Chapter 2
Protective Effects of Cannabis in Neuroinflammation-Mediated Alzheimer's Disease

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ABSTRACT

In recent years, Alzheimer's disease (AD) has been recognized as an age-related neurological disorder wherein neurons degenerate and exhibit abnormal structure and function. Aging is the primary factor in the progression of AD from mild to severe cognitive impairment. No effective targeted therapies are presently available, and treatment is limited to symptomatic management. The neuropathologic hallmarks of the disease include the accumulation of amyloid-beta (Aβ) plaques in brain tissues and the aggregation of hyperphosphorylated-tau proteins (tangles) within neurons. Associated hyperactivation of neuroinflammation results in release of inflammatory molecules from neurons, microglia, and astrocytes, which have been linked with neuronal loss and the worsening neurodegeneration. The anti-inflammatory and neuroprotective properties of cannabis-based medicines may offer benefits in delaying the progression of neurodegenerative diseases including AD. This chapter explores the role of cannabinoids in countering neuroinflammation-mediated AD pathology.

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INTRODUCTION

Dementia has been rising globally among the older population and causes memory impairment with incapability of doing daily tasks (Atri, 2019). Many neurological disorders have been associated with memory impairment, and AD is one of them. The cellular and molecular alterations that contribute to AD progression generally begin many years before the symptoms appear (Jack Jr et al., 2013). The chances of dementia are approximately 3.9% before the age of 60 years and above. The pervasiveness of Alzheimer's disease cases in the US, Germany, France, Italy, United Kingdom, Japan, China, and India has increased from 12.53 million cases in 2012 to 16.72 million cases by 2022. Approximately 6.2 million Americans of 65 age and above have AD-related dementia. It is also expected that the number of AD patients could reach up to 13.8 million by 2060 (Alzheimer's association 2021). Hence, there it is the need of the hour to find therapeutic targets to protect AD and its associated behavioral and biochemical changes.

The extracellular deposited form of Amyloid β (Aβ) and intracellularly located hyperphosphorylated form of tau protein are the major hallmarks in the disease progression. The aberrant cleavage activity of β-Amyloid Cleaving Enzyme-1 (BACE-1) cleaves the Amyloid Precursor Protein (APP) at the C-terminus and forms soluble Amyloid precursor protein beta (sAPP β), which further causes dementia and neuronal cell death (Yuksel & Tacal, 2019). The aggregated form of Aβ triggers the activation of microglia and astrocytes, which produces cytokine storms on the site of damage and attracts other immune cells. This leads to inflammation and increases in the amount of ROS further leading to an increase in the expression of kinases, including Protein kinase C, A, and Extracellular signal-regulated kinase/2(ERK2), which hyper-phosphorylates tau protein, destabilizes microtubules and leads to the formation of NFTs and even neuronal cell death (Hooper et al., 2008).

Increasing shreds of evidence has shown that the amyloid cascade is not a single player in the progression of AD. Other events also play a significant role in its onset, and neuroinflammation is one of them. Inflammation a general process involved in repairing tissue injury and protecting cells from infection. The interconnected network of the brain and immune system allows immune cells to work efficiently. Generally, neuroinflammation is a protective mechanism, but its hyperactivation and increased inflammatory mediators cause neuronal cell death. The interconnected networks of activated microglia, astrocytes, and Aβ plaques contribute to neuroinflammation and neuronal cell death, leading to AD progression.

In the past, various studies have reported that cannabinoids are being used as a protective agent to treat AD pathology by targeting Aβ and hyper-phosphorylated tau protein (Iuvone et al., 2004a; Ramírez et al., 2005). A combination treatment with three synthetic cannabinoids - HU-210, WIN55,212-2, and JWH-133, blocked the Aβ-mediated regulation and activation of microglia cells and inhibited TNF- α release (Ramírez et al., 2005). Many studies have shown that it also neutralizes ROS via antioxidant properties and protects the neuronal cells from damage. CB1 receptor involved in the endocannabinoid system is highly expressed in the brain, specifically within the hippocampus, basal ganglia, and cerebellum area. It has an affinity for cannabinoids in the hippocampus and is associated with solid synapse regulation and is linked with cognitive functions that disrupts AD progression (Riedel & Davies, 2005). CB2 is another receptor with low expression in the brainstem, cerebellum, and microglia cells (Ashton et al., 2005; van Sickle et al., 2005), and a potential to control AD pathology.