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PERSPECTIVE

Treatment with Cannabidiol Results in an Antioxidant and Cardioprotective Effect in Several Pathophysiologies

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Abstract: *Cannabis sativa* has chemically active compounds called cannabinoids, where Δ9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) are the major ones responsible for the various pharmacological effects. The endocannabinoid system is an endogenous system considered a unique and widespread homeostatic physiological regulator. It is made up of type 1 (CB1) and type 2 (CB2) cannabinoid receptors. CBD, in turn, has a low affinity for CB1 and CB2 receptors, and regulates the effects arising from THC as a CB1 partial agonist, which are tachycardia, anxiety, and sedation. It also acts as a CB2 inverse agonist, resulting in anti-inflammatory effects. Furthermore, its anticonvulsant, neuroprotective, antipsychotic, antiemetic, anxiolytic, anticancer, and antioxidant effects seem to be linked to other discovered receptors such as GRP55, 5TH1a, TRPV I, TRPV II and the regulation of the intracellular concentration of Ca^{2+}. Regarding oxidative stress, O^{2-} can act as an oxidizing agent, being reduced to hydrogen peroxide (H_2O_2), or as a reducing agent, donating its extra electron to NO to form peroxynitrite (ONOO-). The ONOO- formed is capable of oxidizing proteins, lipids, and nucleic acids, causing several cell damages. In this sense, CBD can prevent cardiac oxidative damage in many conditions, such as hypertension, diabetes, or even through the cardiotoxic effects induced by chemotherapy, which makes it a potential target for future clinical use to minimize the deleterious effects of many pathophysiologies.

Keywords: Cannabidiol, oxidative stress, heart, cardiotoxicity, antioxidant, pathophyriologies.

1. INTRODUCTION

Cannabis sativa, popularly known as maconha, marijuana, hashish, charas, bhang, sinsemilia, among others, has been used for centuries by many different people for various purposes [1]. It is known that *Cannabis sativa*. has chemically active compounds called cannabinoids, which are divided into three groups of molecules: endocannabinoids, synthetic cannabinoids, and phytocannabinoids. Phytocannabinoids are the most studied because they have a similar pharmacological action to endocannabinoids, cannabinoids produced by the human body itself. Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the main compounds responsible for such pharmacological effects [1].

In this review, we discuss the beneficial effects of CBD treatment on different and common conditions of cardiac oxidative stress such as hypertension, diabetes, or even the cardiotoxic effects induced by chemotherapy. For the selection of articles, a MEDLINE-based search was performed using the following keywords: “Cannabidiol”, “Oxidative stress”, “Heart”, “Antioxidant”, and “Anti-inflammatory”. The list of articles was subsequently narrowed down to those containing abstracts and articles published in the English language. Information analysis started with the title, followed by the abstract, and then the complete report.

2. ENDOCANNABINOID SYSTEM

The endocannabinoid system is an endogenous system considered a unique and widespread homeostatic physiological regulator. It consists of cannabinoid receptors type 1 (CB1) and 2 (CB2), endogenous ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), enzymes of synthesis and degradation of the ligands and the AEA transporter. AEA and 2-AG are endocannabinoids produced in postsynaptic neurons that bind to cannabinoid receptors in presynaptic neurons, when released, constituting a retrogressive neurotransmission [1, 2].

Both receptors are linked to G protein, which is responsible for signal transduction, a process of activation of intracellular events through external stimuli. CB1 receptors are located mostly in the Central Nervous System (CNS), mainly in the hypothalamus, cortex, cerebellum, and spinal cord, where they modulate actions in memory, cognition and movement. However, they also constitute to the peripheral system, being present in nerve endings. On the other hand,

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CB2 receptors are located peripherally connecting to the cells of the immune system [2]. Activation of these receptors inhibits the action of the adenyl cyclase enzyme, decreases the production of the cyclic adenosine monophosphate (cAMP), in addition to closing the Ca^{2+} channels and activating the K^{+} channels, which end up causing changes in cell functions and decreasing the release of neurotransmitters [2].

3. CANNABIDIOL AND ITS THERAPEUTIC APPLICATIONS

The application of *Cannabis sativa* as a focus of research has become increasingly frequent, especially regarding its use for medicinal and therapeutic purposes. The therapeutic potential of this plant is due to more than 400 chemical compounds it has, among which the most important and studied are THC and CBD. CBD gained great prestige in medicine due to its benefits as an analgesic and immunosuppressive action and for not causing, in principle, chemical dependence [3].

For that reason, a portion of patients suffering from serious illnesses such as epilepsy, Alzheimer's disease, Parkinson's disease, fibromyalgia, schizophrenia, cancer and HIV have chosen to use *Cannabis sativa* as a form of alternative treatment, in order to minimize the adverse effects of the disease, or the side effects arising from specific treatments, such as radiotherapy and chemotherapy, in the case of cancer [3].

In this sense, pharmacologically, CBD presents different targets according to the cell type and its therapeutic effect must depend on its dose administration [4]. About its different molecular target, CBD has a low affinity with CB1 and CB2 receptors, and CBD regulates the effects arising from THC as a CB1 partial agonist, which are tachycardia, anxiety and sedation. It also acts as a CB2 inverse agonist resulting in anti-inflammatory effects. Furthermore, its anticonvulsant, neuroprotective, antipsychotic, antiemetic, anxiolytic, anticancer, and antioxidant effects seem to be linked to other receptors discovered as GRP55, 5HT1a, TRPV I, TRPV II and the regulation of the intracellular concentration of Ca^{2+} [5]. Also, regarding the antioxidant effect, CBD may have a scavenging property, capable of neutralizing ROS arising from a redox imbalance [6].

4. OXIDATIVE STRESS

NAD(P)H oxidase is the main ROS-producing enzyme in the cardiovascular system, like O_2^- and H_2O_2. There are seven members of the Nox family, which comprise different isoforms of NAD(P)H oxidase, including Nox 1-5 and Duox 1 and 2 [7, 8]. Among them, the isoforms expressed in cardiomyocytes are Nox2 and Nox4. Nox2 is a quiescent isoform, but it is activated acutely after a stimulus such as increased blood pressure, inflammatory processes, ischemia, and reperfusion, among others [7, 8]. The activation of Nox2 through these stimuli induces the translocation of the p47 phox subunit from the cytosol to the membrane, coupling to cytochrome b558, originating the active form of NAD(P)H oxidase, responsible for catalyzing the production of O_2^- [8-12]. On the other hand, Nox4 has a basal activity regulated by changes in its expression and, in addition, its production is predominantly H_2O_2 [7, 8]. It is noteworthy that the location of the two isoforms in the cardiomyocyte is different. Nox2 in its active form is believed to be located in the plasma membrane, while Nox4 is found in the intracellular environment, including endoplasmic reticulum, mitochondria and perinuclear region [7, 8]. O_2^- can act as an oxidizing agent, being reduced to H_2O_2, or as a reducing agent, donating its extra electron to NO to form peroxynitrite ($ONOO^-$). The $ONOO^-$ formed is capable of oxidizing proteins, lipids, and nucleic acids, causing several cell damages [13].

In contrast to the activity of NAD(P)H oxidase, the production of ROS is regulated by an antioxidant system that can be divided into two main groups, the enzymatic and the non-enzymatic group. The main enzymes of the antioxidant machinery are SOD, Catalase and Glutathione Peroxidase (GPx) [14-16]. SOD is considered the first line of defense against ROS, as it catalyzes the dismutation of O_2^- into H_2O_2. Catalase is able to break down H_2O_2 into O_2 and H_2O. Glutathione peroxidase (GPx), in turn, defends the body from oxidative stress by reducing H_2O_2 to H_2O and lipoperoxides to alcohols. For this, GPx uses GSH as a substrate for its reaction, leading to the formation of GSSG [16-18].

5. CANNABIDIOL AND ITS CARDIOPROTECTIVE EFFECTS

Several studies have already demonstrated the ability of CBD to reduce oxidative stress and inflammation in cardiac tissue in a variety of pathophysiological conditions (Fig. **1**). In this sense, Fouad *et al*., (2013) observed that animals undergoing treatment with doxorubicin, at a dose of 2.5 mg/kg intraperitoneally, for two weeks, with intervals between doses of 48 hours, showed increased serum CK-MB levels and troponin T, in addition to high malondialdehyde (MDA), TNF-α and NO values in cardiac tissue. Doxorubicin also elevated the expression of inducible nitric oxide synthase, nuclear factor-κB, Fas ligand and caspase-3. From this, it was demonstrated that the parallel administration of CBD, at a dose of 5 mg/kg, intraperitoneally, was able to prevent all these cardiotoxicity responses induced by the chemotherapy in question [3].

Also, following this line, Hao *et al*., (2015), have evaluated again the potential of CBD to prevent oxidative and nitrative stress and inflammation that generates cardiomyopathy in animals treated with doxorubicin. The authors demonstrated that CBD decreased iNOS levels, thus attenuating the myocardial nitrotyrosine formation induced by this drug, reduced the decline in myocardial mitochondrial copy number, and increased mitochondrial biogenesis in injured hearts. In addition, CBD attenuated lipid peroxidation and increased levels of GSH and the activity of GPx, which attenuated the formation of cardiomyopathy [19].

More recently, Remiszewski *et al*. (2020) [5] evaluated the effect of CBD in different models of hypertension, such as in nephrectomized animals submitted to treatment with deoxycorticosterone acetate (DOCA-Sal), as well as in spontaneously hypertensive rats (SHR). In this sense, CBD, at a dose of 10 mg/kg, intraperitoneally, daily, was not able to change blood pressure and heart rate values in hypertensive animals, but the drug in question caused a reduction in tissue

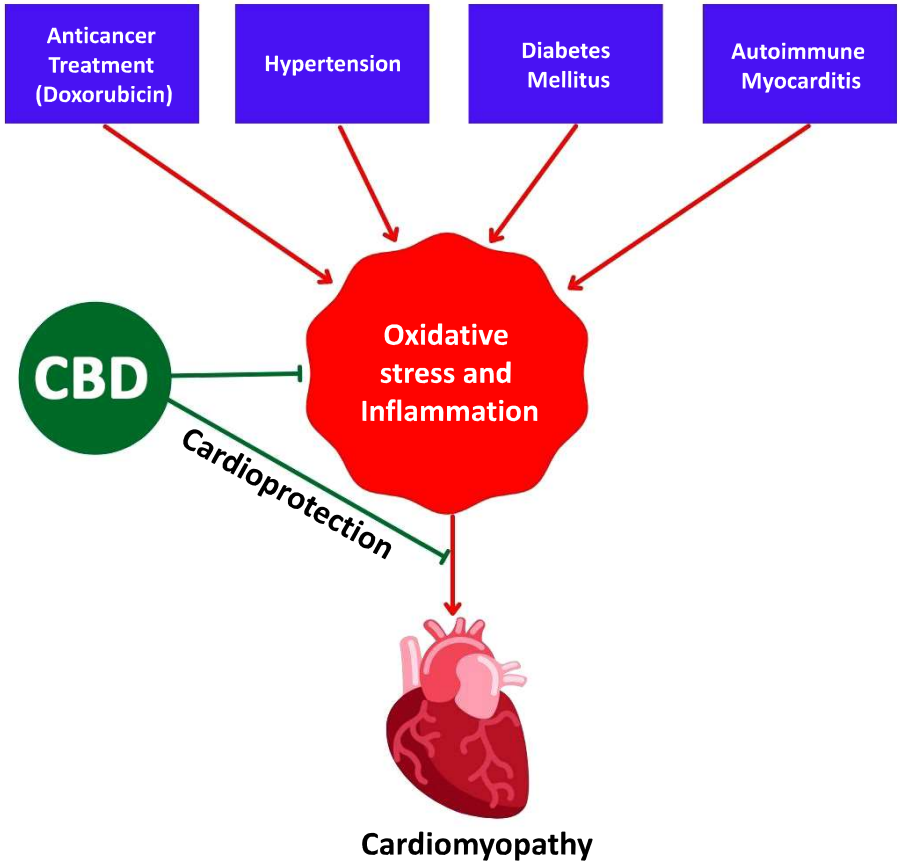

Fig. (1). Schematic resume about cardioprotective effect of Cannabidiol (CBD). Anticancer treatment with doxurubicin, hypertension, diabetes mellitus and autoimmune myocarditis is able to induce oxidative stress and inflammation in the heart resulting in cardiomyopathy. CBD treatment is responsible for reducing these damages demonstrating cardioprotective effects in these diseases. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

and plasma levels of products of lipid peroxidation such as MDA and 4-Hydroxynenal (4-HNE). Furthermore, CBD was responsible for increasing tissue and plasma concentrations of GSH. The authors believe that the antioxidant effect demonstrated by the treatment with CBD can occur directly, through the action of an scavanger, or even *via* the endocannabinoid system [5].

Garcia-Martin *et al.*, (2021) observed the effects of CBD on angiotensin II-induced inflammation in mice. In this sense, the authors implanted an osmotic pump of angiotensin-II (1000 ng/kg/min), for 28 days which resulted in increased expression of IL-6, IL-1α, IL-1β and higher infiltration of T cells and macrophages in cardiac tissue. The treatment with CBD (20 mg/kg) during all the period of pump implantation prevented all these angiotensin-II inflammatory effects in the hearts of mice [20].

The cardioprotective effect of CBD was also evaluated by Matouk *et al.*, (2017), in an animal model of diabetes mellitus, induced by a single injection of streptozotocin, at a dose of 55 mg/kg, intraperitoneally. Thereafter, treatment for 2 weeks with CBD (100 μg/kg/day, intraperitoneal), despite not interfering with high glucose and reduced insulin levels, it was still able to reduce oxidative parameters in cardiac tissue. Thus, diabetic rats showed a reduction in NO levels, in parallel with an increase in MDA values and catalase activity in cardiac tissue, and all these responses were reversed by treatment with CBD. The authors further add that these responses can occur *via* activation of the GPR-18 receptor [21].

More recently, Fouda *et al.* (2020) also evaluated the effects of CBD in models of diabetes mellitus. The authors used cultures of Chinese hamster ovary (CHO) cells, transfected with the gene responsible for the synthesis of the Nav 1.5 ion channel, which is the main cardiac sodium channel and, in conditions of hyperglycemia and, consequently, oxidative stress is responsible for inducing arrhythmias. Afterwards, the transfected cells were submitted to a control condition or to high concentrations of glucose (50 or 100 mM for 24 hours), in order to mimic hyperglycemic conditions. In this sense, the exposure of cells to high levels of glucose resulted in an increase in the generation of ROS and, consequently, hyperexcitability, in addition to an increase in the rate of cell death. In this sense, parallel incubation with CBD at a concentration of 5 μM was able to prevent all the deleterious effects caused by hyperglycemia [22].

Rajesh *et al.*, (2010) also studied the CBD cardioprotective effects in an animal model of diabetes mellitus, induced by streptozotocin, at a dose of 55 mg/kg, intraperitoneally, for 5 consecutive days. Thus, diabetic mice presented increased cardiac levels of lipid peroxides, ROS generation, expression of mRNA of NAD(P)H subunits (p22phox, p67phox, gp91phox), accumulation of 3-nitrotyrosine and reduced activity of SOD. Diabetes mellitus also caused myocardial inflammation demonstrated by elevated degradation of IκB-α in the cytosol, higher activation of NF-κB and increased expression of adhesion molecules as ICAM-1 and VCAM-1, pro-inflammatory cytokine TNF-α, and iNOS. The oral treatment with CBD (20 mg/kg/day) for 11 weeks attenuated all these oxidative and inflammatory parameters on cardiac tissue, confirming its cardioprotective effect [23].

Lee *et al*., (2016) evaluated the cardioprotective effect of CBD in the T-Cell-mediated autoimmune myocarditis. The mice model of myocarditis was characterized by myocardial T-cell infiltration and increased levels of pro-inflammatory proteins as IL-6, IL-1β, INF-γ and MCP-1. Elevated oxidative stress parameters were also observed in the hearts of mice with myocarditis as p47phox protein expression, 4-HNE and 3-NT. In this sense, the treatment with CBD (10 mg/kg) for 46 consecutive days prevented all these cardiac inflammatory and oxidative alterations, demonstrating that this phytocannabinoid may represent a promising novel treatment for managing autoimmune myocarditis [24].

CONCLUSION

In summary, from the data presented, it is possible to observe that CBD has several therapeutic properties, with emphasis on its antioxidant and anti-inflammatory effects. Thus, it was possible to demonstrate that the phytocannabinoid in question can prevent cardiac oxidative and inflammatory damages in various conditions, such as hypertension, diabetes, auto-immune disease or even through the cardiotoxic effects induced by chemotherapy. Thus, CBD presents itself as an important target for future clinical applications, with the intention of minimizing cardiac damage induced by various pathophysiologies.

LIST OF ABBREVIATIONS

cAMP	=	Cyclic Adenosine Monophosphate
CBD	=	Cannabidiol
CNS	=	Central Nervous System
DOCA-Sal	=	Deoxycorticosterone Acetate
MDA	=	Malondialdehyde
THC	=	Tetrahydrocannabinol

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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