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Review

# Cannabinoid pharmacology in cancer research: A new hope for cancer patients?

Farideh A. Javid [a,*], Roger M. Phillips [a], S. Afshinjavid [b], Roberta Verde [c], Alessia Ligresti [c]

[a] Department of Pharmacy, School of Applied Sciences, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, UK
[b] Faculty of Science and Engineering, University of Chester, Pool lane, Chester CH2 4NU, UK
[c] Endocannabinoid Research Group, Institute of Biomolecular Chemistry, National Research Council of Italy, Pozzuoli, NA, Italy

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ABSTRACT

Cannabinoids have been used for many centuries to ease pain and in the past decade, the endocannabinoid system has been implicated in a number of pathophysiological conditions, such as mood and anxiety disorders, movement disorders such as Parkinson's and Huntington's disease, neuropathic pain, multiple sclerosis, spinal cord injury, atherosclerosis, myocardial infarction, stroke, hypertension, glaucoma, obesity, and osteoporosis. Several studies have demonstrated that cannabinoids also have anti-cancer activity and as cannabinoids are usually well tolerated and do not produce the typical toxic effects of conventional chemotherapies, there is considerable merit in the development of cannabinoids as potential anticancer therapies. Whilst the presence of psychoactive effects of cannabinoids could prevent any progress in this field, recent studies have shown the value of the non-psychoactive components of cannabinoids in activating apoptotic pathways, inducing anti-proliferative and anti-angiogenic effects. The aforementioned effects are suggested to be through pathways such as ERK, Akt, mitogen-activated protein kinase (MAPK) pathways, phosphoinositide 3-kinase (PI3K) pathways and hypoxia inducible factor 1 (HIF1), all of which are important contributors to the hallmarks of cancer. Many important questions still remain unanswered or are poorly addressed thus necessitating further research at basic pre-clinical and clinical levels. In this review, we address these issues with a view to identifying the key challenges that future research needs to address.



**Contents**



*Abbreviations:* ABCC1, ATP-binding cassette (ABC) transporter; AC, adenylyl cyclase; AEA, anandamide; AKt, protein kinase B; AM251, a $CB_1$ receptor antagonist; AM630, a $CB_2$ receptor antagonist; AMPK, 5′-adenosine monophosphate-activated protein kinase; ATF-4, activating transcription factor-4; AR, androgen receptors; CBD, cannabidiol; $CB_1$IR, $CB_1$ receptor immunoreactivity; Cdk, cyclin-dependent kinase; Chk 1, cell cycle checkpoint; COX2, cyclooxygenase-2; CXCR4, chemokine receptor 4; CXCL12, a chemokine protein encoded by the CXCL12 gene; $\Delta^9$-THC, Δ9-tetrahydrocannabinol; EGFR, epidermal growth factor receptor; ER, estrogen; ERK, extracellular signal-regulated kinase; FAAH, fatty acid amide hydrolase; FAK, focal adhesion kinase; GBM, glioblastoma multiform; Gi/o, a subunit of G protein; GTPγS, guanosine 5′-O-[gamma-thio] triphosphate; HER2, human epidermal growth factor receptor 2; HIF-α, hypoxia-inducible factor; HU-210, highly potent cannabinoid receptor agonist, 96aR0-trans-3–91, 1-Dimethylheptyl)-6a, 7, 10, 10a-tetrahydro-1-hydroxy-6, 6-dimethyl-6H-dibenzo [b,d]pyran-9-methanol; ICAM, intracellular adhesion molecule; JWH-015, a selective $CB_2$ agonist, 2-Methyl-1-propyl-1H-indol-3-yl)-1-naphthalenylmethanone; JWH-133, a potent selective $CB_2$ agonist, (6aR, 10aR)-3-(1,1-dimethylbutyl)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-6H-dibenzo [b,d]pyran MAPK, mitogen activated protein kinase; LAK, lymphokine-activated killer; LPI, lysophosphatidylinositol; MAGL, monoglycerol lipase; MMP-2, matrix metallopeptidase 2; MMP-9, matrix metallopeptidase 9; MRP1, Multidrug resistance-related protein 1; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NGF, nerve growth factor; PD98059, p42/44 inhibitor, 2-(2-Amino-3-methoxyphenyl)-4/h-1-benzopyran-4-one; $PGE_2$, prostaglandine E-2; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PCNA, proliferating cell nuclear antigen; PPARs, peroxisome proliferator-activated receptors; PR, progesterone; PRLr, prolactin receptor; PSA, prostate specific antigen; PyMT, polyoma middle T oncoprotein; RAF-1, a proto-oncogene, serine/threonine kinase; ROS, reactive oxygen species; RXRα, retinoid X receptor; SB203580, a p38/MAPK inhibitor, 4-[5-(4-Fluorophenyl)-2-[4-(methylsulphonyl)phenyl]-1H-imidazol-4-yl] pyridine; SC58236, COX-2-specific inhibitor, 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide; siRNA, small interfering RNA; SR141716, Rimonabant, a selective $CB_1$ receptor antagonist or an inverse agonist; Src gene, a family of proto-oncogenic tyrosine kinases; Th1, a type of T helper cells; Th2, a type of T helper cells; TIMP-1, tissue inhibitor of matrix metalloproteinases-1; TrK A, tropomyosin receptor kinase A; TRPM8, transient receptor potential channels of melastatin-type 8; TRPVA1, transient receptor potential A1; TRPV1, transient receptor potential vanilloid 1; TRB3, tribbles homologue that inhibits Akt/PKB activation; 2-AG, 2-arachidonoyl glycerol; VEGF, vascular endothelial growth factor; WIN 55,212–2, a $CB_1$ and $CB_2$ receptor agonist [(R0-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphtalenylmethanoneesylate]

* Correspondence to: Department of Pharmacy, School of Applied Sciences, University of Huddersfield, Queensgate, Huddersfield, HD1 3DH, UK.
*E-mail address:* fajavid@hud.ac.uk (F.A. Javid).

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## 1. Introduction

It is known that cannabinoids, the active components of Cannabis sativa, act by mimicking the endogenous substances (the endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG)) by activating specific cell-surface cannabinoid receptors (Devane et al., 1992). Currently, the cannabinoid receptor ligands are generally divided into three main categories known as phytocannabinoids, endogenous cannabinoids and synthetic cannabinoids (Fig. 1). After the clarification of the chemical structure of (-)-$\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) which is the primary psychoactive component of the cannabis plant (Gaonia and Mechoulam, 1964a, 1964b), other chemically related terpenophenolic compounds were identified in Cannabis sativa, including cannabichromene (CBC) (Gaoni and Mechoulam, 1966) and cannabigerol (CBG) (Gaoni and Mechoulam, 1964c). Although the pharmacology of most of the cannabinoids is unknown, $\Delta^9$-THC is the most widely studied owing to its high potency and abundance in cannabis (Pertwee et al., 2010). Among the herbal cannabinoids, other relevant plant-derived cannabinoids include $\Delta^8$-THC, which is almost as active as $\Delta^9$-THC but less abundant and cannabinol (CBN), which is produced in large amounts but is a weak cannabomimetic agent. Cannabidiol (CBD), CBG and CBC are devoid of psychoactive potential. The chemical structures of some cannabinoids are shown in Fig. 1.

So far, two cannabinoid-specific receptors $CB_1$ and $CB_2$ have been cloned and characterized from mammalian tissues (Howlett et al., 2002). Mouse $CB_1$ receptor and $CB_2$ receptor share 66% overall homology and 78% in the transmembrane region (Shire et al., 1996). Human $CB_1$ receptor and $CB_2$ receptor share an overall homology of 44%, and 68% in the transmembrane region respectively (Munro et al., 1993). Homology (96%) has been reported between human and mouse $CB_1$ receptor (Chakrabarti et al., 1995), whilst human and mouse $CB_2$ receptors share 82% homology (Shire et al., 1996). Many central and peripheral effects have been associated with the activation of $CB_1$-receptors (Matsuda et al., 1990; Munro et al., 1993; Pertwee, 2006; Pertwee et al., 2010). The $CB_2$ receptor, originally thought of as being exclusively present in the immune system, is highly expressed in B and T lymphocytes, macrophages and in tissues such as the spleen, tonsils and lymph nodes (Herkenham et al., 1991; Howlett et al., 2002; Porter and Felder, 2001; Pertwee et al., 2010). Recently $CB_2$ receptors have been shown to be also located in the brain stem (Van Sickle et al., 2005). Further studies using $CB_1$ knockout mice demonstrated that $CB_1$ receptors are involved in a variety of different behavioural disorders such as depression, anxiety, feeding and cognition as well as pain at the peripheral, spinal and supraspinal levels (Valverde et al., 2005). Such studies using $CB_1$ knockout mice also revealed the interactions between different systems such as opioids, gamma aminobutyric acid (GABA) and cholecystokinin (CCK) via $CB_1$ receptors (Valverde et al., 2005). $CB_2$ knockout mice have also been developed and revealed/confirmed the involvement of $CB_2$ receptors in a variety of different systems such as immune system, inflammation, apoptosis, chemotaxis, bone loss, liver disorder, pain and atherosclerosis (Buckley, 2008).

Both $CB_1$ and $CB_2$ receptors are metabotropic and belong to the G-protein coupled receptor family (Howlett et al., 2002). Activation of $CB_1$ and $CB_2$ receptors stimulates cellular signalling via alpha subunit of G protein (Gi/o), leading to inhibition of adenylate cyclase and the subsequent activation of many other pathways such as mitogen-activated protein kinase (MAPK) pathways, phosphoinositide 3-kinase (PI3K) pathways, modulation of ion channels (through $CB_1$ receptors), protein kinase B (Akt), ceramide signalling pathways in tumour cells and modulation of cyclooxygenase-2 (COX-2) signalling pathway (Demuth and Molleman, 2006; Galve-Roperh et al., 2000; Glass and Northup, 1999; Guzman et al., 2001; Qamri et al., 2009).

There is also pharmacological evidence that non-$CB_1$ and non-$CB_2$ receptors mediate the actions of cannabinoids located in the brain (Breivogel et al., 2001; Di Marzo et al., 2000). The hypothesis that putative $CB_3$ or non-$CB_1$/$CB_2$ receptor exist is supported by the fact that some of the anandamide (AEA)-mediated effects were neither inhibited by selective CB antagonists nor fully abolished in knockout mice lacking $CB_1$ receptors (De Petrocellis and Di Marzo, 2010). Recent advances suggest, at least for AEA, that the transient receptor potential vanilloid 1 receptor (TRPV1) channel may be considered as the "third" receptor involved in endocannabinoid signalling (Di Marzo et al., 2001; Ross, 2003). For example, it has been shown that the endocannabinoids exert their apoptotic effect by binding to TRPV1, a non-selective cation channel targeted by capsaicin, the active component of hot chilli peppers (Smart and Jerman, 2000). However, the precise role of this receptor in cannabinoid signalling is still unclear and this uncertainty extends into the cancer field where its potential role in cancer biology (proliferation and migration of cancer cells) and cancer pharmacology (resistance to chemotherapeutic agents) needs further investigation (Lehen'kyi and Prevarskaya, 2011; Liberati et al., 2013). Evidence also exists supporting a role for peroxisome proliferator-activated receptors (PPARs) in the actions of cannabinoids (Sun and Bennett, 2007). More recent studies have provided evidence for the interaction of cannabinoids with the orphan receptors such as G protein receptor 55 (GPR55) (Andradas et al., 2011; Pineiro et al., 2011). Thus in addition to $CB_1$ and $CB_2$ receptors other targets might be involved in mediating an effect to cannabinoids and endocannabinoids.

The potential of cannabinoids to alleviate pain has been recognised for many centuries. The antinociceptive actions are mediated via both the $CB_1$ and $CB_2$ receptors (Pacher et al., 2006). This does not negate a role for other receptors such as TRPV1, transient receptor potential cation channel A1(TRPA1), orphan GPCR (*i.e.* GPR55) or PPAR-γ (Maione et al., 2006, 2013; Perez-Gomez et al., 2013; Moreno et al., 2014). For a long time, the development of cannabinoids as anticancer agents has been restricted to two therapeutic avenues (antiemetic and analgesic). They have therefore been evaluated in terms of palliative care as cannabinoids can play an important role in the relief of pain, nausea, vomiting, and stimulation of appetite in cancer patients. However, the involvement of CB receptors in pain and their use in the palliative care in cancer patients are not the focus of this review. In the present review, the aim is to focus on the anti-tumour