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DELVE INTO THE SYNTHESIS AND CHEMISTRY OF PHYTOCANNABINOIDS, EMPHASIZING THEIR POTENTIAL AS THERAPEUTIC ALTERNATIVES FOR NEUROPSYCHOLOGICAL DISORDERS, INCLUDING ALZHEIMER

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ABSTRACT:

Introduction: Alzheimer's disease, a progressive neurodegenerative condition, induces memory loss and cognitive impairments, posing significant challenges for patients, families, and caregivers. Cannabidiol (CBD), derived from cannabis, exhibits neuroprotective properties and influences cognition and behavior. Its therapeutic potential in Alzheimer's treatment is increasingly recognized, aiming to alleviate symptoms and improve patient outcomes.

Objectives: This study aims to conduct an integrative review of cannabinoids' effects, particularly CBD, in treating Alzheimer's disease.

Methods: An integrative literature review was conducted to explore the impact of cannabis-based treatments on Alzheimer's patients. Key health science databases such as LILACS, PubMed, Scopus, Web of Science, and Google Scholar were systematically searched using relevant descriptors (e.g., Cannabidiol, Tetrahydrocannabinol, Alzheimer's, Treatment).

Results: Forty studies were identified from selected databases, with 37 meeting eligibility criteria for inclusion in this review.

Discussion: CBD emerges as a complementary therapeutic option for managing neurological symptoms in Alzheimer's disease. Tetrahydrocannabinol (THC) demonstrates potential in altering patients' static balance and improving gait parameters. Other cannabinoids like cannabigerol (CBG)

and cannabichromene (CBC) exhibit anti-inflammatory and anticonvulsant properties, respectively. However, further research is warranted to validate their efficacy in psychiatric disorders, including Alzheimer's disease.

Conclusion: Phytocannabinoids exhibit promising neuroprotective effects in various neuropsychological conditions, including Alzheimer's disease. Although the use of cannabinoids shows tolerability among patients, rigorous studies are necessary to establish their true effectiveness and benefits in dementia management.

KEYWORDS: Cannabidiol; Tetrahydrocannabinol; Alzheimer's Disease; Treatment.

INTRODUCTION:

Alzheimer's disease (AD) is a progressive neurodegenerative disease that manifests as cognitive memory impairment and is characterized by progressive worsening of symptoms, which include inappropriate motor behaviors, psychosis, personality changes, and behavioral changes, such as aggression, anxiety, agitation, apathy and hallucinations. AD is characterized by low levels of acetylcholine (ACh) and accumulation of amyloid-β (Aβ) in the brain. Despite treatment, it is still a very difficult disease for the patient and especially for his family (Tamaddonfard, Erfanparast, Tamaddonfard, & Soltanalinejad, 2024).

Due to the pathophysiology of the disease, a significant reduction in the quality of life of affected elderly people can be observed, as memory loss makes social, emotional and family bonds difficult, as well as causing an emotional and physical burden on healthcare workers. The cognitive changes caused by AD trigger various feelings in both older adults and their caregivers, such as helplessness, helplessness, frailty, and lack of perspective for the future, as well as the loss of autonomy to care for them and enable relationships social and family (Tamaddonfard et al., 2024).

Functional capacity and loss of autonomy in elderly people suffering from Alzheimer's disease may be related to the presence of bradykinesia and a sedentary lifestyle, which, associated with the lack of stimulation and the absence of an active life, favor a greater probability of developing falls, triad fracture, dependence, which leads many elderly people to reduce their quality of life (Al-Khazaleh et al., 2024).

With the epidemiological transition that occurred in Brazil, there was an increase in the prevalence of chronic non-communicable diseases (NCDs) to the detriment of infectious diseases, due to the improvement of the economic, social and cultural conditions of the country. These improvements have led to an increase in life expectancy, which in turn has culminated in the predominance of progressive morbidities, without the possibility of cure and which is influenced by genetic, behavioral, age and gender factors (Zhang et al., 2024).

With increasing life expectancy, an increase in the prevalence of dementia can be observed, the most common of which is Alzheimer's disease (AD). The course of the disease can vary between 5 and 10 years and life expectancy can be reduced by 50% (Pandey & Hoda, 2024).

By 2050, the number of people living with dementia is expected to triple, from 50 million to 152 million. And among people who develop Alzheimer's disease, nearly six million live in low- and middle-income countries. The annual cost of AD is estimated at $818 billion, which is equivalent to approximately more than 1% of global gross domestic product, with these costs directly related to medical expenses, social assistance and informal care (loss of income for healthcare workers) (Silva, 2024).

While there is no cure for AD, it can be treated, and the quicker the disease is identified, the lower the chance of progression. Current treatments for AD are currently questionable as to their effectiveness as they currently only relieve symptoms and do not prevent progression, as well as being related to numerous side effects. Existing therapeutic options are pharmacological and non-pharmacological; pharmacological medications include drugs such as acetylcholinesterase inhibitors, as well as anxiolytics, antipsychotics, or antidepressants. Non-drug options are physiotherapy and occupational

therapy to stimulate the brain and memory; however, these options only limit the delay of the disease and not its improvement (Ross-Munro, Isikgel, & Fleiss, 2024; Yu, Jia, & Dong, 2024).

Although medications can help relieve some signs and symptoms, such as agitation, anxiety, depression, confusion, and insomnia, these medications are only effective for a limited number of patients and short periods. Although medications can help relieve some signs and symptoms, such as agitation, anxiety, depression, confusion, and insomnia, these medications are only effective for a limited number of patients and short periods. The side effects of these drugs can be harmful, including drug-induced Parkinsonism (Pinapati, Vidya, Khan, Mandal, & Banerjee, 2024).

Non-drug options are physiotherapy and occupational therapy to stimulate the brain and memory; however, these options only limit the delay of the disease and not its improvement.

Due to the need for new therapies, another solution has been sought for the treatment of AD and Cannabis is now one of the main drugs studied for a new treatment strategy. The first reference found on the use of cannabis sativa in 2,700 (Arthur, Kalvala, Surapaneni, & Singh, 2024; Laws III & Smid, 2024)

BC in the pharmacotherapy of the Chinese emperor Shen-Nung, which he recommended in the treatment of malaria, rheumatic pain and irregular and painful menstrual cycles, cannabis has proven effects against diseases such as epilepsy, anxiety, depression, Parkinson's disease, multiple sclerosis and headaches, it was initially widely used for recreational purposes and became illegal due to political and economic factors, while today new uses for cannabis are being discovered (Duncan, Riordan, Gernon, & Koulen, 2024).

Cannabis is classified into two species; C. sativa which has a high concentration of THC (delta-9-tetrahydrocannabinol) and C. indica with a higher percentage of cannabidiol (CBD), there are currently more than 60 different types of pharmacologically active cannabinoids, the THC has a depressant effect on the central nervous system and may represent a health risk, CBD is responsible for the anticonvulsant activity and has recently been released by ANVISA, under medical supervision and prescription (Wang, Sui, Liu, Ren, & Ma, 2024).

Cannabidiol (CBD) is a substance derived from cannabis that acts on the central nervous system, having neuroprotective properties that help improve individuals' cognition and behavior. The Regional Council of Medicine lists cannabidiol as one of the 80 cannabinoids present in the Cannabis Sativa plant that does not produce the psychoactive effects typical of the plant (Abroudi et al., 2024).

The use of Cannabis sativa as a therapeutic resource for AD has led to the growth of research into the pharmacological effects of cannabis. Derived from Cannabis sativa, CBD is effective in various pathologies, including neurocognitive disorders. CBD has an inhibitory action on acetyl-cholinesterase and butyrylcholinesterase, which have a protective action on cells and an inhibitor of oxidative stress, as well as stimulating hippocampal neurogenesis. The combination of THC+CBD is more effective than CBD or THC alone when administered alone (Zarouki et al., 2024).

An integrative review is extremely important to demonstrate existing knowledge on the therapeutic use of Cannabis in the treatment of patients with Alzheimer's disease. This study aimed to carry out an integrative review of cannabinoids, relating their effects in the treatment of Alzheimer's (Teixeira, Rocha, & Gatchel, 2024).

METHODOLOGY:

This study is an integrative review of the literature regarding the impact of cannabis-based treatment on patients with Alzheimer's disease. Data collection began with the research question “What are the effects of cannabis on patients with Alzheimer's disease?” From then on the research developed in five successive phases: 1) search for scientific articles in the selected databases, 2) data selection, 3) data extraction, 4) evaluation of the studies considered according to the eligibility criteria, 5) interpretation of the extracted data, 6) summary of the main aspects of the work, 7) discussion of the studies deemed suitable after the evaluation phases (Calleja, Szijj, Serracino-Inglott, & Azzopardi, 2024).

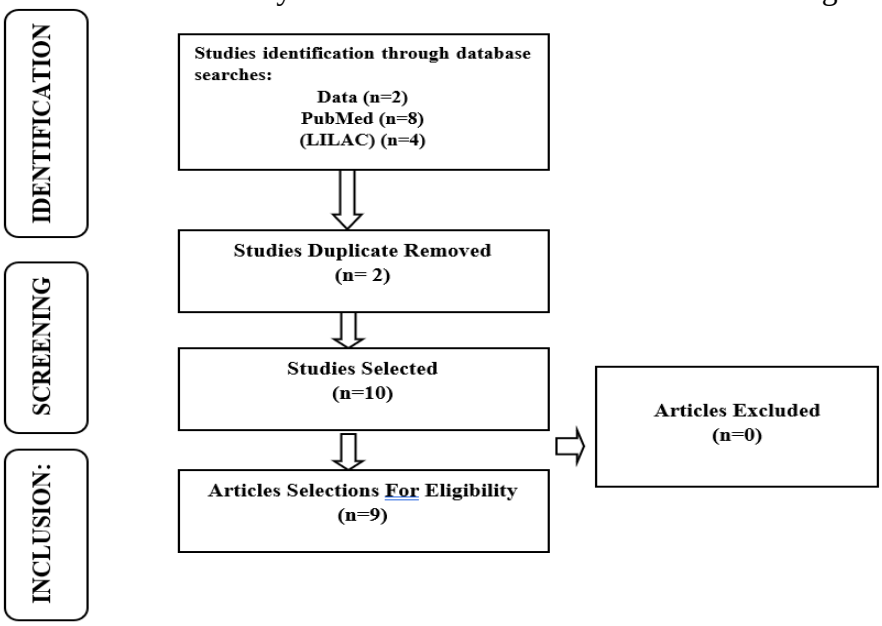
Electronic data for this work were collected in the LILACS (Latin American and Caribbean Literature in Health Sciences) and Pubmed (National Library of Medicine; National Institutes of Health) databases. Inclusion criteria included fully published articles, published from 2013 to 2023, in English, Portuguese, and Spanish. Systematic review studies, meta-analysis, randomized clinical trials, prospective and retrospective studies. Narrative reviews, integrative reviews, course completion studies such as theses and dissertations, editorial letters, and works that did not discuss the effects of cannabis on Alzheimer's patients were ignored (Tsiogkas et al., 2024).

To facilitate the localization of studies in the databases, the Health Sciences Descriptors (DeCs) were used, and applied to LILACS and the Medical Object Headings Section (MeSH) was applied to Pubmed. The DeCs used were: “Cannabidiol”, “Tetrahydrocannabinol”, “Alzheimer” and “Treatment”. MeSH were applied to Pubmed based on their respective English translations “Cannabidiol”, “Tetrahydrocannabinol”, “Alzheimer” and “Treatment”. Keywords were matched using the Boolean operator AND (Gupta et al., 2024).

After collection, the data were organized in Microsoft® Office Excel 2013 into a table with elements based on the structure of each article, including year of publication, authorship, study design, objective, population characteristics, and main findings. Flowchart 1 represents the study selection steps for discussion of this work (Guo, Wei, Deng, & Guo, 2024).

RESULTS:

Flowchart 1 represents the selective synthesis of the studies included in this integrative review.



Flowchart 1: Flowchart for item selection.

Table 1 represents a summary of the characteristics of the studies considered eligible for discussion in this integrative review.

YEAR	AUTHORSHIP	STUDY DESIGN	OBJECTIVE	MAIN RESULTS
2020	Stone et al.	Systematic review	Gather results on the neuroprotective effects of tetrahydrocannabinol acid, tetrahydrocannabivarin, cannabidiol acid, cannabidivarin, cannabichromene (CBC), cannabichromenic acid (CBCA), cannabichromevarin	All phytocannabinoids tested have some degree of neuroprotective activity. More studies are needed to evaluate the neuroprotective activity of these compounds.

			(CBCV), cannabigerol (CBG), cannabigerolic acid (CBGA), cannabigerivarin (CBGV), cannabigerovarinic acid (CBGVA), cannabicromevarinic acid (CBCVA), cannabidivarinic acid (CBDVA) and cannabinol (CBN).	
2020	Charernboon et al.	Systematic review	The present study aimed to examine the evidence on the effectiveness of cannabinoids in treating dementia.	One study used dronabinol 5 mg/day to target anorexic symptoms of dementia, which had a positive impact on weight. Results from two trials investigating the efficacy of tetrahydrocannabinol (THC) 1.5-4.5 mg/day for treating agitation indicated no significant differences between THC and placebo. The most recent study reported significant improvement in agitation using nabilone at 1-2 mg/day. However, the levels of evidence for these agents were classified as low and very low due to the small sample size and methodological issues. There were no studies available that investigated the use of cannabinoids to moderate cognitive symptoms in dementia.
2015	Elsen et al.	A randomized, double-blind, placebo-controlled study	To study the efficacy and safety of low-dose oral tetrahydrocannabinol (THC) in the treatment of dementia-related neuropsychiatric symptoms (NPS).	Oral THC at 4.5 mg daily showed no benefit on NPS but was well tolerated, which adds valuable knowledge to the scant evidence on THC in dementia. The benign adverse event profile of this dose allows us to study whether higher doses are effective and equally well tolerated.
2019	Sugarman et al.	Randomized, double-blind, parallel-group study.	To investigate the feasibility of administering galantamine to individuals with cannabis use disorder (CUD) and the effects of galantamine on cognition.	There were no significant differences in demographic and baseline variables between groups (galantamine vs. placebo). There were no significant adverse effects of galantamine. Withdrawal and craving for cannabis steadily decreased throughout the study. We saw evidence of a modest improvement in cognitive outcomes over the 10 months days, exemplified by a statistically significant increase in measures of response

				inhibition (increased mean reaction time in the stop signal task) and a trend towards improvement in measures of attention (increased RVP A'), for both groups. Analyzes did not, however, show a significant main effect for treatment or treatment by time interactions.
2021	Kuharic et al.	Randomized clinical trial (RCT)	Determine the efficacy and safety of cannabinoids for the treatment of dementia.	It cannot be certain whether cannabinoids have any beneficial or harmful effects on dementia. If there are benefits from cannabinoids for people with dementia, the effects may be too small to be clinically significant. Adequately powered and methodologically robust trials with longer follow-ups are needed to adequately evaluate the effects of cannabinoids in dementia.
2016	Wilkinson et. al	Systematic review	Examine the strength of the evidence for the efficacy of marijuana and other cannabinoids for these psychiatric indications.	To date, no RCTs have examined the effectiveness of marijuana for Tourette's disorder, PTSD, or Alzheimer's disease. Lower-quality studies have examined the efficacy of marijuana, Δ^9-tetrahydrocannabinol, and nabilone; The strength of evidence for the use of cannabinoids for these conditions is very low at this time. Consequences of chronic exposure to cannabinoids include tolerance, dependence, and withdrawal. Early and persistent use of marijuana has been associated with the onset of psychosis. Marijuana impairs attention, memory, IQ and driving ability.
2020	Stone et al.	Systematic review	Gather and summarize all current data on the neuroprotective potential of phytocannabinoids other than Δ9-THC and CBD.	Despite the lack of available studies in this area, all tested phytocannabinoids were found to exhibit neuroprotective properties in a variety of disorders. CBG and its derivatives showed significant anti-inflammatory effects and were particularly effective in models of Huntington's disease. CBDV, Δ9-THCV, and CBC were effective as anticonvulsant agents, while CBN exhibited antioxidant activity and Δ9-THCA had anti-inflammatory effects.

				CBG and Δ9-THCA, like CBD, mediate their anti-inflammatory effects through
2017	Elsen et al.	Randomized placebo-controlled study	Evaluate the benefits of THC on stable motor symptoms associated with dementia	THC also promoted an increase in stride length during gait and trunk oscillation. No falls were observed during the studied period. The authors concluded that THC at a dose of 3mg per day may have beneficial effects on mobility, in addition to having good tolerability among patients.
2021	Sánchez et al.	Systematic review	Review reports of therapeutic applications with the use of cannabis derivatives, emphasizing the role that cannabinoids play, and understand the likely therapeutic use of this plant and its derivatives.	Current knowledge suggests that cannabinoids appear to be a new alternative to combat pain and other symptoms that do not respond or partially respond to classic drug treatment. The scope of cannabinoid drugs appears to range from palliative use to therapeutic purposes. New lines of research point to a likely antitumor effect, which would open up an alternative for cancer treatment; however, more evidence is needed in this field. Thus, cannabinoids appear promising in a wide range of pathological entities.

Table 1: Summary of characteristics of included studies

DISCUSSION:

In a systematic review, Stone et al. (2020) discussed the neuroprotective effect of tetrahydrocannabinolic acid, tetrahydrocannabivarin, CBC, CBCA, CBCV, CBG, CBGA, CBGV, CBGVA, CBCVA, CBDVA, and cannabinol. These phytocannabinoids can promote an antioxidant action and act in an anti-inflammatory manner at the level of the Central Nervous System (CNS). It has been observed that all phytocannabinoids tested present a certain degree of neuroprotective activity, however, new studies are needed to understand the real neuroprotective effect of these substances and also their effects in combinations (Karimi, Zahra, & Martin, 2024; Patel, Paliwal, Sawant, & Prajapati, 2024).

Charernboon et al. (2020) also reviewed the evidence regarding the effectiveness of cannabinoids in treating dementia. It has been recorded that THC (tetrahydrocannabinol) administered at a dose between 1.5 and 4.5 mg/day does not present significant differences in the control of agitation between the group using the substance and the placebo group. The administration of 1-2 mg/day of nabilone was able to improve agitation. A positive effect of using 5 mg/day of dronabinol to control dementia has also been reported, with a positive impact on patients' weight. Despite the results found, the authors state the limited availability of evidence to support the use of cannabinoids in the control of cognitive symptoms in dementia patients (Artimagnella et al., 2024).

The research results of Kuharic et al. (2021) confirm that there is no concrete evidence of the benefits or harms of cannabinoids in dementia. The authors determined the efficacy and safety of cannabinoids for the treatment of dementia in a systematic review. The analysis of 126 participants with Alzheimer's disease revealed that it is unclear whether cannabinoids are harmful or beneficial in treating Alzheimer's disease compared to the placebo group. One study showed significant sedation with nabilone. The research reinforces the fact that, using this method, the available placebo-controlled

studies however have a very small sample size GRID analysis, and the risk of bias is considered low or very low (Chang, Niu, & Jiang, 2024).

In a systematic review, Wilkinson et al. (2016) studied the available evidence regarding the use of marijuana and other cannabinoids for psychiatric indications, such as Alzheimer's disease. Chronic use of cannabinoids can promote tolerance, withdrawal and dependence. Furthermore, it is associated with the development of psychosis among users, damaging areas of memory, attention and locomotive driving ability. The authors reinforce the need for new studies that can guarantee the real effectiveness and benefits of marijuana in psychiatric conditions (Cherninskyi, Hermann, Lukyanetz, & Krishtal, 2024; Wilds & Riddell, 2024).

Elsen et al. (2015), in a randomized, double-blind, placebo-controlled study, evaluated the efficacy and safety of low-dose oral THC (tetrahydrocannabinol) in the treatment of neuropsychic symptoms associated with dementia. The evaluation was carried out based on the analysis of vital signs, adverse events and the application of the neuropsychiatric symptom rating scale (Neuropsychiatric Inventory-NPI). The authors stated that no benefit was observed using THC at a dose of 4.5 mg per day. Despite this, the use of the drug was well tolerated by patients, which can be considered promising in the search for further evidence on the impact of this substance on dementia diseases (Loan, Syal, Lui, He, & Wang, 2024; Pyka et al., 2024).

A new randomized double-blind study was conducted by Elsen et al. (2016) to evaluate the benefits of THC on stable motor symptoms associated with dementia. Eighteen patients with an average age of 77 years were recruited, and divided into two groups, to receive 1.5 mg of oral THC twice daily and a placebo for three consecutive days separated by 4 days. THC was observed to alter the static balance of Alzheimer's disease patients by altering standing (static) balance and increasing the balance of patients with their eyes open. THC also promoted an increase in stride length during gait and trunk swing. No falls were observed during the studied period. The authors concluded that THC at a dose of 3 mg per day can have beneficial effects on mobility, as well as having good tolerability among patients (Ansari, Singh, & Singh, 2024; Pereira et al., 2024)

From this point of view, cannabidiol can be considered a complementary therapeutic alternative for the control of symptoms associated with neurological changes. Cannabis derivatives, such as CBD, can promote relief of motor and non-motor symptoms, especially in the early stages of treatment, without significant adverse events (Delgado-Sequera, Garcia-Mompo, Gonzalez-Pinto, Maria, & Esther, 2024).

Sanchez et al. (2021) reviewed reports on therapeutic applications using cannabis derivatives, emphasizing the therapeutic use of the plant. The effects of cannabidiol have been considered promising and considered an alternative to combat pain, nausea and vomiting in patients undergoing chemotherapy who partially respond to conventional treatment. In Alzheimer's disease, available evidence demonstrates lower biological strength (Suzuki et al., 2024).

In a systematic review, Stone et al. (2020) collected current data on the neuroprotective potential of phytocannabinoids. It has been discussed that phytocannabinoids have neuroprotective properties in several neuropsychological disorders, including Alzheimer's. CBG (cannabigerol), for example, has anti-inflammatory effects and THC and CBC (cannabichromene) have anticonvulsant activity. It was concluded that phytocannabinoids and terpenes present in the cannabis plant may have a neuroprotective effect (Modi, Prajapati, Singh, Singh, & Maheshwari, 2024; Yang et al., 2024).

Galantamine is an acetylcholinesterase inhibitor (AChEI) also widely used in the management of neurocognitive disorders associated with Alzheimer's disease. In a randomized double-blind study, Sugarman et al (2019) evaluated 30 individuals with cannabis use disorder and the effects of galantamine on these patients' cognition. Patients were assigned to two groups where group 1 was randomized to receive 8 mg galantamine daily for 10 days for comparison with the placebo group. No significant differences were observed between the galantamine and placebo groups, and no major adverse effects were associated with the galantamine group (Lahyaoui, Bouyahya, El Menyiy, Bakrim, & Dakka, 2024; Tyagi, Awasthi, Dhiman, Sharma, & Kulkarni, 2024).

Sugarmann et al. (2019) observed a slight improvement in attention measures, which led to a positive impact for ten days. Moreover, abstinence and the desire to change were discovered during the research (Gujarathi et al., 2024; Nayak et al., 2024).

FINAL CONSIDERATIONS:

Phytocannabinoids have neuroprotective properties in several neuropsychological disorders, including Alzheimer's. CBG (cannabigerol), for example, has anti-inflammatory effects and THC and CBC (cannabichromene) have anticonvulsant activity. The authors reinforce the need for new studies that can guarantee the real effectiveness and benefits of marijuana in psychiatric pathologies. Despite this, the use of cannabinoids was well tolerated by patients and can be considered promising in the search for further evidence on the impact of this substance on dementia diseases. In future studies, it is suggested to conduct research that can analyze the real effect of cannabinoids on patients diagnosed with Alzheimer's disease and also the impact of long-term use of the substance.

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