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REVIEW ARTICLE

Review of delta-8-tetrahydrocannabinol (Δ^8-THC): Comparative pharmacology with Δ^9-THC

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[Correction added on 16 June 2022, after first online publication: Linda Klumpers' ORCID ID has added in this version.]

The use of the intoxicating cannabinoid delta-8-tetrahydrocannabinol (Δ^8-THC) has grown rapidly over the last several years. There have been dozens of Δ^8-THC studies dating back over many decades, yet no review articles have comprehensively covered these findings. In this review, we summarize the pharmacological studies of Δ^8-THC, including receptor binding, cell signalling, *in vivo* cannabimimetic activity, clinical activity and pharmacokinetics. We give special focus to studies that directly compared Δ^8-THC to its more commonly studied isomer, Δ^9-THC. Overall, the pharmacokinetics and pharmacodynamics of Δ^8-THC and Δ^9-THC are very similar. Δ^8-THC is a partial agonist of the cannabinoid CB_1 receptor and has cannabimimetic activity in both animals and humans. The reduced potency of Δ^8-THC in clinical studies compared with Δ^9-THC can be explained by weaker cannabinoid CB_1 receptor affinity, although there are other plausible mechanisms that may contribute. We highlight the gaps in our knowledge of Δ^8-THC pharmacology where further studies are needed, particularly in humans.

KEYWORDS
delta-8-THC, pharmacodynamics, pharmacokinetics, Δ^8-THC

1 | INTRODUCTION

Delta-8-tetrahydrocannabinol (Δ^8-THC) is a cannabinoid that is a double bond isomer of the more well-known **Δ^9-THC** (Figure 1). Δ^8-THC was first derived from the cyclization of **cannabidiol (CBD)** and it was discovered to be highly psychoactive in human studies (Adams, 1942). By 1966, it was realized that Δ^8-THC was present in only negligible amounts in cannabis and cannabis-derived products, such as hash (Hively et al., 1966). Δ^9-THC was determined to be the compound, almost entirely, responsible for the intoxicating properties of cannabis, including alterations in mood, perception and cognition. Subsequent research focused much more on Δ^9-THC, but the effects of Δ^8-THC continued to be characterized throughout the following decades. One reason for this is the better thermodynamic stability of Δ^8-THC relative to Δ^9-THC (Hanuš et al., 2016). Note that early studies referred to Δ^8-THC as Δ^6 or $\Delta^{1(6)}$ and Δ^9-THC as Δ^1. This review will follow the modern ring numbering system even when the original publication used the old numbering.

There is currently debate about the regulatory status of Δ^8-THC in the United States (e.g. Koski, 2021). The Agriculture Improvement Act of 2018 (informally called the 'Farm Bill') removed hemp and hemp products containing less than 0.3% Δ^9-THC from the legal definition of marijuana in the Federal Controlled Substances Act (*Agriculture Improvement Act of 2018*, 2018). Importantly for Δ^8-THC, hemp was defined as including 'all derivatives, extracts, cannabinoids, isomers, acids, salts and salts of isomers'. Because Δ^8-THC is both an isomer of CBD and a derivative of CBD when obtained from the cyclization

Abbreviations: C_{max}, maximal concentration; CYP, cytochrome P450; P-gp, P-glycoprotein; T_{max}, time to maximal concentration; Δ^8-THC, delta-8-tetrahydrocannabinol.

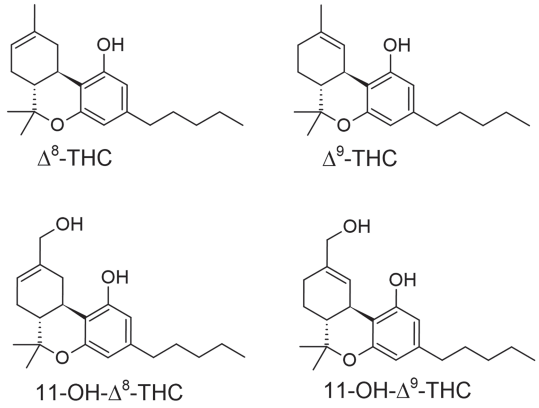

FIGURE 1 The structures of the cannabinoids, (−)-Δ^8-tetrahydrocannabinol (Δ^8-THC) and (−)-Δ^9-tetrahydrocannabinol (Δ^9-THC), and their active metabolites, (−)-11-hydroxy-Δ^8-tetrahydrocannabinol (11-OH-Δ^8-THC) and (−)-11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-Δ^9-THC)

reaction, it may be considered to fall under this definition. On the other hand, there is an argument that the cyclization reaction makes the resultant Δ^8-THC a synthetic cannabinoid and therefore a controlled substance.

This quasi-legal status has resulted in an explosion in sales of Δ^8-THC, including where Δ^9-THC sale and possession is not permitted by state law. Δ^8-THC is present in negligible levels in the cannabis plant, regardless of the chemovar (Wang et al., 2018). Therefore, the source of virtually all Δ^8-THC sold to consumers comes from the cyclization of CBD. This cyclization reaction has been known since 1964 (Gaoni & Mechoulam, 1964), although both Δ^8-THC and Δ^9-THC can be produced, depending on the conditions (Gaoni & Mechoulam, 1966).

Δ^8-THC has been studied quite extensively over the last 80 years, but many people have an impression that it is 'new and unstudied'. To the best of our knowledge, no comprehensive review articles have been published that focus exclusively on Δ^8-THC. To fill this gap, this review will focus on the pharmacology of Δ^8-THC and how its actions compare to those of the better known cannabinoid Δ^9-THC. The scope of this review will include pharmacology studies at the *in vitro*, *in vivo* and clinical levels. We will not focus on toxicology or potential therapeutic use, which will be the subject of future reviews. We will also identify knowledge gaps in Δ^8-THC pharmacology that should be addressed with further studies.

2 | RECEPTOR BINDING AND SIGNALLING

The human endocannabinoid system contains two receptor subtypes, cannabinoid receptor type 1 and 2 (**CB1** and **CB2**, respectively). Most studies using functional assays have reported that Δ^9-THC acts as a partial agonist at both receptors. Clinical studies with antagonists have shown that the psychoactive effects of Δ^9-THC are dependent on the CB_1 receptor (e.g., Klumpers et al., 2013). Its relatively low intrinsic activity explains why it has weaker effects than many synthetic agonists with high intrinsic activity (Pinson et al., 2020).

2.1 | CB_1 receptor

2.1.1 | Ligand binding

Both Δ^8-THC and Δ^9-THC can competitively bind to the orthosteric site of the CB_1 receptor with K_i values in the nM range (Table 1). The ranges of K_i values for Δ^8-THC were similar between species:- 28.5 to 251 nM for the human receptor (Govaerts et al., 2004; Husni et al., 2014; Nadipuram et al., 2003), 44 to 295 nM for the rat receptor (Busch-Petersen et al., 1996; Charalambous et al., 1991; Compton et al., 1993; Govaerts et al., 2004; Hirst et al., 1996; Martin et al., 1993) and 123 to 179 nM for the mouse receptor (Busch-Petersen et al., 1996; Compton et al., 1991, 1993; Govaerts et al., 2004).

Of the publications that measured the binding of both Δ^8-THC and Δ^9-THC, the mean Δ^8-THC:Δ^9-THC ratios of K_i values were 6.0 for human receptors ($n = 2$ studies), 3.3 for rat receptors ($n = 3$ studies) and 1.04 for mouse receptors ($n = 2$ studies). These results indicate that Δ^8-THC binds to the CB_1 receptor with less affinity than Δ^9-THC at human and rat receptors, but they are equipotent at mouse receptors. It is not clear if this is a true species difference or due to differences in experimental conditions. Experiments with the human receptor were performed in transfected cells, whereas all experiments with the rodent receptor were performed in membrane preparations from brain tissue. To date, no species differences have been reported in binding of Δ^9-THC to the CB_1 receptor. Studies that assessed binding of Δ^9-THC to mouse and rat receptors under equivalent experimental conditions did not report any difference in affinity (Wiley et al., 2021). Furthermore, binding of Δ^9-THC to the rat CB_1 receptor was equivalent between transfected cells and brain tissue (Pertwee, 1999). Future studies should compare human and rodent receptors under equivalent experimental conditions, which is important for assessing translatability of *in vivo* studies to humans.

Binding of the active 11-OH-THC metabolite was also assessed in some publications. Eleven-OH-Δ^8-THC had 2.3-fold stronger binding than parent Δ^8-THC at rat CB_1 receptors (Compton et al., 1993). This ratio is slightly greater than that of Δ^9-THC at rat receptors, where the ratio was 1.06 (Compton et al., 1993) and 1.48 (Wiley et al., 2021). Eleven-OH-Δ^8-THC had comparable binding to parent Δ^9-THC at rat receptors, with a range from 1.35-fold weaker to 3.1-fold stronger binding than Δ^9-THC (Compton et al., 1993; Rhee et al., 1997). Binding of 11-OH-Δ^8-THC has not yet been reported at human CB_1 receptors. This information is crucial to interpreting results of clinical studies where Δ^8-THC was administered orally, because this route produces high plasma levels of the 11-OH metabolite.

2.1.2 | Signalling

Δ^9-THC is capable of activating several intracellular signalling pathways through the CB_1 receptor, including activation of $G\alpha_{i/o}$ proteins resulting in the inhibition of **adenylyl cyclase** and β-arrestin1 recruitment (Al-Zoubi et al., 2019; Ye et al., 2019). Table 2 shows studies that have assessed cell signalling stimulated by Δ^8-THC.

TABLE 1 Studies of Δ^8-THC radioligand binding to CB_1/CB_2 receptors

Study[a]	Species	Tissue	Radioligand	Results	Δ^8-THC:Δ^9-THC ratio
CB_1 receptor					
Radwan et al., 2015 Husni et al., 2014	Human	HEK293 (transfected)	[^{3}H]**CP55,940**	Δ^8-THC: K_i = 78 nM Δ^9-THC: K_i = 18 nM	4.3
Govaerts et al., 2004	Human	CHO (transfected)	[^{3}H]CP55,940	Δ^8-THC: K_i = 251 nM (pKi = 6.6) Δ^9-THC: K_i = 32.4 nM (pKi = 7.49)	7.7
Nadipuram et al., 2003	Human	HEK293 (transfected)	[^{3}H]CP55,940	Δ^8-THC: K_i = 28.5 nM Δ^9-THC: K_i = ND	
Rhee et al., 1997	Rat	COS-7 (transfected)	**[^{3}H]HU-243**	Δ^9-THC: K_i = 80.3 nM 11-OH-Δ^8-THC: K_i = 25.8 nM	
Rhee et al., 1997	Rat	Brain	[^{3}H]HU-243	Δ^9-THC: K_i = 66.5 nM 11-OH-Δ^8-THC: K_i = 33.4 nM	
Govaerts et al., 2004	Rat	Cerebellum	**[^{3}H]SR 141716A**	Δ^8-THC: K_i = ND Δ^9-THC: K_i = 209 nM (pKi = 6.68)	
Hirst et al., 1996	Rat	Cerebellum	[^{3}H]SR 141716A	Δ^8-THC: K_i = 295 nM (pKi = 6.53) Δ^9-THC: K_i = 51.3 (pKi = 7.29)	5.75
Martin et al., 1993 Huffman et al., 2003 Huffman et al., 1999 Huffman et al., 2003	Rat	Cortex	[^{3}H]CP55,940	Δ^8-THC: K_i = 44 nM Δ^9-THC: K_i = 41 nM	1.07
Charalambous et al., 1991	Rat	Cortex	[3H]CP55,940	Δ^8-THC: K_i = 219 nM	
Compton et al., 1993	Rat	Cortex	[^{3}H]CP55,940	Δ^8-THC: K_i = 126 nM Δ^9-THC: K_i = 40.7 nM 11-OH-Δ^8-THC: K_i = 54.9 nM 11-OH-Δ^9-THC: K_i = 38.4 nM	3.10
Busch-Petersen et al., 1996 Papahatjis et al., 2002 Papahatjis et al., 2006 Lu et al., 2008	Rat	Forebrain	[^{3}H]CP55,940	Δ^8-THC: K_i = 47.6 nM	
Govaerts et al., 2004	Mouse	Cerebellum	[^{3}H]**WIN 55,212–2**	Δ^8-THC: K_i = 123 nM (pKi = 6.91) Δ^9-THC: K_i = 97.7 nM (pKi = 7.01)	1.26
Compton et al., 1991	Mouse	Cortex	[^{3}H]CP55,940	Δ^8-THC: IC_{50} = 179 nM Δ^9-THC: IC_{50} = 218 nM	0.82
CB_2 receptor					
Radwan et al., 2015 Husni et al., 2014	Human	HEK293 (transfected)	[^{3}H]CP55,940	Δ^8-THC: K_i = 12 nM Δ^9-THC: K_i = 42 nM	0.29
Huffman et al., 1999 Showalter et al., 1996	Human	HEK293 (transfected)	[^{3}H]CP55,940	Δ^8-THC: K_i = 44 nM Δ^9-THC: K_i = 36 nM	1.22
Nadipuram et al., 2003	Human	HEK293 (transfected)	[^{3}H]CP55,940	Δ^8-THC: K_i = 25.0 nM	
Govaerts et al., 2004	Human	CHO (transfected)	[^{3}H]-WIN 55,212–2	Δ^8-THC: K_i = 417 nM (pKi = 6.38) Δ^9-THC: K_i = 309 nM (pKi = 6.51)	1.35
Rhee et al., 1997	Human	COS-7 (transfected)	[^{3}H]HU-243	Δ^9-THC: K_i = 32.2 nM 11-OH-Δ^8-THC: K_i = 7.4 nM	
Busch-Petersen et al., 1996 Papahatjis et al., 2002 Papahatjis et al., 2006 Lu et al., 2008	Mouse	Spleen	[^{3}H]CP55,940	Δ^8-THC: K_i = 39.3 nM	

Abbreviation: NA, not assessed; ND, not determined.

[a]Multiple references are listed when the same results have been presented in multiple publications.

Inhibition of stimulated **cAMP** accumulation was demonstrated with both Δ^8-THC and Δ^9-THC at human, rat and mouse receptors (Gérard et al., 1991; Howlett, 1987a, 1987b; Little & Martin, 1991; Matsuda et al., 1990; Rhee et al., 1997). There was some variation in their relative potencies, with Δ^8-THC reported to be 6.3-fold less potent than Δ^9-THC at the human receptor (Gérard et al., 1991), 2-fold less potent at the rat receptor (Matsuda et al., 1990) and approximately equipotent at the mouse receptor (Howlett, 1987a, 1987b). This species pattern matches very well with differences in Δ^8-THC binding affinity (6-fold, 3.3-fold and 1-fold lower weaker binding in human, rat and mouse receptors, respectively). Because the binding affinity was determined by distinct groups from those reporting the cAMP results, this may indicate a true inter-species difference.

The intrinsic activity of Δ^8-THC and Δ^9-THC in this assay was consistently in a similar range, based on either the reported E_{max} values or our qualitative assessment of the concentration–response curve (Gérard et al., 1991; Howlett, 1987a, 1987b; Little & Martin, 1991; Matsuda et al., 1990). The maximum effect of Δ^8-THC has not yet been fully characterized in clinical studies, but this result provides evidence that it is likely to be similar to Δ^9-THC.

The 11-OH metabolites were also tested in several cAMP accumulation experiments. One study reported that 11-OH-Δ^8-THC was 3.6-fold less potent than Δ^9-THC at the rat receptor (Rhee et al., 1997). In mouse receptors, 11-OH-Δ^8-THC was 2-fold more potent than Δ^9-THC, although 2.6-fold less potent than 11-OH-Δ^9-THC (Howlett, 1987a, 1987b). These authors also reported that both 11-OH metabolites produced E_{max} values similar to parent molecules.

Activity of Δ^8-THC at the CB_1 receptor has also been assessed using the **GTPγS** binding assay. Two studies performed with CB_1 receptors from rat cerebellar homogenates produced conflicting results. One study reported no concentration-dependent stimulation of GTPγS binding by Δ^8-THC (Griffin et al., 1999), whereas another reported stimulation of GTPγS binding with an EC_{50} of 117 nM (Govaerts et al., 2004). This value indicated approximately 2-fold stronger potency than Δ^9-THC, but with a similar E_{max}. These contradictory results are not entirely surprising because intrinsic activity of Δ^9-THC in rat cerebellar membranes has ranged from 0% to 54% in past studies that used this assay (Pertwee, 1999). Experimental conditions can have a strong effect on GTPγS binding, particularly with agonists such as THC that have relatively low intrinsic activities (Howlett, 2002). However, no Δ^8-THC-stimulated binding was detected in the study of Griffin et al. despite testing various assay conditions with different **guanosine 5'-diphosphate** (**GDP**; 100 and 10 μM) and sodium ion concentrations.

A similar GTPγS binding assay was performed using HEK-293 cells transfected with the human CB_1 receptor (Husni et al., 2014). This study calculated an EC_{50} value of 5820 nM for Δ^8-THC, which was much less potent than Δ^9-THC with an EC_{50} of 269 nM. The potency of at least one other CB_1 agonist appears to be different between cells transfected with the human receptor and rat cerebellar membranes. The EC_{50} of **WIN 55,212** determined using the GTPγS assay ranged from 360 to 617 nM in transfected CHO cells ($n = 3$ studies) and 99 to 180 nM using rat cerebellar membranes ($n = 4$ studies) (Pertwee, 1999). So, although it is not without precedent to have a weaker potency in cells transfected with the human receptor compared with rat tissue, the extremely high EC_{50} of 5820 nM reported by Husni et al. does not appear consistent with any other study. This publication did not report the specific THC concentrations tested nor show the data or curve fits, making further interpretation difficult. Replication of this experiment would be useful given the inconsistency with other studies, especially those using the cAMP accumulation assay.

2.2 | CB_2 receptor

2.2.1 | Ligand binding

Both Δ^8-THC and Δ^9-THC can competitively bind to the orthosteric site of the CB_2 receptor with K_i values in the nM range (Table 1). The K_i values for Δ^8-THC ranged from 12 to 417 nM at the human receptor (Govaerts et al., 2004; Husni et al., 2014; Nadipuram et al., 2003; Showalter et al., 1996) and a single study reported a value of 39.3 nM for the mouse CB_2 receptor (Busch-Petersen et al., 1996). Of the publications that measured binding of both Δ^8-THC and Δ^9-THC, the mean Δ^8-THC:Δ^9-THC ratio of K_i values was 0.95 for human receptors (Govaerts et al., 2004; Husni et al., 2014; Showalter et al., 1996). These results indicate that Δ^8-THC binds to the human CB_2 receptor with similar affinity compared with Δ^9-THC. Equivalent comparative binding data between Δ^8-THC and Δ^9-THC at rodent CB_2 receptors would be helpful for interpreting results of animal assays.

2.2.2 | Signalling

Δ^9-THC can activate several intracellular signalling pathways through the CB_2 receptor (Ye et al., 2019). Table 2 shows studies that have assessed CB_2 cell signalling stimulated by Δ^8-THC or its metabolites. Two studies assessed GTPγS binding in human CB_2 receptors transfected into cultured cells. In the first study, both Δ^8-THC and Δ^9-THC acted as inverse agonists at the CB_2 receptor as indicated by decreased GTPγS binding (Govaerts et al., 2004). Δ^8-THC was estimated to be an order of magnitude more potent than Δ^9-THC, but the very weak GTPγS binding response may have biased the estimate of EC_{50}. The second study reported that both Δ^8-THC and Δ^9-THC acted as agonists (Husni, 2014). Although EC_{50} values for the two molecules were fairly similar, this publication did not report E_{max} values.

The reason for the discrepancy of THC molecules acting as either an agonist or inverse agonist is not entirely clear. The experimental conditions were significantly different between the two studies, including cell lines (CHO and HEK-293 cells), assay buffers, GDP concentrations (20 and 50 μM) and incubation times. Past studies have reported inconsistent effects of Δ^9-THC in functional assays of the CB_2 receptor. Using the cAMP accumulation assay, Δ^9-THC was reported to be an antagonist (i.e. no intrinsic activity) or a partial agonist with a wide range of different intrinsic activities (Pertwee, 1999). More recent studies

TABLE 2 Studies of Δ^8-THC-induced signalling at the CB_1/CB_2 receptors

Study[a]	Species	Tissue	Assay	Results	Δ^8-THC:Δ^9-THC ratio
CB_1 receptor					
Husni et al., 2014	Human	HEK293 (transfected)	GTPγS binding	Δ^8-THC: EC_{50} = 5820 nM Δ^9-THC: EC_{50} = 269 nM	22
Gérard et al., 1991	Human	CHO-K1 (transfected)	Forskolin-stimulated cAMP	Δ^8-THC: EC_{50} = 82 nM Δ^9-THC: EC_{50} = 13 nM	6.3
Matsuda et al., 1990	Rat	CHO-K1 (transfected)	Forskolin-stimulated cAMP	Δ^8-THC: EC_{50} = 27.4 nM Δ^9-THC: EC_{50} = 13.5 nM	2.0
Rhee et al., 1997	Rat	COS-7 (transfected)	Forskolin-stimulated cAMP	Δ^9-THC: EC_{50} = 11 nM 11-OH-Δ^8-THC: EC_{50} = 39.9 nM	
Griffin et al., 1999	Rat	Cerebellar homogenate	GTPγS binding	Δ^8-THC: No concentration-dependent stimulation	
Govaerts et al., 2004	Rat	Cerebellar homogenate	GTPγS binding	Δ^8-THC: EC_{50} = 117 nM (E_{max} = 41%) Δ^9-THC: EC_{50} = 245 nM (E_{max} = 48%)	0.48
Howlett, 1987a, 1987b	Mouse	N18TG2 neuroblastoma cells	Secretin-stimulated cAMP	Δ^8-THC: K_{inh} = 430 nM (E_{max} = 1)[b] Δ^9-THC: K_{inh} = 530 nM[c] (E_{max} = 0.9) 11-OH-Δ^8-THC: K_{inh} = 260 nM (E_{max} = 1) 11-OH-Δ^9-THC: K_{inh} = 100 nM (E_{max} = 1)	0.81 2.6
Little & Martin, 1991	Mouse	Whole brain synaptosomes	Forskolin-stimulated cAMP	Δ^8-THC: U-shaped response with E_{max} of 13% inhibition at 1 μM Δ^9-THC: U-shaped response with E_{max} of 18% inhibition at 1 nM	
CB_2 receptor					
Govaerts et al., 2004	Human	CHO (transfected)	GTPγS binding	Δ^8-THC = 1.32 nM (E_{max} = −16%) Δ^9-THC = 23.4 nM (E_{max} = −27%)	0.056
Husni et al., 2014	Human	HEK293 (transfected)	GTPγS binding	Δ^8-THC = 524 nM Δ^9-THC = 327 nM	1.6
Rhee et al., 1997	Human	COS-7 (transfected)	Forskolin-stimulated cAMP	Δ^9-THC: 21% inhibition at 1 μM 11-OH-Δ^8-THC: 19% inhibition at 1 μM	

[a]Multiple references are listed when the same results have been presented in multiple publications.
[b]E_{max} values are a ratio relative to THC.
[c]Value comes from Howlett (1987b). It was reported slightly differently in the original publication.

using cells transfected with the human CB_2 receptor have found that Δ^9-THC acts as an agonist with the GTPγS binding assay (e.g. Gamage et al., 2020; Rosati et al., 2014). However, a CB_2 ligand can appear as both an inverse agonist or an agonist in the GTPγS assay depending on concentrations of GDP (Gonsiorek et al., 2007).

Significant gaps remain in characterizing the functional interaction of Δ^8-THC with the CB_2 receptor. Besides replication of experiments where results were inconsistent (e.g. GTPγS binding), the cAMP accumulation assay has never been reported for Δ^8-THC. Furthermore, these experiments should also be performed with rat and mouse CB_2 receptors, which would be useful for interpretation of rodent *in vivo* results. Ideally, all experiments should include both Δ^8-THC and Δ^9-THC for a direct comparison of the two molecules.

2.3 | Other targets

A number of other targets of Δ^9-THC have been discovered apart from the CB_1 and CB_2 receptors. These include **peroxisome proliferator-activated receptor-γ (PPARγ; NR1C3)** (O'Sullivan et al., 2005, 2006),

G protein-coupled receptor (GPR) 18 (McHugh et al., 2012), **GPR55** (Lauckner et al., 2008; Ryberg et al., 2007) and **glycine receptors** (Hejazi et al., 2006). GPR55 may have importance for the subjective effects of THC because receptor GPR55 knockout or antagonism enhanced the tetrad test effects of THC in mice (Wang et al., 2020). To the best of our knowledge, there are no reports of the effects of Δ^8-THC at these targets. Photoaffinity labelling was used to identify other possible target proteins of Δ^8-THC in neuroblastoma cells (Soethoudt et al., 2018). Although three potential protein targets were identified, it remains unclear what role, if any, these have in Δ^8-THC effects.

2.4 | Implications of different receptor potencies

Putting aside the uncertainty in some *in vitro* results, it appears that Δ^8-THC has a lower potency then Δ^8-THC at the human CB_1 receptor and a similar potency at the human CB_2 receptor. Because cannabis users titrate the dose to the effect they want, equivalent CB_1 receptor activation is likely to occur in the real world regardless of which cannabinoid is used. However, at a dose that produces equivalent CB_1 receptor activation, Δ^8-THC will likely produce greater CB_2 receptor activation than Δ^9-THC.

Although the CB_1 receptor mediates the majority of Δ^9-THC effects, the CB_2 receptor can modulate specific THC responses in animals. For example, the CB_2 receptor is involved in the biphasic reward response of animals to Δ^9-THC, where lower doses are rewarding, but higher doses are aversive (Jordan & Xi, 2019). In rats, the rewarding aspect was mediated by CB_1 receptors and the aversive aspect was mediated by CB_2 receptors (Spiller et al., 2019). This effect may be due to the regulation of extracellular **dopamine** release in the nucleus accumbens (Li et al., 2021). CB_2-null mice also have a different response to some tetrad tests compared with wild-type mice, particularly the analgesic and catalepsy tests (Liu et al., 2017, 2020; Wang et al., 2020). Thus, understanding the relative potency and intrinsic efficacy of Δ^8-THC and Δ^9-THC at the human and rodent receptors is important for interpretation of *in vivo* studies and potentially human effects.

3 | EFFECTS IN ANIMALS

Central CB_1 activity in rodents has been described by effects of hypolocomotion, hypothermia, catalepsy and analgesia, collectively referred to as the tetrad tests (Wiley, Balster, & Martin, 1995). These effects are discussed in the following four sections. Anaesthesia "sleeping" time, discriminative stimulus, dog ataxia and monkey behaviour are assays that have also been used to characterize *in vivo* cannabimimetic activity and a brief overview of these results is given.

3.1 | Locomotor activity

Spontaneous locomotor activity has been tested in mice following administration of Δ^8-THC via intravenous (i.v.), intraperitoneal (i.p.) and intracerebroventricular (i.c.v.) routes (Table 3). Like Δ^9-THC, Δ^8-THC reduced locomotor activity in a dose-dependent fashion with all administration routes tested (Christensen et al., 1971; Compton & Martin, 1990; Compton et al., 1991; Dewey et al., 1970; El-Alfy et al., 2010; Karniol & Carlini, 1973; Martin et al., 1975; Robertson et al., 1984). In the studies that calculated an ED_{50} for both molecules, the potency of Δ^8-THC was in a similar range to Δ^9-THC, with a mean ratio of 1.3 and a range of 0.4 to 2.2 ($n = 6$ studies). One study observed that the maximal effect was similar for both molecules. Other studies that did not calculate ED_{50} and E_{max} values confirmed that the decrease in locomotor activity was similar between Δ^8-THC and Δ^9-THC at equivalent high doses. In particular, two studies with i.c.v. administration, which should minimize the effect of metabolism, showed similar effects between Δ^8-THC and Δ^9-THC, with an ED_{50} value that was 25% higher for Δ^8-THC.

The 11-hydroxy metabolites of Δ^8-THC and Δ^9-THC were also tested in the spontaneous locomotor activity assay following both i.v. and i.c.v routes of administration (Christensen et al., 1971). The potency was equivalent between 11-OH-Δ^8-THC and 11-OH-Δ^9-THC with both routes. The 11-OH-Δ^8-THC metabolite was 2-fold more potent than its parent Δ^8-THC when administered i.v., but 14-fold more potent when administered i.c.v.

3.2 | Hypothermia

The hypothermic effects of Δ^8-THC have been tested in mice following i.v. and i.p. administration (Table 3). Δ^8-THC induced a dose-dependent hypothermia with both administration routes (Compton & Martin, 1990; El-Alfy et al., 2010; Haavik & Hardman, 1973; Karniol & Carlini, 1973; Martin et al., 1981, 1993; Razdan, 1986; Robertson et al., 1984; Watanabe et al., 1980; Watanabe et al., 1990). In the studies that calculated an ED_{50} for both molecules, the potency of Δ^8-THC was weaker than Δ^9-THC in two studies with potency ratios of 11.1 and 2.3 (Compton & Martin, 1990; Karniol & Carlini, 1973), although another study reported them to be equipotent (Martin et al., 1993). One series of studies that reported an E_{max} value for both molecules reported a temperature decrease of 5.9°C with Δ^8-THC and 4.2°C with Δ^9-THC, indicating a maximal effect approximately in the same range. Other studies that did not report ED_{50} and E_{max} values showed mixed results for the effects of Δ^8-THC and Δ^9-THC when tested at the same dose. In one case, Δ^8-THC produced a greater hypothermic effect (Martin et al., 1981), but most often Δ^9-THC produced a greater hypothermic effect (El-Alfy et al., 2010; Radwan et al., 2015; Razdan, 1986; Watanabe et al., 1990).

The 11-hydroxy metabolites of Δ^8-THC and Δ^9-THC produced hypothermic effects that were comparable with each other (Haavik & Hardman, 1973; Watanabe et al., 1990). The 11-oxo-Δ^8-THC metabolite was also active, but the 11-COOH-Δ^8-THC metabolite was inactive (Watanabe et al., 1980).

3.3 | Catalepsy

The cataleptic effects of Δ^8-THC have been tested in mice following i.v., i.p. and p.o. administration and in rats following i.p. administration

TABLE 3 Studies of Δ^8-THC *in vivo* cannabimimetic activity

Study[a]	Species	Route	Results	ED_{50} ratio (Δ^8-THC/Δ^9-THC)
Locomotor activity				
Christensen et al., 1971	Mouse	i.v.	Δ^8-THC: 1.1[b] Δ^9-THC: 1 (reference) 11-OH-Δ^8-THC: 0.50 11-OH-Δ^9-THC: 0.50	1.1
Compton & Martin, 1990 Charalambous et al., 1991 Martin et al., 1993 Huffman et al., 2003	Mouse	i.v.	Δ^8-THC $ED_{50} = 0.9$ mg·kg^{-1} ($E_{max} = 79\%$) Δ^9-THC $ED_{50} = 1$ mg·kg^{-1} ($E_{max} = 78\%$)	0.9
Compton et al., 1991 Compton et al., 1992	Mouse	i.v.	Δ^8-THC $ED_{50} = 1.9$ mg·kg^{-1} ($E_{max} = 79\%$) Δ^9-THC $ED_{50} = 1$ mg·kg^{-1} ($E_{max} = 78\%$)	1.9
Robertson et al., 1984 Razdan, 1986	Mouse	i.v.	Δ^8-THC: $ED_{50} = 7.1$ mg·kg^{-1} Δ^9-THC: $ED_{50} = 3.2$ mg·kg^{-1}	2.2
Dewey et al., 1970	Mouse	i.p.	Δ^8-THC: 70% decrease @ 10 mg·kg^{-1} Δ^9-THC: 70% decrease @ 10 mg·kg^{-1}	
Karniol & Carlini, 1973	Mouse	i.p.	Δ^8-THC: $ED_{50} = 18.5$ mg·kg^{-1} Δ^9-THC: $ED_{50} = 44.8$ mg·kg^{-1}	0.4
Martin et al., 1975 Wilson et al., 1976	Mouse	i.p.	Δ^8-THC: 85% reduction @ 10 mg·kg^{-1}[c] Δ^9-THC: 52% decrease @ 10 mg·kg^{-1}	
Radwan et al., 2015 El-Alfy et al., 2010	Mouse	i.p.	Δ^8-THC: 87% decrease @ 20 mg·kg^{-1}[c] Δ^9-THC: 82% decrease @ 20 mg·kg^{-1}	
Christensen et al., 1971	Mouse	i.c.v.	Δ^8-THC: 1.25[b] Δ^9-THC: 1 (reference) 11-OH-Δ^8-THC: 0.071 11-OH-Δ^9-THC: 0.067	1.25
Compton & Martin, 1990	Mouse	i.c.v.	Δ^8-THC: 69% reduction @ 100 μg Δ^9-THC: 62% reduction @ 100 μg	
Temperature				
Haavik & Hardman, 1973	Mouse	i.v	Δ^9-THC: −10.2°C @ 32 mg·kg^{-1}[c] 11-OH-Δ^8-THC: −6.0°C @ 32 mg·kg^{-1} 11-OH-Δ^9-THC: −6.6°C @ 32 mg·kg^{-1}	
Martin et al., 1981	Mouse	i.v.	Δ^8-THC: −5.7°C @ 16 mg·kg^{-1}[c] Δ^9-THC: −4.9°C @ 16 mg·kg^{-1}	
Robertson et al., 1984	Mouse	i.v.	Δ^8-THC: −3.4°C @ 20 mg·kg^{-1}	
Razdan, 1986	Mouse	i.v.	Δ^8-THC: −0.7°C @ 10 mg·kg^{-1}[c] Δ^9-THC: −5.0°C @ 10 mg·kg^{-1}	
Compton & Martin, 1990 Compton et al., 1991 Charalambous et al., 1991 Compton et al., 1992	Mouse	i.v.	Δ^8-THC: $ED_{50} = 15.5$ mg·kg^{-1} ($E_{max} = -5.9$°C) Δ^9-THC: $ED_{50} = 1.4$ mg·kg^{-1} ($E_{max} = -4.2$°C)	11.1
Martin et al., 1993 Huffman et al., 2003	Mouse	i.v.	Δ^8-THC: $ED_{50} = 1.4$ mg·kg^{-1} Δ^9-THC: $ED_{50} = 1.4$ mg·kg^{-1}	1
Watanabe et al., 1980	Mouse	i.v.	Δ^8-THC: −1.98°C @ 5 mg·kg^{-1} 11-OH-Δ^8-THC: −3.49°C @ 5 mg·kg^{-1} 11-oxo-Δ^8-THC: −3.05°C @ 5 mg·kg^{-1} 11-COOH-Δ^8-THC: Inactive @ 10 mg·kg^{-1}	
Watanabe et al., 1990	Mouse	i.v.	Δ^8-THC: −2.45°C @ 10 mg·kg^{-1} Δ^9-THC: −2.79°C @ 10 mg·kg^{-1} 11-OH-Δ^8-THC: −2.84°C @ 5 mg·kg^{-1} 11-OH-Δ^9-THC: −2.60°C @ 5 mg·kg^{-1}	
Karniol & Carlini, 1973	Mouse	i.p.	Δ^8-THC: $ED_{50} = 44.8$ mg·kg^{-1} Δ^9-THC: $ED_{50} = 19.1$ mg·kg^{-1}	2.3
Radwan et al., 2015 El-Alfy et al., 2010	Mouse	i.p.	Δ^8-THC: −1.96°C @ 20 mg·kg^{-1}[c] Δ^9-THC: −3.87°C @ 20 mg·kg^{-1}	

(Continues)

TABLE 3 (Continued)

Study[a]	Species	Route	Results	ED_{50} ratio (Δ^8-THC/Δ^9-THC)
Catalepsy				
Compton & Martin, 1990 Charalambous et al., 1991 Compton et al., 1991 Compton et al., 1992	Mouse	i.v.	Δ^8-THC: ED_{50} = 5.2 mg·kg^{-1} (E_{max} = 58%) Δ^9-THC: ED_{50} = 1.5 mg·kg^{-1} (E_{max} = 49%)	3.5
Martin et al., 1993	Mouse	i.v.	Δ^8-THC: ED_{50} = 1.5 mg·kg^{-1} Δ^9-THC: ED_{50} = 1.5 mg·kg^{-1}	1
Yoshimura et al., 1978 Watanabe et al., 1980 Narimatsu et al., 1987 Watanabe et al., 1990	Mouse	i.v.	Δ^8-THC: ED_{50} = 3.3 mg·kg^{-1} (Yoshimura et al., 1978) Δ^9-THC: ED_{50} = 2.6 mg·kg^{-1} (Narimatsu et al., 1987) 11-OH-Δ^8-THC: ED_{50} = 0.66 mg·kg^{-1} (Watanabe et al., 1980) 11-OH-Δ^9-THC: ED_{50} = 0.46 mg·kg^{-1} (Watanabe et al., 1990) 11-oxo-Δ^8-THC: ED_{50} = 2.25 mg·kg^{-1} (Watanabe et al., 1980) 11-COOH-Δ^8-THC: ED_{50} = Inactive (Watanabe et al., 1980)	1.3
Karniol & Carlini, 1973	Mouse	i.p.	Δ^8-THC: ED_{50} = 79 mg·kg^{-1} Δ^9-THC: ED_{50} = 37 mg·kg^{-1}	2.1
Radwan et al., 2015 El-Alfy et al., 2010	Mouse	i.p.	Δ^8-THC: 47.9 s catalepsy @ 20 mg·kg^{-1}[c] Δ^9-THC: 5.3 s catalepsy @ 20 mg·kg^{-1}	
Burstein et al., 1988	Mouse	p.o.	Immobility fraction per 5 min: Vehicle: 0.07 Δ^8-THC: 0.17 @ 12.5 mg·kg^{-1}[d] Δ^8-THC: 0.21 @ 25 mg·kg^{-1} Δ^9-THC: 0.22 @ 12.5 mg·kg^{-1} Δ^9-THC: 0.34 @ 25 mg·kg^{-1} 11-COOH-Δ^8-THC: 0.11 @ 40 mg·kg^{-1} 11-COOH-Δ^9-THC: 0.09 @ 40 mg·kg^{-1}	
Grunfeld & Edery, 1969	Rat	i.p.	Δ^8-THC: 3 h catalepsy @ 20 mg·kg^{-1} Δ^9-THC: 5 h catalepsy @ 20 mg·kg^{-1}	
Tail flick				
Compton & Martin, 1990 Charalambous et al., 1991 Compton et al., 1991 Compton et al., 1992 Martin et al., 1993	Mouse	i.v.	Δ^8-THC: ED_{50} = 1.5 mg·kg^{-1} (E_{max} = 100%) Δ^9-THC: ED_{50} = 1.4 mg·kg^{-1} (E_{max} = 100%)	1.1
Martin et al., 1975	Mouse	i.p.	Δ^8-THC: No effect at 10 mg·kg^{-1}[c] Δ^9-THC: No effect at 10 mg·kg^{-1}	
Dewey et al., 1970	Mouse	i.p.	Δ^8-THC: 24% analgesia @ 10 mg·kg^{-1} Δ^9-THC: 28% analgesia @ 10 mg·kg^{-1}	
Radwan et al., 2015 El-Alfy et al., 2010	Mouse	i.p.	Δ^8-THC: 28% analgesia @ 20 mg·kg^{-1} Δ^9-THC: 6% analgesia @ 20 mg·kg^{-1}	
Welch et al., 1995	Mouse	i.c.v.	Δ^8-THC: ED_{50} = 126 μg Δ^9-THC: ED_{50} = 16 μg	7.9
Welch & Stevens, 1992	Mouse	i.t.	Δ^8-THC: ED_{50} = 72 μg Δ^9-THC: ED_{50} = 45 μg	1.6
Hot plate				
Uliss et al., 1975	Mouse	i.v.	Δ^8-THC: ED_{50} = 34.7 mg·kg^{-1} Δ^9-THC: ED_{50} = 54.0 mg·kg^{-1}	0.64
Dewey et al., 1970	Mouse	i.p.	Δ^8-THC: 54% analgesia @ 10 mg·kg^{-1} Δ^9-THC: 46% analgesia @ 10 mg·kg^{-1}	
Martin et al., 1975	Mouse	i.p.	Δ^8-THC: No effect at 10 mg·kg^{-1}[c] Δ^9-THC: No effect at 10 mg·kg^{-1}	
Radwan et al., 2015	Mouse	i.p.	Δ^8-THC: 42% of max @20 mg·kg^{-1}[c] Δ^9-THC: 47% of max @ 20 mg·kg^{-1}	

TABLE 3 (Continued)

Study[a]	Species	Route	Results	ED_{50} ratio (Δ^8-THC/Δ^9-THC)
Wilson & May, 1975	Mouse	s.c.	Δ^8-THC: ED_{50} = 8.8 mg·kg^{-1} Δ^9-THC: ED_{50} = 9.6 mg·kg^{-1} 11-OH-Δ^8-THC: 1.9 mg·kg^{-1} 11-OH-Δ^9-THC: 1.9 mg·kg^{-1}	0.9
Chesher et al., 1973	Mouse	p.o.	Δ^8-THC: ED_{50} = 5 mg·kg^{-1} Δ^9-THC: ED_{50} = 5 mg·kg^{-1}	1
Burstein et al., 1988 Doyle et al., 1990	Mouse	p.o.	11-COOH-Δ^8-THC: 54% increase @ 20 mg·kg^{-1}[c] 11-COOH-Δ^9-THC: 21% increase @ 20 mg·kg^{-1} Δ^9-THC: 51% increase @ 20 mg·kg^{-1}	
Welch & Stevens, 1992	Mouse	i.t.	Δ^8-THC: ED_{50} = 28 μg Δ^9-THC: ED_{50} = 37 μg	0.73

Abbreviations: i.c.v., intracerebroventricular; i.p., intraperitoneal; i.t., intrathecal; i.v., intravenous; NS, not significant; p.o., oral (per os); s.c., subcutaneous.
[a]Multiple references are listed when the same results have been presented in multiple publications.
[b]Potency values were reported as ratios relative to Δ^9-THC based on the dose required to produce a significant decrease in spontaneous activity. We are reporting the inverse of the original ratio so that a lower number indicates greater potency.
[c]Results of one dose are shown in table, but publication tested additional doses.
[d]Values represent fraction of time during a 5-min period that mice remained immobile.

(Table 3). Δ^8-THC induced a dose-dependent cataleptic effect with all administration routes (Burstein et al., 1988; Compton & Martin, 1990; El-Alfy et al., 2010; Grunfeld & Edery, 1969; Karniol & Carlini, 1973; Martin et al., 1993; Yoshimura et al., 1978). In the studies that calculated an ED_{50} for both molecules, the potency of Δ^8-THC was sometimes reported to be weaker than Δ^9-THC but sometimes reported to be equipotent. The ED_{50} ratio of Δ^8-THC to Δ^9-THC ranged from 3.5-fold to 1 (Compton & Martin, 1990; Karniol & Carlini, 1973; Martin et al., 1993; Yoshimura et al., 1978). Other studies that tested limited dose ranges also had inconsistent results. For example, one study showed that Δ^8-THC had greater cataleptic activity than Δ^9-THC in mice at 20 mg·kg^{-1}, whereas another study showed the opposite in rats (El-Alfy et al., 2010; Grunfeld & Edery, 1969; Radwan et al., 2015). The maximum cataleptic effect appeared to be in a similar range for both Δ^8-THC and Δ^9-THC (58% vs. 49% of the maximum time) (Compton & Martin, 1990).

The 11-OH-Δ^8-THC metabolite was about 40% less potent than 11-OH-Δ^9-THC (Narimatsu et al., 1987; Watanabe et al., 1980, 1990). In both cases, the 11-hydroxy metabolites were about 5-fold more potent than their respective parent molecules, whereas the 11-oxo-Δ^8-THC metabolite was slightly less potent than its parent. Contradictory results were found for the 11-COOH-THC metabolites. One study found that 11-COOH-Δ^8-THC was inactive following i.v. dosing (Watanabe et al., 1980), whereas another reported slight activity of both 11-COOH-Δ^8-THC and 11-COOH-Δ^8-THC at an oral dose of 40 mg·kg^{-1} (Burstein et al., 1988).

3.4 | Tail flick

The analgesic effects of Δ^8-THC have been tested in the tail flick assay in mice following i.v., i.p., i.c.v. and intrathecal (i.t) administration (Table 3). Δ^8-THC induced a dose-dependent analgesic effect with i.v., i.c.v. and i.t. administration (Compton & Martin, 1990; Welch et al., 1995; Welch & Stevens, 1992). Studies with i.p. administration did not test a wide enough dose range to evaluate dose-related effects. Two studies did show an analgesic effect at doses of 10 and 20 mg·kg^{-1} (Dewey et al., 1970; El-Alfy et al., 2010), but a third study did not see any effect with 1 or 10 mg·kg^{-1} i.p. dosing of either Δ^8-THC or Δ^9-THC (Martin et al., 1975). The most likely explanation for this was using a formulation with poor absorption.

Potency was similar between Δ^8-THC and Δ^9-THC following i.v. administration, with the ED_{50} of Δ^8-THC reported to be only 10% higher (Compton & Martin, 1990). The E_{max} of both was reported to be 100%, which reflects that the limit of the assay was reached (Charalambous et al., 1991). Contradictory results have been reported with i.p. administration. Although one study observed similar levels of analgesia at 10 mg·kg^{-1}, another reported much greater levels of analgesia with Δ^8-THC compared with Δ^9-THC following a 20 mg·kg^{-1} dose (Dewey et al., 1970; El-Alfy et al., 2010; Radwan et al., 2015). These inconsistent results may represent the variable absorption of THC that can occur with i.p. dosing. Following i.t. dosing, Δ^9-THC was 1.6-fold more potent than Δ^8-THC (Welch & Stevens, 1992). This contrasts with i.c.v. dosing, where Δ^9-THC was 7.9-fold more potent than Δ^8-THC (Welch et al., 1995).

3.5 | Hot plate

The analgesic effects of Δ^8-THC have been tested in the hot plate assay in mice following i.v., i.p., subcutaneous (s.c.), oral (p.o.) and i.t. administration (Table 3). Δ^8-THC induced a dose-dependent analgesic effect with all administration routes (Burstein et al., 1988; Chesher et al., 1973; Dewey et al., 1970; Radwan et al., 2015; Uliss et al., 1975; Welch & Stevens, 1992; Wilson & May, 1975). The exception was a single study that did not see any effect with 1 and 10 mg·kg^{-1} i.p. dosing of either Δ^8-THC or Δ^9-THC, possibly owing to poor absorption (Martin

et al., 1975). Interestingly, Δ^8-THC was typically more potent in this assay than Δ^9-THC. The ED_{50} ratio of Δ^8-THC to Δ^9-THC was 0.64 with i.v. dosing, 0.9 with s.c. dosing, 1 with p.o. dosing and 0.73 with i.t. dosing (Chesher et al., 1973; Uliss et al., 1975; Welch & Stevens, 1992; Wilson & May, 1975). An ED_{50} was not determined with i.p. dosing, but similar analgesic effects of Δ^8-THC and Δ^9-THC were reported at 10 and 20 $mg{\cdot}kg^{-1}$ (Dewey et al., 1970; Radwan et al., 2015).

The 11-hydroxy metabolites of Δ^8-THC and Δ^9-THC were both active in the hot plate assay and were equipotent following s.c. administration (Wilson & May, 1975). These metabolites were both approximately 5-fold more potent than their respective parent THC. The 11-COOH-THC metabolites also had activity in the hot plate assay when administered orally to mice (Burstein et al., 1988; Doyle et al., 1990). Eleven-COOH-Δ^8-THC had a maximal increase in latency of 54% at 20 $mg{\cdot}kg^{-1}$, whereas 11-COOH-Δ^9-THC had a maximal increase in latency of 67% at 10 $mg{\cdot}kg^{-1}$. These values were in a similar range to parent Δ^9-THC, which resulted in a 51% increase at 20 $mg{\cdot}kg^{-1}$.

3.6 | Anaesthesia sleeping time

Both Δ^8-THC and Δ^9-THC have demonstrated dose-dependent effects in the anaesthesia sleeping time assay in mice. When tested at 5 $mg{\cdot}kg^{-1}$ i.v. or 10 $mg{\cdot}kg^{-1}$ p.o., Δ^8-THC and Δ^9-THC had similar sleep-prolonging effects (Chesher et al., 1974; Watanabe et al., 1990). However, Δ^9-THC had significantly greater effects than Δ^8-THC at the lower dose of 1 $mg{\cdot}kg^{-1}$ (1.3-fold vs.1.9-fold), indicating greater potency of Δ^9-THC with a similar maximal effect between the two molecules. A similar trend was seen with 11-hydroxy metabolites except that the effects were about 50% stronger compared with the parent molecules (Watanabe et al., 1980, 1990). Eleven-oxo-Δ^8-THC was also stronger than its parent, whereas 11-COOH-Δ^8-THC did not have significant activity (Watanabe et al., 1980).

3.7 | Discriminative stimulus

Various studies have evaluated the ability of Δ^8-THC and its metabolite to induce responding after animals were trained on Δ^9-THC in discriminative stimulus studies (Balster & Prescott, 1992). Δ^8-THC was able to fully substitute for Δ^9-THC in rats, although it was approximately 2-fold less potent on average. A similar effect was detected in two pigeons (Järbe et al., 1977). The 11-OH-Δ^8-THC metabolite also fully substituted with approximately 2-fold greater potency than Δ^9-THC on average (Balster & Prescott, 1992). Similarly, Δ^8-THC was able to fully substitute for Δ^9-THC in rhesus monkeys, although with at least 10-fold lower potency (Wiley, Huffman, et al., 1995).

3.8 | Dog ataxia

Ataxia of Δ^8-THC and Δ^9-THC has been tested in dogs (Compton & Martin, 1990; Dewey et al., 1970; Grunfeld & Edery, 1969; Martin et al., 1975, 1981; Wilson & May, 1975). Both molecules produced dose-dependent ataxia with qualitatively similar effects, but the dose that produced ataxia was about twice as high with Δ^8-THC (0.4 $mg{\cdot}kg^{-1}$) compared with Δ^9-THC (0.2 $mg{\cdot}kg^{-1}$).

3.9 | Monkey behaviour

The effects of both Δ^8-THC and Δ^9-THC have been tested in monkeys following i.v. administration (Edery et al., 1971; Grunfeld & Edery, 1969; Ho et al., 1972; Scheckel et al., 1968) and were subjectively similar. Although they were not quantitatively evaluated, the effects of 2 mg Δ^8-THC were approximately equal to 0.5 mg Δ^9-THC (Ho et al., 1972). The 11-COOH-Δ^8-THC metabolite had no behavioural effects in monkeys at doses up to 10 $mg{\cdot}kg^{-1}$ (Mechoulam et al., 1973).

3.10 | Comparison between animal assays

All tetrad assays (hypolocomotion, hypothermia, catalepsy and analgesia) indicated that Δ^8-THC has potent cannabimimetic effects. This is supported by additional studies of anaesthesia "sleeping" time, dog ataxia and monkey behaviour. The results show potential species differences, although the different assays used in each species cannot be compared directly. The dose that affected monkey behaviour was approximately 4-fold different between Δ^8-THC and Δ^9-THC with a 10-fold difference for Δ^8-THC to fully substitute for Δ^9-THC in discriminative stimulus assays. The potency difference in dogs and rats was approximately 2-fold. For the tetrad assays, which were almost entirely performed in mice, there was significant variability between individual experiments. However, most studies showed that Δ^8-THC was only slightly less potent than Δ^9-THC. These results are not inconsistent with *in vitro* CB_1 receptor studies, where little difference was seen between Δ^8-THC and Δ^9-THC with the mouse receptor and a 2-fold difference was seen with the rat receptor. Non-human primate versions of the receptor have not been tested, but the human version showed the greatest difference (about 6-fold) in binding and signalling.

Results were generally consistent across tetrad assays, although the hot plate assay appeared to be an outlier. Δ^8-THC was equipotent or slightly more potent than Δ^9-THC in all four experiments and for all administration routes (i.v., s.c., p.o. and i.t.) in the hot plate assay. This inconsistency could reflect differences in mechanism of action, because tail flick is predominantly a spinal response and hot plate predominantly reflects supraspinal effects (South & Smith, 1998). Another contributing factor could be the THC-COOH metabolite, which was active in the hot plate assay (Burstein et al., 1988; Doyle et al., 1990), but generally had little activity in other cannabimimetic tests such as catalepsy, hypothermia, anaesthesia sleeping time and monkey behaviour (Burstein et al., 1988; Mechoulam et al., 1973; Watanabe et al., 1990). However, Δ^8-THC was more potent than Δ^9-THC even when administered

intrathecally, which argues against the contribution of a metabolite. Another possibility is a difference in potency at a receptor other than CB_1. Mouse tetrad tests generally depend on the CB_1 receptor (Metna-Laurent et al., 2017; Zimmer et al., 1999). Despite a selective CB_2 receptor agonist having little effect on tetrad assays (Valenzano et al., 2005), the CB_2 receptor can influence the effects of non-selective cannabinoid receptor agonists (Liu et al., 2017, 2020; Wang et al., 2020). In particular, the hot plate assay was the only one where the effects of intracerebroventricular Δ^9-THC were completely abolished by knocking out the CB_2 receptor (Wang et al., 2020).

4 | EFFECTS IN HUMANS

The first report of the effects of Δ^8-THC in humans was in 1942 (Adams, 1942). Adams studied oral Δ^8-THC derived from CBD in a group of 77 voluntary subjects from a prison population. Subjects started with 30 mg and escalated the dose in 30 mg increments every 2 days. When a non-tolerated dose was reached, the dose was reduced to the tolerable one and escalation was continued at 15 mg·day^{-1}. Although no modern psychometric scale was available to use, the reported effects were remarkably similar to Δ^9-THC:

The observed psychiatric effects are (a) apprehension and anxiety, (b) euphoria, (c) loquaciousness, (d) lowering of inhibitions, (e) hunger and thirst, (f) feeling of being 'high', (g) uncontrollable bursts of laughter or giggles and (h) drowsiness, languor, lassitude and a pleasant feeling of fatigue.

We have identified six additional publications describing the effects of Δ^8-THC or its 11-OH metabolite in humans, including three where Δ^8-THC and Δ^9-THC were compared within the same study (Table 4). Three routes of administration were tested, including intravenous, smoked and oral.

4.1 | Intravenous

Intravenous dosing of Δ^8-THC (1 to 9 mg) and Δ^9-THC (1 to 6 mg) demonstrated that both cannabinoids have very similar qualitative effects (Hollister & Gillespie, 1973). Both resulted in an increase in heart rate and significant increases in a visual analogue scale (VAS) of feeling high, which are CB_1-mediated effects. The small number of subjects per dose makes a quantitative comparison impossible, but it is notable that subjects reported a VAS feeling high of 8/10 after receiving intravenous Δ^8-THC doses of 6 and 9 mg. This indicates that Δ^8-THC may have a maximal subjective effect very similar to Δ^9-THC. This is consistent with functional assays of the human CB_1 receptor, which generally showed a similar *in vitro* maximal effect between the two cannabinoids.

A limited number of subjects were also administered 11-OH-Δ^8-THC (1 to 8 mg) intravenously (Hollister, 1974). The qualitative effects of this compound were described as similar to other THC compounds. Overall, the 11-OH metabolite was judged to be 20% more potent than its parent Δ^8-THC, yet only 25% as potent as 11-OH-Δ^9-THC. One subject received an equivalent 5 mg dose of both 11-OH-Δ^8-THC and Δ^9-THC. The 11-OH-Δ^8-THC had a similar time to onset of action, but it 'reached a peak much faster and was more severe and longer in duration'. These results are qualitatively similar to 11-OH-Δ^9-THC, which had a stronger effect that was achieved more rapidly than parent Δ^9-THC (Lemberger et al., 1973).

4.2 | Inhaled

Two clinical studies have examined Δ^8-THC administered by inhalation via smoking. The first study compared placebo to Δ^8-THC (10 and 20 mg) and Δ^9-THC (5, 10 and 20 mg) (Karniol & Carlini, 1973). Both the 10 and 20 mg doses of Δ^9-THC resulted in stronger ratings of high on a graded interview compared with the equivalent Δ^8-THC dose. The 10 mg dose of Δ^8-THC resulted in similar ratings of high as the 5 mg dose of Δ^9-THC, indicating that smoked Δ^9-THC is approximately 2-fold more potent. The second study assessed 8.3 mg of Δ^8-THC compared with placebo cannabis but reported few details (Levander et al., 1974). A 'highly significant increase' in heart rate was observed following Δ^8-THC administration.

4.3 | Oral

Besides the aforementioned study by Adams (1942), three other clinical studies have examined the effects of Δ^8-THC following oral administration, although only two reported on changes in heart rate and subjective effects. An oral dose of 20 mg Δ^9-THC resulted in stronger subjective effects than an equivalent dose of Δ^8-THC (3.5 vs. 2.2 on a 0–10 global rating) (Hollister & Gillespie, 1973). However, a higher 40 mg dose of Δ^8-THC resulted in a stronger subjective effect than the 20 mg dose of either molecule (6.3/10). These results would indicate that Δ^9-THC is less than twice as potent as Δ^8-THC.

Results of another study appeared to conflict with this (Gong et al., 1984). Both 50 and 75 mg oral doses of Δ^8-THC had weaker effects than a 20-mg dose of Δ^9-THC on a 0–7 peak high rating (Gong et al., 1984). This would indicate that Δ^9-THC is at least 3.75-fold more potent than Δ^8-THC. The reason for this discrepancy is not clear. The Hollister study used a crossover design, whereas the Gong study tested Δ^8-THC and Δ^9-THC in separate groups of subjects. Both studies also used a low number of subjects, which could produce spurious results considering the large variability in THC effects across subjects and even across testing days. Other experimental details were not reported that could help interpretation, such as whether subjects were dosed in a fasted or fed state.

The final study tested oral Δ^8-THC in eight children undergoing chemotherapy for hematologic malignancies in order to evaluate its antiemetic properties (Abrahamov et al., 1995). Dosing at 18 mg·m^{-2} (equivalent to approximately 31 mg in the typical adult) every 6 h was reported to almost completely prevent vomiting. Side effects were observed in two of eight subjects and included mild irritability and euphoria.

TABLE 4 Studies of Δ^8-THC clinical activity

Study[a]	Subjects	Dose	*n*	Heart rate[b]	Subjective effects[c]
Intravenous					
Hollister & Gillespie, 1973	Healthy adult males n = 4 total)	Δ^9-THC 1 mg	3	+9	1–2/10
		Δ^9-THC 2 mg	3	+12	3–4/10
		Δ^9-THC 3 mg	3	+26	6/10
		Δ^9-THC 4 mg	1	+16	6/10
		Δ^9-THC 5 mg	1	+24	9/10
		Δ^9-THC 6 mg	1	+17	9/10
		Δ^8-THC 1 mg	1	+7	1/10
		Δ^8-THC 2 mg	1	+27	2/10
		Δ^8-THC 3 mg	1	+37	6/10
		Δ^8-THC 6 mg	2	+35	7–8/10
		Δ^8-THC 9 mg	2	+41	8/10
Hollister, 1974	Healthy adult males (*n* = 4 total)	11-OH-Δ^8-THC (1–8 mg)	4	NA	1 mg: 'Minimal effect' 2–3 mg: 'Moderate effect' 5 mg: More severe than 5 mg of Δ^9-THC Overall, 20% more potent than Δ^8-THC and 75% as potent as 11-OH-Δ^9-THC
		Δ^9-THC 5 mg	1		
Smoked					
Karniol & Carlini, 1973	Healthy cannabis-naïve male medical students (*n* = 35 total)	Placebo	7	+8%	0.33/4
		Δ^9-THC 5 mg	5	+19%	0.86/4
		Δ^9-THC 10 mg	4	+29%	1.89/4
		Δ^9-THC 20 mg	5	+52%	2.20/4
		Δ^8-THC 10 mg	4	+28%	0.89/4
		Δ^8-THC 20 mg	5	+24%	1.21/4
Levander et al., 1974	Healthy cannabis-experienced adults (*n* = 5 total)	Placebo	5	'Highly significant increase'	NA
		Δ^8-THC 8.3 mg	5		
Oral					
Hollister & Gillespie, 1973	Healthy adult males (*n* = 6 total)	Δ^9-THC 20 mg	6	+10	3.5/10
		Δ^8-THC 20 mg	6	+7	2.2/10
		Δ^8-THC 40 mg	6	+12	6.3/10
Gong et al., 1984	Healthy male cannabis users	Placebo	18	+19%	0.3/7
		Δ^9-THC 20 mg	18	+34%	4.2/7
		Δ^8-THC 50 mg	8	+21%	2.8/7
		Δ^8-THC 75 mg	8	+28%	2.0/7
Abrahamov et al., 1995	Paediatric haematologic cancer patients	Δ^8-THC 18 mg·m^{-2}	8	NA	NA

Abbreviation: NA, not assessed.

[a]The study by Adams (1942) was not included in the table due to lack of experimental details and results.

[b]Heart rate represents the maximum change from baseline in beats per minute, or as a percentage (indicated by %).

[c]Subjective effects represent either a self-rated global impression or a peak effect from multiple timepoints, except for Karniol & Carlini (1973), which used a graded interview.

4.4 | Limitations of clinical studies

Δ^8-THC is clearly less potent in humans relative to Δ^9-THC, regardless of route of administration. Both intravenous and smoked routes, where a negligible level of the 11-OH-THC metabolite is formed, result in a lesser subjective effect of Δ^8-THC compared with the same dose of Δ^9-THC. Similarly, the oral route resulted in less effect of Δ^8-THC at an equal dose or even a significantly higher dose. However,

these clinical studies must be interpreted with caution. The number of subjects was very low in all studies, especially considering the high inter-subject variability observed with cannabinoids. There was also significant heterogeneity between studies in the subjects used (cannabis-naïve, vs. cannabis-experienced vs. regular cannabis users) and the subjective effect scale utilized. At the same time, the subject demographics were not diverse and included almost entirely males in their 20s and 30s. None of the studies measured pharmacokinetics with the exception of one, which included almost no results in their publication (Levander et al., 1974). This information is critical for interpreting results, especially with oral dosing, where both the parent and active metabolite can contribute to the effects.

There are not yet enough clinical data to determine if the potency difference between Δ^8-THC and Δ^9-THC changes with route of administration. However, there are plausible mechanisms of how this could occur because the oral route produces much higher plasma levels of the 11-OH-THC metabolite that can contribute to the perceived high. First, the potency difference between the 11-OH metabolites may not be equivalent to the potency difference between the parent Δ^8-THC and Δ^9-THC molecules. There is some support for this from signalling studies of the mouse CB_1 receptor (Howlett, 1987a, 1987b), but confirmation is needed in human receptors. Second, different plasma levels of the 11-OH metabolite could be produced with Δ^8-THC and Δ^9-THC, which requires clinical pharmacokinetic studies. Furthermore, the studies of oral dosing did not report whether the drugs were administered in a fasted state or following a meal, which can significantly influence the timing and intensity of THC effects (e.g., Lunn et al., 2019).

One more clinical aspect of Δ^8-THC that has hardly been explored is whether it has any differences from Δ^9-THC in qualitative effects. The overall subjective effects of Δ^8-THC and Δ^9-THC are reported to be similar in clinical studies. However, some anecdotal reports claim, for example, that Δ^8-THC produces less anxiety than Δ^9-THC. This may be a result of generally weaker effects at equivalent doses or it could be due to an actual difference in subjective effects even when the overall intensity of cannabimimetic effects is the same. Human studies have not yet explored detailed subjective effects beyond basic rating scales of overall intensity. For example, the effects of Δ^8-THC on mood and cognition are relatively unknown and could potentially have some differences from Δ^9-THC.

5 | PHARMACOKINETICS

5.1 | Absorption

No publications have yet reported a pharmacokinetic profile of Δ^8-THC in humans. One study collected pharmacokinetic samples after smoking 8.3 mg of Δ^8-THC in six subjects (Levander et al., 1974). The authors reported 'rather uniform plasma THC levels, corresponding to an absorption of about 50%'. However, no specific pharmacokinetic results were presented, and it is not clear how the determination of 50% was made because they did not also perform intravenous dosing for comparison. One study described the pharmacodynamic effects of Δ^8-THC and Δ^9-THC after smoking (Karniol & Carlini, 1973). Both compounds produced effects on heart rate within minutes smoking, indicating rapid drug absorption from the lungs as was previously described for Δ^9-THC (see Huestis, 2007, for a review).

Oral absorption in humans is virtually unstudied for Δ^8-THC. No pharmacokinetic data have been published with oral dosing, although some information can be inferred based on pharmacodynamic data from two studies. In the first study, Δ^8-THC (20 and 40 mg) and Δ^9-THC (20 mg) were administered in the form of a cookie. Although a full-time course was not reported, subjective and objective pharmacodynamic effects were higher at 2 h compared with 4 h for all conditions, indicating that the time to maximum plasma concentration (T_{max}) occurred prior to 4 h (Hollister & Gillespie, 1973). In the second study, Δ^8-THC (50 and 70 mg) and Δ^9-THC (20 mg) were administered suspended in sesame oil. The pharmacodynamic effects peaked at 4 to 6 h with 50 and 70 mg doses of Δ^8-THC, compared with 4 h for a 20-mg dose of Δ^9-THC (Gong et al., 1984). These data on human absorption are limited but show that absorption appears to be similar between Δ^8-THC and Δ^9-THC. The small difference in Gong et al. (1984) could be due to the low number of subjects per group or the different doses tested.

In contrast to Δ^8-THC, the oral absorption of Δ^9-THC is very well characterized. Under fasted conditions, it appears to exhibit solubility-limited absorption with a T_{max} of several hours that is also highly variable. For example, the T_{max} of **dronabinol** (oral Δ^9-THC) varies between 0.5 and 4 h according to the FDA label of Marinol® (Δ^9-THC; U. S. Food and Drug Administration [FDA], 2017). There is a strong food effect for Δ^9-THC, where a high fat meal increased bioavailability by about 2.8-fold (Lunn et al., 2019; Oh et al., 2017; Stott et al., 2013). It also increases the fraction of THC absorbed by the lymphatic pathway, which bypasses first-pass metabolism (Zgair et al., 2017). So, despite the higher bioavailability of THC, a high fat meal only increased levels of 11-OH-THC by approximately 25% (Lunn et al., 2019; Oh et al., 2017; Stott et al., 2013). Because they possess equivalent physiochemical properties, we anticipate that these aspects of absorption will be the same between Δ^8-THC and Δ^9-THC.

5.2 | Distribution

The distribution of Δ^8-THC and Δ^9-THC appears to be very similar, which is not surprising given their identical physiochemical properties. Whole body autoradiography in monkeys (*Callithrix jacchus*) following a single intravenous dose showed identical radiographic distribution of Δ^8-THC and Δ^9-THC in all organs tested, including bile, liver, kidney, stomach, lung, adrenal gland, parotid gland and pancreas (Just, Erdmann, et al., 1975; Just, Werner, et al., 1975). Similar results have been reported in mice (Ryrfeldt et al., 1973). Brain levels of Δ^8-THC and Δ^9-THC were equivalent from 15 to 60 min following a single intravenous dose of each compound to rats (Ho et al., 1973). After administering multiple doses of Δ^8-THC to rats, extensive accumulation was observed in fat, but not in plasma or brain (Nahas

et al., 1981, 2002). This is a similar pattern to Δ^9-THC distribution, which is characterized by extensive distribution to fat tissue, driven by its high lipophilicity (Lucas et al., 2018).

The active 11-OH-Δ^9-THC metabolite distributed to the brain more extensively than parent Δ^9-THC (Schou et al., 1977). The same phenomenon appears to be true of Δ^8-THC and its 11-OH metabolite. When both Δ^8-THC and its 11-OH metabolite were administered as 10 mg·kg^{-1} intravenous doses, the peak brain concentration of 11-OH-Δ^8-THC was 3-fold higher than parent Δ^8-THC in mice (Watanabe et al., 1981). However, conflicting results were found in rats, where 11-OH-Δ^8-THC brain levels were similar to parent when each compound was administered at the same dose (Ho et al., 1973).

Δ^9-THC is 95%–99% bound to plasma proteins (Huestis, 2007). The active 11-OH-Δ^9-THC metabolite is also 99% protein bound (Widman et al., 1974). The majority of this binding is to lipoproteins, although Δ^9-THC also binds to albumin (Klausner et al., 1975). Binding characteristics of Δ^8-THC to lipoprotein fractions appear to be similar (Capelle et al., 1976), but the actual unbound fraction of Δ^8-THC and its metabolite have not yet been determined in plasma.

No studies have yet examined whether Δ^8-THC is a substrate for any drug transporters, although Δ^9-THC is a substrate for several. In vitro studies conflict on whether Δ^9-THC is a substrate for **P-glycoprotein (P-gp; ABCB1)** (Tournier et al., 2010; Zhu et al., 2006), but it has been confirmed by *in vivo* studies. A strain of mice naturally deficient in P-gp have higher absorption of Δ^9-THC (Bonhomme-Faivre et al., 2008) and brain penetration is higher in both P-gp and **BCRP(ABCG2)** knockout mice (Spiro et al., 2012). In humans, a functional polymorphism in the gene for P-gp was associated with plasma Δ^9-THC level modulation (Kebir et al., 2018) and cannabis dependence (Benyamina et al., 2009). Daily administration of THC to mice induced P-gp expression in various brain regions and reduced brain penetration of the P-gp substrate **risperidone** (Brzozowska et al., 2017). Given the similar structure between Δ^8-THC and Δ^9-THC, it is possible that Δ^8-THC is also a P-gp substrate and could induce P-gp expression.

5.3 | Metabolism

The metabolism of Δ^9-THC is complex, with over 100 metabolites identified (Huestis, 2007). Many of the same *in vivo* metabolites were found in mice with Δ^8-THC (Harvey & Paton, 1980). The pathways for the most abundant metabolites are similar between Δ^8-THC and Δ^9-THC. In human liver microsomes, both Δ^8-THC and Δ^9-THC are oxidized at the 11 position to form 11-OH-Δ^8-THC and 11-OH-Δ^9-THC, respectively (Burstein et al., 1970; Watanabe et al., 2007). These 11-hydroxy metabolites are pharmacologically active, which is discussed in the pharmacodynamic sections. The 11-hydroxy metabolites are both formed by **CYP2C9**, demonstrated by sulfaphenazole inhibition in liver microsomes and efficient catalysis by the expressed CYP2C9 enzyme (Watanabe et al., 2007). The 11-OH metabolites can be subsequently metabolized to the non-psychoactive 11-carboxy metabolites (Huestis, 2007).

Human CYP2C9 formed 11-OH-Δ^8-THC less efficiently than 11-OH-Δ^9-THC (7.60 vs.19.2 nmol·min^{-1}·nmol^{-1} CYP) (Watanabe et al., 2007). This may depend on genotype, because the CYP2C9*2 form of the enzyme showed an opposite pattern. The slower formation of the 11-hydroxy metabolite with Δ^8-THC compared with Δ^9-THC has been observed *in vivo* with *C. jacchus* monkeys (Erdmann et al., 1976; Just, Erdmann, et al., 1975). The ratio of 11-OH-THC to THC at 30 min after an i.v. dose was on average two to three times lower following Δ^8-THC administration compared with Δ^9-THC in both blood and brain. However, the ratio of 11-OH-THC to THC in rat and mouse brain was similar between Δ^8-THC and Δ^9-THC, indicating a possible species difference (Ho et al., 1973; Ryrfeldt et al., 1973). The reduced formation of the 11-hydroxy metabolite may be one of the mechanisms by which Δ^8-THC has reduced activity *in vivo* relative to Δ^9-THC, but this requires further study.

Several other monohydroxylated metabolites are formed from both Δ^8-THC and Δ^9-THC, although there are some minor differences between the two. Expressed human **CYP3A4** catalysed the 7α- (5.34 nmol·min^{-1}·nmol^{-1} CYP) and 7β-hydroxylation (1.39 nmol·min^{-1}·nmol^{-1} CYP) of Δ^8-THC. With Δ^9-THC, it catalysed 8β-hydroxylation (6.10 nmol·min^{-1}·nmol^{-1} CYP) and 9α,10α-epoxidation (1.71 nmol·min^{-1}·nmol^{-1} CYP) (Watanabe et al., 2007).

5.4 | Excretion

Very few studies have examined the excretion of Δ^8-THC. In rabbits, Δ^8-THC urinary elimination was similar to Δ^9-THC in that little of the 11-OH-Δ^8-THC was excreted but that 11-COOH-Δ^8-THC was eliminated in urine as a conjugate that we now know to be a glucuronide (Mechoulam et al., 1973). However, the route of elimination was highly species dependent, as rabbits excreted Δ^8-THC drug material primarily through urine and rats primarily through faeces (Agurell et al., 1969, 1970). Despite the minimal excretion data, we can reasonably assume that the excretion pattern of Δ^8-THC is very similar to Δ^9-THC because its patterns of metabolism and distribution are equivalent.

The excretion of Δ^9-THC in humans has been well characterized with radiolabel studies after both i.v. and oral dosing (Hunt & Jones, 1980; Lemberger et al., 1970; Wall et al., 1983). The excretion of the 11-OH-Δ^9-THC metabolite has also been studied (Lemberger et al., 1972). Approximately half of the radioactivity was recovered in faeces (range from 28% to 65%). Virtually no parent Δ^9-THC was recovered in the faeces, although 11-OH, di-OH, COOH and glucuronide metabolites were detected. Approximately 25% of radioactivity was recovered in the urine (range from 15% to 30%). The majority of this was recovered as the glucuronide metabolite of 11-COOH-Δ^9-THC, with only trace amounts of parent Δ^9-THC detected. Thus, the majority of Δ^9-THC is converted to inactive metabolites prior to excretion.

The terminal elimination half-life of Δ^8-THC has not been reported in humans. The terminal half-life of Δ^9-THC is up to 4 days in chronic users (Huestis, 2007). This long half-life is driven primarily by redistribution to plasma from fat tissue. Given the similar distribution to fat tissue, we anticipate that Δ^8-THC will have a similarly long terminal half-life.

6 | CONCLUSIONS

The pharmacology of Δ^8-THC is generally very similar to Δ^9-THC *in vitro*, *in vivo* and in humans, but a few key differences have been identified. The most obvious difference is that Δ^8-THC has weaker potency than Δ^9-THC in many assays, even though it appears to have similar intrinsic efficacy *in vitro* and maximal effects *in vivo*. The metabolism of Δ^8-THC is similar to Δ^9-THC and both have an active 11-OH metabolite that is more potent than its respective parent. There are several plausible mechanisms by which Δ^8-THC could have lower *in vivo* potency, including a different potency at the CB_1 receptor, a different balance of CB_1 versus CB_2 receptor activation and a different formation rate of the active 11-OH metabolite.

Several gaps remain in characterizing the pharmacology of Δ^8-THC. For example, there are conflicting reports of its effects at the cannabinoid receptors using the GTPγS assay and activity at GPR55 and other receptors is unknown. The clinical dose–response and concentration–response of Δ^8-THC have not been studied in detail and human pharmacokinetics has not been reported at all. Further clinical pharmacology studies should be performed to understand the pharmacokinetics/pharmacodynamics of Δ^8-THC and how it is distinct from Δ^9-THC.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander et al., 2021).

CONFLICT OF INTEREST

No conflict of interest to declare.

AUTHOR CONTRIBUTIONS

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