

Chapter 6

Cannabinoid Neurobiology and Medical Cannabis Intervention for Amyotrophic Lateral Sclerosis (ALS): Understanding the Molecular Mechanisms of Action

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ABSTRACT

Amyotrophic lateral sclerosis (ALS), a neurodegenerative condition that leads to muscle wasting, weakness, and stiffness, is characterized by progressive loss of upper and lower extremity muscle cells. The development of therapies that do more than just slow disease progression is essential. Cannabinoids with a broad-spectrum neuroprotection profile appear to have the potential to manage ALS. Cannabinoids can reduce excitotoxicity and neuroinflammation via activating CB1 and CB2 receptors. To increase treatment efficacy and reduce side effects, cannabinoids, particularly THC and CBD, can effectively alleviate ALS-related symptoms, including spasticity and neuropathic pruritus. This chapter aims to provide a comprehensive summary of the effectiveness and the molecular pathways that cannabis activates to exert its potential pharmacotherapeutic effects for alleviating ALS-related symptoms.

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INTRODUCTION

Cannabis and Medical Cannabis

Cannabis belongs to the Cannabaceae family, with *Cannabis sativa* and *Cannabis indica* being the common species. For 5000 years, cannabis was exploited as an abused substance for recreational use. The controversial debates remain prevalent on legal or illegal cultivation across different countries (Bridgeman & Abazia, 2017). In terms of global cultivation, production volume, and consumer population, the cannabis market has been the largest illicit drug market. Cannabis is native to Central and South Asia, and currently, 200.4 million individuals consume cannabis per annum. Cannabis produces hemp, cannabis (from flower buds), and hashish (resin), which are used for recreational use and consumed by smoking and inhaling (Donnan et al., 2022). Apart from abuse, cannabis also has various medicinal uses, such as cramps and pain management; therefore, regarded as medical cannabis. Cannabis use for recreational and medical purposes, is becoming increasingly accepted globally, and several nations have legalized it under strict regulations. Cannabis's medical use appears to be supported by the general population, even though many people are deeply concerned about its recreational use and abuse (Fragoso et al., 2020).

CANNABINOIDS: PHYTOCONSTITUENTS OF CANNABIS

The cannabis plant contains over 560 identified chemical constituents and secondary metabolites with more than 104 termed cannabinoids; including Cannabidiol (CBD), Δ^9 -tetrahydrocannabinol (THC), cannabigerol, cannabidivarin, tetrahydrocannabivarin, cannabichromene, etc. (Gonçalves et al., 2019). CBD and THC are the most abundant cannabinoids. THC has high psychoactive activity (such as anxiety and paranoia), while CBD, a non-euphoria molecule, has less psychoactive activity but stimulant effects on CNS. The therapeutic potential of these substances has been extensively recognized due to the clinical application of cannabis and the non-psychoactive nature of most phytocannabinoids, excluding THC (Lafaye et al., 2017). Although highly debated, several phytocannabinoids, particularly cannabidiol (CBD), have been suggested to have potential benefits in several pathological conditions such as inflammation, cancer, addiction, and epilepsy (Legare et al., 2022). The CBD and THC ratio in cannabis varies from species to species, i.e., *C. Sativa* has a higher CBD to THC ratio, whereas *C. indica* has a higher THC to CBD ratio. THC content, which also determines cannabis potency, also varies in different parts of plants; 15-25% in flowers, 1-2% in leaves, 2% in the stem, and >0.03% in roots (Jin et al., 2020). CBD, a non-psychoactive molecule with a 21-carbon terpenophenolic skeleton, accounts for 40% that account for approximately 40% of the plant extract portion.

Pharmacological applications of Cannabinoids

The endocannabinoid system regulates synaptic transmission, neuron-glia interactions, glial function, neural cell proliferation and differentiation, and protein homeostasis, among other processes in the central nervous system (CNS). Therefore, the endocannabinoid system is a potential modulator for a variety of CNS disorders that entail dysregulation of these mechanisms (Cristino et al., 2020; Zou & Kumar, 2018). CBD or THC alone or the combination can influence the common variables implicated in neuronal degradation and death because of the wide-ranging therapeutic actions of cannabinoids, which

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