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Review article

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The relationship between cannabis and cardiovascular disease: clearing the haze

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Abstract

Cannabis has been consumed for centuries, but global regulatory changes over the past three decades have increased the availability and consumption of cannabis. Cannabinoids are touted to have therapeutic potential for many diseases and could be a replacement for opioids for analgesia and sedation. However, cannabinoids can cause substantial adverse cardiovascular events that would mitigate any potential benefit. The endocannabinoid system regulates mood, satiety and memory, and modulates the cardiovascular system. The link between cannabinoids and cardiovascular disease, which used to be limited to evidence from preclinical studies, case reports and case series, is now evident in epidemiological studies. Cannabinoids adversely affect the cardiovascular system, causing myocardial infarction, cerebrovascular accidents, arrhythmia and heart failure. The effects of novel cannabinoids are unknown, and synthetic cannabinoids have the potential to cause even more substantial harm than traditional cannabinoids. Therefore, with the increasing availability and use of cannabis, the acute and chronic effects of this drug are becoming apparent.

Sections

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Key points

- Cannabis use has increased as a result of decriminalization and legalization, but the cardiovascular effects need research to inform public health policies.
- Cannabis, via cannabinoid receptor 1 (CB_1)-mediated oxidative stress and inflammation, is linked to adverse cardiovascular outcomes, including myocardial infarction, arrhythmias and cardiomyopathy.
- CB_1 antagonists and CB_2 agonists are promising novel treatments for cardiovascular risk factors and cardiovascular disease, but clinical translation is complicated by adverse effects and limited data.
- Synthetic cannabinoids (such as 'K2' and 'Spice') are an emerging public health concern owing to their potent toxicity and cardiovascular implications.
- The co-use of cannabis and tobacco has synergistic adverse effects on cardiovascular health and addiction potential.
- Induced pluripotent stem cell modelling and genetic tools should be used to discover novel cannabinoid signalling pathways and potential new therapeutic targets for cardiometabolic disease.

Introduction

Cannabis has been cultivated for thousands of years for recreational and medicinal uses and is consumed in various modalities, including smoking, hookah, vaping and edibles[1–4]. In the early twentieth century, government prohibition limited its widespread consumption. Since the 1988 United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, decriminalization and legalization have increased the availability of cannabis, and its use is expected to increase dramatically worldwide[1,2].

The effects of cannabis are mediated by cannabinoid receptor 1 (CB_1) and CB_2, which belong to the G protein-coupled receptor (GPCR) superfamily[5] (Fig. 1). CB_1, the most abundant GPCR in the brain[6], is also expressed in peripheral tissues, including the heart and vasculature, and is implicated in atherosclerosis[7]. CB_2 is expressed largely in immune cells and the vasculature, and loss of the CB_2 receptor exacerbates atherosclerosis[8,9].

Cannabis is a complex mixture of more than 500 compounds, including more than 100 cannabinoids. Δ^9-Tetrahydrocannabinol (Δ^9-THC), the main psychoactive component of cannabis, and cannabidiol (CBD) are the most abundant cannabinoids in cannabis. Novel synthetic cannabinoids were developed as research tools but shifted to recreational use in 2008 (ref. 10). Medical cannabinoids are being studied for treating chronic pain, epilepsy, sleep disorders, chemotherapy-induced nausea and vomiting, HIV-induced cachexia and neurodegenerative disorders[11–13]. Cannabis has been proposed as an alternative to opioids, which are associated with addiction and overdose, with some concerns that cannabis can increase opioid addiction[14,15]. The development of CB_1 antagonists and CB_2 agonists might further the treatment of a broad range of diseases, including obesity, metabolic syndrome and atherosclerosis, but legal restrictions continue to limit research. Of particular interest to cardiovascular health are medical marijuana and synthetic cannabinoids[11,16], the use of which is associated with adverse cardiovascular effects[17]. Although the long-term cardiovascular effects of using cannabis are emerging, several gaps in our knowledge merit further investigation[18].

In this Review, we focus on the following areas: the evolution in cannabis regulation that has changed public perceptions of cannabis and increased cannabis use; the endocannabinoid system, cannabinoid receptors and cannabinoid receptor therapies that might ameliorate cardiovascular disease; the effects of cannabis on cardiovascular risk factors, atherosclerotic cardiovascular disease, cardiomyopathies and arrhythmias; and the impact of traditional, hemp-derived and synthetic cannabinoids on cardiovascular health.

Cannabis regulation

Cannabis is one of the most popular recreational drugs, and its regulation has changed dramatically over time. In the twentieth century, various prohibition movements around the world banned the consumption of alcohol, cannabis and other recreational drugs[19,20]. With changing societal perceptions towards cannabis use, global restrictions on the medicinal and recreational use of cannabis have eased (Fig. 2). The compassionate use of medical marijuana has been permitted for individuals with chronic pain, neurodegenerative disorders, cachexia and epilepsy. For example, the FDA has approved the clinical use of dronabinol, nabilone and CBD. Medical marijuana is legal in 38 states in the USA, and recreational use is legal in 24 states, two territories and the District of Columbia[4]. Nonetheless, federal laws criminalizing and restricting cannabis are still in effect, thereby conflicting with state laws in most of the USA.

Until it is reclassified, cannabis is a Schedule I drug under federal law in the USA, and the FDA's scientific determination guides the Drug Enforcement Agency[21]. The 2018 Agriculture Improvement Act (or 'Farm Bill') legalized hemp with <0.3% Δ^9-THC. The Farm Bill has added substantial ambiguity to the use of hemp-derived CBD, as well as synthetic cannabinoids such as Δ^8-THC, which can be derived from CBD. The US Department of Justice reported potential plans to reclassify cannabis as a Schedule III drug, which would allow more research, but the production, distribution, sale and possession of recreational cannabis would probably remain illegal under these proposed changes[22].

Worldwide, cannabis regulation and enforcement are highly heterogeneous. In the Far East, Middle East and former Soviet republics, cannabis remains illegal[23]. However, over the past five decades, cannabis regulation in other regions has eased considerably. In Netherlands, cannabis was decriminalized in 1972. To date, nine other countries have legalized recreational cannabis use: Canada, Georgia, Germany, Luxembourg, Malta, Mexico, South Africa, Thailand and Uruguay. More than 40 countries have legalized the medical use of cannabis, but regulations vary depending on the type of cannabis pharmaceutical agent[24].

With less stigma and greater acceptance, cannabis use has increased relative to other illicit drugs[25,26]. *Forbes* estimates that revenues from legitimate sales of cannabis rose to US $54 billion in 2022 in the USA alone[27]. After legalization, the Government of Canada found that cannabis use increased from 22% in 2018 to 27% in 2022 (ref. 28). Cannabis use rose around the world during the coronavirus disease 2019 pandemic, with corresponding increases in adverse psychiatric and clinical outcomes[29].

The endocannabinoid system

CB_1 and CB_2 are the most abundant GPCRs in the central nervous system and are also found throughout the body, including in the cardiovascular system[7]. Endocannabinoids are arachidonic acid derivatives and

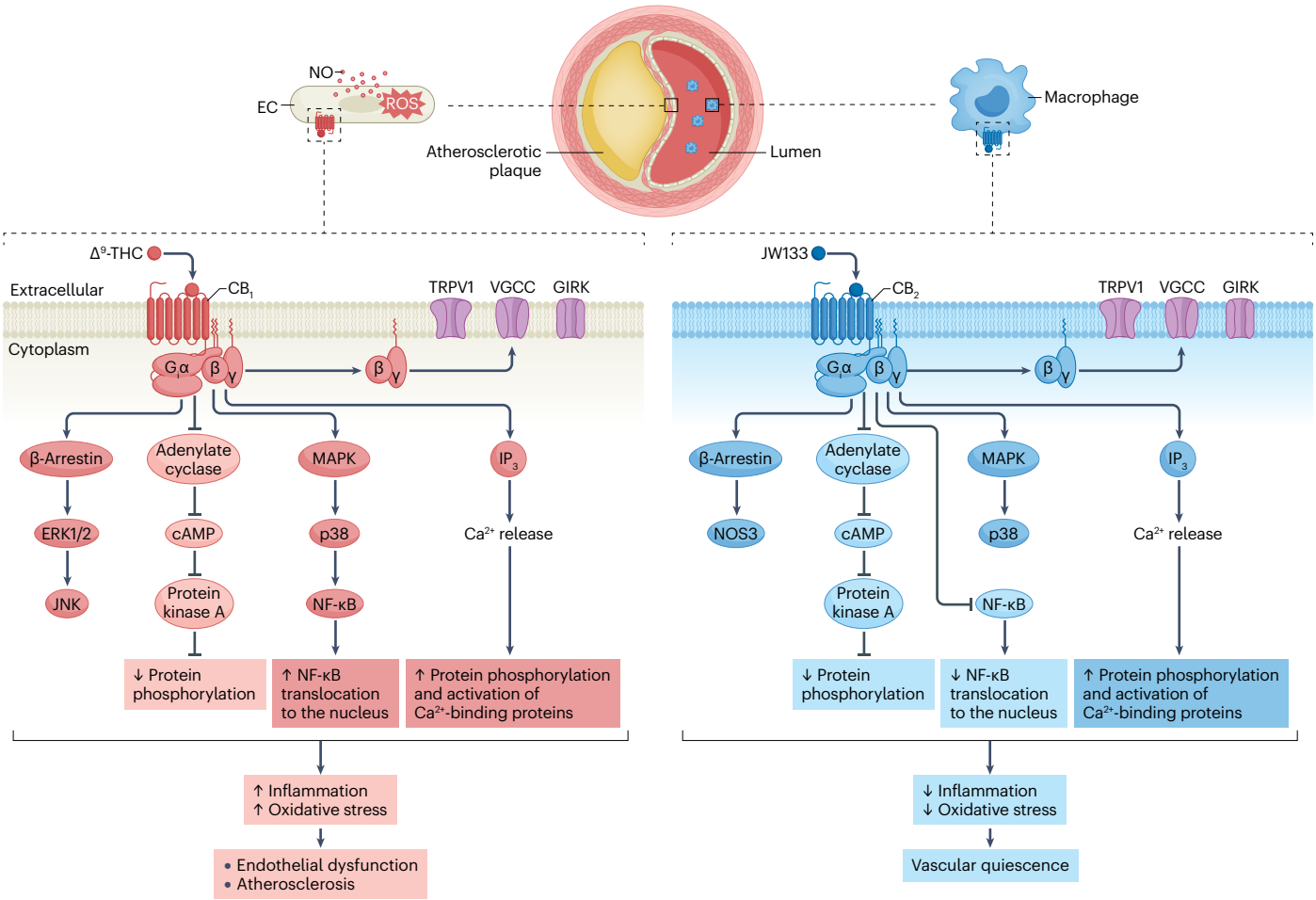


Fig. 1 | Mechanism of action of cannabinoids on cardiovascular health. When Δ^9-tetrahydrocannabinol (Δ^9-THC) binds to cannabinoid receptor 1 (CB_1), the G protein-coupled receptor (GPCR) is activated, and the $G_{i/o}$ complex dissociates into the $G_i\alpha$, βγ and β-arrestin subunits, which regulate heart rate, blood pressure, hypertension, atherosclerosis and cardiomyopathy[145]. The $G_i\alpha$ subunit inhibits adenylate cyclase and blocks cAMP production, which prevents phosphorylation of protein kinase A and downstream effects of protein kinase A on transcription. β-Arrestin modulates extracellular signal-regulated kinase 1 and 2 (ERK1/2; also known as MAPK3 and MAPK1, respectively) and c-JUN amino-terminal kinase (JNK) pathways. The βγ subunit activates the mitogen-activated protein kinase (MAPK) pathway, promotes the translocation of nuclear factor-κB (NF-κB) to the nucleus, activates the transcription of genes encoding pro-inflammatory factors and suppresses the transcription of genes encoding factors that protect against oxidative stress. Therefore, CB_1 agonists promote endothelial dysfunction and atherosclerosis. Cannabinoid receptor 2 (CB_2) agonists, such as JW133, activate the GPCR and cause dissociation of the subunits. The βγ subunit activates the MAPK–p38 pathway but prevents translocation of NF-κB to the nucleus. Consequently, the transcription of pro-inflammatory genes is not activated, and the transcriptional status of oxidative stress-protective genes is not perturbed. CB_2 agonism causes endothelial cells (ECs) to produce nitric oxide (NO) and other vasoactive substances that modulate blood pressure. β-Arrestin promotes nitric oxide synthase 3 (NOS3) production and, consequently, NO release, leading to vascular quiescence. The binding of agonists to CB_1 and CB_2 also modulates various channels, including transient receptor potential cation channel subfamily V member 1 (TRPV1), voltage-gated calcium channel (VGCC), G protein-coupled inwardly rectifying potassium channel (GIRK), and sodium and potassium channels, activating the inositol trisphosphate (IP_3) pathway that causes calcium release, protein phosphorylation and activation of calcium-binding proteins. ROS, reactive oxygen species.

endogenous ligands for cannabinoid receptors. The principal endocannabinoids are 2-arachidonoylglycerol and anandamide (arachidonoyl ethanolamide), which are synthesized on demand. Endocannabinoid signalling is important for maintaining physiological homeostasis. Endocannabinoids affect memory, mood and pain in the central nervous system[30]. Endocannabinoids are also important for regulation of metabolism and the cardiovascular system[31].

CB_1 stimulation has acute haemodynamic effects, including increasing heart rate and blood pressure, myocardial contractility and vascular tone[10]. These effects are dose-dependent and can be both central and peripheral[32]. In pathological conditions such as shock, cardiomyopathies and heart failure, elevated plasma endocannabinoid levels can exacerbate hypotension[33,34]. CB_1 is expressed at low levels in various cardiac cell types, including cardiomyocytes, endothelial cells, vascular smooth muscle cells, fibroblasts and neural elements in mouse and human hearts[35]. Under pathological conditions, CB_1 expression can be upregulated, contributing to stress signalling, cell death, inflammation, oxidative stress and fibrogenesis[36–38].

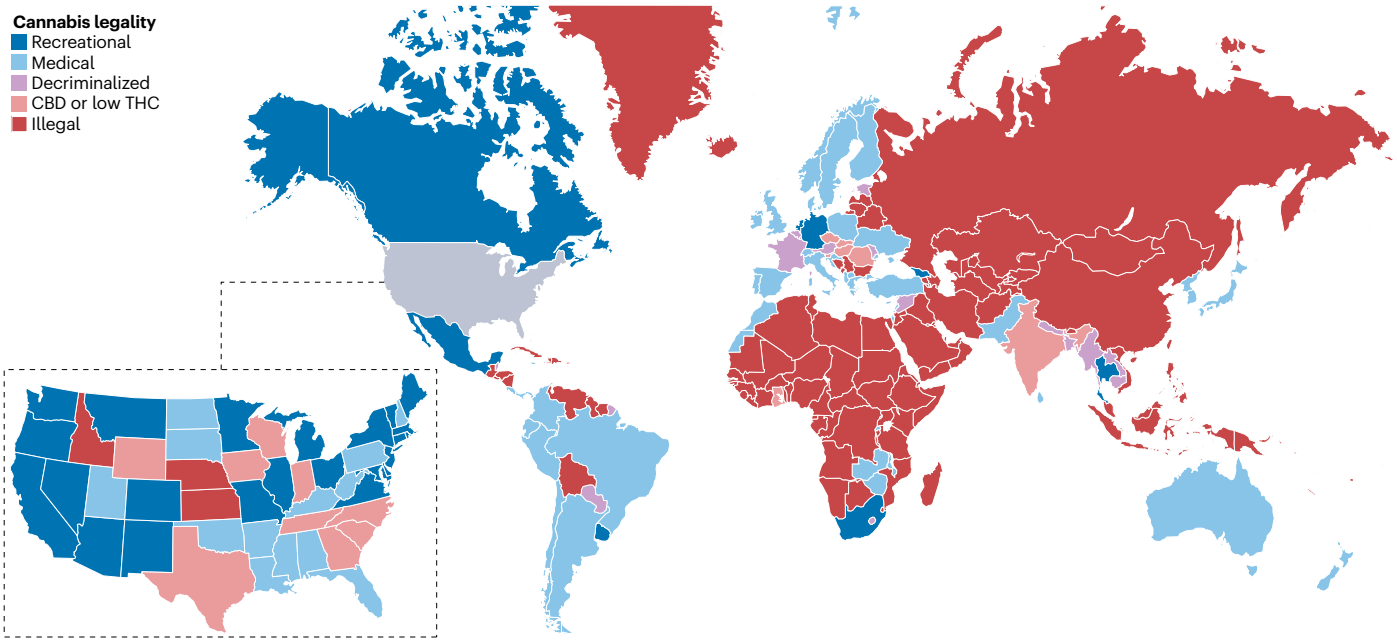


Fig. 2 | The legal status of cannabis around the world. The regulation of cannabis varies considerably worldwide and is changing together with perceptions of the safety and usage of the drug. CBD, cannabidiol; THC, tetrahydrocannabinol.

By contrast, CB_2 stimulation does not produce substantial haemodynamic effects. Healthy mouse or human hearts have negligible CB_2 expression[39,40]. However, under pathological conditions, CB_2 can be upregulated in endothelial cells and infiltrating immune cells, attenuating vascular inflammation, inflammatory cell infiltration and pro-inflammatory responses[39–41].

Other putative receptors for cannabinoids exist, such as the transient receptor potential (TRP) channels such as TRPV1. These channels are a superfamily of transmembrane ion channels that function in signal transduction in response to physical and chemical stimuli. TRP channels are implicated in sensory perception and cellular physiology[42]. Other non-cannabinoid receptors include orphan GPCRs such as GPR18 and GPR55, nicotinic acetylcholine receptors, 5-HT_3 receptors, glycine receptors, calcium channels, potassium channels, sodium channels, and peroxisome proliferator-activated receptor-α (PPARα) and PPARγ[43].

Cannabinoid receptor therapeutics

CB_1 antagonists can attenuate cannabis-induced adverse cardiovascular effects. In preclinical models and clinical trials, CB_1 antagonists were shown to ameliorate obesity, metabolic syndrome, diabetes mellitus and atherosclerosis[7]. However, CB_1 antagonists have not been translated from preclinical models into the clinic. Rimonabant (an inverse agonist of CB_1) was approved for treating obesity[44], but was later withdrawn from phase II clinical trials when participants reported anxiety and depression[45]. Rimonabant has high penetration into the central nervous system and is likely to antagonize CB_1 activity implicated in mood and affect. Second-generation CB_1 antagonists were developed with lower penetrance into the central nervous system, thereby avoiding adverse psychiatric effects, but these modifications also decreased efficacy. Third-generation CB_1 antagonists are designed with alternative mechanisms of action to reduce cardiovascular adverse effects[46]. So far, these CB_1 antagonists have not entered clinical use because of concerns about adverse psychiatric effects. However, the peripherally restricted CB_1 inverse agonist INV-202 has been tested in a phase Ib clinical trial and reduced body weight and improved metabolic function without serious adverse effects, presenting a potential novel therapy for metabolic syndrome[47].

CB_2 agonists are promising pharmacological agents for treating inflammatory diseases such as cardiovascular disease, pain, inflammatory bowel disease and neurodegenerative disease, with further therapeutic potential in metabolic disease, diabetes, osteoporosis and cancer[48–50]. CB_2 has low levels of expression in the central and peripheral nervous systems[51]. Therefore, the effects of CB_2 agonists are predominantly peripheral, and preclinical investigations have not suggested adverse psychiatric effects. However, because of concerns about the capacity of assays to detect CB_2 and possible neuropsychiatric and off-target effects, CB_2 agonists are not in clinical use.

Cardiovascular risk factors

A strong association exists between cannabis-associated risk factors and cardiovascular disease[52]. Endocannabinoids regulate learning, memory, mood and satiety, so exogenous cannabis use can influence behaviour in ways that contribute to the development of obesity, metabolic syndrome, type 2 diabetes and other health problems. The effects of cannabinoids on various risk factors are emerging, and their mechanistic role in the pathogenesis of cardiovascular disease is distinct from that of traditional tobacco smoking.

Hypertension

The clinical effects of cannabis on hypertension are controversial. In one study, cannabis use was associated with a dose-dependent increase in systolic blood pressure[53], and there is evidence from small-animal models that endocannabinoids cause hypertension[54]. Multiple animal and human studies have shown that Δ^9-THC initially causes a transient

increase in heart rate and blood pressure, followed by bradycardia and hypotension[10,55,56]. However, cross-sectional data from the National Health and Nutrition Examination Survey from 2009 to 2018 indicated that cannabis use is not associated with a clinically significant increase in blood pressure, defined as systolic blood pressure >130 mmHg or diastolic blood pressure >90 mmHg, or the initiation of antihypertension medications in middle-aged adults[57]. In addition, multivariate linear regression analyses of the UK Biobank database of participants who used cannabis have shown that cannabis is negatively associated with hypertension ($P < 0.001$)[58]. CB_1 antagonists have been reported to increase blood pressure and left ventricular contractile performance in spontaneously hypertensive rats[59]. The hypotensive effects of cannabinoids and the endocannabinergic system are mediated by TRPV1 and might be a therapeutic target[33]. Inhibitors of fatty acid amide hydrolase 1 (FAAH) block the degradation of endocannabinoids and are associated with reduced blood pressure and improved cardiac contractility in spontaneously hypertensive rats[60]. FAAH inhibitors are a potential therapeutic strategy for treating hypertension by amplifying endogenous anandamide levels.

The nervous system, renin–angiotensin–aldosterone system, natriuretic peptide system, vascular endothelium and immune system all influence blood pressure regulation[52] (Fig. 3). CB_1 is expressed

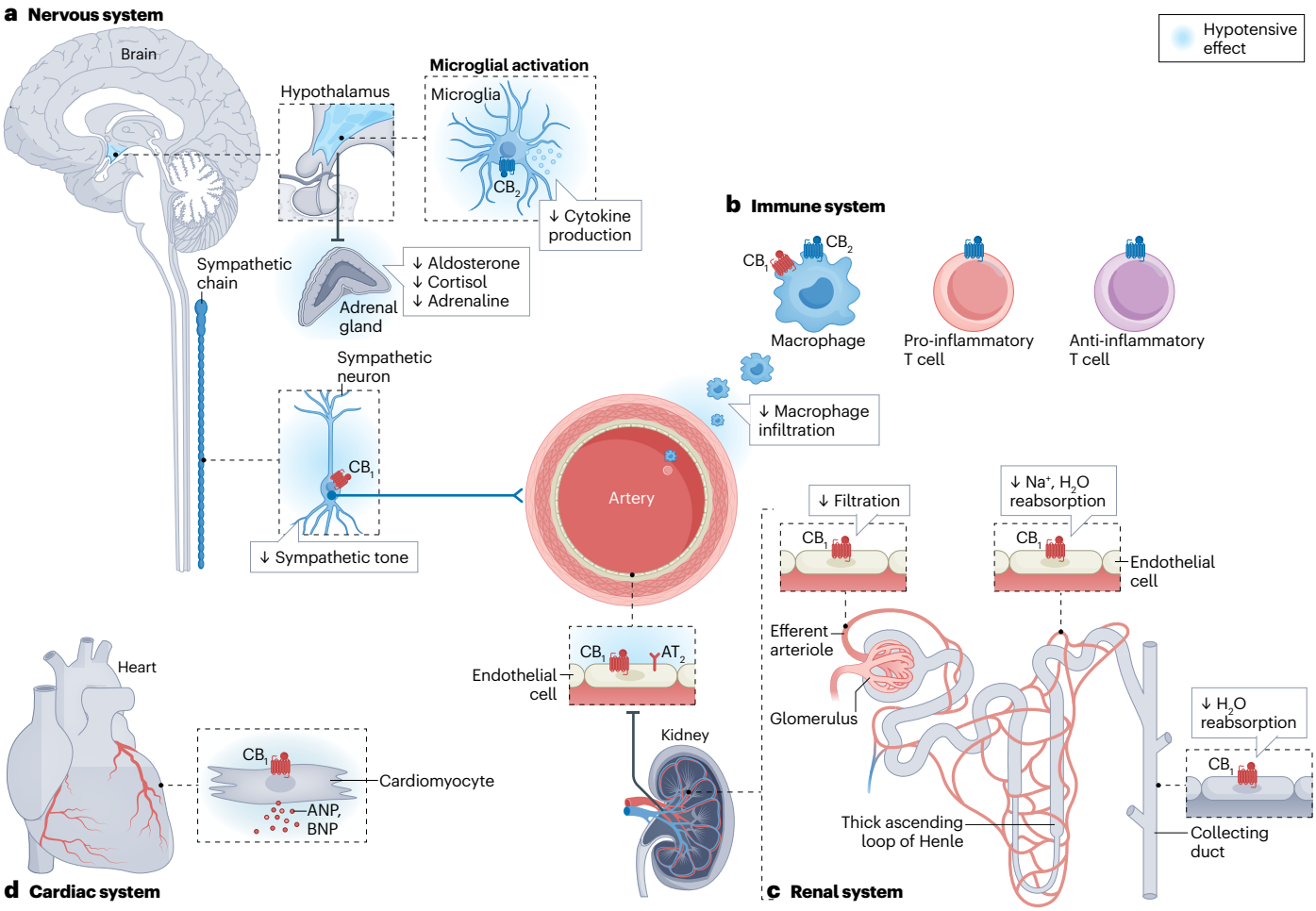


Fig. 3 | Cannabis modulates blood pressure via the nervous system, with immune, cardiac and renal inputs. a, The nervous system modulates blood pressure via the sympathetic nervous system (SNS) and hypothalamus–pituitary–adrenal axis. Acute use of cannabis is associated with transient hypertension; when baroreceptors detect arterial stretch, the SNS reduces sympathetic tone, leading to hypotension[146]. Activation of cannabinoid receptor 2 (CB_2) in the microglia of the hypothalamic paraventricular nucleus reduces neuroinflammation and promotes hypotension[65]. Cannabinoid receptor 1 (CB_1) is on parasympathetic neurons, and CB_1 has inhibitory effects on both sympathetic and parasympathetic neurons. **b**, Cannabinoids modulate immune cell function and innate and adaptive immunity via CB_1 and CB_2. CB_1 activation of macrophages is associated with hypotension. Macrophage infiltration into the artery wall is associated with hypertension, and CB_2 activation prevents macrophage infiltration, contributing to hypotension. The interplay between pro-inflammatory and anti-inflammatory T cells also modulates blood pressure. **c**, Cannabinoids are speculated to cause hypotension via CB_1-mediated inflammation and oxidative stress, leading to reduced glomerular filtration, impaired resorption of sodium and water in the ascending loop of Henle, and reduced water reabsorption in the collecting ducts. With reduced perfusion in the juxtaglomerular apparatus, the renin–angiotensin–aldosterone system is not activated, leading to reduced binding of angiotensin II to the angiotensin II receptor type 2 in the vasculature, promoting vasoconstriction[54], as well as reduced aldosterone production, causing more diuresis. **d**, In the heart, CB_1 activation causes inflammation and oxidative stress in cardiovascular cells, causing impaired myocardial contractility and the release of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), which promote diuresis and hypotension.

in macrophages and might have a role in regulating blood pressure. Macrophage-derived endocannabinoids acting on CB_1 are implicated in haemorrhagic shock[61], septic shock[62], and the hypotension associated with advanced liver cirrhosis[63,64]. CB_2 is also expressed in immune cells and might affect blood pressure regulation. The CB_2 agonist JWH133 has been reported to reduce the levels of tumour necrosis factor, IL-1β and IL-6 by inhibiting aerobic glycolysis in angiotensin II-treated BV-2 cells (a mouse microglia cell line) and to activate microglia in the paraventricular nucleus of C57BL/6J mice treated with angiotensin II, thereby suppressing neuroinflammation and ameliorating hypertension[65]. Therefore, cannabinoids can modulate the immune system and autonomic nervous system to promote hypotension and protect against aortaopathy[66].

Metabolic dysfunction

Obesity, insulin resistance, metabolic syndrome and type 2 diabetes are important risk factors for developing cardiovascular disease. The effects of cannabis on these metabolic risk factors are emerging from clinical and basic science data. Cannabis use has known links to obesity from studies in preclinical models, and clinical trials suggest that the CB_1 antagonist rimonabant could reduce body weight in individuals with obesity[44]. In one study, rimonabant was associated with significant reductions in mean body weight and waist circumference[44]. A Cochrane review found a modest reduction in body weight in four studies involving 6,635 individuals taking rimonabant, but also found substantial adverse psychiatric effects that ultimately led to its removal from the market[67]. Epidemiological studies have suggested that cannabis might protect against metabolic risk factors[68], and a meta-analysis of seven studies found that users were less likely than non-users of cannabis to develop type 2 diabetes (OR 0.48, 95% CI 0.39–0.59)[69]. However, the International Prospective Register of Systematic Reviews (PROSPERO) found no clear link between cannabis use and metabolic disease, owing to the poor quality of the evidence and the inadequate assessment of cannabis exposure[70].

Dyslipidaemia

Trials of CB_1 antagonists have suggested that cannabis use might promote dyslipidaemia. The RIO-Lipids and ADAGIO-Lipids trials[44,71] found that rimonabant treatment improves plasma lipid profiles. In a cross-sectional, case–control study, cannabis users were found to have lower plasma levels of HDL[72]. However, PROSPERO found no link between cannabis use and dyslipidaemia[70]. Further investigation is needed to clarify the effects of cannabis on plasma lipid profiles.

Cardiovascular diseases

Robust evidence from basic science and clinical studies supports the association between cannabis use and cardiovascular diseases[1,10,11,16,18]. Before the legalization and decriminalization of cannabis, only small and retrospective studies suggested that cannabis is linked to myocardial infarction (MI)[73]. Cannabis has now been shown to be associated with adverse cardiovascular events, and heavier use is associated with a greater risk[74]. In a cross-sectional study, the adjusted odds ratios for coronary heart disease (CHD), MI and cerebrovascular accident were 1.16 (95% CI 0.98–1.38), 1.25 (95% CI 1.07–1.46) and 1.42 (95% CI 1.20–1.68), respectively, for daily cannabis users compared with non-users[74]. However, less frequent use of cannabis was also associated with an increased risk of CHD, MI and cerebrovascular accident[74]. In the YOUNG-MI registry, a retrospective cohort study of young adults (aged ≤50 years) with MI, cannabis users were more likely than non-users to have a premature MI[18]. Cannabis users were more likely than non-users to concomitantly smoke tobacco (70.3% versus 49.1%; $P < 0.001$) but had a lower incidence of diabetes (10.7% versus 20.4%; $P = 0.007$), hypertension (34.4% versus 47.3%; $P = 0.006$) and hyperlipidaemia (60.0% versus 60.8%; $P = 0.022$)[18]. After adjusting for age, sex, diabetes, hypertension, peripheral vascular disease, smoking, plasma HDL cholesterol level, plasma triglyceride level, revascularization, creatinine level, medications at hospital discharge and length of hospital stay, cannabis users had an adjusted hazard ratio of 2.09 (95% CI 1.25–3.50; $P = 0.005$) for all-cause death, and an adjusted hazard ratio of 2.13 (95% CI 1.03–4.42; $P = 0.042$) for cardiovascular death[18]. The researchers attributed the increased risk of premature MI to the cannabis-induced generation of reactive oxygen species, which decreases myocardial contractility and increases vascular smooth muscle cell proliferation[18].

Prospective clinical trials have found compelling evidence that cannabis use is linked to heart disease. The Determinants of MI Onset Study (MIOS)[75] prospectively followed up 3,886 patients with MI and found that mortality was 29% higher in chronic users of cannabis than in non-users. In the UK Biobank, cannabis users had a higher incidence of premature MI (age ≤50 years) than non-users (0.53% versus 0.45%)[17]. A logistic regression model found that frequent cannabis use is a risk factor for MI when controlling for age (<50 years), BMI and sex[17]. Inflammation and oxidative stress are hypothesized to initiate the pathophysiology of atherosclerosis[76]. Using an Olink inflammation panel, blood plasma from recreational cannabis smokers was found to have higher levels of atherosclerosis-related cytokines, including CCL1, CCL4, CCL8 (also known as MCP2), CCL13 (also known as MCP4), CCL19, CXCL6, CXCL10, CXCL11, IL-8, transforming growth factor-β and tumour necrosis factor[17].

The adverse effects of cannabis and endocannabinoids on the cardiovascular system occur via CB_1, mitogen-activated protein kinase (MAPK) activation and nuclear factor-κB pathways[17,36–38]. CB_1 activation was implicated in endothelial dysfunction in a mouse model of streptozotocin-induced diabetic retinopathy[77,78] and diabetic cardiac dysfunction[36]. Human induced pluripotent stem (iPS) cells are a powerful tool for disease modelling and toxicity testing[17,79]. Previous studies on human coronary artery endothelial cells have demonstrated CB_1-mediated adverse effects[77]. In iPS cell-derived endothelial cells (iPSC-ECs), Δ^9-THC caused toxicity, inflammation and oxidative stress[17]. Knockdown of CB_1 expression in iPSC-ECs with small interfering RNA or CRISPR interference demonstrated that the Δ^9-THC-mediated vascular dysfunction was dependent on CB_1[17]. Pharmacological inhibition with the CB_1 inverse agonist rimonabant also mitigated the adverse effects of Δ^9-THC on iPSC-ECs[17]. Because of the adverse effects associated with CB_1 antagonists, the researchers performed experiments of virtual ligand binding and molecular docking with the crystal structure of CB_1 and found that genistein (a naturally occurring isoflavone that structurally resembles oestrogen) is a neutral antagonist of CB_1[17]. Testing in iPSC-ECs validated that genistein binds to CB_1 and attenuates Δ^9-THC-mediated vascular inflammation and oxidative stress[17]. Genistein has a low penetrance into the central nervous system and might function as a peripheral CB_1 antagonist to ameliorate cannabis-induced cardiovascular disease. Genistein has been studied extensively for various ailments and has no serious adverse effects[80]. Despite its low bioavailability, genistein could be a peripherally restricted CB_1 antagonist with no substantial adverse effects, and further investigation is warranted.

Pharmacological blockade of CB_1 using rimonabant was reported to reduce atherosclerosis in *Ldlr*$^{-/-}$ mice[81]. Therefore, CB_1 agonists

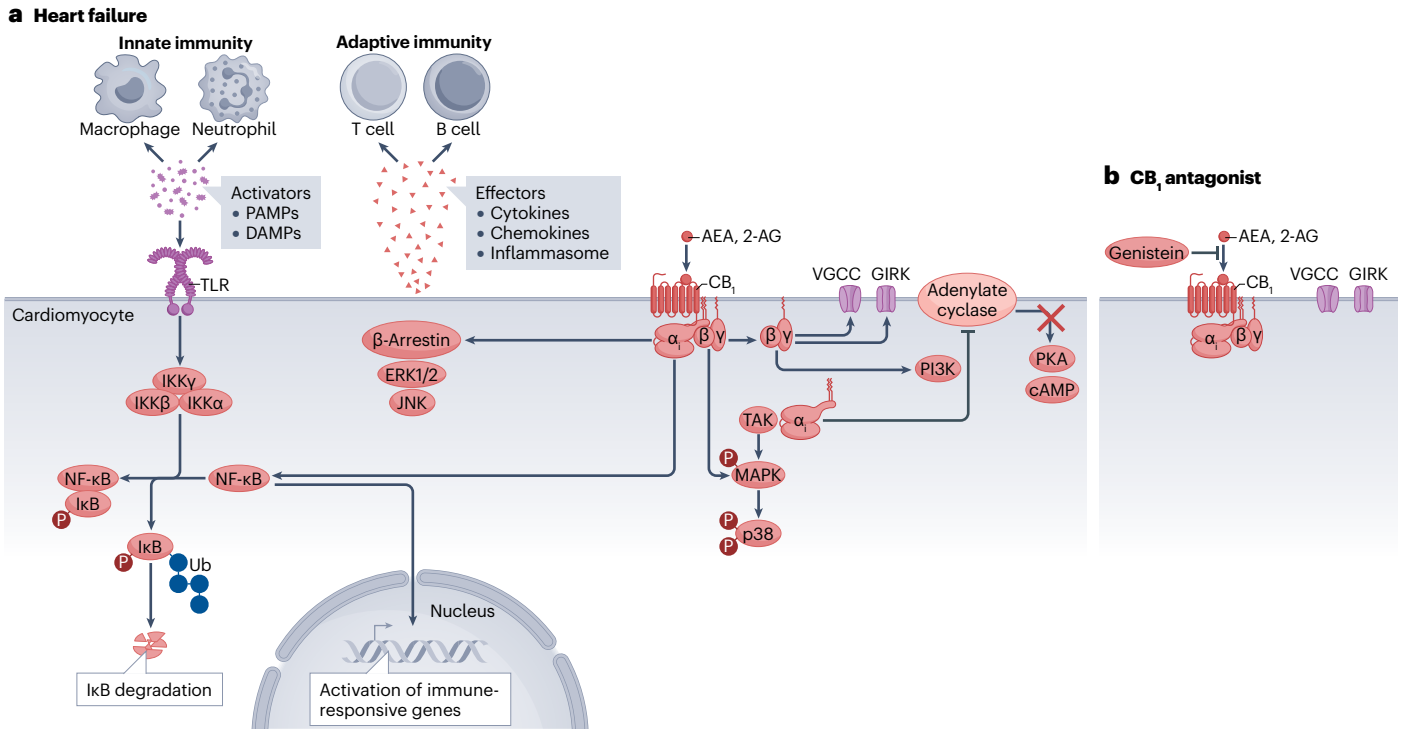


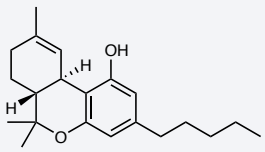
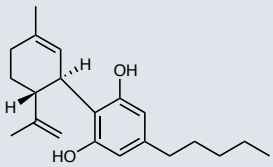
Fig. 4 | Cannabinoid receptor 1 and heart failure. a, Cannabinoid receptor 1 (CB_1) activation, myocardial inflammation and oxidative stress. Endogenous ligands such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) bind to CB_1 and activate the G protein-coupled receptor, leading to activation of the mitogen-activated protein kinase (MAPK), nuclear factor-κB (NF-κB) and β-arrestin pathways, as well as inhibition of the adenylate cyclase pathway. CB_1 activation also activates voltage-gated calcium channels (VGCC) and G protein-coupled inwardly rectifying potassium channels (GIRK), which might cause electromechanical dyssynchrony or arrhythmia. Therefore, CB_1 activation upregulates immune-response genes and downregulates oxidative stress-protective genes implicated in heart failure. The inflamed cardiomyocytes release cytokines and chemokines that in turn activate resident and adaptive immune cells, such as T cells and B cells. Myocardial damage releases pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) that bind to and activate Toll-like receptors (TLRs) on cardiomyocytes and resident immune cells, such as neutrophils and macrophages, exacerbating inflammation. **b**, The CB_1 neutral antagonist genistein ameliorates CB_1-mediated cardiomyocyte inflammation and oxidative stress. Genistein blocks endogenous binding of cannabinoids to their cognate receptor, without modulating CB_1 activity and thereby attenuates CB_1-mediated inflammation and oxidative stress to ameliorate myocardial inflammation and heart failure. ERK1/2, extracellular signal-regulated kinase 1 and 2; IκB, nuclear factor-κB inhibitor; IKKα, inhibitor of NF-κB kinase subunit-α; IKKβ, inhibitor of NF-κB kinase subunit-β; IKKγ, inhibitor of NF-κB kinase subunit-γ; JNK, c-JUN amino-terminal kinase; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; TAK, transforming growth factor-β-activating kinase; Ub, ubiquitin.

such as Δ^9-THC would be expected to exacerbate atherosclerosis. However, studies in *Ldlr*$^{-/-}$ mice revealed that low doses of Δ^9-THC (1 mg/kg per day) administered via oral gavage could reduce atherosclerotic plaque size and that this effect was mediated via CB_2[82]. When Δ^9-THC was delivered by oral gavage, the maximum concentration of the drug in the serum was 6 ng/ml owing to the limiting effects of gastrointestinal absorption and the first-pass effect of the liver[17]. By contrast, the maximum serum concentration of Δ^9-THC is estimated to be 45.6–187.8 ng/ml after smoking a 3% Δ^9-THC marijuana cigarette[83,84]. When an intraperitoneal dose of 1 mg/kg per day of Δ^9-THC was administered to C57BL/6J mice, the maximum serum concentration was 100 ng/ml[17], which is equivalent to the effect of smoking a marijuana cigarette. The thoracic aorta of these mice had impaired endothelial function, as measured on wire myograph, which could be partially rescued with administration of genistein (50 mg/kg per day)[17]. In *Ldlr*$^{-/-}$ or *Apoe*$^{-/-}$ mice fed a high-fat diet, administration of Δ^9-THC resulted in increased atherosclerotic plaque size compared with control mice, which could be ameliorated by the CB_1 antagonist genistein[17].

Arrhythmias

In a retrospective study from a Danish registry in 5,391 patients with chronic pain who used cannabis, a link was reported between cannabis use and new-onset arrhythmias (atrial fibrillation or flutter, conduction disorders, paroxysmal tachycardias and ventricular arrhythmias)[85]. Cannabis users had an absolute risk of new-onset arrhythmias of 0.8% (95% CI 0.6–1.1%), whereas non-users had an absolute risk of 0.4% (95% CI 0.3–0.5%)[85]. The annual risk ratio was 1.36 (95% CI 1.00–1.73)[85]. Cannabis use disorder, defined as an inability to stop using marijuana despite adverse health effects or social problems, is associated with increased occurrence of atrial fibrillation, hospital admissions for uncontrolled atrial fibrillation and thromboembolic events[86,87]. Moreover, cannabis use disorder and associated arrhythmias are more common in younger patients[86]. After cannabis exposure, heart rate transiently increases due to increased sympathetic tone and decreased parasympathetic tone[10]. The chronic use of cannabis results in bradycardia due to reversal of autonomic tone. Moreover, the burden of cannabis-related arrhythmic events is exacerbated in individuals with ischaemic heart disease compared with those without[88].

Table 1 | Traditional cannabinoids

Compound	Structure	Uses	Cardiovascular effects	Legal status in the USA
Δ^9-THC		Pain management[11,13,85], nausea and vomiting[11,13], appetite stimulation[11], glaucoma[13], muscle spasticity[11,13], sleep disorders[11,12], anxiety and post-traumatic stress disorder[11,12], neuroprotection[13], mood disorders[13], recreational[10]	Tachycardia[2,17,85], arrhythmias[2,17,85], vasodilatation and subsequent vasoconstriction[2,17,85], risk of developing cardiovascular disease[2,17,85]	Hemp Δ^9-THC is banned in Idaho and is restricted in California; three states (Colorado, North Dakota and Washington) have banned hemp cannabinoid conversions[106]
CBD		Pain management[11,13], anxiety and depression[11,13], sleep disorders[11,13], neurological disorders[11,13], inflammatory conditions[11,13], skin conditions[11,13], cancer symptom management[11,13], heart health[11,13], substance abuse management[11,13]	Suppression of ischaemia-induced ventricular arrhythmias[103]; protection against autoimmune myocarditis[98], diabetic and doxorubicin-induced cardiomyopathies[99,100], myocardial ischaemia–reperfusion injury[34], vascular damage[104]; vasodilatation[104,105], reduction of blood pressure[105]	Legal medical use in all states, except Idaho, Kansas and Nebraska[106]

CBD, cannabidiol; THC, tetrahydrocannabinol.

Cannabis-induced arrhythmias have multiple mechanisms associated with cannabinoid receptor activation[89]. CB_1 activation might trigger arrhythmias by modulating sodium, potassium or calcium ion channels, vasoconstriction of coronary arteries, compromised microcirculation to atrial and ventricular conduction paths, or inhibition of the mitochondrial electron transport chain[89]. CB_2 activation can also cause dysrhythmias as a result of autonomic nervous system modulation, hypothalamic–pituitary–adrenal axis effects, blocking of sodium, calcium or potassium ion channels, or elevated levels of oxidative stress[89].

Cardiomyopathy

Cannabis-induced cardiomyopathy has been described in case reports[90]. An observational study using the UK Biobank found that cannabis was associated with changes in cardiac structure and function[91]. Cardiac MRI analyses have revealed that cannabis use is associated with larger indexed left ventricular end-diastolic volume, left ventricular end-systolic volume and impaired global circumferential strain after adjustment for age, sex, BMI, systolic blood pressure, use of cholesterol-lowering medication, diabetes, smoking and alcohol consumption[91]. In addition, cannabis use has been linked to heart failure, with an underlying ischaemic mechanism[92].

Preclinical data suggest that endocannabinoids can cause cardiac dysfunction via CB_1 activation, whereas CB_2-mediated signalling might mitigate adverse cardiac remodelling (Fig. 4). In a mouse model of streptozotocin-induced diabetic cardiomyopathy, myocardial levels of the endocannabinoid anandamide were elevated compared with non-diabetic mice[36]. Pharmacological inhibition of CB_1 or genetic deletion of *Cnr1* (which encodes CB_1) decreases levels of oxidative stress and inflammation[93], which are implicated in diabetic cardiomyopathy and endothelial dysfunction[36]. In a C57BL/6J mouse model of doxorubicin-induced cardiomyopathy, CB_1 activation in cardiomyocytes produced reactive oxygen species and activated the MAPK-related cell death pathway[38,94]. However, treatment with the CB_1 antagonist rimonabant or AM281 ameliorated cardiac dysfunction and lowered doxorubicin-mediated myocardial apoptosis[37]. Therefore, CB_1 activation seems to contribute to diabetic and doxorubicin-induced cardiomyopathy. In a Wistar rat model of chronic ischaemic cardiomyopathy induced by permanent ligation of the left coronary artery, treatment with rimonabant improved systolic and diastolic function[95]. Rimonabant treatment in these animals was also associated with a reduction in cardiac fibrosis, which correlated with in vitro observations of decreased matrix metalloproteinase 9 activity and transforming growth factor-β1 expression in cardiac primary fibroblasts[95]. CB_2 also has a role in cardiomyopathy induced by ischaemia–reperfusion, a condition characterized by tissue damage after the restoration of blood flow to oxygen-deprived organs[96]. Compared with wild-type mice, *Cnr2*$^{-/-}$ mice (which lack CB_2) had a larger infarct size after ischaemia–reperfusion injury[96]. Treatment with a CB_2 agonist decreased infarct size in C57BL/6J mice[96]. CB_2 activation also improved diabetes-induced cardiac dysfunction[39] and hepatic cardiomyopathy in mice[40].

Despite these results, few preclinical data link cannabinoids with cardiotoxicity. Primary cardiomyocytes are not affected by exposure to Δ^9-THC according to dose–response curves and viability assays, and iPS cell-derived cardiomyocytes in engineered heart tissues are not affected by exposure to Δ^9-THC in functional and transcriptomic analyses[17]. Treatment of C57BL/6J mice with 1 mg/kg per day of Δ^9-THC via intraperitoneal delivery for 1 month did not affect cardiac function as measured by echocardiography, and histological analysis showed no evidence of increased cardiac fibrosis[17]. Therefore, the cardiac dysfunction and heart failure observed in clinical studies after cannabis exposure are likely to have resulted from ischaemic cardiomyopathy.

Types of cannabinoids and their uses

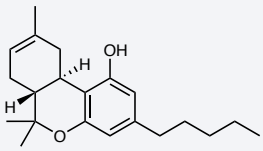
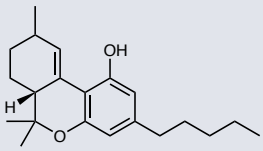
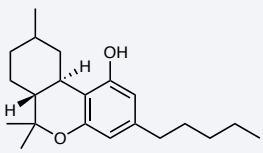
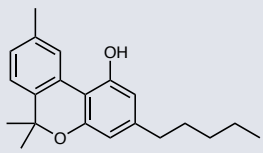
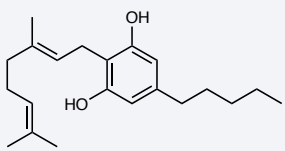
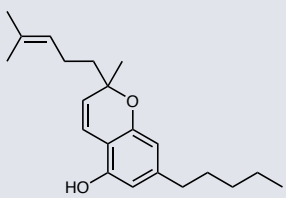
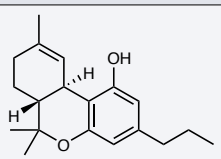
Traditional cannabinoids

Traditional cannabinoids, including CBD and Δ^9-THC, have emerged as compounds of interest for their potential therapeutic properties (Table 1). Directly extracted from the cannabis plant, these compounds are being studied for their diverse pharmacological effects and therapeutic potential for various cardiovascular conditions. Central to understanding the pharmacological effects of traditional cannabinoids are their interactions with cellular receptors. Whereas CBD has a low affinity for CB_1 and CB_2, Δ^9-THC acts as a partial agonist of these receptors, exerting its psychotropic effects primarily through CB_1 activation[97]. In addition, CBD and Δ^9-THC engage with many other receptors, including PPARs, TRP channels and opioid receptors[97] (Fig. 1). These receptor interactions trigger downstream signalling pathways that modulate various physiological processes,

ranging from the regulation of vascular tone to the modulation of inflammation and cellular stress response[10]. Understanding the intricate interaction between cannabinoid receptors and downstream pathways is essential for deciphering the therapeutic mechanisms of traditional cannabinoids and exploring their potential applications in cardiovascular health and disease[10].

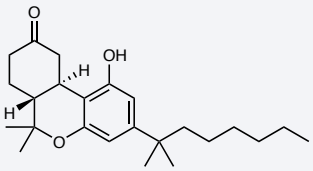
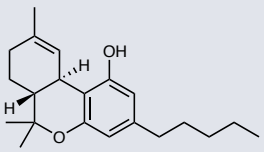
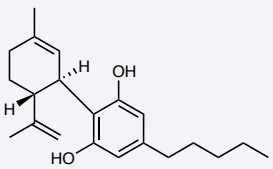
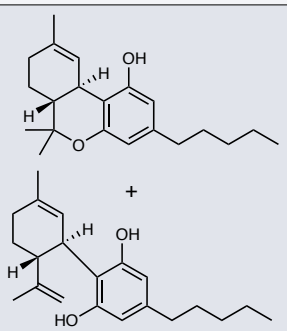
Several studies have suggested that CBD is a promising therapeutic agent for cardiomyopathies, including diabetic and doxorubicin-induced cardiomyopathy, as well as autoimmune myocarditis[98–100]. CBD might improve these cardiomyopathies as a redox modulator[100,101]. CBD does not have psychoactive effects like those of Δ^9-THC, but profoundly influences cardiovascular function through a diverse array of mechanisms that extend beyond interactions with CB_1 and CB_2 to effects on TRP and other ion channels and PPARs[102]. To treat ischaemia–reperfusion injury, CBD can modify immunomodulatory responses and mitigate inflammation, oxidative stress and infarct size[34]. Moreover, by activating adenosine A_1 receptors, CBD has been shown to suppress ventricular arrhythmias induced by

Table 2 | Hemp-derived cannabinoids

Compound	Structure	Extraction or synthesis	Cannabinoid receptor binding	Uses	Cardiovascular effects	Legal status in the USA
Δ^8-THC		Synthesized from CBD[113]	CB_1 and CB_2 partial agonist	Self-treatment for medical conditions, reduction of anxiety and stress, recreational psychoactive	Slow heart rate, tachycardia, hypotension	Legal if it contains <0.3% Δ^9-THC but specifically banned in 17 states and restricted in 7 states
Δ^{10}-THC		Synthesized from CBD or converted from Δ^9-THC[113]	CB_1 antagonist; CB_2 undetermined	Reduction of stress	Unreported (insufficient studies)	Legal if it contains <0.3% Δ^9-THC but illegal in 11 states
HHC		Synthesized from CBD[113]	CB_1 partial agonist; CB_2 partial agonist, agonist and inverse agonist	Anxiety and relaxation, pain management, anti-inflammatory, sedative, recreational psychoactive	Tachycardia	Legal if it contains <0.3% Δ^9-THC but illegal in 9 states
CBN		Synthesized from Δ^9-THC[113]	CB_1 agonist; CB_2 agonist and inverse agonist	Sleep aid, sedative, pain management, anti-inflammatory	Decreased heart rate, tachycardia	Legal if it contains <0.3% Δ^9-THC
CBG		CBGA decarboxylation in plants or yeast biosynthesis[113]	CB_1 partial agonist; CB_2 partial agonist	Reduces intraocular pressure, antioxidant, anti-inflammatory, antitumoural, anti-anxiety, neuroprotective, dermatological conditions, appetite stimulant	Unreported (insufficient studies)	Legal if it contains <0.3% Δ^9-THC
CBC		Synthesized from CBCA[113]	CB_1 partial agonist; CB_2 partial agonist	Anti-inflammatory, pain relief, neuroprotection, antidepressant, acne relief, antitumoural, bone growth, antimicrobial	Unreported (insufficient studies)	Legal if it contains <0.3% Δ^9-THC
Δ^9-THCV		Synthesized from CBGVA[113]	CB_1 antagonist at lower doses; CB_1 agonist at higher doses; CB_2 partial agonist	Appetite suppression, weight loss, diabetes mellitus, neuroprotection, bone health, anti-inflammatory, anticonvulsant, mood modulation	Unreported (insufficient studies)	Legal if it contains <0.3% Δ^9-THC

CB_1, cannabinoid receptor 1; CB_2, cannabinoid receptor 2; CBC, cannabichromene; CBCA, cannabichromenic acid; CBD, cannabidiol; CBG, cannabigerol; CBGA, cannabigerolic acid; CBGVA, cannabigerovarinic acid; CBN, cannabinol; HHC, hexahydrocannabinol; THC, tetrahydrocannabinol; THCV, tetrahydrocannabivarin.

Table 3 | Medicinal cannabinoids

Compound	Structure	Composition	Cannabinoid receptor binding	Uses	Cardiovascular effects
Nabilone		Δ^9-THC synthetic analogue	Partial agonist of CB_1 and CB_2	Pain management, reduction of nausea and vomiting, appetite stimulation, spasticity control	Dose-related tachycardia, palpitations, orthostatic hypotension
Dronabinol		Δ^9-THC synthetic analogue	Partial agonist of CB_1 and CB_2	Reduction of nausea and vomiting, appetite stimulation, management of chronic pain	Dose-related tachycardia, increased heart rate, hypotension
Epidiolex		Purified, pharmaceutical-grade CBD	CB_1 negative allosteric modulator (weak); CB_2 antagonist (weak)	Epilepsy management	Vasodilatation of isolated vessels, reduced effects of cardiac ischaemia–reperfusion, reduced resting systolic blood pressure
Nabiximols		Δ^9-THC and CBD (1:1 ratio)	Δ^9-THC is a partial agonist of CB_1 and CB_2; CBD is a CB_1 negative allosteric modulator (weak) and a CB_2 antagonist (weak)	Spasticity control, neuropathic pain management	Tachycardia

CB_1, cannabinoid receptor 1; CB_2, cannabinoid receptor 2; CBD, cannabidiol; THC, tetrahydrocannabinol.

ischaemia–reperfusion injury[103]. In individuals with hypertension, CBD might modulate vascular tone, causing vasodilatation[104] and blood pressure reduction[105].

Because of its therapeutic promise, CBD is legal in all but three states of the USA[106] (Fig. 2). However, the use of CBD might be associated with interactions with other drugs, such as selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, β-blockers and opioids, and cause adverse effects[107]. In addition, the pain management effects of CBD might be due to a placebo effect, and the use of CBD can lead to severe hepatoxicity and pulmonary inflammation[108,109]. Rigorous research is imperative to ensure that the benefits of CBD are safely harnessed without incurring unintended adverse cardiovascular effects.

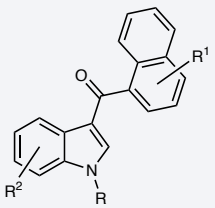
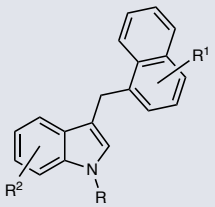
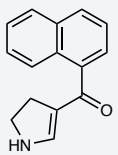
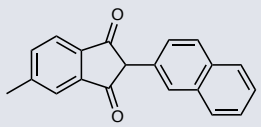
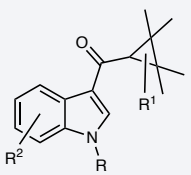
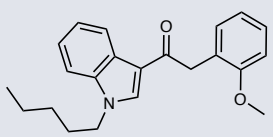
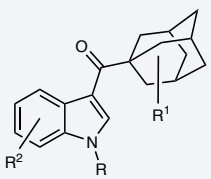
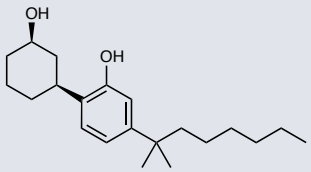
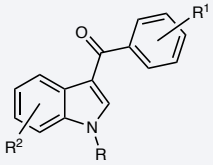
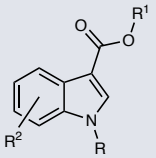
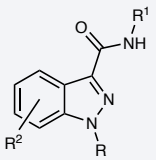
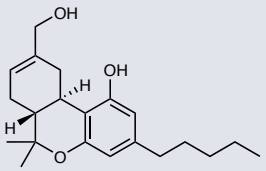
Hemp-derived cannabinoids

Cannabinoids such as Δ^8-THC, Δ^{10}-THC and hexahydrocannabinol (HHC) have become popular among recreational users[21,110,111] and are found in hemp or can be synthesized from CBD (Table 2). After the 2018 Farm Bill in the USA, demand for Δ^8-THC, Δ^{10}-THC and HHC surged because they are hemp-derived and, therefore, fell outside regulation at the time. However, some jurisdictions subsequently began to regulate Δ^8-THC, Δ^{10}-THC and HHC to reduce their usage[112].

Each of these cannabinoids has distinct psychoactive properties, offering users varied experiences. Δ^8-THC is often reported to produce a milder 'high' than Δ^9-THC, with reduced anxiety and paranoia, making it potentially appealing to individuals who are sensitive to the effects of traditional Δ^9-THC. However, the consumption of Δ^8-THC and HHC might be associated with psychotic symptoms[88]. Nevertheless, Δ^8-THC, Δ^{10}-THC and HHC are often sold for therapeutic applications, although research in this area is limited. These cannabinoids are speculated to have anti-emetic, analgesic, anxiolytic, anti-inflammatory and neuroprotective properties. However, Δ^8-THC, Δ^{10}-THC and HHC might confer cardiovascular risks, and further investigation of their use is warranted.

Cannabinol (CBN), cannabigerol (CBG), cannabichromene (CBC) and tetrahydrocannabivarin (THCV) can be found in trace amounts in hemp and are legal as hemp-derived products (Table 2). However, CBN, CBG, CBC and THCV have to be synthesized for commercial applications, which can be done by various methods[113]. CBN, CBG, CBC and THCV have no known psychoactive properties, which limits their recreational use. CBN can be used for sedation, analgesia and as an anti-inflammatory therapeutic agent[114]. CBG is speculated to have anti-inflammatory properties for treating inflammatory bowel disease, neuroprotective effects for managing neurodegenerative disorders, utility for ameliorating metabolic syndrome and an

Table 4 | Synthetic cannabinoids

Class of compound	Structure	Examples
Naphthoylindoles		JWH-018, JWH-073, JWH-398
Naphthyl-methylindoles		AM-2201, JWH-081, JWH-175
Naphthoylpyrroles		JWH-030
Naphthyl-methylindenes		JWH-175, JWH-176
Tetramethylcyclo-propanoylindoles		XLR-11, UR-144
Phenylacetylindoles		JWH-250, RCS-8
Adamantoylindoles		AB-001, AKB-48, STS-135
Cyclohexylphenols		CP 47,497, CP-55,940
Benzoylindoles		RCS-4, AM-694, AM-1220
Indole-3-carboxylate esters		PB-22
Indazole-3-carboxamides		AB-CHMINACA, AB-FUBINACA
Classic cannabinoids		HU-210, HU-211

antimicrobial effect[115]. CBC has also been shown to be effective as an anti-inflammatory agent in treating neurodegenerative disease, with additional analgesic, antidepressant and antimicrobial properties[116]. THCV might cause appetite suppression and can be used to treat obesity, metabolic syndrome and type 2 diabetes[117,118]. However, the cardiovascular effects of CBN, CBG, CBC and THCV are largely unknown and require preclinical and clinical analysis[119]. Of note, cannabinoids can modulate the pharmacokinetics of other drugs and cause harm[120].

Medicinal cannabis

Medicinal cannabinoids, such as dronabinol and nabilone, are possible effective therapeutics for anorexia, nausea and vomiting (Table 3). However, their use has also been associated with increased heart rate and decreased systolic blood pressure[121]. A meta-analysis found that medical cannabis use is associated with adverse cardiovascular events, including increased emergency department visits, MI and cerebrovascular accident[122]. Epidiolex, a type of purified, pharmaceutical-grade CBD, has FDA approval for the treatment of seizures in early-onset epilepsy, such as Lennox–Gastaut syndrome[123] and Dravet syndrome[124]. CBD is a CB_1 and CB_2 receptor antagonist[125] and might have a protective effect on the cardiovascular system, but further research is needed for paediatric use, given findings that prenatal exposure to CBD can cause depressed cardiac activity in mice[126].

Finally, nabiximols, an oral spray containing Δ^9-THC and CBD in a 1:1 ratio, is approved for managing spasticity in patients with multiple sclerosis and for the management of neuropathic pain[127,128]. Because nabiximols contains both Δ^9-THC and CBD, the spray might have adverse cardiovascular effects, and further monitoring is advised.

Next-generation synthetic cannabinoids

Synthetic marijuana, sold under trade names such as 'Spice' and 'K2', mimics the psychoactive effects of Δ^9-THC[129] and was originally composed of synthetic cannabinoids such as JWH-018 and CP 47,497 (Table 4). However, newer synthetic cannabinoids have been developed, including AB-FUBINACA, ABM-FUBINACA and MDMB-FUBINACA, the use of which has been associated with numerous overdoses and fatalities via CB_1 activation and selectivity mechanisms (cannabinoids targeting specific receptors, cells or pathways)[6]. These synthetic cannabinoids exert strong depressant effects when combined with alcohol, they do not have legal medical use status in the USA, and the Drug Enforcement Agency lists many of them as Schedule I substances. The synthetic cannabinoids are far more potent than traditional cannabinoids, being full agonists and having a higher binding affinity to CB_1 and CB_2[130], and their potential adverse effects are concerning. Clinical reports and case studies provide insight into the acute adverse effects and potential complications associated with the recreational use of synthetic cannabinoids, including respiratory depression, cardiovascular events, neuropsychiatric symptoms and death[131]. The use synthetic cannabinoids has also been linked to MI, myocardial ischaemia and other cardiovascular complications, particularly in paediatric patients[132].

Combined cannabis and tobacco consumption

The co-use of cannabis and tobacco is prevalent, boosting health risks compared with the use of either substance alone[133]. Studies have found that the co-use of these substances is associated with heightened risks of various harmful health outcomes[134–137]. For instance, the maternal use of both cannabis and tobacco is associated with adverse infant health and neonatal death and increased maternal and infant morbidity[138]. Whereas the adverse effects of tobacco are well described, the long-term effects of combined tobacco and cannabis use on the cardiovascular system are largely unknown. Cannabis is more difficult to inhale than tobacco, so combining tobacco with cannabis allows deeper inhalation and exposure[135]. In addition, combining cannabis with tobacco might increase vulnerability to addiction and hinder smoking cessation[139,140].

Gateway drug

The gateway drug hypothesis posits that the use of cannabis could lead to the use of other addictive substances, such as cocaine or heroin[15]. According to studies in rats, cannabis produces neurobiological changes that potentially make the brain more susceptible to the effects of other drugs[141]. However, how these findings apply to humans is uncertain. Epidemiological studies are confounded by socioeconomic and psychiatric factors that might predetermine polysubstance abuse. In addition, the gateway drug hypothesis might not account for potential genetic predisposition to polysubstance abuse[142]. For example, single-nucleotide polymorphisms located in the *CHRNA5–CHRNA3–CHRNB4* locus might make a person susceptible to early tobacco use[143] and possibly cannabis, alcohol and cocaine use[144]. Therefore, genetic polymorphisms might exacerbate exposure to polysubstance abuse and increase the risk of adverse cardiovascular events.

Conclusions

Cannabis is emerging as a risk factor for adverse cardiovascular health. With changing public perceptions and an overall decline in tobacco use, cannabis is poised to replace tobacco as a legal drug of choice. Previous restrictions are ending with the widespread decriminalization and legalization of cannabis, boosting use of the drug. A public perception that cannabis is harmless and therapeutically beneficial persists, despite mounting evidence from preclinical and clinical studies showing that cannabis use can harm the cardiovascular system and pose other serious health problems, not unlike tobacco. To resolve remaining uncertainties and better inform policymakers and the public, the effects of cannabis and natural and synthetic derivatives on the cardiovascular system need to be rigorously investigated.

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Competing interests

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