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THE ROLE OF CANNABIDIOL IN THE TREATMENT OF ATHEROSCLEROSIS: THERAPEUTIC POTENTIALS AND REGULATORY CHALLENGES IN MEDICINE

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Maria Eduarda Carneiro Rizzatti[1], Graziela Torres Blanch[2], Ana Elisa de Figueiredo Miranda Mundim[3] and Kesia Morais de Lima[4].

ABSTRACT

Introduction: Cardiovascular diseases are one of the main causes of global mortality, and atherosclerosis, characterized by the accumulation of fatty plaques in the arteries, is one of the most common variants. Recently, Cannabidiol has sparked interest as a potential preventive approach to atherosclerosis. **Objective**: The present study aims to explore the therapeutic potential of Cannabidiol in this context, reviewing relevant clinical and experimental studies, in order to promote an interdisciplinary dialogue between researchers and health professionals. **Methodology**: For this, the PubMed Advanced database was used to conduct a literature review, with specific inclusion criteria that aimed to find direct studies on the therapeutic use of Cannabidiol in atherosclerosis. **Results**: The results highlight Cannabidiol's ability to reduce inflammation and mitigate complications associated with atherosclerosis, such as endothelial dysfunction and myocardial infarction. However, despite the promising findings, validating the efficacy and safety of Cannabidiol requires rigorous clinical trials. **Conclusion**: The study concluded that Cannabidiol demonstrates great potential as a therapeutic agent for atherosclerosis, and therefore, more research should be done on this substance so that we can fully use and understand its effects.

Keywords: Cardiovascular diseases. Atherosclerosis. Cannabidiol. Inflammation. Clinical trials.

[1] Medical student
Pontifical Catholic University of Goiás
School of Medical and Life Sciences - Medical Course
[2] Dr. in Physiological Sciences
Pontifical Catholic University of Goiás
School of Medical and Life Sciences - Medical Course
[3] Master of Science in Environmental and Health Sciences
Pontifical Catholic University of Goiás
School of Medical and Life Sciences - Medical Course
[4] Medical student
Pontifical Catholic University of Goiás
School of Medical and Life Sciences - Medical Course

Revista ARACÊ
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INTRODUCTION

Cardiovascular diseases (CVD) are a group of diseases of the heart and blood vessels, such as: coronary heart disease, cerebrovascular disease, and other conditions. On average, 4 out of 5 CVD deaths are due to heart attacks and strokes.[1] CVD, according to the WHO (World Health Organization), is the leading cause of death in the world, with about 17.9 million victims annually.[1,2] The WHO estimated that, as of 2015, there would be 20 million deaths each year from CVD, consolidating the estimate, in 2016, there were 17.9 million deaths from cardiovascular diseases. [2,3] Brazil reflects this global pattern, since, according to the Mortality Information System (SIM), in 2022 more than 400 thousand deaths were caused by cardiovascular events, and of this total, 835 deaths were caused by atherosclerosis. [4]

The main risk factors for CVD are intrinsically linked to the age group between 50 and 70 years, with gender being more predominant in men,5 in addition to other aggravating factors such as hyperlipidemia, smoking (increases the risk by nine times), hypertension, sedentary lifestyle, and social components, such as stress and poverty.[3,5,6] It is observed that certain determinants manifest themselves as a reflection of the main forces that govern social, economic and cultural changes, some of them being globalization, the internet and the increase in working hours.[3,5,6]

Among the various cardiovascular conditions, atherosclerosis deserves to be highlighted. This condition involves the slow and progressive accumulation of fatty plaques in the arteries, known as atheroma, which accumulate in a diffuse or localized way.[5,6] The growth of these plaques can culminate in the rupture of the atheroma or in the narrowing of the vessel, and for the first ischemic symptoms to appear, the obstruction of the vessel must reach about 75% of its caliber, compromising the blood flow in the affected region, the supply of oxygen and nutrients, and its functionality.[5]

As it is a worldwide problem, atherosclerosis arouses the interest of pharmaceutical companies in the search for effective preventive treatments. In this context, cannabidiol (CBD) has currently emerged as a possible therapeutic candidate. [7] Its anti-inflammatory and antioxidant action are attributes that have awakened the possibility of preventing or reducing some risk factors associated with atherosclerosis and cardiovascular conditions, such as blood pressure and Diabetes Mellitus.[8]

After the scientific proof of several still unknown benefits of Cannabis Sativa, there was a worldwide wave of release of its medicinal use. And although it has been used for

Revista ARACÊ
ISSN: 2358-2472

more than five thousand years by the Chinese pharmacopoeia, its recreational use has made the plant immoral and stigmatized.[9] In this sense, Brazil followed the world and in 2015 there was an initial milestone in the acceptance of the plant for therapeutic purposes with the authorization of the controlled prescription of CBD-based medicines by the National Health Surveillance Agency (Anvisa), [10] which is a significant step towards the integration of alternative and complementary treatments in the Brazilian health scenario.

Scientists Lumír Hanuš and William Devane (1992) triggered the discovery of the Endocannabinoid System (ECS) by isolating the first endocannabinoid, anandamide.[11] Since then, its clinical importance has increased due to its stimulatory and productive factor of endocannabinoids through the CB1 receptor, and its main function is the regulation of learning, memory, sleep, pain control and inflammatory and immunological responses, and the activity of the CB2 receptor.[11.12]

Contrary to social prejudices involving CBD, several studies have reinforced the therapeutic potential of Cannabidiol. In the meantime, the pharmacological industry has analyzed its possibility in reducing atherosclerotic plaques, acting as an agonist of the peripheral receptor CB211 or as an antagonist of CB1, Genistein, inhibiting the activation of the receptor, resulting in the reduction of atheromas.[13]

The hypothesis around CBD has been evidenced by scientific research regarding the reduction of risk markers, regulation of inflammatory molecules and protection of the cardiovascular system, making relevant the discussion around these studies, their therapeutic potential, the medical interest in these products and the conflicts that emerge around the effectiveness of alternative medicine.[10,14,15]

OBJECTIVES

This study aims to explore and analyze the therapeutic potential of CBD in the treatment of atherosclerosis, emphasizing a holistic approach that unites multiple facets of medical research. It is intended to investigate the biological and pharmacological mechanisms through which CBD can influence the progression of atherosclerosis.

This review seeks not only to consolidate and expand the current knowledge about the effects of CBD on atherosclerosis, evaluating its potential as an innovative therapeutic agent in the treatment of this condition, but also to discuss the practical implications of these findings, offering a new perspective on the treatment and clinical management of

Revista ARACÊ
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atherosclerosis, considering CBD as a possible addition or alternative to existing treatment regimens

In addition, this study aims to stimulate an interdisciplinary dialogue between researchers, clinicians, and policymakers. The intention is to advance the clinical applications of CBD, overcoming the obstacles that restrict its therapeutic use. By establishing a constructive dialogue, it is possible to establish a solid foundation for future research and promote a broader understanding of the effective incorporation of CBD into treatment protocols for atherosclerosis, with the ultimate goal of improving healthcare and outcomes for patients globally.

METHODOLOGY

The methodology adopted for this literature review was conducted using the PubMed Advanced database, using the search terms DeCS MeSH ("*Cannabidiol*" OR "*Cannabis*" AND "*atherosclerosis*"). Initially, the search resulted in a total of 67 articles. These were submitted to an initial analysis phase, where 27 articles were selected after applying the predefined inclusion criteria. The article selection process was governed by specific inclusion criteria, which focused on studies that directly explored the therapeutic use of Cannabidiol in the context of atherosclerosis. With regard to exclusion, the criteria adopted aimed to discard studies that did not address these themes directly.

The 27 selected articles were then subjected to a detailed analysis, aiming to extract relevant information about the use of Cannabidiol in the treatment of atherosclerosis. Among the aspects analyzed were the proposed mechanisms of action, preclinical and clinical studies, results obtained and pertinent conclusions. The information was organized and synthesized in an Excel spreadsheet.

It is crucial to emphasize that this literature review may have some limitations inherent to the process, including the possibility that specific studies on the subject may be limited. All articles included in this review were evaluated under the ethical and legal guidelines pertinent to scientific research, ensuring the integrity and ethical rigor of this study.

RESULTS

Research in cannabinoids and cardiovascular health is unlocking new perspectives on the complex interaction between these compounds and the cardiovascular system. This

Revista ARACÊ
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emerging area is crucial as it investigates the therapeutic benefits and risks associated with the use of cannabinoids, with a particular focus on CVD such as atherosclerosis.

Several findings point to the risks of recreational marijuana use, as demonstrated in Desai, who associates its recreational use with hospital admissions.[16] In this context, an increase in cardiovascular and cerebrovascular events was observed among these patients, underlining the need for greater awareness of the health risks associated with recreational marijuana use.

Among the various side effects caused by the use of such a substance, the risks to the cardiovascular system deserve to be highlighted, as highlighted by the author Subramaniam [17] in his work carried out in 2019. The research highlights the adverse effects of THC on the cardiovascular system, specifically pointing to arteritis, vasospasms, and platelet aggregation. This study is crucial as it underlines the need for a deeper understanding of how marijuana use may influence CVD progression. This disease can also be potentiated by the release of a neurotransmitter directly influenced by the use of Cannabis, as mentioned in Skipina. [18] This article also explores the central role of the endocannabinoid N-arachidonoyl ethanolamine (anandamide) in increasing atherosclerosis, proving the direct relationship between its release in the body and the occurrence of atherosclerotic plaques.

Accordingly, the influence of cannabinoids on the occurrence of heart attacks was also investigated. According to the study by El-Dahan,19 the actions of cannabinoids, including the modulation of adipocyte biology, directly affect regional fat distribution and atherosclerosis. Therefore, cannabinoids can influence hemodynamic stressors in the context of a myocardial infarction. In addition, some studies aim to alert users about the extent of the consequences of the use of the substance in question.

In this sense, in his article published in 2012, Singla.[20] explores the relationship between marijuana use and cardiovascular effects, such as arrhythmias. The role of cannabinoid receptors in the modulation of cellular elements in blood vessels and their potential contribution to atherosclerosis is evidenced.

Liberale's study [21] discusses the pharmacological properties of plant-derived cannabinoids and their impact on cardiovascular health. This research highlights the need for additional research to fully understand the cardiovascular effects of phytocannabinoids and how they can be utilized to benefit patients with cardiovascular disease.

Revista ARACÊ
ISSN: 2358-2472

Several scientific studies have explored the therapeutic potential of Cannabis Sativa with regard to cardiovascular health. This fact is also observable in the scientific production of researcher Liberale [21], since the pharmacological properties of plant-derived cannabinoids and their impact on cardiovascular health have been shown to be promisingly favorable. This study highlights the need for additional research to fully understand the cardiovascular effects of phytocannabinoids and how they can be used to benefit patients with cardiovascular disease.

From this perspective, the benefits in relation to the treatment and especially with regard to the prevention of Atherosclerosis, are prominent in several articles. In the first instance, the study carried out at Mach[22] deserves to be highlighted for the topic, as it examines C-reactive protein (CRP) and cannabis in the context of the development, diagnosis or treatment of atherosclerosis. In this same perspective, the study "Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress", also pointed to CBD as a reducer of oxidative stress of immune cells, revealing its potential to treat diseases such as rheumatoid arthritis, atherosclerosis, Alzheimer's and neuropathic pain. Still on this, the idea explored in the article by Teichmann[23] demonstrates that both CBD and THCV have great potential to reduce inflammation in cardiovascular tissues.

The benefits of CBD are widely explored in Kleiner[24], which brings in its text the use of cannabidiol as an adjuvant therapy for metabolic syndrome. In the meantime, CBD demonstrates effects as an antagonist of serotonin receptors and cannabinoids, relieving hyperphagia without side effects associated with other therapies. In addition, its immunomodulatory effect may help reduce the progression of atherosclerosis induced by high glucose, suggesting a potential role in ischemic complications associated with metabolic syndrome.

Other promising notes were made by Huang[25], who reinforced in his work the use of Cannabidiol for both the treatment and prevention of atheromatous plaques. Therefore, this article demonstrates the anti-atherosclerotic effects of cannabis seed oil, suggesting a preventive strategy in the progression of atherosclerosis.

It is worth noting that the author Rajesh[26] evidenced in his work that CBD also demonstrates the ability to mitigate endothelial barrier dysfunction and monocyte adhesion and migration, suggesting its therapeutic potential against diabetic complications and atherosclerosis. The study investigated the effects of CBD on endothelial dysfunction

Revista ARACÊ
ISSN: 2358-2472

induced by high glucose concentrations. The results suggest the potential of CBD to attenuate mitochondrial superoxide generation, NF-kappaB activation, and endothelial barrier dysfunction associated with high glucose levels, indicating a possible therapeutic application in this context.

In addition, in the article carried out by Kaushal[27] he evidenced that the use, not only of Cannabidiol, but of components of the plant itself from which CBD is extracted, demonstrated efficiency in reducing factors that potentiate the appearance of atherosclerosis. The study investigates the impact of hemp seeds on cardiovascular health in models of hypercholesterolemia. In this context, results indicated improvements in lipid profiles and aortic tissue health, suggesting that the inclusion of hemp seeds in the diet may have protective effects against cardiovascular changes associated with hypercholesterolemia.

Also on this, another study by researcher Takeda[28] was selected that reinforces the benefits of Cannabidiol by exploring the ability of cannabidiol-2',6'-dimethyl ether (CBDD) to inhibit low-density lipoprotein (LDL) oxidation mediated by 15-lipoxygenase, being a critical factor in atherosclerosis. The results provide evidence that CBD-derived compounds can be effective therapeutic agents in the prevention and treatment of atherosclerosis.

In addition, the research carried out by Scharf[29] suggests CBD as a therapeutic candidate for stroke prevention, enhancing endocannabinoid signaling and improving metabolic syndrome while delaying the development of atherosclerosis. In his research, Liberale[21] discusses the pharmacological properties of plant-derived cannabinoids and their impact on cardiovascular health. This study highlights the need for additional research to fully understand the cardiovascular effects of phytocannabinoids and how they can be used to benefit patients with cardiovascular disease. These collective studies illustrate the complexity and vast potential of cannabinoids in modulating cardiovascular health and beyond. They underscore the potential therapeutic role of these compounds and emphasize the need for in-depth understanding of their effects in different clinical contexts. Continued research is essential to fully unravel the benefits and risks of cannabinoids in cardiovascular health and other areas.

DISCUSSION

Research on CBD in the treatment of atherosclerosis, a prevalent cardiovascular condition, reveals an emerging field in medicine. CBD's anti-inflammatory and antioxidant

Revista ARACÊ
ISSN: 2358-2472

properties, along with its interaction with the endocannabinoid system, offer significant therapeutic potential for cardiovascular diseases, including atherosclerosis.[9,10,11] Studies suggest that CBD may attenuate the progression of atherosclerosis by reducing inflammation and improving lipid profile, two critical factors in atherosclerotic plaque formation.[4,26,30]

Research on CBD is still in its early stages, and while initial results are promising, rigorous clinical trials and long-term analyses are needed to validate the efficacy and safety of CBD in patients with atherosclerosis.[10] In addition, the standardization and quality of CBD products are crucial to the reliability of study results, given the variation in cannabis-based products.[13,31,32]

The progressive legalization of the medical use of cannabis and the growing acceptance of CBD in conventional medicine are opening up new research opportunities.[13] This could lead to the development of new CBD-based drugs for the treatment of atherosclerosis, offering therapeutic alternatives for patients with cardiovascular disease.

However, understanding the effects of CBD in the cardiovascular context requires a holistic approach. In addition to its therapeutic application, it is crucial to consider the regulatory, ethical, and practical challenges associated with the use of cannabis-based products, including issues of standardization, quality, and public perception.[13,31,32]

In conclusion, CBD has significant potential as a therapeutic agent for atherosclerosis. However, future research is key to overcoming the current limitations and establishing CBD as an effective and safe therapy for cardiovascular disease. Continued collaboration between researchers, healthcare professionals, and policymakers will be crucial to advancing the understanding and application of CBD in cardiovascular medicine.

CONCLUSION

The investigation of Cannabidiol (CBD) in the treatment of atherosclerosis opens up new horizons in cardiovascular medicine. Recent studies indicate that CBD, with its anti-inflammatory, antioxidant properties and beneficial effects on the endocannabinoid system, can be an innovative therapeutic path to combat the progression of atherosclerosis and other cardiovascular diseases.

CBD has the potential to influence risk factors for atherosclerosis, such as hyperlipidemia, inflammation, and oxidative stress. Studies show that CBD can reduce

Revista ARACÊ
ISSN: 2358-2472

atherosclerotic plaque formation, decrease inflammatory markers, and improve lipid profile, highlighting its potential as a valuable therapeutic agent.

However, research on CBD is still in its early stages. Despite the promising results, more studies are needed to fully understand its impact on the cardiovascular system. This includes well-designed clinical trials to evaluate the efficacy and safety of CBD in different populations, as well as studies to determine optimal dosages and methods of administration.

The research should also address regulatory concerns and challenges associated with the use of cannabinoid-based products. The standardization of CBD extracts, the quality and purity of the products are crucial aspects that need strict regulation to ensure the safety and effectiveness of the treatment. It is equally important to clearly differentiate CBD from other compounds in the Cannabis sativa plant, such as THC, which has psychoactive effects and can have negative implications for cardiovascular health.

Another crucial point is the improvement of the collection of information on cannabis in Brazil, since the scarcity of data on the use and commercialization of cannabis, along with endocannabinoids, presented itself as a significant obstacle. The recent legalization of the medicinal use of the plant in Brazil has brought with it a substantial lack of consolidated and updated information. The absence of specific surveys on cannabis in key databases, such as Datasus, reflects the lack of epidemiological information that could support a more comprehensive analysis.

The lack of up-to-date records compromises the accuracy and generalizability of this study's conclusions, since the dynamics surrounding cannabis use are constantly evolving. Therefore, there is an urgent need for more extensive and comprehensive research to fill in the gaps in understanding the role of cannabidiol in atherosclerosis. In parallel, it is essential to encourage the collection of specific data on cannabis users to provide a solid basis for future investigations and promote significant advances in the management of this valuable resource.

The increased acceptance of CBD in conventional medicine and the progressive legalization of the medical use of cannabis in various countries provide opportunities for the expansion of clinical research. This could lead to the development of new CBD-based drugs for the treatment of atherosclerosis, potentially improving the quality of life and health outcomes of millions of people around the world.

Revista ARACÊ
ISSN: 2358-2472

Finally, it is crucial for the medical and scientific community to continue to address the outstanding issues related to CBD and its role in treating atherosclerosis. Collaboration between cardiologists, pharmacologists, botanists, and other experts is essential to advancing our understanding and application of CBD in cardiovascular medicine. With an ongoing commitment to rigorous and ethical research, CBD can become a valuable tool in the fight against cardiovascular disease, offering new hope for patients around the world.

Revista ARACÊ
ISSN: 2358-2472

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