Research, Society and Development, v. 13, n. 2, e6513245006, 2024
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v13i2.45006

Therapeutic analysis of cannabidiol for Alzheimer treatment

Análise terapêutica do canabidiol para o tratamento de Alzheimer

Análisis terapéutico del cannabidiol para el tratamiento de Alzheimer

Recebido: 31/01/2024 | Revisado: 11/02/2024 | Aceitado: 13/02/2024 | Publicado: 17/02/2024

Maria Vitória Frota Magalhães
ORCID: https://orcid.org/0000-0001-7597-0616
Faculdade Ciências Médicas de Minas Gerais, Brazil
E-mail: vitoriafrotam@gmail.com
Ruymara Candal Nogueira
ORCID: https://orcid.org/0009-0005-5780-723X
Faculdade Multivix Cachoeiro de Itapemirim, Brazil
E-mail: ruymaracandalnogueira@gmail.com
Joana Baschung Bertazzon
ORCID: https://orcid.org/0000-0001-8386-1049
Universidade da Região de Joinville, Brazil
E-mail: joanabaschung@gmail.com
Andressa Gonçalves Vicente
ORCID: https://orcid.org/0009-0001-0988-0425
Centro Universitário Fundação Assis Gurgacz, Brazil
E-mail: andressa.agv@gmail.com
Marcos Gabriel Bastos Sereno
ORCID: https://orcid.org/0000-0003-3976-0501
Centro Universitário FAMINAS, Brazil
E-mail: gabriel.extremer@hotmail.com
Carlos Vinícius Teixeira Palhares
ORCID: https://orcid.org/0000-0002-1790-6226
Faculdade Ciências Médicas de Minas Gerais, Brazil
E-mail: carlos.palhares@cienciasmedicasmg.edu.br
Marina Rodrigues e Silva
ORCID: https://orcid.org/0009-0001-1433-279X
Faculdade Ciências Médicas de Minas Gerais, Brazil
E-mail: marinarscbb@gmail.com

Abstract
Objective: To analyze therapeutic evidence regarding the potential antioxidant, anti-inflammatory and neuroprotective effects of cannabidiol (CBD) and its effectiveness for the treatment of Alzheimer's Disease (AD). Methodology: Data collection, in the Virtual Health Library, targeting the primary databases *Medical Literature Analysis and Retrieval System Online (*Medline) and *Latin American and Caribbean Literature in Health Sciences* (Lilacs) to answer the research question: is the therapeutic use of cannabidiol effective in improving the treatment of patients with Alzheimer's Disease? Results: 14 articles were selected, after analyzing the inclusion and exclusion criteria, all after 2017, with the largest number concentrating on systematic literature review or meta-analysis. Conclusion: Cannabidiol has clear potential to reduce the symptoms of AD given its action on the Central Nervous System. Therefore, its therapeutic use in the treatment of AD emerges as a promising field of investigation, highlighting its relevance as a safe and effective treatment option. Therefore, an in-depth understanding of the antioxidant, anti-inflammatory and neuroprotective properties of CBD is necessary, not only for a better clinical definition of AD, but also for a series of neurological diseases that still have undefined treatments. The potential of CBD, therefore, represents a valuable alternative in the context of neurology, offering significant perspectives for the treatment of neurodegenerative conditions.
Keywords: Alzheimer disease; Therapeutic; Cannabidiol; Treatment.

Resumo
Objetivo: Analisar as evidências terapêuticas quanto aos potenciais efeitos antioxidantes, anti-inflamatórios e neuroprotetores do canabidiol (CDB) e sua eficácia para o tratamento da Doença de Alzheimer (DA). Metodologia: Levantamento de dados, na Biblioteca Virtual em Saúde, com direcionamento às bases primárias *Medical Literature Analysis and Retrieval System Online* (Medline) e Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) para responder à pergunta de pesquisa: o uso terapêutico do canabidiol é eficaz para melhorar o tratamento de pacientes com Doença de Alzheimer? Resultados: Foram selecionados 14 artigos, após análise dos critérios de inclusão e exclusão, todos posteriores ao ano de 2017, concentrando-se o maior número em revisão sistemática da literatura ou

metanálise. Conclusão: O canabidiol possui potencial evidente para diminuir a sintomatologia da DA tendo em vista sua atuação no Sistema Nervoso Central. Desta forma, seu uso terapêutico no tratamento de DA emerge como um campo de investigação promissor, destacando sua relevância como uma opção de tratamento seguro e efetivo. Portanto, faz-se necessária a compreensão aprofundada das propriedades antioxidantes, anti-inflamatórias e neuroprotetoras do CBD, não apenas para a melhor definição clínica da DA, mas também para uma série de doenças neurológicas que ainda possuem tratamentos indefinidos. O potencial do CBD, assim, representa uma valiosa alternativa no contexto da neurologia, oferecendo perspectivas significativas para o tratamento de condições neurodegenerativas.
Palavras-chave: Doença de Alzheimer; Terapêutico; Canabidiol; Tratamento.

Resumen
Objetivo: Analizar la evidencia terapéutica sobre los potenciales efectos antioxidantes, antiinflamatorios y neuroprotectores del cannabidiol (CBD) y su efectividad para el tratamiento de la Enfermedad de Alzheimer (EA). Metodología: Recolección de datos, en la Biblioteca Virtual en Salud, dirigidos a las bases de datos primarias *Medical Literature Analysis and Retrieval System Online* (Medline) y *Literatura Latinoamericana y del Caribe en Ciencias de la Salud* (Lilacs) para responder a la pregunta de investigación: ¿es efectivo el uso terapéutico del cannabidiol para mejorar el tratamiento de pacientes con Enfermedad de Alzheimer? Resultados: Se seleccionaron 14 artículos, luego de analizar los criterios de inclusión y exclusión, todos posteriores a 2017, concentrándose el mayor número en revisión sistemática de literatura o metanálisis. Conclusión: El cannabidiol tiene un claro potencial para reducir los síntomas de la EA dada su acción sobre el Sistema Nervioso Central. Por tanto, su uso terapéutico en el tratamiento de la EA emerge como un campo de investigación prometedor, destacando su relevancia como una opción de tratamiento segura y eficaz. Por tanto, es necesario un conocimiento profundo de las propiedades antioxidantes, antiinflamatorias y neuroprotectoras del CBD, no sólo para una mejor definición clínica de la EA, sino también de una serie de enfermedades neurológicas que aún tienen tratamientos indefinidos. El potencial del CBD, por tanto, representa una alternativa valiosa en el contexto de la neurología, ofreciendo importantes perspectivas para el tratamiento de enfermedades neurodegenerativas.
Palabras clave: Enfermedad de Alzheimer; Terapéutico; Cannabidiol; Tratamiento.

1. Introduction

The term dementia is defined as a neurocognitive disorder characterized by memory impairment, accompanied by other impaired cognitive functions such as language, praxis (difficulty performing gestures), agnosia (difficulty recognizing objects), or executive functions. These impairments compromise the normal functioning of the body and lead to occupational and social difficulties (Bitencourt *et al.*, 2018).

According to the United Nations (2022), dementia is one of the greatest public health challenges of our time. Studies have shown that in 2019, dementia affected 55 million people worldwide, and this number is projected to increase to 78 million by 2030 and 139 million by 2050. Among the diseases associated with cognitive loss, Alzheimer's Disease (AD) is the most prevalent, accounting for 70% of dementia cases. Most Alzheimer's cases begin after the age of 65.

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder characterized by cognitive and memory deterioration, as well as impairment in daily life activities. It is also associated with a variety of neuropsychiatric symptoms and behavioral changes (Jiang *et al.*, 2021; Leszko *et al.*, 2021).

The disease significantly impacts not only the quality of life of patients but also that of their closest family members. This is due to the care that must be provided, especially as the disease progresses, to address temporary or permanent functional incapacity associated with Alzheimer's disease (AD). Patients often experience social challenges as they forget how to perform basic activities and become unable to go out alone. These difficulties make it challenging for patients to maintain friendships and result in increased reliance on family members. In some cases, patients may even struggle with carrying out basic hygiene activities in isolation, necessitating comprehensive care (Borghi *et al*., 2011).

There is no concrete evidence regarding the exact triggers of Alzheimer's disease. It is believed that as life expectancy increases, the number of individuals developing dementia also rises. However, there is evidence suggesting that Alzheimer's is a multifactorial syndrome. Studies demonstrate various risk factors associated with the disease, such as genetic factors, exposure to infectious agents, hypertension, diabetes, obesity, and stress (Bittes *et al.*, 2021).

During a post-mortem anatopathological examination of a patient with AD, extracellular deposits of the beta-amyloid protein were discovered. These deposits are known to contribute to the formation of neural plaques. Additionally, an increase in hyperphosphorylated Tau proteins, which normally play a role in organizing the cytoskeleton, was observed within the intracellular environment. These changes, coupled with the presence of inflammation and oxidative stress, collectively contribute to the symptoms and progression of Alzheimer's disease (Camargo Filho *et al.*, 2019).

Since the disease currently has no cure, early diagnosis is crucial for prolonging the progression of the disease and preserving neurocognitive capabilities. One approach to treating AD involves using drugs that inhibit the degradation of acetylcholine. However, it's important to note that these drugs are designed to only delay the progression of the disease and improve the patient's quality of life (Jiang *et al.*, 2021).

The studies of Camargo Filho *et al.* (2019), it is widely acknowledged that drug therapy for Alzheimer's relies on medications with questionable efficacy, as they primarily aim to alleviate cognitive symptoms. As a result, the treatment does not intend to delay the progression of the disease and may be associated with adverse effects. One such drug used in Alzheimer's is donepezil (Eranz), an acetylcholinesterase inhibitor. However, the therapeutic benefits of donepezil are experienced by, at most, 20% of patients with the disease. Moreover, to manage the typical symptoms of AD, it is sometimes necessary to employ a broad range of medications, which increases the likelihood of adverse reactions and drug interactions.

As studies continue to investigate the pathophysiology of neurodegenerative diseases, the endocannabinoid system (ECS) has garnered significant attention for its potential in treating these conditions. This interest arises from its potential antioxidant, anti-inflammatory, and neuroprotective effects. Cannabidiol (CBD), a substance found in the Cannabis sativa plant, has been shown to act on the central nervous system and provide neuroprotection. Consequently, it has emerged as a therapeutic option for delaying the progression of these diseases (Jiang *et al.*, 2021; Leszko *et al.*, 2021; Dash *et al.*, 2021; Cooray *et al.*, 2020).

The objective of this study is to analyze the therapeutic evidence regarding the potential antioxidant, anti-inflammatory, and neuroprotective effects of cannabidiol, as well as its effectiveness in treating Alzheimer's Disease.

2. Methodology

This is an integrative literature review study, a method recognized for providing the synthesis of knowledge compared to other review studies, which makes it possible to approach different methodological variables, enabling a categorical understanding of the outlines and objectives established based on the information found in the literature, whether observational or theoretical (Souza et al., 2010).

The PICO strategy was utilized as a guiding tool for the research. The acronym represents the following methodology: Population/Patients, Intervention, Control, and Outcome (Garcia *et al*., 2016). In this case, the element (P) refers to patients with AD, while the element (I) represents the intervention. However, since this study was not an interventional study, the specific intervention element was not used. Element (C) involves a comparison with other methods already employed in AD therapy. Lastly, element (O) pertains to the therapeutic use of cannabidiol and its clinical implications.

Therefore, the study's research question was: “Is the therapeutic use of cannabidiol effective in improving the treatment of patients with Alzheimer's Disease?”

With the aim of achieving this purpose, a search for references began on the secondary information platform called the Virtual Health Library (VHL) and then access to (Medline) Medical Literature Analysis and Retrieval System Online and (Lilacs) *Literatura Latino-Americana e do Caribe em Ciências da Saúde*, classified as primary bases. Four keywords were recognized as descriptors in the Health Sciences Descriptors (DeCS) were used: Treatment, Therapeutic, Cannabidiol and Alzheimer's

Disease. The terms were searched in English and Portuguese, simultaneously interspersed with the Boolean operators AND and OR, as shown in (Table 1) below:

Table 1 - Combination of Boolean connectors in English and Portuguese.

DeCS in English language	DeCS in Portuguese language
"Treatment" OR "Therapeutics" AND "Cannabidiol" AND "Alzheimer disease".	*"Tratamento" OR "Terapêutico" AND "Canabidiol" AND "Doença de Alzheimer"*

Source: Magalhães, *et al*. (2023).

The literature search was conducted using virtual access to databases, with the search period limited to September 2023. Exclusion and inclusion criteria were applied to the articles found. The inclusion criteria consisted of complete articles available online for free, published between 2013 and 2023, in English or Portuguese, and addressing the use of Cannabidiol for the treatment of AD. As an additional exclusion criterion, articles unrelated to the proposed topic were excluded even after applying the filters.

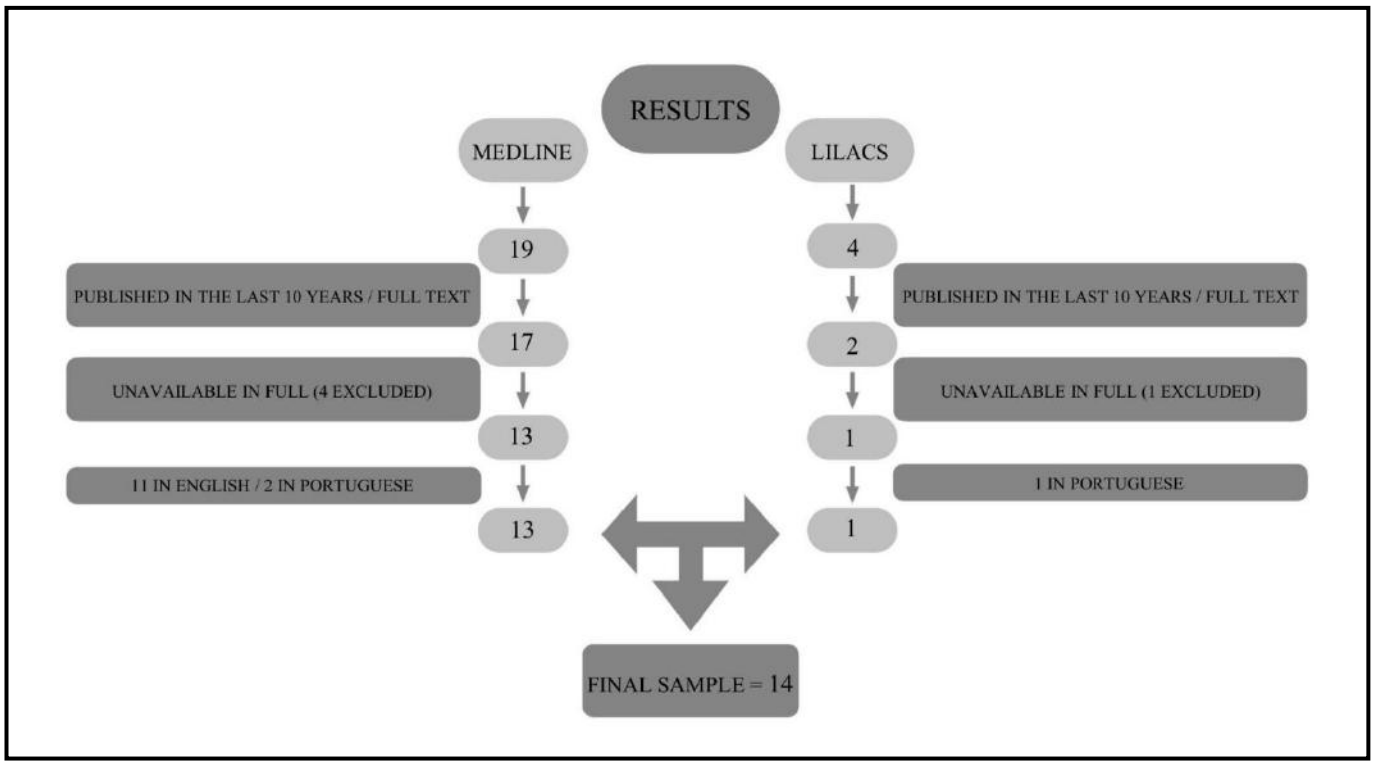
The levels of evidence recommended by Melnyk and Fineout-Overholt (2005) were used for the qualitative analysis of the literary findings of the final sample, these are divided into seven categories in ascending order. In an illustrative way, these levels are represented in a pyramid, studies that are at the top mean that they have a higher level of evidence and at the bottom there are studies with a lower level of evidence.

In this context, as the category number decreases, the quality of the study's justification increases, and vice versa. Thus, the support levels include: I - Systematic analysis of the literature or meta-analysis; II - At least one randomized controlled clinical trial with a well-designed structure; III - At least one well-designed, but non-randomized, clinical trial; IV - Case-control investigation and cohort study; V - Systematic analysis of descriptive or qualitative studies; VI - Descriptive or qualitative studies; VII - Expert opinion article or report from committees of experts in the field. After reading the articles in full, the data were described in tables and organized within the levels proposed by Melnyk and Fineout-Overholt (2005).

3. Results

By utilizing the combination of descriptors and Booleans described previously, a total of 23 articles were initially identified in the databases. After applying further delimitations, including narrowing the publication period to 2013-2023 and filtering by full text availability, 4 articles were excluded, resulting in a remaining set of 19 articles. Subsequently, a comprehensive reading of the texts was conducted, revealing that 4 articles were not accessible for free and 1 article was duplicated. Consequently, the final sample of articles included 14 studies. Among these, 3 were published in Portuguese, while the remaining 11 were published in English, as illustrated in Figure 1.

Figure 1 - Articles selected after searching the databases according to the inclusion and exclusion criteria.



Source: Magalhães, *et al*. (2023).

All (N=14) articles included in the study's final sample have publication dates from 2017 or later, with the highest number of publications (4 articles) occurring in 2021. Table 2 displays the distribution of articles by year of publication, along with their corresponding relative percentages.

Table 2 - Final sample of articles according to year and percentages.

PUBLICATION YEAR	N	%
2017	3	21,4
2019	2	14,2
2020	2	14,2
2021	4	28,5
2022	1	7,1
2023	2	14,2
TOTAL	**14**	**100**

Source: Magalhães, *et al*. (2023).

Regarding the type of design, the largest number was concentrated in systematic literature review or meta-analysis as shown in (Table 3).

Table 3 - Framing of articles according to level of evidence.

Design	**Level of evidence**	**N**	**%**
Systematic literature review or meta-analysis.	I	7	50
At least one well-designed randomized controlled trial.	II	3	21,4
At least one well-designed non-randomized clinical trial.	III	2	14,2
Case-control study and cohort study.	IV	0	0
Systematic review of descriptive or qualitative studies.	V	0	0
Descriptive or qualitative studies.	VI	2	14,2
Expert opinion article or report from committees of experts in the field.	VII	0	0
Total	**-**	**14**	**100**

Source: Magalhães, *et al*. (2023).

4. Discussion

4.1 First analyzes of Alzheimer's Disease

During post-mortem anatomopathological examinations of patients with AD, extracellular deposits of the beta-amyloid protein (βA), which are responsible for forming neural plaques, were identified. Additionally, an accumulation of hyperphosphorylated Tau proteins, which normally play a role in organizing the cytoskeleton, was observed intracellularly. These findings, along with the inflammatory process and oxidative stress, represent the changes that contribute to the symptoms and progression of Alzheimer's disease (Camargo Filho *et al.*, 2019).

However, drug therapy currently used to treat AD faces significant challenges. Camargo Filho *et al*. (2019), highlights that drug therapy for Alzheimer's uses drugs with questionable efficacy, as they act exclusively to relieve symptoms. Therefore, the treatment does not seek to prevent the progression of the disease and, in addition, is related to adverse effects. Donepezil (Eranz) is an acetylcholinesterase inhibitor and one of the drugs used to treat the disease, but the individuals who experience its therapeutic benefits are, at most, 20% of patients with the disease. Furthermore, it is sometimes necessary to use broad classes of medications to control the typical symptoms of AD and, consequently, the chances of adverse reactions to the drug and a drug interaction increase.

4.2 Endocannabinoid system

As for the Endocannabinoid System (ECS), this was a relatively recent discovery, in the 90s, by Raphael Mechoulam, the same researcher responsible for the discovery of CBD and THC, a few decades earlier, in 1964 (Crippa *et al*., 2023). The SEC (Second Extracellular Loop) is closely linked to G protein receptors. The CB1 cannabinoid receptor is the most abundant present in the brain, also found in the peripheral nervous system, while the CB2 receptor is present mainly in cells of the immune system. Currently, there is knowledge of different endocannabinoids capable of activating these receptors, with Anandamide being the first discovered, followed by 2-arachidonylglycerol and the others.

Endocannabinoids are synthesized from membrane precursors and are only produced in response to stimulation. Once produced, they undergo rapid degradation. Once synthesized, endocannabinoids perform various functions in different organs. In neurons, for example, the stimulation of CB1 receptors in the pre-synaptic region leads to the inhibition of neurotransmitter

release. Considering this mechanism, the possibility of conducting studies using cannabinoids to modulate this system emerged. The first drugs developed were analogues of THC (Fonseca *et al.*, 2013).

The activation of the endocannabinoid system occurs through the cannabinoid receptors already mentioned, which lead to the release of neurotransmitters, especially glutamate. Two types of receptors are found in the human body, these are identified in our system as CB1 present in the central nervous system (CNS) and CB2 present in peripheral tissues. These are coupled to the G protein and have Δº-THC as an endogenous agonist, which is derived from di-benzopyran. The binding of such agonists to their receptor generates an intracellular signaling cascade and, consequently, inhibits adenylate cyclase and voltage-sensitive calcium channels. On the other hand, the activation of potassium channels and mitogen-activated protein kinases (MAPKs) was noticed. CBD therefore prevents neurotoxicity and histoperphosphorylation of Tau protein. Δº-THC reduces agitation and involuntary motor activity in AD patients (Camargo Filho *et al.*, 2019).

Considering the importance of AD pathophysiology as the basis of the present studies, other pathologies permeate its existence, not only the basis of ECS (Endocannabinoid System) dysfunctions. Jørgensen, J. T. *et al.* (2020) consider that the altered circadian cycle can contribute to the development of dementia, just as a history of depression can increase the risk of future development of AD (Ownby *et al.*, 2006). Adding to the previous information, the effectiveness of antidepressants in certain patients is directly proportional to the regularity of the circadian cycle (Silva *et al.*, 2021).

Associated with the information described above, the study of Fonseca *et al.* (2023) highlights the interconnected pathophysiology of depressive disorder and Alzheimer's disease associated with ECS disorders, subsequently concluding that the medicinal use of cannabinoids has a pleiotropic effect on the diseases presented; Furthermore, CBD acts as a modulator of neuroinflammation, which leads to a decrease in the formation and aggregation of βA. It achieves this by promoting the ubiquitination of the amyloid precursor protein and modulating the hyperphosphorylation of TAU protein, thus reducing memory deficits induced by βA. On the other hand, CBN and CBC primarily modulate neuroinflammation and the formation of βA plaques. However, there is still a scarcity of studies examining the effects of phytocannabinoids and synthetic cannabinoids on neurotrophic factors, neurotransmission, and bone density. Further scientific evidence is needed in these areas.

Just like the study of Fonseca *et al.* (2023) exposed the modulation of neuroinflammation with the use of CBD, Zhang *et al.* (2022) discovered in their research that the substance's phenolic hydroxyl groups are critical for eliminating ROS (Reactive Oxygen Species) both *in vitro* as *in vivo*, attenuating βA aggregation in vivo, consequently improving associated neurotoxicity.

4.3 Therapeutic benefits of cannabidiol in the context of the treatment of Alzheimer's Disease

Investigations into the potential therapeutic properties of Cannabis, specifically CBD, in the treatment of AD have produced notable results. In a study of Zhang *et al.* (2022), using as a model organism *Caenorhabditis elegans*, whose gene sequences are 38% homologous to those of human genes, including amyloid precursor protein (APP) and TAU, it was shown that CBD acted to alleviate the progression of AD induced by βA. Furthermore, this study highlighted CBD's ability to eliminate reactive oxygen species in vivo without inducing overexpression of antioxidant genes. It also demonstrated that CBD can increase the resistance of the model organism to oxidative stress. These findings suggest a potential relationship with CBD's intrinsic antioxidant properties.

Several mechanisms have been proposed to explain this neuroprotection, including the reduction of oxidative stress and prevention of apoptosis. Additionally, CBD can induce the ubiquitination of the APP protein, thereby reducing the production of βA. It also inhibits neuroinflammation induced by βA and promotes neurogenesis through selective activation of peroxisome proliferator-activated receptor-γ (PPARγ). CBD achieves this by concurrently inhibiting iNOS and IL-1β. However, there is still a lack of conclusive clinical evidence supporting the isolated use of CBD, without the presence of THC, in the treatment of AD. (Mannucci *et al*., 2017).

In a recent *in vivo* study, using rats as models, Kim *et al.* (2023) raises that, in addition to decreasing levels of βA and TAU protein in primary neurons and hippocampus, treatment with CBD and THC decreases cell death and modulates calcium levels. In patients with AD, elevated calcium concentration interferes with signaling pathways, resulting in impaired learning and memory. Consequently, in homeostatic environments, the long-term consequences of memory formation could be reduced. Additionally, by normalizing calcium concentration, therapy would enable an increase in the levels of BDNF (brain-derived neurotrophic factor) through the regulation of CREB (cyclic AMP response element binding protein) phosphorylation. This balanced environment is of great importance for learning, memory, synaptic plasticity, and neuroprotection.

According to the study of Elsaid *et al.* (2019), CBD activates and increases the protein expression of the PPAR-ÿ receptor, such activation has anti-inflammatory and antioxidant effects. The same study highlights CBD as an antagonist of the GPR55 protein receptor. When this receptor is active, it triggers the release of intracellular calcium, which in turn stimulates the calcineurin nuclear factor of activated T cells (NFAT). This process leads to an increase in the immune response and neurodegenerative processes. Therefore, CBD acts by providing negative feedback on this inflammatory pathway, preventing its stimulation.

Neuronal degeneration, a central process in the progression of AD, often correlates with iron accumulation. In the study conducted by Flores *et al.* (2017), an experiment was selected which correlates the neuronal damage caused by iron accumulation and the restorative effects of CBD. During the investigation, the incorporation of excessive levels of iron in young mice promoted changes in mitochondrial regulatory proteins, DNM1L and OPA1. Simultaneously, an increase in caspase 3 levels and a reduction in synaptophysin levels were observed in the hippocampus and cerebral cortex. These events ultimately led to the loss of synapses and neuronal death through apoptosis. However, the administration of CBD to adult rats reversed these deleterious effects, restoring protein and synaptophysin levels to normal.

The study of Li *et al.* (2020), these findings indicate that exposure of cortical and hippocampal neurons to AB peptides leads to the phosphorylation and activation of Glycogen Synthase Kinase 3B (GSK-3B). This, in turn, disrupts the Wnt signaling pathway and results in the hyperphosphorylation of the Tau protein and the formation of neurofibrillary tangles, which are characteristic features observed in patients with AD. CBD can prevent the phosphorylation of GSK-3B. By doing so, it positively regulates the wnt/b-catenin signaling pathway. Activation of this pathway leads to mechanisms that promote the transcription of genes related to neuronal survival and homeostasis response. Finally, Camargo Filho *et al.* (2019) complement in their study that, in a group treated with CBD, it was possible to observe "*Downregulation*" of the GSK-3B gene and, in this way, contributes to the wnt/b-catenin pathway.

Astrocytes, which are responsible for maintaining brain homeostasis and modulating the inflammatory response, play a crucial role in AD. Dysfunction of astrocytes can lead to oxidative stress and neuroinflammation, contributing to neuronal degeneration. Hence, the development of therapies aimed at regulating astrocytic activity is of utmost importance. Studies have demonstrated that CBD has the ability to reduce neuroinflammation and suppress astrocyte activation induced by Aβ. This reduction occurs through the inhibition of inflammatory cytokine production, such as tumor necrosis factor alpha (TNF-α) and interleukin-1β (IL-1β), as well as the downregulation of proteins associated with astrocyte activation, such as glial fibrillary acidic protein (GFAP) and S100β protein. However, further research is still needed to elucidate the precise mechanism of action and the connection between CBD and astrocytes. (Kozela *et al.*, 2017).

4.4 Adverse effects

Like any medication, cannabis also has its side effects, especially when the therapeutic dose is exceeded. Exceeding the therapeutic dose may lead to toxic adverse events in the patient's body. However, studies indicate that when the therapeutic dose is properly administered, the adverse consequences are minor. On the other hand, direct administration of dry cannabis leaves

has shown serious effects, highlighting the importance of proper usage and attention to the method of drug administration (Cooray *et al.*, 2020).

The serious adverse effects discovered included fatalities resulting from the toxicity exerted on the neurodegenerated brain. This finding has sparked controversy regarding the use of these compounds as a clinical therapy. Consequently, researchers have conducted studies on the endocannabinoid system (ECS) and its natural components, such as cannabinoid receptors and ligands (anandamides and 2-AG), at the molecular and biochemical levels. These studies aim to understand the effects of these components on the neurodegenerated brain and the central nervous system (Cooray *et al.*, 2020).

Therefore, considering the data mentioned above, it is important to highlight that cannabinoid-based therapeutic medicines have both advantages and disadvantages. Due to the cultural beliefs and diverse perspectives found in the developing world, there might be hesitancy in accepting cannabinoids for treatment purposes (Cooray *et al.*, 2020).

5. Conclusion

Cannabidiol has clear potential to reduce the symptoms of AD given its action on the central nervous system. Therefore, its therapeutic use in the treatment of AD emerges as a promising field of investigation, underscoring its relevance as a safe and effective treatment option. Therefore, it is crucial to have an in-depth understanding of the antioxidant, anti-inflammatory, and neuroprotective properties of CBD. This understanding is necessary not only for a better clinical definition of AD but also for a range of neurological diseases that currently lack defined treatments. The potential of CBD, therefore, presents a valuable alternative in the field of neurology and offers significant prospects for the treatment of neurodegenerative conditions.

Cannabinoid-based therapeutic medicines can have both benefits and potential risks. It is important to consider that in the developing world, cultural beliefs and diverse perspectives may lead to hesitancy in accepting cannabinoids for treatment purposes. On the other hand, the administration of cannabinoid drugs requires strict regulation to prevent adverse effects resulting from possible overdose. The treatment should be closely monitored by a healthcare professional to assess the necessity of therapy, determine appropriate dosage, and establish the duration of use. This approach helps reduce the risk of dependence on the medication. With a thoughtful, evidence-based approach, the utilization of cannabinoids in Alzheimer's treatment offers significant hope for enhancing the quality of life for patients and their families.

The Extracellular Communication System (ECS) is a new system that is currently under study. It is possible that CBD has numerous connections with other important body systems, which suggests potential therapeutic advantages for a variety of non-communicable diseases (NCDs). The implementation of new technologies, such as Genome-Wide Association Studies (GWAS) and epigenetics, holds potential for addressing significant challenges in drug development, not only for non-communicable diseases (NCDs) but also for other diseases. However, there are caveats, as our understanding of the genetics of the Endocannabinoid System (ECS) is not well-established. To fully comprehend the results, patients need to be monitored over an extended period, and the safety of these treatments should be verified at higher dosages.

Consistent with current literature, this study further supports the therapeutic potential of CBD in Alzheimer's Disease. It is recommended to adopt a continuous, comprehensive, and cautious approach, both in research and in the regulation of cannabidiol use. This approach will enable effective translation of promising discoveries into noticeable clinical benefits for patients.

Scientific evidence suggests that CBD and THC, components of cannabis, exhibit anti-inflammatory and neuroprotective effects. Nevertheless, there is an urgent need for robust, long-term clinical studies to further elucidate their efficacy and safety. Additionally, future research could focus on identifying specific biomarkers that can predict individual patient responses to treatment, enabling a more personalized approach to Alzheimer's treatment. Investigating the effects of CBD

and THC at various stages of the disease, considering the progression of the condition and the variability of symptoms over time, will undoubtedly provide valuable insights into the effectiveness of these substances across different clinical scenarios.

References

Bitencourt, E. M., Kuerten, C. M. X., Budny, J., & Tuo, T. (2018). Alzheimer's Disease: physiopathological aspects, quality of life, therapeutic strategies of physiotherapy and biomedicine. *Revista Inova Saúde*, 8(2), 2317-2460. https://doi.org/10.18616/inova.v8i2.3573

Bittes, Y. P., Ribeiro, L. B., Anselmo, G. S. Dantas, T. C. L., Ferreira, M. V. R., Neves, W. C., Barbosa, J. S. P., Silva, D. F. (2021). Use of cannabinoids in the treatment of persons with Alzheimer. *Revisa (online)* 10 (2), 887-899. https://pesquisa.bvsalud.org/portal/resource/pt/biblio-1354211

Borghi, A. C., Sassá, A. H., Matos, P. C. B., Decesaro, M. N., & Marcon, S. S. (2011) Quality of life of elders with Alzheimer's disease and of their caregiver. *Revista Gaúcha de Enfermagem*, 32(4), 1983-1447. https://doi.org/10.1590/S1983-14472011000400016

Camargo Filho, F. M. A., Romanini, A. P., Pyrich, B. C. *et al*. (2019) Canabinoides como uma nova opção terapêutica nas doenças de Parkinson e de Alzheimer: uma revisão de literatura. *Revista Brasileira de Neurologia*, 55(2), 17–32. https://fi-admin.bvsalud.org/document/view/nsxb2

Cooray, R., Gupta, V., & Suphioglu, C. (2020). Current Aspects of the Endocannabinoid System and Targeted THC and CBD Phytocannabinoids as Potential Therapeutics for Parkinson's and Alzheimer's Diseases: a Review. *Molecular neurobiology*, 57(11), 4878–4890. https://doi.org/10.1007/s12035-020-02054-6

Crippa, J. A. S., Guimarães, F. S., Zuardi, A. W., & Hallak, J. E. C. (2023). Dr. Raphael Mechoulam, cannabis and cannabinoids research pioneer and his legacy for Brazilian pharmacology. *Revista brasileira de psiquiatria* (Sao Paulo, Brasil: 1999), 45(3), 201–202. https://doi.org/10.47626/1516-4446-2023-0047

Dash, R., Ali, M. C., Jahan, I., Munni, Y. A., Mitra, S., Hannan, M. A., Timalsina, B., Oktaviani, D. F., Choi, H. J., & Moon, I. S. (2021). Emerging potential of cannabidiol in reversing proteinopathies. *Ageing research reviews*, 65, 101209. https://doi.org/10.1016/j.arr.2020.101209

Elsaid, S., Kloiber, S., & Le Foll, B. (2019). Effects of cannabidiol (CBD) in neuropsychiatric disorders: A review of pre-clinical and clinical findings. *Progress in molecular biology and translational science*, 167, 25–75. https://doi.org/10.1016/bs.pmbts.2019.06.005

Flores, E. L., & Zamin, L. L. (2017). Potencial neuroprotetor, antioxidante e anti-inflamatório do Canabidiol: relevância e perspectivas para o tratamento de doenças neurodegenerativas. *Revista De Ciências Médicas E Biológicas*, 16(2), 224–229. https://doi.org/10.9771/cmbio.v16i2.20568

Fonseca, B.M.; Costa, M. A.; Almada, M. *et al*. (2013). O Sistema Endocanabinóide – uma perspetiva terapêutica. *Acta Farmacêutica Portuguesa*, v. 2, n. 2, p. 37–44. https://actafarmaceuticaportuguesa.com/index.php/afp/article/view/5

Fonseca, C., Ettcheto, M., Bicker, J., Fernandes, M. J., Falcão, A., Camins, A., & Fortuna, A. (2023). Under the umbrella of depression and Alzheimer's disease physiopathology: Can cannabinoids be a dual-pleiotropic therapy? *Ageing research reviews*, 90, 101998. https://doi.org/10.1016/j.arr.2023.101998

Garcia, A. K. A., Fonseca, L. F., Aroni, P., & Galvão, C. M. (2016). Strategies for thirst relief: integrative literature review. *Revista Brasileira de Enfermagem - REBEn*, 69(6), 1215-1222. https://doi.org/10.1590/0034-7167-2016-0317

Jiang, X., Zhang, Z., Zuo, J., Wu, C., Zha, L., Xu, Y., Wang, S., Shi, J., Liu, X. H., Zhang, J., & Tang, W. (2021). Novel cannabidiol-carbamate hybrids as selective BuChE inhibitors: Docking-based fragment reassembly for the development of potential therapeutic agents against Alzheimer's disease. *European journal of medicinal chemistry*, 223, 113735. https://doi.org/10.1016/j.ejmech.2021.113735

Jørgensen, J. T., Hansen, J., Westendorp, R. G. J., Nabe-Nielsen, K., Stayner, L. T., Simonsen, M. K., & Andersen, Z. J. (2020). Shift work and incidence of dementia: A Danish Nurse Cohort study. *Alzheimer's & dementia: the journal of the Alzheimer's Association*, 16(9), 1268–1279. https://doi.org/10.1002/alz.12126

Kim, J., Choi, P., Park, Y. T., Kim, T., Ham, J., & Kim, J. C. (2023). The Cannabinoids, CBDA and THCA, Rescue Memory Deficits and Reduce Amyloid-Beta and Tau Pathology in an Alzheimer's Disease-like Mouse Model. *International journal of molecular sciences*, 24(7), 6827. https://doi.org/10.3390/ijms24076827

Kozela, E., Juknat, A., & Vogel, Z. (2017). Modulation of Astrocyte Activity by Cannabidiol, a Nonpsychoactive Cannabinoid. *International journal of molecular sciences*, 18(8), 1669. https://doi.org/10.3390/ijms18081669

Leszko, M., & Meenrajan, S. (2021). Attitudes, beliefs, and changing trends of cannabidiol (CBD) oil use among caregivers of individuals with Alzheimer's disease. *Complementary therapies in medicine*, 57, 102660. https://doi.org/10.1016/j.ctim.2021.102660

Li, H., Liu, Y., Tian, D., Tian, L., Ju, X., Qi, L., Wang, Y., & Liang, C. (2020). Overview of cannabidiol (CBD) and its analogues: Structures, biological activities, and neuroprotective mechanisms in epilepsy and Alzheimer's disease. *European journal of medicinal chemistry*, 192, 112163. https://doi.org/10.1016/j.ejmech.2020.112163

Mannucci, C., Navarra, M., Calapai, F., Spagnolo, E. V., Busardò, F. P., Cas, R. D., Ippolito, F. M., & Calapai, G. (2017). Neurological Aspects of Medical Use of Cannabidiol. *CNS & neurological disorders drug targets*, 16(5), 541–553. https://doi.org/10.2174/1871527316666170413114210

Melnyk B. M., & Fineout-Overholt, E. (2005) *Making the case for evidence-based practice. Evidence-based practice in nursing & healthcare. A guide to best practice.* Lippincot Williams & Wilkins, Philadelphia, p.3-24.

Organização das Nações Unidas (2022). Demência pode afetar 78 milhões de pessoas até 2030, diz OMS. *ONU News. Perspectiva Global Reportagens Humanas*. https://news.un.org/pt/story/2022/10/1804302

Ownby, R. L., Crocco, E., Acevedo, A., John, V., & Loewenstein, D. (2006). Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Archives of general psychiatry*, 63(5), 530–538. https://doi.org/10.1001/archpsyc.63.5.530

Silva, S., Bicker, J., Falcão, A., & Fortuna, A. (2021). Antidepressants and Circadian Rhythm: Exploring Their Bidirectional Interaction for the Treatment of Depression. *Pharmaceutics*, 13(11), 1975. https://doi.org/10.3390/pharmaceutics13111975

Souza, M. T., Silva, M. D., & Carvalho, R. (2010). Revisão integrativa: o que é e como fazer Integrative review: what is it? How to do it? *Einstein*, 8(1), 102–108. https://doi.org/10.1590/S1679-45082010RW1134

Zhang, Y., Li, H., Jin, S., Lu, Y., Peng, Y., Zhao, L., & Wang, X. (2022). Cannabidiol protects against Alzheimer's disease in C. elegans via ROS scavenging activity of its phenolic hydroxyl groups. *European journal of pharmacology*, 919, 174829. https://doi.org/10.1016/j.ejphar.2022.174829