which is often incorporated into phospholipids is well known (39, 143, 144), the extent and route of excretion of unmetabolized PEA is yet to be characterized (39). As with CBD, further human studies of PEA pharmacokinetics in diverse populations are required.

As PEA's lipophilicity and large particle size are the primary hindrances to dissolution, micronized (m-) and ultramicronized (um-) PEA formulations have been

developed using air-jet milling, which effectively reduces particle size and increases the total surface area available to the gastrointestinal milieu (21, 91, 110, 130, 131). This results in a faster dissolution rate, especially as the absorption of smaller particles is not influenced by gastrointestinal tract hydrodynamics (21).

Several studies have shown m- and um-PEA formulations to possess superior therapeutic actions and greater absorbability compared to non-micronized PEA in animals and humans (31, 91, 130). Petrosino et al. found that m-PEA formulations increased plasma PEA levels by up to six-fold in beagle dogs and twofold in human volunteers respectively 2 h after oral administration (93). Plasma PEA levels were found to be higher in carrageenan-injected (CAR) injured rats given um-PEA compared to healthy controls. Plasma PEA levels in injured rats rapidly fell 5 min post treatment, as PEA was distributed from the blood to the CAR-injected paw. This may be reflective of an “on-demand” distribution of PEA to injured tissue, similar to its “on-demand” synthesis in the face of stressors (130). PEA levels in the spinal cord of CAR rats were also significantly higher than in healthy rats, potentially reflective of changes in the blood-spinal cord-barrier that may occur during peripheral inflammation (130).

A recently developed PEA formulation, using a novel crystalline dispersion technology (LipiSpense®), increased plasma PEA concentrations above baseline by 1.75 times ($p < 0.05$) that of standard PEA in healthy adults (47). LipiSpense® comprises surfactants, polar lipids and solvents which prevent lipophilic crystals from agglomerating, increasing the surface area available to the gastrointestinal tract and improving absorption (47, 145). The C_{max} of a single 300 mg dose of Levagen+® in healthy adults was similar to that found in Petrosino et al.’s human trial (91), which showed a twofold increase in plasma PEA concentration after administration of a 300 mg micronized PEA formulation. Unexpectedly, Levagen+® elevated plasma PEA levels above baseline even after 4 h, demonstrating a more sustained period of therapeutic action. As data was only collected for 4 h in this study, the exact time point at which plasma PEA levels return to baseline after Levagen+® administration is yet to be determined. The collection of more data points may increase the change in AUC between the two groups above the currently documented 1.75-fold increase (47). For both Levagen+® and the standard PEA formulation, two plasma peaks of equal height were found (at 90 and 180 min for Levagen+® and 70 and 120 min for standard PEA), further supporting potential hepatic recycling (47).

Safety and side effects

CBD

Several reviews have described the safety of CBD in in-vitro, pre-clinical and clinical studies.

In rodents, a wide range of acute doses (3–30 mg/kg bw) did not produce emesis (146), affect physiological parameters (blood pressure, glucose level, body temperature, hematocrit or heart rate), or gut transit time in rodents (147–149). Even at 60 mg/kg bw there was no evidence of ataxia, tremor, kyphosis, tail stiffness or kyphosis (150).

Longer-term dosing in pre-clinical models has been reported to cause AE’s at doses between 15–300 mg/kg bw. These include developmental toxicity, central nervous system

inhibition and neurotoxicity, hepatocellular injuries, spermatogenesis reduction, organ weight alterations, embryo-fetal mortality, reduction in hyperphagia and body weight, male reproductive system alterations, and hypotension (37, 151–161). A study in rhesus monkeys found a dose- and time-dependent worsening of hyperpnea and bradycardia (155). Various animal studies have reported increased liver weights and elevated liver enzymes with doses as low as 2 mg/kg bw (162–165).

Some mild to moderate adverse effects have been reported in humans with chronic administration (112, 166). In humans, oral administration of CBD at 10–300 mg/day to 17 subjects for 21 days (167) and at 3 mg/kg/day to 23 subjects for 30 days (168), induced no changes in neurological, physical, blood and urine examinations. The reviewed research suggests that doses up to 1,500 mg/day CBD are well tolerated (112, 166). In a phase 1/2 clinical trial of CBD in 61 children with drug-resistant epilepsy, considerably higher doses of up to 40 mg/kg/day were given for a period of ten days (169). Although SAE's (apnoea, skin eruption, thrombophlebitis) occurred in one patient at 20 mg/kg/day and one at 40 mg/kg/day, treatment was described as generally safe and well-tolerated (169).

It is important to note that these studies' primary objectives were to investigate cannabinoid activity rather than CBD's safety. Further work on CBD's long-term safety profile in humans is required. Nevertheless, with its low potential for abuse and good tolerability, CBD is a promising treatment for use in clinical settings (33, 37, 65, 170).

In other clinical trials, CBD at 10–50 mg/kg/day, commonly reported side-effects included tiredness, diarrhea, pyrexia, somnolence, hepatic abnormalities and changes in appetite and weight (38, 70, 162, 166, 171, 172). Patients who took single (1500–6000 mg) and multiple doses (750 and 1500 mg) reported 75% and 96% of these AE's, respectively (113). One case study reported that 370 mg CBD caused neurologic and cardiopulmonary depression, suggesting that doses relevant to non-diseased patients may lead to negative health outcomes (173). Pregnant women should be wary when taking CBD, as cannabinoids cross the placental barrier and may have a profound effect on the maternal and fetal immune systems (174).

The development of medicinal CBD (175, 176), has generated a greater awareness of drug interactions (165, 177–182). Co-administration of CBD with antiepileptic or anticoagulant drugs should be monitored carefully since CBD has been shown to inhibit enzymes involved in drug metabolism, particularly the cytochrome P450 enzyme system (165, 177–182). Negative effects in other diseases have also been noted; at 300–600 mg CBD per day worsened the symptoms of hypokinesia and tremor in patients with coexisting Parkinsonian features (165, 183).

PEA

Five decades of literature documenting PEA's therapeutic efficacy show good safety and tolerability in humans and animals (107, 184). Numerous clinical trials involving more than 1,500 subjects have demonstrated no adverse effects (107, 184), with doses of 300–1,200 mg per day being studied extensively in both healthy and sick populations (97, 102, 131, 185). Furthermore, PEA carries a minimal risk of toxicity and genotoxic potential (185, 186). Results from an acute oral toxicity study determined PEA's LD50 to be >2000 mg/kg body weight (185), while 14 and 90-day repeat dose toxicity studies

reported its No Observed Adverse Effect Level (NOAEL) to be >1000mg/kg body weight/day (185), the highest dose tested which is equivalent to a human dose of >9.7g/day (185, 186). A recent prenatal developmental toxicity study found PEA to be well tolerated and safe in pregnant rats at doses up to 1,000mg/kg body weight/day (186). This dose was thus determined as the no-observed-adverse-effect level (NOAEL) of PEA for maternal toxicity, embryotoxicity, fetotoxicity and teratogenicity (186). PEA has not been found to produce any drug-drug interactions (187, 188), further supporting its safety in a range of populations.

The lack of adverse effects is likely due to PEA being an endogenous autocoidal compound (107), and a natural component of the human diet (107). For treatment duration up to 49 days, current clinical trials deem the frequency of PEA ADRs to be less than 1/200, which is classified as ‘uncommon’. There is insufficient data to determine whether ADRs at these time frames are ‘uncommon’ or ‘rare’ (131). However, there is a lack of longer-term PEA dosing studies and insufficient patients to rule out an ADR frequency of less than 1/100 for 60 days or greater (131).

Finally, and in contrast with a number of pre-clinical reports of CBD-induced reproductive and developmental toxicity (38), the screening of PEA in multi-generational models has not yet found similar problems (186).

Efficacy and future applications of PEA

Over the last 60 yrs a large body of research, including pre-clinical and clinical studies, has established PEA’s protective actions in multiple therapeutic areas including pain states (95, 131, 184), eczema (105, 189), influenza and common cold (107), psychopathologies (190, 191), neurodegenerative disorders (46, 192, 193) and muscle damage (106). More recently, a number of reviews and meta-analyses have noted the efficacy of PEA in depression (194), pain management (131, 184, 195) and neuro-inflammatory conditions (196). The degree of clinical efficacy is comparable to that of CBD.

Several clinical studies have utilized of the currently most highly bioavailable form of PEA, Levagen+®. This has been shown to be effective in facilitating muscle recovery after repeated bouts of exercise (106), reducing joint pain in healthy adults (197) and improving sleep disturbance in adults (198). A further study comparing the efficacy of Levagen+ to ibuprofen in reducing pain, duration and severity of tension-type headaches is currently in peer review.

Considering the overlap between CBD and PEA pharmacology, it is not unexpected that many of the reported actions/applications of PEA resemble those of CBD. Given PEA’s status as an endogenous molecule and its related safety record, it may eventually find a number of applications in the general area of minor analgesia. Its legal status (see below) supports this.

Regulatory framework for CBD and PEA

CBD extracted from *Cannabis Sativa* is not a controlled substance and there are at least 12 potential controlled contaminants in CBD products, including THC. This

causes confusion among the general population and various companies relating to the regulatory status of products containing hemp, CBD and other cannabinoids. Regarding products on the market, the FDA has approved only one CBD product, Epidiolex® - a highly purified CBD as a prescription drug for treating Dravet Syndrome. However ever since the 2018 Farm Bill federally legalized the production of industrial hemp-derived CBD to contain no more than 0.3% THC, the demand for CBD has surged. Various products containing CBD are currently sold online, despite the US Food & Drug Administration (FDA) prohibiting sales of CBD as a dietary supplement (35). Most states have not been able to update their laws to match this federal law, leaving them without answers to CBD's legalities. Similar confusion is taking place in Europe, where in January 2019 the European Food Standards Agency (EFSA) added extracts of *Cannabis sativa*, including CBD, to the Novel Food catalogue providing they contain less than 0.2% THC (36). In order to be legally sold in the majority of EU member states, CBD products must acquire pre-market authorization. Unfortunately, the European Food Standards Agency (EFSA) has yet to approve any CBD suppliers, adding to the complexity of CBD's legal status in Europe.

Unapproved CBD products are still being sold across the globe with a lack of standardization, unapproved health claims, and a high rate of mislabeling (165). This creates inherent risks for manufacturers and the general public as CBD products may contain compounds harmful to human health or which may lead to inadvertent doping (199, 200). Numerous tests conducted by the FDA found a large number of commercially available products either did not contain the content of CBD as claimed on the labels or were contaminated with THC (201). Specifically, 21% of products tested were contaminated with THC, 43% contained more CBD than labeled, and 26% contained less (202). Further adding to the number of mis-labeled products on the market, the Food Safety Authority of Ireland (FSAI) reported 37% of products to contain more THC than the safety limits set by EFSA (1 µg/kg body weight/day) and 50% making unauthorized health claims (203). Similar reports from the Netherlands and Italy are also available (204, 205). This potentially increases the risk of AE's and intoxication among the general population with consumers purchasing CBD products. Moreover, an independent test performed by ConsumerLab.com found a wide range of CBD dosages in CBD products sold on the marketplace, from as low as 2.2 mg to as high as 22.3 mg (206).

At this time, PEA is approved to be marketed and sold globally. In the US, PEA was introduced in 2015 as a dietary supplement under the brand name Levagen®, which received self-affirmed Generally Recognized As Safe (GRAS) status. Levagen® and Levagen®+ have since received approval from the Therapeutic Goods Administration (TGA) in Australia, Food Safety and Standards Authority of India (FSSAI), Natural Health Products Directorate (NDPD) in Canada, and the Brazilian Health Regulatory Agency (ANVISA). Previously considered a Food for Special Medical Purpose [FSMP] in Europe, PEA was then reclassified as a Food Supplement in 2017 when Italy added PEA to the list of substances for use in food supplements. Normast® was the first product introduced into the European market by Epitech as a finished product, where now multiple brands are sold in that region (OptiPEA®, Levagen®, and Levagen®+).

Conclusion

The therapeutic actions of CBD and PEA overlap in their biochemical roles in humans. There is a need for further investigation of their pharmacokinetics, specifically regarding definitive bioavailability and volume of distribution, and safety and efficacy when used long-term in diseased and healthy populations. At this time PEA's safety, tolerability, consistency and regulatory profile confer certain advantages (107, 184).

Disclosure statement

S.S., M.H. and N.B. are employed by Gencor Pacific Limited. There are no other conflicts of interest involved.

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Author's contributions

P.C. prepared and edited the manuscript. S.S., M.H., R.V. and N.B. prepared the manuscript. All authors have read and agreed to the published version of this manuscript

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