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Adverse Impact of Cannabis on Human Health

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Abstract

Cannabis, the most commonly used recreational drug, is illicit in many areas of the world. With increasing decriminalization and legalization, cannabis use is increasing in the United States and other countries. The adverse effects of cannabis are unclear because its status as a Schedule 1 drug in the United States restricts research. Despite a paucity of data, cannabis is commonly perceived as a benign or even beneficial drug. However, recent studies show that cannabis has adverse cardiovascular and pulmonary effects and is linked with malignancy. Moreover, case reports have shown an association between cannabis use and neuropsychiatric disorders. With growing availability, cannabis misuse by minors has led to increasing incidences of overdose and toxicity. Though difficult to detect, cannabis intoxication may be linked to impaired driving and motor vehicle accidents. Overall, cannabis use is on the rise, and adverse effects are becoming apparent in clinical data sets.

INTRODUCTION

Cannabis has been cultivated by humans for thousands of years for recreational and medicinal uses (1). Consumed in various modalities, including smoking, hookah, vaping, and edibles, cannabis is one of the most commonly used recreational drugs and is illicit in many areas of the world (2). With growing decriminalization and legalization, cannabis use has increased worldwide (3, 4).

There are over 500 chemicals in cannabis, and the chief psychoactive component, delta-9-tetrahydrocannabinol (Δ^9-THC), is the most abundant cannabinoid (5). However, cannabis contains more than 100 other cannabinoids that are structurally similar to Δ^9-THC, including cannabidiol (CBD), the second most abundant component, which is nonpsychotropic. The effects of cannabinoids are mediated by cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2), which belong to the G protein–coupled receptor (GPCR) superfamily (6). CB1, the most abundant GPCR in the mammalian brain, regulates the psychoactive effects of Δ^9-THC (**Figure 1**). CB1 is also expressed in other peripheral cells, tissues, and organs such as the heart, vasculature, and smooth muscle. CB2 is expressed in immune cells, particularly in macrophages. The cannabinoid receptors modulate adenylyl cyclase, ion channels, mitogen-activated protein (MAP) kinases [p44/42 MAP kinases, p38, extracellular signaling-regulated kinases (ERK), Janus N-terminal kinase (JNK)], and ceramide signaling (7).

BENEFICIAL EFFECTS OF CANNABIS

A recent systematic review and meta-analysis found that cannabinoids such as Δ^9-THC and CBD might be of benefit for chronic pain, spasticity, epilepsy, cancer, and neurological disorders (8). There are several reports describing the anti-inflammatory effects of cannabis and Δ^9-THC (9). Δ^9-THC has been reported to have apoptotic effects on immune cells (10, 11). Inflammatory cytokine production is also reduced after treatment with Δ^9-THC (12, 13). In neurological disorders such as multiple sclerosis, Δ^9-THC is also thought to exert beneficial effects due to immunosuppression (14). Indeed, several reports show that Δ^9-THC can induce cytotoxicity in cancer, including acute lymphoblastic leukemia (15, 16).

CBD is reported to have anti-inflammatory properties (17) and might ameliorate inflammatory arthropathies (18). CBD is also described as having a neuroprotective effect (19) and is used for neurodegenerative disorders such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease (20, 21). Cannabinoids are known to induce sedation and analgesia and could be an alternative to opioids (22, 23). The adverse effects of opioids include constipation, overdose causing bradypnea, bradycardia, and death, as well as cardiovascular disease. Opioid misuse is exacerbated by the propensity for addiction and highlighted by the ongoing and unrelenting opioid crisis.

Medicinal marijuana has been used in HIV and cancer patients (24). Several forms of synthetic Δ^9-THC have been approved by the US Food and Drug Administration (FDA) for treating chemotherapy-induced nausea and vomiting, as well as for HIV and anorexia: Marinol® (dronabinol), Syndros® (dronabinol), and Cesamet® (nabilone). More recently, synthetic cannabinol, Epidiolex®, has been approved for treating epilepsy in children (25). However, while medicinal cannabis might be beneficial, its adverse effects are becoming evident with increased usage (24, 26).

The assumption that marijuana has pleiotropic benefits without any adverse consequences lacks supporting evidence in clinical practice (49). Some cannabinoids, such as CBD, might have beneficial effects; however, the overwhelming evidence from in vitro, in vivo, and clinical studies indicates that Δ^9-THC is proinflammatory in the context of overall cardiovascular disease risk and likely a precipitant for myocardial infarction and increased mortality.

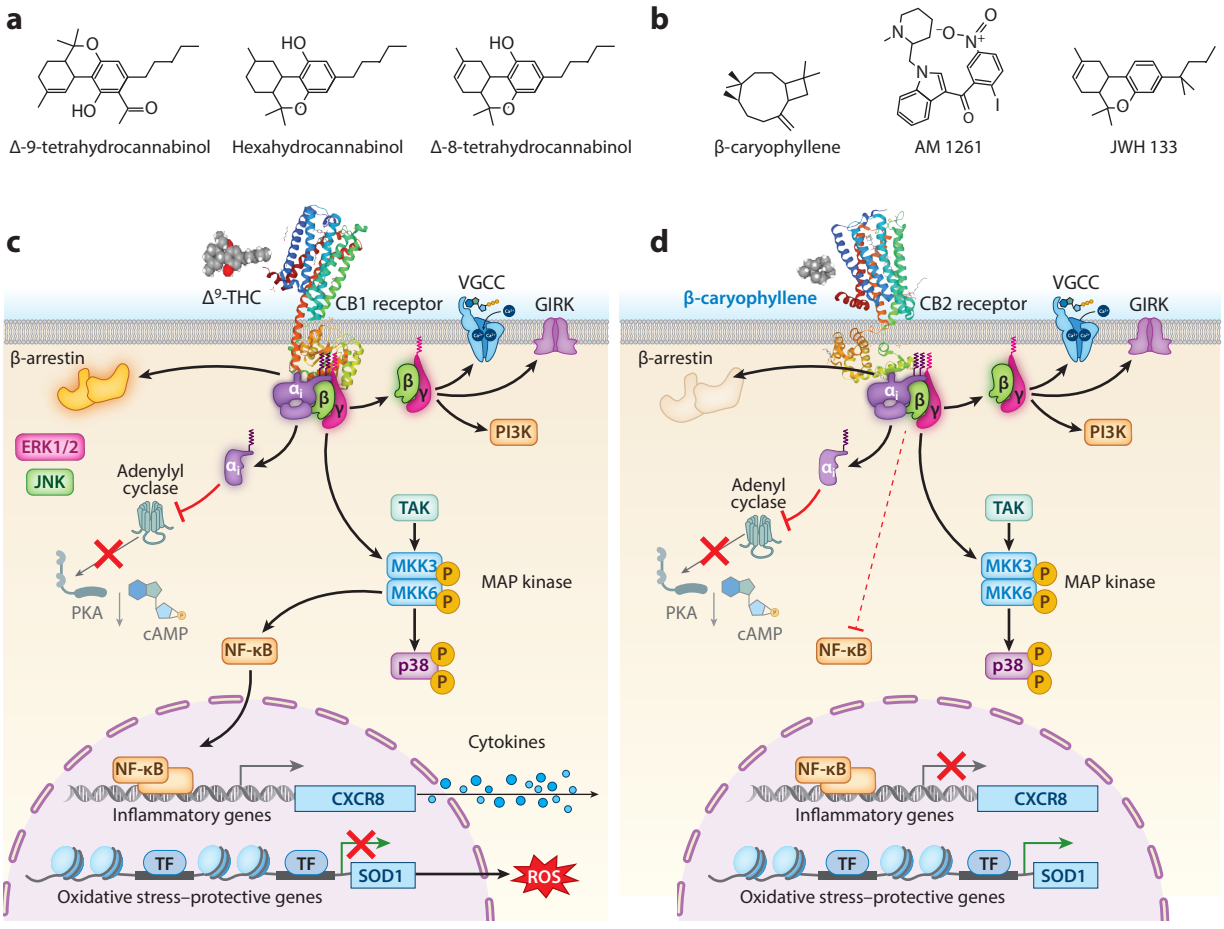


Figure 1

Cannabinoids and cognate receptors. (*a*) The molecular structures of three representative cannabinoid receptor 1 (CB1) agonists that cause psychoactive effects: Δ-9-tetrahydrocannabinol (Δ^9-THC), hexahydrocannabinol (HHC), and Δ-8-tetrahydrocannabinol (Δ^8-THC). (*b*) The molecular structures of three cannabinoid receptor 2 (CB2) agonists: β-caryophyllene (BCP), 2-iodo-5-(nitrophenyl)(1-((1-methylpiperidin-2-yl)methyl)-1H-indol-3-yl)methanone (AM 1261), and (6AR,10AR)-3-(1,1-Dimethylbutyl)-6A,7,10,10A-tetrahydro-6,6,9-trimethyl-6H-dibenzo[B,D]pyran (JWH 133). Chemical structures adapted from the National Center for Biotechnology Information. (*c*) CB1 activation causes inflammation and oxidative stress via multiple signaling pathways. Δ^9-THC binding to the CB1 receptor activates the G protein–coupled receptor (GPCR). The Gi/o complex dissociates into the α_i, βγ, and β-arrestin subunits. The α_i subunit inhibits adenylyl cyclase, thereby decreasing cyclic AMP (cAMP) production and preventing protein kinase A (PKA) phosphorylation, which modulates transcription. The βγ subunit activates the mitogen-activated pathway (MAP) and p38, which activate nuclear factor–kappa B (NF-κB), thus leading to the activation of inflammatory genes and downregulation of oxidative stress-protective genes. The βγ subunit simultaneously affects voltage-gated calcium channels (VGCC), G protein−gated potassium channels (GIRK), and the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway. (*d*) CB2 activation prevents inflammation and oxidative stress. BCP binding to the CB2 receptor activates the GPCR. The α_i subunit of the Gi/o complex dissociates into the α_i, βγ, and β-arrestin subunits. As in CB1 activation, the α_i subunit inhibits adenylyl cyclase, thereby decreasing cAMP production, and prevents PKA phosphorylation to modulate transcription. The βγ subunit activates MAP and p38. However, CB2 activation prevents NF-κB translocation to the nucleus, thus blocking the expression of inflammatory genes and downregulating oxidative stress-protective genes. The βγ subunit simultaneously affects VGGC, GIRK, and the PI3K/AKT pathway. Figure adapted from Reference 46 with permission, modified using BioRender.com.

ADVERSE CARDIOVASCULAR EFFECTS OF CANNABIS

The cardiovascular effects of cannabis are both acute and chronic. Acutely, the psychoactive component of cannabis, Δ^9-THC, is associated with tachycardia, hypertension, platelet activation, and endothelial dysfunction (2). The chronic effects of cannabis are revealed in epidemiological studies that support the link between recreational cannabis use and heart disease, generally finding that cannabis increases the risk of cardiovascular disease, cardiomyopathy, and arrhythmias (2, 27, 28). Medical marijuana and synthetic cannabinoids are also associated with adverse cardiovascular effects (24, 26).

Inflammation plays a central role in the pathophysiology of atherosclerosis (29, 30). Chronic inflammation is speculated to accelerate atherosclerosis in diseases such as HIV, rheumatoid arthritis, and systemic lupus erythematosus (31–33). Δ^9-THC has been described as promoting inflammation and oxidative stress via the CB1, MAP kinase activation, and NF-κB pathways.

In addition to being the most abundantly expressed GPCR in the central nervous system, CB1 is also expressed in peripheral cells, tissues, and organs such as the heart and vasculature, and it has been implicated in atherosclerosis (34). CB1 activation occurs via the MAP kinase pathway, which causes oxidative stress, inflammation, and cell death in human coronary artery endothelial cells (35, 36). In contrast, CB2, while also expressed in the vasculature, is antiatherogenic (7). Preclinical studies have found that CB1 activation mediates increased oxidative stress and inflammation, which are implicated in diabetic retinopathy, cardiomyopathy, and endothelial dysfunction (36–38). Animal studies have shown a causal link between Δ^9-THC via the atherogenic CB1 receptor (28, 39). The loss of the atheroprotective CB2 receptor exacerbates the progression of atherosclerosis (40, 41).

Historically, clinical associations between marijuana and cardiovascular disease were limited to case reports or case series (28), and these studies showed that even low doses of Δ^9-THC are associated with adverse cardiovascular events (42, 43). A meta-analysis found an association between marijuana and cardiovascular disease. Frost et al. followed patients who were chronic marijuana users and found increased mortality (44). The landmark study by DeFilippis et al. showed a significant association between marijuana and cardiovascular disease in young patients with index myocardial infarction (27). Those using cannabis had a lower incidence of cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia when compared to nonusers. However, after adjusting for age, sex, diabetes, hypertension, peripheral vascular disease, smoking, high-density lipoprotein cholesterol, triglycerides, revascularization, creatinine, medications at discharge, and length of stay, DeFilippis et al. found that the adjusted hazard ratio for cardiovascular events was 2.09 [95% confidence interval (CI) 1.25−3.50; $p = 0.005$] for marijuana (27). They also noted the confounder of cigarette smoking with marijuana users significantly more likely to use tobacco (70.3% versus 49.1%; $p < 0.001$) than other participants. While cigarette smoking was strongly linked to marijuana use, the hazard ratio for marijuana and cardiovascular events was higher than for smoking tobacco cigarettes alone. Compared to a healthy nonsmoker, the adjusted hazard ratio in a current smoker was 1.7 (95% CI 1.3–2.2) for all-cause cardiovascular disease (45). The study was conducted in Massachusetts between 2000 and 2016, when recreational cannabis use was illicit there. Despite consequent concerns about participants not disclosing cannabis use, an increased incidence of cardiovascular events with a worse prognosis was observed among cannabis users.

In a recent study, Wei et al. described the adverse effect of Δ^9-THC on the cardiovascular system using data from the UK Biobank, as well as from in vitro and in vivo models (46). Previous studies that showed a link between cannabis and cardiovascular disease were small and retrospective (27). The largest prospective cohort study to date, the UK Biobank, includes genetic and phenotypic data on 500,000 individuals ages 40 to 69 (47), thus providing a unique opportunity to

characterize relationships among clinical phenotypes. The UK Biobank analysis revealed an increased incidence of myocardial infarction for cannabis users under age 50 (0.53% versus 0.45%). Prior studies demonstrating an association between cannabis use and myocardial infarction were conducted on individuals who developed myocardial infarction before age 50 (27). Wei et al. (46) controlled for age, body mass index, and sex and developed a logistic regression model revealing that cannabis use was a statistically significant positive predictor for myocardial infarction. O-link analysis of blood from acute marijuana smokers found that 13 inflammatory cytokines associated with cardiovascular disease were elevated (46).

Using induced pluripotent stem cell (iPSC) disease modeling (48), Wei et al. (46) discovered that Δ^9-THC caused toxicity, inflammation, and oxidative stress in iPSC-derived endothelial cells. Using siRNA and CRISPR interference knockdown of CB1 expression, they showed that the effects of Δ^9-THC were dependent on CB1. The adverse effects of Δ^9-THC were attenuated by CB1 antagonists such as rimonabant, which is associated with psychiatric side effects. However, virtual ligand modeling discovered that genistein is also a CB1 antagonist and could attenuate Δ^9-THC-mediated inflammation and oxidative stress in iPSC-derived endothelial cells. Previous studies by Steffens et al. showed that low-dose Δ^9-THC (1 mg/kg administered orally) was associated with reduced progression of atherosclerosis in *LDLR*$^{-/-}$ mice (49). At low doses, the maximum concentration (c_{max}) of Δ^9-THC was 6 ng/mL and acted as an agonist of CB1 and CB2; CB2 antagonists abrogated these effects. However, in a 3.5% marijuana cigarette, the c_{max} concentration of Δ^9-THC was 169 ng/mL (50). Moreover, marijuana is now cultivated to produce higher concentrations of Δ^9-THC, and e-cigarettes allow for vaping up to 85% Δ^9-THC. Using the *LDLR*$^{-/-}$ and *ApoE*$^{-/-}$ mouse model, Wei et al. showed that intraperitoneal administration of Δ^9-THC at 1 mg/kg achieved a c_{max} dose of 130 ng/mL and caused endothelial dysfunction and atherosclerosis (46). More importantly, genistein ameliorated Δ^9-THC-mediated inflammation, oxidative stress, and inflammation. This study was significant as it provided a mechanistic link between Δ^9-THC and atherosclerotic cardiovascular disease.

Cardiomyopathy

Case reports and case series have described cannabis-induced cardiomyopathy (51). The link between cardiovascular disease and cannabis suggests that ischemic cardiomyopathy will increase with cannabis use. However, preclinical evidence that cannabinoids cause cardiotoxicity is conflicting. Rajesh et al. found that CB1 activation promoted the pathogenesis of diabetic cardiomyopathy in a mouse model of diabetic cardiomyopathy (37). However, Wei et al. found that Δ^9-THC had no toxicity in primary cardiomyocytes, iPSC-derived cardiomyocytes, or a mouse model (46). Δ^9-THC had minimal or no effect on contractility or beat rate in engineered heart cells composed of iPSC-derived cardiomyocytes and endothelial cells. RNA sequencing data sets found no significant effects on iPSC-derived cardiomyocytes or endothelial cells. Moreover, C57BL/6J mice exposed to 1 mg/kg Δ^9-THC via intraperitoneal delivery for 1 month showed no evidence of cardiovascular dysfunction as assessed by echocardiography that interrogated systolic function and diastolic function using speckle tracking strain imaging.

Arrhythmias

Cannabis is associated with both supraventricular and ventricular arrhythmia. Multiple animal models and clinical data demonstrate immediate effects of tachycardia and hypertension, followed by bradycardia and hypotension with marijuana use (52). Despite lower blood pressure, cannabis users are at risk for dysrhythmias, including atrial fibrillation, atrial flutter, atrioventricular block, premature ventricular contractions, premature atrial contractions, ventricular tachycardia, and

ventricular fibrillation (53). With legalization and increased use of cannabis, cannabis use disorder is now associated with more arrhythmias, such as atrial fibrillation, requiring hospitalization and placing patients at a higher risk of stroke and embolic events (54, 55). Interestingly, the arrhythmias are more common in younger patients with cannabis use disorder, suggesting that the effects are due to the toxicity of cannabis. The precise mechanisms of the cannabis-induced arrhythmias are unclear and therefore merit further investigation given the severe consequences of arrhythmias, such as atrial fibrillation causing stroke with potentially significant changes in quality of life for younger users.

ADVERSE PULMONARY EFFECTS OF CANNABIS

Widespread use of marijuana has highlighted the need to learn more about its potential deleterious side effects, particularly those affecting the respiratory system. Smoking is a major cause of cardiopulmonary disease, the leading cause of death worldwide (56). The harm from conventional cigarettes is from the combustion of tobacco products, exacerbated by long-term use due to nicotine addiction, which can lead to acute and long-term adverse changes in the lung, including chronic obstructive pulmonary disease (COPD), emphysema, idiopathic pulmonary fibrosis, and pulmonary hypertension (57). Smoking cannabis increases the respiratory burden of carbon monoxide and tar compared to traditional cigarettes (58). Moreover, cannabis and tobacco are often consumed together (59). Hancox et al. speculate that by mixing tobacco and cannabis, smokers can inhale more deeply and experience enhanced psychoactive effects and increased acute exposure to toxins (60). With deeper inhalation, cannabis users are at a higher risk of developing COPD and experiencing a more rapid decline in pulmonary function (61). The combined or synergistic effects of nicotine and Δ^9-THC on the cardiopulmonary system are unclear and need further investigation. While the detrimental effects of conventional cigarette smoke are now well documented, the toxicities of e-cigarettes remain poorly understood (62).

E-cigarettes and other electronic nicotine dispenser systems are popular particularly among younger users (62). E-cigarettes do not produce carbon monoxide or toxins associated with conventional cigarettes. Because e-cigarettes do not involve combustion, they are speculated to aid in smoking cessation without some of the adverse effects of conventional cigarettes (62). However, the debate about whether e-cigarettes will provide long-term benefits or harm is ongoing, with limited data on the pulmonary effects (63). Although the components are toxic, the potentially adverse effects of e-cigarette liquids on the cardiopulmonary system are largely unknown. Given the increasing popularity of flavored e-cigarettes, their components and potential health risks must be studied systematically. E-cigarette and vaping-related acute lung injury (EVALI) has recently emerged as an urgent crisis (64). Illicit e-cigarettes are linked to the EVALI crisis. The content of illicit e-cigarettes is unknown because they do not undergo rigorous testing for contaminants as compared to commercially available sources. The US Centers for Disease Control and Prevention (CDC) estimates that over 2,500 patients have developed EVALI, with over 60 deaths from this mysterious illness (65). A breakthrough by the CDC eventually revealed the components associated with EVALI. While studying bronchoalveolar lavage specimens, investigators discovered nicotine, Δ^9-THC, and vitamin E acetate as the most common components of e-cigarettes in EVALI patients (66). However, the mechanism by which these components and others affect the pulmonary tissue is unclear.

ADVERSE NEUROPSYCHIATRIC EFFECTS OF CANNABIS

Cannabinoids are used to treat various neurological disorders, including chronic pain, neurodegenerative diseases, and epilepsy. However, cannabinoids can also cause adverse neuropsychiatric

effects. The effects are both acute and chronic, and their incidence is increasing as a consequence of legalization.

Acute cannabis use causes sedation, analgesia, hypothermia, and hypomobility (67). Cannabis intoxication can impair motor coordination and judgment while producing euphoria and anxiety. Heavy cannabis use may alter neurological pathways and lead to addiction via the psychoactive component of cannabis, Δ^9-THC (68). Withdrawal symptoms are also reported in a subset of patients (69).

Cannabis misuse has increased incidences of intoxication and cannabis hyperemesis syndrome (70). Chronic cannabis use causes dysregulation of the neuronal pathways in the central and enteric nervous systems, resulting in cyclical nausea, vomiting, and abdominal pain after cannabis use (71). The presentation resembles cyclical vomiting and can resolve with cannabis cessation.

Cannabis use disorder is the continued use of cannabis despite harm to the user or impaired social functioning (72). Cerda et al. found an increase in cannabis use disorder with legalization (73). Cannabis use disorder rose from 2.18% to 2.72% in respondents aged 12 to 17. In comparison, among respondents over 26 years of age, the proportion who reported an increase in frequent recreational cannabis use grew from 2.13% to 2.62%, and the proportion reporting cannabis use disorder increased from 0.9% to 1.23%.

Cannabinoids are associated with psychiatric conditions, including psychosis and mood disorders. Patients who use cannabis are more likely to have anxiety, depression, and bipolar disorder (74). Acutely, cannabis causes euphoria, but chronic use might perturb neurological pathways and cause mood disorders. However, cannabis use might be confounded with bipolar disorder and mitigate impulsive behavior (75), although cannabis use is associated with a higher rate of suicide in bipolar disorder.

Cannabis is also linked with psychosis. Using logistic regression analysis, Di Forti et al. found a link between high-potency cannabis use and the development of psychotic disorders (76). Exogenous cannabinoids affect the development of the central nervous system in rats, cause cognitive deficits, and alter cortical gene expression (77). A genetic variation of *AKT1* that affects dopamine signaling was found to increase the risk of psychosis in chronic cannabis users (78).

TRAUMA AND OVERDOSE

In the United States, motor vehicle accidents are a leading cause of mortality. Alcohol intoxication and, more recently, distracted driving while using cellular phones and other personal devices are associated with increased traffic accidents and fatalities (79). Cannabis intoxication is also associated with motor vehicle accidents (80). While acute alcohol intoxication can be detected with a breathalyzer or blood test, detecting cannabis intoxication is more difficult and requires novel methods (81, 82). Because cannabis can remain detectable in blood, saliva, and urine for hours to days, it is difficult to distinguish between acute intoxication and chronic use.

Misadventure is now being reported with cannabis edibles. Unlike smoking or vaping, edibles appear innocuous and are easy for anyone to ingest regardless of experience or age. A recent report suggests that pediatric emergency department visits have increased in Canada since the legalization of cannabis due to unintentional ingestion of cannabis (83). Pediatric patients present with analgesia and sedation, which can be fatal.

ADVERSE EFFECTS OF CANNABIS ON REPRODUCTION AND FERTILITY

Cannabis affects male fertility and conception. A systematic review found that chronic marijuana exposure reduced male fertility due to lower sperm count and abnormal sperm morphology,

mobility, and viability (84). Harlow et al. report that male preconception use of cannabis is associated with spontaneous abortion (85). Compared to nonusers, male users of cannabis at more than once per week increased the hazard ratio of spontaneous abortion by 2.0 (95% CI 1.2–3.1).

Prenatal exposure to cannabinoids can affect fetal development. Pregnant women frequently experience nausea and vomiting. Hyperemesis gravidarum is protracted nausea and vomiting that is only partly responsive to antiemetic medications. Cannabis is considered a benign herbal antiemetic and was recently found to significantly improve symptoms of hyperemesis gravidarum (86). However, the potential effects on the fetus are concerning. The CDC recommends against using marijuana during pregnancy because it is associated with abnormal neurological development and low birth weight (87). A systematic review found that prenatal exposure to cannabis is associated with maternal anemia, low birth weight, low neonatal length, and premature gestational age (88). Furthermore, Roncero et al. found a link between prenatal cannabis exposure and developmental and mental disorders in children, such as attention deficit hyperactivity disorder and depression (89).

CANNABIS AND MALIGNANCY

Cannabinoids are approved for treating cancer symptoms, including pain, nausea, and vomiting (90). Preclinical evidence suggests that cannabinoids might be effective therapy for glioblastoma multiforme, colon cancer, skin cancer, prostate cancer, and breast cancer (90). However, the clinical data on the efficacy of cannabinoids in cancer are unclear. There is a paucity of clinical trials showing cannabis improves cancer survival. After tumor debulking, only a single study on glioblastoma multiforme showed that Δ^9-THC treatment caused a reduction in angiogenesis and tumor growth when assessed with magnetic resonance imaging on post-treatment biopsies (91).

Recent evidence suggests a link between marijuana use and cancer. A systematic review and meta-analysis found an association between marijuana use and cancer (92); while there was no association with head and neck cancer or oral cancer, testicular germ cell tumor was linked to marijuana use (odds ratio 1.36; 95% CI 1.03–1.81; $p = 0.03$; $I^2 = 0\%$). The study was underpowered to link marijuana use with lung cancer. However, a case-control study found that cannabis was associated with lung cancer (93). After adjusting for tobacco smoking, the risk of lung cancer increased with higher cannabis use. With legalization and increased use, the link between cancer and marijuana is expected to become more pronounced in the future and warrants further investigation.

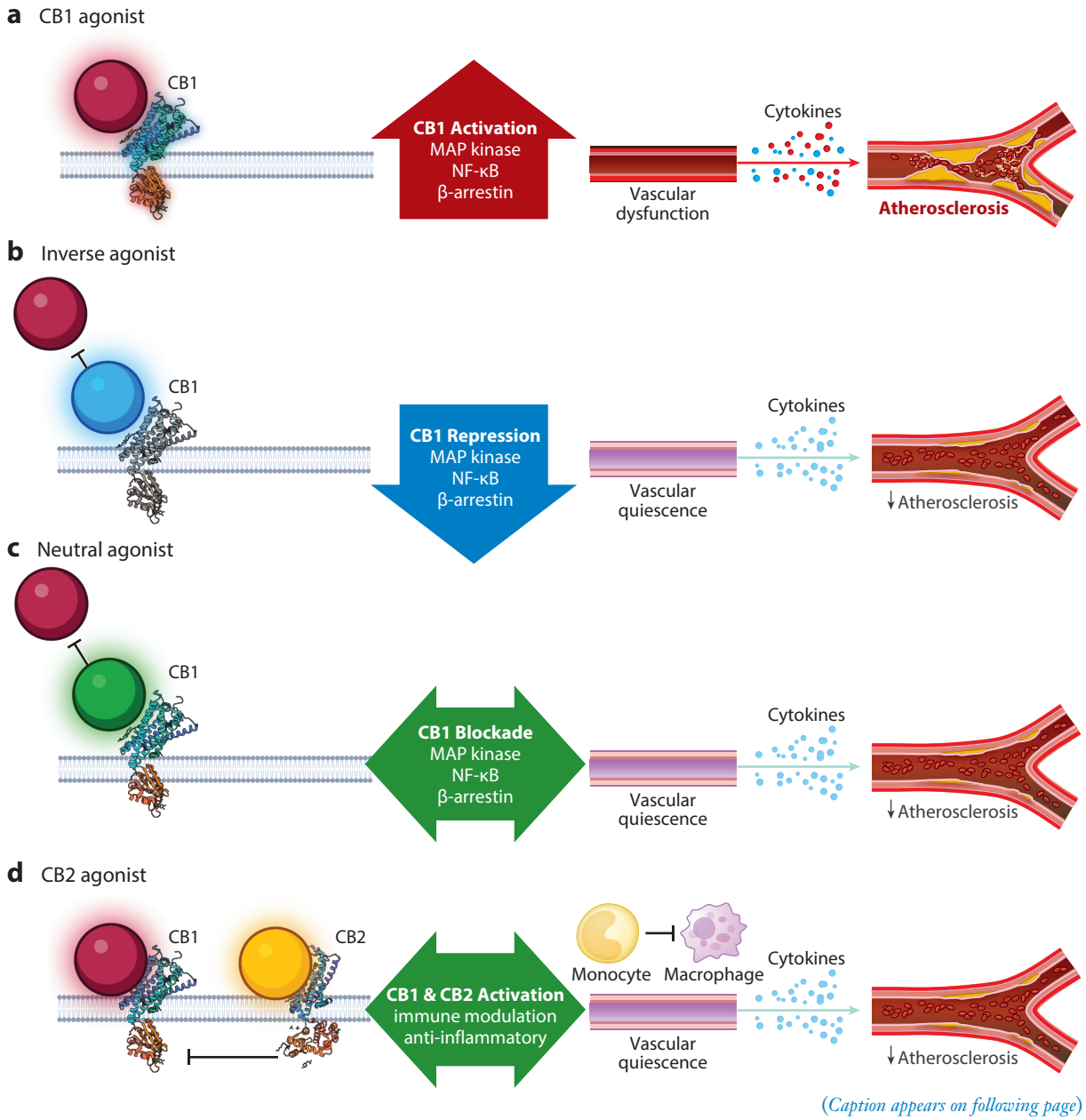
CONCLUSION

Cannabis has been cultivated for thousands of years for recreation and medical therapy. In the early twentieth century, legal restrictions limited its consumption. Over the past 20 years, decriminalization and legalization have increased the availability of cannabis. Medicinal marijuana may benefit patients with chemotherapy-induced nausea and vomiting, HIV-induced cachexia, and neurodegenerative disorders. However, restrictions continue to limit research into the efficacy of medical marijuana. Preclinical studies and emerging epidemiological data suggest cannabis is expected to affect human health adversely in multiple ways.

At the beginning of the twentieth century, tobacco cigarettes were incorporated into the American lifestyle and spread worldwide. We now know this led to dramatic increases in respiratory disease, cancer, and cardiovascular disease that caused millions of deaths. Cannabis might have medicinal benefits, but no medication is without side effects or adverse effects. Growing evidence suggests that expanding cannabis use will likely exacerbate cardiopulmonary disease and malignancy in the future. Historically, criminalizing cannabis has led to a disparity in enforcement

among racial groups. The incremental public health benefit of criminalizing cannabis might be outweighed by the social cost. More importantly, there is a lack of evidence to support such measures. Further research may also point to CB1 antagonists and CB2 agonists as a potential novel class of medical therapies (**Figure 2**).

The CB2 receptor is expressed mainly in immune and hematopoietic cells but also in peripheral cells, tissues, and organs including the central nervous system, enteric nervous system, heart, vasculature, liver, and pancreas (94). CB2 agonists modulate immune function and attenuate



(*Caption appears on following page*)

Figure 2 (*Figure appears on preceding page*)

Modulation of cannabinoid receptor activity. (*a*) Cannabinoid receptor 1 (CB1) agonists activate the CB1 receptor, causing inflammation, oxidative stress, and atherosclerosis. A CB1 agonist such as delta-9-tetrahydrocannabinol (Δ^9-THC) (*red sphere*) binds to the CB1 receptor and activates the G protein–coupled receptor (GPCR), causing inhibition of adenylyl cyclase, phosphorylation of mitogen-activated pathway (MAP) kinase, translocation of nuclear factor–kappa B (NF-κB) to the nucleus, and activation of β-arrestin pathways. CB1 activation ultimately causes increased expression of inflammatory cytokines and oxidative stress, which promote atherosclerosis. (*b*) A CB1 receptor inverse agonist binds the agonists and prevents them from binding the CB1 receptor, modulates receptor function, and attenuates CB1-mediated atherosclerosis. An inverse agonist such as rimonabant (*blue sphere*) blocks CB1 agonist binding (*red sphere*) and downregulates CB1 receptor activity via the GPCR, thus preventing inhibition of adenylyl cyclase, MAP kinase phosphorylation, NF-κB translocation to the nucleus, and β-arrestin pathway activation. Consequently, inverse agonists abrogate inflammation, oxidative stress, and atherosclerosis, which are mediated by CB1 agonist interactions. (*c*) A neutral antagonist blocks CB1 agonist binding and attenuates CB1 mediated atherosclerosis. A neutral antagonist such as genistein (*green sphere*) blocks the CB1 agonist (*red sphere*) without affecting the CB1 receptor or downstream pathways. Neutral antagonists also abrogate CB1-mediated inflammation, oxidative stress, and atherosclerosis. (*d*) CB2 agonists attenuate the adverse effects of CB1 activation by modulating the immune system, inflammation, and oxidative stress, thus preventing atherosclerosis. A CB2 agonist such as JWH 133 (*yellow sphere*) binds the CB2 receptor and counteracts the effects of a CB1 agonist (*red sphere*) binding the CB1 receptor by decreasing MAP kinase phosphorylation, preventing NF-κB translocation, and modulating β-arrestin pathways. Because CB2 receptors are expressed on immune cells and the vasculature, CB2 agonists prevent the transformation of monocytes into macrophages in addition to suppressing vascular inflammation and oxidative stress, thereby promoting vascular quiescence and preventing atherosclerosis. Figure adapted from images created with BioRender.com.

vascular inflammation (95). Thus, CB2 agonists might be beneficial for treating inflammatory diseases such as inflammatory bowel disease, atherosclerosis, sepsis, traumatic brain injury, pain, and neurodegenerative diseases (96).

Novel CB1 antagonist therapies might mitigate the adverse effects of cannabis caused by Δ^9-THC. CB1 signaling is involved in various pathophysiological processes, including smoking cessation, obesity, diabetes, coronary artery disease, atherosclerosis, liver cirrhosis, and cancer (34). CB1 antagonists are capable of attenuating Δ^9-THC-mediated inflammation and oxidative stress. Experimental and clinical evidence supports the therapeutic potential of CB1 antagonists.

In 2006, rimonabant (Acomplia®) became the first CB1 antagonist approved in Europe for treating obesity (97). However, rimonabant was withdrawn in 2008 due to severe psychiatric side effects (98). Second- and third-generation compounds derived from rimonabant thus far have failed to translate to the clinic because of concerns about psychiatric effects and efficacy (99). To reduce the psychiatric side effects, pharmaceutical companies developed peripherally restricted CB1 antagonists with limited blood-brain barrier permeability and, in theory, less central nervous system exposure (100). Despite the restricted bioavailability, psychiatric side effects could not be completely excluded. Therefore, continuing efforts to discover novel CB1 antagonists with therapeutic potential that lack psychiatric side effects will be clinically important with the rapid growth of cannabis use worldwide.

DISCLOSURE STATEMENT

J.C.W. is a cofounder and a member of the Scientific Advisory Board of Greenstone Biosciences, and M.C. is a consultant for Greenstone Biosciences. This article was written independently of Greenstone Biosciences.

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