Evaluation of the Neuro-modulatory Effects of Cannabidiol in Alzheimer's Disease using Brain Imaging Markers: A Systematic Literature Review

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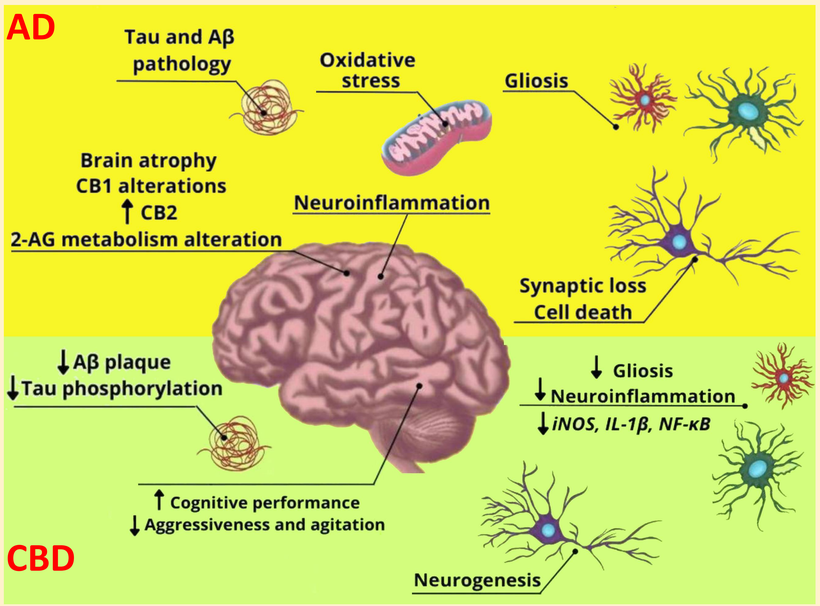
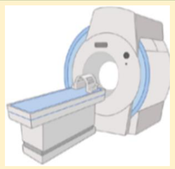
Introduction

Among various mechanisms implicated in the etiology of **Alzheimer's disease (AD), neuroinflammation, oxidative stress, and disruption of the endocannabinoid system (ECS)**, play key roles in the disease onset and progression. Numerous human and animal model in vivo studies have demonstrated the potential of cannabis-based products in modulating these processes, specifically **cannabidiol (CBD)**, due to **its anti-inflammatory, anti-oxidative, ECS modulatory, and neuroprotective properties**.[1,2] However, it is unclear how many studies have used neuro-imaging techniques to examine the effects of CBD on the above processes in the brains of AD patients in vivo and the findings of these studies.



Objective

To perform a systematic literature review to summarize **the impact of CBD treatment in the brains of AD patients using neuroimaging**.



Methods

A literature search was performed in the PubMed library for articles containing the terms "**Alzheimer's disease**", combined with "**cannabidiol**", "**cannabinoid**", "**cannabis**", or "**marijuana**" and with "**MRI**" or "**PET**".

Results

The literature search identified 32 articles. **None of these articles investigated marijuana or its products or their effects on the brains of patients with AD**.

The literature search identified 32 articles. **None of these articles investigated marijuana or its products or their effects on the brains of patients with AD**. Therefore, to the best of our knowledge, there are **no published studies that investigated the effects of CBD in the brains of patients with AD using brain imaging methods** (i.e., MRI and PET).

However, there are two brain MRI and three PET studies that evaluated **the effects of CBD on AD-relevant brain structures (e.g., hippocampus) and function** in healthy human subjects or in animal models.

MRI Studies

One study using **arterial spin labeling (ASL) MRI** showed that CBD increased cerebral blood flow in healthy subjects and associated with improved reaction time and working memory, particularly in the hippocampus and other brain structures affected by AD.[3]

Another study using **structural MRI** showed that CBD treatment in cannabis consumers restored the hippocampal structure, as evidence of the differential effect of CBD compared to other cannabis compounds.[4]

PET Studies

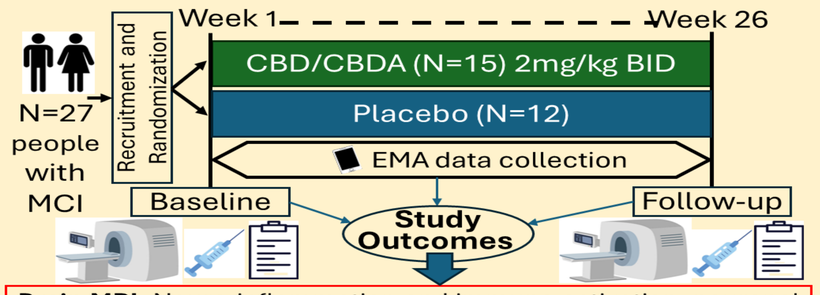
Three studies evaluated the use of cannabinoids in AD animal models; **two studies** showed that CBD improved fluorodeoxyglucose metabolism and memory.[5-6]

One study showed that synthetic cannabinoids (WIN-55-212-2 and JWH-133) reduced TNF-α (inflammatory cytokine produced by macrophages/monocytes during acute inflammation) expression and β-amyloid levels.[7]

Current Proposal

In a recently submitted proposal to the Consortium for Medical Marijuana Clinical Outcomes Research (MMJCOR), we proposed **to evaluate the efficacy of a 26-week long CBD + cannabidiolic acid (CBDA) intervention in individuals who meet clinical criteria for MCI and considered at risk for developing AD** (65-85 y.o.; CBD group n=15; placebo group n=12). The CBD group will be given CBD+CBDA-rich hemp extract (1:1 ratio; 2mg/kg, BID). Procedures will include a **urine drug screen, a blood draw, a brain MRI brain scan, and quality of life (QoL)** at baseline and after 26-weeks.

We propose to use advanced MRI techniques: whole-brain **MR spectroscopic imaging (MRSI), diffusion tensor/kurtosis imaging (DTI/DKI) with free-water elimination (FWE) and neuromelanin (NM)-MRI**. Biomarkers obtained from these methods can evaluate changes in neuro-inflammation and -immune activation, neuronal integrity, structural integrity, and neurotransmitters.



Brain MRI: Neuro-inflammation and immune activation, neuronal Viability and microstructure, neurotransmitters, volumetrics.
Blood samples: Inflammation, immune activation, neuronal injury, CBD/CBDA metabolites.
Physical/mental health: CBD+CBDA intake, quality of life.

Data from Ongoing MMJCOR-funded Study

In an ongoing study funded by MMJCOR (PI: Govind), we utilized the above proposed MRI techniques to **investigate the effects of HIV infection and marijuana use in the brain of people with HIV infection (PWH)**. We enrolled n=11 subjects with n=14 additional subjects to be enrolled within the next 2 weeks.

Sample whole-brain MRSI and NM-MRI data obtained on a 3T MRI from a subject are shown here to demonstrate the feasibility of the MRI protocol proposed for the new study on AD.

Conclusion

Despite CBD showing promising results in restoring hippocampal structure and function and reducing neuroinflammation in the brains of healthy subjects, **evidence-based knowledge on the effects of CBD on the brains of AD patients using advanced in vivo MRI techniques is still lacking**. Future studies should focus on gathering comprehensive brain imaging data in AD patients who are taking cannabis products.

Our current proposal seeks to fill this knowledge gap by **investigating the role of CBD and CBDA intervention in people with MCI at risk for developing AD**.

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