Chapter 1
Medicinal Cannabis for Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia, and currently there is no cure. New therapeutic strategies that have the potential to address the complex pathophysiology of AD are urgently required; medicinal cannabis offers this possibility. Several potential leads can be extracted from Cannabis sativa (cannabis) that can target AD pathophysiology and alleviate symptoms, making it a prime candidate for AD drug discovery research. To date, most cannabis and AD research has focused on the major cannabinoids Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), paying little attention to other plant constituents with therapeutic properties for AD. This chapter will highlight emerging evidence on the therapeutic potential of medicinal cannabis going beyond CBD and THC to discuss cannabinol (CBN), cannabigerol (CBG), cannabichromene (CBC), cannabinoid acids, and other cannabinoid homologs, terpenes, and flavonoids that may have relevance to AD therapy. Further, the entourage effect, clinical implications, and directions for future research will be discussed.

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INTRODUCTION

Cannabis sativa (cannabis) has been used since the Neolithic period to treat cognitive decline and maximise longevity (Bonini et al., 2018; Sinclair, 2020). Contemporary drug discovery has built on these ethnobotanical roots, harnessing the potential of cannabis to manage the broad ranging symptoms and multifaceted pathophysiology of Alzheimer's disease (AD), the most common form of dementia. AD is associated with the aggregation of extracellular amyloid-β (Aβ) peptides and hyperphosphorylated tau protein in a neurotoxic pro-inflammatory environment of oxidative stress and excitotoxicity resulting in neurodegeneration (Ballard et al., 2011). To date, a large portion of research on cannabis as a treatment for AD has focused on Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). A range of potential therapeutic properties relevant to AD have been demonstrated, such as reducing neurotoxicity, neuroinflammation, oxidative stress, tau hyperphosphorylation, Aβ production, and improving microglia function, while promoting the brain's intrinsic repair mechanisms (Coles et al., 2022). However, cannabis contains >550 phytochemicals that may have relevance to AD prevention and treatment, some of which may have synergistic potential via the entourage effect (Lewis et al., 2017; Rock & Parker, 2021).

The objective of this chapter is to highlight the emerging preclinical and clinical evidence on the therapeutic potential of medicinal cannabis for AD symptoms and pathology beyond CBD and THC to appraise cannabinol (CBN), cannabigerol (CBG), cannabichromene (CBC), cannabinoid acids (e.g., tetrahydrocannabinolic acid; THCA, and cannabidiolic acid; CBDA), and other cannabinoid homologs (e.g., cannabidivarin; CBDV), terpenes, and flavonoids. These compounds were pragmatically selected for discussion due to the existing evidence base, which is in part due to their relevance to AD and their abundance (or their precursors) in *Cannabis sativa*.

The chapter will begin with a discussion on AD's clinical and pathological presentation and lack of available treatments. Following this, endocannabinoid system (ECS) dysfunction in AD will be reviewed. The core of this chapter will focus on cannabis-derived therapeutics for AD. Here, key compounds with relevance to AD that are present in *Cannabis sativa* or can be derived via (for example) decarboxylation will be appraised including mechanisms of action, available *in vitro* and *in vivo* evidence, followed by clinical evidence on efficacy and safety, and a discussion on the entourage effect and how various cannabis botanicals may synergistically work together to improve efficacy and safety. As a closing note to the chapter, clinical considerations and directions for future research will be discussed.

BACKGROUND

Dementia and Alzheimer's Disease (AD)

Dementia is a syndrome clinically characterised by cognitive decline that interferes with independent function. It is estimated that over 55 million people live with dementia worldwide, and without a medical breakthrough, this number will increase to 139 million by 2050 (Alzheimer's Association, 2021). Dementia's annual global cost is currently USD $1.3 trillion and is forecast to rise to USD $2.8 trillion by 2030 (Alzheimer's Association, 2021; Alzheimer's Disease International, 2015). In Australia, dementia is the number one cause of disability and the second leading cause of death (the leading cause for women) in people over the age of 65 years (Australian Bureau of Statistics, 2017). Dementia may be attributable to over 100 different diseases, for which there are no cures and no way to stop their degenerative course.