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Mini Review

The Potential of Cannabidiol in the Treatment of Cardiovascular Disease -

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ABSTRACT

Cannabidiol (CBD) is a naturally occurring compound extracted from the hemp plant, Cannabis sativa L. CBD is chemically similar to delta-9-tetrahydrocannabinol (THC) but does not have the same euphoric side effects. Previous studies have suggested that CBD has anti-inflammatory and cardio-protective properties, indicating that CBD may be a potential therapeutic option for cardiovascular diseases (CVD). While there has been a great deal of speculation about the medicinal value of this drug, actual research in the field of cardiovascular health is currently very limited. Investigations into the potential medicinal properties of CBD may uncover new therapeutic options for the treatment of CVD.

CARDIOVASCULAR DISEASE (CVD)

CVD is the leading cause of death worldwide [1]. The major underlying cause of CVD is atherosclerosis, a chronic inflammatory disease characterized by arterial plaque accumulation in the sub-endothelial layer, leading to narrowing of the artery. The progression of atherosclerosis can span decades and patients are generally asymptomatic before manifestation of clinical symptoms [2]. Risk factors associated with the development of atherosclerosis include hypertension, dyslipidemia, diabetes, stress, smoking and diet [3]. CVD risk factors induce endothelial injury [3,4] that results in the expression and/or presentation of cell surface receptors including, intracellular adhesion molecule 1 (ICAM1), vascular cell adhesion molecule 1 (VCAM1), P-selectin and E- selectin [5]. These surface receptors interact with circulating monocytes and initiate monocyte rolling and transmigration into the sub-endothelial layer [4]. When monocytes enter the sub-endothelial layer they differentiate into macrophages and internalize oxidized low-density lipoproteins forming lipid engorged macrophages called foam cells [4]. Foam cells can undergo apoptosis resulting in the formation of a lipid rich necrotic core in the vessel wall. As the necrotic core expands, the plaque is vulnerable to rupture [4].

Currently there is no cure for atherosclerosis and interventions mainly focus on controlling risk factors associated with atherosclerosis in order to slow its progression. Though generally effective, pharmaceutical interventions aimed at lowering cholesterol and blood pressure do not completely eliminate CVD risk and are often associated with undesirable side effects. CBD could represent an alternative treatment option.

CANNABIDIOL (CBD)

Plants have always been an important source of drug leads and novel drugs for the treatment of many different conditions and diseases. The hemp plant, Cannabis sativa L., was classified in 1975 and is commonly used for its euphoric mood altering effects [5]. Cannabis sativa L. contains phytocannabinoids, which are bioactive compounds extracted from the plant that are capable of interacting with cannabinoid receptors found on many different cell types [5]. Phytocannabinoids have recently gained a lot of attention for their potential medical properties and uses in western medicine [5]. To date, over 100 phytocannabinoids have been isolated from the Cannabis sativa L. plant [6]. The most abundant, well-known, and well-studied phytocannabinoid is tetrahydrocannabinol (THC) [7]. Although THC has been shown to help with conditions including multiple sclerosis [8], chronic pain [9] and chemotherapy-induced nausea [10], the drawback is its psychoactive effect. CBD is another abundant plant-derived phytocannabinoid isolated from Cannabis sativa L [11]. Structurally, CBD is very similar to THC, however it is devoid of the psychoactive symptoms making it a more desirable pharmaceutical compound. In 2018, the Food and Drug Administration approved Epidiolex, an oral CBD solution, as an anti-epileptic drug [12]. Many other medicinal properties of CBD are currently being examined. A major area of CBD research is focussed upon investigating the anti-inflammatory properties of CBD and its potential medicinal contribution to cardiovascular diseases [11,13]. CBD has also been shown to induce vasorelaxation in normotensive rat models [14] and human mesenteric arteries [15].

CBD RECEPTORS IN THE ENDOCANNABINOID SYSTEM (ECS)

There are two major G-protein coupled receptors for cannabinoids, cannabinoid receptor 1 (CB_1) and cannabinoid receptor 2 (CB_2) [16]. CB_1 is highly expressed in the central nervous system and to some extent in peripheral tissues. CB_2 is located in many peripheral tissues, including the cardiovascular system, and is also highly expressed in immune cells [16]. The endocannabinoid system (ECS) is a homeostatic regulator of many physiological systems in the body, including energy balance, appetite, pain-sensation, blood pressure, mood, embryogenesis, nausea and vomiting control, memory, learning and immune response [16]. CBD's association with cannabinoid receptors is not well defined, however, it is believed that CBD is a partial antagonist for CB_1 and partial agonist for CB_2 [17]. CB_2 was initially thought to be an optimal target for inhibiting atherosclerosis progression. However, genetic knockout of CB_2 did not affect the size of atherosclerotic plaques in high cholesterol diet fed low-density lipoprotein receptor knockout mouse model [18].

CBD can also interact with non- cannabinoid receptors including the peroxisome proliferator-activated receptors (PPAR) [19,20]. PPARs are nuclear receptors that control gene transcription by forming heterodimers with the retinoid X receptor and binding to the peroxisome proliferator hormone response element (PPRE) of target genes [20]. PPARs are present in 3 isoforms, PPARα/β/γ, and are widely expressed in the body [20]. They have a large ligand binding domain and interact with various compounds [20]. Recent evidence, from binding studies, reporter gene assays, the use of selective antagonists, siRNA knockdown studies, and knockout animals suggest that therapeutic effects of CBD are mediated through CBD-PPARγ binding [20]. Myeloid-specific genetic PPARγ-deficient mice have increased aortic atherosclerosis, suggesting that PPARγ is an important receptor for slowing the progression of atherosclerosis [21]. PPARγ has been the focus for many anti-diabetic drugs and is known to regulate adipocyte differentiation, fatty acid storage and glucose metabolism [23]. Additionally, PPARγ activators have been shown to inhibit the expression of ICAM and VCAM and therefore may contribute to reduced monocyte attachment to endothelial cells, resulting in attenuated plaque development [24,25]. Other agonists of PPARγ, including the thiazolidinediones (TZD), have also shown promise in pre-clinical studies as anti-atherogenic drugs [22].

CBD AND ATHEROSCLEROSIS

CBD has been approved for recreational and medical use in Canada and several States, and is currently being tested in the treatment of a plethora of diseases. One major advantage of CDB is that it appears to lack any major detrimental side effects. Despite the limited research on CBD and its effects on the vascular system and atherosclerosis, CBD is currently being marketed as a natural vasorelaxant compound with potential anti-atherogenic effects. A number of studies have discovered an anti-inflammatory and cardio-protective function of CBD when tested in animal models of diabetes [26,27], myocardial infarction [28] and stress [29]. However, the effects of CBD administration on atherosclerosis have not yet been definitively assessed. More research is required to explore the therapeutic potential of CDB in the treatment of atherosclerotic cardiovascular disease.

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