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CANNABIS AND CANNABINOIDS

Phytocannabinoids and endocannabinoids: different in nature

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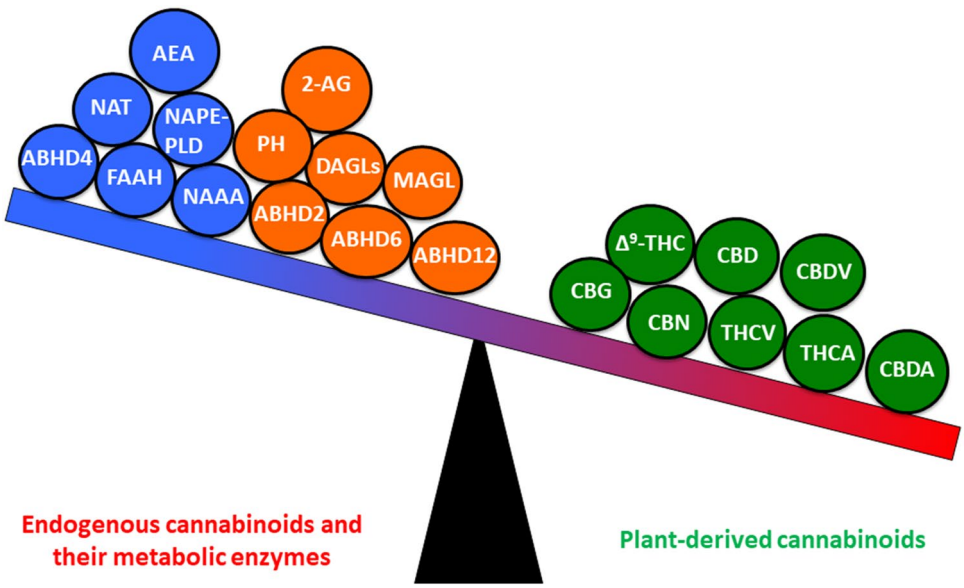
Abstract

Cannabis is one of the earliest cultivated plants, of which *Cannabis sativa* and *Cannabis indica* are the most widespread and best characterized species. Their extracts contain (phyto)cannabinoids (pCBs) of therapeutic interest, such as Δ^9-tetrahydrocannabinol and cannabidiol, along with many other compounds, so that there is no "one cannabis" but several mixtures even from the same plant. This complexity is mirrored, or even exceeded, by the complexity of the molecular targets that pCBs find in our body, most of which belong to the so-called "endocannabinoid (eCB) system". Here, we describe the major pCBs and the main components of the eCB system to appreciate their differences and mutual interactions, as well as the potential of using pCB/eCB-based drugs as novel therapeutics to treat human diseases, both in the central nervous system and at the periphery. Moreover, we address the question of the evolution of pCBs and eCBs, showing that the latter compounds were the first to appear in nature, and that the former substances took a few million years to mimic the three-dimensional structures of the latter, and hence their biological activity in our body.

Graphic abstract



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Keywords Cannabinoid receptor · Bioactive lipid · Metabolic enzyme · Pharmacophore · Signal transduction · Vanilloid receptor

1 Introduction

Cannabis is one of the earliest cultivated plants. When it is of industrial utility and culinary value, it is generally termed hemp; when it is bred for medical or recreational purposes, it is called marijuana. In both cases, the female plant produces a significant amount of bioactive and psychoactive compounds, but the existence of different species and cultivars of cannabis must be taken into account to evaluate their impact on health. *Cannabis sativa* and *Cannabis indica* are the most widespread and best characterized species of cannabis, and their extracts contain (phyto)cannabinoids (pCBs) of therapeutic interest, such as Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD), both shown in Table 1. Yet, the effect of cannabis extracts does not depend only on the amount of Δ^9-THC and CBD, but also on the presence and concentration of > 110 additional pCBs, and > 440 non-phytocannabinoid compounds like terpenoids, flavonoids and sterols (Sohly et al. 2014; Solymosi and Köfalvi 2017). Among the pCBs, the following classes have been clearly detected in cannabis extracts: (1) in abundant amounts Δ^9-THC and its analogs (including Δ^8-tetrahydrocannabinol and Δ^9-tetrahydrocannabivarin), CBD and its analogs (including the propyl derivative cannabidivarin), cannabinol and its analogs (including the propyl derivative cannabivarin), cannabigerol and its analogs; (2) in less abundant amounts cannabinodiol, cannabichromene, cannabicyclol, cannabielsoin, cannabitriol (ElSohly et al. 2017; Morales et al. 2017), as well as others like varinic (short aliphatic chain) and acidic (bearing carboxylic groups) derivatives of the major pCBs. To date, understanding of the pharmacological properties of these pCBs have only scratched the surface (Franco et al. 2020; Russo 2018). Therefore, it should be appreciated that the term "(phyto)cannabinoids" serves to cluster different plant-derived lipophilic compounds, which are clearly distinguishable from other pharmacologically related, but structurally different, natural and synthetic compounds (Ligresti et al. 2016; Pertwee 2014).

It is also remarkable that different cannabis extracts may have a largely different chemical profile (i.e., they may be different "chemovars"), which means that they may contain different components and/or different amounts of the same constituents. In addition, the modes of cultivation, harvest, extraction of active principles, and of their administration routes to subjects, may further affect the final chemical composition, clearly suggesting that there is no "one cannabis" but several mixtures even from the same plant (Friedman et al. 2019). This is the reason why there is still little understanding of the pharmacological efficacy of cannabis extracts, and indeed remaining uncertainties represent a warning for the clinical applications of these natural compounds (Friedman et al. 2019). The pCBs that have been characterized for potential medical applications, and for which cellular targets have been clearly identified, are reported in Table 1 (for more details, see ref. 10).

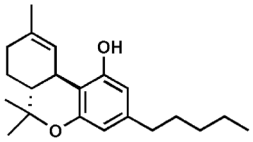
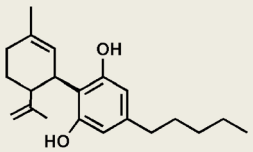
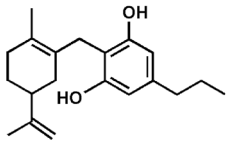
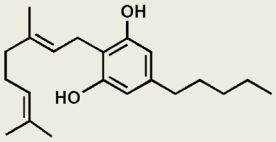
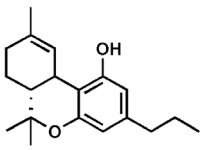
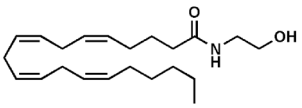
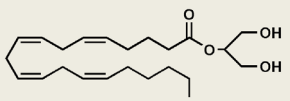
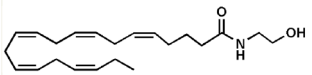
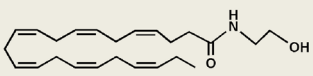
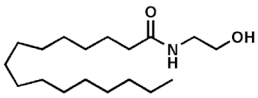
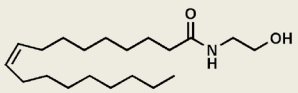
Unsurprisingly, marijuana is surrounded by controversies, debates and misconceptions related to its medical potential, legalization and long-term health consequences. To date, marijuana is the most widely used recreational drug in Western countries, and is consumed by ~ 3% of the world population (~ 185 million individuals) (United Nations Office on Drugs and Crime (2017). The advent of legalized cannabis in multiple regions of the United States, and elsewhere around the world, have raised additional and urgent concerns about its potential hazard to health. Nevertheless, research on the therapeutic potential of cannabis extract-based drugs suggests them to be clinically useful in a wide range of pathological conditions, including neurological (Friedman et al. 2019; Cristino et al. 2020) and psychiatric disorders (Cohen et al. 2019). Conversely, repeated cannabis use has been associated with short-term and long-term side effects, including cognitive alterations, psychosis, schizophrenia and mood disorders (Cohen et al. 2019), as well as with respiratory and cardiovascular diseases (Maccarrone et al. 2015).

2 Metabolism of phytocannabinoids

Phytocannabinoids are synthesized via metabolic pathways that start from farnesyl diphosphate to produce geranyl diphosphate, that is then condensed with olivetolic acid in a reaction catalysed by cannabigerolic synthase. From the cannabigerolic acid product, a number of pCBs are generated (Solymosi and Köfalvi 2017; Schafroth and Carreira 2017), as depicted in Fig. 1a.

It is very important that pCBs cannot be degraded by our body. Yet, biotransformation of Δ^9-THC may occur primarily within the liver by hydroxylation and oxidation reactions catalyzed the cytochrome P450 subfamily 2C9 (CYP2C9) enzymes, which play a major role in rodents and humans (Watanabe et al. 1993, 2007). Such a "phase I metabolism" involves hydroxylation of Δ^9-THC to its primary metabolite 11-hydroxy-Δ^9-tetrahydrocannabinol (11OH-THC), that in turn undergoes further oxidation by other liver enzymes to the inactive secondary metabolite 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (11-COOH-THC, or THC-COOH), as shown in Fig. 2b. The latter substance is then biotransformed further during "phase II

Table 1 Major plant-derived and endogenous cannabinoids

Name (abbreviation)	Chemical structure
Phytocannabinoids	
Δ^9-Tetrahydrocannabinol (Δ^9-THC)	
Cannabidiol (CBD)	
Cannabidivarin (CBDV)	
Cannabigerol (CBG)	
Δ^9-Tetrahydrocannabivarin (THCV)	
ω-6 Endocannabinoids	
N-Arachidonoylethanolamine (Anandamide, AEA)	
2-Arachidonoylglycerol (2-AG)	
ω-3 Endocannabinoids	
N-Eicosapentaenoylethanolamine (EPEA)	
N-Docosahexaenoylethanolamine (DHEA)	
Endocannabinoid-like compounds	
N-Palmitoylethanolamine (PEA)	
N-Oleoylethanolamine (OEA)	

metabolism" by UDP-glucuronosyltransferase (UGTase)-dependent glucuronidation, producing a water-soluble glucuronide which can be more easily excreted by the body. Much in the same way, Δ^9-THC degradation product cannabinol (CBN) can be converted by CYP2C9 into 11OH-CBN (Fig. 1b).

As mentioned above, pCBs are endowed with many pharmacological properties, due to their ability to hit and modulate (as agonists, inverse agonists, antagonists, or even positive or negative allosteric modulators) different cellular targets (Morales et al. 2017; Turner et al. 2017; Friedman et al. 2019; Cristino et al. 2020; Hanuš et al. 2016). Indeed, it should be appreciated that the complexity of cannabis extracts is mirrored, and possibly even exceeded, by the complexity of the molecular targets that they find in our body, most of which belong to the so-called "endocannabinoid system" described in the following section.

3 Metabolism of endocannabinoids

It is well-established that Δ^9-THC binds to and activates specific G protein-coupled receptors, known as type-1 (CB_1) and type-2 (CB_2) cannabinoid receptors, which endogenously are triggered by ligands that were identified in the '90 s as anandamide (*N*-arachidonoylethanolamine, AEA) (Devane et al. 1992) and 2-arachidonoylglycerol (2-AG) (Mechoulam et al. 1995; Sugiura et al. 1995). These two compounds, respectively, an amide and an ester of the ω-6 arachidonic acid (Table 1), are the most active and best studied endocannabinoids (eCBs). Additional members of this family are ω-3 fatty acid derivatives like *N*-eicosapentaenoylethanolamine and *N*-docosahexaenoylethanolamine (Table 1); or the eCB-like compounds *N*-palmitoylethanolamine and *N*-oleoylethanolamine (also shown in Table 1) that do not bind to CB_1 nor to CB_2, but inhibit eCB degradation thus prolonging their biological activity with an "entourage effect" (Maccarrone et al. 2015,2014). AEA and 2-AG are metabolized by a complex array of biosynthetic enzymes and hydrolases, and are transported through the plasma membrane and intracellularly by distinct carriers. Altogether receptors, enzymes and transporters of eCBs form the "eCB system", that has been recently discussed in comprehensive reviews (Friedman et al. 2019; Cristino et al. 2020; Sugiura et al. 1995; Maccarrone et al. 2014; Baggelaar et al. 2018; Maccarrone 2020; Iannotti et al. 2016). The main components of the eCB system are shown in Fig. 2, and support and control the manifold actions of eCBs, both in the central nervous system (Cristino et al. 2020; Maccarrone 2020; Iannotti et al. 2016) and at the periphery (Maccarrone et al. 2015).

In particular, the number of receptors activated by eCBs in the same cell, both on the plasma membrane and in the

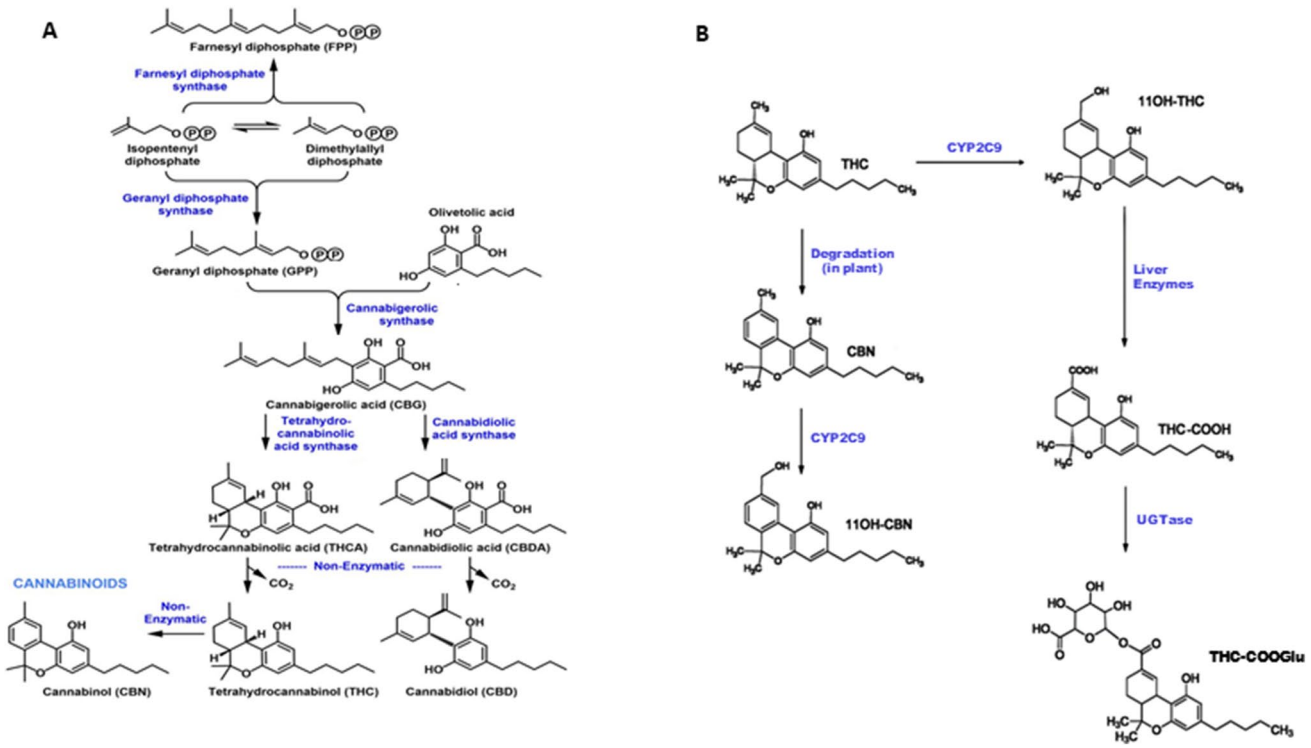


Fig. 1 Metabolism of (phyto) cannabinoids in plants. **a** The main steps of the biosynthesis of (phyto) cannabinoids in plants are shown, starting from farnesyl diphosphate and olivetolic acid. **b** Biotransformation of pCBs in our body by cytochrome P450 subfamily 2C9 (CYP2C9), liver enzymes and UDP-glucuronosyltransferase (UGTase)

nucleus, appears striking. Indeed, these receptors include: (1) CB_1 and CB_2, as well as the G protein-coupled orphan receptor (GPR) 55 (all on the plasma membrane and with an extracellular binding site); (2) transient receptor potential vanilloid 1 (TRPV1) and additional transient receptor potential (TRP) channels (all on the plasma membrane, but with an intracellular binding site); and (3) nuclear peroxisome proliferator-activated receptors (PPARs) α, γ and δ, that are all transcription factors able to regulate gene expression (Maccarrone 2020). It is of paramount importance that receptor-mediated activities of eCBs are subjected to a stringent "metabolic control", which means that their cellular concentration (and hence biological activity) depends on a balance between synthesis and degradation by different biosynthetic and hydrolytic enzymes (Friedman et al. 2019; Cristino et al. 2020; Maccarrone 2020). Among the latter, *N*-acyltransferase (NAT), *N*-acylphosphatidylethanolamines-specific phospholipase D (NAPE-PLD), along with phospholipase A_2 (PLA_2) and α/β hydrolase domain 4 (ABHD4), catalyze parallel routes for the release of AEA from phospholipid precursors; then, fatty acid amide hydrolase (FAAH) and *N*-acylethanolamine acid amidase (NAAA) cleave AEA to ethanolamine and arachidonic acid (AA), terminating its signalling (Maccarrone 2020) (Fig. 2). Much alike AEA, a phosphohydrolase (PH) releases diacylglycerol (DAG) from phospholipid precursors, and DAG lipases (DAGLs) α and β synthesize 2-AG from it; then, 2-AG is cleaved to glycerol and AA through different routes, catalysed mainly by monoacylglycerol lipase (MAGL), but also by ABHD2, ABHD6 or ABHD12 (Baggelaar et al. 2018; Maccarrone 2020) (Fig. 2). In addition to synthesis and degradation, a further level of complexity in eCB metabolism is represented by the addition of molecular oxygen to the fatty acid moiety by cyclooxygenase-2 (COX-2), various lipoxygenase isozymes and cytochrome P450 (Rouzer and Marnett 2011; Fezza et al. 2014). These oxidative derivatives are endowed with biological activities on their own, due to a different ability to recognize enzymes and receptors of eCBs. To date, their pathophysiological roles remain rather elusive, but apparently they include key activities like neuroprotection of the brain against excitotoxicity (Veldhuis et al. 2003). The stringent metabolic control of eCB tone is further modulated by distinct transporters that facilitate the movement of eCBs both across the plasma membrane (via a purported, as yet elusive eCB membrane transporter), and intracellularly, as well as by storage of eCBs in cytosolic organelles like adiposomes (Maccarrone 2020).

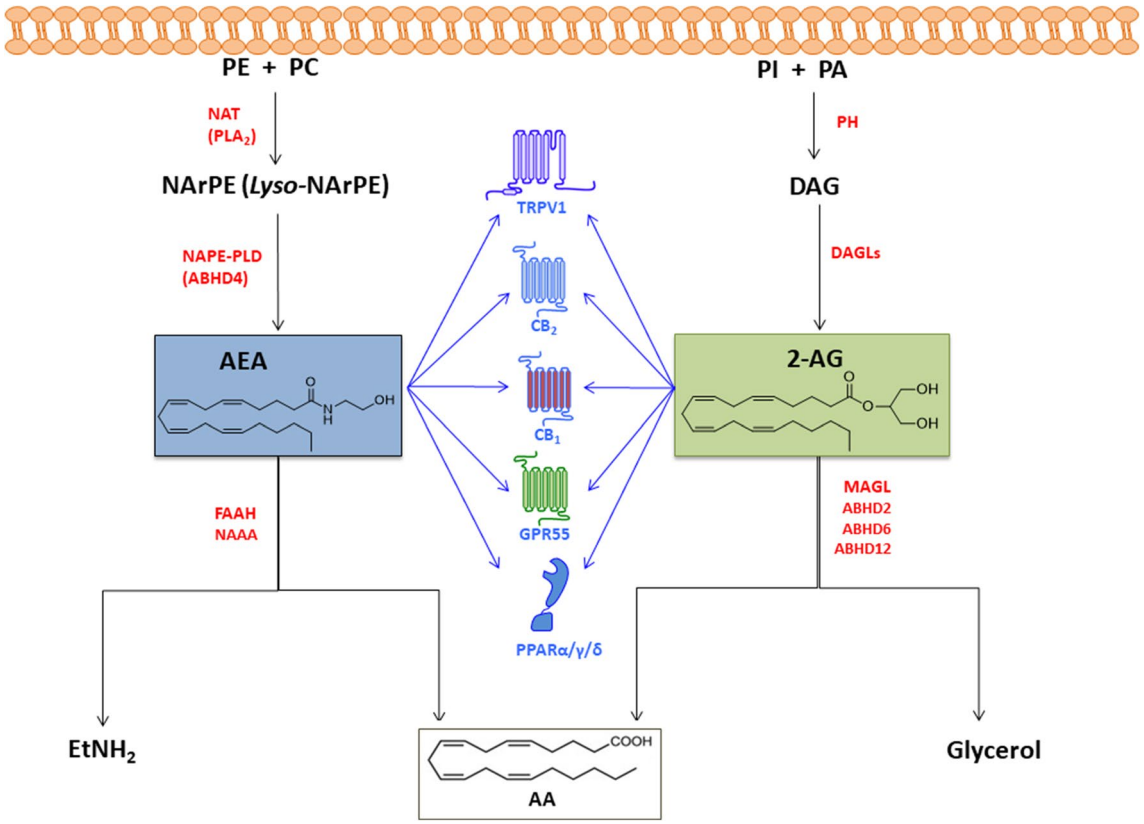


Fig. 2 Metabolism and known receptors of major endocannabinoids. For the biosynthesis of AEA, NAT produces NArPE from membrane PC and PE, and then NAPE-PLD releases AEA; in addition, NArPE can be converted by PLA_2 into *lyso*-NArPE, from which ABHD4 releases AEA. *2-AG* 2-Arachidonoylglycerol, *AA* arachidonic acid, *ABHD* α/β hydrolase domain, *AEA* *N*-arachidonoyl ethanolamine, *CB* cannabinoid receptor, *DAG* diacylglycerol, *DAGL* diacylglycerol lipase, *$EtNH_2$* ethanolamine *FAAH* fatty acid amide hydrolase, *MAGL* monoacylglycerol lipase, *NAAA* *N*-acylethanolamine acid amidase, *NAPE-PLD* *N*-acyl phosphatidylethanolamines-specific phospholipase D, *NArPE* *N*-arachidonoyl phosphatidylethanolamine, *PPAR* peroxysome proliferator-activated receptor, *PA* phosphatidic acid, *PC* phosphatidylcholine, *PE* phosphatidylethanolamine, *PH* phosphohydrolase *PLA_2* phospholipase A_2, *TRPV1* transient receptor potential vanilloid 1

4 Cross-talk between pCBs and eCBs

Based on the observation that activities of pCBs and eCBs overlap to some extent, at the level of target receptors and/or metabolic enzymes, it remains challenging to design effective drugs based on these substances (Marzo and Piscitelli 2015; Jacobson et al. 2019). As yet, it appears that pCBs like Δ^9-THC and CBD modulate CB_1 and CB_2 (and CBD does the same also at the level of TRPV1, PPARs and FAAH), whereas other pCBs like cannabidivarin and CBD acid can modulate DAGLs and COX-2 (Marzo and Piscitelli 2015). In line with this, it is well-established that chronic or recent cannabis exposure leads to down-regulation of CB_1 (Jacobson et al. 2019). Unfortunately, the structural and functional properties of only a few elements of the eCB system have been thoroughly investigated (Maccarrone 2020), and this gap of knowledge must be filled to really appreciate how pCBs can interact with the eCB system, and how novel pCB/eCB-based therapeutics can be designed against human disorders. In this context, one may wonder how two so markedly different compounds like Δ^9-THC (a terpeno-phenol) and AEA (an *N*-arachidonoylethanolamine) can share common cellular targets. This apparently striking feature is due to the unanticipated similarity of their 3D structures, that indeed present three different "pharmacophores" (i.e., spatial arrangements of atoms that are essential to interact with a specific receptor target) at the same positions (Van der Stelt et al. 2002). Stereoviews of these 3D structures are shown in Fig. 3, and clearly explain why pCBs can mimic eCB biological activity.

Another interesting question arises as to whether pCBs appeared in nature before eCBs, or viceversa. This issue has recently found an answer, because mature black truffles (*Tuber melanosporum* Vittad.) were reported to contain AEA and its metabolic enzymes (Pacioni et al. 2015). It should be recalled that the botanical family of truffles (*Tuberaceae*) evolved during or after the first major radiation of Angiosperms in the Jurassic period (140–180 million years ago, Mya) (Soltis

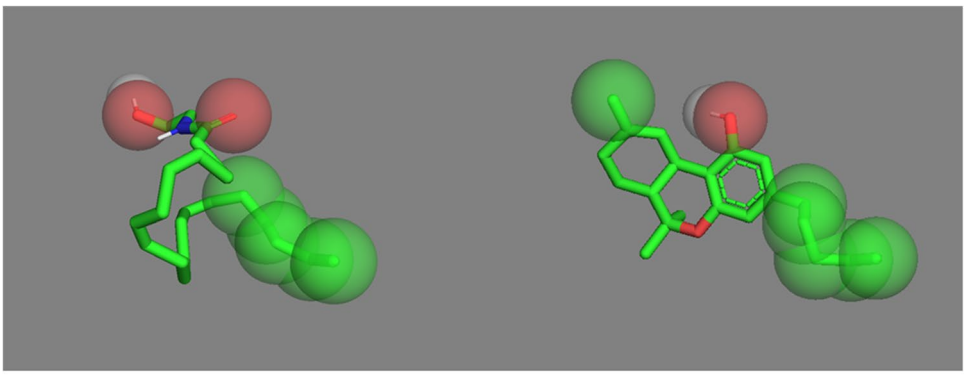


Fig. 3 Three dimensional structures of Δ^9-THC and AEA. Stereoview of anandamide (AEA, PubChem 5281969, on the left) and Δ^9-tetrahydrocannabinol (Δ^9-THC, PubChem 16078, on the right), obtained with the Pymol program (Schrodinger, www.pymol.org) to depict van der Waals surfaces of the pharmacophores and highlight corresponding positions. The center of rotation, calculated with the Chimera program (National Institutes of Health, www.cgl.ucsf.edu), is: x = − 12.68, y = − 3.41 and z = − 4.59, for AEA; x = − 16.89, y = 0.23 and z = − 3.49, for Δ^9-THC (method used: from center models). Carbon atoms are shown in green, oxygen atoms in red, nitrogen atoms in blue and polar hydrogen in white

et al. 2008). Instead *Cannabis* diverged from *Humulus*, both genera of the family *Cannabaceae*, at the end of Paleogene (28 Mya) (McPartland 2018). In keeping with these data, the phylogenetic analysis of cytochrome c oxidase subunit 1 clearly showed that *T. melanosporum* is more ancestral than *C. sativa* (Pacioni et al. 2015). Furthermore, a recent study on the historical biogeography of the genus *Tuber* has estimated its molecular dating at the end of the Jurassic period, that is 156 Mya (Bonito et al. 2013); instead, in the order *Rosales*, that includes the family *Cannabaceae* and the genus *Cannabis*, dates 76–107 Mya (Wikström et al. 2001; Wang et al. 2009). Incidentally, it seems interesting that many animals involved in truffle spore dispersal (e.g., nematodes, arthropoda, mammalia) possess cannabinoid receptors (Trappe and Claridge 2010; Elphick 2012), supporting the concept that AEA has an ancient role in attracting truffle eaters. In this context, it should be recalled that eCBs, unlike other eCB-like molecules devoid of activity at cannabinoid receptors, contain in their structure arachidonic acid, which has been reported in little amounts only in a few higher terrestrial plants (Shanab et al. 2018). Thus, the biosynthesis of arachidonate-containing AEA in *Tuber melanosporum* remains to be further investigated. Moreover, AEA and 2-AG have been described in very simple invertebrates, such as *Hydra vulgaris*, which evolved earlier (> 500 Mya) than cannabis plant (Petrocellis et al. 1999). Finally, AEA and other *N*-acylethanolamines have also been identified in a unicellular eukaryote, such as *Tetrahymena*, which evolved even earlier (Karava et al. 2005; Anagnostopoulos et al. 2010).

Taken together, available evidence clearly supports the view that eCBs are "older" than pCBs, and that the plant-derived compounds took quite a few million years to mimic the biological and pharmacological activity of our endogenous counterparts.

5 Conclusions

Plant-derived and endogenous cannabinoids represent two different but equally complex systems, so that the terms "(phyto) cannabinoids" and "endocannabinoids" are actually used to identify rather heterogeneous groups of lipophilic substances. It is striking how some of these molecules happened to share 3D structures, allowing exogenous pCBs to play so many biological activities in our body. The additional layer of complexity brought about by these structural similarities makes extremely challenging the use of pCBs as potential therapeutics to combat human diseases, and requires deeper knowledge of the structural and functional details of their potential targets in the cell. Overall, understanding these fine molecular clues will allow to turn pCBs from threats to treasure trove for human health.

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Compliance with ethical standards

Conflicts of interests Not applicable.

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