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Dark Classics in Chemical Neuroscience: Δ^9-Tetrahydrocannabinol

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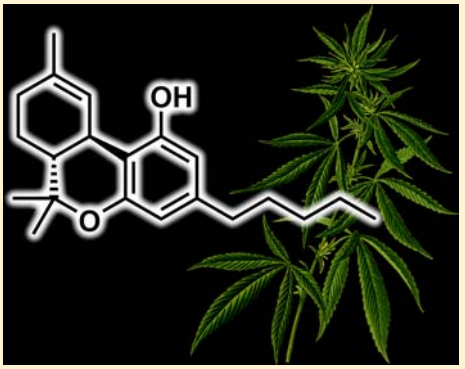
ABSTRACT: Cannabis (*Cannabis sativa*) is the most widely used illicit drug in the world, with an estimated 192 million users globally. The main psychoactive component of cannabis is (−)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC), a compound with a diverse range of pharmacological actions. The unique and distinctive intoxication caused by Δ^9-THC primarily reflects partial agonist action at central cannabinoid type 1 (CB_1) receptors. Δ^9-THC is an approved therapeutic treatment for a range of conditions, including chronic pain, chemotherapy-induced nausea and vomiting, and multiple sclerosis, and is being investigated in indications such as anorexia nervosa, agitation in dementia, and Tourette's syndrome. It is available as a regulated pharmaceutical in products such as Marinol, Sativex, and Namisol as well as in an ever-increasing range of unregistered medicinal and recreational cannabis products. While cannabis is an ancient medicament, contemporary use is embroiled in legal, scientific, and social controversy, much of which relates to the potential hazards and benefits of Δ^9-THC itself. Robust contemporary debate surrounds the therapeutic value of Δ^9-THC in different diseases, its capacity to produce psychosis and cognitive impairment, and the addictive and "gateway" potential of the drug. This review will provide a profile of the chemistry, pharmacology, and therapeutic uses of Δ^9-THC as well as the historical and societal import of this unique, distinctive, and ubiquitous psychoactive substance.



KEYWORDS: *cannabis, cannabinoid, tetrahydrocannabinol, cannabidiol, chemistry, pharmacology*

INTRODUCTION

Use of the cannabis plant (*Cannabis sativa*) as an intoxicant can be traced to China around 2500 BCE, and archeological evidence of *Cannabis* cultivation extends this timeline by several thousand years.[1,2] From Asia, *Cannabis* spread across the globe over several millennia[3] and was known to Western medicine by the 18th century.[4]

Cannabis is a dioecious annual plant that biosynthesizes unique terpenophenolic natural products termed phytocannabinoids. Of the 565 compounds identified in *C. sativa* to date, more than 140 phytocannabinoids have been isolated, belonging to several distinct structural classes.[5,6] The therapeutic potential of a number of these phytocannabinoids in arresting the pathophysiological processes involved in inflammation and pain is increasingly apparent, alongside increased knowledge of their fundamental pharmacological actions.

The enduring popularity of the cannabis plant as an intoxicant (generically "cannabis") can be attributed to the psychoactivity of a single cannabinoid, (−)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC, dronabinol, **1a**, Figure 1). Other major phytocannabinoids obtained from *Cannabis* include (−)-cannabidiol (CBD, **2a**), cannabigerol (CBG, **3a**), and cannabichromene (CBC, **4a**), but although biologically active, these are not intoxicants. Regioisomeric (−)-*trans*-Δ^8-THC (**5a**)[7] and the oxidation product cannabinol (CBN, **6a**)[8] occur naturally and can be intoxicating, albeit with lesser potency than Δ^9-THC. Indeed, CBN was the first pure phytocannabinoid isolated from *Cannabis* (by Wood and colleagues at Cambridge in 1899).[9] By the 1940s, researchers in the United Kingdom and United States had simultaneously prepared isomeric tetrahydrocannabinols, including Δ^8-THC, retaining the same qualitative effects as cannabis in laboratory animals,[10,11] although it would be several decades before the structure of Δ^9-THC was conclusively determined and its activity at CB_1 identified.

Δ^8-THC and CBN are also far less abundant in *Cannabis* than Δ^9-THC and therefore unlikely to contribute substantively to the psychoactivity of the plant. It is worth noting that early cannabinoid literature used several numbering systems (see

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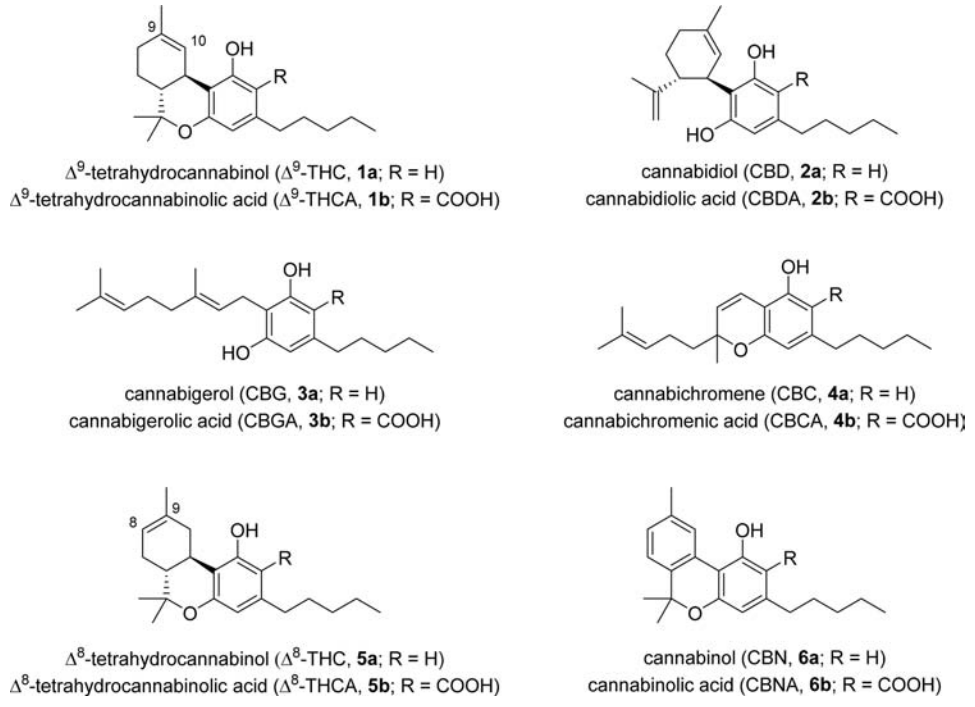

Figure 1. Selected phytocannabinoids obtained from cannabis.

Figure 2), leading to potential confusion for the modern reader attempting to interpret historical data. Throughout this review,

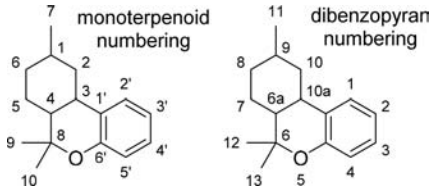

Figure 2. Monoterpenoid and dibenzopyran tetrahydrocannabinol numbering systems.

we used the dibenzopyran numbering now adopted throughout the cannabinoid sciences.

Somewhat counterintuitively, raw cannabis plant material is typically low in Δ^9-THC. Phytocannabinoids accumulate in the glandular trichomes of female *Cannabis* flowers, but the levels of Δ^9-THC are low in comparison to those of its phytochemical precursor tetrahydrocannabinolic acid (THCA, **1b**).[12,13] When cannabis plant material is heated, nonintoxicating THCA is decarboxylated to form Δ^9-THC. For this reason, recreational cannabis use traditionally involves smoking, baking, or vaporization, ensuring maximal conversion of THCA to Δ^9-THC and corresponding psychoactive effects. Analogously, CBD, CBG, CBC, Δ^8-THC, and CBN are obtained by nonenzymatic decarboxylation of naturally occurring acid precursors cannabidiolic acid (CBDA, **2b**), cannabigerolic acid (CBGA, **3b**), cannabichromenic acid (CBCA, **4b**), Δ^8-THCA (**5b**), and cannabinolic acid (CBNA, **6b**). Only recently has interest developed around the therapeutic properties of THCA, motivating the consumption of raw "juiced" cannabis and other cold-processed extracts enriched in the carboxylated (acid) form of Δ^9-THC, while the effects of other

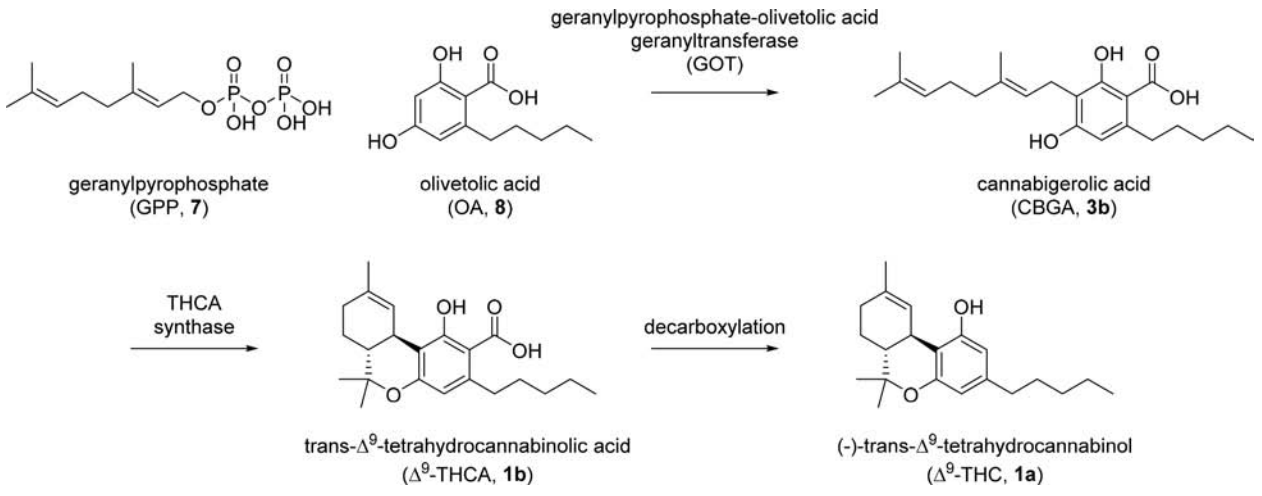

Figure 3. Biosynthesis of Δ^9-tetrahydrocannabinol.

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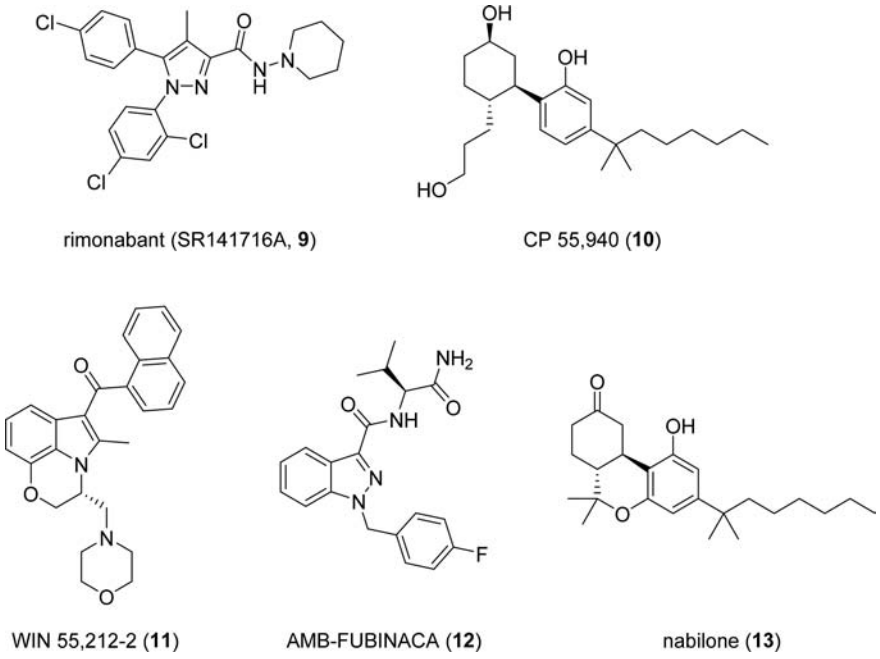

Figure 4. Common cannabinoid ligands used in pharmacology research or as drugs.

phytocannabinoid acids remain pharmacologically unexplored in people.[14]

The biosynthesis of Δ^9-THC[15] and other phytocannabinoids[16,17] has been extensively reviewed. Briefly, coupling of olivetolic acid (OA, **8**, Figure 3) and geranylpyrophosphate (GPP, **7**) is mediated by geranylpyrophosphate:olivetolic acid geranyltransferase to give CBGA.[18] Olivetolic acid itself originates from a hexanoate-derived pentyl tetra-*β*-ketide CoA via olivetolic acid cyclase (OAC), the only known plant polyketide cyclase.[19,20] CBGA serves as the common precursor for several phytocannabinoid acids and is the direct precursor for CBG by nonenzymatic decarboxylation. In the case of Δ^9-THCA, CBGA cyclization is catalyzed by THCA synthase.[21] Although THC(A) is found in many parts of the cannabis plant, accumulation in the glandular trichomes of unpollinated female *Cannabis* flowers ("sinsemilla"), as well as their sieved resin ("hashish"), makes the flowers ("bracts" or "bud") the most popular form of the drug. THCA undergoes nonenzymatic (thermal) decarboxylation to give Δ^9-THC, and further oxidative degradation of Δ^9-THC results in aromatization to the dibenzopyran CBN.

There are more than 700 different plant varieties (chemovars or cultivars) of *Cannabis*, with a diversity of cannabinoid profiles and Δ^9-THC/THCA content.[22,23] For example, fiber hemp varieties of *Cannabis* display a distinctive cannabinoid profile with very low levels of THCA (<0.5%) and Δ^9-THC (<0.5%) but relatively high levels of CBDA and CBD. There are also up to 200 volatile terpenoid compounds found in *Cannabis* (e.g., limonene, pinene, myrcene, *trans*-caryophyllene), and these also vary substantially according to chemovar.[24] Variations in terpenoid content may also conceivably contribute to the psychoactivity or therapeutic action of a particular cultivar, although direct evidence for this is sparse despite anecdotal reports and academic speculation.

For many users seeking pleasurable effects, cannabis essentially *is* Δ^9-THC. In 1970, Mechoulam and coworkers reported that of the cannabinoids, including Δ^9-THC, CBG, CBC and CBN, separated from Lebanese hashish, only Δ^9-THC-containing extracts produced intoxicating-like behavioral effects in monkeys (these included akinesia, apathy, reddening of the eyes, drowsiness, and tameness).[25] Humans injected with Δ^9-THC, or taking pure Δ^9-THC in capsule form, similarly display cannabis-like symptoms and subjective effects.[26] Importantly, these effects, in both humans and laboratory animals, can be prevented with the selective cannabinoid receptor type 1 (CB_1) inverse agonist rimonabant (SR141716A, **9**, Figure 4), giving us a relatively simple mechanistic understanding of what "being stoned" involves.[27,28] Indeed, ligands widely employed in pharmacology research as CB_1 agonists, such as CP 55,940 (**10**) and WIN 55,212-2 (**11**), are cannabimimetic in laboratory animals,[29] and the potent CB_1 agonist AMB-FUBINACA (**12**) was recently associated with a mass intoxication event in New York after it was sold as a "new psychoactive substance" (NPS).[30] The Δ^9-THC analogue nabilone (rac-**13**), used clinically as an antiemetic for the treatment of chemotherapy-induced nausea and vomiting (CINV), is another intoxicating CB_1 agonist.[31]

CHEMICAL SYNTHESIS AND MANUFACTURING INFORMATION

Δ^9-THC is a 21-carbon terpenoid featuring an internal double bond (C9−C10) and two stereocenters (6a, 10a), with the levorotatory trans stereoisomer, (−)-*trans*-Δ^9-THC (6a*R*,10a*R*; **1a**), occurring most abundantly in cannabis. The stereochemistry of Δ^9-THC has been confirmed by synthesis[32] and X-ray crystallography (as a benzenesulfonate ester).[33] Pure Δ^9-THC is described as a "light yellow resinous oil" in The Merck Index[34] and is a highly lipophilic substance with low vapor pressure and poor aqueous solubility (see Table 1).

Many methods have been developed for the synthesis of THCs and their analogues;[37] however, the clandestine synthesis of THCs is uncommon compared to extraction of Δ^9-THC from cannabis.[38] The earliest synthetic methods suffered from the concomitant formation of undesired THC regio- and stereoisomers, and the subsequent difficulty of separating *trans*-Δ^9-THC from these byproducts. The initial synthetic route to

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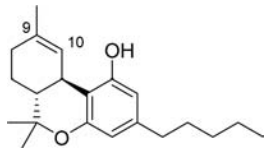
Table 1. Selected Chemical Properties of (−)-*trans*-Δ^9-THC



IUPAC name	(6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-1-ol
CAS registry number	1972-08-3
molecular formula	$C_{21}H_{30}O_2$
formula weight	314.47 g·mol^{-1}
physical state	odorless, light yellow resinous oil[34]
specific optical rotation ([α])	−150.5° at 20 °C (0.53% in chloroform)[34]
boiling point	155−157 °C (0.05 mmHg)[32]
aqueous solubility	2.8 mg·L^{-1} (23 °C)[35]
logP (HPLC method)	6.8[36]
pK_a	10.6[35]
plasma protein binding	97%[35]

racemic Δ^9-THC described by Mechoulam proceeded in 2% overall yield and was primarily concerned with mechanistic details of product formation and identity.[39] Optimization of a method for cyclization of CBD to THC in the presence of boron trifluoride by Taylor[40] enabled Mechoulam and coworkers to generate racemic *trans*- (rac-**1a**, Figure 5) and *cis*-Δ^9-THC (rac-**9**) from citral (**10**) and olivetol (**11**) in one pot.[41]

Many syntheses of stereochemically pure Δ^9-THC have utilized chiral building blocks rather than achiral citral for acid-mediated coupling to olivetol.[42] Of particular note is the production of enantiomeric Δ^9-THC in moderate isolated yields on the preparative scale using *cis*/*trans*-(+)-*p*-methan-2,8-dien-1-ol (*cis*-**12** depicted, Figure 6) from the chiral pool.[43,44] The reaction proceeds via elimination of the hydroxy group with concomitant migration of the internal alkene, so it is the pendant propene unit rather than the relative stereochemistry of the *p*-methan-2,8-dien-1-ol that confers relative configuration in Δ^9-THC.

A biomimetic route to Δ^9-THC was reported for the first time in 1982,[45] and recent approaches have afforded Δ^9-THC enantioselectively from achiral starting materials using modern, asymmetric methodology (reviewed in ref 37). Proof-of-concept production of THCA using synthetic biology has been achieved in yeast.[46]

MEDICINAL CHEMISTRY, SAR, AND PHARMACOLOGY

Elucidation of the pharmacological effects of Δ^9-THC have traditionally focused on the two endogenous cannabinoid receptors, CB_1[47] and CB_2.[48] These two G-protein coupled receptors share approximately 70% homology in their transmembrane regions and bind Δ^9-THC with nanomolar affinity across species.[49] CB_1 is the major central nervous system (CNS) receptor for Δ^9-THC but is also present peripherally in a wide range of tissues,[47,50] while CB_2 is widely expressed in the immune system and only sparsely in the CNS.[48,51] X-ray crystal and cryo-electron microscopy structures of CB_1 bound to Δ^9-THC-like agonists and structurally dissimilar antagonists were recently reported and offer insights into the CB1 receptor activation at the atomic level.[52−55] The endogenous activators of CB_1 and CB_2 are arachidonic acid derivatives, the most well-defined being anandamide (arachidonoylethanolamide, AEA, **13**, Figure 7)[56] and 2-arachidonyl glycerol (2-AG, **14**).[57]

Distinctive dose-dependent physiological and behavioral effects are elicited by Δ^9-THC in most mammals, including humans. The four most commonly studied classical cannabinoid effects in rodents have become known as the cannabinoid tetrad involving: (1) lowered body temperature (hypothermia), (2) antinociception, (3) an inhibition of locomotor activity (sedation), and (4) a characteristic immobility termed catalepsy.[58] The CB_1-dependence of these effects is shown by the ability of CB_1 antagonists to reverse these effects and the absence of such effects in mice genetically engineered to lack the CB_1 receptor.[59] In addition, many structurally disparate CB_1 agonists produce the tetrad effects in laboratory animals as well as a cannabimimetic intoxication in humans.[30,60,61]

In vivo structure−activity relationships (SARs) were established for dozens of synthetic Δ^9-THC analogues prepared since the 1940s based on characteristic pharmacological activity in multiple animal models, including rats, pigeons, dogs, rabbits, and monkeys.[62] To date, hundreds of THC analogues have been synthesized, and the SARs conferring high affinity for CB_1 *in vitro* and high potency *in vivo* are well established (summarized in Figure 8).[63,64] It is worth noting that Δ^8-THC is most commonly used as the scaffold for SAR studies due to the increased stability and isoactivity of this isomer relative to Δ^9-THC.

The (−)-*cis*-Δ^9-THC diastereomer, containing a 6a*S*,10a*R* junction rather than the 6a*R*,10a*R* of (−)-*trans*-Δ^9-THC, is also detected in cannabis but is not psychoactive.[65] Similarly, the non-natural enantiomer of **1a**, (+)-*trans*-Δ^9-THC, was without activity when tested in monkeys at doses up to 20 times higher than (−)-*trans*-Δ^9-THC,[41] and (+)-*cis*-Δ^9-THC was also inactive. Indeed, the stereospecific bioactivity of (−)-*trans*-Δ^9-THC was an early indication of the likely existence of a complementary receptor.

There are five regioisomers of Δ^9-THC differing by position of the internal C9−C10 alkene (**18**−**22**, Figure 9), as well as an exocyclic alkene analogue (**23**).[66] Each of these regioisomers features between one and three stereocenters (at one or more of positions C6a, C9, and C10a), with dozens of isomeric Δ^9-THC analogues possible. Racemic Δ^{6a,10a}-THC (**21**) was the first THC synthesized—simultaneously in 1940 in the US and UK—

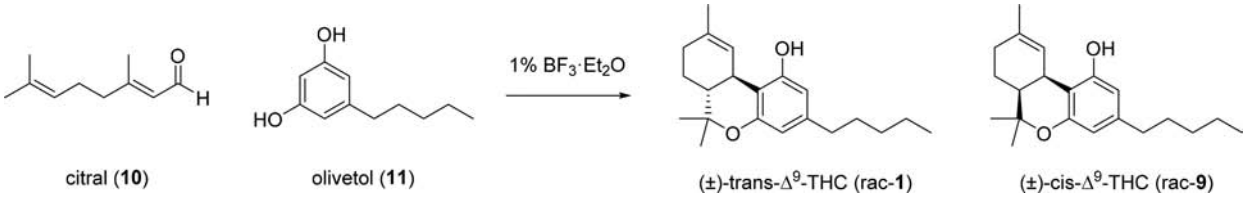


Figure 5. Early one-pot synthesis of racemic Δ^9-THC from citral and olivetol.

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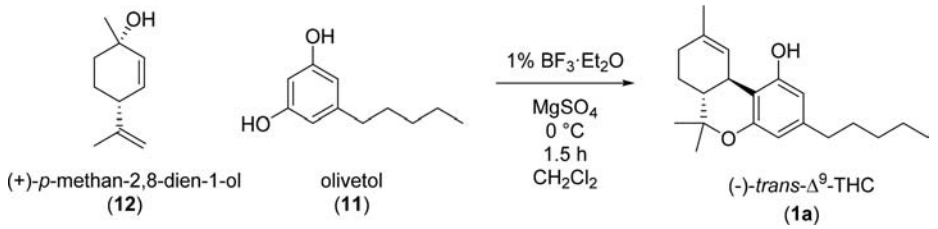

Figure 6. One-pot synthesis of enantiomeric Δ^9-THC.

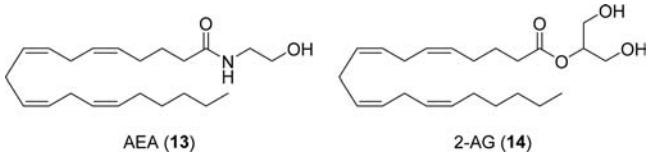

Figure 7. Selected endogenous cannabinoids acting as agonists at CB_1 and/or CB_2.

and possessed qualitative cannabis-like activity.[10,67] Racemic $\Delta^{6a,10a}$-THC was reported to be cannabimimetic in humans when smoked, with potency estimated at 15−30% of Δ^9-THC,[68] and activity was later shown to reside solely in the (*S*)-enantiomer.[69] The early synthetic analogues of Δ^9-THC prepared in the 1940s and 1950s were based on a Δ^8-THC (**18**) scaffold, which is the more thermodynamically stable of the two and relatively more accessible by synthesis. Δ^8-THC has also been isolated from cannabis[7] and is reportedly about two-thirds as potent in humans following oral or intravenous administration.[70] Both Δ^7-THC (**19**) and $\Delta^{9,11}$-THC (**23**) were inactive in monkeys,[71−73] and Δ^{10}-THC (**22**) was inactive in pigeons trained to discriminate Δ^9-THC.[74]

The 1-hydroxy group of Δ^9-THC is essential for cannabinoid activity; conversion to a methyl ether (**24**) abolished activity,[71] as did removal,[75] whereas replacement of the C9 methyl group with an alcohol increased potency.[76] With respect to the 3-pentyl chain, homologation, branching, and increased steric bulk all conferred improved potency, and the SAR of this region has been extensively reviewed.[64] Dimethylheptylpyran (DMHP, **25**) was so potent that it was investigated as an incapacitating agent, EA-2233 (a racemic mixture of the *O*-acetyl esters of all 8 stereoisomers), during the Edgewood Arsenal experiments in the 1960s.[77,78] One of the most potent Δ^9-THC analogues identified to date is the 1′,1′-dimethylheptyl (DMH) derivative of 11-hydroxy-Δ^8-THC, HU-210 (**26**), which is 100−800 times more potent than Δ^9-THC depending on the species.[79,80]

Although the main psychoactive effects of Δ^9-THC are attributed to its activation of central CB_1 receptors as a moderate efficacy agonist, it is also a moderate efficacy agonist at CB_2. Beyond the cannabinoid receptors, Δ^9-THC interacts with several other G protein-coupled receptors (GPCRs) and ligand-gated ion channels (LGICs), with the most well-characterized interactions, including GPR18, GPR55, 5-HT_{3A}, glycine α1 and α3 subunits, PPARγ, TRPA1, TRPM8, TRPV2, TRPV3, and TRPV4 (summarized in Table 2). Some of the actions of Δ^9-THC could also be due to interactions with transporters and enzymes at concentrations in the micromolar range, although these effects are less well characterized than those at the aforementioned GPCRs and LGICs and have been reviewed elsewhere.[81] Like other xenobiotics, Δ^9-THC interacts with various cytochrome P450s (CYPs), and the relevant interactions are described in the drug metabolism and pharmacokinetics section below. The relatively high lipophilicity of Δ^9-THC (logP 6.8)[36] places it outside traditional "drug-like" chemical space, consistent with observed target promiscuity.[82] Ongoing experimentation is beginning to parse some of the diverse functional effects of Δ^9-THC to these disparate noncannabinoid receptors, with examples given below.

CB_1 and CB_2 receptors both couple predominantly to Gi/o-type G proteins, although CB_1 also activates Gs and Gq.[102,103] Δ^9-THC mediated CB_1 stimulation leads to inhibition of adenylyl cyclase (leading to decreased cAMP),[104] inhibition of N-, P/Q-, and L-type calcium channels, and activation of inwardly rectifying potassium channels.[105] Subsequently, downstream pathways such as MAP kinases (ERK1/2, p38 MAPK, JNK, ERK5) are activated, although the extent and exact pathways may vary between cell types.[106] Notably, Δ^9-THC is a moderate efficacy agonist at CB_1 and CB_2 receptors, with the extent of activation varying depending on the pathway being measured.

Like most GPCRs, CB_1 and CB_2 are thought to be desensitized and internalized by activity-dependent receptor phosphorylation and recruitment of β-arrestins.[107] Arrestin recruitment also facilitates non-G protein-mediated signaling, such as activation of ERK. Direct recruitment of β-arrestin 2 (β-arr2) to activated CB_1 has been demonstrated in both AtT20 and HEK293 cells.[108,109] A detailed study of CB_1-arrestin

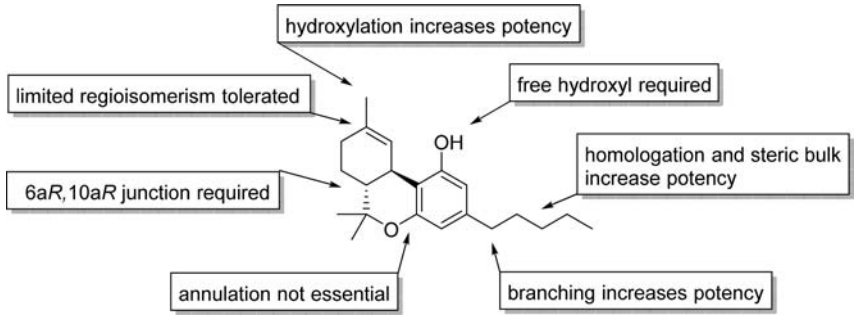

Figure 8. Key structure−activity relationships for Δ^9-THC.

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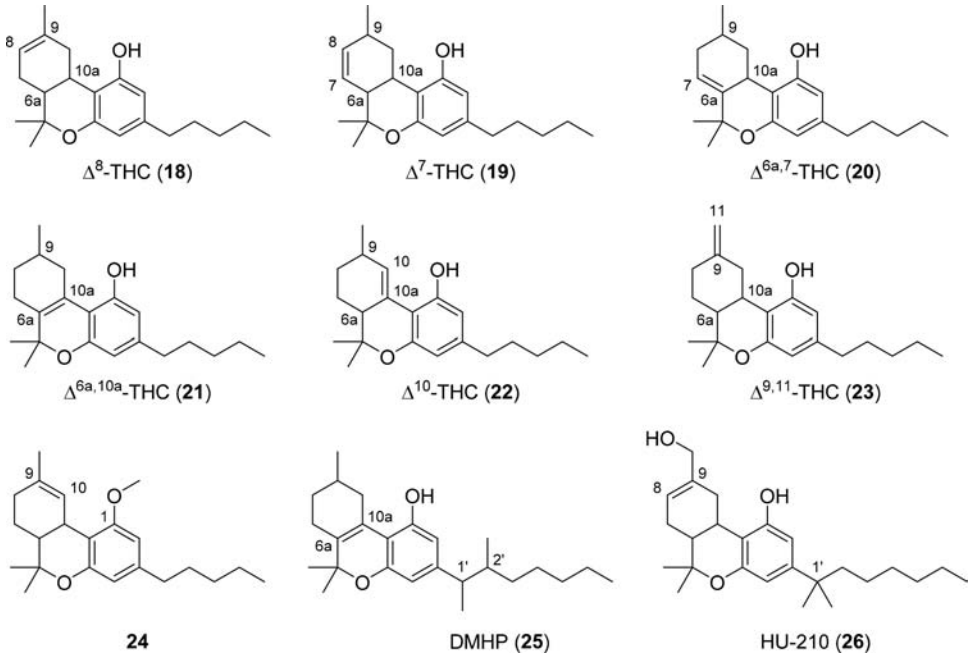

Figure 9. Regioisomers and analogues of Δ^9-THC informing SARs.

Table 2. Interactions of Δ^9-THC with Noncannabinoid Receptors and Ion Channels[a]

target	assay method	effect/potency	references
GPR18	ERK phosphorylation	stimulation, 1 μM	83
		stimulation, 0.1 μM	84
	Ca^{2+} mobilization	stimulation, ~1 μM	84
	arrestin recruitment	stimulation, ~10 μM	84
GPR55	GTPγS binding	activation, 8 nM	85
	Ca^{2+} mobilization	stimulation, 5 μM	86
	arrestin recruitment	no effect up to 30 μM	87
GlyRα1, GlyRα3	electrophysiological measure of glycine current	enhancement of glycine activated current, ~3 μM for both	88, 89
		enhancement of glycine activated current in recombinant systems and rat neurons ~100 nM	90
5-HT_{3A}	electrophysiological measure of 5-HT_3 current	inhibition, ~40 nM	91
		inhibition, 320 nM	92
PPARγ	transactivation reporter assay PPARy binding assay	stimulation ~100 nM	93
		stimulation ~25 μM	94
		inhibition, K_i 5.5 μM	94
TRPA1	electrophysiology in *Xenopus* oocytes	stimulation, EC_{50} 12 μM	95
	elevation of Ca^{2+} in HEK293 cells	stimulation, 230 nM (rat)	96
	electrophysiology in HeLa cells	stimulation: inside-out patches, 670 nM, outside-out, >20 μM	97
TRPM8	elevation of Ca^{2+} in HEK293 cells	inhibition, 150 nM (against menthol), rat	96
TRPV1	elevation of Ca^{2+} in HEK293 cells	no effect	98
		no effect	99
TRPV2	elevation of Ca^{2+} in HEK293 cells	stimulation, 43 μM	100
		stimulation, 0.8 μM (rat)	99
TRPV3	elevation of Ca^{2+} in HEK293 cells	stimulation, 10 μM, low efficacy (rat)	101
TRPV4	elevation of Ca^{2+} in HEK293 cells	no effect (rat)	101

[a]Values are for human proteins unless otherwise noted.

interactions suggested a low affinity, transient interaction between CB_1 and β-arr2, while recruitment of β-arrestin 1 (β-arr1) was not observed.[110] However, structural studies have suggested an interaction between β-arrestin-1 with a synthesized CB_1 C-terminus.[111,112] In whole cells, Δ^9-THC was suggested to be selective for β-arr1 recruitment over G protein signaling, although extent of the bias was not quantified.[113]

Δ^9-THC inhibits voltage-gated calcium channels (I_{Ca}) through CB_1 receptors but also directly affects all 3 members of the Ca_V3 (T-type I_{Ca}) family at concentrations greater than 100 nM in vitro.[114,115] Δ^9-THC also dramatically slows the deactivation of $Ca_V3.1$ and $Ca_V3.2$, which will lead to prolonged Ca entry when cells expressing these channels repolarize[115] We can only speculate how the effects of Δ^9-THC on Ca_V3 channels might contribute to the actions of Δ^9-THC in humans, but

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inhibition of Ca_V3 channels in sensory neurons is likely to be antinociceptive, and it has also been suggested that Δ^9-THC actions on thalamic Ca_V3 channels may contribute to cannabis-induced psychosis.[116] THC also inhibits recombinant Kv1.2 channels with an EC_{50} of 2.4 μM.[117]

Δ^9-THC was one of the first ligands described for the cold- and noxious chemical-activated channel TRPA1 (originally called ANKTM1), and robustly activates the native and recombinant channel at concentrations above 3−10 μM.[95,118] Δ^9-THC activates TRPV2 with similar potency as TRPA1, inhibits TRPM8 activation, and has not been reported to modulate other TRP channels.[96,99,100] The functional correlates of the TRPA1 and TRPM8 effects are not clear at present.

At concentrations from 30 nM to 1 μM, Δ^9-THC strongly potentiates the activation of ionotropic glycine receptors (GlyR), particularly those containing α1 and α3 subunits.[90,89] Altered Δ^9-THC antinociception in GlyRα3 receptor knockout mice has been reported, suggesting that Δ^9-THC modulation of spinally mediated tail-flick responses to noxious thermal stimuli are mediated via GlyR rather than CB_1 or CB_2.[88] The supraspinal analgesic and hypothermic effects of Δ^9-THC associated with CB_1 were not altered in these GlyRα3 knockout animals, consistent with the predominantly spinal expression of the receptors. The concentrations of glycine most effectively potentiated by Δ^9-THC correspond to ambient levels of the neurotransmitter. Glycine receptors are found in many regions of the CNS, suggesting the possibility of subtle but widespread interactions between Δ^9-THC and these channels.

Δ^9-THC is also a noncompetitive inhibitor of native and recombinant 5-HT_3 receptors at concentrations between 100 nM and 1 μM,[91] but it is not known if Δ^9-THC affects 5-HT_3-mediated synaptic currents. Interestingly, 5-HT_3 antagonists are antiemetic, as is Δ^9-THC, although it is believed that the antinausea effects of Δ^9-THC may be mediated by CB_1 rather than 5-HT_3 receptors.[119]

The historical discovery that Δ^9-THC produces many of its characteristic effects via activation of a neuronal GPCR motivated the neuroanatomical mapping of binding sites. In humans, Δ^9-THC induces characteristic effects: euphoria, appetite stimulation, sedation, impaired cognitive function, analgesia, anxiety, and hypothermia. These effects can be parsed across the neuroanatomical distribution of CB_1 receptors first mapped by Miles Herkenham using tritiated CB_1 agonist CP 55,940 (**10**).[50] CB_1 receptors are densely expressed in the cortex and hippocampus, consistent with modulation of cognitive function and perceptual experience by Δ^9-THC. Indeed, infusion of Δ^9-THC directly into the hippocampus promoted CB_1-mediated memory impairment in rats.[120] CB_1 receptors are also abundant in the basal ganglia and the molecular layer of the cerebellum, consistent with the cataleptic effects of high-dose Δ^9-THC in laboratory animals and the ataxia and heavy sedation reported in overdose cases featuring cannabis "edibles".[121] The orexigenic effects of Δ^9-THC are well-known in popular culture as "the munchies" and appear to involve activation of CB_1-mediated endocannabinoid pathways in the mesolimbic reward system, gut−brain axis, discrete hypothalamic nuclei, and main olfactory bulb.[122−124]

Although Δ^9-THC has been used clinically to reduce nausea and vomiting, there are also paradoxical reports of cannabinoid hyperemesis syndrome (CHS); episodes of severe, cyclic nausea and vomiting in regular cannabis users that resolve with cessation.[125−127] Pharmacological intervention for CHS has most frequently and effectively employed benzodiazepines, haloperidol, ondansetron, morphine, or capsaicin.[128] Curiously, hot water hydrotherapy appears to be highly effective, leading many CHS sufferers to compulsively bathe or shower.[129] Although the underlying pathophysiology remains unclear, the efficacy of capsaicin and hot water as CHS treatments has invited speculation of a common mechanism involving TRPV1.[129−131]

DRUG METABOLISM AND PHARMACOKINETICS

Δ^9-THC undergoes rapid and extensive hepatic metabolism, and more than 80 metabolites have been identified.[132] Limited extrahepatic metabolism also occurs, including in brain microsomes.[133] In humans, phase I oxidation of Δ^9-THC by CYP 2C9, 2C19, and 3A4 produces the active metabolite 11-hydroxy-Δ^9-THC (11-OH-Δ^9-THC, **27**, Figure 10), which is

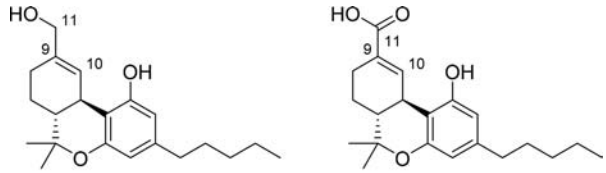

Figure 10. Prominent human metabolites of Δ^9-THC.

approximately equipotent with Δ^9-THC as a CB_1 agonist,[134] and Δ^9-THC itself is a potent inhibitor of CYP1A1, CYP1A2, and CYP1B1.[135] Further oxidation of 11-OH-Δ^9-THC gives nonpsychoactive 11-nor-9-carboxy-Δ^9-THC (11-COOH-Δ^9-THC, **28**), with 11-COOH-Δ^9-THC and its glucuronide conjugate representing the terminal products of Δ^9-THC biotransformation in humans. For this reason, 11-COOH-Δ^9-THC is a common target analyte in forensic urine immunoassays; however, the pharmacology of this abundant metabolite is relatively unexplored.[136]

The route of administration of Δ^9-THC plays an important role in the time course of its psychoactive effects and the detectable blood, urine, and saliva concentrations of Δ^9-THC and its metabolites.[137,138] Smoking or vaporizing Δ^9-THC-containing cannabis produces a rapid spike in blood Δ^9-THC concentrations, followed by a precipitous drop as Δ^9-THC undergoes hepatic metabolism and sequestration into fat. With the inhaled routes (both smoking and vaporizing), there is clear dose-related cognitive impairment on relevant tests such as digit-symbol substitution test, divided attention test, and paced serial addition test, with 10 mg Δ^9-THC causing modest cognitive impairment and subjective effects, while 25 mg produces more serious impairment.[139] Notably, this impairment can persist for several hours while Δ^9-THC concentrations become minimal in blood and autonomic changes, such as increased heat rate, return to baseline. Generally, vaporization produces more pronounced effects than smoking, presumably because less Δ^9-THC is lost to pyrolysis when using the vaporization route.[139]

When Δ^9-THC is delivered orally via dronabinol capsules or edibles, or buccally via product such a nabiximols (a oromucosal spray formulated from a standardized cannabis extract containing 2.7 mg Δ^9-THC, 2.5 mg CBD, and trace levels of other phytocannabinoids and terpenoids per 100 μL spray), it has a very different pharmacokinetic profile: there is no initial spike in blood THC concentrations; rather, a steady increase in plasma Δ^9-THC occurs which peaks 3−4 h after administration.[140,141] Higher concentrations of the metabolite 11-

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COOH-Δ^9-THC accumulate than with smoked or vaporized Δ^9-THC. Additionally, subjective feelings of intoxication and objective signs of impairment are delayed relative to inhaled routes. Importantly, users can report very high levels of intoxication and display cognitive impairment in the presence of relatively low levels of blood Δ^9-THC following administration of Δ^9-THC via the oral route. This is one of several issues that confounding use of *per se* limits (i.e., a fixed prohibited concentration of blood Δ^9-THC) as a legal definition of intoxication in driving laws. Another confounding factor is that frequent cannabis users frequently show chronic low levels of blood Δ^9-THC (presumably slowly released from adipose stores) in the absence of acute intoxication or impairment.

Δ^9-THC is preferentially stored in adipose tissue, where it accumulates with repeated exposure and persists for weeks.[142] Δ^9-THC could be detected in fat biopsies of human users 28 days after smoking cannabis.[143] The sequestration of Δ^9-THC in fat helps explain the long elimination half-life of the drug and why people may test positive for blood Δ^9-THC long after many weeks of drug abstinence.[144] Research in adipocytes, rats, and humans indicates that the increased fat utilization caused by fasting or exercise can elevate Δ^9-THC blood levels due to release of Δ^9-THC from fat stores.[145−147]

Brain uptake of Δ^9-THC is subject to regulation by the ABC transporters P-glycoprotein (P-gp) and breast cancer resistance protein (Bcrp) with P-gp and Bcrp knockout mice displaying greater brain concentrations of Δ^9-THC than wild-type mice.[148] Loss of function single nucleotide polymorphisms (SNPs) in the genes encoding P-gp and Bcrp, *MDR1* and *ABCG2* respectively, can affect plasma levels of Δ^9-THC in human users and modulate the risk of cannabis dependence.[149,150] Beyond individual pharmacogenomic differences, the pharmacology of Δ^9-THC following cannabis consumption can be confounded by interaction with other phytocannabinoids. For example, CBD can increase brain and plasma concentrations of Δ^9-THC in rats and humans[151] and may also function as a negative allosteric modulator of CB_1.[152]

■ ADVERSE EFFECTS AND DOSAGE

The toxicity of Δ^9-THC has been explored in many species, and is very low compared to most other recreational and pharmaceutical drugs.[153−155] The median lethal dose (LD_{50}) following oral administration has been determined in rats (800−1910 mg/kg depending on sex, strain, and vehicle), but higher doses in dogs (up to 3000 mg/kg) and monkeys (up to 9000 mg/kg) were evaluated without lethality.[153,156] No cases of fatal overdose in humans following acute Δ^9-THC consumption have been conclusively identified, and extrapolated estimates of lethal human doses have ranged from 4 g to greater than 15 g.[154,157] Typical human doses of Δ^9-THC (1−20 mg) are 3 orders of magnitude lower than the estimated lethal dose range, suggesting a very large therapeutic index. Despite low acute toxicity, Δ^9-THC intoxication was deemed to be a contributing factor in several reported fatalities due to idiosyncratic drug reactions or accidental death by misadventure.[158−161]

The most commonly reported adverse effects following Δ^9-THC administration are generally transient and not serious. The adverse effects of Δ^9-THC are dose-dependent, and higher doses are associated with anxiety, panic, confusion, and disorientation.[162] In one clinical study, acute intravenous Δ^9-THC induced conceptual disorganization, fragmented thinking, suspiciousness, paranoid and grandiose delusions, and perceptual distortions; however, these effects were modest in magnitude and reversible.[163] The psychosis-like "hallucinatory" reaction to Δ^9-THC occasionally experienced by a minority of users is qualitatively distinct from that of other hallucinogens such as psilocybin, dextromethorphan, and salvinorin A.[164] Clinical trials involving daily administration of Δ^9-THC to participants for periods of months—or even years—produced a low incidence of serious adverse events.[165,166] A systematic meta-review of medical cannabinoid safety studies found that 96.6% of adverse effects were not serious, with dizziness the most commonly reported side effect.[167]

Acute Δ^9-THC or cannabis administration in humans promotes a mild, transient tachycardia and increased supine blood pressure, with tolerance to these effects developing with repeated exposure.[168,169] Interestingly, chronic exposure to Δ^9-THC was reported to lower blood pressure and heart rate to below baseline; effects opposed to its acute cardiovascular actions.[170] An association between cannabis use and adverse cardiovascular events is evident from various case reports of cannabis-related myocardial infarction and sudden death.[171,172] Such cardiovascular complications appear to be extremely rare. For example, only a single case of a coronary event and fatality was reported out of 2198 emergency hospital admissions related to cannabis use recorded across 14 European countries over a 6 month period.[173]

The intoxicating effects of Δ^9-THC present a barrier to widespread adoption as a therapeutic drug. Above a certain threshold Δ^9-THC can impair cognitive processes and human performance in a detrimental fashion. Although tolerance to some of these effects is sometimes reported to occur in heavier users,[174] it is unlikely that daily dosing with standard doses of Δ^9-THC (i.e., 5−10 mg and upward) will become universally acceptable as a medicament for employees in the workplace or for drivers on the roads. One intriguing possibility, however, is that Δ^9-THC may retain important therapeutic effects at doses far below those that cause intoxication. Both acute and chronic low doses of Δ^9-THC were recently reported to reversed age-related cognitive impairments in multiple assays of learning and memory in rodents, seemingly through modulation of glutamatergic CB_1 receptors and histone acetylation.[175,176] In other studies, similarly low doses were found to protect the mouse brain, heart, and liver from a variety of toxic insults via an attenuation of apoptotic, oxidative, and inflammatory mechanisms.[177−179]

Like many other drugs of abuse, Δ^9-THC triggers dopamine release in the nucleus accumbens.[180] In the case of Δ^9-THC, the mechanism involves CB_1 receptors located in the ventral tegmental area and nucleus accumbens.[181] Self-administration models are routinely employed to study many addictive drugs, however, obtaining Δ^9-THC self-administration in laboratory animals has proved challenging. Place conditioning studies suggest that rats tend to find cannabinoid agonists (including Δ^9-THC) aversive, particularly at higher doses,[182−184] although aversion can be mitigated by using young adolescent rodents, lower doses of Δ^9-THC, and pre-exposure to Δ^9-THC.[185] Robust intravenous self-administration of Δ^9-THC was achieved in squirrel monkeys via infusion of lower doses than those used in preceding studies, in an attempt to mirror human dose titration when smoking cannabis.[186]

The notion of cannabis or Δ^9-THC addiction in humans is controversial. Although cannabis use disorder is reported in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; 305.20, 304.30), with cannabis users seeking treatment to overcome habitual use, withdrawal signs during abstinence of

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Δ^9-THC are very mild (irritability, insomnia, appetite disruption, craving) compared to those experienced during withdrawal from opioids, alcohol, or benzodiazepines. Clinical interventions for cannabis dependence are primarily psychosocial,[187] although there are some indications that substitution therapy with nabiximols (buccal Δ^9-THC/CBD spray) or oral dronabinol could be an effective intervention for those trying to reduce or cease their cannabis use.[188−191]

Also controversial is the notion that use of cannabis may serve as a gateway in increasing vulnerability to later initiation into use of "harder" drugs such as heroin and cocaine.[192] A recent review concluded that there is only limited evidence of a causal association between cannabis use and changes in the rates and use patterns of other licit and illicit substances.[193] Some studies in laboratory animals suggest that pre-exposure to cannabinoids such as THC may make adult opioids or stimulants more rewarding, but such effects, when seen, are generally small in size.[194,195]

In contrast, there is now substantial interest in the "reverse gateway" whereby use of medicinal cannabis products, including Δ^9-THC and CBD, may promote reductions in the use of opioid and stimulant drugs.[196] This notion is in many ways just as controversial as the original gateway hypothesis but also achieves some support from animal models[197] and from epidemiological[198] and observational[199] studies. Ongoing clinical studies will be the key in more precisely describing the therapeutic efficacy of cannabinoids in treating addictions.

Human population studies have consistently reported that cannabis use is associated with an increase in the risk of developing schizophrenia by around twofold.[200] This equates to regular cannabis use increasing rates of schizophrenia from 7 in 1000 to about 14 in 1000.[201] Recent analyses suggest that schizophrenia may be a risk for cannabis use rather than vice versa.[202]

HISTORY AND IMPORTANCE IN NEUROSCIENCE

In the 19th and twentieth centuries, cannabis tinctures were produced by the largest US pharmaceutical firms of the time (e.g., Parke Davis & Co, Lilly, Sharp & Dohme) until the US Marihuana Tax Act of 1937 effectively prohibited such products.[203] Although *Cannabis* was cultivated and used without restriction for most of its history, efforts to control the plant began in the late 19th century.[204] In 1961, the United Nations (UN) Single Convention on Narcotic Drugs limited "the production, manufacture, export, import, distribution of, trade in, use and possession" of cannabis and other drugs. Cannabis was placed in the most restrictive category—Schedule I, along with heroin and cocaine—for substances that are highly addictive and liable to abuse. Cannabis was also added to Schedule IV, an additional category for certain Schedule I drugs with "particularly dangerous properties" and little or no medical utility. In the United States, the federal Controlled Substances Act (CSA) of 1970 designated cannabis ("marijuana"; originally spelled "marihuana") and its chemical constituents, including Δ^9-THC obtained from cannabis, Schedule I substances. Analogously to the Convention, Schedule I substances are those with a high potential for abuse, no currently accepted medical use in the US, and lack of accepted safety for use under medical supervision. All cannabinoids found in the cannabis plant are Schedule I substances because they fall under the definition of "marijuana" within the Act.

The isolation and conclusive structural elucidation of Δ^9-THC from cannabis was reported in 1964 by Yehiel Gaoni and Raphael Mechoulam at the Weizmann Institute of Science in Rehovoth, Israel, using nuclear magnetic resonance (NMR) spectroscopy techniques unavailable to earlier researchers.[32] A total synthesis of racemic Δ^9-THC was reported by the same researchers a year later.[39] When the UN convened in 1971 to establish a system of international control for newer synthetic psychoactive drugs that had emerged since 1961 (the 1971 Convention on Psychotropic Substances), Δ^9-THC (since given the international nonproprietary name dronabinol) and its isomers were specifically classified in Schedule I.

Today there are an estimated 192 million annual cannabis users in 164 countries, approximately 3.9% of the global population, making cannabis the most widely used illicit drug in the world.[205] Raw cannabis plant material is processed into an enormous variety of Δ^9-THC-containing products ranging from relatively low potency blends of dried flowers, leaves, stems, and trimmings to the more potent flowering tops of the female cannabis plant ("bud", "sinsemilla"). The most Δ^9-THC-rich cannabis product historically was the compressed, sieved trichomes of the female flowers, pressed into a resin known as "hash" or "hashish". Raw herbal cannabis is the most popular form of the drug in the US and elsewhere and typically contains approximately 10−30% Δ^9-THC/THCA,[206−208] with similar potencies reported in Australia,[12] France,[209] Japan,[210] and The Netherlands.[211] However, modern industrial extraction methods (e.g., supercritical carbon dioxide), and the more dangerous butane extraction, have facilitated the isolation of resinous Δ^9-THC concentrates for vaporization ("wax", "shatter", "dabs") with Δ^9-THC content exceeding 80−90%.[212] Other Δ^9-THC-containing products from commercial vendors include "edibles" (e.g., baked goods, gummy candies, infused chocolate), chewing gum, transdermal patches, beverages, and suppositories, while pharmaceutical companies have developed, or are currently developing, gels, nasal sprays, buccal sprays, and sub-buccal/lingual wafer formulations.

The first contemporary, pharmaceutical Δ^9-THC product was developed by Unimed; a capsule containing synthetic Δ^9-THC (INN: dronabinol) in sesame oil (Marinol) for the treatment of anorexia in acquired immune deficiency syndrome (AIDS) and nausea and vomiting associated with cancer chemotherapy. Marinol received marketing approval in the US from the Food and Drug Administration (FDA) in 1985 and entered the market as a Schedule II substance (the second most restrictive category; for medically approved substances with high potential for abuse). Nabilone (Cesamet, **13**), a synthetic analogue of Δ^9-THC, was developed by Eli Lilly and Company for the same indications and received marketing approval in the same year.

Despite the federal prohibition of cannabis in the US for most of the twentieth century, a small cohort of seriously ill patients in the 1980s were granted legal access to cannabis cigarettes (provided by the National Institute on Drug Abuse, NIDA) under the supervision of a physician via the Compassionate Investigational New Drug (IND) program of the FDA.[213] Some of these patients were already using cannabis illegally for medical purposes, and had been arrested for cultivation or possession. As of January 2019, the medical use of cannabis (with recommendation from a physician) is legal in 33 US states, as well as the District of Columbia, and the territories of Guam, the Northern Mariana Islands, Puerto Rico, and the US Virgin Islands, and recreational use of cannabis is legal in 10 of those states (Alaska, California, Colorado, Maine, Massachusetts, Michigan, Nevada, Oregon, Vermont, and Washington), as well as the District of Columbia and the Northern Mariana

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Islands.[214] Additionally, 15 states have laws permitting the restricted use of low Δ^9-THC cannabis or industrial hemp products for specified medical conditions.

Beyond the US, an increasing list of countries have legalized medical and/or recreational cannabis in recent years. Consistent with changing attitudes toward cannabis, the World Health Organization (WHO) made history in 2018 by conducting a critical review of the risks and benefits of cannabis and Δ^9-THC at the forty-first meeting of the Expert Committee on Drug Dependence (ECDD).[215] WHO is currently deliberating a potential rescheduling recommendation to the UN regarding the status of cannabis and Δ^9-THC under international drug control treaties.

Historical prohibitions around cannabis products have led to difficulty in conducting clinical trials and subsequent lack of evidence for efficacy in specific diseases. As medicinal cannabis products become legally and commercially available in an increasing number of jurisdictions around the world, there is a strong contemporary focus on the therapeutic potential of cannabinoids, including Δ^9-THC, and the evidence supporting use of Δ^9-THC and other cannabinoids for the treatment of various diseases. For example, there is widespread self-medication with Δ^9-THC products for conditions such as insomnia, back pain, arthritis, depression, and post-traumatic stress disorder (PTSD), despite a paucity of high-quality clinical evidence to support such use.[216] Stronger signals are evident in the current literature for the use of Δ^9-THC in such conditions as CINV, chronic pain, and spasticity in multiple sclerosis.[193,217] There are also emerging indications supporting the use of Δ^9-THC in Tourette's syndrome, sleep apnoea, agitation in dementia, and anorexia nervosa, although further studies are needed.

The complexity of the effects of cannabis and Δ^9-THC have been described by countless writers, artists, and musicians. The dichotomy of subjective effects following Δ^9-THC administration are perhaps best illustrated by the juxtaposed statements of author William Burroughs and neurologist Oliver Sacks.

> *The effects of this drug have been frequently and luridly described: disturbance of space-time perception, acute sensitivity to impressions, flight of ideas, laughing jags, silliness. Marijuana is a sensitizer, and the results are not always pleasant. It makes a bad situation worse. Depression becomes despair, anxiety panic. I have already mentioned my horrible experience with marijuana during acute morphine withdrawal. I once gave marijuana to a guest who was mildly anxious about something ("On bum kicks" as he put it). After smoking half a cigarette he suddenly leapt to his feet screaming "I got the fear!" and rushed out of the house.—William S. Burroughs, Letter from a Master Addict to Dangerous Drugs, British Journal of Addiction, 1957.*[218]
>
> *"I was fascinated that one could have such perceptual changes, and also that they went with a certain feeling of significance, an almost numinous feeling. I'm strongly atheist by disposition, but nonetheless when this happened, I couldn't help thinking, 'That must be what the hand of God is like."—Oliver Sacks, interview with Terry Gross, Fresh Air on NPR, 2013.*[219]

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ABBREVIATIONS

β-arr2, β-arrestin 2; 2-AG, 2-arachidonyl glycerol; 5-HT, 5-hydroxytryptamine; AEA, arachidonoylethanolamide; AIDS, acquired immune deficiency syndrome; Bcrp, breast cancer resistance protein; cAMP, cyclic adenosine monophosphate; CBC, cannabichromene; CBCA, cannabichromenic acid; CBD, cannabidiol; CBDA, cannabidiolic acid; CBG, cannabigerol; CBGA, cannabigerolic acid; CBN, cannabinol; CBNA, cannabinolic acid; CHS, cannabinoid hyperemesis syndrome; CINV, chemotherapy-induced nausea and vomiting; CNS, central nervous system; CSA, Controlled Substances Act; CYP, cytochrome P450; DEA, Drug Enforcement Administration; DMH, 1′,1′-dimethylheptyl; DMHP, dimethylheptylpyran; ECDD, Expert Committee on Drug Dependence; ERK, extracellular signal-regulated kinases; FDA, Food and Drug Administration; GPP, geranylpyrophosphate; HEK, human embryonic kidney; INN, international nonproprietary name; IUPAC, International Union of Pure and Applied Chemistry; JNK, Jun N-terminal kinase; LD_{50}, median lethal dose; LGIC, ligand-gated ion channel; MAPK, mitogen-activated protein kinases; NIDA, National Institute on Drug Abuse; NMR, nuclear magnetic resonance; OA, olivetolic acid; OAC, olivetolic acid cyclase; P-gp, P-glycoprotein; PPAR, peroxisome proliferator-activated receptor; PTSD, post-traumatic stress disorder; SAR, structure−activity relationship; SNPs, single nucleotide polymorphisms; THC, tetrahydrocannabinol; TRPA, transient receptor potential ankyrin; TRPM, transient receptor potential melastatin; TRPV, transient receptor potential vanilloid; UN, United Nations; WHO, World Health Organization

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