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USE OF CANNABINOIDS IN ALZHEIMER'S DISEASE: INTEGRATIVE SYNTHESIS OF THE LITERATURE

***Tereza Raquel Xavier Viana and José Eduardo Martinelli**

Faculdade de Medicina de Jundiaí (FMJ), Rua Francisco Telles, 250 Vila Arens, Jundiaí, São Paulo, Brasil

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****Corresponding Author:***
Tereza Raquel Xavier Viana,

ABSTRACT

Introduction: Alzheimer's disease (AD) is an incurable neurodegenerative condition with limited therapeutic options. Cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC), derived from *Cannabis sativa*, show therapeutic potential due to their neuroprotective properties and interaction with the endocannabinoid system (ECS). ***Objectives:*** Synthesize and evaluate the available scientific evidence on the use of cannabinoids in the treatment of AD. ***Methodology:*** This is an integrative literature review using the PubMed, SciELO, BVS, Cochrane Library and Lilacs databases, focusing on studies published between 2019 and 2024 in English and Portuguese. Articles that did not meet the inclusion criteria were excluded. ***Results:*** Initially, 31 articles were identified, 13 of which were selected after reviewing the titles and abstracts, excluding one duplicate study. The 13 articles selected were read in their entirety to compose the research. ***Conclusion:*** Cannabinoids, CBD and THC, have shown promising potential in the treatment of AD, suggesting benefits in reducing neurodegenerative symptoms and neuronal protection via ECS. However, more clinical studies are needed to validate these findings and establish safe and effective therapeutic protocols.

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INTRODUCTION

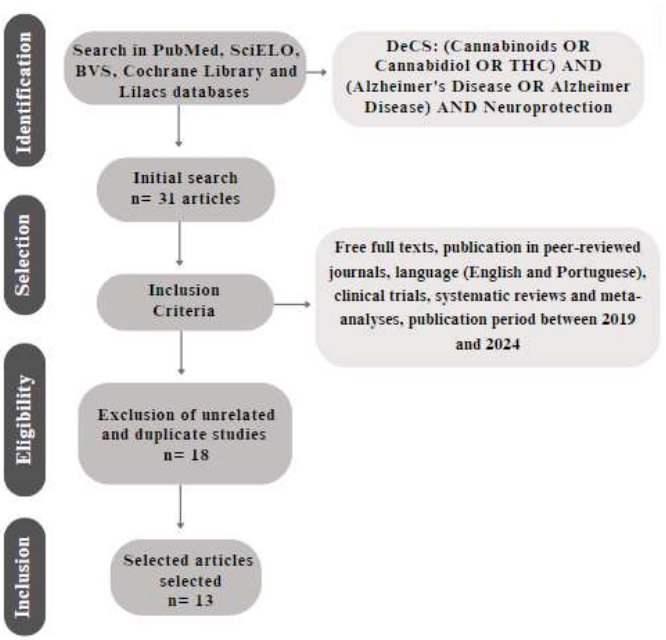
Alzheimer's disease (AD) is a neurodegenerative condition of the nervous system that causes a progressive decline in memory and cognitive-behavioral manifestations (Chung*et al*., 2000). It is one of the leading causes of dementia and increasingly affects more people, becoming a significant challenge for both the economy and Society (Dong *et al*., 2017). Additionally, the progression of the disease is characterized by the emergence of neuropsychiatric and non-cognitive symptoms, which have a significant impact on the patient's life and their caregivers. Among the various symptoms are memory loss, motor agitation, depressive episodes, affective disorders associated with social isolation, and difficulty in facial recognition, among others (Itagaki *et al*., 1989; Chung *et al*., 2000). This condition is characterized by the accumulation of senile plaques (beta-amyloid peptide), hyperphosphorylated tau protein neurofibrillary tangles, selective neuronal loss, and cognitive deficits. The behavioral symptoms of AD can be managed with various medications, such as antipsychotics, anticonvulsants, antidepressants, and benzodiazepines; however, these may have adverse reactions and/or drug interactions, resulting in new symptoms (Camargo Filho *et al*., 2019). Additionally, acetylcholinesterase inhibitors such as Donepezil, Rivastigmine, and Galantamine are used in the treatment of the disease, but they can cause adverse effects such as nausea, vomiting, diarrhea, weight loss, insomnia, agitation, anxiety, and urinary tract infection (Maroon & Bost, 2018). These effects can lead patients to discontinue or stop the medication (Russo, 2018). Memantine hydrochloride, another medication used, may cause gastrointestinal disturbances, agitation, dizziness, drowsiness, confusion, and headache (Cassano *et al*., 2017). Although they do not provide clinically significant benefits, these medications are indicated when more effective resources are unavailable (Cassano *et al*., 2020). According to projections by the United Nations, it is estimated that there are currently 36 million individuals affected by dementia worldwide, with the possibility of this number reaching 115 million by 2050. This condition impacts not only the patients but also their families, caregivers, and even the healthcare system (Ahmed *et al*., 2015). However, there are no available treatments that slow the progression of AD or any other neurodegenerative disease related to aging. There are likely several reasons for this lack of success, such as the complex nature of the diseases and their connection to the primary risk factor, which is aging (Schubert *et al*., 2019). In light of this urgent need, there has been growing interest in researching new therapeutic approaches for AD. In this context, cannabidiol (CBD), one of the primary active compounds derived from the *C. sativa* plant, has been the subject of study and debate due to its potentially beneficial pharmacological properties. CBD has a favorable safety profile and exhibits neuroprotective, antioxidant, anti-inflammatory, and immune-regulating properties (Fernández-Ruiz *et al*., 2015). It is believed that CBD, through its multifaceted mechanisms of action, may modulate fundamental pathological processes such as

neuroinflammation, oxidative stress, and synaptic dysfunction, which play a central role in the progression of the disease (Cheng *et al*., 2014; Campos *et al*., 2016). Preclinical and clinical studies have investigated the therapeutic potential of CBD in AD, with promising results. CBD has shown the ability to modulate neuroinflammation, reduce neurodegeneration, and improve cognitive function in animal models of AD (Cheng *et al*., 2014; Esposito *et al*., 2011). Additionally, anecdotal reports and early clinical studies suggest that CBD may have positive effects in reducing behavioral and psychological symptoms associated with AD, such as agitation, aggression, and anxiety (Chagas *et al*., 2014; Crippa *et al*., 2018). In the treatment of neurodegenerative diseases such as AD, studies indicate that CBD has promising properties. CBD may reduce beta-amyloid (Aβ) protein deposits, a hallmark of AD, due to its ability to cross the blood-brain barrier (Brazilian Alzheimer's Association, 2023). Additionally, CBD may act as a neuroprotective, anti-inflammatory, and antioxidant agent, which could have beneficial effects in the treatment and slowing of disease progression (Camargo Filho *et al*., 2019). The synergy of *Cannabis*, known as the "entourage effect," suggests that the therapeutic and industrial potential of the plant cannot be fully realized by a single molecule alone, highlighting the importance of the plant as a complete source of phytochemicals (Russo, 2019). Recent evidence indicates that both CBD and Δ9-tetrahydrocannabinol (THC) have neuroprotective properties that may be beneficial in the treatment of dementias (Costa, 2022).

Results from an investigation based on spontaneous and non-systematic observations revealed that *Cannabis* extract diluted in oil showed efficacy and safety in patients diagnosed with AD (Palmieri & Vadalà, 2023). CBD components have proven promising in the treatment and prevention of AD by suppressing key causal factors of the disease. Additionally, it is suggested that the combination of CBD and THC may be more beneficial than using each component in isolation (Kim *et al*., 2019). Cannabinoids have been identified as potentially beneficial in managing symptoms associated with AD, particularly agitation, as well as manifestations such as aggression, impulsivity, circadian rhythm disturbances, nocturnal activity, and sleep disorders (Outen *et al*., 2021). Based on these preliminary indications, the therapeutic use of balanced CBD and THC emerges as a promising strategy for treating AD. The elements of CBD, THC, and other compounds present in *C. sativa* interact synergistically, enhancing their therapeutic potential when combined, rather than being used in isolation. Therefore, the approach of treating AD through a combination of cannabinoids, such as the use of *Cannabis* extracts or specific proportions of CBD:THC, may be more effective than strategies involving only a single cannabinoid compounds (American Psychiatric Association, 2021). This study aims to synthesize and evaluate scientific evidence on the use of cannabinoids, such as CBD and THC, in the treatment of AD. Analyzing this evidence is crucial for guiding the development of more innovative and effective approaches to managing AD, with the goal of significantly improving the quality of life for both patients and their families.

MATERIALS AND METHODS

This is an integrative review, a systematic methodology for gathering secondary data. Recognized for its comprehensiveness in synthesizing knowledge, this approach facilitates the integration of various perspectives on a specific topic by extensively utilizing available evidence. Its ability to include a range of studies is particularly valued, providing a substantial contribution to evidence-based practice(Whittemore & Knafl, 2005).The methodological process was conducted in six distinct stages: first, the topic of interest was identified and the research question was formulated. Next, relevant databases were selected, and inclusion and exclusion criteria for primary studies were established. Subsequently, the categories of information to be extracted were defined, and the methodological quality of the studies was assessed. Finally, the results were interpreted, and the review was presented with a synthesis of the acquired knowledge. The first stage involved defining the central research question using the PICO acronym. The target population was elderly individuals diagnosed with AD. The intervention focused on cannabinoids CBD and THC. There was no specific comparison in this study. The outcome evaluated the effects of cannabinoids CBD and THC on AD, with an emphasis on neuroprotection and interaction with the endocannabinoid system (ECS) (Santos *et al*., 2007).The guiding question resulting from this was: "What is the impact of cannabinoids CBD and THC on neurodegenerative symptoms and neuronal protection in elderly individuals with AD?" The objective was to synthesize and evaluate studies to explore the therapeutic potential of cannabinoids in this neurodegenerative condition. Based on this question, eligibility criteria were established to search for and select studies, includingclinical trials, systematic reviews, and meta-analyses published in the last five years (2019 - 2024), available in English and Portuguese, peer-reviewed, and with free full text. Exclusion criteria were established to include studies specifically addressing cannabinoids such as CBD and THC. Articles without available full text, not peer-reviewed, or published before 2019 were excluded. The search for articles used keywords indexed in the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH), combined with the Boolean operators "OR" and "AND". The general search key was (Cannabinoids OR Cannabidiol OR THC) AND (Alzheimer's Disease OR Alzheimer Disease) AND Neuroprotection, adapted for specific databases such as PubMed, SciELO, BVS, Cochrane Library, and Lilacs. The bibliographic search was conducted on June 26, 2024. Initially, 31 articles were identified, of which 13 were selected after reviewing titles and abstracts, excluding one duplicate study. After a complete analysis, the 13 studies were included in this review, meeting the study's objectives. The studies were selected following the flowchart (Figure 1) in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guide (Page *et al*., 2020). Due to the secondary nature of this study, it was not necessary to submit it to the Research Ethics Committee (CEP). However, all ethical principles were strictly followed to ensure the legitimacy in the collection, analysis, and discussion of the data.



Source: Literature search process - developed by the authors.

Figure 1. Flowchart of the scientific articles search process

RESULTS

The thirteen studies included in this review were predominantly published in international English-language journals, with the exception of two studies from China, translated into English, and one study in Spanish. The studies originated from various countries,

distributed as follows: United States (5 studies), China (2 studies), United Kingdom (2 studies), Spain (1 study), Mexico (1 study), India (1 study), and Germany (1 study). Regarding the distribution by year of publication, two studies were published in 2019, accounting for 15.4% of the total. In 2020, three studies were published, representing 23.1%. The years 2021 and 2022 each had two studies published, equating to 15.4% respectively. In 2023, the year with the highest number of publications, four studies were released, totaling 30.8% of the analyzed period. Of the 13 studies reviewed, there was a significant predominance of qualitative systematic reviews, representing approximately 61.5% of the total. Additionally, two meta-analyses were identified, corresponding to about 15.4% of the reviewed studies. To a lesser extent, three original quantitative studies were found, totaling approximately 23.1% of the reviewed studies. The review highlighted a strong evidence base regarding cannabinoids in the treatment of neurodegenerative diseases. Studies consistently demonstrated the therapeutic potential of cannabinoids, showcasing neuroprotective effects such as the removal of intraneuronal amyloid, reduction of oxidative damage, and protection against energy loss. Combinations of THC and CBD were effective in neuroprotection, particularly in diseases like Parkinson's and Alzheimer's. However, the studies also discussed challenges related to toxic effects and the need for a better understanding of the molecular pathways involved to optimize therapies.

Other findings included the efficacy of cannabigerol (CBG), cannabidivarin (CBDV), and cannabichromene (CBC) in models of various neurological disorders such as Huntington's Disease (HD), Epilepsy, and Parkinson's. Partially elucidated mechanisms of action, such as the involvement of the Peroxisome Proliferator-Activated Receptor Gamma (PPARγ), were suggested as contributors to these effects, indicating the need for further research to confirm and explore these findings. Additionally, the review highlighted the role of cannabinoid receptors, such as CB2R, in mediating the neuroprotective effects of cannabinoids in experimental models. The discussion on the clinical use of *Cannabis* extracts, such as Sativex TM, illustrated the potential implications of *Cannabis* legalization in medical and pharmacological practice.

Regarding CBD, studies demonstrated its ability to mitigate cognitive deficits, modulate microglial activity, promote the release of neurotrophic factors, and regulate inflammatory genes. It also showed protective effects against Aβ toxicity, underscoring its therapeutic potential in neurodegenerative diseases such as Alzheimer's. These results suggest that cannabinoids offer promising therapeutic avenues for the treatment and management of various neurological disorders, although additional challenges need to be addressed to translate these findings into effective clinical treatments, as shown in Table 1.

Table 1 - Presentation of the articles included in the review

Author / Year	Objectives	Methods	Results
Plancarte-Sánchez *et al*., 2019	To review the historical and current interest in cannabinoids, from their synthesis to therapeutic applications in various medical conditions.	Systematic review of studies on cannabinoids, including controlled and uncontrolled clinical trials.	Demonstration of the therapeutic potential of cannabinoids in various conditions, such as AD.
Schubert *et al*., 2019	To evaluate the efficacy of various non-psychoactive cannabinoids as neuroprotectants in a new preclinical screening platform for AD and neurodegeneration.	Systematic review. Screening for neuroprotection in assays including proteotoxicity, oxidative stress, energy loss and inflammation. Structure-activity analysis (SAR) to identify functional requirements for neuroprotection.	Nine of the 11 cannabinoids tested showed neuroprotective capacity in neurodegeneration assays, including removal of intraneuronal amyloid, reduction of oxidative damage and protection against energy loss. Combinations of THC and CBN showed synergistic neuroprotective interaction.
Cooray *et al*., 2020	To review the literature on ESA and phytocannabinoids (THC and CBD) as potential therapies for Parkinson's disease (PD) and AD.	Systematic review. Analysis of published work on the use of ECS as a therapeutic target for neurodegeneration, including genetic modifications and studies in animal models.	Identification of the potential neuroprotection of THC and CBD phytocannabinoids in animal models of PD and AD. Discussion of challenges associated with toxic effects and the need to better understand the molecular cascade in order to develop effective therapies.
Li *et al*., 2020	Describe 11 types of natural cannabinoids from *C. sativa* and 50 (-)-CBD analogues with therapeutic potential. Clarify the underlying molecular mechanisms of CBD in epilepsy and neurodegenerative diseases.	Comprehensive systematic review of the mechanisms of action of CBD as an indirect agonist of endogenous cannabinoid receptors. Evaluation of the signal transduction pathways affected by CBD. Investigation of CBD's potential to prevent GSK-3 ß hyperphosphorylation associated with AD.	Demonstration of CBD's neuroprotective potential through indirect activation of cannabinoid receptors, prevention of GSK-3 ß hyperphosphorylation and positive impact on neurodegenerative diseases such as epilepsy and Alzheimer's.
Stone *et al*., 2020	To investigate the neuroprotective properties of minor phytocannabinoids in experimental models.	Systematic review of articles obtained from Embase and PubMed, focusing on specific phytocannabinoids.	Thirty-one studies were analyzed from a total of 2,341 articles, highlighting the therapeutic potential of cannabinoids such as CBG, CBDV and CBC in neurodegenerative disorders. Some mechanisms of action, including PPAR-γ, have been identified, but more research is needed to validate these effects.
Pérez-Olives *et al.,* 2021	To explore the potential of cannabinoids for neuroprotection in neurodegenerative conditions such as AD.	Systematic review of advances since 2016 in the use of cannabinoids in animal models, with an emphasis on CB1, CB2, GPR55, GPR3/GPR6/GPR12/GPR18, and PPARγ receptors.	Identification of the neuroprotective potential of cannabinoids through receptors such as CB2R in experimental models. Highlighting SativexTM as a clinical example of *Cannabis* extract, addressing pharmacological implications in the face of the trend towards legalization of *Cannabis*.
Bosnjak *et al*., (2021)	To evaluate the efficacy and safety of cannabinoids in the treatment of dementia, including Alzheimer's.	Systematic review of randomized clinical trials (RCTs) using THC (Namisol), dronabinol, nabilone and placebo/active control.	Inclusion of 4 studies (126 participants), predominantly with THC, dronabinol and nabilone. Very low to low certainty evidence for benefits in cognition and behavioral symptoms in dementia.

.....Continue

Laws e Smid, (2022)	To evaluate the neuroprotective potential of the active constituents of *C. sativa* in AD and dementia.	Systematic review of pre-clinical studies (in vitro and in vivo) on phytocannabinoids and other phytochemicals from *C. sativa*.	Phytocannabinoids, terpenes and flavonoids from *C. sativa* have shown efficacy in protecting against neurodegeneration, including antioxidant action, anti-aggregation and modulation of cannabinoid receptors, with emphasis on their efficacy against ß amyloid in AD.
Yousaf *et al*., (2022)	To evaluate the neuroprotective potential of CBD, its synthetic derivatives and combined preparations against microglia-mediated neuroinflammation in neurological disorders.	Review of pre-clinical and clinical studies on CBD and its derivatives, focusing on the molecular mechanisms of action against neuroinflammation.	Inhibitory effects of CBD on neurotoxic molecules and inflammatory modulators, highlighting its action through the ROS pathways mediated by NADPH oxidase, TLR4-NFκB, and IFN-ß-JAK-STAT. Indication of the therapeutic potential of CBD and its derivatives for neurological disorders, including enhanced anti-neuroinflammatory synergy with other biomolecules.
Chen *et al.* (2023)	To investigate the therapeutic efficacy of CBD in AD. Elucidate underlying mechanisms of CBD in AD neurodegeneration. Contribute to nutritional guidelines for the prevention of AD with CBD.	Use of the Aß1-42 peptide for in vivo and in vitro models. Treatment with CBD to evaluate therapeutic efficacy. RNA-seq analysis to elucidate therapeutic mechanisms. Evaluation of cognitive deficits, microglial activity, neurotrophic factor release and regulation of inflammatory genes.	CBD attenuated Aβ-induced cognitive deficits by modulating microglial activity and promoting neurotrophins. In addition, CBD protected against Aβ toxicity in in vitro and in vivo models, suggesting its potential to prevent AD.
Rapaka *et al*., (2023)	To investigate the role of CB1 cannabinoid receptors in astrocytes in synaptic plasticity and cognition in AD.	Literature review focused on studies exploring the function of CB1 receptors in astrocytes.	CB1 receptors regulate brain functions, including synaptic plasticity and cognition, with a crucial role for astrocytes in neuroprotection and AD.
Tambe *et al*., (2023)	To investigate the molecular mechanisms by which CBD exerts neuroprotective effects and their clinical implications.	Systematic literature review focused on the neuropharmacological impacts of CBD on the central nervous system.	Demonstrated effects of CBD in reducing neuroinflammation, oxidative stress and protein misfolding, without inducing psychotropic effects. Emphasis on the therapeutic potential of CBD in neurological diseases such as AD, PD and epilepsy.
Kamaruzzaman *et al*., (2023)	Evaluating the role of cannabinoids in modulating ECS in glial cells and its influence on cognitive function in animal models of AD.	Systematic review and meta-analysis of pre-clinical studies in rodents investigating the effects of cannabinoids on AD, with a focus on glial cells.	Inclusion of 26 studies (1050 rodents) with symptoms similar to AD. Rodents treated with cannabinoid agonists showed significant improvements in cognition and a reduction in Aβ plaques.

Source: Literature research process - prepared by the authors.

DISCUSSION

This review demonstrated the therapeutic potential of cannabinoids in treating neurodegenerative and neurological diseases, such as AD. The studies revealed significant neuroprotective effects of these compounds, highlighting their importance in mitigating neuronal damage. However, challenges arise, including concerns about toxicity and the need for a better understanding of the underlying molecular mechanisms. These observations underscore the relevance of cannabinoids in neuroprotection and the urgency of future research to optimize available therapies. To contextualize the evolution and current interest in cannabinoids, it is essential to explore their history from the early syntheses in the 1940s to recent advancements in therapeutic applications. The trajectory of these compounds was analyzed, from the initial discovery of CBN to the characterization of CBD by Mechoulam and Shvo. This historical timeline culminates in the contemporary exploration of the medicinal potential of *Cannabis*, particularly in treating AD and other significant medical conditions. Initially, compounds with activity similar to cannabinoids were synthesized and studied both in animals and clinically, with notable examples being Δ6a,10a-THC hexyl and Δ6a,10a-THC dimethylheptyl (DMHP), the latter known for its antiepileptic effects(Plancarte-Sánchez *et al*., 2019). The efficacy of non-psychoactive cannabinoids as neuroprotective agents against AD and neurodegeneration was assessed through the testing of eleven cannabinoids in preclinical assays that replicated aspects of neurodegenerative pathology. These included aging-associated toxicity, oxidative stress, trophic support loss, and inflammation. Among the eleven cannabinoids tested, nine demonstrated protective effects on cells, including the removal of intraneuronal amyloid, reduction of oxidative damage, and protection against trophic support loss. Structural-activity analysis suggested that antioxidant groups, such as aromatic hydroxyls, play a crucial role in neuroprotection, indicating potential mechanisms of action. Additionally, synergy between cannabinoids such as THC and CBN was observed in neuronal protection, highlighting their therapeutic potential in neurodegenerative diseases like AD (Schubert *et al*., 2019). Neurodegenerative diseases such as AD and Parkinson's disease (PD) represent significant global health challenges, necessitating effective therapies to prevent neurodegeneration. The endocannabinoid system (ECS) emerges as a promising therapeutic target, particularly through the CB1 and CB2 receptors in regulating neuroinflammation and providing neuronal protection. Phytocannabinoids like THC and CBD show promise in animal models, demonstrating reductions in neuroinflammation and protection of neurons. However, further studies are required to better understand their mechanisms of action and to minimize potential adverse effects before their definitive clinical application in conditions such as PD and AD (Cooray *et al*., 2020). CBD and its analogs are discussed extensively, exploring their structures, biological activities, and neuroprotective mechanisms, particularly in contexts such as AD and epilepsy. CBD acts as an indirect agonist of endogenous cannabinoid receptors, exerting neuroprotective effects through various molecular signaling pathways, including modulation of inflammation, regulation of oxidative stress, and promotion of synaptic plasticity—critical for neuronal protection. Notably, CBD has demonstrated the ability to prevent the hyperphosphorylation of GSK-3β, which is relevant in the pathogenesis of AD, suggesting potential to modulate neurodegenerative processes associated with Aβ plaques and neurofibrillary tangles. Thus, CBD emerges as a promising therapeutic option not only for epilepsy but also for Alzheimer's, offering new perspectives in modifying the course of these neurodegenerative diseases (Li *et al*., 2020). Phytocannabinoids such as CBG, CBDV, CBC, THC, and THCV are recognized for their potential neuroprotective effects. Studies indicate that CBG and CBDV are effective in experimental models of Huntington's disease

(HD) and epilepsy, while CBC, THC, and THCV have shown promise in treating seizures, hypomobility, and conditions like Huntington's and Parkinson's diseases. Despite limitations in available mechanistic data, there are indications that CBG and THC may exert their effects through the PPAR-γ receptor, suggesting potential molecular mechanisms for their therapeutic benefits. This study highlights the urgent need for further research to fully elucidate the mechanisms of action of these compounds and explore their clinical potential across a range of neurodegenerative disorders (Stone *et al*., 2020).

Cannabinoids emerge as promising neuroprotective agents in neurodegenerative diseases such as AD, Parkinson's disease (PD), and Huntington's disease (HD), which present significant challenges due to their progressive nature and the lack of effective disease-modifying treatments. These compounds act through key receptors like CB1 and CB2, as well as orphan receptors (GPR55, GPR3/GPR6/GPR12/GPR18) and PPARγ, influencing critical molecular pathways involved in neuroinflammation and neuronal survival. Notably, CB2 receptors have the capability to modulate glial cells, including activated microglia, potentially fostering a neuroprotective environment. The approval of Sativex TM for human therapy marks a significant advancement, potentially driving the medicinal legalization of *Cannabis* in various countries and expanding therapeutic options for patients with neurodegenerative conditions (Pérez-Olives *et al*., 2021). The reviewed studies on cannabinoid use in dementia treatment included four randomized clinical trials investigating natural THC, dronabinol, and nabilone. The research revealed very low evidence that cannabinoids significantly improve cognitive function, as measured by the sMMSE, and have minimal impact on the overall behavioral and psychological symptoms of dementia. Adverse events, such as sedation, were common with nabilone. Due to the limitations of small and heterogeneous studies, there is no certainty regarding the benefits or harms of cannabinoids in dementia treatment. More robust clinical trials are needed to elucidate their true therapeutic potential and guide future clinical practices more effectively (Bosnjak *et al*., 2021). The neuroprotective potential of the active constituents of *C. sativa*, particularly in neurodegenerative diseases like AD, is emphasized. There is an urgent need for disease-modifying treatments, as current therapies only provide transient symptomatic improvements. Phytocannabinoids, terpenes, and flavonoids from the plant have shown efficacy in preclinical models of neurodegeneration, acting through various molecular pathways, including cannabinoid receptors and antioxidant properties. The review highlights the importance of clinical studies to validate these findings and explore synergies among the plant's phytochemicals (Laws *et al*., 2022).

Neurological disorders face a significant gap in effective treatments, with neuroinflammation emerging as a crucial therapeutic target. Microglial activation plays a central role in this process, releasing neurotoxic molecules that exacerbate conditions such as epilepsy, multiple sclerosis, and AD. CBD has shown promising therapeutic effects in both clinical and preclinical studies by inhibiting neurotoxic molecules and modulating inflammatory mediators. Molecular mechanisms involving NADPH oxidase, TLR4-NFκB, and IFN-ß-JAK-STAT pathways indicate its capacity to reduce inflammation and modulate immune responses, thus protecting neurons from damage. In addition to CBD, synthetic derivatives and combinations with other biomolecules are being investigated for their potential synergy in anti-neuroinflammatory activity, expanding therapeutic prospects for complex neurological disorders (Yousaf *et al*., 2022). Neuroinflammation has been studied as a crucial target in AD pathology due to synaptic and neuronal damage associated with the Aβ peptide. Using in vivo and in vitro models with Aβ1-42, CBD was evaluated for its ability to mitigate cognitive deficits and its molecular mechanisms through RNA-seq analysis. CBD demonstrated a reduction in Aβ-induced toxicity by modulating microglial activity, promoting neurotrophic factors, and regulating inflammatory genes. This resulted in a significant protective effect against cognitive impairment in mice. These findings underscore CBD's potential as part of future therapeutic strategies for preventing AD, highlighting its neuroprotective and anti-inflammatory properties (Chen *et al*., 2023). The growing role of CB1 cannabinoid receptors in astrocytes highlights their influence on synaptic plasticity and cognitive function, particularly relevant in AD. Astrocytes, which are central to the tripartite synapse, modulate neuronal communication and support synaptic plasticity—processes crucial for cognition and learning. Disruptions in CB1 receptor regulation in astrocytes in AD may impair synaptic plasticity and contribute to the observed cognitive decline. Understanding how cannabinoids affect these astroglial processes could open new therapeutic perspectives in AD, underscoring the need for further research to explore clinical applications (Rapaka *et al*., 2023). CBD, a non-psychoactive phytocannabinoid, stands out for its neuroprotective and therapeutic effects on the central nervous system, including reducing neuroinflammation and protecting against oxidative stress. These properties are particularly relevant for neurodegenerative diseases such as Alzheimer's, Parkinson's, and epilepsy. Although CBD does not strongly bind to cannabinoid receptors, it modulates these pathological processes, suggesting potential for neuronal protection. Further studies are needed to elucidate its molecular mechanisms and validate its clinical applications, promoting the development of more effective and safe treatments for neurological disorders (Tambe *et al*., 2023).

A recent study investigated the role of ECS agonists on cognitive function and neuroinflammation in animal models of AD. Treated rodents exhibited improvements in cognitive function, reduction in Aβ plaques, and decreased levels of neuroinflammation markers, such as glial fibrillary acidic protein and pro-inflammatory cytokines. However, responses to cannabinoids varied among the AD models, highlighting the complexity of the interaction between these substances and the genetic heterogeneity of the animals (Kamaruzzaman *et al*., 2023). In conclusion, the reviewed data strongly suggest that stimulation of the ECS may enhance cognitive function by modulating glial cells and reducing neuroinflammation in animal models of AD. However, to fully validate the therapeutic potential of cannabinoid agents, well-designed clinical studies involving human populations are necessary. These studies will be crucial for elucidating the efficacy and safety of cannabinoids as a treatment for AD in real-world contexts.

CONCLUSION

Based on the comprehensive analysis of the therapeutic use of cannabinoids, particularly THC and CBD, in neurodegenerative diseases such as AD, it can be concluded that both have significant potential. THC shows effectiveness in managing symptoms such as pain and sleep disturbances, along with possible benefits in modulating neuroinflammation. Conversely, CBD holds promise in reducing brain inflammation, improving cognitive function, and providing neuroprotection. The combination of THC and CBD may enhance their therapeutic properties, offering a more comprehensive approach for patients with complex symptoms of neurodegenerative diseases. However, it is crucial to consider adverse effects, such as drowsiness, fatigue, and potential psychoactive alterations, and to tailor the treatment to individual needs under medical guidance. Future research should focus on detailed mechanisms of action, optimized formulations, and ideal dosages to improve the efficacy and safety of cannabinoid-based treatments. These efforts are essential to provide more effective and personalized therapeutic options, thereby enhancing the quality of life for patients affected by neurodegenerative diseases.

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