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Cannabinoids as a Therapeutic Alternative in Alzheimer's disease: A Brief Review of the Literature

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Abstract

Alzheimer's disease (AD) is a pathophysiological condition characterized by progressive neurodegeneration that leads to decline in cognitive functions and dementia. Although pharmacotherapy represents the main strategy in the clinical treatment of AD, currently available drugs have limited therapeutic effects and the undesirable effects of these drugs can often outweigh their beneficial effects. Studies with cannabinoid compounds have increased greatly in recent decades and the results of these studies point to the therapeutic potential of these substances in different pathophysiological conditions, including AD. The present work aimed to perform a comprehensive literature review on the analysis of the efficacy/effectiveness of cannabinoid derivatives in AD. The search for articles was carried out in the databases PubMed (NCBI), Virtual Health Library (VHL), Scientific Online Electronic Library (SciELO), Medical Literature Analysis and Retrieval System Online – MedLine (PubMed), Scientific Electronic Library – SciELO and Latin American and Caribbean Literature in Health Sciences – LILACS. Despite the limitations found in most studies and described in this work, medicinal *Cannabis* and its derivatives have beneficial effects in the treatment of AD, where the combination of specific *Cannabis* derivatives described in this review may represent a potential therapeutic option both in controlling symptoms and mitigating disease progression. However, more robust evidence that proves the real efficacy and safety of these compounds may support the idea of using these substances in the treatment of AD.

Keywords: Alzheimer's disease, Cannabinoid system, *Cannabis*, Cannabidiol, Tetrahydrocannabinol

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1. Introduction

Worldwide, the demographic transition process in recent decades has been marked by significant population aging. Specific studies indicate that elderly people will reach billions in the next two decades, as life expectancy has increased considerably [1-2]. Unfortunately, in this context, the incidence of chronic degenerative pathophysiologies, such as Alzheimer's disease (AD), is also increasing [3]. Epidemiological studies estimate that tens of millions of people worldwide suffer from AD and this number could reach hundreds of millions in the next thirty years and may be prevalent in low and middle income countries, but regardless of the financial situation, the disease will inexorably affect the lives of patients, families, caregivers and even the health system [4-6]. AD is a debilitating neurodegenerative disease characterized primarily by a progressive decline in cognitive ability, leading to ongoing memory loss and cognitive-behavioral symptoms [3]. The slow and progressive loss of cognitive functions, such as memory, language, attention, and behavioral changes, becomes more significant and impactful over time [6]. AD can currently be classified into two types: familial AD (FAD), which has an early onset and usually occurs before the age of 60, and late-onset AD (LOAD), which is sporadic and usually

occurs after the age of 60. Less than 10% are FAD and the prevalent form is LOAD [6].

Furthermore, according to the AD Clinical Protocol and Treatment Guidelines and the International Statistical Classification of Diseases and Related Health Problems, there is a third classification of the disease, classified as other forms of AD [7-8]. Currently, some classes of drugs are used to treat AD symptoms, aiming to slow the clinical progression of the disease. However, they provide limited benefits on cognitive function and, in many patients, can cause considerable undesirable effects [9-10]. In Brazil, main class of drugs used to treat mild and moderate forms of AD is class of reversible acetylcholinesterase (AChE) inhibitors, such as rivastigmine, donepezil, and galantamine [3-7]. However, clinical significance of the pharmacological efficacy of these drugs is questionable, as they provide limited therapeutic benefits since they are lost when treatment is discontinued [3-5-9-11]. Regarding treatment of symptoms of severe AD, memantine, a non-competitive antagonist of NMDA (N-methyl-D-aspartate) glutamate receptors, has been used in Brazil. This drug prevents excessive glutamate stimulation of NMDA receptors and thus reduces the influx of extracellular calcium into neurons in different brain structures. However, the intensity of effect determined by this drug on the cognitive, behavioral, and functional fields of AD is very subtle [7].

In this way, it is clear that full knowledge or complete elucidation of the pathophysiology of AD is crucial for the development of potential drugs that are effective in containing the progression of AD and that are not only useful in treating the symptoms of the disease [12]. Currently, studies on the use of *Cannabis* for therapeutic purposes in the treatment of chronic pain, chemotherapy-induced nausea and vomiting, multiple sclerosis, anorexia nervosa, anxiety, dementia, dystonia, Huntington's disease, Parkinson's disease, post-traumatic stress disorder, Tourette's syndrome, epilepsy and AD itself have increased significantly [9-10-13]. The Δ9-tetrahydrocannabinol (THC) and CBD are two phytocannabinoids produced by the *Cannabis sativa* plant and are related to the activation of the endocannabinoid system [3]. Stimulation of the endocannabinoid system appears to negatively modulate the pathophysiological processes related to neuroinflammation observed during AD. Thus, the use of cannabidiol (CBD) has shown great promise and can be considered a leading candidate and a new therapeutic strategy in the treatment of AD [9-10]. The aim of this study was to carry out an integrative review of works related to the efficacy and effectiveness of medicinal *Cannabis* and its derivatives on the main pathophysiological aspects of Alzheimer's disease.

2. Methodology

The present work is a literature review where the identification of articles of interest was performed using the PubMed databases of the US National Library of Medicine (https://pubmed.ncbi.nlm.nih.gov/), database Medical Literature Analysis and Retrieval System Online (MEDLINE), Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature on Health Sciences (LILACS), and the search tool attached to the Virtual Health Library (VHL). The Institutional Repository of different Brazilian Universities for researching articles along with theses, dissertations, and monographs was also consulted. The predefined keywords “Alzheimer's disease”, “Cannabinoid system”, “*Cannabis*”, “Cannabidiol”, “Tetrahydrocannabinol” were used in the searches. The search expression was the Boolean operator "AND", limiting the searches to the words of the title or abstract of articles, in English, Portuguese and Spanish, studies with human beings and/or experimental animals, as well as *in vivo* studies and/or *ex-vivo*. To ensure the quality of articles, only indexed publications were included in this database and articles that presented title and abstract according to the theme were included and those that did not fit were excluded.

3. Results and discussion

3.1. Pathophysiology of AD

Biomarkers are represented by measurable biological parameters such as cellular and even biochemical components that may indicate cellular and/or molecular changes, for example, a pathological process or severity of a disease. In this way, known pathophysiological markers of AD can be represented by the accumulation of β-amyloid proteins that give rise to senile plaques specifically in the hippocampus and adjacent areas of the cerebral cortex, and the intracellular presence of neurofibrillary tangles formed by hyperphosphorylation of the tau protein [14]. In addition, the accumulation of senile plaques leads to chronic and prolonged activation of microglial cells and astrocytes, resulting in an environment rich in inflammation and oxidative stress [15]. All these factors contribute to the worsening and progression of the disease. Thus, the β-amyloid peptide is formed from the erroneous cleavage of the amyloid precursor protein (APP) by the enzymes β-secretase, followed by γ-secretase, which results in insoluble proteins (step 1). β-amyloid peptides can be eliminated by two different pathways: by apolipoprotein E (APOE) or by astrocytes through low-density lipoprotein receptor-related protein 1 (LRP1) (step 2).

The accumulation together with the decreased clearance of these fragments causes aggregation and formation of senile plaques (step 3). The plaques formed can be cleared by phagocytic or endocytic degradation or by proteolytic enzymes such as neprelysin, in addition to absorption by astrocytes and microglia (step 4) [14-16]. The tau protein is responsible for the organization of the cytoskeleton of neurons. Under normal conditions, it acts as a stabilizing protein associated with microtubules in neuronal axons, but in pathology, it is dissociated [4-6-12]. The aggregation of the tau protein may occur, by mechanisms still unknown, due to the formation of some conformational oligomers that dissociate from the β-amyloid fibrils and plaques, being toxic to adjacent synapses (stage 5). In addition, hyperphosphorylation of this protein may occur, in which it loses its ability to bind to microtubules, leading to its destabilization and the formation of neurofibrillary tangles, causing damage mainly to neurons, extending to the dendrites (stage 6) [16]. Finally, the elimination of tau protein fibrils may occur by healthy neurons and through absorption, causing damage to the captured cell (stage 7) [14].

3.2. Clinical Manifestations of AD

AD presents a progressive pattern of cognitive and functional deterioration, which can be classified into three main stages: initial, moderate, and severe/terminal. The initial stage or preclinical phase is usually observed in the first or second year after the onset of the disease, where brain

changes are detectable, but clinical symptoms have not yet manifested significantly. In this way, biomarkers, such as changes in cerebrospinal fluid and blood, can indicate the presence of AD, although memory is not affected at this stage [17-18]. During the moderate stage, it is characterized by mild cognitive impairment and develops between the second and fifth year of the disease [17-18]. Patients begin to present more evident cognitive deficits, such as difficulty in naming objects and gradual worsening of memory. Biomarkers become more pronounced, including elevated levels of the β-amyloid protein. Furthermore, symptoms affect autonomy in daily activities, such as eating and dressing, and may include disinterest, apathy, and loss of identity [17–18]. The last stage of AD is the severe or terminal stage (dementia), where from the fifth year onwards the symptoms become severe, with significant impairment of cognitive and motor function.

This stage is characterized by the total dependence of the patient in daily activities and the presence of symptoms such as loss of speech, facial recognition, and self-care. In addition, significant behavioral changes occur, including agitation and irritability [9-19]. Histopathological studies reveal that during AD, senile plaques and neurofibrillary tangles form, impairing the functioning of different areas of the brain throughout the stages of the disease. In the initial stage, the changes are subtle; in the moderate stage, there is more evident brain atrophy; and in the terminal stage, the changes are extensive and affect areas related to movement and swallowing [18]. These clinical manifestations reflect the complexity of AD and its profound impact on quality of life of affected individuals. Appropriate management requires a multidisciplinary approach to optimize support for the patient and their caregivers throughout the disease course [20-21].

3.3. Current pharmacological treatment and its limitations

During AD, pathophysiological and biochemical changes are observed in the hippocampus and cortex, where a reduction or hypoactivity of cholinergic neurotransmission is observed. Current pharmacological treatments for AD determine limited and short-term beneficial effects. These drugs do not prevent or stop the progression of the disease, that is, they reduce the symptoms of the disease and, therefore, have limited efficacy, in addition to determining the occurrence of considerable adverse reactions [22]. In this way, AChE inhibitors determine the occurrence of adverse effects that compromise the patient's quality of life, such as nausea, vomiting and diarrhea, muscle spasms, bradycardia, and nightmares, among other pathophysiological conditions. In addition, these drugs should be used with caution in individuals with a history of gastrointestinal disorders and the combination of two or more of them should be avoided due to the lack of studies demonstrating the efficacy and safety of this procedure. Regarding the use of NMDA receptor blockers, most common adverse effects caused by memantine are dizziness, severe headache, and lethargy [14]. Thus, it can be deduced that one of the ideal pharmacological treatments for AD would be to limit and/or prevent formation of senile plaques and neurofibrillary tangles and to reestablish healthy cholinergic neurotransmission with more specific drugs that determine a lower incidence of serious adverse effects.

3.4. The endocannabinoid system and AD

"Maconha", as *Cannabis* is known in Brazil, through its main psychoactive component, tetrahydrocannabinol (THC), exerts a variety of disruptive effects on the central nervous system (CNS). These effects can be classified as acute and chronic, covering a range of neurological, psychic, and physiological reactions. Based on specific studies on phytocannabinoids, the human endocannabinoid system was discovered in 1990, where anandamide and 2-arachidonoylglycerol are the main neurotransmitters of this system and through the stimulation of transmembrane receptors (CB1 and CB2) modulate different physiological effects such as pain, mood, appetite, synaptic plasticity and memory [23]. The CB1 receptor is widely distributed in the CNS and poorly distributed in peripheral tissues. Stimulation of this receptor is related to motor control, emotional response, learning, memory, and goal-oriented behaviors. In turn, CB2 receptors are widely distributed in the immune system, microglial cells, and postsynaptic neurons, and, therefore, their stimulation does not imply changes in mood, behavior, or cognitive-motor changes [23].

In this way, *in vivo* studies have shown that stimulation of the cannabinoid system by phytocannabinoids determines reductions in oxidative stress and neuroinflammation, decrease in the formation of amyloid plaques and neurofibrillary tangles, regulation of microglial cell activation and release of macromolecules [4-9-13]. Population studies indicate a reduction in symptoms related to dementia, such as behavioral disorders, and unlike current therapies, medicinal *Cannabis* and its derivatives cause mild adverse reactions and can be safe and effective in the elderly population [4-9-13].The literature also reports that cannabinoid derivatives can be considered safe, as overdose can cause drowsiness and confusion, euphoria and hallucinations, but does not cause potentially fatal respiratory and/or cardiovascular events, and thus risk inherent in their clinical use is outweighed by their therapeutic benefits [23].

3.5. Medicinal Cannabis in Brazil

In Brazil, the use of medicinal *Cannabis* and its derivatives is still debated and quite limited, which makes it difficult for patients with different neurodegenerative diseases to access these substances. In 2015, the Collegiate Board Resolution (RDC) No. 17/2015 [24] was published, introducing rules for the import of CBD-based medicines on an exceptional basis, allowing the substance to be prescribed by doctors and facilitating the import process. In 2016, therefore, medicinal *Cannabis* became part of the list of plants and substances subject to special control, contained in list C1 of Ordinance 344/98 [25]. Only in 2017, the first medicinal *Cannabis*-based medicine was approved in Brazil, composed of CBD and THC, Mevatyl® [26], and is indicated for the symptomatic treatment of moderate to severe spasticity related to multiple sclerosis [24-26-27]. In 2019, as a major step forward, the commercialization of *Cannabis*-derived products was permitted according to RDC number 327/2019 [28].

Which grants health authorization for the manufacture and import of the product, as well as the commercialization in pharmacies and drugstores with retention of prescription, prescription, monitoring, and inspection of products with the active ingredient. Recently, the Superior Court of Justice (STJ) granted authorizations for the cultivation of *Cannabis* for medicinal purposes. These decisions allow patients to cultivate the plant without being penalized, as long as they prove medical need. In November

2024, the STJ authorized the cultivation of the *Cannabis sativa* with low THC content (less than 0.3%) for the manufacture of medicines, establishing a six-month deadline for regulation by the National Health Surveillance Agency. Despite all these procedures, the acquisition and use of the medicinal *Cannabis* is still a delicate matter and those who are most negatively impacted are the patients who need the medicines [24-27].

3.6. In vivo studies

The table 1 presents the main aspects covered in the *in vivo* studies selected to be further discussed. In the literature review carried out by Camargo Filho *et al.* [3], it was possible to identify the benefits of using THC and CBD for Parkinson's disease and also for AD. In vivo, studies suggested that there was recovery of social deficits and object recognition, in addition to modification in the composition of β-amyloid plaques, while studies in humans suggested an improvement in emotional well-being, mobility, psychotic symptoms, and Rapid Eye Movement (R.E.M) sleep, with no reports of adverse effects when compared to the administration of placebo. In this way, the authors concluded that these compounds have a possible potential for therapeutic use in patients with AD, requiring new studies that evaluate long-term use, as well as an evaluation of higher doses about effects and safety. According to Crunfli *et al.* [29], a study was conducted to evaluate the protective effect of a cannabinoid agonist arachidonyl-2′-chloroethylamide (ACEA) in experimental models of sporadic AD *in vivo* for 7 days. The drug streptozotocin (STZ) was administered intracerebroventricularly to animals so that it could generate a condition of β-amyloid protein deposition. Subsequently, an object recognition test was performed to evaluate the animals' memory, assessing both short-term and long-term memory.

After administration of ACEA through intraperitoneal administration, it was observed that it was able to improve the short- and long-term memory deficits caused by STZ injection. Furthermore, a significant increase in the anti-apoptotic protein Bcl-2 (Bcl-2) was observed, in the expression of the insulin receptor, improving brain insulin signaling, in addition to the modulation of nitric oxide induced by STZ, actions that revealed a possible neuroprotective mechanism of ACEA. In this way, the data collected during the study suggest an important role of the CB1 receptor as a therapeutic target for the treatment of neurodegenerative diseases such as AD, with cannabinoids being a possible new therapeutic strategy against AD. According to Kim *et al.* [30], treatment with the combination of CBD and THC in AβPP/PS1 transgenic mice was shown to improve experimental parameters related to memory; furthermore, this combination was more effective than treatment with CBD or THC alone. Therefore, according to the authors, these results showed that marijuana components may be useful for treating and preventing AD, since they can suppress the main causal factors of the disease [30].

According to Watt and Karl [9], it was shown that in vivo studies performed in established experimental and transgenic animal models for AD provided evidence of the therapeutic benefits of CBD and its combinations (CBD-THC) in AD, showing the ability to reduce reactive gliosis, the inflammatory response, and promote neurogenesis. Furthermore, CBD can also reverse and prevent the development of cognitive deficits in animal models, and it is shown that the combination may be even more beneficial and provide greater therapeutic benefits than CBD alone, and the advantage of the combination is that CBD can antagonize the psychoactive effects caused by THC. Therefore, the studies provide evidence that CBD and the THC-CBD combination may be valid candidates for the development of new therapies for AD, while additional studies on the long-term effects of CBD and its therapeutic mechanisms need to be carried out. The limitations found were that the studies were conducted in young mice (3 to 6 months), which contradicts diagnosis of AD that usually occurs late, and need to conduct studies in murine models of AD-specific tauopathy and in female mice since reviewed studies were carried out in male mice [9].

In a study conducted by Aso *et al.* [34] the efficacy of botanical extracts enriched with THC (containing 67.0% THC, 0.8% CBD, 1.2% cannabigerol, 0.9% cannabichromene and 3.2% other phytocannabinoids) and enriched with CBD (containing 62.7% CBD, 3.6% THC, 1.4% cannabigerol, 5.7% cannabichromene and 1.8% other phytocannabinoids) in APP/PS1 transgenic mice in advanced stages of AD. The extracts were administered in a single injection via the intraperitoneal route, corresponding to the administration of a single Sativex® oromucosal spray (2.8 mg THC + 2.8 mg CBD) in a 70 kg human being, a dose at which it has no psychoactivity. The duration was 5 weeks, with administration once a day, and after a washout period of 10 days, the animals underwent a behavioral evaluation. The results obtained were the reduction of memory impairment in mice at 12 months of age in the advanced stages of the disease. However, the combination of compounds did not modify the processing of β-amyloid proteins, nor did it reduce glial reactivity associated with the deposition of aberrant β-amyloid proteins, as occurs when administered in the early stages of the disease. Thus, it was suggested that the action of these compounds may occur through the modulation of mechanisms other than glial processing and reactivity.

Furthermore, these authors observed that the combination of THC and CBD can induce changes in markers of synaptic function, normalizing the levels of presynaptic synaptosome-associated protein 25 kDa (SNAP-25), but not of postsynaptic density protein 95 (PSD-95), in which this increase in synaptic proteins has previously been associated with the emergence of brain areas affected by the synthesis and deposition of β-amyloid proteins in AD. Another effect observed was the decrease in the expression levels of glutamate receptor subunits (GluR2/3) and an increase in the expression of the α1 subunit of the γ-aminobutyric acid receptor A (GABA-A Rα1) in treated APP/PS1 mice, suggesting that the compounds may decrease glutaminergic activity due to chronic stimulation of the CB1 receptor, neutralizing neural excitability and consequently improving cognitive performance. Although more specific studies relating THC and CBD to AD are needed, it is clear that these compounds may represent safe and effective therapeutic alternatives in the advanced stages of AD. Cheng *et al.* investigated the effect of long-term CBD treatment in APPxPS1 transgenic mice. They observed that CBD could determine the restoration of social recognition memory and improve object recognition deficits without affecting fear-associated memory or anxiety-like behavior.

In this way, Chan *et al.* suggested that CBD may have therapeutic potential for the treatment of AD patients and that future studies to clarify mechanisms of therapeutic effects are indispensable and essential [32]. In another study,

conducted by Cheng et al. [33], effects of long-term oral treatment with CBD on social recognition memory and pathophysiology in an APP/PS1 double transgenic mouse model of AD were first demonstrated in 2014. Control mice and transgenic models were treated orally from 2.5 months of age with CBD (20 mg/kg) daily for 8 months. According to study, CBD can prevent development of social recognition deficit, which was not associated with changes in amyloid burden or oxidative damage. Nevertheless, it caused a subtle impact on neuroinflammation in the brains of AD mice, cholesterol, and dietary phytosterol retention, requiring further investigation. Thus, it demonstrated that CBD can prevent social recognition deficit, a process that may be related to an environmentally beneficial effect of dietary phytosterol retention caused by CBD, revealing a possible interaction of this compound in pathophysiology of AD, increasing retention of specific phytosterols. Consequently, study provides evidence that above-mentioned compound could be considered a long-term preventive treatment option for AD and relevant for symptoms of social withdrawal and facial recognition [33].

In another study, conducted by Aso *et al.* [34], male APP/PS1 mice were used as an animal model to evaluate botanical extracts of THC or CBD, as well as the combination of both natural cannabinoids, with the administration of THC-enriched botanical extract (containing 67.1% THC, 0.3% CBD, 0.9% cannabigerol, 0.9% cannabichromene, and 1.9% other phytocannabinoids) and CBD-enriched botanical extract (containing 64.8% CBD, 2.3% THC, 1.1% cannabigerol, 3.0% cannabichromene, and 1.5% other phytocannabinoids). Aso *et al.*, found that natural cannabinoids reduced cognitive deficits in AD models using non-psychoactive doses, in addition, they preserved memory when administered chronically during early symptomatic stage. Furthermore, the researchers also found that the combination of THC and CBD alters the processing of β-amyloid protein, providing levels of the 42-residue β-amyloid protein (Aβ1-42), but not of 40-residue β-amyloid protein (Aβ1-40). These results suggest a protective effect of the compound by reducing amount of more toxic soluble form A (Aβ1-42), since when enzymes γ-secretase and β-secretase cleave APP into different parts, β-amyloid protein fragments of different sizes generated, with residues 40 and 42, latter being more hydrophobic, having greater amyloidogenic potential, although both can combine and give rise to protofibrils, fibrils and, finally, insoluble plaques [6-34].

Changes in the composition of amyloid plaques were also observed in mice treated with the combination, since there was an increase in the Aβ1-42/Aβ1-40 ratio, which could be explained by a facilitated composition of Aβ1-42 caused by cannabinoids, reducing the soluble form and possibly its toxicity [34]. Also in the same study, Aso *et al.*, observed that after the administration of THC, CBD, or a combination of both, these natural cannabinoids reduced astrogliosis related to the deposition of β-amyloid protein and expression of cytokines related to disease, with combination being more effective than compounds alone. In addition, a reversal of thioredoxin 2 (Trx2) deficiency was evidenced in mice, a situation also observed in patients with AD. This gene encodes an essential protein of mitochondrial antioxidant system that is responsible for release of reactive intermediates and replacement of proteins that have suffered oxidative damage, which ensures protection against deleterious and oxidative effects in animal model [34]. In this way, results obtained in these studies provide valuable information so that an additional clinical study can eventually be carried out to test efficacy of compounds and then for development of *Cannabis*-derived drugs for treatment of AD [34].

During the studies by Martín-Moreno *et al.* [35], effects of chronic administration of WIN 55,212-2 and JWH-133 (CB2 cannabinoid receptor agonists) at a dose of 0.2 mg/kg/day for 4 months in transgenic mice (Tg APP) verified. The agonists were administered orally and determined a decrease in microglial activation, a decrease in neuroinflammation, and a reduction in brain levels of β-amyloid proteins, which resulted in improvement of cognitive deficits and a decrease in release of cytokines in CNS [35]. In this context, Esposito *et al.* [36] evaluated relationship between peroxisome proliferator-activated receptor gamma (PPARγ) and genesis of AD pathophysiology and effects of CBD administration in experimental rodent models of AD induced by intrahippocampal administration of β-amyloid peptide (Aβ1-42). The results showed that, under physiological conditions, PPARγ receptors are expressed at low levels in the CNS.

However, during AD, the expression of these receptors is elevated, and may therefore be associated with the etiology of the pathophysiological characteristics of AD [36]. Furthermore, results obtained by Esposito *et al.* showed that intrahippocampal administration of β-amyloid peptide causes severe neuronal loss and marked astrocytic activation in experimental animals, mainly at the site of application, implying appearance of AD symptoms [36]. The researchers also found that administration of CBD (10 mg/kg) for 15 consecutive days led to almost complete recovery of integrity of pyramidal neurons in the most affected area and inhibition of reactive gliosis [36]. Also concerning hippocampus, during same study, it was observed that treatment with CBD causes restoration of neurogenesis in dentate gyrus through selective activation of PPARγ in animals with AD symptoms induced by injection of β-amyloid peptide, and this restoration induced by CBD is almost completely abolished by PPARγ receptor antagonists, which suggests that stimulation of these receptors may represent a probable mechanism of action of CBD in restoring neurogenesis in the hippocampus [36].

3.7. Population studies

The main aspects observed in the results of population studies are presented in Table 2 and the discussion of these results will be described below. According to Peprah and McCormack [37], the selected studies (primary studies and an uncontrolled prospective pilot study—a “before and after” study) showed positive but limited evidence that medical *Cannabis* may be effective in treating neuropsychiatric symptoms (NPS) associated with dementia, such as agitation, disinhibition, irritability, aberrant motor behavior, nocturnal behavior disorders, and aberrant vocalizations. In addition, limited evidence was observed regarding improvements in rigidity and cognitive scores assessed by the mini-mental state examination (MMSE, which is a test used for a rapid assessment of cognitive function, which lasts around 10 minutes and is divided into two parts, the first covering orientation, memory, and attention, and the second assessing specific skills such as naming and comprehension). However, data are inconclusive due to low quality of the evidence and the non-randomization

of patients, meaning that further studies, such as controlled and randomized studies, are needed to prove its efficacy.

A prospective observational study was conducted by Broers *et al.* [38] in patients with severe dementia and behavioral problems in a specialized nursing home in Geneva. The study was conducted on ten patients, who received an average of 7.6 mg THC oil + 13.2 mg CBD daily for two months. In this study, it was found that oral treatment with the THC + CBD combination was acceptable, well tolerated, and improved rigidity and general behavior, in addition, it allowed the reduction or discontinuation of other psychotropic medications in half of patients, in whom polypharmacy is quite common. Positive effects of medication also benefited the staff, who observed in almost all patients less general rigidity, such as more relaxed faces, necks, shoulders, & limbs (reduced rigidity), which facilitated daily care and transfers, direct contact with patients, and improved behavior. In addition, nurses described patients as calmer, more relaxed, less irritable, and more smiling. Despite limitations and difficulties of study, such as influence of several factors on behavior and symptoms of patients, low number of patients included, and absence of pharmacological data, study showed that oral oily extract of *Cannabis* containing THC + CBD determines significant improvement in behavioral problems, rigidity and facilitates daily care in patients with severe dementia, but still, study in a randomized clinical trial is indispensable [38]. In a systematic review and meta-analysis article published by Bahji [39] efficacy of cannabinoids in treatment of SNPs in patients with dementia evaluated in 9 studies (85% of which were AD), of which THC, dronabinol, and nabilone used.

In this systematic review meta-analysis, it was suggested that treatment with dronabinol and nabilone determines significant improvements in SNPs without evaluating the occurrence of serious adverse events in these patients. However, the small sample size in the study does not allow an adequate conclusion on subject, which is dependent on more population studies. In another prospective open-label study by Shelef *et al.* [40], patients with AD received low (2.5 mg) and high (5.0 mg) doses of medicinal *Cannabis* oil that added to conventional AD pharmacotherapy. Results showed that patients had a significant decrease in the following symptoms: delusions, agitation/aggression, irritability, apathy, sleep, and caregiver distress. The main adverse effect determined by the treatment was shown to be dose-dependent and was mental confusion, which was observed in only 1 of 11 patients who participated in studies. Although the sample size was small and the lack of a control group may negatively impact studies, Shelef *et al.* concluded that addition of medicinal *Cannabis* oil to patients' pharmacotherapy could be considered a possible and promising treatment option in patients suffering from AD and patients with behavioral and psychological symptoms of dementia [40].

Regarding THC's safety, pharmacodynamics, and pharmacokinetics, a randomized, double-blind, placebo-controlled crossover study was conducted by Ahmed *et al.* [41] in ten patients with dementia (mean age 77.3 ± 5.6) for 12 weeks. Patients were randomly assigned to receive oral THC or placebo twice daily for 3 days, separated by a 4-day washout period. During the period, 98 adverse events were reported. Data obtained in the study also showed that THC is rapidly absorbed, which suggests a short latency of its pharmacological effect. However, Ahmed *et al.* concluded that studies with higher doses are needed to evaluate these same parameters in elderly patients with dementia [41]. In a randomized, double-blind, placebo-controlled, crossover study divided into six treatment blocks of two weeks each, Elsen *et al.* [42] conducted in patients with dementia and clinically relevant NSD selected from two hospitals in Netherlands. The study aimed to evaluate the efficacy and safety of orally administered THC in the treatment of NSD. The results obtained showed that, although THC did not reduce behavioral disturbances in patients with dementia when compared to the placebo group and did not show any benefit in the treatment of AD symptoms in any of measures during the study, THC was well tolerated by patients.

Thus, Elsen *et al.*, suggest that THC presents good safety in elderly patients with dementia when administered in a short period and that future studies with higher doses in a gradual manner to evaluate efficacy and safety of THC in patients with dementia are essential. In a review conducted by Liu *et al.* [43], efficacy of synthetic cannabinoids, dronabinol or nabilone, was evaluated concerning agitation and aggression in AD. Six studies were included, including letters, case studies, and controlled trials, resulting in a total of 67 participants, of whom a significant proportion had used or were using psychoactive medication to control symptoms of disease. The results showed significant benefits of use concerning symptoms and may offer a therapeutic alternative with a low-risk profile when compared to antipsychotic medications, however, these data were limited due to the small sample size and number of studies included, short study duration and the lack of placebo control in some studies. Therefore, according to high prevalence of these symptoms in AD and adverse events of current therapies, authors concluded that more controlled clinical studies are needed, with more rigorous methods to evaluate safety and efficacy of cannabinoids for treatment of agitation and aggression, in addition to better understanding roles of CB1 and CB2 receptors, DA and mechanism of action of these compounds.

Finally, in addition to studies focused on AD, it is valid to verify efficacy and safety of medicinal cannabinoids in the elderly, issues that can be seen in the review carried out by Elsen *et al.*, who showed that THC may be useful in treatment of anorexia and behavioral symptoms of dementia, and adverse events were more common during cannabinoid treatment when compared to control groups, the most frequent being sedation [44]. However, the study by Elsen *et al.* does not clarify whether there is a relationship between age and, consequently, the efficacy and safety of medicinal cannabinoids, since many of studies were conducted in adult patients and included older individuals, and are therefore not exclusive. Furthermore, there was high heterogeneity among included studies and regarding sample size, which was generally very small. Therefore, review shows that there is a lack of evidence on use of these compounds in elderly, data that is extremely important due to age of patients with AD. The authors concluded that more planned studies needed that consider risk-benefit ratio regarding dementia symptoms, considering initial positive results obtained in review regarding weight loss and agitation in these patients, which would result in more available and reliable information that can guide and support treatment decisions [44].

Table 1. *In vivo* studies on cannabinoid use and its relationship with AD signs and symptoms

Cannabinoid receptor agonists	Main scientific findings	References
THC CBD	-Significant recovery of deficits in social interaction assessment parameters and a beneficial modification in the composition of β-amyloid plaques in experimental animals. -Improvement of emotional well-being, REM sleep, and general mobility in addition to reducing psychotic symptoms in humans	[3]
Arachidonyl-2′-chloroethylamide	- Improvement of short- and long-term memory deficits; - Significant increase in the anti-apoptotic protein Bcl-2 and inhibition of programmed cell death; - Increased expression of the insulin receptor, improving brain insulin signaling; - Modulation in nitric oxide production.	[29]
CBD + THC	-Treatment with the combination of CBD + THC is more effective in improving memory-related parameters during AD than the isolated administration of each compound; - Both the isolated administration of CBD and the administration of CBD + THC reduce the processes of reactive gliosis, the inflammatory response and stimulate neurogenesis; - CBD reverses and prevents the development of cognitive deficits.	[30]

To be continued

Table 1. *In vivo* studies on cannabinoid use and its relationship with AD signs and symptoms

Continuation

Cannabinoid receptor agonists	Main scientific findings	References
Botanical extracts enriched with THC and/or CBD	-Both the isolated administration of THC and the isolated administration of CBD reduce memory impairment in advanced stages of the disease, decrease the expression levels of glutamate receptor subunits (GluR2/3), and increase the expression of the α1 subunit of the γ-aminobutyric acid receptor A (GABA-A Rα1), resulting in the neutralization of neural excitability. - Treatment with the THC + CBD combination does not modify the processing of β-amyloid proteins, nor does it reduce glial reactivity associated with the deposition of aberrant β-amyloid proteins; - The combination of THC + CBD can induce changes in markers of synaptic function, normalizing the levels of the presynaptic synaptosome-associated protein 25 kDa (SNAP-25), but not of the postsynaptic density protein 95 (PSD-95).	[31]
CBD	Rescue of social recognition memory improved object recognition deficits and did not affect fear-associated memory or anxiety behavior.	[32]
CBD	- Prevents the development of social recognition deficit; - Reduces neuroinflammation, reduces plasma cholesterol levels, and reduces the retention of phytosterols from the diet.	[33]

To be continued

Table 1. *In vivo* studies on cannabinoid use and its relationship with AD signs and symptoms ***Continuation***

Cannabinoid receptor agonists	Main scientific findings	References
Botanical extracts enriched with THC or with CBD	-Both the isolated administration of THC and the isolated administration of CBD determine a reduction in cognitive deficits; preservation of memory in the initial symptomatic stage of AD -The combination of THC + CBD determines neuroprotective effects characterized by the reduction of the levels of the 42-residue β-amyloid protein (soluble form A) and reduction of its toxicity; reduction of astrogliosis related to the deposition of β-amyloid protein; reduction of cytokine expression and reversal of thioredoxin 2 (Trx2) deficiency, a pathophysiological condition also observed in patients with AD.	[34]
WIN 55.212-2 JWH-133	- Decreased microglial activation, and consequently inflammation and brain levels of β-amyloid proteins; - Decreased cognitive deficits and cytokine release.	[35]
CBD	-Selective interaction and activation of PPARγ that determines anti-inflammatory and neuroprotective effects, inhibition of reactive gliosis and neurodegeneration; - Possible stimulation of hippocampal neurogenesis in vivo.	[36]

Abbreviations: Aβ1-42 - Amyloid β Protein Fragment 1-42 / CBD – Cannabidiol / AD - Alzheimer's Disease / PPARy - Peroxisome Proliferator-Activated Receptor Gamma / THC - Tetrahydrocannabinol

Table 2. Aspects observed in the results of population studies

Cannabinoid receptor agonists	Main scientific findings	References
Dronabinol THC Nabilone *Cannabis* essential oil	-Positive evidence regarding the efficacy of treating dementia-associated SNPs in improving stiffness and cognitive scores.	[37]
THC + CBD	-Improves patients' rigidity and general behavior after approximately 2 months of treatment; -Favors the reduction or interruption of the administration of psychotropic medications conventionally used in the treatment of AD.	[38]
THC preparations Dronabinol Nabilone	- Significant improvements in SNPs; -Individual tolerability to drug administration -Absence of serious adverse events.	[39]
Medical *Cannabis* Oil	-Highly effective in reducing various signs and symptoms related to dementia; - Low occurrence of significant adverse events	[40]

To be continued

Table 2. Aspects observed in the results of population studies ***Continuation***

Cannabinoid receptor agonists	Main scientific findings	References
THC	- Rapidly absorbed after oral administration; - Low doses of THC are considered safe and well tolerated by frail elderly people with dementia; - The occurrence of adverse effects is very low.	[41]
THC	- Does not reduce behavioral disorders in patients with dementia compared to placebo; - Adverse effects determined to be very well tolerated Does not modify vital signs and mobility in a clinically significant way; - Shows a high safety rate in elderly patients with dementia when administered over a short time.	[42]
Synthetic cannabinoids Dronabinol Nabilone	Significant reduction in AD symptoms and may represent a therapeutic alternative, as they present a low risk of adverse events when compared to antipsychotic medications.	[43]
THC	Effective in the treatment of anorexia and behavioral symptoms of dementia, however sedation is a very commonly observed undesirable effect.	[44]

Abbreviations: CBD – Cannabidiol / THC – Tetrahydrocannabinol / SNPs – Neuropsychiatric symptoms.

3.8. Limitations of population studies

Given all results found in population studies, limitations and low quality of evidence were noted, a fact that occurred due to several factors, including non-randomization of patients and, consequently, the lack of a control group; the impossibility of feedback by patients due to limitations of disease itself and cognitive impairment; influence of several factors on behavior and symptoms, being elderly patients who often have several comorbidities and use several medications (polypharmacotherapy). The limited number of studies included; low doses used and short duration (the last two factors can be considered a limitation, but they guarantee the safety of patients since they are elderly, which also ends up being a justification for the limitations found). Other factors were the different pharmaceutical inputs used in the studies, such as *Cannabis* oil, synthetic medications, extracts, etc., which makes analysis and conclusions on the subject difficult; and finally, the legislation of the countries themselves regarding the legalization of the use of compounds for academic purposes, becoming a limiting factor for the number of studies included.

3.9. Final considerations

With the rapid and progressive aging of the world population, neurodegenerative diseases such as AD have become more prevalent and a concern for everyone. As it is an incurable disease, in which treatments are palliative to reduce and control symptoms, the results found in studies carried out on medicinal *Cannabis* are of extreme importance. The review gathered studies published in the literature, both in vivo and in humans, which demonstrated that medicinal *Cannabis* and its derivatives have several actions and therapeutic benefits for AD and mechanisms that are still unknown, but have also been shown to play an important role in the pathophysiology of disease. In addition, combination of CBD-THC proved to be more effective than the isolated compounds, and the psychoactive effects caused by THC were antagonized by CBD. Although the results found are promising and cannabinoids and their derivatives have great potential to be considered as a new therapeutic option for AD in the future, selected population studies presented limitations and low-quality evidence. Therefore, the verification of the results found depends on several factors, and it is not possible to concretely state the efficacy of medicinal *Cannabis* and cannabinoid derivatives as a therapeutic alternative for AD. There is a need for additional studies on the long-term effects of the compounds, as well as larger doses, controlled and randomized studies, in addition to greater knowledge about the mechanisms of action and their adverse effects, since the target audience is the elderly, a population more vulnerable to pharmacodynamic and pharmacokinetic effects. In short, all these points would result in more robust evidence that could prove the efficacy and safety of these compounds.

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