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REVIEW ARTICLE

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Dissecting the role of cannabinoids in vascular health and disease

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Abstract

Cannabis, often recognized as the most widely used illegal psychoactive substance globally, has seen a shift in its legal status in several countries and regions for both recreational and medicinal uses. This change has brought to light new evidence linking cannabis consumption to various vascular conditions. Specifically, there is an association between cannabis use and atherosclerosis, along with conditions such as arteritis, reversible vasospasm, and incidents of aortic aneurysm or dissection. Recent research has started to reveal the mechanisms connecting cannabinoid compounds to atherosclerosis development. It is well known that the primary biological roles of cannabinoids operate through the activation of cannabinoid receptor types 1 and 2. Manipulation of the endocannabinoid system, either genetically or pharmacologically, is emerging as a promising approach to address metabolic dysfunctions related to obesity. Additionally, numerous studies have demonstrated the vasorelaxant properties and potential atheroprotective benefits of cannabinoids. In preclinical trials, cannabidiol is being explored as a treatment option for monocrotaline-induced pulmonary arterial hypertension. Although existing literature suggests a direct role of cannabinoids in the pathogenesis of atherosclerosis, the correlation between cannabinoids and other vascular diseases was only reported in some case series or observational studies, and its role and precise mechanisms remain unclear. Therefore, it is necessary to summarize and update previously published studies. This review article aims to summarize the latest clinical and experimental research findings on the relationship between cannabis use and vascular diseases. It also seeks to shed light on the potential mechanisms underlying these associations, offering a comprehensive view of current knowledge in this evolving field of study.

KEYWORDS

atherosclerosis, cannabinoid receptors, cannabis, vascular diseases, VSMCs

1 | INTRODUCTION

Cannabis, commonly known as marijuana, is the most frequently used illicit substance globally. To date, cannabinoids have been approved for the treatment of chemotherapy-induced gastrointestinal symptoms, multiple sclerosis (MS), and two rare forms of epilepsy. With the trend of global legalization of cannabis for both recreational and medical purposes, the prevalence of cannabis use has increased markedly over the past few years. Hence, it is necessary for healthcare providers to understand the effects of cannabinoids on human physiology. Here, we will focus on vascular diseases.

Based on their source of production, cannabinoids can be classified into three groups: phytocannabinoids produced primarily by cannabis, synthetic cannabinoids (SCs) that are made artificially in the lab, and endocannabinoids produced by the human body. The two major constituents of cannabis, delta-9-tetrahydrocannabinol (THC, the primary psychoactive cannabinoid) and cannabidiol (CBD), are the best-characterized cannabinoids. The mechanism of cannabinoid effects on vascular diseases became clear with the identification of two classical cannabinoid receptors (CBRs; CB1 and CB2), and nonclassical cannabinoid receptors such as transient receptor potential vanilloid (TRPV1 and TRPV4) and G protein-coupled receptors (GPR18 and GPR55). CB1 is located mainly in the central nervous system (CNS), and its variants are associated with dyslipidemia, obesity, and insulin resistance. In contrast, CB2, referred to as "the peripheral CBR" is highly expressed in the peripheral immune system.

Over the past several decades, considerable evidence from both animal and human studies has demonstrated that the endocannabinoid system (ECS) participates in the regulation of atherogenic dyslipidemia (Bluher et al., 2006; Boon et al., 2014; Hu et al., 2011; Jiang et al., 2009). Sugamura et al. reported that serum endocannabinoids and mRNA expression of CB1 in coronary atheroma were significantly increased in patients with coronary artery disease (Sugamura et al., 2009). Interestingly, although rimonabant (30 mg/kg/d), a selective CB1 inhibitor, did not affect serum total cholesterol, it still had antiatherosclerotic effects in low-density lipoprotein receptor $(LDLR)^{-/-}$ mice (Sugamura et al., 2009). This study shows that CB1 blockade may inhibit atherosclerosis progression by multiple mechanisms independent of cholesterol metabolism. CB2 is expressed in atherosclerotic lesions of mice and humans and a growing body of research has revealed that CB2 activation has a protective effect against atherosclerosis (Steffens et al., 2005; Zhao, Liu, et al., 2010; Zhao, Yuan, et al., 2010). CB2 is also associated with matrix metalloproteinase-9 (MMP-9) activity, collagen degradation, and subsequent plaque vulnerability (Montecucco et al., 2009, 2012; Netherland et al., 2010).

Many clinical cases have also linked cannabis use to cannabis arteritis (Combemale et al., 2005; Desbois & Cacoub, 2013; Peyrot et al., 2007; Pilitsi et al., 2023; Sterne & Ducastaing, 1960), reversible arterial vasospasm (Adamson et al., 2020; Baskaran et al., 2019; Bliss et al., 2021; Gunawardena et al., 2014; Hodcroft et al., 2014; Robert et al., 2013; Uhegwu et al., 2015; Wolff et al., 2011) and spontaneous artery dissection (Ibn Hadj Amor et al., 2021; Lou et al., 2015; Mason et al., 2019; Sarmiento et al., 2021; Schmid & Auer, 2011), especially in young healthy men with no other risk factors. With the rise in cannabis use among older adults, it is expected that these reports will increase in the next decades. Although existing literature has not found a significant association between marijuana smoking and vascular calcification (VC) (Murtha et al., 2023), cannabinoids may contribute to VC via impaired calcium homeostasis, autophagic flux, and increased endoplasmic reticulum (ER) stress in vascular smooth muscle cells (VSMCs).

In several multicenter trials, selective blocking of CB1 with rimonabant not only reduced body weight, but also improved cholesterol profile and reduced high-sensitivity C-reactive protein (hsCRP), blood glucose, fasting insulin, and leptin in overweight patients with dyslipidemia (Despres et al., 2005). However, rimonabant was removed from the market due to its adverse psychiatric events. Therefore, peripherally restricted second-generation or hybrid CB1 blocker third-generation (Cinar et al., 2020) treatments that do not cause CNS-mediated side effects represent a new therapeutic strategy for metabolic diseases.

Previous studies demonstrated that balloon injury increased endocannabinoid levels and the expression of CB1/2 in injured arteries (Molica et al., 2012, 2013). A further study revealed that CB1 activation contributes to VSMC proliferation and neointima formation in response to arterial injury (Molica et al., 2013). In contrast, CB2 activation attenuates tumor necrosis factor-α (TNF-α)-induced proliferation and migration of VSMCs and reduces neointima formation in injured arteries (Rajesh et al., 2007; Rajesh, Mukhopadhyay, Haskó, Huffman, et al., 2008). Therefore, blocking CB1 together with selective activation of CB2 could be an attractive therapeutic strategy for the treatment of in-stent restenosis (ISR).

In previous studies, CBD has been proven to modify endocannabinoid levels via the inhibition of fatty acid amide hydrolase (FAAH) (De Petrocellis et al., 2011). CBD inhibited the hyperproliferation of pulmonary artery smooth muscle cells (PASMCs) and ameliorated Sugen + hypoxia-induced pulmonary arterial hypertension (PAH) in mice and monocrotaline (MCT)-induced PAH in rats via improved PASMCs mitochondrial function (Lu et al., 2021) and activation of the transforming growth factor β1 (TGF-β1) signaling pathway (Krzyżewska et al., 2023). CBD may also attenuate PAH by decreasing CB1 expression and levels of inflammatory mediators. Additionally, CBD also showed therapeutic effects for PAH by inhibiting platelet aggregation (Walsh et al., 2010) and decreasing plasminogen activator inhibitor-1 (PAI-1) expression (Ramer et al., 2010), and ameliorating MCT-induced PAH. The pleiotropic properties of CBD may prove useful as a therapeutic tool for the treatment of PAH.

Based on these findings, it is reasonable to speculate that the growing popularity of cannabis for both recreational and medical purposes will be associated with a parallel rise in the incidence of vascular complications. Therefore, a thorough understanding of the effects of cannabis on the vascular system is warranted. Here we provide a review of the cannabis and cannabinoid receptors followed by examining the effects of cannabis on the vascular system,

including the occurrence of atherosclerosis, arterial vasospasms, cannabis arteritis (CA), and spontaneous artery dissection. Additionally, accumulating studies suggest that CBRs are present in vascular tissues and cells, and may play a pivotal part in various vascular diseases. Therefore, the pharmacologic regulation of CBRs is a promising therapeutic strategy for vascular diseases. We also briefly summarize the recent evidence in experimental and human studies relating to the therapeutic potential of CBR agonists/antagonists in various pathological conditions, including atherosclerosis, ISR, and PAH.

2 | CANNABIS AND CANNABINOIDS

Following increased recreational use of marijuana in the mid-1960s, Raphael Mechoulam and his colleagues in Israel isolated THC and other phytocannabinoids. Based on their source of production, cannabinoids can be classified into three groups: phytocannabinoids produced primarily by cannabis, synthetic cannabinoids that are made artificially in the lab, and endocannabinoids produced by the human body. All three groups of cannabinoids have a similar structure (Figure 1).

2.1 | Phytocannabinoids

Cannabis is an herb that has three major subspecies: *sativa*, *indica*, and *ruderalis*. Cannabis is a complex mixture of over 500 cannabinoids, of which 120 cannabinoids have been identified, including THC, CBD, cannabinol (CBN), and cannabigerol (CBG). Among them, THC and CBD are the best characterized. THC is the major psychoactive compound in cannabis and two synthetic THC cannabinoids (Dronabinol and Nabilone) have been approved by the Food and Drug Administration (FDA) in the United States for the

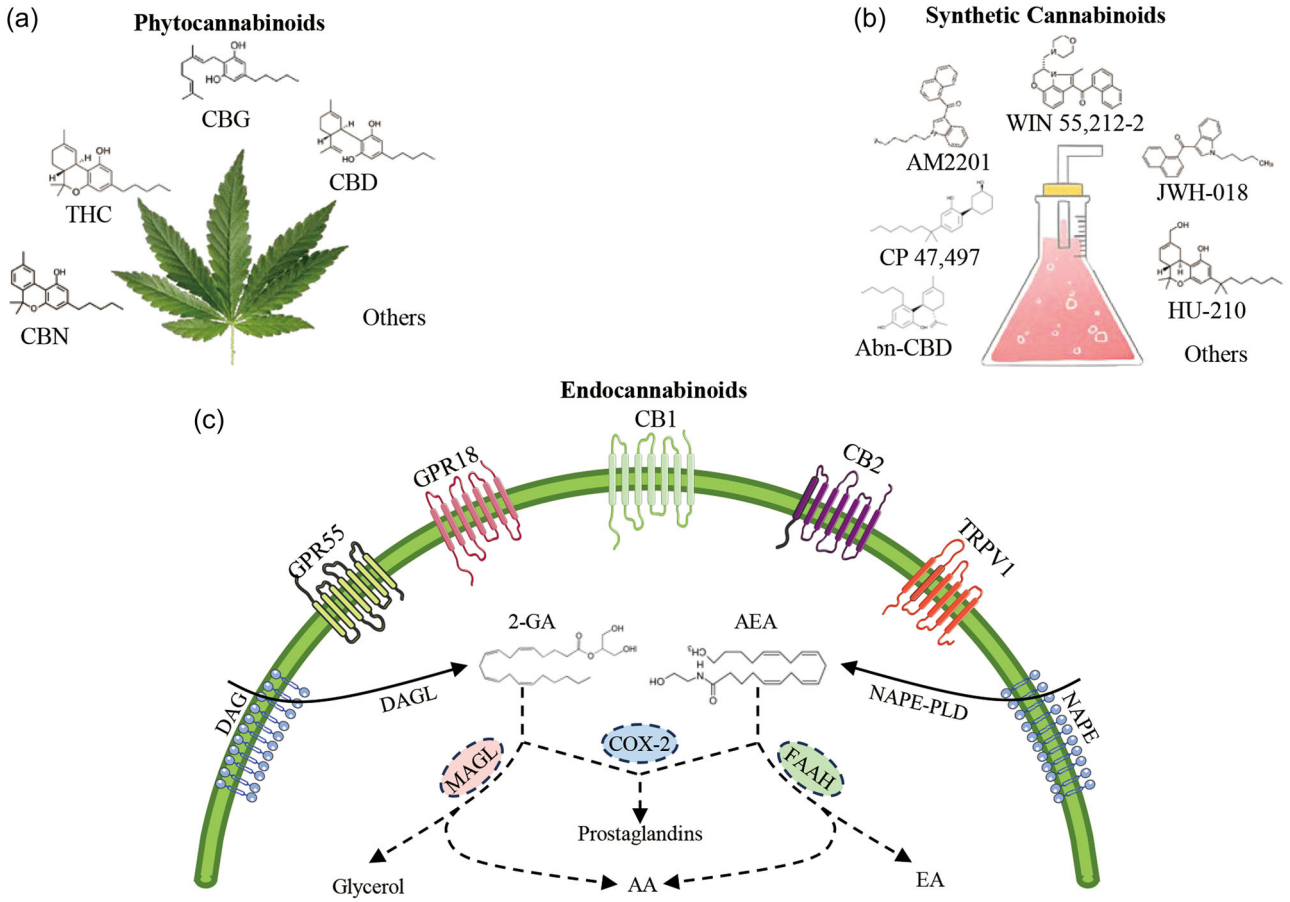

FIGURE 1 Classification of cannabinoids and chemical structures of the main representative phyto-, endo- and synthetic cannabinoids. (a) Phytocannabinoids are bioactive natural products found in cannabis plants. (b) Synthetic cannabinoids are manmade chemicals that have a chemical structure similar to those of phytocannabinoids. (c) Endocannabinoids 2-AG and AEA are biosynthesized by DAGL and NAPE-PLD, respectively. MAGL and FAAH are the metabolizing enzymes that degrade AEA to produce AA and EA, and 2-AG to AA and glycerol. Both AEA and 2-AG can also be oxidized by COX-2, to create prostamides. 2-GA, 2-arachidonoylglycerol; AA, arachidonic acid; Abn-CBD, abnormal cannabidiol; AEA, anandamide; CBD, cannabidiol; CBG, cannabigerol; CBN, cannabinol; COX-2, oxidized by cyclooxygenase-2; DAGL, diacylglycerol lipase; EA, ethanolamine; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; NAPE-PLD, N-acylphosphatidylethanolamine phospholipase D; THC, 9-tetrahydrocannabinol.

treatment of chemotherapy-induced nausea and vomiting and human immunodeficiency virus/acquired immunodeficiency syndrome-induced anorexia. Additionally, the FDA approved Sativex, an oral spray containing THC and CBD in a 1:1 ratio, for easing spasticity in adult MS patients. CBD is the major nonpsychotropic ingredient in cannabis, and the FDA has approved Epidiolex (highly purified CBD) for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome. CBD was also found to exert beneficial effects in many preclinical disease models ranging from MCT-induced PAH (Lu et al., 2021), cardiac ischemia/reperfusion injury (Walsh et al., 2010), and doxorubicin- and diabetes-induced cardiomyopathies (Hao et al., 2015; Rajesh et al., 2010). Of note, safety concerns have arisen regarding the potential conversion of CBD to psychotropic cannabinoids under in vitro and in vivo conditions.

2.2 | Synthetic cannabinoids

SCs were initially synthesized following the discovery of THC in 1964. With the growing popularity of medical and recreational consumption, numerous synthetic analogs have been produced. Most SCs are agonists of CBRs, and have a higher affinity for CB1 (Table 1). Because of the risk of psychiatric side effects, CB1 antagonists have evolved from first-generation brain penetrance (e.g., rimonabant, Taranabant, and Otenabant) to second-generation peripherally restricted antagonists (e.g., TM38837 and AM6545), to a third-generation multitargeting approach (e.g., MRI-1867 and MRI-1569) (Cinar et al., 2020).

Early SCs were named after either the scientist who first synthesized them or the institution or company where they originated. For example, the JWH and AM series of SCs are derived from the scientists John W. Huffman and Alexandros Makriyannis, and the HU and CP series of SCs were developed at the Hebrew University and Charles Pfizer. Additionally, recreational SCs have been marketed under brand names, such as Spice, K2, K3, and many others. In recent years, SCs have been assigned names derived from their four pharmacophore components termed the linked group, linker, core, and tail, using the following arrangement: LinkedGroup-TailCoreLinker. In addition, many nonclassical SCs have been synthesized to simplify the classical SCs structure, presenting challenges to nomenclature.

2.3 | Endocannabinoid system

The ECS is a widespread neuromodulatory network that plays important roles in the CNS regulation of food intake, emotional behavior, cognition, memory, and pain sensation. The ECS includes endocannabinoids, the enzymes that synthesize and degrade endocannabinoids, and G-protein-coupled CB1/2. Over the past decade, substantial evidence has accumulated demonstrating that alterations and dysfunctions of the ECS modulate several processes critical in the pathophysiology of metabolic cardiovascular risk factors, and atherosclerosis (Cristino et al., 2020). Patients with obesity or type 2 diabetes-related hyperglycemia exhibit higher concentrations of endocannabinoids in visceral fat or serum (Engeli et al., 2005; Matias et al., 2006), indicating that the ECS is upregulated in patients with obesity and those with multiple cardiovascular risk factors.

Endocannabinoids are lipophilic molecules synthesized in biological membranes on demand. The arachidonic acid derivatives anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the most characterized endocannabinoids. AEA is mainly synthesized by the catabolism of the phospholipid hormone precursor N-acyl-phosphatidylethanolamine (NAPE) via NAPE phospholipase D (NAPE-PLD). 2-AG is almost exclusively catalyzed from the hydrolysis of diacylglycerol (DAG) by diacylglycerol lipase (DAGL), releasing a free fatty acid and 2-AG (Figure 1). Once taken up through a specific anandamide transporter, AEA is hydrolyzed by FAAH into arachidonic acid (AA) and ethanolamine (EA), whereas 2-AG is mostly degraded by monoacylglycerol lipase (MAGL) into AA and glycerol. Additionally, both AEA and 2-AG can also be oxidized by cyclooxygenase-2 (COX-2), to create prostamides.

3 | CANNABINOID RECEPTORS

Owing to their lipophilic nature, cannabinoids were initially thought to exert various biological effects by disrupting the cell membrane nonspecifically. In the early 1990s, the mechanism of cannabinoids became clear with the subsequent identification of two classical CBRs, CB1 and CB2, which are seven-transmembrane G-protein coupled receptors (GPCRs). In recent years, other nonclassical cannabinoid receptors such as transient receptor potential vanilloid (TRPV1 and TRPV4) and G protein-coupled receptors (GPR18 and GPR55) were found to have affinity for cannabinoids. Additionally, an as yet unidentified endothelial cannabinoid receptor was reported to partially participate in the vasodilatory effects of endocannabinoids. CB1 is located mainly in the CNS, while CB2 is primarily found in the periphery, especially the immune system. In addition to their well-established roles in the CNS and immune system, CB1 and CB2 are also present in vascular tissues and cells, including endothelial cells (ECs), VSMCs, and macrophages, and may play a pivotal part in various vascular diseases, as summarized in Table 2.

3.1 | Cannabinoid receptor type 1

CB1 and CB2 are both members of the superfamily of metabotropic GPCRs. CB1 is the most abundant GPCR in the CNS and was immediately recognized as the receptor responsible for the effects of cannabis on the CNS. CB1 is also abundantly expressed in the peripheral nervous system and tissues, and its expression is upregulated in the vascular system under pathological conditions, which promotes vascular diseases progression (Baranowska-Kuczko et al., 2016; Gestrich et al., 2015; Molica et al., 2013; Sugamura et al., 2009).

TABLE 1 Agonist and antagonist/inverse agonists of several cannabinoid receptors.

	Agonist	Antagonist	Inverse agonists
CB1	JWH-018, −019, −030, −073, −122, −200, −251 AM-1220, −2201, −679, −694, −251, −281 CP-47,497, −55244 PB-22, 5F-PB-22 O-1812 MDMB-FUBINACA, MAM-2201, APINACA, ACEA	SR141716 (Rimonabant) SR147778 (Surinabant) O-1248, −2050 SLV-319 LY-320, 135 WIN55, 212-2 AM-6545 JD5037 CP945598	AM-251, −281
CB2	HU-308 JWH-015, −133, −151 UR-144 AM-1241	SB-705498, −366791 AMG-9810, −517 AP-18 A-784168 HC-030031 JNJ-17203212 JYL1421 BCTC	SR144528 AM-630 WIN54,461 JTE 907 GP 1a COR 170 SCH 336 SR144528
CB1 and CB2	HU-210 JWH-081, −203, −250, −307 AM-2232, −2233, −1248 EAM-2201 CP-55,940		
TRPV1	Capsaicin 20-HETE	Capsazepine HC-067047 GSK2193874 RN-9893, −1734 GSK1016790A SB-366791 Ruthenium red AMG-9810	
TRPV4	4α-PDD	PSB CB5 HC067047 CID-85469571 RN1734	
GPR18	PSB-KD107 PSB-KK-1415	O-1918	
GPR55	O-1602 Lysophosphatidylinositol	ML-193	CID16020046

Like the majority of GPCRs, CB1 is primarily localized in the cell membrane. Typically, CB1 can be coupled to different G proteins, such as Gi/o and/or Gq proteins, to modulate ion-channel function and several signaling cascades, including the phosphatidylinositol-3-kinase (PI3K)-protein kinase B (AKT), mitogen-activated protein kinase (MAPK), and protein kinase A (PKA) cascades. Interestingly, considerable observations have shown that CB1 is functionally localized in the intracellular milieu, including endo/lysosomes and mitochondrial membranes (mtCB1). Follow-up studies discovered that intracellular CB1 may come from the agonist-induced internalization of plasma membrane or a distinct pool of intracellularly localized CB1 (Zou & Kumar, 2018). Intracellular-localized CB1 does not translocate to the plasma membrane and exerts its pharmacological properties distinct from plasma membrane-localized CB1. Endo/lysosome-located CB1 can increase intracellular calcium concentrations from the endoplasmic reticulum and lysosomes. mtCB1 has been shown to be present in different cell types and regulates the motility of sperm, progesterone production in ovarian cells, cognitive functions in brain, and oxygen consumption in skeletal and myocardial muscles.

CB1 is encoded by the *CNR1* gene, and consists of 472 amino acids in humans, and 473 amino acids in rats and mice, with 97%–99% amino acid sequence identity among them. *CNR1* is located on human chromosome 6q14-15 and has one promoter and four exons that are spliced into six variants. The entire protein coding region of *CNR1* is contained within the single Exon 4. Two isoforms (CB1a and CB1b) result from intra-exonal splicing of Exon 4. A number of polymorphisms has demonstrated that genetic variability

TABLE 2 Role of cannabinoid receptors in vascular cells/tissues.

CBRs	Cell type/tissue	Species	Agents/models	Specific observations
CB1	VSMCs	Mice	WIN55212-2 O-2050	CB1 inhibition enhances vasoconstriction induced by Ang II, and augmented Ang II-induced blood pressure rise in mice (Szekeres et al., 2015).
	VSMCs	Mice	AM-281 Carotid balloon injury model	Endogenous CB1 activation contributes to VSMC proliferation and neointima formation in response to arterial injury (Molica et al., 2013).
	HCASMCs	Human	Rimonabant	Rimonabant attenuates PDGF-induced Ras and ERK 1/2 activation, and decreases proliferation and migration of HCASMCs (Rajesh, Mukhopadhyay, Haskó, & Pacher, 2008).
	ECs	Rat	AM-251	CBD-induced relaxation in mesenteric artery is inhibited by AM-251 in SHR and DOCA-salt hypertensive rats (Baranowska-Kuczko et al., 2020).
	ECs	Mice	Rimonabant AM-251	CB1 blockade reduces oxidative stress, improves endothelial function and exerts anti-atherosclerotic effects by downregulation of the AT1-R (Tiyerili et al., 2010).
	Aortic ECs	Human	AM-251	CBD causes endothelium-dependent vasorelaxation of mesenteric artery via CB1 activation (Stanley et al., 2015).
	Macrophages	Mice	Rimonabant	CB1 blockade reduces atherosclerosis in ApoE$^{-/-}$ mice through an increase in serum adiponectin levels and activation of the reverse cholesterol transport system (Sugamura et al., 2010).
	Macrophages	Mice	Rimonabant	Rimonabant (20 mg/kg/d) attenuates dyslipidemia and atherosclerosis in APOE*3-Leiden. CETP mice (van Eenige et al., 2021).
	Macrophages	Mice	Rimonabant	Rimonabant (30 mg/kg/d) reduces food intake, macrophage recruitment, and lesion size without affecting serum cholesterol levels (Dol-Gleizes et al., 2009).
	Macrophages RAW264.7	Human Mice	Rimonabant ACEA JWH-015	CB1 promotes pro-inflammatory responses of macrophages through ROS production and p38-MAPK activation, while CB2 suppresses the signal by the activation of Rap1 (Han et al., 2009).
	Macrophages RAW264.7	Mice and Rat	AM-251 WIN55212-2	CB1 blockade reduces ox-LDL accumulation in macrophages (Jiang et al., 2009).
	Macrophages coronary artery	Human	Rimonabant	CB1 levels are increased in coronary atheroma of patients with unstable angina, and CB1 blockade exhibited anti-inflammatory effects on macrophages (Sugamura et al., 2009).
	Aortic aneurysm specimens	Human	N/A	The expression of CB1, CB2, TRPV1, and GRP55 are increased in aortic aneurysm (Gestrich et al., 2015).
	Mesenteric artery aorta	Rat	AM-6545	Upregulated CB1 in resistance mesenteric arteries plays a protective role in DOCA-salt hypertension rats (Baranowska-Kuczko et al., 2016).
	Pulmonary artery	Human Rat	AM-251	Ang II-induced vasoconstriction contributes to the synthesis of 2-AG, and 2-AG induces vasorelaxation via CB1 (Karpinska et al., 2017).
	Pulmonary artery	Rat	JD5037	Polytherapy with metformin and JD5037 improve lung hypertrophy in MCT-induced PH (Remiszewski et al., 2022).
	Aorta	Rat	CBD	CBD increases the expression of endocannabinoids, CB1 and CB2 in the aortas of DOCA-salt or SHR hypertensive rats (Baranowska-Kuczko et al., 2021).

TABLE 2 (Continued)

CBRs	Cell type/tissue	Species	Agents/models	Specific observations
CB2	HCASMCs	Human	JWH-133 HU-308	CB2 agonists attenuate TNF-α-triggered proliferation and migration of HCASMCs and the activation of Ras, MAPK, ERK 1/2, SAPK/JNK and Akt (Rajesh, Mukhopadhyay, Haskó, Huffman, et al., 2008).
	VSMCs macrophages	Mice	JWH-133 Carotid balloon injury model	*CB2* deficiency contributes to neointima formation via enhanced VSMC proliferation and macrophage infiltration (Molica et al., 2012).
	SMCs macrophages aorta	Mice	SR144528	*CB2* deficiency affects atherogenesis by increasing lesional macrophage and SMC content, reducing lesional apoptosis, and reducing extracellular matrix components by upregulating MMP-9 levels (Netherland et al., 2010).
	Coronary artery ECs	Human	JWH-133	CB2 activation attenuates TNF-α-induced human EC activation, transendothelial migration of monocytes, and monocyte-endothelial adhesion (Rajesh et al., 2007).
	Macrophages	Mice	WIN55212-2 AM-630	CB2 activation ameliorates atherosclerosis by reducing macrophage accumulation and adhesion molecule expression with little effect on lipid profiles (Zhao, Yuan, et al., 2010).
	Macrophages	Mice	JWH133	Deficiency of *CB2* in bone marrow-derived cells aggravates atherogenesis and causes increased leukocyte infiltration in atherosclerotic plaques (Hoyer et al., 2011).
	Macrophages	Mice	N/A	*CB2* deficiency reduces the susceptibility of macrophages to ox-LDL/oxysterol-induced apoptosis (Freeman-Anderson et al., 2008).
	Macrophages	Mice	WIN55212-2 AM-630	WIN55212-2 inhibits atherosclerosis by the suppression of pro-inflammatory responses (Zhao, Liu, et al., 2010).
	Macrophages	Mice	SR144528	Enhanced 2-AG levels in atherosclerotic plaques trigger the inflammatory process by recruiting macrophages and inducing extracellular matrix degradation via CB2 (Montecucco et al., 2009).
	Macrophages	Mice	AM-281 AM-630	Enhanced 2-AG levels promote atherogenesis. CB1 and CB2 are implicated in 2-AG-induced macrophage migration (Jehle et al., 2018).
	Macrophages RAW264.7	Mice	AM-251 SR144528	CB1 and CB2 blockade reduce cholesteryl ester synthesis in unstimulated and acetylated LDL-stimulated RAW264.7 cells (Thewke et al., 2009).
	Macrophages RAW264.7	Rat Mice	WIN55212-2 AM-630	WIN55212-2 protects against ox-LDL-induced inflammation and oxidative stress in macrophages (M. X. Hao et al., 2010).
	Monocytes	Human	JWH-015	CB2 activation reduces monocyte recruitment via CB2-dependent PI3K/Akt and ERK1/2 signaling (Montecucco et al., 2008).
	Monocytes	Human	JWH-015 SR144528	CB2 activation reduces CD36-dependent oxLDL accumulation and modulates production of inflammatory cytokines (Chiurchiu et al., 2014).
	Immune cells	Mice	N/A	*CB2* deficiency in immune cells aggravates early atherosclerosis development in $LDLR^{-/-}$ mice (Delsing, 2011).
	Aorta	Mice	SR144528	THC or cannabinoids with activity on CB2 may be valuable targets for treating atherosclerosis (Steffens et al., 2005).
	Pulmonary artery	Mice	HU-210	CB2 is prominently expressed in murine lungs, but HU-210 does not alter pulmonary arterial tone (Wenzel et al., 2013).

(Continues)

TABLE 2 (Continued)

CBRs	Cell type/tissue	Species	Agents/models	Specific observations
TRPV1	Microvascular ECs	Human	WIN55212-2	Cannabinoids may change TRPV1 in microvascular ECs from being anti-inflammatory to being proinflammatory (Wilhelmsen et al., 2014).
	Mesenteric artery	Rat	SB-366791 Capsazepine	AEA elicits an acute release of NO via the activation of endothelial TRPV1 (Poblete et al., 2005).
TRPV4	ECs	Mice	AEA	TRPV4 is highly expressed in ECs, and AEA exerts relaxant effects via the activation of TRPV4 (Watanabe et al., 2003).
	Coronary ECs	Human	HC067047 RN1734 Ruthenium red	2-AG can directly activate endothelial TRPV4 and partly participate in endothelium-dependent relaxation due to 2-AG (Ho et al., 2015).
GPR18	Pulmonary artery	Human	O-1918 Abn-CBD	GPR18 mRNA is detectable in human pulmonary artery and GPR18 elicits endothelium-dependent vasorelaxation of human isolated pulmonary artery (Kozłowska et al., 2022).
GPR55	Peritoneal neutrophils	Mice	CID16020046 Abn-CBD	GPR55 antagonism with CID16020046 does not affect atherosclerotic plaque size, but increases neutrophil activation and recruitment in early atherogenesis (Montecucco et al., 2016).

Abbreviations: 2-AG, 2-arachidonoylglycerol; AEA, anandamide; Ang II, Angiotensin II; AT1-R, angiotensin II type 1 receptor; CB1, cannabinoid receptor type 1; CBD, cannabidiol; DOCA-salt, 11-deoxycorticosterone acetate; ECs, endothelial cells; HCASMCs, human coronary artery smooth muscle cells; LPS, lipopolysaccharide; MCT, monocrotaline; PH, pulmonary hypertension; SHR, spontaneously hypertensive; TXA2, thromboxane A2.

in the *CNR1* gene is associated with common obesity and its related metabolic disorders, including dyslipidemia and insulin resistance (Figure 2). In the coming era of personalized medicine, genetic variants and haplotypes in *CNR1* associated with metabolic disorders may help identify specific targets in conditions of endocannabinoid dysfunction.

Endogenous CB1 signaling plays a critical role in regulating energy homeostasis by increasing food intake (Bellocchio et al., 2010; Di Marzo et al., 2001), modulating the release of adipose-derived hormones (Balsevich et al., 2018; Cota et al., 2003), promoting lipogenesis in the liver (Kunos & Osei-Hyiaman, 2008; Osei-Hyiaman et al., 2005) and insulin secretion in the pancreas (Matias et al., 2006), and regulating digestion from salivation to nutrient absorption in the intestinal tract (Lee et al., 2016). Therefore, increased CB1 activation can lead to excessive weight gain, insulin resistance and dyslipidemia, and CB1 antagonists appear to be efficacious in facilitating weight reduction, and improving glucose homeostasis and lipid homeostasis. Several clinical trials have demonstrated the efficacy of rimonabant, the first commercially available CB1 blocker, in improving obesity and its associated metabolic abnormalities (Despres et al., 2005). However, the drug was quickly withdrawn due to psychiatric effects in 2008. Therefore, peripherally restricted second generation or hybrid CB1 blocker third generation treatments that do not causing CNS-mediated side effects represents a new therapeutic strategy for mitigating obesity and its multiple metabolic disorders (Cinar et al., 2020).

3.2 | Cannabinoid receptor type 2

CB2 is highly expressed in cells of the peripheral immune system, thus it is referred to as "the peripheral CBR." Due to its low expression in the vascular system, CB2 does not exert direct vascular effects under physiological conditions. However, CB2 can be induced in ECs (Rajesh et al., 2007) and VSMCs (Rajesh et al., 2007; Rajesh, Mukhopadhyay, Haskó, Huffman, et al., 2008) under pathological conditions such as inflammatory stimulation or tissue injury. For example, increased CB2 expression has been described in atherosclerotic plaques (Netherland et al., 2010; Steffens et al., 2005), neointimal lesions following balloon injury (Molica et al., 2012), and in aortic aneurysms (Gestrich et al., 2015).

CB2 is encoded by *CNR2* and was first cloned from the human leukemia cell line HL-60 in 1993. *CNR2* is located in human chromosome 1p35-p36.1 and contains four exons alternatively transcribed and spliced to yield two isoforms (Figure 2). With two separate promoters (P1 and P2) and four exons, *CNR2* (87.7 kb) is over three times as large as *CNR1* in genomic size (26.5 kb). *CNR2* has CB2a with Exons 3 and 4, and CB2b with Exons 1 and 2. Human CB2a is found primarily in the testis and in the brain, while the CB2b isoform is expressed primarily in the immune differential tissues. Despite sharing 44% homology, CB1 and CB2 appear to be functionally distinct. CB1 has a *yin-yang* relationship with CB2 structurally and functionally. CB1 promotes proinflammatory

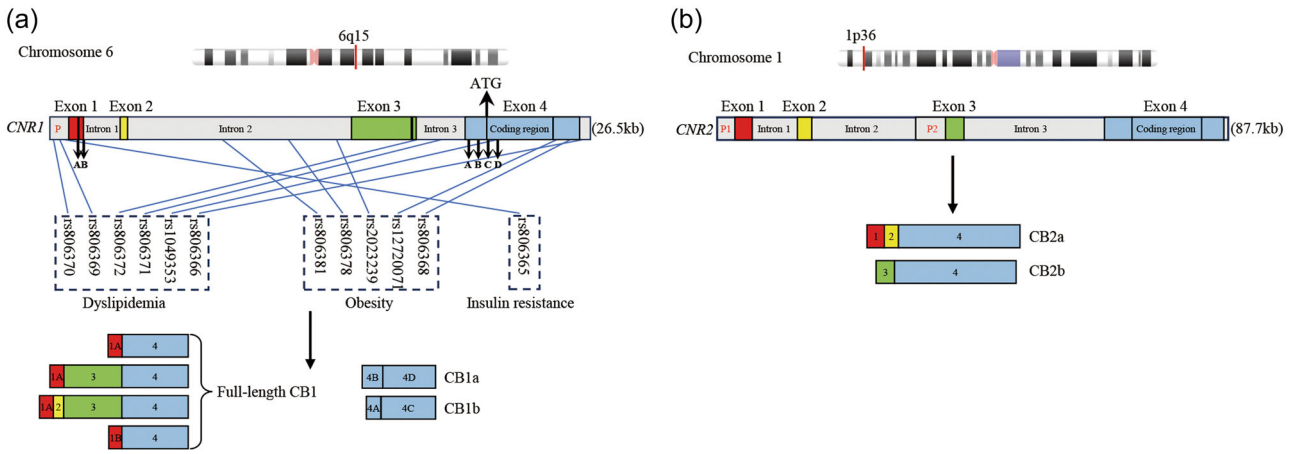

FIGURE 2 Schematic representation of human *CNR1* (a) and *CNR2* (b) genomic structure, their alternative spliced transcripts (mRNAs), and the effects of *CNR1* mutations on metabolism. The coding region of *CNR1* and *CNR2* is contained within Exon 4. (a) *CNR1* is on human chromosome 6q15. It has one promoter (P), four exons, and six splice sites in Exon 1 (a) and (b) and Exon 4 (4A-D) indicated by downward arrows and capital letters. *CNR1* can be spliced into six transcripts including four full-length CB1 transcripts and two N-terminal altered and deleted isoforms (CB1a and CB1b). A number of polymorphisms associated with metabolism have been identified and the positions of some of the polymorphisms are indicated by thin blue lines. (b) *CNR2* is located on human chromosome 1p36. *CNR2* has two separate promoters (P1 and P2) and four exons that are spliced into CB2a and CB2b transcripts, encoding the same peptide sequences. *CNR2* contains human-specific Exons 1 and 2 encoding CB2a that is under control of P1, whereas P2 controls expression of Exons 3 and 4 encoding CB2b that is preferentially expressed in the immune system. P (red font) represents promoters. CNR1, cannabinoid receptor type 1; CNR2, cannabinoid receptor type 2.

responses of macrophages through reactive oxygen species (ROS) production, which is negatively regulated by CB2 through Rap1 activation (Han et al., 2009). Strong evidence supports a protective role of CB2 in mouse models of atherosclerosis (Montecucco et al., 2012; Netherland et al., 2010; Steffens et al., 2005; Zhao, Liu, et al., 2010; Zhao, Yuan, et al., 2010), restenosis (Molica et al., 2012), and ischemia/reperfusion injury (Defer et al., 2009). Considering basic research data, CB2 activation may be a promising approach against atherosclerosis and acute ischemic complications.

3.3 | Transient receptor potential channels

Transient receptor potential (TRP) channels constitute a superfamily of cation-permeable ion channels located mostly on the plasma membrane. Among them, the TRP vanilloid (TRPV1-TRPV4), TRP ankyrin (TRPA1), and TRP melastatin (TRPM8) have been reported to mediate cannabinoid activity, and are often referred to as ionotropic cannabinoid receptors. TRPV1 is predominantly expressed in peripheral sensory neurons and is also expressed in SMCs, ECs, and the immune system. It participates in the regulation of vascular tone and blood pressure, and is involved in the pathogenesis of atherosclerosis development (Li et al., 2014; Ma et al., 2011), pulmonary hypertension (Song et al., 2017), and abdominal aortic aneurysm (Wang & Jia, 2020). There is evidence suggesting that endogenous, phytogenic, and synthetic cannabinoids can modulate vascular tone via the activation of TRPV1. TRPV4 shares over 40% sequence homology with TRPV1. Watanabe et al. have shown that TRPV4 is highly expressed in ECs, and may partly participate in the endothelium-dependent relaxation in response to AEA (Watanabe et al., 2003) and 2-AG (Ho et al., 2015) (Table 2). Although cannabinoids may cause vasorelaxation via endothelial TRPV1/4, it is not clear whether cannabinoids can exert other vascular effects through the activation these TRP channels.

3.4 | G protein-coupled receptor

GPR55 shares numerous cannabinoid ligands but low sequence homology with classical CBRs, therefore, it has emerged as a putative "type 3" CBR. Previous studies have demonstrated that GPR55 participates in oxidized LDL (oxLDL)-induced foam cells, and may be associated with the formation of unstable plaques (Montecucco et al., 2016). However, its physiological role and underlying mechanism remain unclear. Additionally, GPR18, which shares moderate identity with GPR55 (21%), was reported to cause vasorelaxation in human-isolated pulmonary arteries (Kozlowska et al., 2022). However, there are no reports on GPR18 activation in vascular diseases.

4 | CANNABIS AND VASCULAR DISEASES

4.1 | Cannabis and atherosclerosis

Since the ECS participates in the regulation of atherogenic dyslipidemia in mice (Boon et al., 2014; Hu et al., 2011; Jiang et al., 2009) and humans (Blüher et al., 2006), evidence from previous studies has demonstrated that blocking CB1 can attenuate

atherosclerosis development through activating the reverse cholesterol transport system in ApoE$^{-/-}$ mice (Sugamura et al., 2010) and reversing dyslipidemia in APOE*3-Leiden.CETP mice (van Eenige et al., 2021). In a human study, Sugamura et al. reported that blood endocannabinoids and mRNA expression of CB1 in coronary atheroma are significantly increased in patients with coronary artery disease, and rimonabant exerts anti-inflammatory effects on macrophages through modulation of the activation of cyclic adenosine monophosphate (cAMP) and phosphorylation of c-Jun N-terminal kinase, JNK (Sugamura et al., 2009) (Figure 3).

Subsequently, Dol-Gleizes et al. demonstrated that rimonabant (50 mg/kg/d) significantly reduces weight gain, serum total cholesterol, and atherosclerotic lesion development in LDLR$^{-/-}$ mice (Dol-Gleizes et al., 2009). Interestingly, although a low dosage of

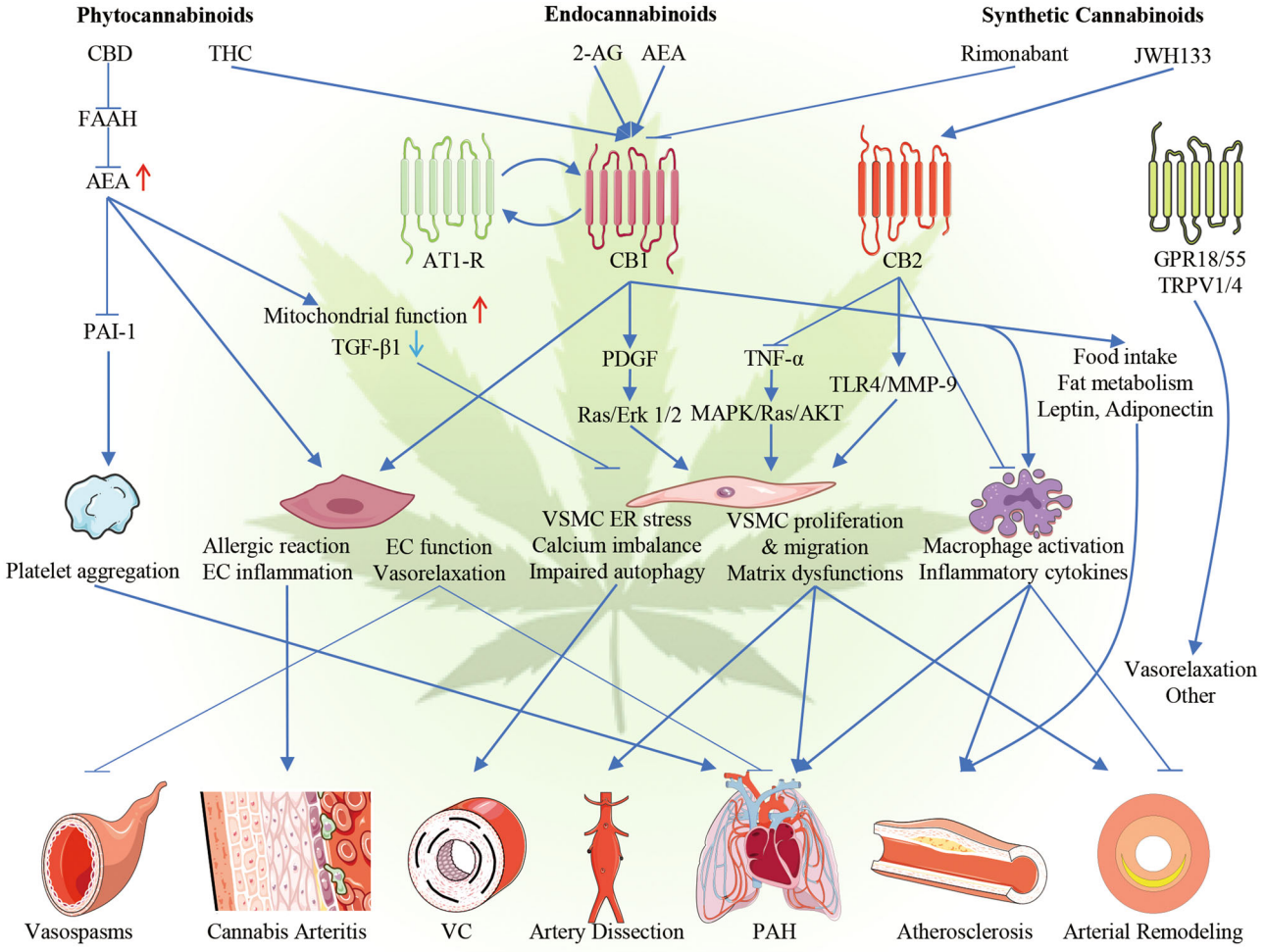

FIGURE 3 Hypothetical effects of cannabinoids on vascular cells and subsequent vascular diseases. Cannabis use is associated with atherosclerosis and triggers vasospasm, arteritis, aortic dissection, and VC. Cannabinoids may also represent a new therapeutic strategy for PAH and arterial remodeling. CB1 activation promotes atherosclerosis development by increasing food intake, modulating fat metabolism and the release of adipose-derived hormones. Additionally, cannabinoids can ameliorate atherosclerosis progression via immunomodulatory effects of CB1 on macrophages. CB1 activation contributes to VSMC proliferation and neointima formation. By contrast, CB2 activation inhibits proliferation and migration of VSMCs, and reduces neointima formation. Mechanically, CB1 inhibition and CB2 activation can attenuate PDGF- and TNF-α-induced proliferation and migration of VSMCs by the activation of the Ras-Erk 1/2 and MAPK/Ras/AKT pathways, respectively. The mechanisms underlying cannabis arteritis may be associated with allergic reactions and EC inflammation. Cannabinoids may promote the progression of VC via dysfunctional calcium homeostasis, impaired autophagy, and ER stress in VSMCs. Cannabis use may also contribute to spontaneous artery dissection/aneurysm formation through the mutual interaction of CB1 and AT1-R and CB2-induced TLR4/MMP-9 signaling. CBD can increase endocannabinoid levels via the inhibition of FAAH, and then ameliorate PAH progress by improving endothelial function. CBD may also attenuate PAH progress by inhibiting the CB1-induced inflammatory response and hyperproliferation of PASMCs via improved PASMC mitochondrial function and activation of the TGF-β1 signaling pathway. Additionally, CBD may also show therapeutic usage in PAH by inhibiting PAI-1-induced platelet aggregation. 2-GA, 2-arachidonoylglycerol; AEA, anandamide; AT1-R, angiotensin II type 1 receptor; CBD, cannabidiol; ECs, endothelial cells; ER, endoplasmic reticulum; FAAH, fatty acid amide hydrolase; MMP-9, matrix metalloproteinase-9; PAH, pulmonary arterial hypertension; PAI-1, plasminogen activator inhibitor-1; PASMCs, pulmonary arterial smooth muscle cells; TGF-β1, transforming growth factor β1; THC, 9-tetrahydrocannabinol; TNF-α, tumor necrosis factor-α; VC, vascular calcification; VSMCs, vascular smooth muscle cells.

rimonabant (30 mg/kg/d) did not affect serum total cholesterol, it still had antiatherosclerotic effects in LDLR$^{-/-}$ mice. Moreover, rimonabant was shown to decrease lipopolysaccharide (LPS)-and IL-1β-induced proinflammatory gene expression in vitro as well as thioglycolate-induced recruitment of macrophages in vivo (Dol-Gleizes et al., 2009). In another study, Lim et al. found that chronic treatment with rimonabant reduces myocardial infarct size in a model of ischemia-reperfusion injury and the cardioprotective effects appeared to be independent of weight loss (Lim et al., 2009). The above studies indicate that CB1 may participate in the regulation of atherosclerosis by multiple mechanisms independent of cholesterol metabolism.

The Rimonabant in Obesity–Lipids (RIO–Lipids) study revealed that selective blockage of CB1 with rimonabant not only reduces body weight, but also improves several metabolic risk factors by increasing concentrations of high-density lipoprotein (HDL) cholesterol and adiponectin, and reducing hsCRP, triglycerides, blood glucose, fasting insulin, and leptin in overweight patients with dyslipidemia (Despres et al., 2005). Despite the benefit obtained in weight reduction, the favorable effects of rimonabant on cardiovascular diseases remain unclear. The Strategy To Reduce Atherosclerosis Development In-Volving Administration of Rimonabant—the Intravascular Ultrasound Study (STRADIVARIUS) found that rimonabant (20 mg/day) administered over 18 months did not reduce coronary disease progression in patients with abdominal obesity and metabolic syndrome as assessed by intravascular ultrasound (Nissen et al., 2008). The Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial demonstrated that rimonabant did not improve adverse cardiovascular outcomes, and the trial was prematurely terminated after a mean of 14 months follow-up owing to serious neuropsychiatric side effects (Topol et al., 2010).

CB2 is expressed in atherosclerotic lesions of mice and humans and a growing body of research has revealed a link between the activation of CB2 signaling and atherosclerosis (Meletta et al., 2017; Montecucco et al., 2012; Steffens et al., 2005; Zhao, Liu, et al., 2010). CB2 is expressed primarily in immune cells, and in vitro studies have shown that CB2 modulates macrophage migration, adhesion, differentiation, accumulation, and oxLDL-induced apoptosis. In vivo studies suggest that oral administration of THC (Steffens et al., 2005) (1 mg/kg/d) or WIN55212-2 (Zhao, Liu, et al., 2010; Zhao, Yuan, et al., 2010) ameliorates atherosclerosis progression in ApoE$^{-/-}$ mice via immunomodulatory effects of CB2 on macrophages. Moreover, Delsing et al. reported that *CB2* deficiency in hematopoietic cells aggravates early atherosclerosis in LDLR$^{-/-}$ mice (Delsing, 2011). Additionally, CB2 was reported to be associated with MMP-9 activity (Montecucco et al., 2009, 2012; Netherland et al., 2010), collagen degradation, and subsequent plaque vulnerability. In an in vivo study, Montecucco et al. found that CB2 was downregulated in human vulnerable plaque, and its expression was inversely correlated with MMP-9 expression (Montecucco et al., 2012). Subsequent in vitro investigations suggested that CB2 colocalized with neutrophils and MMP-9 in ApoE$^{-/-}$ mice, and JWH-133, a selective CB2 agonist, prevented neutrophil release of MMP-9 in vivo and in vitro by reducing TNF-α-induced ERK1/2 phosphorylation in human neutrophils (Montecucco et al., 2012). Therefore, CB2 may serve as a new marker for the diagnosis (Meletta et al., 2017) and treatment of atherosclerosis. Conversely, although JWH-133 reduced lesion formation by improving endothelial function, *CB2* deficiency had no impact on plaque formation in ApoE$^{-/-}$ mice (Hoyer et al., 2011). Furthermore, although *CB2* deficiency results in increased macrophage content and elastin fiber fragmentation and reduced lesional apoptosis in atherosclerotic plaques, both genetic deficiency and pharmacological blockage of CB2 do not relevantly modulate atherogenesis in LDLR$^{-/-}$ mice (Freeman-Anderson et al., 2008) and ApoE$^{-/-}$ mice (Montecucco et al., 2009). These conflicting results may be partly explained by several factors including the atherosclerotic genetic background, the composition of the atherogenic diets, and/or the methods for lesion quantitation.

At present, angioplasty with balloon predilatation followed by drug-eluting stent placement has been an effective therapeutic option for coronary artery disease. Despite improvements in stent design, drugs, and polymers, ISR in second-generation drug-eluting stents still happens in 5%–10% of patients and continues to pose a therapeutic challenge. Although the detailed mechanisms are yet to be determined, it is generally believed that aggressive neointimal proliferation and late neoatherosclerosis are the predominant pathogenic mechanisms of the ISR process. Thus, inhibiting VSMC proliferation is critical for preventing ISR. Previous studies demonstrated that balloon injury increases systemic endocannabinoid levels and induces expression of cannabinoid receptors (CB1 and CB2) in injured arteries of ApoE$^{-/-}$ mice (Molica et al., 2012, 2013). A further study revealed that endogenous CB1 activation contributes to VSMC proliferation and neointima formation in response to arterial injury, and CB1 antagonist AM-281 or *CB1* deficiency significantly reduces proliferation rates of VSMCs in vitro (Molica et al., 2013). By contrast, *CB2* deficiency resulted in increased intima formation compared with the control group, whereas pharmacological CB2 activation using JWH-133 reduces neointima formation in injured arteries of ApoE$^{-/-}$ mice (Molica et al., 2012). In in vitro studies, CB1 inhibition with rimonabant (Rajesh, Mukhopadhyay, Haskó, & Pacher, 2008) and CB2 activation with JWH-133 (Rajesh, Mukhopadhyay, Haskó & Huffman, Mackie, et al., 2008) attenuated PDGF- and TNF-α-induced proliferation and migration of human coronary SMCs by the activation of Ras-ERK and Ras/MAPK/AKT pathways, respectively (Figure 3). Taken together, these preclinical data appear to support that blocking CB1 together with selective activation of CB2 could be an attractive therapeutic strategy for the treatment of ISR.

Although blocking CB1 may protect against neointima formation, in two double-blind, randomized controlled trials, STRADIVARIUS and AUDITOR, despite treatment with rimonabant reducing body weight, waist circumference, and total atheroma volume, it did not significantly reduce percent atheroma volume and carotid intima-media thickness progression in patients with abdominal obesity and metabolic syndrome. To date, only two clinical trials have been conducted, therefore more clinical trials with suitable drugs should be

performed to confirm the role of cannabinoid receptors in neointimal proliferation.

4.2 | Cannabis and pulmonary arterial hypertension

PAH is a progressive condition characterized by pulmonary vasoconstriction and vascular remodeling leading to elevated pulmonary arterial pressures and right-heart failure. Despite current therapies improving the quality of patients' lives, PAH remains an incurable disease that urgently needs new strategies and better therapeutic interventions. In recent years, the vasorelaxation of human and rat pulmonary arteries caused by abnormal CBD and endocannabinoids suggests the potential therapeutic significance of CBD in PAH treatment.

CBD has multipotent beneficial effects. First, CBD has been shown to modify endocannabinoid levels via the inhibition of FAAH (De Petrocellis et al., 2011). CBD (10 mg/kg/d for 3 weeks) also increases lung concentration of endocannabinoids and ameliorates MCT-induced PAH in rats by improving endothelial function and reducing leukocyte count (Sadowska et al., 2020). Second, CBD inhibits the excessive proliferation of PASMCs in preclinical models. In a recent study, Lu et al. demonstrated that CBD improved PASMC mitochondrial function, inhibited the hyperproliferation of PASMCs, and ameliorated Sugen + hypoxia-induced PAH in mice and MCT-induced PAH in rats (Lu et al., 2021). In addition, Krzyzewska et al. found that chronic administration of CBD (10 mg/kg) to MCT-treated rats decreased the proliferation of PASMCs (Krzyżewska et al., 2023) through the TGF-β1 signaling pathway. Third, CBD may attenuate PAH progress by reducing the CB1-induced inflammatory response. In a recent study, Krzyzewska et al. found that MCT-induced PAH increased CB1 expression in rat lung tissues, and CBD attenuated PAH by decreasing CB1 expression and levels of inflammatory mediators (Krzyżewska et al., 2022).

Pulmonary thromboembolic hypertension usually manifests in patients due to recurrent or incomplete resolution of pulmonary embolism. In previous studies, CBD was shown to inhibit platelet aggregation induced by collagen, adenosine, or epinephrine. Moreover, CBD was found to decrease PAI-1 in lung (Ramer et al., 2010), and ameliorate MCT-induced PAH (Sadowska et al., 2020). Therefore, CBD may also show therapeutic usage in PAH by inhibiting platelet aggregation. The pleiotropic properties of CBD may prove useful as a therapeutic tool for the treatment of PAH, but a large-scale clinical investigation on CBD in PAH patients is needed.

4.3 | Cannabis and vascular calcification

VC, which is categorized by intimal and medial calcification, is linked to increased cardiovascular risks. Intimal calcification is associated with atherosclerosis and increased risk for plaque rupture, while medial calcification is prevalent in certain pathologic conditions, including genetic diseases, diabetes, and diseases with disturbances of calcium metabolism (e.g., chronic kidney disease), and may be related to increased arterial stiffness. Despite clinical trials conducted to evaluate the efficacy of drug therapies for VC, none have been successful.

It is well-established that dysfunctional calcium homeostasis, defective autophagy or mitophagy, and ER stress, may all contribute to VC. CB1 and CB2 play a crucial role in the regulation of bone metabolism, and *CB1* knockout mice have increased bone mass (Idris et al., 2005). All this evidence suggests that cannabinoids may promote the progression of VC via multiple mechanisms. However, one small retrospective case-control study found no significant association between marijuana smoking and VC (43% vs. 26%; $p = 0.06$) (Murtha et al., 2023). Therefore, more large-scale clinical investigations should be conducted to clarify the effect of cannabinoids on VC.

Aortic valve calcification (AVC) is considered a potential cause of cerebral embolism or subclinical valve thrombosis after surgical or transcatheter aortic valve replacement. Warfarin is the most widely prescribed oral anticoagulant used in the prophylaxis and treatment of thromboembolism. Warfarin consists of two optically active isomers (R and S) and is mainly metabolized via cytochrome P450 2C9 (CYP2C9), a major cytochrome P450 isoform. Recent reports suggest medical cannabis (Epidiolex [Cortopassi, 2020] and THC/CBD mixture [Thomas et al., 2022]) or recreational marijuana may interact with warfarin, resulting in increased international normalized ratio (INR) levels and risk of overanticoagulation. In an in vitro study, Yamaori et al. reported that three major cannabinoids (THC, CBD, and CBN) potently cause a concentration-dependent inhibition of CYP2C9 activity (Yamaori et al., 2012). Additionally, synthetic cannabinoids may be contaminated with warfarin-like anticoagulants or rodenticide. Therefore, new oral anticoagulants may serve as treatment alternatives to warfarin in patients using medical cannabis products.

4.4 | Cannabis and arteritis

CA was first reported by Sterne and Ducastaing in 1960. Since then, a large number of new cases and several comprehensive reviews have been published in the literature (Combemale et al., 2005; Desbois & Cacoub, 2013; Peyrot et al., 2007; Pilitsi et al., 2023). Notably, both heavy and light cannabis users can develop CA. Clinically, CA manifests with claudication, Raynaud's phenomenon, ischemic ulcers or digital necrosis, and sometimes venous thrombosis (Desbois & Cacoub, 2013; Peyrot et al., 2007). The mechanisms underlying CA are currently not fully understood, but several mechanisms, including immune-allergic vasculitis, arsenic-containing byproducts, and associated endothelial inflammation, have been proposed as essential for the progression of CA.

CA is probably underdiagnosed because of its clinical resemblance to Buerger's disease. Therefore, the diagnosis of CA should be suspected in all young patients with peripheral arterial disease.

Treatment of CA is mainly medical. Anticoagulant and vasodilator therapy can be given in the acute phase, followed by platelet aggregation inhibitors. Hyperbaric oxygen therapy and complete revascularization can also be used to treat CA. Cannabis-associated arteriopathy had a poor prognosis without cannabis weaning, as 58% of patients underwent limb amputation (Desbois & Cacoub, 2013). Therefore, the most effective treatment of CA is to stop cannabis consumption immediately and definitively.

4.5 | Cannabis and other vascular diseases

In experimental conditions, the vasorelaxation of cannabinoids is well documented; however, this is not always the rule. A growing body of evidence suggests cannabis use causes reversible arterial vasospasms, which is considered the most common cannabis-induced vascular event, responsible for transient ischemic attack (Bliss et al., 2021; Robert et al., 2013; Uhegwu et al., 2015; Wolff et al., 2011) and acute coronary syndrome (Baskaran et al., 2019; Gunawardena et al., 2014; Hodcroft et al., 2014). The underlying mechanisms are still uncertain, but may be associated with baseline autonomic dysfunction coupled with THC-induced irritation of the vascular endothelium.

Spontaneous artery dissection is a rare vasculopathy, and there have been previous reports of cannabis-induced artery dissection in young people, particularly in patients with other predisposing risk factors, affecting coronary artery (Schmid & Auer, 2011), renal artery (Lou et al., 2015), carotid artery (Ibn Hadj Amor et al., 2021), and thoracic aorta (Mason et al., 2019; Sarmiento et al., 2021). The pathophysiology is postulated to be associated with increased hemodynamic and oxidative stress (Ibn Hadj Amor et al., 2021). Additionally, Gestrich et al. found that the mRNA levels of cannabinoid receptors (CB1, CB2, TRPV1, and GRP55) in human aortic aneurysm samples and endocannabinoid concentrations were significantly higher in aneurysms than in controls (Gestrich et al., 2015) (Table 3). Furthermore, the mutual interaction of CB1 and angiotensin II type 1 receptor (AT1-R) in the paraventricular nucleus of the hypothalamus plays an important role in blood pressure (Mińczuk et al., 2022) and heart rate control (Grzeda et al., 2017). Moreover, rimonabant was reported to decrease AT1-R expression in VSMCs and reduce angiotensin II-mediated ROS production and NADPH oxidase activity (Tiyerili et al., 2010). As AT1-R was proven to enhance vascular inflammation and aortic aneurysm formation, it may be speculated that activation of the ECS leads to aortic aneurysm by upregulation of AT1-R and thus increased vascular oxidative stress. Additionally, previous studies demonstrated that *CB2* deficiency alters atherosclerotic lesion formation by inhibiting MMP-9 expression, and exogenous activation of CB2 by JWH-133 could attenuate rat spinal cord ischemia-reperfusion by inhibiting the expression of TLR4/MMP-9. As MMP-9 levels correlate significantly with aortic dissection formation, we speculated that CB2 may also participate in aortic dissection formation by modulating TLR4/MMP-9 expression.

TABLE 3 Summary of clinical studies associated with cannabinoids and vascular diseases.

Vascular diseases	Study	Cannabinoids	Relevant findings
Atherosclerosis	Cross-sectional study	NA	Levels of blood endocannabinoids is increased in patients with coronary artery disease (Sugamura et al., 2009).
	RIO-Lipids study	Rimonabant	Rimonabant significantly reduces body weight and improves the profile of metabolic risk factors (Despres et al., 2005).
	STRADIVARIUS study	Rimonabant	Rimonabant does not reduce coronary disease progression in patients with metabolic syndrome (Nissen et al., 2008).
	AUDITOR study	Rimonabant	Rimonabant does not significantly reduce carotid intima-media thickness progression (O'Leary et al., 2011).
	CRESCENDO study	Rimonabant	Rimonabant does not improve adverse cardiovascular outcomes (Topol et al., 2010).
Vascular calcification	Cross-sectional study	NA	There is no significant difference in coronary artery calcification rates between marijuana smokers and nonsmoker control patients (Murtha et al., 2023).
Cannabis arteritis	Case series study	NA	Cannabis use can lead to cannabis arteritis (Desbois & Cacoub, 2013; Peyrot et al., 2007; Pilitsi et al., 2023).
Reversible arterial vasospasms	Case series study	NA	Cannabis use may be associated with the occurrence of reversible arterial vasospasm (Baskaran et al., 2019; Robert et al., 2013; Wolff et al., 2011).
Artery dissection	Case series study	NA	Marijuana may be a contributing risk factor for acute aortic dissection (Baskaran et al., 2019).
Aortic aneurysms	Cross-sectional study	NA	Levels of endocannabinoid concentration are significantly higher in aneurysms than in controls (Gestrich et al., 2015).

Abbreviation: NA, not applicable.

5 | CONCLUSIONS

Cannabis use has increased tremendously over the past decade, however, the effects of cannabinoids on vascular diseases are not fully understood. Current case series or observational studies have shown that cannabis use is associated with atherosclerosis and triggers arteritis, reversible vasospasm, and aortic aneurysm/dissection. However, large-scale clinical investigations still need to be conducted to clarify the relationship between cannabinoids and vascular diseases. Conversely, CBD, a nonintoxicating cannabis component, was reported to exhibit a wide therapeutic potential on the vascular system. However, translational studies that explore the effectiveness of CBD in human populations are needed. Additionally, cannabinoids exert their physiological and pathophysiological effects on vascular diseases mainly by binding to various CBRs and activating different signaling pathways. Increased CB1 and CB2 expression has been described in atherosclerotic plaques, neointimal lesions following balloon injury, and aortic aneurysms. CB1 has been shown to have a *yin-yang* relationship with CB2 structurally and functionally, and existing CB1 agonists have psychiatric side effects so they are no longer used. Thus, a peripherally restricted CB1 antagonist or polytherapy with a CB1 antagonist and CB2 agonist are promising candidates for the management of metabolic syndrome and vascular diseases. However, the absence of data regarding this polytherapy in preclinical models and clinical studies necessitates future well-designed studies.

AUTHOR CONTRIBUTIONS

Xi-Long Zheng and Yanan Guo have made substantial contributions to conception and design. Yanan Guo drafted the manuscript. Xiaoyun Wei provided writing assistance. Junyu Pei was involved in revising it critically for important intellectual content. Xi-long Zheng and Haibo Yang gave the final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors agreed on the order in which their names will be listed in the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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