Middle East Research Journal of Medical Sciences
ISSN: 2789-7699 (Print) & ISSN: 2958-2024 (Online)
Frequency: Bi-Monthly
DOI: https://doi.org/10.36348/merjms.2025.v05i03.003

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Study of the Relationship between Cannabidiol and Motor Neuron Disease

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Abstract: The main functions of motor neurons include regulating muscle contraction, controlling posture and balance, coordinating movements, and transmitting sensory information to the central nervous system. They are essential for carrying out daily motor activities and maintaining homeostasis in the body. Their unique structure and vital functions make them fundamental parts of the functioning of the nervous system and the regulation of the body's motor activities. Motor Neuron Disease(MND), the target mechanism of cannabinoids, to provide an antispastic effect, occurs through receptors in the synapses of the Central Nervous System(CNS). This mechanism allows the inhibition of the pre-synapses and reduces the release of glutamatergic neurotransmitters. Thus, it was shown that cannabidiol was well tolerated and presented the first evidence of providing control of spasticity. The manuscript aims to study the relationship between cannabinoids and motor neuron disease. A literature review is a study based on collecting selected materials and bibliographies, through a precise search in the scientific community's available databases.

Keywords: Amyotrophic Lateral Sclerosis, Cannabidiol, Degeneration, Neuroplasticity, Receptors.

Review Paper

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How to cite this paper:
Ronaldo Freua Bufaíçal Filho *et al* (2025). Study of the Relationship Between Cannabidiol and Motor Neuron Disease. *Middle East Res J. Med. Sci*, *5*(3): 259-268.

Article History:
| Submit: 23.04.2025 |
| Accepted: 24.05.2025 |
| Published: 27.05.2025 |

INTRODUCTION

Motor neurons are nerve cells that are specialized for transmitting nerve impulses from the central and peripheral nervous systems to the muscles and glands of the body. They play a crucial role in coordinating movement and regulating body functions. These neurons have a unique structure, with a cell body that contains the nucleus and extensions called dendrites and axons. Dendrites receive nerve impulses from other nerve cells, while axons transmit these impulses to target cells, such as muscles (Figure 1) (Porto, 2004; Porto, 2013; Freire *et al.*, 2020; Sanar, 2022; Guy-Evans, 2023; Varella, 2024).

There are two main types of motor neurons: upper motor neurons, which originate in the cerebral cortex and control voluntary movements, and lower motor neurons, which originate in the spinal cord and control involuntary movements such as reflexes (Biologydictionary.net Editors, 2021; Varella, 2024).

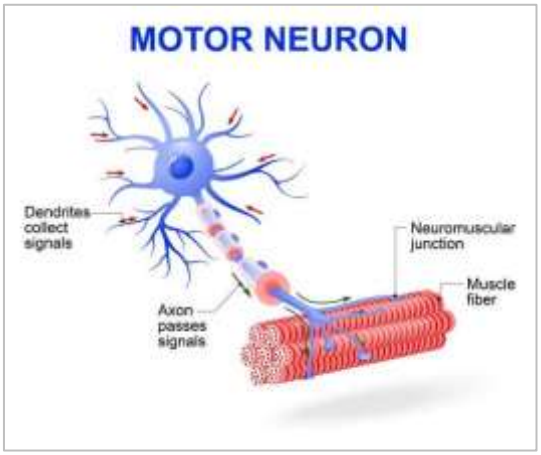

Figure 1: Motor neurons control all of our muscle movements
Sources: Kate Latham, and https://biologydictionary.net/nerve-cell/

The main functions of motor neurons include regulating muscle contraction, controlling posture and balance, coordinating movements, and transmitting sensory information to the central nervous system. They are essential for carrying out daily motor activities and maintaining homeostasis in the body. Their unique structure and vital functions make them fundamental parts of the functioning of the nervous system and the regulation of the body's motor activities. Motor neurons are a type of neuron responsible for transmitting nerve impulses from central neurons to muscles or glands. They are crucial in controlling voluntary movements and coordinating muscle activities (Sanar, 2019; Sanar, 2022; Varella, 2024).

1.1. OBJECTIVE

The manuscript aims to study the relationship between cannabinoids and motor neuron disease.

2.0. METHOD

A literature review is a study based on collecting selected materials and bibliographies, through a precise search in the scientific community's available databases. Related keywords are used to collect the material in the databases. to the subject of the study, so that the use of operators and, or not, allows for further refinement of the results and, consequently, the corpus of the research. The bibliography and collection of material on the agenda for this integrative review of specific literature were carried out in the following databases: PubMed, BVS, and Lilacs. To search for articles, the following descriptors were used in the English language: "Cannabidiol'', "neurodegenerative diseases", and "Motor Neuron Disease". The descriptors were combined in different strategies to ensure a more comprehensive search. For this review, 53 articles were selected, and inclusion criteria were defined for an exhaustive search.

3.0. SELECTED STUDIES

3.1. Motor Neuron Disease(MND)

Motor Neuron Diseases(MND), or motoneuronopathies, correspond to a broad group of diseases characterized by involvement of the upper or lower motor neurons, or both. It is characterized by the primary participation of the cell body of the motor neuron, the cortical, brainstem, and spinal motor neurons. For this reason, it has exclusively motor manifestations, which include loss of strength and muscle atrophy (Figure 2) (Porto, 2004; Porto, 2013; Freire *et al.*, 2020; Montenegro, 2021; Péladeau *et al.*, 2021; Sanar, 2022; Varella, 2024; Lennon, 2025).

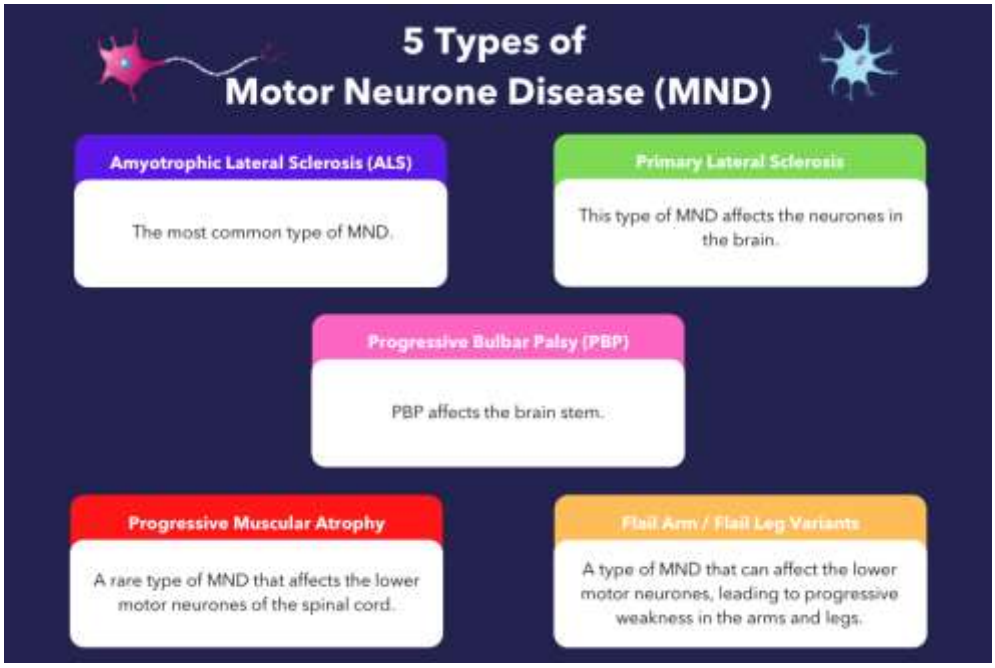

Figure 2: Five Types of Motor Neurone Disease (MND)
Source : https://www.homage.com.au/health/motor-neurone-disease/

The pyramidal system consists of upper motor neuron fibers that descend from the cerebral cortex through the internal capsule, traverse the medullary pyramid, and then decussate for the most part to descend in the lateral corticospinal tract on the side opposite their origin, where they synapse with interneurons and lower motor neurons in the spinal cord. All other descending influences on the lower motor neurons belong to the extrapyramidal system and originate primarily in the basal ganglia and cerebellum. The motor fibers that form

the cranial and peripheral nerves originate in the lower motor neurons (Sanar, 2022; Varella, 2024).

The two main representatives of this group are Amyotrophic Lateral Sclerosis (ALS) in adults and Spinal Muscular Atrophy (SMA) in children. Motor neuron disease is the name given to a group of diseases in which the nerve cells neurons that control muscles undergo degeneration and die (ALS), Progressive Muscular Atrophy (PMA), Progressive Bulbar Palsy (PBP), and Primary Lateral Sclerosis (PLS) are subtypes of Motor Neuron Disease (MND) (Porto, 2004; Porto, 2013; Bickley, 2015; Freire *et al.*, 2020; Sanar, 2022; Varella, 2024).

Neurologic examinations reveal specific signs associated with upper and lower motor neuron degeneration. Signs of upper motor neuron damage include spasticity, active reflexes, and plantar reflexes. Signs of lower motor neuron damage include muscle weakness and atrophy. The main symptoms are muscle weakness, accompanied by muscle hardening, sclerosis, initially on one side of the body, and amyotrophic muscle atrophy. However, there are others: cramps, muscle tremors, sharp reflexes, spasms, and loss of sensation. Symptoms usually begin to appear after age 50, but can also appear in younger people. ALS is a disease that affects the nervous system in a degenerative and progressive way, leading to irreversible motor paralysis (Porto, 2004; Porto, 2013; Freire *et al.*, 2020; Sanar, 2022; Burchill *et al.*, 2023; Varella, 2024).

Neurons extend from the brain to the spinal cord and from the spinal cord to the muscles of the body. They control voluntary movement and muscle power, allowing control of the muscles that make us speak, walk, breathe, and swallow. As motor neurons progressively degenerate and die, the brain's ability to initiate and control muscle movement is lost. Without neurons to activate them, muscles gradually weaken and lose their function. Patients with ALS suffer gradual paralysis and early death as a result of the loss of crucial abilities such as speaking, moving, swallowing, and breathing (Porto, 2004; Porto, 2013; Freire *et al.*, 2020; Sanar, 2022; Varella, 2024).

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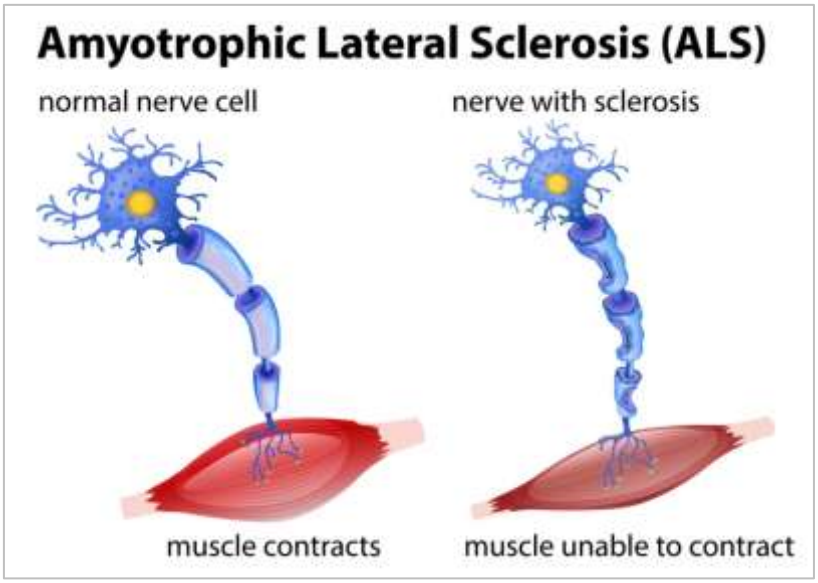

Figure 3: Amyotrophic Lateral Sclerosis (ALS)
Sources: © 2025 - AZ Institute of Neurology & Polysomnography. Habib Khan, MD, and https://neurologycasagrande.com/amyotrophic-lateral-sclerosis-als-causes-and-symptoms/

Motor neurons' progressive degeneration and death cause the brain to lose its ability to initiate and control muscle movement. Without neurons to activate muscles, they gradually weaken and lose their function. Patients with ALS suffer gradual paralysis and early death as a result of the loss of crucial abilities, such as speaking, moving, swallowing, and breathing (Porto, 2013; Freire *et al.*, 2020).

SMA has well-understood pathophysiology; the pathology is caused by homozygous deletion or mutation of the Motor Neuron Survival(MND) Gene 1 (SMN1),

located in the telomeric region of chromosome 5q13, and the number of copies of a gene similar to it Motor Neuron Survival Gene 2 (SMN2), located in the centromeric region, is the main determinant of the severity of the disease (Figure 4) (Porto, 2013; Bickley, 2015; Singh *et al.*, 2021; Sanar, 2022; Varella, 2024).

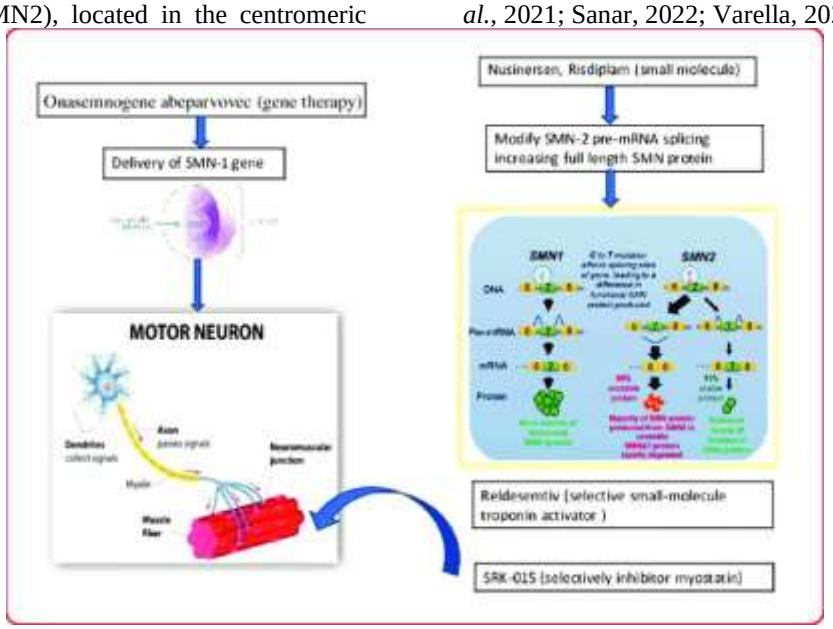

Figure 4: Core existing therapeutic options and their mechanism of action SMN1 = Survival Motor Neuron 1; SMN2= Survival Motor Neuron 2; SMN = Survival Motor Neuron
Source: Doi:10.5937/scriptamed52-31529

This genetic alteration in the SMN1 gene is responsible for the reduction in levels of the Motor Neuron (SMN) protein. The SMN2 gene does not completely compensate for the absence of SMN1 expression because it produces only 25% of the SMN protein. The lack of SMN protein leads to the degeneration of alpha (α) motor neurons located in the anterior horn of the spinal cord, which results in progressive and symmetrical proximal muscle weakness and paralysis (Freire *et al.*, 2020; Sanar, 2022; Varella, 2024).

3.2. MND - Cnnabinoids (CDB)

MND, the target mechanism of cannabinoids, to provide an antispastic effect, occurs through the CB1 receptors located in the synapses of the Central Nervous System (CNS). This mechanism allows the inhibition of the influx of calcium presynapses and reduces the release of glutamatergic neurotransmitters. Thus, it was shown that CBD was well tolerated and presented the first evidence of providing control of spasticity (Figure 5) (Ożarowski *et al.*, 2021; Cannabis & Health, 2022; Raïch, 2024).

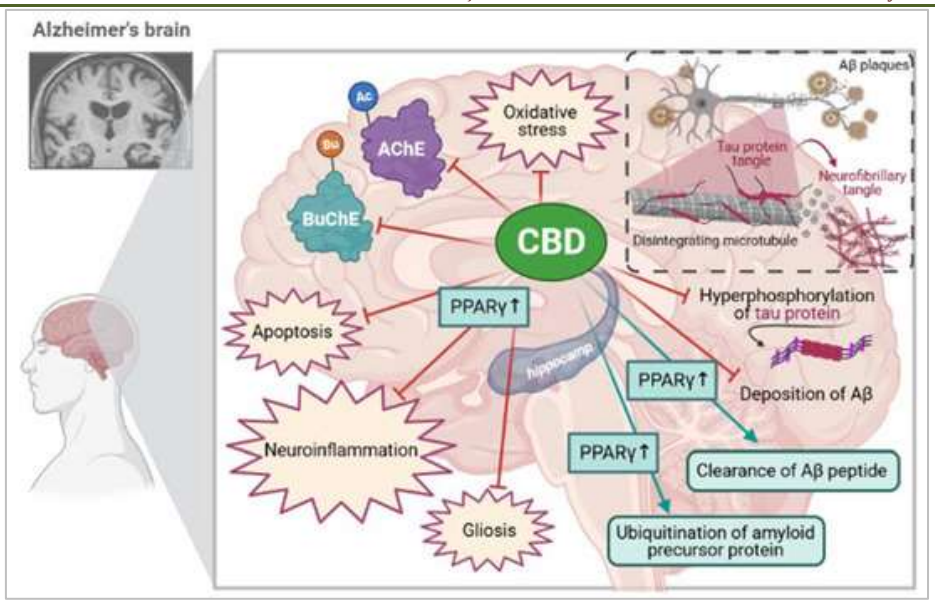

Figure 5: The role of CBD in the pathogenic mechanism of Alzheimer's disease [own drawing]. Legends: CBD: Cannabidiol; AChE: Acetylcholinesterase; BuChE: Butyrylcholinesterase; Aβ: beta-amyloid; PPAR-γ: peroxisome proliferator-activated receptor-gamma
Source: https://doi.org/10.3390/ijms220942 94

Cannabis-derived chemicals used as an adjunct treatment could potentially help alleviate symptoms of motor neuron disease, such as tight or stiff muscles [Researchers at the San Raffaele Scientific Institute in Milan, Italy] found that Patients in the study took anti-spasticity medications and were then treated with an oral spray nabiximols containing equal parts delta-9 Tetrahydrocannabinol (THC) and Cannabidiol (THC-CBD) derived from the *Cannabis sativa* Linnaeus (Rosales: Cannabacea), plant (Figure 6) (Ożarowski *et al.*, 2021; Silva *et al.*, 2022; Wei *et al.*, 2022; Vanin, 2023; Raïch, 2024).

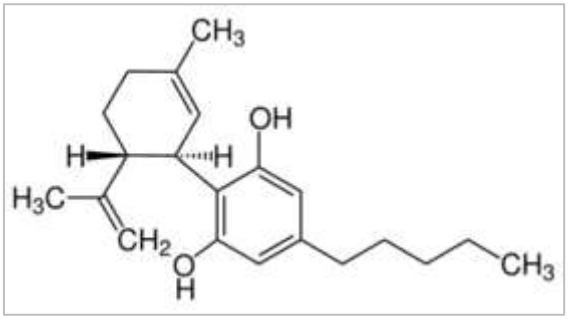

Figure 6: The structural formula of Cannabidiol (CBD, $C_{21}H_{30}O_2$)
Source : https://doi.org/10.3390/ijms220942 94

3.3. Neurodegeneration

Neurodegenerative disease is a broad term for some diseases that attack the nervous system. A common characteristic of all diseases in this group is the death of neurons, which are essential for the brain and do not regenerate or multiply. In addition, this group of diseases usually affects areas considered vulnerable, not just the brain but the upper part of the central nervous system as a whole (Barbosa *et al.*, 2006; Britch *et al.*, 2017; Boldrini, 2018; Gavioli *et al.*, 2024).

Currently, due to the increase in life expectancy of the population, there is a growing interest in the study of neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and ALS. One aspect of these studies demonstrates that oxidative stress plays an important role and can even trigger the process of neurodegeneration. This aspect is strengthened by the fact that neurons are highly prone to oxidative stress (Barbosa *et al.*, 2006; Britch *et al.*, 2017; Boldrini, 2018; Gavioli *et al.*, 2024).

Oxidative stress is defined as the situation in which the formation of reactive species significantly exceeds the antioxidant defense and repair capacity of the organism, resulting in increased damage to biomolecules such as DNA, lipids, and proteins. This damage, when not repaired, ends up compromising the functioning of the cell and leading to its death by apoptosis or necrosis (Barbosa *et al.*, 2006; Britch *et al.*, 2017; Boldrini, 2018; Gavioli *et al.*, 2024).

3.4. Neuroplasticity

The importance of neuroplasticity is that it stimulates the brain's adaptation to a wide variety of situations. This also means that an individual does not completely lose their ability to perform certain tasks, even if some areas of their nervous system are damaged. Traumatic events can also generate psychological disorders, such as panic syndrome and other anxiety disorders. By stimulating neuroplasticity, it is possible to help a person face these problems and minimize their effects on their life (Britch *et al.*, 2017; Boldrini, 2018; Cognitivo, 2020; Gavioli *et al.*, 2024).

In one of the most recent definitions, spasticity was described as involuntary muscle hyperactivity in the presence of central paresis. Three mechanisms play a central role in the development of spasticity: **(i)** changes in the afferent input reaching spinal motor neurons; **(ii)** changes in reflex arcs that affect the excitability of motor neurons; and **(iii)** changes in the internal characteristics of motor neurons. Spasticity occurs in stroke, traumatic brain injury, spinal cord injury, and cerebral palsy. It may also be present in neoplasms of the nervous system and hereditary degenerative and demyelinating diseases (Schünemann *et al.*, 2013; Oussama *et al.*, 2016; Trompetto *et al.*, 2014; Abate *et al.*, 2021; Brazil, 2021; Silva *et al.*, 2022; Vanin, 2023).

3.5. Neuroprotection

Many substances with neuroprotective, antioxidant, and anti-inflammatory properties have been described and used in studies related to the process of synaptic regeneration and plasticity, to prevent neuronal death after injuries. In this scenario, CBD has been gaining prominence, as a large number of pharmacological effects have been attributed to the molecule, including anticonvulsant, sedative, anxiolytic, antipsychotic, anti-inflammatory, antioxidant, and neuroprotective effects, as well as effects on the immune and circulatory systems (Zuardi, 2008; Scuderi *et al.*, 2009; Perez, 2013; Alline *et al.*, 2016; Flores and Zamin, 2017).

Using neonatal rats, through the suppression of oxygen and glucose and decreased blood flow, ischemic hypoxia leads to functional and cognitive impairment. In the first 7 and 30 days after the injury, all rats were subjected to neurobehavioral tests such as rotarod, rear cylinder test, and object recognition. It was observed that rats treated with CBD presented better functional behavior concerning the execution of activities, both on the seventh day and after the first month following treatment. This fact indicates that CBD exerted its neuroprotective action in a prolonged and effective manner (Zuardi, 2008; Scuderi *et al.*, 2009; Perez, 2013; Flores and Zamin, 2017).

3.6. Neuromodulation

CBD's modulation of serotonin, dopamine, glutamate, and GABA levels can provide relief for a range of conditions, from depression and anxiety to insomnia and even certain neurodegenerative diseases. CBD binds to serotonin receptors (5-HT1a receptors), contributing to the sense of well-being and antidepressant effect of CBD. In addition to influencing serotonin regulation, cannabidiol can also affect dopamine through its medicinal use, since endocannabinoids are important for modulating neurotransmitter responses. CBD regulates the way this neurotransmitter is transmitted, absorbed, and transported in the brain (Russo *et al.*, 2005; Resstel *et al.*, 2009; Pandolfo, 2011; Montoya *et al.*, 2020).

Glutamate acts like a switch in the brain: it controls arousal and is involved in the processes of learning and reasoning. It is the main excitatory neurotransmitter in the brain, and CBD regulates its transmission. CBD helps regulate the way glutamate activates neurons. GABA is an inhibitory neurotransmitter that reduces neuronal excitability. It is the opposite or complementary effect of glutamate. CBD may increase the efficiency and release of GABA in certain parts of the brain, which is related to the relaxing effects of CBD (Pandolfo, 2011; Ibeas *et al.*, 2015; Renard *et al.*, 2017; Montoya *et al.*, 2020; Burelo, 2024).

The effects of CBD on neurotransmitters allow for a better understanding of the effects of cannabis and CBD on feelings of calm, well-being, relaxation, mental health, mood, anxiety, pain relief, improved sleep, and a sense of well-being (Burelo, 2024; Carrascosa *et al.*, 2024).

3.7. Cannabidiol has anti-inflammatory and antioxidant activities

Many neuroprotective, antioxidant, and anti-inflammatory compounds have been described and used in synaptic regeneration and plasticity, to prevent neuronal death after injuries. In this scenario, Cannabidiol (CBD) has been gaining prominence, as a large number of pharmacological effects have been attributed to the molecule, including anticonvulsant, sedative, anxiolytic, antipsychotic, anti-inflammatory, antioxidant, and neuroprotective effects, as well as on the

immune and circulatory systems (Scuderi *et al.*, 2009; Perez, 2013).

"The Cannabidiol acts on different skin cells to release its antioxidants. It has been found to induce the expression of heme oxygenase 1, an enzyme with antioxidant and anti-inflammatory properties, in the main cells of the upper layer of the skin, called keratinocytes" [Maurizio Pupo, Director of Research. and development at Ada Tina Italy] (Figure 7) (Zuardi, 2008; Belem *et al.*, 2017; Pisanti *et al.*, 2017; Ożarowski *et al.*, 2021).

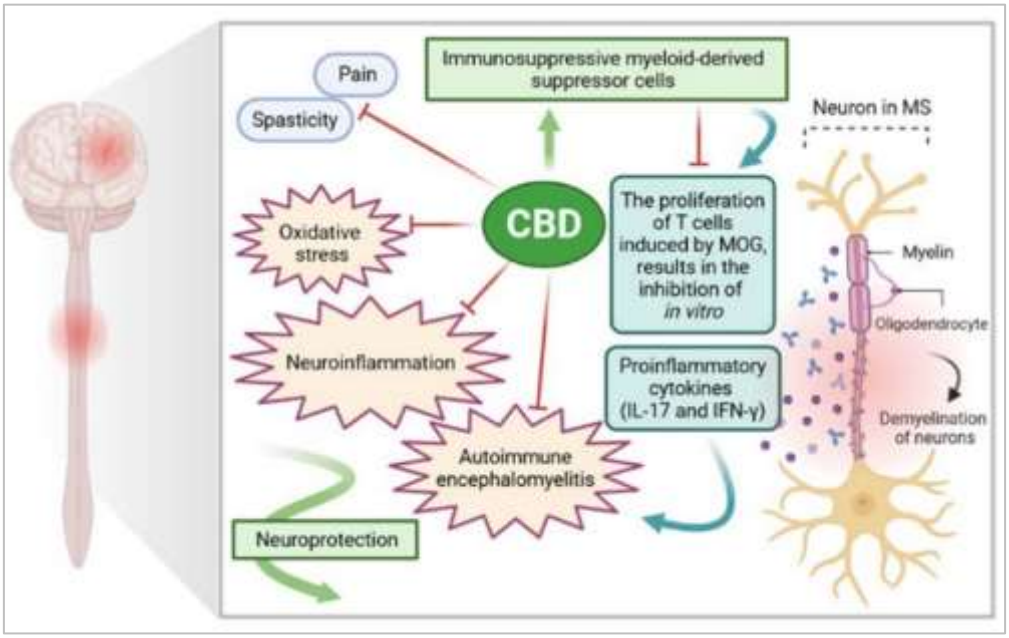

Figure 7: The role of CBD in the pathogenic mechanism of multiple sclerosis [own drawing]. Legends: CBD: Cannabidiol; MOG: Myelin Oligodendrocyte Glycoprotein; IL-17: Interleukin-17; IFN-γ: Interferon-Gamma
Source : https://doi.org/10.3390/ijms220942 94

CBD exerts, in a combined way, neuroprotective, anti-inflammatory, and anti-apoptotic effects, inhibiting Caspase 3 and acting on the toxicity of β-peptide, which may play an important role in neutralizing or slowing the progression of neuronal cell death. CBD has been emerging as a therapeutic agent in several pathologies such as cancer, anxiety, immunological diseases, and cardiovascular disease, because it presents high tolerability, low toxicity, and does not present psychoactive effects, in addition to presenting anti-inflammatory, antiepileptic and antioxidant activities (Zuardi, 2008; Belem *el al.*, 2017; Pisanti *et al.*, 2017; Atalay *et al.*, 2020).

3.8. Relationship between cannabinoids and motor neuron death

Cannabis contains cannabinoids with different effects on the body, in this case, CBD and THC. As an agonist, presynaptic CB1 receptors have the potential to hyperpolarize neurons in the CNS, causing relaxation. THC, despite being psychoactive, when given in an adequate dose and in a balanced way with CBD, can be responsible for improving motor function in some diseases. More clearly, THC is a partial CB1 agonist, being responsible for hyperpolarization. It can also generate tolerance and impair memory and learning; however, benzodiazepines also have these side effects (Valdeolivas *et al.*, 2012; Silva, 2018; Silva *et al.*, 2020; Joshi and Onaivi, 2019; Cannabis & Health, 2022).

Although there are over a hundred cannabinoids produced by *Cannabis*, THC and CBD are the two main compounds present in the plant. They have the most predominant therapeutic properties, are widely used in the production of medicinal oils, and are also the most widely used in clinical studies for various pathologies. Our brain has mechanisms that connect to these substances organically. It is naturally prepared to bind to these cannabinoids through the CB1 and CB2 receptors endogenous to the endocannabinoid system, which regulates a series of physiological processes in the human body leading to interaction with cellular metabolism and, in this way, modulating synaptic functions [Ana Paula Vanin - Federal University of the Southern Border (UFFS)] (Fusar-Poli, 2009; Chiricosta, 2019; Cassano *et al.*, 2020; Silva *et al.*, 2020; Abate *et al.*, 2021; Cannabis & Health, 2022; Silvam, 2023; Vanin, 2023).

With motor neuron disease, the target mechanism of cannabinoids, to provide an antispastic

effect, occurs through CB1 receptors located in the synapses of the CNS. This mechanism inhibits the influx of calcium presynapses and reduces the release of glutamatergic neurotransmitters. Thus, it was shown that CBD was well tolerated and provided the first evidence of control of spasticity (Figure 8) (Riva *et al.*, 2019; Abate *et al.*, 2021; Śledziński *et al.*, 2021; Cannabis & Health, 2022; Silva *et al.*, 2022; Vanin, 2023).

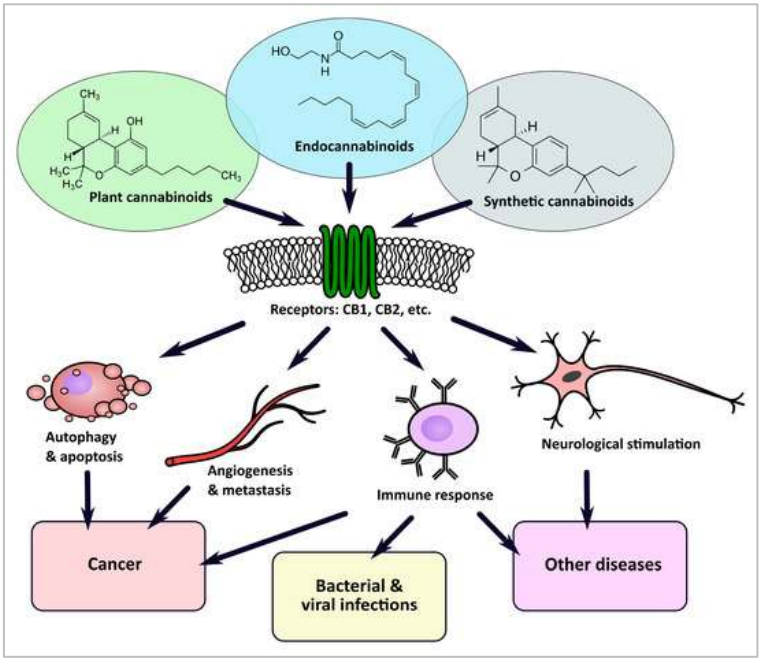

Figure 8: The involvement of the endocannabinoid system in a variety of modulatory processes makes it a promising target in the therapy of many conditions
Source: https://doi.org/10.3390/ijms22010263

The lack of significant clinical variations suggesting a relevant therapeutic response was associated with a lack of changes in essentially all biomarkers examined, except for an elevation of CB2 receptor gene expression in peripheral lymphocytes. This elevation can be interpreted as a positive response initiated by the treatment and possibly to potentiate the cytoprotective and anti-inflammatory role of this type of cannabinoid receptor in the harmful conditions existing in TV HD (high definition)**.** TV HD its interface allows viewing of the power and quality of the captured signal, instructing possible adjustments of the antenna's pointing to improve the signal. It comes with smart control, which allows synchronization of the TV's control with the receiver's control (Faria *et al.*, 2020; Freire *et al.*, 2020; Almeida *et al.*, 2021; Gustavsen, 2021; Burgaz *et al.*, 2021).

However, a longer treatment period is needed to allow the benefits derived from CB2 receptor activation to be visible in disease progression in patients. It is suggested that the study drug is well tolerated and provides the first evidence of efficacy in terms of spasticity control in patients with motor neuron disease (Fusar-Poli, 2004; Moreno, 2016; Chiricosta, 2019; Riva *et al.*, 2019; Abate *et al.*, 2021; Silva *et al.*, 2022).

The canabidiol interacts with some types of receptors that are not part of the endogenous cannabinoid system and is even capable of activating serotonin 5-HT1A receptors. Serotonin is a neurotransmitter that regulates mood, sleep, appetite, heart rate, and body temperature, and studies show that it is involved in pain, depression, and anxiety. Furthermore, CBD activates vanilloid receptors of the TRPV1 type, which are also involved in pain, anxiety, and depression responses (Gregorio *et al.*, 2018; Elsaid *et al.*, 2019; Ferreira, 2024; Gavioli, 2024).

It was observed that with acute administration of CBD, there was a decrease in the activity of Serotonergic Neurons (DRN) by activation of 5-HT1A receptors and Vanilloid Receptors (TRPV1), while repeated treatment with CBD increased this activity through desensitization of serotonin receptors. Repeated treatment was also able to decrease mechanical allodynia, reverse anxiety-like behavior, and improve serotonin neuronal activity in animals exposed to nerve injury, but through different mechanisms (Gregorio *et al.*, 2018; Elsaid *et al.*, 2019; Ferreira, 2024; Gavioli, 2024).

4.0. CONCLUSION

Clinical studies prove the beneficial action of CBD in controlling motor neuron disease. The control provided by phytocannabinoids in some of the symptoms that usually accompany patients can provide a better quality of life. The chemical compounds derived from CBD as an additional treatment could help alleviate motor neuron disease symptoms, such as tight or rigid muscles. Cannabidiol is a viable substance in treating neurodegenerative diseases, given its promising therapeutic properties in the field of neuronal health, and its positive approach to the recovery, symptomatic improvement, and quality of life of patients.

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