***Review Article***

**Therapeutic Interaction of Cannabis sativa in the Treatment of Alzheimer's Disease**

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**ABSTRACT**

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| **Introduction:** The use of cannabinoids from Cannabis sativa has shown promising effects in treating cognitive and behavioral symptoms of Alzheimer's disease. The endocannabinoid system may offer relevant neuroprotective and anti-inflammatory properties.  **Objective:** To investigate the effects of Cannabis sativa, particularly THC and CBD, on symptom management and disease progression in Alzheimer's, considering potential side effects.  **Methodology:** An exploratory-descriptive bibliographic research with a qualitative approach was conducted in databases such as LILACS, SciELO, and PubMed between 2013 and 2023. The study selection considered thematic relevance and publications in Portuguese, English, and Spanish. The analysis of the articles was guided by three key questions related to the study objectives.  **Results and Discussion:** Studies indicated that the combination of THC and CBD can significantly reduce agitation and aggression in Alzheimer's patients. CBD demonstrated neuroprotective potential, attenuating neuroinflammation and β-amyloid plaque formation. However, the side effects of prolonged cannabinoid use, such as drug interactions and dependence, require further research. CBD stood out for its safety profile.  **Conclusion:** Cannabis sativa is a promising alternative for Alzheimer's treatment, alleviating neuropsychiatric symptoms and slowing disease progression. However, caution is necessary regarding long-term effects, with more studies essential to validate its safe use. |

*Keywords:**Cannabis sativa, Alzheimer's Disease, Cannabinoids, Neuroprotection, CBD and THC*

**1. INTRODUCTION**

Therapeutic cannabis has garnered growing scientific interest due to its potential in managing various medical conditions, particularly neurodegenerative diseases. Cannabis sativa is rich in compounds such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which interact with the endocannabinoid system—a key player in physiological processes including appetite regulation, pain, inflammation, memory, and neuroprotection (FRAGUAS-SÁNCHEZ; TORRES-SUÁREZ, 2018). Although initially associated with recreational and psychoactive use, the therapeutic properties of cannabis have been progressively explored in clinical trials, especially for conditions like chronic pain, epilepsy, multiple sclerosis, and neurodegenerative diseases such as Alzheimer's disease (LIM; SEE; LEE, 2017).

Specifically in Alzheimer's disease (AD), studies suggest significant benefits of medicinal cannabis. Research has shown that the combined use of THC and CBD can reduce behavioral symptoms such as agitation, aggression, and sleep disturbances (PALMIERI; VADALÀ, 2023). Additionally, in silico studies indicate that CBD may attenuate tau protein hyperphosphorylation and beta-amyloid protein accumulation, both hallmark neuropathological features of AD (CHOI; LEE; KIM, 2023). These effects are associated with the anti-inflammatory and antioxidant properties of the active compounds in cannabis, suggesting a promising role in the treatment of neurodegeneration (CHIURCHIÙ; LEUTI; MACCARRONE, 2015).

Epidemiological aspects highlight the relevance of medicinal cannabis, especially due to the growing elderly population and the increasing incidence of neurodegenerative diseases. Globally, it is estimated that over 36 million people have some form of dementia, with AD accounting for up to 80% of these cases. Projections indicate that this number could reach 115 million by 2050, reflecting the importance of developing effective therapeutic strategies (PALMIERI; VADALÀ, 2023). Furthermore, symptoms such as agitation—present in approximately 50% of institutionalized patients—increase the need for safe and effective treatment options (TIMLER et al., 2020).

In the United States, AD is already recognized as a qualifying condition for the use of medicinal cannabis in some states, especially for agitation management. However, despite the expanding therapeutic indications, the number of specific certifications for AD remains low. This scenario suggests a need for further clarification and scientific investigation into the efficacy and safety of this therapeutic option for AD patients (MAUST et al., 2016).

In this context, the present study aims to identify the neurodegenerative mechanisms involved in the progression of AD and the interactions of cannabis's active compounds with neurotransmitters such as acetylcholine, glutamate, and dopamine. Moreover, it seeks to analyze how the anti-inflammatory and antioxidant properties of these compounds affect the neurodegenerative processes characteristic of AD. This investigation is essential, given the significant impact of AD on the quality of life of both patients and caregivers, as well as the current lack of effective treatments with fewer side effects—thereby justifying a deeper exploration of the therapeutic use of medicinal cannabis.

**2. METHODOLOGY**

This was a bibliographic, exploratory-descriptive study with a qualitative approach, and the collected data were used for the development of the scientific article. According to Gil (2022), bibliographic research is developed based on already existing material, consisting mainly of books and scientific articles—in other words, it involves a theoretical survey on a given subject by gathering information about what different authors report on the topic.

A study is exploratory in nature when it involves bibliographic research, interviews with people who have (or had) practical experiences related to the issue being investigated, and the analysis of examples that stimulate understanding. Its main purpose is to develop, clarify, and modify concepts and ideas to support future approaches. In this way, this type of study aims to provide the researcher with deeper knowledge on the subject, allowing them to formulate more precise problems or create hypotheses to be examined in subsequent studies (GIL, 2022).

According to Gonçalves (2003), descriptive research records, analyzes, classifies, and interprets observed facts, often establishing relationships between them. Regarding the approach, this study is qualitative. Minayo (1994) describes qualitative research as one in which the researcher’s concern is not with the quantitative profile of the data, but rather with the value of the information that can be collected, correlating phenomena and variables to reality, to better understand the lived experience in its deeper dimensions. This includes creativity and aims to build new perspectives and scenarios within the same reality.

Data collection was carried out through a bibliographic review of scientific literature on the proposed topic, covering the period from 2014 to 2024. The inclusion criteria for content selection were: full-text publications related to the theme, documents, regulations, and guidelines from health organizations on the topic, and articles published in Portuguese, English, and Spanish.

The exclusion criteria included articles not relevant to the topic, duplicate or incomplete materials, debates, reviews, abstracts, and materials unavailable in full. The literature search was conducted in the following databases: Latin American and Caribbean Literature in Health Sciences (LILACS), the Scientific Electronic Library Online (SciELO), and PubMed. It is worth noting that the LILACS and BDENF databases were accessed through the Virtual Health Library (BVS). The searches were carried out using Health Sciences Descriptors (DeCS) from the Regional Library of Medicine (BIREME): Cannabis sativa, Alzheimer’s Disease, Cannabinoids, Neuroprotection, CBD, and THC, in both Portuguese and English, using the Boolean operators “AND” and “OR”.

The methodology used in this study began with the careful selection of keywords from DeCS (Health Sciences Descriptors), followed by searches in the previously mentioned indexed databases. Using both the selected keywords and their alternative terms, tables were created containing all relevant articles identified in each database. Duplicate articles were removed from each table, and a title-based relevance selection was conducted. After this screening, abstracts of the selected articles were read, and those that met the relevance criteria were included for in-depth reading.

For comprehensive analysis of the selected articles, three discussion axes were identified, which were defined based on the specific objectives of the study and transformed into guiding questions. These questions guided the reading of the selected articles, providing a conceptual framework for the critical and in-depth analysis of the information contained in them. The answers obtained for each question, derived from the thorough reading of the articles, formed the basis for drafting the results and conducting the discussion, thereby enriching the analysis and interpretation of the data. This structured and meticulous methodology enabled a systematic and well-founded investigation of the relevant literature, reinforcing the validity and robustness of the results presented in this scientific study.

**3. RESULTS AND DISCUSSION**

**NEURODEGENERATIVE MECHANISMS INVOLVED IN THE PROGRESSION OF ALZHEIMER'S DISEASE**

Alzheimer's disease (AD) is a progressive neurodegenerative pathology characterized by the accumulation of beta-amyloid (Aβ) plaques in the extracellular space and neurofibrillary tangles of hyperphosphorylated tau protein within neurons, resulting in synaptic dysfunction, neuronal loss, and neuroinflammation (CHOI; LEE; KIM, 2023). These alterations compromise brain circuits fundamental to memory and cognition, such as the hippocampus, leading to significant cognitive and functional deficits (PLANCARTE-SÁNCHEZ et al., 2018). Dysregulation of the autonomic nervous system and decreased acetylcholine also play an essential role in the progression of the disease (ROM; PERSIDSKY, 2013). Furthermore, chronic activation of microglia and astrocytes promotes an inflammatory cycle that intensifies neurodegeneration (CHEN et al., 2023).

Oxidative stress and neuroinflammation are central factors in the pathogenesis of AD, aggravating Aβ aggregation and tau hyperphosphorylation (GROH, 2022). Activation of the nuclear factor κB (NF-κB) pathway in astrocytes increases the production of C3, which interacts with microglia and neurons, causing synaptic damage and continuous neuroinflammation (CHEN et al., 2023). Neuronal degeneration is also influenced by impaired energy metabolism and mitochondrial dysfunction (TROJAN et al., 2023). Low glucose utilization in the brain is one of the first signs of AD and contributes to progressive cognitive decline (KUHARIC et al., 2021). Increased reactive oxygen species (ROS) accentuates damage to neuronal membranes and DNA, intensifying neuronal loss (SUERO-GARCÍA; MARTÍN-BANDERAS; HOLGADO, 2015).

Cognitive deficits in AD often begin with difficulties in forming new memories, progressively compromising other executive functions and communication (LESZKO; MEENRAJAN, 2021). Degeneration of the hippocampus and CA1 area is among the first neuropathological signs observed (ELSAID; KLOIBER; LE FOLL, 2019). The accumulation of Aβ activates microglia, leading to the release of pro-inflammatory cytokines, such as IL-1β and TNF-α, which exacerbate synaptic dysfunction and neurodegeneration (CHARERNBOON et al., 2021). Aβ aggregation also induces gliopathy and insulin resistance in the brain, contributing to neuronal loss (RUVER-MARTINS et al., 2022). Furthermore, dysfunction of the cholinergic system, essential for memory and cognition, aggravates neuropsychiatric symptoms (MOOKO et al., 2022).

The endocannabinoid system (ECS) has been investigated as a potential therapeutic target for AD, due to its influence on neuroinflammation, oxidative stress, and synaptic dysfunction (RUSSO, 2018). The increase in CB2 receptors in microglial cells and astrocytes near senile plaques suggests a regulatory role in the inflammatory response (MACCARRONE et al., 2017). Studies indicate that CB2 activation reduces the production of inflammatory cytokines and promotes the removal of Aβ by macrophages (CRISTINO; BISOGNO; DI MARZO, 2020). Furthermore, cannabinoids demonstrate the ability to reduce oxidative stress, excitotoxicity, and the aggregation of neurotoxic proteins (LIM; SEE; LEE, 2017). Thus, compounds such as cannabidiol (CBD) have neuroprotective potential by modulating multiple pathological pathways of AD (NOREEN et al., 2018).

Studies in experimental models have shown that CBD reduces Aβ production and tau hyperphosphorylation, primary targets of AD (FRANCO; SMID; VIEGAS, 2021). Furthermore, CBD increases cerebral blood flow to the hippocampus, improving memory function (BLOOMFIELD et al., 2020). The neuroprotection provided by CBD is attributed to its ability to attenuate neuroinflammation and oxidative stress, key processes in the progression of AD (HOUNIE; VASQUES, 2019). Furthermore, ECS modulation can reduce neurodegeneration associated with proteostatic and inflammatory dysfunction (DASH et al., 2021). Despite this promising evidence, more research is needed to elucidate the exact mechanisms and clinical efficacy of cannabinoids in AD (INGLET et al., 2020).

Activation of CB1 and CB2 modulates inflammatory and neuroprotective processes in AD, reducing neurotoxicity and promoting neuronal homeostasis (COSTA et al., 2022). Furthermore, cannabinoids can improve neuropsychiatric symptoms, such as agitation, frequently observed in patients with AD (MAUST et al., 2016). The relationship between ECS and AD also extends to the regulation of energy metabolism, since changes in CB1 signaling impact glucose utilization in the brain (SHELEF et al., 2016). The therapeutic potential of ECS in AD is based on its influence on neuroinflammation, neuronal metabolism, and synaptic plasticity (GONÇALVES et al., 2020). However, the long-term effects of cannabinoids on cognition still require further investigation (SUGARMAN et al., 2019).

Chronic neuroinflammation in AD involves hyperactive microglia and leukocyte infiltration, exacerbating neuronal degeneration (CHIURCHIÙ; LEUTI; MACCARRONE, 2015). Microglial activation in Aβ plaques is associated with increased CB2 expression, suggesting that the ECS may play an immunomodulatory role in the disease (ROM; PERSIDSKY, 2013). Furthermore, cannabinoids demonstrate antioxidant effects, reducing oxidative stress and lipid peroxidation associated with AD (AHMED et al., 2015). ECS modulation may also influence pathways related to autophagy and protein metabolism, potentially reducing the aggregation of neurotoxic proteins (FRAGUAS-SÁNCHEZ; TORRES-SUÁREZ, 2018). However, the heterogeneity of the results suggests that further clinical studies are essential to establish the therapeutic efficacy of cannabinoids in AD (BONINI et al., 2018).

AD is a multifactorial pathology characterized by the accumulation of Aβ, tau hyperphosphorylation, neuroinflammation, and oxidative stress, culminating in neuronal loss and cognitive deficits (COORAY; GUPTA; SUPHIOGLU, 2020). The endocannabinoid system presents itself as a promising target for modulating neuroinflammation and neuroprotection, but there are still challenges in its clinical application (CALABRESE; RUBIO-CASILLAS, 2018). Growing experimental evidence suggests that cannabinoids can mitigate neurodegenerative processes in AD, improving synaptic function and reducing oxidative damage (CHIURCHIÙ; LEUTI; MACCARRONE, 2015). However, further studies are needed to clarify the exact mechanisms and validate their clinical efficacy (WATT; KARL, 2017).

**INTERACTIONS OF ACTIVE COMPOUNDS IN CANNABIS SATIVA WITH NEUROTRANSMITTERS ASSOCIATED WITH ALZHEIMER'S DISEASE**

Cannabis sativa compounds, such as tetrahydrocannabinol (THC) and cannabidiol (CBD), interact with the endocannabinoid system, modulating neurotransmitters essential for cognitive function, such as acetylcholine, dopamine, glutamate, serotonin and gamma-aminobutyric acid (GABA) (LIM; SEE; LEE, 2017). THC acts as a partial agonist of CB1 receptors, regulating the release of neurotransmitters and influencing processes such as memory and learning (MANDELBAUM; DE LA MONTE, 2016). CBD, in turn, modulates glutamate-mediated excitotoxicity and promotes neuroprotection, being potentially beneficial for Alzheimer's disease (TOMMASO; KUNZ; VALERIANI, 2016). Furthermore, THC has demonstrated the ability to increase acetylcholine availability and inhibit acetylcholinesterase-induced beta-amyloid aggregation, suggesting neuroprotective effects (AHMED et al., 2015).

CB1 and CB2 receptors are expressed in the central nervous system and play a fundamental role in the regulation of neurotransmitters, influencing neurodegenerative processes (MANDELBAUM; DE LA MONTE, 2016). While CB1 modulates the release of acetylcholine and glutamate, affecting cognition, CB2 is related to the modulation of inflammatory responses and neuroprotection (ROM; PERSIDSKY, 2013). Studies indicate that CB2 agonists can alter cytoskeletal reorganization and regulate inflammatory pathways, presenting therapeutic potential for neuroinflammatory diseases, including Alzheimer's (ROM; PERSIDSKY, 2013). The activation of CB1 receptors has been shown to be neuroprotective by preventing electrophysiological changes associated with Alzheimer's disease, such as the neuronal firing frequency induced by Aβ deposition (TROJAN et al., 2023).

CBD has also demonstrated anti-inflammatory and antioxidant properties by modulating the expression of enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), in addition to interacting with vitamin D receptors, contributing to the reduction of inflammation and aging (TROJAN et al., 2023). Furthermore, CBD administration increased the expression of essential synaptic proteins such as GluA1, GluA2 and synaptophysin, indicating positive effects on neurotransmission (CHEN et al., 2023). The modulation of neurotrophic factors such as BDNF and GDNF by CBD also suggests its protective action on neuronal survival and regeneration (CHEN et al., 2023). The use of CBD oil by caregivers of Alzheimer's patients has been associated with improvements in quality of life, including reduced agitation, anxiety and insomnia (LESZKO; MEENRAJAN, 2021).

THC has demonstrated positive effects on mitochondrial function and reduced beta-amyloid aggregation in animal models of Alzheimer's, suggesting a therapeutic potential for the disease (MACCARRONE et al., 2017). Furthermore, the combination of THC and CBD increased the expression of synaptic markers such as GluR2/3 and GABA-A Rα1, promoting a balance in neurotransmission in APP/PS1 mice (ASO; ANDRÉS-BENITO; FERRER, 2016). Studies indicate that CBD can act as a multimodal agent for the treatment of Alzheimer's, interacting with NMDA receptors, serotonergic 5-HT1A and TRPV1 channels (WATT; KARL, 2017). The activation of the PPARγ receptor by CBD has also been shown to be relevant in reducing neuroinflammation and improving hippocampal neurogenesis (HOUNIE; VASQUES, 2019).

In addition to acting on CB1 and CB2 receptors, CBD regulates the release of neurotransmitters such as dopamine, serotonin, and GABA, contributing to neuroprotection and reducing excitotoxicity (FRANCO; SMID; VIEGAS, 2021). The inhibition of acetylcholinesterase by THC and CBD reinforces their potential therapeutic application in Alzheimer's disease (SENIYA; KHAN; UCHADIA, 2014). Studies indicate that activation of CB1R can protect hippocampal pyramidal neurons against beta-amyloid-induced damage (COORAY; GUPTA; SUPHIOGLU, 2020). CBD also influences intracellular calcium homeostasis, regulating T-type calcium channels and modulating apoptotic and inflammatory processes (MANDELBAUM; DE LA MONTE, 2017).

THC and CBD have demonstrated the ability to reduce beta-amyloid deposition and regulate neuroinflammatory processes through interaction with CB1 and CB2 receptors (SUERO-GARCÍA; MARTÍN-BANDERAS; HOLGADO, 2015). Furthermore, modulation of the Wnt/β-catenin axis by CBD has been shown to reduce tau protein hyperphosphorylation, one of the main pathological processes associated with Alzheimer's (VALLÉE et al., 2017). Activation of PPARγ by CBD suppresses pro-inflammatory signaling, reducing the production of TNF-α and IL-1β, key markers in neuroinflammation (RUSSO, 2018). Combined administration of THC and CBD showed significant improvement in cognitive performance in aged mice, suggesting a synergy between the compounds (CALABRESE; RUBIO-CASILLAS, 2018).

Studies indicate that cannabinoids can modulate synaptic plasticity and protect against beta-amyloid toxicity by activating the PI3K/Akt system through interaction with CB1 receptors (VALLÉE et al., 2017). The action of cannabinoids in neuroprotection also involves the inhibition of microgliosis and the release of pro-inflammatory cytokines, reducing neuronal damage in experimental models of Alzheimer's (ABATE; UBERTI; TAMBARO, 2021). Furthermore, CBD has been shown to interact with TRPV1 and 5-HT1A receptors, contributing to the regulation of neurotransmitter systems in the brain (NOREEN et al., 2018). These effects reinforce the therapeutic potential of cannabinoids in neurodegenerative diseases.

The growing scientific evidence base suggests that Cannabis sativa compounds may offer therapeutic benefits in Alzheimer's disease through modulation of the endocannabinoid system and regulation of neurotransmitters. However, despite the promising effects observed in animal models and in vitro studies, controlled clinical trials are still needed to confirm these benefits in humans. Although the use of THC for neuropsychiatric symptoms of dementia has been evaluated, the results remain inconclusive (Maust et al., 2016). Continued research is essential to better understand the mechanisms of action of cannabinoids and their clinical potential in neuroprotection and treatment of Alzheimer's.

**THE ANTI-INFLAMMATORY AND ANTIOXIDANT MECHANISMS OF CANNABIS SATIVA INFLUENCE THE NEURODEGENERATIVE PROCESSES OF ALZHEIMER'S DISEASE**

Neurodegeneration associated with Alzheimer's disease (AD) is largely influenced by oxidative stress and neuroinflammation, factors that contribute to disease progression and cognitive decline. Cannabinoids, especially cannabidiol (CBD) and tetrahydrocannabinol (THC), have antioxidant and anti-inflammatory properties capable of attenuating these deleterious effects. Studies show that CBD reduces the production of reactive oxygen species (ROS) and limits damage to DNA and cell membranes (MANDELBAUM; DE LA MONTE, 2016). Furthermore, CBD improves mitochondrial functionality and optimizes neuronal energy metabolism (CHOI; LEE; KIM, 2023). Microglial modulation by CBD also reduces the release of pro-inflammatory cytokines, such as TNF-α and IL-1β, preventing neuronal damage (KUHARIC et al., 2021).

The interaction between cannabinoids and the endocannabinoid system plays a crucial role in neuroprotection. Activation of CB1 and CB2 receptors modulates the inflammatory response, reduces excitotoxicity, and favors neuronal survival (LIM; SEE; LEE, 2017). CBD activates TRPV2, promoting microglial phagocytosis of beta-amyloid (Aβ) and reducing neuroinflammation (TROJAN et al., 2023). CBD also inhibits the expression of NFkB p50/p65, reducing pro-inflammatory transcriptional activity in a PPARγ-dependent mechanism (HUGHES; HERRON, 2018). CB2 stimulation reduces iNOS production via inhibition of ERK-1/2 phosphorylation in microglia, attenuating inflammation in the central nervous system (ROM; PERSIDSKY, 2013).

Cannabinoids also demonstrate a direct effect on Aβ-induced neurotoxicity, preventing the formation of amyloid plaques and blocking its neuronal proteolysis (RUVER-MARTINS et al., 2022). CBD negatively regulates pro-inflammatory genes, such as Slamf8, Grn and Prdx2, reducing oxidative stress and brain neuroinflammation (CHEN et al., 2023). These effects are reinforced by its ability to improve the elimination of Aβ by the glymphatic system (CRISTINO; BISOGNO; DI MARZO, 2020). Furthermore, THC has been shown to inhibit beta-amyloid aggregation by binding to acetylcholinesterase, preventing the toxic accumulation of the protein (SENIYA; KHAN; UCHADIA, 2014).

Microglial modulation is one of the main mechanisms by which cannabinoids promote neuroprotection. CBD induces gene expression towards a less harmful M2 phenotype, reducing the neurotoxic effects of microglial activation (COORAY; GUPTA; SUPHIOGLU, 2020). In addition, it reduces neuroinflammation by modulating the release of pro-inflammatory cytokines, such as IL-1 and TNF-α, and protecting synaptic function (CHARERNBOON et al., 2021). These effects are enhanced by CBD's ability to reduce hyperphosphorylated tau, preventing the formation of neurofibrillary tangles (CASSANO et al., 2020).

The antioxidant effects of cannabinoids also play an essential role in mitigating oxidative stress in AD. CBD significantly reduces free radical formation, attenuates lipid peroxidation, and improves mitochondrial homeostasis (ABATE; UBERTI; TAMBARO, 2021). Studies indicate that CBD also improves Wnt/β-catenin signaling, inhibiting GSK-3β activation and preventing neuronal apoptosis (LI et al., 2020). Furthermore, CBD activates autophagy via ERK1/2, aiding in the removal of toxic protein aggregates (TROJAN et al., 2023).

Despite the beneficial effects observed in preclinical models, the therapeutic use of Cannabis sativa in AD still faces challenges. A randomized clinical trial found no positive effects of marijuana in treating dementia symptoms (MAUST et al., 2016). Furthermore, marijuana can have short- and long-term cognitive adverse effects, which raises questions about its use in patients with Alzheimer's (PLANCARTE-SÁNCHEZ et al., 2018). In some US states, agitation in Alzheimer's dementia is a qualifying condition for the use of medical marijuana, but the decision often rests with caregivers (MAUST et al., 2016).

Recent studies indicate that CBD can attenuate mitochondrial changes related to brain aging, preserving ATP production and neuronal function (VALLÉE et al., 2017). Furthermore, cannabinoids act by reducing reactive microglial activation and promoting the removal of neurotoxins (NOREEN et al., 2018). Therefore, its therapeutic potential should be further explored through robust clinical studies to evaluate safety and efficacy in patients with AD.

Cannabinoids, especially CBD, have promising neuroprotective effects in AD, acting through multiple mechanisms, including inflammatory modulation, oxidative stress, autophagy, and synaptic regulation. However, the lack of conclusive clinical studies and potential adverse effects still limit their clinical application. Future investigations should focus on elucidating the molecular mechanisms and developing safe and effective cannabinoid therapies for AD-associated neurodegeneration.

**4. CONCLUSION**

The neurodegenerative mechanisms involved in the progression of Alzheimer’s disease include the extracellular accumulation of beta-amyloid (Aβ), tau protein hyperphosphorylation, mitochondrial dysfunction, and energy impairment, all of which are associated with specific neuroinflammatory processes and oxidative stress. In this context, the active compounds of Cannabis sativa, especially cannabidiol (CBD) and tetrahydrocannabinol (THC), interact significantly with key neurotransmitters affected by the disease, including acetylcholine, glutamate, dopamine, serotonin, and GABA. These compounds positively modulate neurotransmission by enhancing acetylcholine release, alleviating glutamatergic excitotoxicity, and protecting neurons from damage caused by pathological protein accumulation.

Moreover, the anti-inflammatory and antioxidant mechanisms of Cannabis sativa, mainly mediated by the endocannabinoid system (CB1 and CB2), directly impact neurodegenerative processes by reducing chronic microglial activation, modulating the production of inflammatory cytokines, and promoting the clearance of neurotoxic aggregates such as beta-amyloid plaques and hyperphosphorylated tau proteins. The modulation of these processes, along with the optimization of neuronal energy metabolism, demonstrates the therapeutic potential of cannabinoids in mitigating cognitive deficits and slowing the progression of Alzheimer’s disease.

However, despite promising preclinical results, clinical findings remain inconclusive, highlighting the urgent need for further investigations to fully elucidate the molecular mechanisms involved and ensure the safety and therapeutic efficacy of cannabinoids for patients with Alzheimer’s disease.

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