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USE OF CANNABIDIOL IN PATIENTS WITH DEMENTIA: AN INTEGRATIVE REVIEW

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Ana Beatriz Almeida Monteiro[1], Laura Siqueira Bolzani[2], Maria Eduarda Martinelli Rocha[3], Wagner de Brito Véras[4]

ABSTRACT

Cannabidiol (CBD), one of the main non-psychoactive compounds in Cannabis sativa, has aroused growing interest in research as a potential therapeutic agent for the treatment of dementia. Some studies claim that CBD may have neuroprotective and anti-inflammatory effects on neuromodulatory systems related to neurodegenerative diseases such as Alzheimer's disease. Although results are still limited, the use of this drug represents a promising approach in managing the symptoms associated with dementia, especially when conventional therapies are ineffective for patients. This integrative review aims to evaluate the use of cannabidiol for the treatment of dementia, examining the available literature without year restrictions. Through a systematic search in the PubMed, EBSCO and SCIELO databases, 159 studies were initially found in PubMed, 65 in EBSCO and 4 in the SCIELO database. After screening, 10 relevant studies were selected for the assembly of the article, including randomized controlled trials, case reports, and meta-analyses. The results suggest that cannabidiol is a potential drug to be used in the treatment of dementia, showing significant improvement in symptoms. However, studies suggest the need for careful monitoring of doses in order to avoid adverse effects of the medication.

Keywords: Cannabidiol. Treatment. Dementias.

[1] Medical Student
University Center of Espírito Santo
Email: anabeatrizalmeidam@gmail.com
Lattes: https://lattes.cnpq.br/4831198254753770
[2] Medical Student
University Center of Espírito Santo
Email: laurabolzani10@gmail.com
Lattes: https://lattes.cnpq.br/1199657366480597
[3] Medical Student
University Center of Espírito Santo
Email: dudamrocha83@gmail.com
Lattes: http://lattes.cnpq.br/9562002779769155
[4] PhD in Health Sciences
University Center of Espírito Santo
Email: wveras@unesc.br
Lattes:https://lattes.cnpq.br/1676312093014678

1 INTRODUCTION

Dementia, characterized by a progressive decline in cognitive and functional abilities and challenging behavioral symptoms, is a leading cause of disability and addiction among older adults. Neuropsychiatric symptoms (NPS) occur in up to 90% of patients with dementia and are associated with a reduced quality of life (HERMUCHE et al., 2022). Currently, options for treating psychological and behavioral symptoms of dementia (BPSD) include pharmacologic and nonpharmacologic therapies. Psychotropic medications are often used to reduce the frequency and severity of BPSD, but in most patients, they provide only modest control of symptoms and major side effects. The interest of cannabinoids in Alzheimer's disease and other forms of dementia first increased as neuroprotective drugs in animal studies. In fact, some studies suggest a potential beneficial effect of CB1 and CB2 receptor agonists in reducing the harmful action of β-amyloid peptide and tau phosphorylation seen in Alzheimer's disease, as well as increasing intrinsic brain repair mechanisms (BROERS et al., 2019).

Regarding the positive effects and restrictions related to the use of cannabidiol, according to Pautex (2022), despite the limitations of this study, the overall positive results on rigidity, care, and behavior in this population are encouraging. In addition, the pharmacokinetic profile is promising. In addition, the sociological perspective of medical *cannabis* prescription was highly favorable. Caregivers, initially reluctant, particularly appreciated the improved quality of contact with their patients. In addition, families were enthusiastic about offering their relatives an alternative and accepted the treatment without worries. According to SHELEF et a (2016), only 3 of the 11 patients who started the study had adverse events. One patient discontinued Medical Cannabis Oil (MCO) after three days due to dysphagia, likely unrelated to MCO intake. A second patient, who already had recurrent falls before admission, suffered a simple fracture of the pelvis during the study, with no observable functional impairment. The third patient had greater confusion with the MCO dose of 5mg THC (tetrahydrocannabinol) twice daily. The dose of MCO was reduced to the minimum dose of 2.5 mg twice daily, and patient confusion improved.

Overall, studies have shown that cannabidiol (CBD)-rich oil is an effective and safe therapy to treat NPS in dementia patients, while reducing the suffering of family members and caregivers. Between July 2020 and July 2023, 59 (93.5%) patients completed ≥ 3 months of follow-up. According to Navarro and Perez (2024), for patients who were on treatment for an average of 23.2 months, they received the median dose of CBD of 111 mg/day. The median NPI-Q severity and caregiver distress scores at baseline were 24 and 29, respectively. At 3 months, the median NPI-Q severity score changed to 12 ($p < 0.001$) and

14 ($p < 0.001$), respectively. The proportion of patients who achieved a reduction in NPI-Q severity score of > 30% was 94.9%, while a reduction of >50% was achieved by 54.2%. The improvement was maintained for up to 24 months.

1.1 DEMENTIA: DEFINITION, ETIOLOGY AND RISK FACTORS

Dementia can be defined as a clinical syndrome characterized by the progressive decline in memory, thinking, behavior, and the ability to perform activities of daily living independently. According to data from the World Health Organization (WHO), in 2017 there were approximately 50 million people in the world living with this condition, a number that tends to grow due to the population aging observed globally. Although several pathologies can lead to dementia, Alzheimer's Disease (AD) represents the main cause, accounting for about two-thirds of cases (BROERS et al., 2019).

The etiology of agitation often seen in individuals with dementia is complex, involving psychological and social factors; however, anatomical and neurochemical changes in the brain predominate (HERMUSH et al., 2022). AD, the most prevalent neurodegenerative disease in the elderly population, is widely studied due to its high incidence and impact. With life expectancy increasing, experts warn that AD could become a global epidemic by 2050. Pathological mechanisms, such as neurochemical dysfunction, glucose, neuroinflammation, oxidative stress, insulin resistance, and alterations in autophagy processes are well described in the literature as factors associated with AD progression (RUVER-MARTINS et al., 2022).

Another condition that deserves attention is rapidly progressive dementia (PRD), defined by accelerated cognitive deterioration that culminates in dementia in less than two years. Certain conditions, such as encephalitis or metabolic encephalopathies, can lead to even faster progression, occurring within weeks. Despite the absence of specific diagnostic criteria for PKD, adaptations based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the Clinical Classification of Dementia (CDR) have been used as auxiliary instruments. Currently, there is no established standard treatment for PKD; however, cannabis medicine has been proposed as a promising therapeutic approach for the management of different types of dementia (VALQUEZ-BARRETO et al., 2024).

1.2 PROPERTIES OF CANNABIDIOL

The discovery of the endocannabinoid system, in the early 1990s, revealed the neuronal mechanisms that underlie the use of cannabinoids, giving way to the description of multiple molecules, both endogenous and exogenous (VALQUEZ-BARRETO, Mareli et al.

2024). The endocannabinoid system is associated, in the central nervous system, with the regulation of psychomotor activation, mood, the sleep-wake cycle, and eating behavior. All these functions are impaired in the moderate and severe stages of dementia (SHELEF, Assaf et. al.2016).

More than 100 phytocannabinoids have already been identified in the *Cannabis sativa* plant, the most studied being tetrahydrocannabinol (THC) and cannabidiol (CBD). THC regulates synaptic transmission and promotes neuroprotection by acting as an agonist of CB1R and CB2R, also known for its psychoactive and potent analgesic effects. In the brain, CB1R is expressed primarily in neurons, which regulate the release of neurotransmitters, while CB2R is expressed in immune cells (e.g., T cells and microglia), reducing inflammation. (RUVER-MARTINS et al.2022).

CBD acts as an agonist for CB1, CB2, TRPV1, TRPV2, TRPA1, 5Ht1α receptors, and glycine receptors. On the other hand, it is an antagonist of melastatin type 8 TRP channels, voltage-gated T-type calcium channels, and the receptor coupled to GPR55 proteins. As a result, CBD exerts a dynamic control over intracellular calcium, which depends on cellular excitability (VALQUEZ-BARRETO, Mareli et al. 2024).

In addition to the classic receptors of the endocannabinoid system, CBD also regulates GPR55, and transporters such as ENT-1. TRPV1 activation is associated with modulation of affective, memory, and appetite functions through interaction with AMPA receptors, while GPR55 inhibition and ENT-1 modulation favor anti-inflammatory responses and mitochondrial protection. Another relevant property of CBD is its antagonistic action on the N-methyl-D-aspartate (NMDA) receptor, similar to the pharmacological activity of memantine, used in the treatment of Alzheimer's disease (AD) (NAVARRO; PÉREZ, 2024). The mechanisms of action underlying CBD's direct and indirect effects on agitation involve the regulation of serotonin receptor 1A, CB1Rs, the hypothalamic-pituitary-adrenal axis, anandamide, CB2Rs, and GABAA receptors (HERMUSH, Vered et al.2022).

Thus, the growing evidence on the role of cannabinoids in the central nervous system and neuroinflammation justifies in-depth investigation of their therapeutic potential in dementia, especially considering the scarcity of effective options for the management of behavioral, cognitive, and affective symptoms in advanced stages of the disease.

2 METHODOLOGY

The present study is an integrative review, whose objective is to gather and critically analyze all available evidence on the use of cannabidiol in the treatment of dementia. To achieve this objective, a detailed and careful search strategy was developed, involving the

PubMed, EBSCO and Scielo databases. The research focused on identifying studies that addressed the relationship between treatment with the use of cannabidiol and dementia.

The search strategy combined terms related to the use of cannabidiol and the treatment of dementia. The terms included "treatment", "dementia" and "cannabidiol", associated with the Boolean descriptors and operators (cannabis OR cannabis indica OR cannabis sativa OR hemp plant OR marihuana OR marijuana) AND (treatment OR therapeutic action OR therapeutic measure OR curative procedure OR therapeutic procedure OR therapy procedure OR treatment procedure OR procedures OR treatment) AND (dementia OR dementia). The search was carried out without language and time restrictions, thus ensuring the inclusion of different studies and updates on the subject over the years.

This integrative review included retrospective, analytical, observational, and spontaneous clinical trials, a long-term pilot observational study, a prospective, open-label, single-center cohort study, a randomized, double-blind, single-center, placebo-controlled clinical trial, a pilot, complementary, open-label study, a prospective observational study, and case reports, which specifically investigate the relationship between the use of cannabidiol and its relationship with dementia. Studies that focus on various types of treatment and form of this substance, such as cannabis extract and oil were also included, as long as they presented relevant data on its impact on the course of these diseases as an object of analysis. Articles dealing with other forms of *cannabis* use (such as recreational use), in *vitro* and *in vivo experimental studies*, studies that did not establish a direct relationship between the use of cannabidiol, the nervous system and the various types of dementia, as well as news abstracts, poster presentations, simple abstracts and review synopses were excluded. After selection, the articles were read in full and the data were collected and tabulated

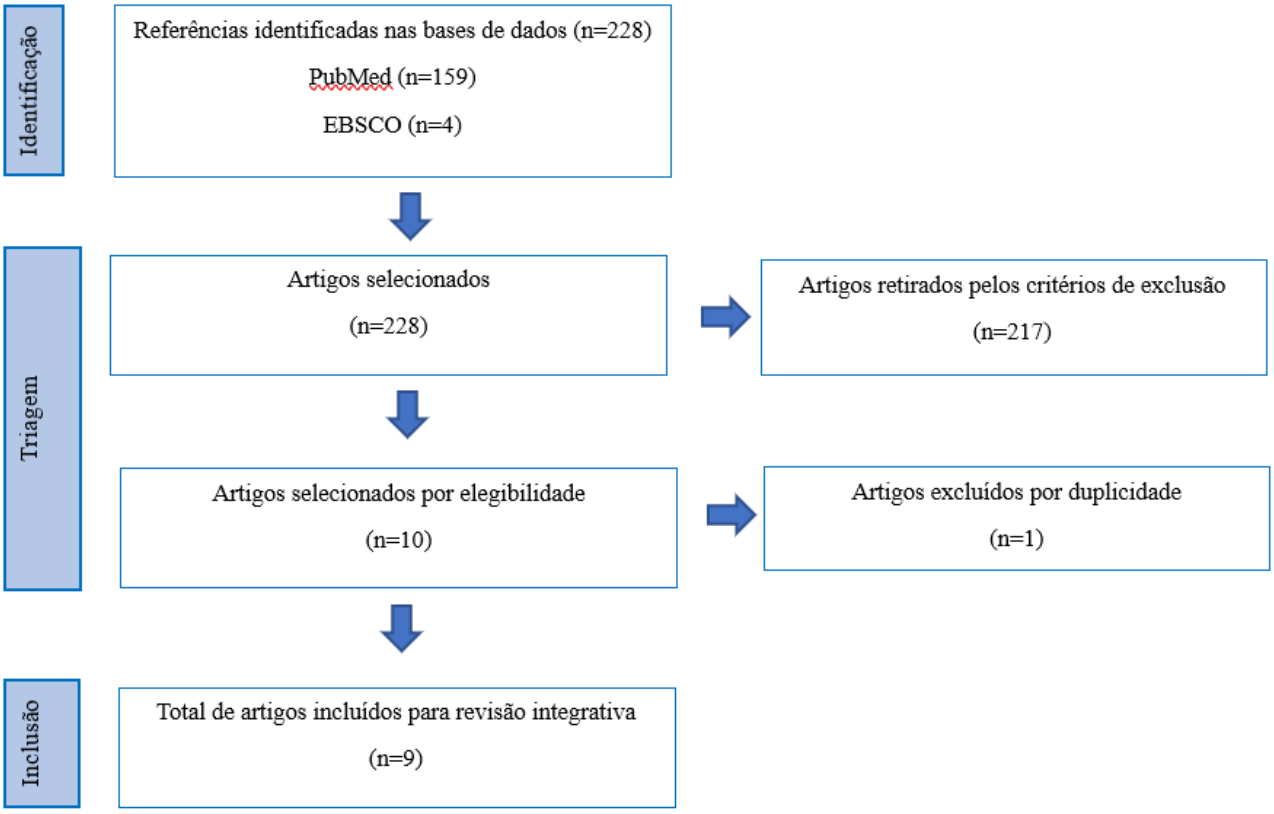
Critical analysis of the evidence was performed individually for each article, taking into account the study design and the evidence pyramid, as well as the best evaluation for each study design. The synthesis of evidence was prepared in such a way as to ensure a careful and rigorous analysis, taking into account both the methodological quality and the risk of bias of each study analyzed.

3 RESULTS

The initial search for the review identified 159 articles in the PubMed database, 65 in EBSCO and 4 in SCIELO, totaling 228 scientific papers. After judicious application of the eligibility criteria and removal of duplicates, only 9 articles were considered suitable for inclusion. These inclusion criteria included double-blind and placebo-controlled clinical trials, randomized, double-blind, placebo-controlled crossover trial, long-term pilot observational

study, double-blind exploratory study, and case reports analyzing the relationship between the use of cannabidiol and therapeutic effects in patients with dementia. The study population should include patients who had some type of dementia. In addition, the intervention considered was the use of cannabidiol, with or without comparison with other conventional treatments, focusing on the advantages and disadvantages in the results obtained with treatment with cannabidiol.

Figure 1. Flowchart of the study selection process



Source: Survey Data.

The exclusion criteria included studies that did not specify the relationship between cannabidiol and any of the types of dementia, articles that did not cover the topic of cannabis, that dealt with diseases other than dementia, studies carried out on animals, cells, or molecular studies, studies that dealt with the recreational use of cannabis, studies that were outside the design model, and duplicate studies in different databases. Studies to which it was not possible to have access were also excluded, in addition to book chapters. Likewise, review articles, review abstracts and synopses, news and other textual genres were excluded. All selected studies underwent a critical evaluation, carried out by two independent reviewers, with consultation with a third reviewer, in case of disagreement, thus ensuring rigor and methodological consistency in the selection process.

Table 1: Results of the articles searched (n=9)

AUTHOR/YEAR	TITLE	DESIGN OF STUDY	STUDY POPULATION	INTERVENTION	DENOUEMENT
B. Palmieri, M. Vadalà. 2023	Oral THC: CBD *cannabis* extract in the main symptoms of Alzheimer's disease: agitation and weight loss	Retrospective, analytical, observational, and spontaneous clinical trial	Thirty patients diagnosed with mild, moderate or severe AD, aged between 65 and 90 years, who attended the Second Opinion Medical Consultation	Use of *cannabis* extract diluted in oil, Bedrocan® (22% THC, 0.5% CBD, 50 ml olive oil), twice a day, for 12 weeks	Reduction in agitation, apathy, irritability, sleep disturbances and eating disorders, levels of physical and verbal aggressive behaviors, and cognitive impairment.
PAUTEX, Sophie et al. 2022	Cannabinoids for behavioral symptoms in severe dementia: safety and feasibility in a long-term pilot observational study in nineteen patients	Long-term pilot observational study	19 patients with severe dementia residing in a nursing home for the elderly	Patients receiving an average of 12.4 mg THC/24.8 mg CBD per day for up to 13 months	Significant and stable improvement, with deprescribing of medications and facilitation of treatment, with no reports of problems or relevant adverse reactions.
NAVARRO, Cristian E.; PÉREZ, Juan C.2024	Treatment of Neuropsychiatric Symptoms in Alzheimer's Disease With a Masterful Cannabis-Based Formulation *:* An Open-Label, Prospective Cohort Study	Prospective, open-label, single-center cohort study	Patients with AD onset after 65 years of age and untreated SPN.	CBD-rich oil was administered 0.1 mL sublingually every 8-12 h, with weekly titration	CBD-rich oil is an effective and safe therapy to treat NPS in AD patients while reducing the distress of caregivers.
HERMUSH, Vered et al.2022	Effects of Cannabidiol-Rich Oil on Behavioral Disorders in Patients With Dementia: A Randomized Placebo-Controlled Clinical Trial	Randomized, double-blind, single-center, placebo-controlled clinical trial	Patients with a minimum age of 60 years, with a diagnosis of severe neurocognitive disorder and associated behavioral disorders	Randomized 2:1 to receive "Avidekel," a broad-spectrum cannabis oil (30% cannabidiol and 1% tetrahydrocannabinol: 295mg and 12.5mg per ml, respectively; n=40) or a placebo oil (n=20) three times daily for 16 weeks.	Avidekel oil significantly reduced agitation in dementia patients, with only mild side effects.
SHELEF, Assaf et. al.2016	Safety and Efficacy of Medical Cannabis Oil for	Pilot, complementary, open-label	Eleven AD patients	Eleven AD patients were recruited for a 4-	Adding MCO to the pharmacotherapy

	Behavioral and Psychological Symptoms of Dementia: A Pilot, Complementary, Open-label Study	study		week open-label prospective study.	of AD patients is a safe and promising treatment option.
RUVER-MARTIS et al.2022	Microdose Cannabinoid Extract Improves Mnemonic and Non-Mnemonic Symptoms of Alzheimer's Disease: Case Report	Case report	A 75-year-old man with Alzheimer's disease presented with memory loss, disorientation in time and space, and difficulties in daily activities.	The experimental therapeutic intervention was carried out for 22 months with microdoses of a cannabinoid-containing cannabis extract	Microdosing cannabinoids can be effective in treating Alzheimer's disease by preventing major side effects.
VALQUEZ-BARRETO, Mareli et al. 2024	Cannabinoid Treatment for Rapidly Progressing Dementia	Case report	A 45-year-old woman with a current diagnosis of MRP, epilepsy, and sequelae of cerebrovascular events	Palliative treatment was started with adjustments in diet and use of cannabidiol (CBD), starting with 20mg daily and extra doses in case of epileptic seizures.	Cannabinoid derivatives, especially CBD and THC, have neuroprotective and anticonvulsant effects, and can reduce early damage and slow the progression of neurodegenerative diseases, improving quality of life
BROERS, Barbara et al.2019	Prescribing a THC/CBD-based drug for dementia patients: a pilot study in Geneva	This is a prospective observational study.	Ten female patients with dementia and severe behavioral problems	Oral medication with an average of 7.6mg THC/13.2mg CBD daily after 2 weeks, 8.8mg THC/17.6mg CBD after 1 month, and 9.0mg THC/18.0mg CBD after 2 months.	Oral cannabis extract with THC/CBD in high doses was well tolerated and significantly improved behavior, rigidity, and daily care in patients with severe dementia.
CONSORE, Paul et. al, 1991	Controlled Clinical Trial of Cannabidiol in Huntington's Disease	Double-blind, placebo-controlled, crossover clinical trial	15 patients (8 men and 7 women) with a confirmed diagnosis of Huntington's disease stages 1 to 4, without the use of neuroleptics.	Oral administration of cannabidiol (CBD) at 10 mg/kg/day for 6 weeks, followed by 6 weeks of placebo (sesame oil), with 1 week of washout between treatments. The study used capsules identical in appearance to maintain blinding.	The study concluded that CBD was well tolerated and safe, but did not show significant clinical efficacy in improving the symptoms of Huntington's disease.

4 DISCUSSION

4.1 EFFICACY, SAFETY AND TOLERANCE

Palmieri and Vadalà (2023) investigated, in their study, the use of an oral cannabis extract, containing THC and CBD in patients with Alzheimer's disease, focusing on symptoms, such as agitation and weight loss, and obtained as a result the improvement of these symptoms, suggesting that the combination of cannabinoids may represent a significant therapeutic approach, especially in more advanced stages of the disease. The study by Navarro and Pérez (2024) also evaluated patients with Alzheimer's disease and reported improvement in several neuropsychiatric symptoms, especially aggression and communication with caregivers. The study conducted by Hermush et al. (2022) showed a significant improvement in behavioral disorders, such as agitation, irritability, and sleep disorders, with a safety profile considered satisfactory. Ruver-Martins et al. (2022) presented a case report in which small doses of cannabinoid extract were used in a patient with Alzheimer's disease, resulting in improvement in both memory-related symptoms and anxiety and irritability.

The study by Consroe et al. (1991) evaluated the efficacy and safety of cannabidiol in patients with Huntington's disease (HD), whose main objective was to verify a reduction in chorea.

Pautex et al. (2022) showed that long-term use of cannabinoids was well tolerated and safe, with few adverse effects. Similarly, Broers et al. (2021) explored the use of a THC:CBD formulation in institutionalized dementia patients, indicating that prescribing should be done safely and reinforcing that there is adequate clinical monitoring. The study reported improvement in symptoms, such as agitation, anxiety, and insomnia, with good patient adherence and no serious adverse events. In addition, the study by Broers et al. (2021) demonstrated the importance of strict clinical follow-up when prescribing THC/CBD-based medications to elderly patients with dementia.

4.2 METHODOLOGICAL LIMITATIONS

Some methodological limitations involved the absence of a placebo group, as in the study by Palmieri and Vadalà (2023) and in the work by Navarro and Pérez (2024), which reduces the reliability of the effects attributed to the intervention, as they may be subject to expectancy biases, and makes it difficult to exclude confounding factors, and also the use of an open methodology, as in the study by Broers et al. (2021), which weakens the conclusions on efficacy, in addition to the heterogeneity of the patients (age, stage of dementia, and comorbidities of the patients), which limits the control of confounding variables.

Hermush et al. (2022) stand out for having conducted a randomized, double-blind, placebo-controlled clinical trial, offering greater methodological safety. However, this study had limitations, such as relatively short follow-up time and a population limited to a single center.

The long-term observational study, conducted by Pautex et al. (2022), suffers from a small sample size, lack of standardization in diagnostic criteria, and lack of validated cognitive and behavioral assessment instruments. Consroe et al. (1991), in addition to the small sample, presented a relatively short treatment time (6 weeks), and the use of standardized and non-individualized doses may not have reflected the optimal dose for each patient.

In the case report presented by Ruver-Martins et al. (2022), although it brings an innovative approach when using microdoses of cannabinoids, it is a very low-level evidence, with validity limited to that single patient. The absence of replication or control prevents generalization of findings.

In general, most studies suffer from a lack of standardization in THC and CBD doses and formulations, variability in administration times, differences in dementia diagnostic criteria, and a lack of long-term follow-up. In addition, there is a gap in the representation of different genotypes, ethnicities, and sociocultural contexts, which are important factors in the clinical response and pharmacokinetics of cannabinoids.

Regarding patient assessment, some studies have used the application of standardized scales to assess patients' symptoms, such as Hermush et al. (2022), with the Neuropsychiatric Inventory (NPI) scale. The other scientific articles addressed in this review were based on subjective clinical indicators, reports from caregivers and attending physicians, and longitudinal clinical observations, such as the study by Pautex et al. (2022) and Navarro and Pérez (2024).

Consroe et al. (1991) was the most complete in terms of symptom assessment after medication use, using the Marsden and Quinn Chorea Severity Scale (M&Q), Shoulson and Fahn Functional Scale (S&F), Motor tests (tongue protrusion, finger tapping, bolt and nut test), SCL-90R for psychological symptoms, Memory tests (Buschke-Fuld), subjective evaluation of doctor and patient (from -100% to +100%), checklist of Cannabis side effects (69 items) and standardized clinical laboratory tests and vital signs.

4.3 PHARMACODYNAMICS AND PHARMACOKINETICS

As for pharmacodynamics, the studies analyzed highlight the therapeutic effects of CBD and THC, based on their actions on the endocannabinoid and non-endocannabinoid systems. CBD acts predominantly as a negative allosteric modulator of CB1 receptors, with

anxiolytic, antipsychotic, and anti-inflammatory effects, while THC is a partial agonist of CB1 and CB2 receptors, being related to more pronounced effects on mood, appetite, and sensory perception. Thus, this distinction is key to understanding why combination formulations, such as extracts with a THC:CBD ratio, have been chosen in some clinical approaches for symptoms such as agitation, anxiety, sleep disturbances, and weight loss.

Palmieri and Vadalà (2023) used a combined oral formulation of THC:CBD and attributed its effectiveness to both the action of THC on appetite and behavior and the modulating action of CBD on neuropsychiatric symptoms. The pharmacodynamics reported in the study suggest synergism between these compounds, which may explain the positive results in symptoms such as agitation and weight loss in Alzheimer's patients.

Hermush et al. (2022) used CBD-rich oil and reported significant improvement in behavioral disorders with no major psychotropic effects, which corroborates the anxiolytic and antipsychotic pharmacodynamics of CBD at moderate doses. The study by Broers et al. (2021) also used the THC:CBD formulation, demonstrating that THC, even at low doses, helps relaxation and sleep regulation, while CBD seems to have a greater action in stabilizing mood.

From a pharmacokinetic point of view, there is little standardization among studies regarding composition, route of administration, doses, and bioavailability. Most of these studies used oral formulations in oil, which has variable absorption and relatively low oral bioavailability, caused by the extensive first-pass hepatic metabolism, especially for THC. Hermush et al. used sublingual oil with potentially more efficient absorption, but without a clear description of the exact formulation.

Consroe et al., (1991) administered cannabidiol orally and encapsulated in sesame oil, having low absorption, with plasma levels between 5.9 and 11.2 ng/mL during treatment, which reinforces the low oral bioavailability and, after one week of washout, plasma levels dropped to 1.5 ng/mL. No THC was detected in the patients, and CBD was considered non-psychoactive.

Pautex et al. (2022) and Broers et al. (2021) reported the chronic use of oral formulations in microdoses, with individualized titration according to tolerance. This approach aims to minimize adverse effects, in addition to introducing variability in individual pharmacokinetics. Ruver-Martins et al. (2022), in their case report, denote benefits with microdoses of cannabinoid extract, proposing that even very low concentrations, if well absorbed, have the ability to modulate neurological and behavioral symptoms.

4.4 THC and CBD

In addition, the studies analyzed point out, in general, positive signs of clinical efficacy of the use of cannabinoids – especially in combined formulations of THC and CBD – in reducing behavioral and psychological symptoms of dementia, with an emphasis on improving agitation, aggressiveness, sleep disorders, anxiety, and loss of appetite/weight. At different levels of methodological rigor, the authors highlight favorable effects on patients' quality of life, in addition to an indirect impact on caregiver burden.

Palmieri and Vadalà (2023), in their study, through a combined oral formulation of THC and CBD, noticed an important reduction in agitation, as well as an improvement in appetite and weight gain in patients with Alzheimer's disease. This study highlights the synergy between the two cannabinoids as essential for therapeutic success, being pointed out as a promising alternative in cases refractory to conventional medications.

Consroe et al. (1991) reported that there was no notable difference between the CBD and placebo group for the primary (chorea) or secondary (function, memory, and psychiatric symptoms) outcomes, however, despite the therapeutic ineffectiveness, CBD was well tolerated by patients, and the absence of serious side effects, due to the use of the medication, It is a positive point of the use of cannabidiol.

Hermush et al. (2022), in a randomized clinical trial, reported a statistically relevant improvement in behavioral disorders in patients with dementia who used CBD-rich oil, when compared to the placebo group. In addition, the authors emphasized the good acceptance of the treatment by patients and the low incidence of adverse effects, which increases the clinical applicability of the product in institutional settings.

Pautex et al. (2022), in a long-term observational study with 19 patients, demonstrated sustained improvement in agitation and irritability in cases of severe dementia, in addition to reports of better sleep quality and reduced need for psychotropic medications, which have a higher risk of adverse effects in the elderly, evidencing the feasibility and safety of prolonged use.

The study by Navarro and Pérez (2024), with a masterful formulation of cannabis, highlights the simplicity of administration as a positive point, especially in patients with severe cognitive limitations.

Ruver-Martins et al. (2022), in a case report, noted that microdoses of cannabinoid extract promoted a reduction in both mnemonic symptoms (such as memory loss) and disruptive behaviors, suggesting a potential neuroprotective or modulating effect on clinical progression.

The study by Broers et al. (2021) confirmed that a THC:CBD formulation administered in a controlled manner brought significant improvement in agitation, anxiety, and sleep

disorders, and contributed to greater tranquility and cooperation of patients in the institutional setting. The possibility of individualized dose adjustment was pointed out as a crucial factor for the success of the treatment.

Therefore, studies show that cannabinoids are promising as a complementary strategy in the management of behavioral symptoms in dementia, especially in patients who do not respond well or have contraindications to the use of traditional psychotropic drugs. In addition, the more favorable safety profile of cannabinoids, especially CBD, compared to medications such as antipsychotics, denotes a potential therapeutic and ethical benefit in vulnerable populations.

Despite the growing interest in the use of cannabinoids, particularly cannabidiol (CBD), in the management of neuropsychiatric symptoms associated with dementia, the literature still has important limitations regarding the safety and efficacy of this approach. One of the main obstacles is the absence of robust and statistically significant clinical evidence. Although experimental studies and case reports suggest beneficial effects, many clinical trials have small sample sizes and inconclusive results due to methodological bias and heterogeneity in the formulations used (B. Palmieri, M. Vadalà, 2023).

From a pharmacokinetic point of view, there is concern about the modulation of cytochrome P450 liver enzymes. Studies indicate that CBD can inhibit the activity of isoenzymes such as CYP1A2 and CYP2C19, which can interfere with the metabolism of drugs often used by dementia patients, such as antidepressants, antipsychotics, and cardiovascular medications. Such interaction can lead to the accumulation of active substances and an increased risk of toxicity, and is especially relevant in polymedicated patients. Although this inhibition has been found to be weak or limited in some studies, it cannot be ruled out that higher doses of CBD or different proportions of THC/CBD amplify these effects (PAUTEX et al., 2022).

4.5 ADVERSE EFFECTS

In addition, direct adverse effects have been documented, although mostly mild and reversible. The most common include drowsiness, confusion, disorientation, and, less frequently, hallucinations and falls—events that can be especially dangerous in an already cognitively and functionally vulnerable population (HERMUSH et al., 2022; SHELEF et al., 2016). In a randomized clinical trial, 48.6% of participants experienced drowsiness and 45.9% confusion, with a trend toward a higher occurrence of hallucinations in the CBD-treated group, although without statistical significance (HERMUSH et al., 2022).

Other reported adverse reactions included oral pain and gingivitis related to the medication formulation (tincture diluted in syrup), which were resolved by switching to a THC/CBD oil formulation (PAUTEX et al., 2022). In addition, according to Valquez-Barreto et al., 2024, although the clinical case did not specifically describe blood pressure changes, the literature points out that tetrahydrocannabinol (THC) can cause elevated blood pressure and hypertensive uncontrol in certain patients. These effects seem to be associated with the interaction of anandamide and cannabidiol (CBD) itself with neuronal α-1 adrenergic receptors, promoting a slow depolarization mediated by potassium channels (K^+), in addition to the activation of the c-fos gene in hypothalamic neurons. Such activation can stimulate the hypothalamic-pituitary-adrenal axis, contributing to adverse cardiovascular changes, especially in individuals with greater hemodynamic vulnerability.

It should also be noted that many studies exclude patients with multiple comorbidities or using psychotropic medications, which may limit the generalization of the results to the real population of elderly people with dementia, who are often polymedicated and frail (NAVARRO, Cristian E.; PÉREZ, Juan, 2024). In one case, worsening of mental confusion was observed with a higher dose of THC, which was later reversed with a reduction in dosage (SHELEF et al., 2016).

Additionally, practical obstacles related to the route of administration were observed. For example, the administration of nabiximols via oromucosal spray proved difficult in patients with agitation, who bit the applicator or moved their head, compromising the proper dosage (BROERS et al., 2019).

Thus, although cannabinoids have promising therapeutic potential, the adverse effects, drug interactions, and methodological limitations of existing studies require caution. Future clinical trials need to strictly control variables such as formulation, dose, route of administration, and pharmacological profile of patients in order to more reliably establish the role of CBD in dementia management.

Consroe et al. (1991) showed few laboratory abnormalities due to the use of CBD, and most of them were mild and without clinical relevance and did not show any important difference in blood pressure, heart rate or body weight, concluding that CBD was safe, even at high daily doses (~700 mg/day).

5 CONCLUSION

The present integrative review allowed us to critically analyze the available evidence on the use of cannabinoids in the management of neuropsychiatric symptoms in patients with dementia. The reviewed studies point out that both tetrahydrocannabinol (THC) and

cannabidiol (CBD), alone or in combination, can positively modulate clinical manifestations such as agitation, aggressiveness, sleep disorders, anxiety, and depression.

The findings suggest a trend towards clinical efficacy, with gradual improvement of behavioral symptoms refractory to conventional pharmacological approaches. In particular, CBD's more favorable profile in terms of safety and tolerability stands out, with fewer adverse effects than THC, whose side events — although generally mild to moderate — include excessive sedation, appetite changes, diarrhea and, in some cases, transient worsening of cognition. However, variability in study methodological designs, scarcity of high-quality randomized controlled trials, small number of participants, and short duration of interventions limit the generalization of results and the formulation of robust clinical recommendations.

In addition, there are still gaps regarding ideal dosages, forms of administration, duration of use, and potential drug interactions, especially in polymedicated elderly patients. The lack of standardization in therapeutic protocols and the heterogeneity of the instruments for assessing outcomes make it difficult to compare studies and consolidate evidence-based clinical guidelines.

Thus, although cannabinoids represent a promising pharmacological alternative in the context of dementia, their use should be considered with caution, restricted to supervised contexts, with individualized risk-benefit assessment, and always respecting the principles of person-centered medicine. New randomized clinical trials, with larger samples, prolonged duration, and standardized methodologies, are strongly recommended in order to elucidate the real efficacy, safety, and applicability of cannabinoids in the management of behavioral and psychological symptoms of dementia.

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