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Review Article

Therapeutic use of *Cannabis sativa* in the treatment of Alzheimer's Disease: an integrative review

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Objective: to investigate, in light of the scientific literature, the efficacy of the therapeutic use of *Cannabis sativa* in the treatment of Alzheimer's Disease. **Methodology:** this is an integrative literature review that gathered articles based on a systematized methodology. The search for studies was conducted through the following databases: Latin American and Caribbean Health Sciences Literature (*Literatura Latino Americana e do Caribe em Ciências da Saúde*), SciVerse Scopus, and Web of Science, using Health Sciences Descriptors. **Results:** the sample included 16 scientific articles, all indicating a growing trend in exploring *Cannabis sativa* compounds for symptomatic treatment of the disease. Experimental laboratory studies stand out among the findings, as well as the analysis of the optimal non-toxic dose for treatment efficacy. Treatment efficacy is demonstrated by the delay and/or reduction of behavioral symptoms of the disease, resulting in improved quality of life for the involved family context. **Conclusion:** the use of *Cannabis sativa* compounds demonstrated efficacy in the symptomatic treatment of individuals with Alzheimer's, revealing medical advancements and a paradigm shift regarding the plant. The presented evidence sheds light on specific nuances that may impact not only the life of the person with the disease but also the entire family dynamic.

Descriptors: Alzheimer Disease; Cannabis; Medical Marijuana; Neurobehavioral Manifestations.

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Uso terapêutico da *Cannabis sativa* no tratamento da Doença de Alzheimer: revisão integrativa

Objetivo: investigar à luz da literatura científica a eficácia do uso terapêutico da *Cannabis sativa* no tratamento da Doença de Alzheimer. **Metodologia:** trata-se de uma revisão integrativa da literatura que reuniu artigos a partir de uma metodologia sistematizada. A busca dos estudos se deu através das bases de dados Literatura Latino Americana e do Caribe em Ciências da Saúde, *SciVerse Scopus* e *Web of Science*, utilizando Descritores em Ciências da Saúde. **Resultados:** a amostra incluiu 16 artigos científicos, todos indicando uma crescente tendência na exploração dos compostos da *Cannabis sativa* para o tratamento sintomático da doença. Estudos experimentais em laboratório são destaques nos achados, bem como a análise da dose ideal não tóxica para eficácia no tratamento. A eficácia no tratamento mostra-se no retardo e/ou diminuição de sintomas comportamentais da doença com consequente melhora da qualidade do contexto familiar envolvido. **Conclusão:** o uso dos compostos da *Cannabis sativa* demonstrou eficácia para o tratamento sintomático da pessoa com Alzheimer, o que revela um avanço da medicina e a quebra de paradigmas sobre a planta. As evidências apresentadas lançam luz sobre nuances específicas que podem repercutir não apenas na vida da pessoa com a doença, mas em toda dinâmica familiar.

Descritores: Doença de Alzheimer; Cannabis; Maconha Medicinal; Manifestações Neurocomportamentais.

Uso terapéutico del *Cannabis sativa* en el tratamiento de la Enfermedad de Alzheimer: revisión integradora

Objetivo: investigar, a la luz de la literatura científica, la eficacia del uso terapéutico del *Cannabis sativa* en el tratamiento del Alzheimer. **Metodología:** revisión integradora de la literatura que reunió artículos sobre la base de una metodología sistematizada. La búsqueda de estudios se llevó a cabo a través de las bases de datos Literatura Latinoamericana y del Caribe en Ciencias de la Salud, *SciVerse Scopus* y *Web of Science*, utilizando Descriptores de Ciencias de la Salud. **Resultados:** la muestra incluyó 16 artículos científicos, que indicaban una tendencia creciente en la exploración de compuestos de *Cannabis sativa* para el tratamiento sintomático de la enfermedad. En los hallazgos se destacan los estudios experimentales en el laboratorio, así como el análisis de la dosis no tóxica ideal para la eficacia del tratamiento. La eficacia del tratamiento se demuestra por el retraso y/o reducción de los síntomas conductuales de la enfermedad con la consiguiente mejora de la calidad del contexto familiar implicado. **Conclusión:** el uso de compuestos de *Cannabis sativa* demostró eficacia para el tratamiento sintomático de personas con Alzheimer, lo que revela un avance de la medicina y una ruptura de paradigmas respecto a la planta. La evidencia presentada demuestra matices específicos que pueden impactar no sólo en la vida de la persona que padece la enfermedad, sino en toda la dinámica familiar.

Descriptores: Enfermedad de Alzheimer; Cannabis; Marihuana Medicinal; Manifestaciones Neuroconductuales.

Introduction

Alzheimer's Disease (AD) is a progressive and degenerative neuropathology that affects millions of people worldwide, being one of the main dementias affecting individuals in senile and pre-senile age groups. Regarding gender, it shows higher prevalence in the female population[1].

The pathophysiology of AD presents a neuroinflammatory and degenerative cascade supposedly triggered by the accumulation of Aβ peptide and neurofibrillary tangles (NFT), composed of aggregated hyperphosphorylated microtubules associated with the Tau protein. This cascade induces neuroinflammation and oxidative stress, creating a neurotoxic brain environment that potentiates neurodegeneration and eventually leads to cognitive decline[2].

Regarding the symptomatology of AD, three phases are identified: the initial phase, characterized by recent memory loss; the intermediate phase, marked by motor difficulties, reasoning, and language impairments; and finally, the terminal stage, characterized by muscle rigidity, urinary or fecal incontinence, dysphagia, difficulty walking, or maintaining a seated position, potentially leading the individual to a vegetative state[3].

The treatment of AD emerged from the identification of decreased acetylcholine neurotransmitter levels; however, current medications only aim to slow disease progression, inhibit its evolution, and improve patients' quality of life. Currently, there are few medications available for treatment, and they only address cognitive, behavioral, and psychological dementia-related disorders[4-5].

In today's pharmaceutical market, *Cannabis sativa*-based medications have gained prominence in pain condition treatments, acting directly on the nervous system to provide muscle relaxation and stiffness relief[6]. This progress is driven by recent technological advances that have facilitated the development of new products derived from this plant. Research emphasizes the importance of *Cannabis sativa* extracts in treating various central nervous system (CNS) disorders[7], aiming to enhance therapeutic approaches and patients' quality of life.

To maximize the potential benefits of *Cannabis sativa*-derived compounds in AD treatment, it is essential to intensify studies and expand knowledge in this area. Based on this need, the present study is justified by considering the promising therapeutic properties of *Cannabis sativa*, where rigorous research becomes crucial to validate the efficacy of these treatments. Thus, this study was developed with the objective of investigating, in light of the scientific literature, the efficacy of the therapeutic use of *Cannabis sativa* in the treatment of AD.

Methodology

Type of study

This is an integrative literature review that gathered published scientific works, analyzing them under the method of research systematization to synthesize knowledge on the topic[8]. For this purpose, the six methodological stages foreseen in this type of study were followed: a) formulation of the research question; b) development of strategies for data collection; c) selection, by two reviewers, of the studies composing the final sample; d) observation, evaluation, and comparison of the findings from the selected articles; e) synthesis and elaboration of the review results; f) presentation of the review.

Sample selection criteria

In the first stage, the PICo strategy was used to formulate the research question, an acronym corresponding to: P = Population, I = Phenomenon of Interest, and Co = Context. In this regard, the research question was formulated as "What do scientific studies indicate about the therapeutic use of *Cannabis sativa* in the treatment of Alzheimer's Disease?" where the population consists of individuals with AD, the therapeutic use of *Cannabis sativa* is the Phenomenon of Interest, and the symptomatic treatment of AD is the Context.

The search for scientific articles was conducted in national and international libraries and databases: Latin American and Caribbean Health Sciences Literature (*Literatura Latino Americana e do Caribe em Ciências da Saúde* - LILACS), SciVerse Scopus, and Web of Science, during the period from June to August 2023. As inclusion/exclusion criteria for the articles, descriptors were selected based on Health Sciences Descriptors (*Descritores em Ciências da Saúde* - DeCS) and Medical Subject Headings (MeSH), related to the PICo strategy, combined using the Boolean operators *AND* and *OR* (Figure 1).

PICo	Health Sciences Descriptors and Medical Subject Headings (DeCS/MeSH)
P (Population): People with Alzheimer's Disease	Alzheimer OR "Alzheimer's Disease" OR dementias OR "Alzheimer-type dementia"
I (Phenomenon of Interest): Therapeutic use of *Cannabis*	marijuana OR "medical marijuana" OR THC OR cannabidiol OR "cannabis sativa" OR Cannabis
Co (Context): symptomatic treatment of Alzheimer's disease	"Alzheimer's symptoms" OR Treatment OR "cognitive symptoms of Alzheimer's"
Combined descriptors	
Alzheimer OR "Alzheimer's disease" OR dementias OR "Alzheimer-type dementia" AND marijuana OR "medical marijuana" OR THC OR cannabidiol OR "Cannabis sativa" OR Cannabis AND treatment AND "Alzheimer's symptoms" OR "symptomatic manifestations" OR "cognitive symptoms of Alzheimer's" OR "behavioral symptoms of Alzheimer's"	

Figure 1 - PICo strategy and descriptor definition

For identification and selection of the studies, the descriptors were used in Portuguese and English, and filters were applied: English and Portuguese languages, free full-text articles, excluding theses, dissertations, and reviews. No publication year filters were applied, considering the topic's novelty and rising interest, with publications already reflecting current knowledge.

Data collection steps

Initially, 492 articles were identified, leading to the second step, which involved reading titles and abstracts for article selection. The first stage was conducted by two researchers, with a third researcher resolving any disagreements using the *Rayyan* selection tool[9]. In the third step, duplicate articles and those not aligned with the study's objective were removed. Subsequently, the articles were read in full to reach the final selection, totaling 16 articles (Figure 2).

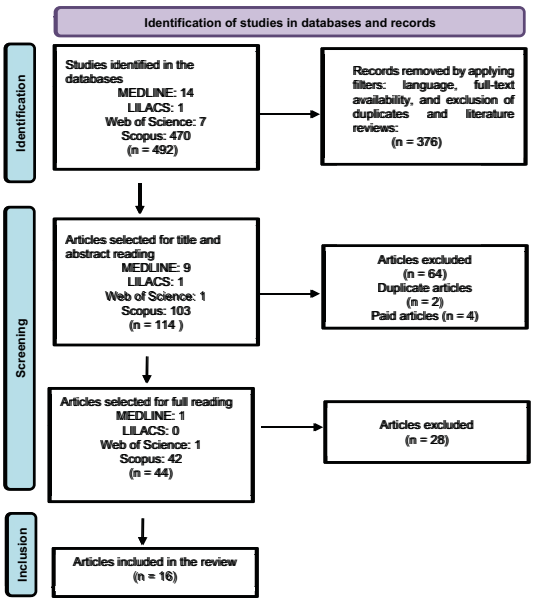

Figure 2 - Flowchart of the selected studies from the database search, following the PRISMA 2020 model[10]

Data treatment and analysis steps

The fourth step consisted of evaluating the final studies (levels of evidence) based on the classification of evidence levels. The six levels of the Agency for Healthcare Research and Quality (AHRQ) were considered: Level 1 - meta-analysis of multiple randomized controlled clinical trials; Level 2 - individual studies with an experimental design; Level 3 - quasi-experimental studies; Level 4 - descriptive (non-experimental) or qualitative approach studies; Level 5 - case reports or experiences; and finally, Level 6 - expert opinions[11]. After grouping, the articles were characterized as follows: author/year, country, level of evidence, and results/conclusions (Figure 3).

In the penultimate step, a full reading of the articles was conducted to identify points of convergence and key discussions for analyzing the findings, using Bardin's categorical analysis[12]. Finally, the last step consisted of preparing the results and discussion of this study.

Results

A total of 16 articles addressing the use of *Cannabis sativa* derivatives in the symptomatic treatment of AD were selected, analyzed, categorized, and presented in Figure 3 below.

Citation article	Country	LE*	Results/Conclusions
Fihurka, et al., 2023	USA†	2	The study results provide the first evidence that the MIT‡ nanoformulation containing melatonin, insulin, and THC§ has potential as a multi-target treatment for AD‖, particularly in improving memory.
Timler, et al., 2023	USA†	2	The study demonstrated that a maximum of 50 mg of THC§/34 mg of CBD❦ per day was safe and well-tolerated in individuals living with dementia, with reduced agitation, increased relaxation, and improved sleep quality.
Ruver-Martins, et al., 2022	BRA**	3	Microdosing of cannabinoids is a potential therapeutic option for AD‖, without significant side effects, with beneficial effects on memory and brain function improvement.
Hermush, et al., 2022	ISR††	2	The findings suggest that CBD❦-rich *cannabis* oil significantly reduced agitation compared to placebo in patients suffering from dementia-related behavioral disorders, with non-serious side effects.
Chesworth, et al., 2022	AUS‡‡	2	The results indicate that preventive treatment with CBD❦ may moderately improve spatial learning in a female mouse model of AD‖, suggesting preventive therapeutic potential in female patients with familial AD‖.
Nitzan, et al., 2022	ISR††	2	Treatment with THC§ improved the cognitive performance of AD‖ mice at 6 months of age (during the early stages of AD‖) and at 12 months of age (advanced AD‖). The research demonstrates for the first time the beneficial effects of an ultralow single dose of THC§ in a mouse model of AD‖ after disease onset.

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Citation article	Country	LE*	Results/Conclusions
Leszko; Meenrajan, 2021	POL[§§]	4	The use of CBD[ʼ] oil was considered effective by most caregivers. There are still gaps in knowledge and stigma regarding the use of CBD[ʼ] among both healthcare professionals and caregivers.
Bittes, et al., 2021	BRA[‡]	4	The use of cannabidiol provides quality of life for individuals with AD[ǁ], making them slightly more independent, improving their appetite, and enabling them to perform simple activities such as combing their hair and even taking a bath on their own.
Coles, et al., 2020	AUS[‡‡]	2	CBD[ʼ] acts against Aβ[ǁǁ]-induced toxicity. In mice, it prevented spatial learning deficits induced by Aβ[ǁǁ]. It has therapeutic value for specific behavioral impairments present in AD[ǁ].
Broers, et al., 2019	SWI[ʼʼ]	2	Oral medication with THC[§]/CBD[ʼ] in patients with severe dementia and behavioral problems is acceptable, well-tolerated, improves rigidity, and alleviates behavioral symptoms.
Schubert, et al., 2019	USA[†]	3	Cannabinoids have the ability to stimulate the degradation and removal of pre-formed and aggregated Aβ[ǁǁ] from neurons and are also potent inhibitors of amyloid toxicity. The combination of multiple cannabinoids may provide a lead compound for AD[ǁ] drug therapy.
Libro, et al., 2017	ITA[***]	2	CBD[ʼ] benefits GMSC[†††] by reducing Tau protein hyperphosphorylation, which is linked to neurofibrillary tangles in AD[ǁ], potentially improving symptom therapy and prevention.
Haug, et al., 2016	USA[†]	3	Teams from institutions distributing medicinal *cannabis* recommend high concentrations of CBD[ʼ] for arthritis and AD[ǁ], and a high concentration of CBD[ʼ] or a 1:1 ratio for ALS[‡‡‡], epilepsy, and muscle spasms.
Ahmed, et al., 2015	USA[†]	2	The findings suggest that low doses of THC[§] are safe and well-tolerated in frail elderly individuals with dementia, presenting minimal adverse effects, although there was considerable interindividual variability.
Seniya; Khan; Uchadia, 2014	USA[†]	2	After a dose of 0.75 mg of THC[§], there was a significant increase in internal perception and heart rate. Body balance with closed eyes improved only after the 1.5 mg dose. Systolic blood pressure changed significantly after both THC[§] doses.
Martín-Moreno, et al., 2012	SPA[§§§]	2	Chronic administration of cannabinoids showed marked beneficial effects, along with reduced inflammation and increased elimination of Aβ[ǁǁ].

*LE = Level of evidence; [†]USA = United States of America; [‡]MIT = Melatonin-insulin-THC; [§]THC = Tetrahydrocannabinol; [ǁ]AD = Alzheimer's disease; [ʼ]CBD = Cannabidiol; **BRA = Brazil; [††]ISR = Israel; [‡‡]AUS = Australia; [ǁǁ]Aβ = Amyloid-beta; [ʼʼ]SWI = Switzerland; **ITA = Italy; [†††]GMSC = Gingival mesenchymal stem cells; [‡‡‡]ALS = Amyotrophic lateral sclerosis; [§§§]SPA = Spain

Figure 3 - Analysis of articles selected for review

Regarding the temporal scope, the studies found were published between 2012 and 2023, with one from 2012, one from 2014, one from 2015, one from 2016, one from 2017, two from 2019, one from 2020, two from 2021, four from 2022, and two from 2023. This reveals an increase in publications over the last five years, as 10 of the 16 selected articles were published during this period.

Concerning the level of evidence, according to the standardization by AHRQ in 2016, 11 articles are at Level 2, three at Level 3, and two at Level 4[11]. Regarding location, the United States stands out for having the highest number of studies compared to other countries, with a total of six, while two were conducted in Brazil, two in Israel, two in Australia, one in Italy, one in Poland, one in Spain, and one in Switzerland.

The results indicate a growing trend in the scientific community toward exploring the therapeutic potential of *Cannabis sativa* compounds[13], both in the context of symptomatic treatment of AD and in investigating the complex mechanisms of cannabinoids in interfering with the disease's pathophysiology and their ability to delay the progression and onset of associated symptoms[13-16].

Some of these studies undertook a detailed analysis, performing comprehensive mapping of the various components present in plant extracts. This analysis revealed a broad spectrum of compounds, each with specific efficacy in mitigating behavioral symptoms such as anxiety, agitation, aggression, and restlessness[17-19], as well as addressing cognitive challenges, including memory and reasoning difficulties[14,16,18,20-23].

Another significant finding is that a substantial portion of this research is still in the experimental stage, aiming to identify the optimal dose that poses no health risks[22,24-28]. In this regard, laboratory studies using animal models, such as mice, have been diligently

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working to determine the non-toxic therapeutic dose, possibly due to the significant social stigma and criminalization of the plant in many countries[13,19-22].

Parallel to these studies, another, more advanced line of investigation involves conducting pilot studies in humans[17-18,23-24], demonstrating notable efficacy in treating neuropsychiatric symptoms associated with AD[19,27].

In addition to the direct benefits in symptom treatment, the factors motivating these investigations are also related to the demystification of prejudices[18]. The authors highlight stigma as a social issue, showing that the use of *Cannabis sativa* products remains underexplored due to a lack of experience and acceptance. Therefore, it is essential to expand knowledge about plant extracts and introduce this resource as a viable alternative, especially through the regulation of its derivatives, particularly cannabidiol oil[18].

Discussion

The analysis of the collected data makes it evident that Cannabis sativa emerges as a promising component in addressing symptoms associated with AD. This section aims to analyze and discuss the research findings to achieve the proposed objectives, based on the collected evidence, highlighted in three thematic categories: *Cannabis sativa* in focus: experimental evidence; analysis of the ideal dosage in experimental studies; effects on symptomatic treatment of AD.

Cannabis sativa in focus: experimental evidence

The findings highlight the development of several laboratory studies in animals, such as mice and rats, demonstrating that cannabidiol has neuroprotective and anti-inflammatory effects that may help reduce symptoms related to AD, such as brain inflammation and memory loss[17,23].

Doses of CBD and/or THC reduce the concentration of Amyloid beta protein (Aβ), as this peptid affects synapses and signals immune cells to trigger neuronal inflammation, leading to the destruction of deficient cells[23]. Therefore, the research demonstrates that the therapeutic use of *Cannabis sativa* is effective as a neuroprotective, anti-inflammatory, and antioxidant agent, slowing the progressive effects of AD.

An innovative study combined insulin, melatonin, and THC *in vitro* to produce the oily phase of *Cannabis sativa*, demonstrating the ability of a melatonin-insulin-THC (MIT) nanoformulation to improve spatial memory in AD mice through its multi-directional effects on Aβ production, tau phosphorylation, and mitochondrial dynamics[20].

In the same direction, another analyzed study shows therapeutic efficacy in the use of a combination of CBD and THC in AD mice. Long-term preventive oral CBD improved spatial memory acquisition, accompanied by changes in speed and locomotion in mice[21].

No effect of CBD was identified regarding reverse learning or recall of previously rewarded locations in transgenic AD mice. It therefore reduced freezing behavior following the presentation of a discrete signal associated with foot shock in the studied genotypes, without manifesting anxiety-like behaviors[21].

Other studies associate the use of CBD with an improved immune response, which may also lead to increased microglial migration and reduced nitrite generation, potentially facilitating Aβ phagocytosis and decreasing Aβ plaque burden in the hippocampus and mesenchymal stem cells (MSCs), attenuating the expression of genes implicated in the etiopathogenesis of AD[21]. Alternatively, it is possible that CBD improves hippocampal synaptic plasticity deficits to enhance spatial learning, and the use of MSC transplantation in the early stages of AD may play a role in preventing or mitigating disease onset[15,20].

Regarding cannabinoid agonists, particularly selective CB2 agonists, one study demonstrates that they interfere with several processes linked to key events in the pathophysiology of AD. These compounds, by directly interacting with cannabinoid receptors, reduce microglial activation, decreasing inflammation and its consequences. Simultaneously, they may indirectly have beneficial effects on microglial activation, lowering amyloid-beta levels in the brain[13].

Preclinical and experimental studies have shown that CBD, whether combined with THC and other compounds or not, possesses neuroprotective, anti-inflammatory, and antioxidant properties. The research suggests that they may help reduce oxidative stress, neuroinflammation, and protect brain cells, specifically slowing disease progression.

Furthermore, *Cannabis sativa* compounds may have effects on neurotransmission regulation and modulation of the endocannabinoid system, which plays a role in brain function and homeostasis. This has led to significant interest in the potential therapeutic medicinal use of this plant to minimize symptoms associated with AD, such as anxiety, agitation, sleep disturbances, and possibly even cognitive decline. However, research is needed to establish appropriate therapeutic dosage protocols.

Analysis of the optimal non-toxic dosage

The studies provide original evidence that microdosing cannabinoids may be effective in treating AD while avoiding major side effects[13]. This is an important step, as it is necessary to dissociate the purpose of cannabinoid use from the idea that it is exclusively associated with narcotic effects. Therefore,

it is crucial to distinguish the therapeutic use of cannabinoids from the perception of the negative effects caused by narcotics.

Although THC-based medications have recently been approved for clinical use, there is limited data on their safety in elderly individuals with dementia. However, research data demonstrate that doses of 0.75 and 1.5 mg of THC twice daily are safe and well-tolerated by older individuals with dementia[27].

Regarding CBD, it was recognized that chronic treatment with 5 mg/kg of this substance was able to reverse object recognition deficits in female mice, suggesting a therapeutic-like effect in this established AD mouse model. Thus, the study helped define potentially effective therapeutic dosage regimens for AD patients[14].

It was found that treatment with lower doses of CBD would not only reduce therapy costs for patients but also minimize potential side effects (especially important for therapeutic *Cannabis sativa* compounds containing not only CBD but also combined use with THC, as in the case of CBD-enriched *Cannabis sativa* extract therapies).

Regarding the route of administration, a recent study adds that a higher preventive oral dose of CBD may result in more pronounced effects on spatial learning. However, the use of oral administration is clinically preferable to intravenous or intramuscular injections, significantly increasing the translational power of these findings[21].

In addition to the safety of microdosing, selected studies demonstrated that treatment with 20 mg/kg of CBD prevents Aβ-induced learning deficits in the Morris Water Maze and reduces Aβ-induced interleukin-6 (IL-6) elevation[13]. A previous study conducted in the same laboratory also revealed that CBD at the same dose reversed social recognition and novel object recognition deficits in transgenic mice with familial AD modulation, when chronically administered after the onset of disease-relevant symptoms[14].

The same study further points out that the use of 50 mg/kg of CBD restores impaired social recognition memory, reverses spatial learning, and tends to reduce insoluble Aβ40 levels in the hippocampus of 12-month-old male mice. It is therefore essential to investigate a range of dosages to determine the therapeutic efficacy window of the medication. Additionally, evaluating lower doses of CBD compared to previous studies may have a positive impact on future financial burdens for individuals with dementia[14].

Another study conducted in mice[21] revealed that the use of low doses of THC (ULD-THC) reduced three inflammatory markers related to AD: tissue inhibitor of metalloproteinase 3 (TIMP-3), glucocorticoid-activated kinase (SGK), and the Nfkbia gene. It also noted that mice treated with ULD-THC showed reduced gliosis (a pathological process associated with AD), suggesting a possible beneficial effect of the treatment in reducing the gliotic response associated with AD.

According to a case report[16], the use of microdoses of cannabinoids is effective in improving memory and brain function, particularly in the mild stage of the disease. In this sense, the research findings highlight an important distinction between the therapeutic and narcotic effects of *Cannabis sativa* extracts, contributing to the acceptability of their use for treatment purposes.

The results largely corroborate the initial expectations of the study, demonstrating the benefits of low-dose cannabinoids as a therapeutic method for the symptomatic treatment of AD.

Symptomatic treatment of Alzheimer's Disease

Regarding the symptomatic treatment of individuals with AD, the main complaints revolve around behavioral changes, agitation, sleep loss, aggression, and severe communication impairments. Thus, some quantitative and qualitative studies in this research demonstrated both positive aspects and concerns regarding the therapeutic use of *Cannabis sativa*.

Some findings suggest that CBD-rich *Cannabis sativa* oil may alleviate agitation in elderly individuals with dementia, highlighting the importance of developing conclusions about the safety and efficacy of broad-spectrum CBD. According to an experiment[16], a potential therapeutic use of a *Cannabis sativa* metabolite in cholinesterase inhibition with minimal side effects was revealed, emphasizing the need for further investigations to understand molecular interactions and develop new pharmacological approaches.

As CBD-rich *Cannabis sativa* oils become increasingly available, there is a growing need for a more in-depth evaluation of them as a possible treatment option for agitation and to identify the characteristics of such treatment[17].

A qualitative study[18] highlights the different perceptions of caregivers regarding the use of CBD oil in individuals with AD. Although most are positive about its use and results, some concerns were also expressed, demonstrating the need for greater dialogue and clarification between caregivers and healthcare professionals to discuss the use and management of this therapy in treating individuals with AD.

In light of the above, findings from another study indicate that oral medication with THC/CBD in patients with severe dementia and behavioral problems is acceptable, well-tolerated, and improves rigidity and overall behavior. Thus, the use of such cannabinoids made it possible to reduce or even discontinue the use of other psychotropic medications in half of the patients. In this regard, the team appreciated the

reduction in rigidity, noting improvements in daily care and transfers, as well as better direct contact with patients and their behavior[19].

We can highlight the positive repercussions of using cannabinoids with the reduction or discontinuation of psychotropic treatments, considering the variety of side effects and adverse reactions that these medications can trigger. Therefore, the importance of advancements in the development of new therapies based on *Cannabis sativa* extracts is evident.

A study[27] conducted to investigate the effects of an alternative cannabinoid treatment pointed out that the main improvements directly related to AD were in sleep and relaxation. This finding underscores the potential of cannabinoids as a promising therapeutic option in managing the symptoms of the disease.

Given the studies already conducted on the benefits of cannabinoids, their use in practice remains an integrative therapy. Although classified as phytotherapeutics and medicinal plants, their utilization is still highly restricted in some countries, including Brazil, further limiting access to this form of non-pharmacological therapy for individuals with AD[23].

The evidence presented in this study guides science toward a path where the therapeutic benefits of this plant are highlighted, which are not limited to CBD but encompass a range of possibilities to be tested and combined, with advancements already demonstrating therapeutic efficacy and safety at non-toxic doses. The study underscores the significant importance of scientific progress, as it fosters innovation in treating the severe symptoms of AD, moving beyond the stigma and social prejudices surrounding *Cannabis sativa*.

As a suggestion for future work, it is proposed to conduct a systematic approach to the safe use of cannabidiol and the feasibility of its legalization in Brazil for the treatment of AD and other diseases.

Conclusion

In conclusion, the use of *Cannabis sativa* compounds has demonstrated efficacy in the symptomatic treatment of AD. The analyzed research highlights significant advantages in its use, such as phytocannabinoids' ability to combat the accumulation of tau and beta-amyloid proteins in the brain, which are involved in the etiopathogenesis of AD. The findings are essential for advancing medicine and breaking paradigms regarding the medicinal use of *Cannabis sativa*.

The evidence not only corroborates previous discoveries in the literature but also sheds light on specific nuances that may influence treatment efficacy. Considering this panorama, it is imperative to recognize the practical implications of these findings, both in the clinical context and in the family and social spheres. It is crucial to expand the contributions of these discussions from the perspective of health and, above all, ethics, aiming for the correct use of *Cannabis sativa* in the treatment of AD to improve the quality of life of individuals with the disease.

The study has limitations regarding the need for a more robust analysis of the results of the identified research, as well as the fact that publications with the highest levels of evidence (Level 1 - AHRQ) were not found, a characteristic of the inclusion criteria of this research, which did not include systematic reviews.

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