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Medicinal Use of Synthetic Cannabinoids—a Mini Review

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Abstract

Purpose of Review This review gives an overview of the medicinal uses of synthetic cannabinoids and other related aspects on the basis of recent as well as earlier studies that the authors considered relevant to the context and scope of the review.

Recent Findings Synthetic cannabinoids are laboratory synthesized products eliciting effects way more than their natural counterparts. These compounds are more potent in generating intoxicating effects and are also difficult to be detected in conventional screening tests. Their clinical side effects are also more pronounced than natural cannabinoids, and their antidotes are also not known. However, they are also therapeutically found to be very effective in many health conditions, as these act by interacting with almost ubiquitously distributed cannabinoid receptors (CB1 and CB2) in the human body and by other mechanisms also that do not involve these receptors.

Summary All the issues related to their appropriate dosage, mode of action, acute and chronic effects in vivo, interaction with other drugs, their metabolism, etc. need much research to be done so that it will be easier to predict their different aspects in human subjects in more appropriate way. Further, development of strict legislation and regulation is required to be done so that their abuse can be curbed, and toxic effects can be reduced, but medicinal benefits and usage can be enhanced.

Keywords Synthetic cannabinoids · *Cannabis sativa* · Cannabinoid receptors · Medicinal uses

Introduction

Cannabis sativa, commonly called Marijuana, is a storehouse of large number of pharmacologically active compounds, with one of the classes being that of cannabinoids. In stringent sense, the term "Cannabinoids" refers to compounds which can activate cannabinoid receptor 1 (CB1) or cannabinoid receptor 2 (CB2) or both, but some other molecules that are structurally similar to tetrahydrocannabinol (a well-known cannabinoid) which do not activate CB1 and CB2 receptors are also included under this term [1]. Further, many cannabis components that do not activate these receptors are referred to as cannabinoids [1]. Cannabinoids are terpeno-phenolic compounds found in *Cannabis sativa* plant which are hydrophobic and psychoactive in their elicited effects. These are fundamentally categorized in to three classes on the basis of their source namely Phytocannabinoids from marijuana plant, Endocannabinoids formed in animals and humans, and synthetic cannabinoids synthesized in the laboratory [2].

The Natural Cannabinoids: Phyto- and Endo-Cannabinoids

Phytocannabinoids are lipid-soluble phytochemicals found in *Cannabis sativa L.* and also in non-cannabis plants [2]. These are oxygen-containing C21 aromatic hydrocarbons, with their number being over 120, isolated from Cannabis plant [3]. There are varieties of phytocannabinoids that bind to cannabinoid receptors and elicit characteristic psychotropic effect (e.g., (-)-trans-Δ9-tetrahydrocannabinol, i.e., Δ9-THC, (-)-trans-Δ8-tetrahydrocannabinol, i.e., Δ8-THC) [4], while some others do not exhibit such effects (e.g., Cannabidiol, i.e.,

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CBD) [5]. These compounds having dibenzopyran ring and a hydrophobic alkyl chain show different affinities towards the cannabinoid receptors (CB1 and CB2 receptors) [3]. These are now considered to be having multiple sites of activity, with molecular targets for some of them being outside the endocannabinoid system also. These compounds also interact with other G-protein-coupled receptors like GPR55 or GPR18, opioid or serotonin receptors, etc. with some of them having the ability to modulate nuclear receptors, transient receptor potential (TRP), or ligand gated ion channels also [3]. Phytocannabinoids are reported to be effective in many health conditions, as they have anti-inflammatory, anti-anxiety, anti-tumor, and analgesic activities [5].

Endocannabinoids or endogenous cannabinoids are derivatives of long-chain fatty acids that comprise a group of naturally occurring members of eicosanoid super-family, which activate cannabinoid receptors. These are formed rapidly from lipid precursors and are released from their source cells upon stimulation and activate cannabinoid receptors on the same or nearby cells or are quickly metabolized (hydrolyzed) by specific serine hydrolase known as fatty acid amide hydrolase [1]. Relevant examples include anandamide, 2-arachidonylglycerol, virodamine, etc. Endocannabinoids seem to be involved in many regulatory functions in animals such as regulation of egg implantation [6], control of sensorimotor and motivational aspects [7], sleep wakefulness cycle, pain perception, memory function, etc. [8]. These perform their actions by interacting with either CB1 or CB2 receptor subtypes, which results in activation of G-proteins (particularly those belonging to G(i/o) family [9].

Synthetic Cannabinoids are lab-generated designer drugs that have emerged as the drugs of abuse as they produce psychoactive effects similar to those of Δ9-THC, by binding to same CB1 and CB2 receptors [10]. These, however, have a higher affinity towards CB1 receptors. These compounds are highly bioactive synthetic cannabinoids most of which are apolar and lipid soluble. Each of these compounds consists of 22–26 carbon atoms and is structurally related to Δ9-tetrahydrocannabinol (THC). Mechoulam et al. and Huffman et al. have significantly contributed to the field of synthetic cannabinoids with Huffman et al. synthesized 450 synthetic cannabinoids [11]. Synthetic cannabinoids produce a wide range of effects such as kidney damage, seizure activity, cardiotoxicity, and even death. Other common toxicities associated with synthetic cannabinoids include irritability, delusions, tachycardia, dizziness, vertigo, chest pain, nausea, hypertension, etc. [12]. On the basis of structure, synthetic cannabinoids have been classified in to seven major groups:

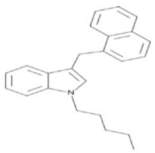
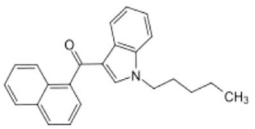
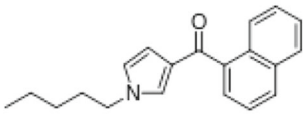
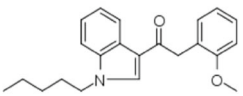
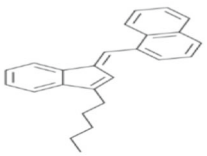
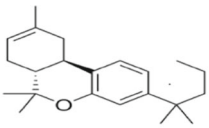
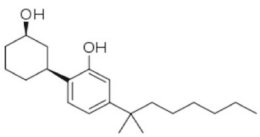
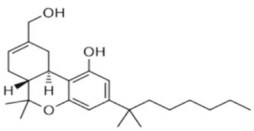
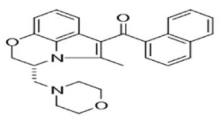
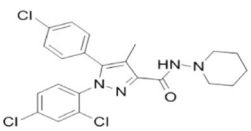
1. Naphthylmethylindoles (e.g., JWH-175, JWH-197)
2. Naphthoylindoles (e.g., JWH-018, JWH-398)
3. Naphthoylpyrroles (e.g., JWH-030, JWH-243)
4. Phenylacetylindoles (e.g., JWH-250, JWH-313)
5. Naphthylmethylindenes (e.g., JWH-176)
6. Cyclohexylphenols (e.g., CP 47,497 and its homologs)
7. Classical cannabinoids (e.g., HU-210)

Some of the major synthetic cannabinoids have been listed in Table 1 with their structure and molecular properties.

Mode of Action of Synthetic Cannabinoids

Natural cannabinoids altogether affect a wide variety of physiological activities of the body as they interact with cannabinoid receptors (CB1 and CB2) distributed throughout the body. The CB1 receptor is, however, mainly distributed in the CNS and also in peripheral nerve terminals, testis, uterus, spleen, and tonsils, while CB2 receptors are mostly restricted to cells and organs of the immune system [13–15] (Fig. 1). Synthetic cannabinoids also elicit wide variety of physiological and pathological effects as they are similar to Δ9-THC (simply THC) on functional grounds, and they bind to the same cannabinoid receptors in the brain and other organs like the endogenous ligands 2-arachidonylglycerol and anandamide, which interact with CB_1 as well as CB_2 receptors [16]. Cannabinoid receptors, as already mentioned, are G-protein-coupled receptors (GPCRs) forming important components of the complex endocannabinoid system. The endocannabinoid system (ECS) is a cooperating network of molecules which regulate the metabolism of the body's own and of exogenously administered cannabinoids [17]. The ECS consists of endogenously produced cannabinoids (endogenous ligands anandamide and archidonoylglycerol), their receptors (the G-protein-coupled cannabinoid (CB) receptors, GPCRs), enzymes which produce and degrade endogenous cannabinoids, and proteins which regulate the uptake and transport of endocannabinoids [18, 19]. Cannabinoids elicit most of their effects in the CNS through the CB1 receptor, which is functionally coupled to inhibition of adenylate cyclase, activation of extracellular signal regulated kinase (ERK), and modulation of ion channels [20] such as those of Ca^{2+} and K^+. The CB2 receptor also signals inhibition of adenylate cyclase and activation of ERK. It has been demonstrated in the Chinese hamster ovary cells transfected with CB1 receptor cDNA that THC induces activation of protein kinase B (Akt (PKB)) and synthetic cannabinoids namely CP-55940 and HU-210 also exert similar effect [20]. Since this kinase (serine-threonine protein kinase B, PKB also called Akt) is an important player in regulation of many basic cellular functions such as proliferation, energy metabolism, etc., cannabinoids (both natural and synthetic) are important modulators in these cellular activities [20] (Fig. 2). Further, in the case of neurons, the activation of GPCRs results in pre-synaptic hyperpolarization by alteration of calcium influx and potassium efflux ultimately

Table 1 Synthetic cannabinoids and their physical properties

Synthetic Cannabinoid	Property	
	Structure	**Physical properties**
JWH-175		Mol. Formula: $C_{24}H_{25}N$ Mass: 327.4 Da
JWH-018		Mol. Formula: $C_{24}H_{23}NO$ Mass: 341.4 Da
JWH-030		Mol. Formula: $C_{20}H_{21}NO$ Mass: 291.38 Da
JWH-250		Mol. Formula: $C_{22}H_{25}NO_2$ Mass: 335.4 Da Lipid soluble, apolar
JWH-176		Mol. Formula: $C_{25}H_{24}$ Mass: 324.4 Da
JWH-133		Mol. Formula: $C_{22}H_{32}O$ Mass: 312.4 Da Lipid soluble, apolar
CP 47, 497		Mol. Formula: $C_{21}H_{34}O_2$ Mass: 318.4 Da
HU-210		Mol. Formula: $C_{25}H_{38}O_3$ Mass: 386.56 Da Lipid soluble, apolar
WIN55,212-2		Mol. Formula: $C_{27}H_{26}N_2O_3$ Mass: 426.5 Da Lipid soluble, apolar
SR141716		Mol. Formula: $C_{22}H_{21}Cl_3N_4O$ Mass: 463.7 Da Lipid soluble, apolar

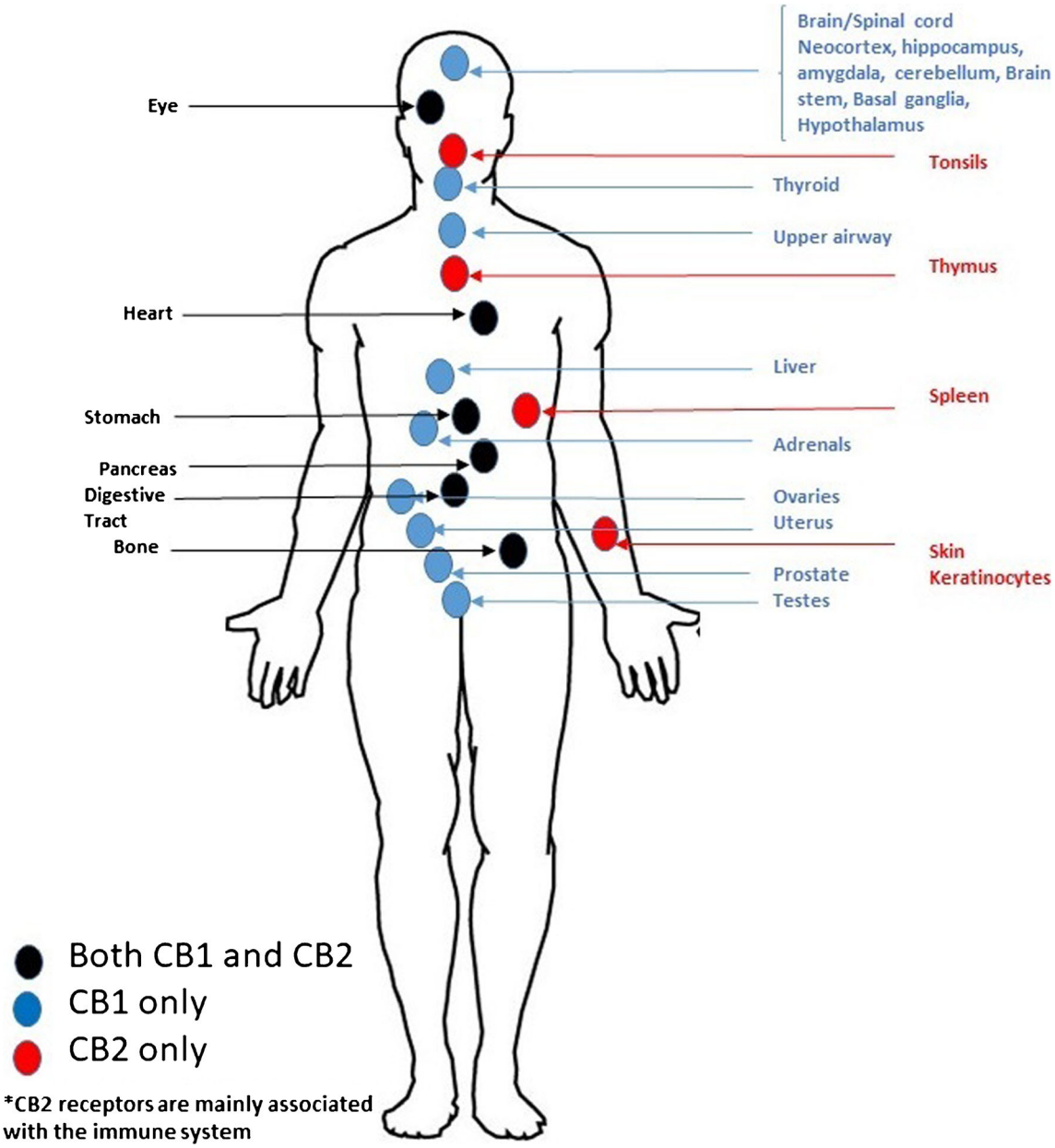


Fig. 1 Location and distribution of CB1 and CB2 receptors in human body. Widely distributed cannabinoid receptors (CB1 and CB2) in the human body are responsible for a number of physiological aspects affected by the cannabinoids that act as agonists or antagonists up to different degrees

leading to neuronal hyper-polarization and decrease in release of neurotransmitters [21].

A very important aspect of synthetic cannabinoid activity is that these compounds are full agonists of the CB_1 receptors. Even THC is a weak CB_1 partial agonist, and hence, no amount of THC can stimulate cannabinoid receptors as that of synthetic cannabinoids. Both in vitro and animal in vivo studies have shown that the pharmacological effects of synthetic cannabinoids are 2–100 times more potent than those of THC along with anti-seizure, anti-inflammatory, analgesic, weight loss, and anti-cancer effects. Synthetic cannabinoids like NNEI, MN-18, CUMYL-PICA, 5F-CUMYL-PICA, MMB-FUBINACA, etc. have been reported to exhibit high affinity for CB_1 and CB_2 receptors in human and produce greater effects than THC in cAMP and [35S] GTPγS signaling. Activation of CB_1 receptors lowers the cAMP activity and discloses cannabimimetic effects (Fig. 2). Further, synthetic cannabinoid agonists interact with voltage-gated ion channels and decrease membrane potential causing inhibition of potassium, sodium, and N- and P/Q-type calcium channels. It has been reported that minor structural modifications done in these drugs can have very large impact on their

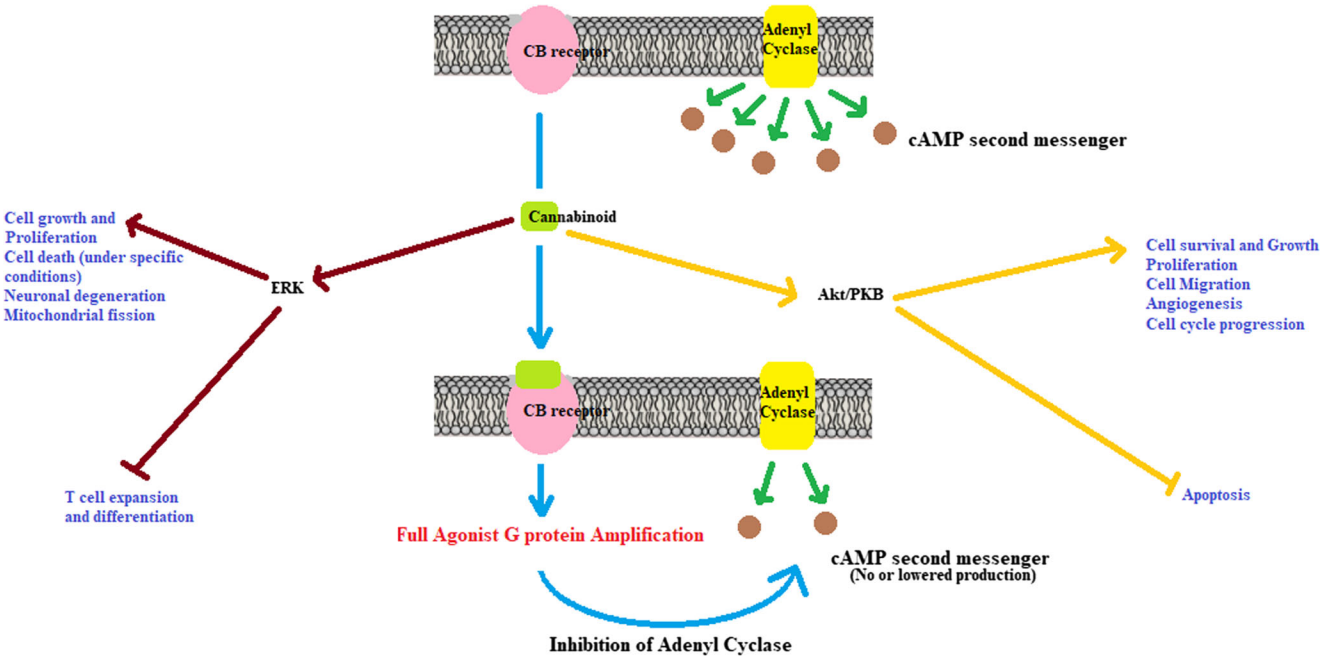


Fig. 2 Mode of action of cannabinoids (both natural and synthetic). At cellular level, cannabinoids upon interacting with appropriate receptors cause inhibition of adenyl cyclase, promotion of ERK, and Akt/PKB signaling pathways, leading to a wide variety of effects on different cellular functions such as growth, proliferation, metabolism, and cell death

pharmacological properties. For instance, methylation of MMB-FUBINACA to form MDMB-FUBINACA leads to increase in its affinity for CB_1 receptors. Further, different chemical structures found in synthetic cannabinoids found in various commercial products may interact in unknown and unpredictable ways, and the commercial products may have unknown contaminants also [12]. An account of differences in activities and effects of some synthetic cannabinoids and natural cannabinoid (THC) is given in Table 2.

Medicinal Uses of Major Synthetic Cannabinoids

The naturally occurring cannabinoids and their synthetic analogues (synthetic cannabinoids) have significant therapeutic potential against many diseases. Marijuana has been used for many medical purposes including management of vomiting and nausea, appetite, and immunological stimulation in HIV-infected patients and those with AIDS, glaucoma, and neurological disorders [51]. Many studies and patents suggest that there are neuroprotective properties in the endocannabinoid system that can be targeted in treatment of neurodegenerative disorders [52]. Many preclinical studies suggest that cannabinoid compounds may act as neuroprotective agents in neonatal and adult ischemia, Alzheimer's disease, brain trauma, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's chorea [53]. Activation of CB1 and CB2 receptors using non-psychoactive doses of natural or synthetic agonists is found to be beneficial in experimental models of Alzheimer's disease, as these decrease the harmful β-amyloid peptide action and tau phosphorylation and promotes brain's intrinsic repair mechanisms [54]. Synthetic cannabinoid such as WIN55,212-2 is found to enhance the expression of antioxidant Cu/Zn SOD and prevents inflammation induced by amyloid β1–42 in the cultured astrocytes obtained from rat fetuses [39]. Synthetic cannabinoids such as WIN55,212-2 are reported to be neuroprotective in Parkinson's disease, as these can suppress excitotoxicity, oxidative injury, and glial activation which cause destruction of dopaminergic neurons [40]. Many pre-clinical studies suggest that cannabinoids elicit their effects at different levels of cancer progression including inhibition of proliferation, invasion, neovascularization, chemoresistance, induction of apoptosis and autophagy, and enhancement of tumor immune surveillance [55]. It has been found in many previous studies that these compounds can inhibit proliferation, migration, adhesion, invasion, and angiogenesis of tumor cells. Two major forms of cancer namely prostate and breast cancers can be very effectively handled using these compounds, as these have direct anti-tumor effects and can also improve the efficacy of traditional anti-tumor drugs. In cancer patients, cannabinoids have been mainly used for palliative care, but many cell culture and animal studies have shown the anti-tumor effects of cannabinoids in different types of cancer [56]. For instance, intratumoral administration of Δ9-THC and synthetic cannabinoid WIN55,212-2 induced a considerable regression of malignant gliomas in mice and Wistar rats, without producing any neurotoxicity. Further,

Table 2 Some important synthetic cannabinoids, their mode of action, pharmacological effects, and comparison of their activity with that of THC, a popular natural cannabinoid

Synthetic cannabinoid	Mode of action	Pharmacological effect	Comparison with natural cannabinoid (THC)
JWH-175	High affinity for CB1 receptor	Hypomotility and abuse potential [22]	More potent than THC [23]
JWH-018 (spice, K2 type herbal blends)	Full agonist for CB1 and CB2 receptors with some selectivity for CB2 receptor	Vomiting, agitation, confusion, tachycardia and hallucinations; increase in blood pressure, myocardial ischemia, impairment of neurocognition at lower doses [24]	Higher potency than THC (four to five times more potent than THC)
JWH-030	Higher affinity for CB1 receptor as compared to CB2; partial agonist of CB1 receptor	Analgesic, severe harmful effects on cardiovascular system; mediates cytotoxicity by acting on CB2 receptor [25]	Nearly half the potency of THC [26]
JWH-250	CB1 and CB2 receptor agonist	Analgesic, severe harmful effects on cardiovascular system [26]	–
JWH-176	High affinity for CB1 receptor	Analgesic	More potent than THC [23]
JWH-133	Potent selective CB2 receptor agonist; has affinity for CB1 receptor also but less as compared to that for CB2 receptor; inhibits VEGF, bFGF, IL-8, MMPs, IL-17, and other cytokines [27]	Effective in Alzheimer's disease prevention, potent analgesic, anti-inflammatory, effective against pathogenesis of psoriasis [27]; chemotherapeutic effect against gliomas [28, 29]; protects heart against ischemia-reperfusion injury [30]	–
CP 47, 497	CB1 agonist	Analgesic, anticonvulscent, hypothermic effects	Equivalent potency to THC [31]
HU-210	Synthetic agonist analog of THC, potent CB1 and CB2 receptor agonists; involves ATP sensitive K+ channels [32]	Effective in prevention of Alzheimer's disease [33], potent analgesic; neuroprotection [34, 35]; anti-arrhythmatic [36]; anti-nociceptive [37]	100–800 times more potent than THC with extended duration of action [38]
WIN55,212-2	Binds with both CB1 and CB2 receptors; full agonist of CB1 receptor with higher affinity for it as compared to THC	Effective in Alzheimer's disease and Parkinson's disease prevention [39, 40], potent analgesic, anti-inflammatory, intra-ocular pressure reduction [41, 42]; reduction of cardiac ischemia-reperfusion injury in rat models [43]; effective against multiple sclerosis in mice model [44, 45], anti-tumor effects [46, 47]	Higher affinity for cannabinoid receptors than THC
SR141716 (“”Rimonab-ant)	Antagonist or inverse agonist for CB1 receptor	Anorectic anti-obesity drug, causes sleep disorders, nausea, skin irritation, diarrhea, fatigue, cramps, and spasms	Opposite activity to THC
Nabilone	CB1/CB2 receptor agonist	Treatment of cannabis dependence [48]; antiemetic, analgesic, Chemotherapy induced nausea, and vomiting [49]	Mimics THC
Dronabinol	CB1/CB2 receptor agonist	Anti-emetic [50], anti-anorexic	Synthetic form of THC; chemically known as Δ^9 tetrahydrocannabinol

cannabinoids signal apoptosis in C6 glioma cells by pathway involving cannabinoid receptors, Raf1/extracellular signal-regulated kinase activation, and ceramide accumulation [46]. Another study revealed that analogue of anandamide that is R(p)-methanandamide and JWH-015 (a synthetic CB2 agonist) exerts anti-proliferative effects in PC-3 cells, with ceramide de novo synthesis being triggered due to JWH-015, which is involved in cannabinoid-induced death [57]. JWH-015 activated JNK pathway and inhibited the Akt pathway leading to significant reduction in tumor growth in mice. Kenyon et al. have also suggested on the basis of their findings that pharmaceutical grade synthetic cannabidiol is a candidate for treatment of gliomas and breast cancer. They found clinical response in 92% of the solid tumor cases along with reduction in size of the tumors and in the number of circulating tumor cells with no side effects of any kind [58]. An earlier study involving study of effect of WIN55,212-2 in different human cancer cell lines (lung cancer cells, testicular cancer cells, and neuroblastoma cells) showed that it elicits apoptotic effect in these cell lines [47]. The mechanism involving ceramide-induced death in cancer cells is shown in Fig. 3.

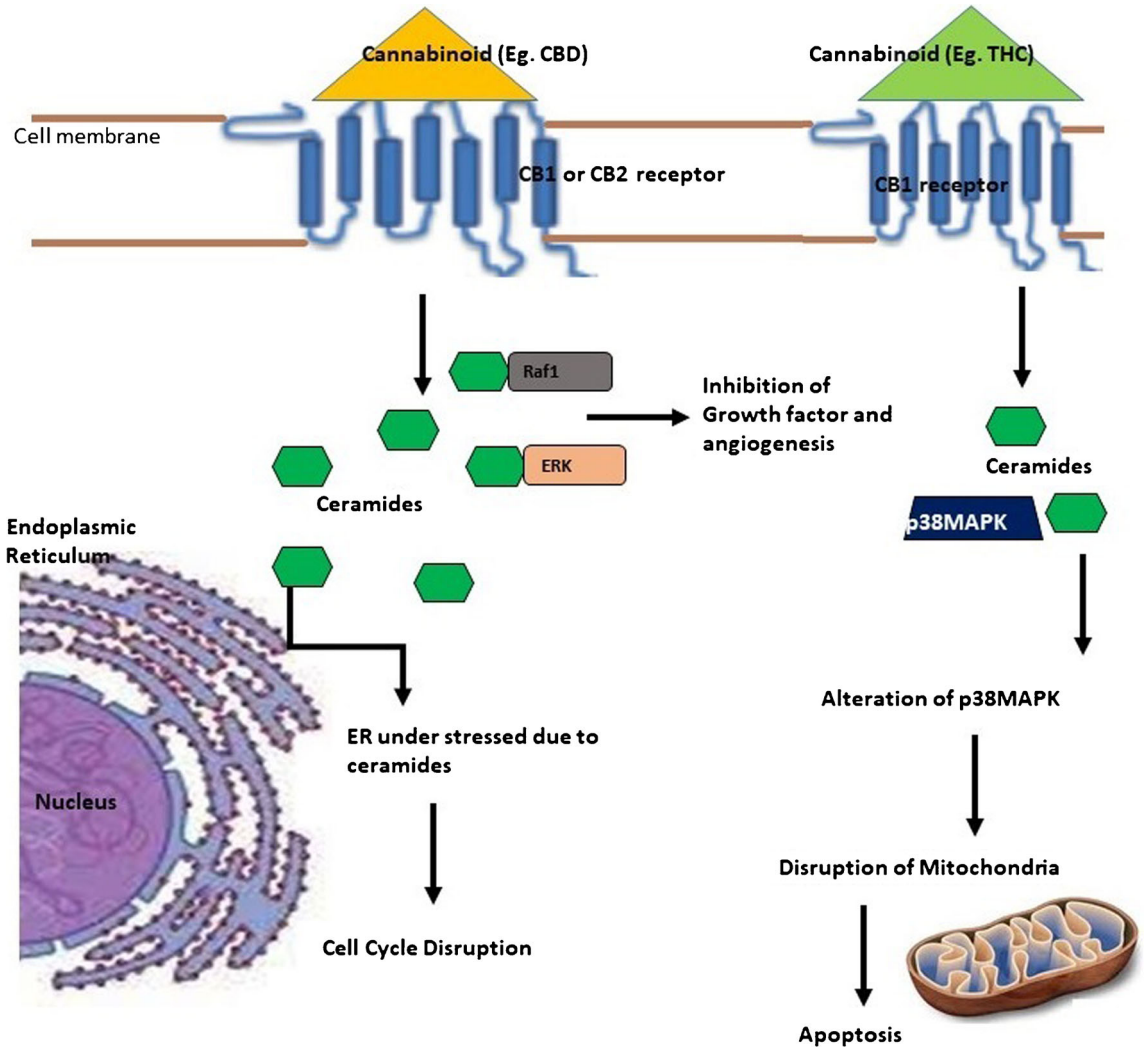


Fig. 3 Mechanism of cancer prevention by cannabinoids through ceramide accumulation in the cells. Cannabinoids upon interaction with suitable receptors lead to accumulation of ceramides in the cancer cells. These ceramide molecules generate ER stress and bind with other cellular factors (ERK, Raf1) to block them and prevent them from participating in the growth, angiogenesis. Upon interaction with p38MAPK, mitochondria are also disrupted. In this way, cannabinoids prevent tumor growth in multiple ways

Synthetic cannabinoids such as JWH015 and BML190, the selective CB_2 receptor agonists, partially inhibited keratinocyte proliferation, while another cannabinoid called HU210, the non-selective CB receptor agonist, inhibited it in a concentration-dependent way. This indicates that these cannabinoids can be effective against psoriasis, a condition that involves epidermal keratinocyte hyper-proliferation, and their activity cannot be blocked by CB_1/CB_2 receptor antagonists [59]. A recent study shows that JWH-133 has a strong anti-angiogenic and anti-inflammatory activities as it inhibits VEGF, IL-8, IL-17, MMPs, HIF-1 α, bFGF, and other cytokines and adhesion molecules in vitro and in vivo, and thus, it can suppress the two major steps of pathogenesis of psoriasis [27]. However, further complementary animal studies and trials involving human are still needed [27].

Kokona et al. have suggested through their review that endocannabinoids like anandamide and synthetic cannabinoids like HU-210 are involved in neuroprotection of early and final events of pathophysiology of retinal ischemia [27]. Many studies also demonstrate the effectiveness of cannabinoids in chronic permanent blinding disease called glaucoma which is caused due to increase in the intra-ocular pressure. A synthetic cannabinoid called 1-nantradol reduces intra-ocular pressure upon acute administration, producing no change in the ocular pressure upon chronic administration in eyes of cats. Another synthetic cannabinoid called HU-211 is also reported to reduce the intra-ocular pressure in rabbits when used in the form of a sub-micron emulsion [60]. A cannabimimetic called WIN55,212-2 is also reported to reduce the intra-ocular pressure with its effect partly mediated by CB_1 receptor; however, contribution of CB_2 receptor up to

certain extent cannot be ruled out. Liu and Dacus suggested on the basis of their experimental study that the reduction in the intraocular pressure due to cannabinoids does not begin in the CNS but originates due to alteration in the blood pressure. CB_1 receptor is specifically associated with anti-glaucomatous activity of cannabinoids as experimentally demonstrated by Porcella et al., who found significantly higher mRNA of CB_1 receptor in different regions of the rat eyes using RT-PCR. Porcella et al. further showed that WIN55,212-2, a CB_1 receptor agonist, decreases the intra-ocular pressure of glaucoma in human that is resistant to conventional therapies, corroborating that CB_1 receptor has direct involvement in regulation of intra-ocular pressure in human.

In another ocular pathology called retinitis pigmentosa, an autosomal dominant disorder, the therapeutic potential of synthetic cannabinoid HU-210 was studied in the transgenic P23H rat model and it was found that HU-210 preserved the structure and function of the rods and cones along with their contact to post-synaptic neurons. Thus, HU-210 can delay retinal degeneration in patients suffering from retinitis pigmentosa. The Muller cells of the retina are also affected by cannabinoids in both receptor-dependent and receptor-independent ways. Cannabinoids like 2-AG and WIN55,212-2 inhibit Ca^{2+} channel currents in the Muller cells in receptor independent way, while AEA (anandamide) suppressed them partially through CB_2 receptors. R(+)WIN55,212-2 is also reported to promote vaso-relaxation of retinal capillaries of rats having pericytes. This effect of R(+)WIN55,212-2 is dependent on CB_1 and NO-cGMP pathway.

Multiple sclerosis (MS), that is a chronic, demyelinating disorder of the CNS, has been widely reported to be slowed down using cannabinoids as reviewed recently by Gado et al. [61]. Kozela et al. also concluded on the basis of their study that synthetic cannabinoids like HU-446 and HU-465 have anti-inflammatory effect in inflammatory and autoimmune diseases like MS and in experimental autoimmune encephalitis (EAE) [62]. Since the beginning of this decade and even earlier, studies have been done to establish the therapeutic effects of cannabinoid in such conditions. For instance, it has been shown in A-172 glioblastoma and 1321N1 astrocytoma cell models that the synthetic cannabinoid R(+)WIN55,212-2 (active chiral form) strongly inhibited IL-1, ICAM-1, VCAM-1, and IL-8 induction without involving cannabinoid receptors (CB_1 and CB_2) and instead, by inhibiting transactivation potential of NFκB. On the other hand, there are reports according to which both CB_1 and CB_2 receptors are involved in protective function in MS due to their anti-inflammatory, anti-excitotoxic, and immune-modulatory properties. The role of CB_2 is particularly of more interest as it has been found to exhibit no psychoactive activity in animal models of MS. de Lago et al. have concluded from their experimental studies in mice models of MS that WIN55,212-2 (a potent CB_1 and CB_2 receptor agonist) administration effectively ameliorated spasticity and thus delayed the progress of MS in these mice. It has also been experimentally demonstrated that R(+)WIN55,212-2 behaves as a novel regulator of TLR3 (Toll like receptor 3) signaling to IRF3 (interferon regulatory factor 3) activation and expression of IFN-β and these are crucial for manifestation of the protective effects of R(+)WIN55,212-2 in a murine MS model. Further, it has been reported in mice models of MS that the CB_2 receptors also have myeloid progenitor trafficking as their target site of action.

There are many studies that have reported the adverse effects of cannabinoids on the heart. A number of recent studies report the cardiac complications that people underwent due to the recreational use of synthetic cannabinoids in the form of K2, spice, Mojo, etc. The complications include sudden cardiac death, stress cardiomyopathy, vascular events, and arrhythmias [63]. However, many studies have reported their therapeutic effects also. For instance, the cannabinoid HU-210 is found to exhibit anti-arrhythmic effect that is mediated through CB_2 receptors' activation. As early as year 2002, Krylatov et al. have demonstrated that intravenous administration of HU-210, a cannabinoid receptor agonist, leads to increased cardiac resistance towards arrhythmogenic effect of aconitine, epinephrine, coronary artery reperfusion, and occlusion in rats, indicating that stimulation of CB_2 receptors enhances the myocardial tolerance for ischemic and reperfusion damage in these animals. Similarly, intravenous administration of synthetic analogue of anandamide called R-(+)-methanandamide prevents ischemic and reperfusion arrhythmia in rats by CB_2 receptor stimulation that raises the tolerance of heart for these conditions.

Another synthetic cannabinoid named O-1602 is reported to be effective against colitis by inhibiting neutrophil recruitment. Synthetic cannabinoids are also reported to protect retinal amacrine neurons in vivo from AMPA excitotoxicity, and the mechanism involves CB_1 receptors with signaling pathways like MEK/ERK1/2 and/or PI3K/Akt. Intravenous administration of the synthetic analogue of anandamide known as R-(+)-methanandamide prevents ischemic and reperfusion arrhythmia in rats by activating CB_2 receptor that increases cardiac tolerance towards conditions such as ischemia and reperfusion. HU-210 is reported to exhibit anti-nociceptive properties that do not depend its effect on the prostaglandin pathway. Further, it is also reported to exhibit infarction-limiting effect during in vitro reperfusion of heart following focal ischemia [64]. Regarding the mechanism followed in HU-210-induced resistance to reperfusion injury, Maslov et al. suggested that ATP-sensitive K^+ channels are involved in it. Inhibition of Na^+/Ca^{2+} exchange by activation of peripheral cannabinoid receptor (CB_2) may also be associated with the anti-apoptotic and cardio-protective effects of these compounds. Another synthetic cannabinoid called HU308 is also found to reduce the infarct size and levels of TNF-α and ROS

in animals with acute myocardial infarction and myocardial ischemia-reperfusion injury [65]. WIN55,212-2 is also reported to reduce cardiac ischemia-reperfusion injury in Zucker diabetic fatty rats by restoration of coronary perfusion pressure and heart rate to pre-ischemic level.

JWH-133 protects the heart from ischemia-reperfusion injury as suggested by Li et al. who observed that administration of JWH-133 (a CB_2 receptor agonist) before ischemia in rats significantly improved recovery of cardiac ventricular activity during reperfusion, decreased size of infarcts, increased coronary flow, prevented the loss of mitochondrial membrane potential and MPTP opening, and enhanced levels of pERK1/2 while decreasing release of cytochrome C from mitochondria [66]. Upon comparing the effect of three different cannabinoid receptor agonists namely anandamide, methanandamide, and CP 55,940 on parameters like cell morphology, cell loss, cell viability, and DNA laddering in human gastric adenocarcinoma cell line, the three agents exhibited similar concentration dependent effects [67]. Further, some more benefits are also provided by compounds related to cannabinoids such as CE-178253, nabilone, HU-210, and oleoylethanolamide that act against bradykinesia and levodopa-induced dyskinesia in Parkinson's disease [40]. HU-21, incorporated into a submicroscopic emulsion, is reported to cause a temporary (for 6 h) decrease in the intra-ocular pressure in rabbits [60].

Negative Aspect of Synthetic Cannabinoids

The naturally occurring cannabinoids have long been associated with human history due to their medicinal and recreational properties. Despite world-wide regulations on their use and abuse, their synthetic synonyms have been marketed under several names and they have gained popularity all over the globe since recent years. These synthetic compounds are termed as "herbal highs" or "legal highs" due to their legal status and herbal make-up [68]. Among forensic practitioners, compounds belonging to HU, JWH, CP, WIN, AM, RCS, UR, and XLR have been found to be of most interest. Many of these compounds are cannabinoid receptor agonists that were synthesized originally for medical research purpose, but they have been used in the illicit drug market. The illicit preparations contain synthetic cannabinoids such as MDMB-FUBINACA, NNEI, MN-18, CUMYL-PICA [O], AKB48, JWH-081, and UR-144. Factors like similarity in the psychoactive effects produced by synthetic cannabinoids to those of cannabis, their easy accessibility and difficult detection in standard urine drug screens contribute to their high usage rate with another frustrating factor being constantly changing composition of commercial synthetic cannabinoid products. In addition to the intoxicating effects of synthetic cannabinoids, there is also a high incidence of adverse effects linked with their use such as confusion, tachycardia, anxiety, dizziness, drowsiness, hypertension, vomiting, chest pain, nausea, acute CNS, and cardiovascular toxicity along with dependence and withdrawal symptoms upon long-term use. Further, studies suggest that there are pharmacokinetic and pharmacodynamics differences between the activities of THC and synthetic cannabinoids that indicate towards greater risk of abuse and development of dependence on these synthetic compounds than cannabis. Synthetic cannabinoids lead to extreme metabolic derangements and widespread destructive effects in multiple organ systems, due to the presence of cannabinoid receptors in these organs. These compounds can cause severe renal, cardio-vascular, and neurologic manifestations. For instance, JWH-133 and HU-308 cause enhancement of cell proliferation rate by activating AKT/PKB pathways in colon cancer both in vitro and in vivo. However, these compounds have demonstrated no adverse effects as reported in many animal studies.

Drugs-Synthetic Cannabinoid Interactions: Recent Studies

The synthetic cannabinoid designer drugs are not only the drugs of abuse producing psychoactive effects similar to THC but also lead to severe intoxication, as these are extensively metabolized. The abuse of these compounds with other drugs with variety of chemical groups has led to large number of poisonings [69]. The problem is further enhanced due to limited knowledge about the enzymes involved in their metabolism [70]. A study done by Holm et al. for instance suggested that adverse drug-drug interactions (DDIs) may occur where a co-intake of strong CYP3A4 inhibitors, like HIV antivirals, azole antifungal agents is done with that of a synthetic cannabinoid called AKB-48, because CYP3A4 is a major enzyme responsible for the oxidative metabolism of AKB-48 [70]. They further suggested that knowledge of specific enzymes that metabolize these designer drugs will help in predicting such drug-drug interactions [70]. Another study done by Kong et al. found that MAM-2201, a potent synthetic cannabinoid agonist for CB receptors, has the potential to trigger in vivo pharmaco-kinetic drug interactions upon getting co-administered with substrates of CYP2C9, UGT1A3, CYP2C8, and CYP3A4 [71]. Zendulka et al. also suggested that direct inhibition or activation of nuclear receptors in liver cells by cannabinoids can lead to alteration in the expression and activity of CYP [72]. Tai and Fantegrossi have recently suggested that synthetic cannabinoids should not be considered safe and legal alternatives to marijuana, as these are relatively more toxic. Further, there is a possibility of enhanced toxicity due to combined activity of complex mixture of different synthetic cannabinoids and their active metabolites that have high binding affinity towards CB1 and CB2 receptors [73]. A recent study by Fantegrossi et al. suggests that

synthetic cannabinoids also elicit pro-psychotic effect leading to schizophrenia and psychosis upon their exposure as these may affect the way neurotransmitters (serotonin, dopamine, etc.) interact with cannabinoid receptors (CB1Rs) [74].

Clinical Studies Involving Cannabinoids: A Field with Many Shortcomings

Synthetic cannabinoid abuse has led to severe clinical illness in different parts of the world since past many years, and their impact may increase further with increase in their abuse and inability of regulatory mechanisms to restrict it. The issue gets further complicated as new combinations and synthetic substances emerge time to time, with little known about their clinical hazards. Limited knowledge about the clinical hazards of synthetic cannabinoids is due to far lesser number of human-subject-based studies being done until now. These synthetic compounds elicit undesirable adverse health effects similar to those seen in the case of cannabis usage but in a more pronounced and long lasting way. In the year 2014, Kucerova et al. highlighted in their review the close relation between the endocannabinoid systems (ECS) and schizophrenia, as the ECS activation affects release of many neurotransmitters in many systems and cytokines from the glial cells. They indicated that use of cannabis in adolescence may alter the ECS signaling and pose a potential risk of psychosis [75]. There is quite a possibility that the synthetic cannabinoids activity will be comparable to the natural cannabinoids. With a rise in accessibility to cannabis, increase in strength, advent of strong synthetic mixtures, and increasing number of cannabis users during pregnancy, there is rising need of thorough studies involving the pre-natal consequences associated with cannabis exposure [74]. There have been reports that activation of CB1 receptors by THC or synthetic cannabinoids significantly modifies neuronal differentiation [76] and affects synapse physiology by disrupting normal patterns of endocannabinoid signaling [77].

Talking about the therapeutic effects and potential of cannabinoids and related compounds, the number of clinical studies done is also limited. Human studies that have been done so far mostly for investigating the pharmaco-therapeutic benefits of cannabinoids focus mainly on reducing pain, spasticity, and cognitive deficits in the disorders of CNS and PNS [78, 79]. For instance, Volz et al. concluded on the basis of their human subject-based study that cannabis may be useful in relieving symptoms of Crohn's disease like pain, nausea, etc. However, they also indicated that studies with high methodological quality, sufficient duration, and sample size are needed to be done to determine therapeutic effects and risks associated with cannabis in gastroenterology [80]. Kucerova et al. highlighted the therapeutic potential of the cannabinoids and related substances in relation to schizophrenia [75]. Many animal studies suggest that synthetic cannabinoids are potent chemotherapeutic agents for gliomas (e.g., JWH-133, HU-210, WIN55,212-2). JWH-133 is effective against human gliomas also as demonstrated in murine C6 xenografts with the mechanism followed being through CB2 receptors (not CB1 receptors) activation, ceramide synthesis [28], and inhibition of glioma cells invasion by downregulation of MMP-2 [29]. Another study done by Singh and Bali showed a 14-year-old female Philadelphia chromosome-positive patient-treated unsuccessfully with conventional therapy for acute lymphoblastic leukemia, experiencing a dose-dependent management of the disease using orally administered cannabinoid extract [81]. An evident limitation of the current human subject-based studies for evaluation of anti-cancer effects of cannabinoid compounds is small patient size which makes replication and comparison of the results in multiple cohorts difficult [82]. Another recent study done to evaluate the effect of JWH-018 on neurocognition and subjective experience in human showed that lower levels of JWH-018 does impair neurocognition, but still, the study is not sufficient as higher doses are required to get more representative risk profile of JWH-018 [24]. All these evidences show that substantial amount of clinical work involving more human subjects and higher doses of the cannabinoids tested are required in order to reach concrete conclusions regarding both positive (therapeutic) and negative aspects of all classes of cannabinoids.

Future Perspective

Synthetic cannabinoids are chemically and pharmacologically different from the naturally occurring cannabinoids. Their structural dissimilarity with THC allows them to evade legal restrictions and also makes them less likely to be detected through standard drug screens. Such structural deviations in these cannabimimetic compounds may result in their increased efficacy and affinity for CB_1 receptor. Further, this may lead to enhancement of adverse reactions and toxicities which are not elicited by natural cannabinoids. There is a lot of scope as well as need to research in the field of synthetic cannabinoids, as the complete understanding of these compounds is still lacking. Little information about the pharmacodynamics and pharmacokinetics of these compounds is available. Further, it is known that these compounds are potent CB_1 agonists, but the exact mode of action underlying their toxic effects is not understood. There is no specific antidote to handle cases of overdose of these designer drugs and no approved curative treatment. Also, there is little or no information about the long-term use and chronic toxicity of these compounds, and speculations have been made mostly on the basis of effects elicited by cannabis. Few studies have associated psychosis and its relapse with their consumption.

Limited availability of epidemiological data related to different aspects of synthetic cannabinoids such as their use, pharmacokinetics, distribution in tissues and organs, elimination, drug-drug interactions, and clinical effects is a major issue in understanding the biology of these compounds, and hence, large-scale investigations are needed to be done regarding these issues of synthetic cannabinoids. Overall, a number of avenues are open for different kinds of studies to improve our understanding of interactions of these compounds with cannabinoid and non-cannabinoid receptors and to better characterize their pharmacological and toxicological aspects. Proper drug scheduling, legislation, and monitoring are also needed to be implemented along with development of treatments for synthetic cannabinoid intoxication. In addition to this, the medicinal use of these compounds in different disease conditions needs attention as well.

Conclusion

Synthetic cannabinoids, like any other drugs, are required to be judiciously used. There is need of extensive research regarding their clinical effects (acute and chronic), mechanism of eliciting intoxication and toxicity, treatments for over doses, etc. Enforcement of regulation and legislation to control their abuse is also a primary concern. There is serious need to develop more effective screening and detection tests for these compounds so that their abuse can be controlled. However, their medical utility should not be belittled due to these negative factors. By regulating their abuse and promoting their utilization for treatment and research purposes can be a boon for human kind.

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Compliance with Ethical Standards

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