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REVIEW

The Endocannabinoid System as a Target for Ischemic Stroke Therapy

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Abstract

Introduction: Cannabinoids are increasingly being explored as a potential treatment for neurodegenerative diseases. This article aims to provide a narrative review of available data on the treatment of neurological disorders with cannabis constituents, focusing on ischemic stroke.

Methods: Selected articles are summarized to describe design, results, limitations, conclusions, and implications about this theme.

Results: The growing understanding of the endocannabinoid system and the cannabinoid receptors distribution in all human body systems and organs and particularly in brain structures importantly involved in myelination processes, suggests potential benefits for stroke symptoms and overall patient improvement. However, the variety of studied compounds, the different administration routes, dosages, and timing complicates data comparison, especially due to limited studies about these compounds, peculiarly in stroke patients. Thereat, this review to showcase disparities in findings and to summarize current advancements in cannabinoid use for potential future treatments.

Conclusion: This article offers a review of the current literature in the field and discuss a pragmatic approach to the clinical use of cannabinoids in patients with ischemic stroke.

Keywords: ischemic stroke; cannabis; neuroprotection; endocannabinoid system

Introduction

Ischemic stroke stands as one of the primary contributors to neurological morbidity worldwide, representing a complex condition necessitating prompt intervention and effective treatment. It is regarded as a disease of immense significance for global public health.[1] Ischemic stroke encompasses multiple risk factors culminating in the interruption or severe reduction of blood flow within cerebral arteries, notably the middle cerebral artery, thereby depriving neurons of essential oxygen and nutrients crucial for maintaining homeostasis. Consequently, cellular demise ensues, setting forth a cascade of deleterious physiological processes.[2]

Pathophysiological mechanisms such as increased permeability of the blood–brain barrier (BBB), neuroinflammation, and oxidative stress are pivotal in ischemic stroke. They are intricately linked to severe brain injury instigated, potentially precipitating pathological advancement of brain damage. Furthermore, survivor patients undergo systemic immunosuppression, rendering them vulnerable to various microorganisms. Therefore, safeguarding vulnerable cells emerges as a paramount goal in ischemic stroke treatment.[3,4]

Despite advancements in comprehending stroke pathophysiology, efficacious treatment remains a major challenge. Recent investigations pivot on exploring

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efficacious strategies for developing neuroprotective agents. However, clinically proven and readily available neuroprotective drugs are yet to materialize. Hence, further research endeavors should be directed toward therapies preventing free radical damage, counteract neuroinflammation, immunosuppression in cerebral ischemia and reperfusion (I/R) injury, in conjunction with revascularization therapy.[5]

The medicinal properties of the *Cannabis sativa* plant and its constituents have been recognized for millennia, yet their substantial therapeutic potential has only recently gained acknowledgment. Consequently, cannabidiol (CBD) and other phytochemical compounds exhibit promise as neuroprotective agents, given their immunomodulatory, neuroprotective, and anti-inflammatory attributes. These compounds could serve as focal points in reducing neuroinflammation and oxidative stress associated with revascularization therapy. Furthermore, the rising medical cannabis market represents a unique landscape in modern medicine, underscoring the promising therapeutic target of neuroprotection in ischemic stroke, offering myriad opportunities for advancement and exploration.[6,7] Thus, this review endeavors to elucidate current advancements in employing cannabinoids as a therapeutic target in stroke therapy.

Definition and Epidemiological Aspects of Ischemic Stroke

It is crucial for the scientific community to establish and formulate diagnostic criteria for diseases to guide medical practices, prevention strategies, and treatment modalities. Therefore, the usual definition for stroke is clinical, and the appearance of focal neurological signs of vascular origin lasting at least 24 h characterizes stroke.[8] Stroke is one of the most devastating and widespread diseases worldwide. It is considered the leading cause of long-term disability, with 80% of survivors suffering some degree of disability. It jeopardizes the health and quality of life of those affected and causes immense public health expenditure worldwide, with not only economic but also social consequences.[5,9–11]

Stroke, also known as cerebrovascular accident or apoplexy, is characterized by the impairment of blood and nutrient flow to the brain, with no identifiable cause other than a vascular origin. It represents the fourth leading cause of death worldwide.[12,13] More than 42 million people suffer a stroke each year and the number of strokes is expected to more than double between 2010 and 2050.[14] This pathological condition can be divided into ischemic stroke and hemorrhagic stroke, of which 85% are ischemic strokes, which represent a major individual, social, and economic impact.[2]

According to the World Stroke Organization, the estimated global cost of stroke is more than USD 721 billion (0.66% of the global Gross Domestic Product - GDP). From 1990 to 2019, the burden (in terms of the absolute number of cases) has increased significantly [70.0% more strokes, 43.0% more deaths from stroke, 102.0% more prevalent strokes, and 143.0% more disability-adjusted life years (DALYs) lost], with most of the global stroke burden (86.0% of deaths and 89.0% of DALYs) occurring in low- and middle-income countries.[15]

Recent studies show that the incidence of stroke is increasing, and that one in four people in the world will suffer a stroke in their lifetime. In addition, the global growth of the elderly population over 65 years of age and the accumulation of risk factors have fueled this increase in recent decades. Strokes currently have a global mortality rate of 5.5 million and a high morbidity rate, which also results in 50% of survivors being considered chronically disabled.[10,16–18] Early recognition and intervention set in motion a chain of survival that is specific to stroke.[19]

Another population group contributing to a steady increase in stroke mortality worldwide is younger adults, as increasing socioeconomic status in developing countries has led to an epidemic risk of risk factors such as atrial fibrillation, hypertension, diabetes, hyperlipidemia, hyperhomocysteinemia, smoking, unhealthy diet, physical inactivity, obesity, and alcohol consumption.[20–22] Nevertheless, older people are among the patients with the highest prevalence, mortality, and disability associated with stroke and have a higher risk of complications associated with thrombolytic treatment compared with younger patients.[23] In this context, the highest incidence of stroke is in the 70–79 age group with 59,706 cases, followed by the 60–69 age group with 52,673 cases, according to the American Heart Association.[24]

The most recent report published by the American Heart Association shows that an additional 3.4 million U.S. adults ≥18 years, or 3.9% of the adult population, are projected to suffer a stroke by 2030, a 20.5% increase in prevalence since 2012.[25] However, the most

important risk factor for the development of a stroke is high blood pressure.[26] In addition, there is the genetic factor, which has received less attention in studies, but nevertheless makes a significant contribution to the ischemic genesis of stroke, especially in the case of an early onset of stroke.[27]

In the epidemiology of stroke, a crucial and relevant factor to consider is the individual biological sex. This factor also depends on age, as the influence of gender on the risk of ischemic stroke changes with age.[28] Functionally, women suffer more severe strokes than men, resulting in more physical limitations, poorer mental health, and greater dependency.[29] The World Health Organization (WHO) has evaluated mortality rates by gender in 39 countries in Europe and Central Asia and reports that mortality rates are higher in women than in men.[30] According to the National Institute of Health Stroke Scale, women (44%) suffer acute and severe strokes and recover more slowly than men (36%).[31] However, these data come from women older than 75 years, most of whom fall into the highest risk range. For young adults, the American Heart Association confirms that the incidence of stroke in men is 62.8 per 100,000, while in women it is 59 per 100,000, suggesting that this comorbidity affects men greater than women.[8,32]

Pathophysiology of Ischemic Stroke

The ischemic stroke cause is the occlusion of a cerebral artery, which leads to a lack of oxygen, glucose, and lipids and thus to necrosis of the brain parenchyma. However, the exact pathophysiology of ischemic stroke is complex and not yet fully understood.[34,35] In general, the ischemic cascade is stimulated by a series of physiological and molecular events, mainly related to neuroinflammation and oxidative stress.[19]

It is important to emphasize that the epicenter of ischemia, the so-called ischemic core, is the central region where blood flow has been interrupted and where cells (neuronal and glial), blood vessels (arteries, veins, and capillaries), and nerve fibers have undergone necrosis.[36] In addition to the central region, there is a transitional area, the so-called ischemic penumbra, in which the intermediate reduction in local cerebral blood flow causes the death of nerve cells through apoptosis.[37]

By the complex stroke pathophysiology, studies of the disease pathogenesis are based on the mechanisms underlying the lesions caused by ischemic stroke, that is, the pathophysiology is a progressive and systemic response to brain injury. Therefore, it is possible to highlight the main mechanisms that composes the basis for the occurrence of a cascade of pathological events. First, one of the most direct causes of neuronal injury in general is the loss of neurons caused by ischemia and infarction. Regarding these mechanisms, studies have focused on regeneration and neuroprotection processes as well as molecular signaling pathways and corresponding biomarkers.[38,39] Second, the vasoconstriction caused by ischemia generates excessive reactive oxygen and nitrogen species (ROS/RNS) that lead to oxidative stress, exacerbate neuronal damage, and result in significant functional deficits. The pathways that respond to and attenuate oxidative stress are being extensively studied to reduce neuronal damage. Ischemia-induced inflammation is another factor leading to further neuronal damage after ischemic stroke. Therefore, effective control of immune responses may help to reduce neuronal damage.[40]

A cascade of physiological events is triggered and contributes to irreversible cellular damage.[41,42] During the first minutes of hypoxia resulting from I/R injury, cellular energy is insufficient due to the lack of adenosine triphosphate (ATP),[43] production, mitochondrial damage, and activation of caspases.[44] Failure of Na+/K+-ATPase pumps and an increase in calcium influx (Ca^{+2}).[45] As a result, there is a homeostasis loss and ischemic depolarization as well as the release of excitatory neurotransmitters such as glutamate, which are responsible for a further increase in intracellular Ca^{+2} levels.[46] In addition, the mitochondria exhibit dysfunction due to Ca^{2+} accumulation. Mitochondrial damage allows the release of cytochrome C and the generation of ROS, which activates caspase-dependent cell death pathways.[47]

Thus, cell death is responsible for the release of damage-associated molecular patterns (DAMPs) that stimulate cellular receptors such as the Toll-like receptors.[48] This creates a cellular stimulus to produce proinflammatory mediators such as interleukins (IL)−1β, IL-6, tumor necrosis factor alpha (TNF-α), and chemokines.[49]

Although the reperfusion process is essential for cell survival, the restoration of O_2 associated with cellular damage events related to ischemia leads to increased production of ROS and RNS.[50,51] In addition to oxidative damage, ROS/RNS in turn activate

matrix metalloproteinases, which are responsible for the extracellular matrix proteins degradation. This leads to permeability changes in the BBB and makes the brain susceptible to inflammatory cells presence from the periphery.[51,52]

Since the ischemic brain inflammation is triggered by the infiltration and subsequent activation of immune cells,[53] the immune system plays an important role in determining the condition of the brain and the survival of individuals after ischemic stroke.[54–56,62]

Therefore, by reason of cerebral artery injury, the ischemic tissue follows a series of secondary events after occlusion, including vascular, cellular, and molecular changes.[66] In general, the resulting interruption of blood flow consequences are diverse and depend on the brain region affected. They lead to the death of the individual or to chronic consequences, which are usually complex and heterogeneous. This situation can lead to problems in various functional areas, such as the ability to carry out everyday activities, to learn and apply knowledge, in communication, in mobility, in self-care, in domestic life, and in interpersonal and social interaction. Even if some people experience a short-term improvement, in most cases sensory, motor, and cognitive impairments can persist in the long term and be associated with dementia, anxiety, and depression.[57,58,67–69]

Neuroinflammation and Peripheral Immunosuppression After Ischemic Stroke

As already described, blood flow to the brain is severely reduced in an ischemic stroke. In a cerebral infarction, where the blood flow is 10–25% below normal, the nerve cells are irreversibly damaged and even die. As a result, the tissue's defense cells release inflammatory factors, meaning the injured regions attract inflammatory cascades to try to repair the damage and restore the injured area. However, it all depends on the severity of the injury, the size of the infarct, and the affected area, where the harmful cascades often outweigh the recovery processes, disrupting the balance of the cellular microenvironment and leading to the activation of harmful signaling pathways.[64,66,70]

Neuroinflammation and oxidative stress are the most important and critical pathological processes in ischemic stroke, and their relationships mediate neuronal damage, BBB damage, and conversion to hemorrhagic stroke.[33] Inflammatory and immune cells are important in the progression of the disease. The energy deprivation and hypoxia that occur after acute cerebral ischemia not only activate the brain immune system but also lead to infiltration and accumulation of peripheral immune cells. Diapedesis of peripheral cells into the central nervous system (CNS) is controlled by the BBB and regulated by immune and endothelial cells.[71,72]

Focal cerebral ischemia can trigger widespread and dynamic activation of inflammatory cytokines (TNF-α, Interferon gamma - IFN-γ, IL-6, and IL-2), chemokines (Monocyte Chemoattractant Protein 1 - MCP-1, Macrophage Inflammatory Protein 2 - MIP-2, Interferon-gamma Inducible Protein 10 - IP-10), and chemokine receptors (Chemokine Receptor 1 - CCR1, CCR2, CCR7, and CCR8) in the peripheral immune system. Cytokines coordinate and interact with each other to complete functions of hematopoiesis and immune regulation. In addition, they play a very important role in the transmission, activation, and regulation of information from immune cells and mediate the activation, proliferation, and differentiation of T and B cells in the inflammatory response. These cytokines and chemokines are mainly directed against resident microglia and infiltrating leukocytes.[59,63]

Thus, many immune cells such as macrophages, monocytes, natural killer cells, dendritic cells, and lymphocytes are involved in the ischemic brain injury process.[33,60,70] Also in this phase, microglia activation induces the expression and activation of TNF-α, IFN-γ, and IL-6 and promotes the recruitment of circulating neutrophils, monocytes, and lymphocytes from the CNS.[73] Consequently, the inflammatory response promotes a crucial role in the development of an ischemic stroke, which significantly exacerbates brain damage and causes severe brain dysfunction.[74]

Cytokines are notably important in the modulation of the immune system developing a pivotal role in the process of cell activation, differentiation, and proliferation. Cytokines, which have a proinflammatory effect, are directly linked to the processes that take place in brain tissue. By the reason of this complicated multistep pathway, they can both increase cell traffic and cause additional damage.[8,75]

Since microglia are the first cells to be recruited to the lesions in ischemic stroke, they are the most important immune cells in the brain parenchyma. Their main secreted proinflammatory cytokines are

IL-1β, IL-6, and TNF-α. Increased systemic inflammation associated with stroke and risk factors is mediated in part by IL-1. In the acute phase, the increase of IL-1β in the brain after ischemic stroke affects the harmful inflammatory process and also contributes to the positive regulation of IL-6, TNF-α, and chemokines in astrocytes, increase in leukocyte infiltration and adhesion molecules, inhibition of neurogenesis, decrease in blood flow through the action of endothelial cells, and decreased BBB integrity, leading to worse outcomes. In addition, IL-1β also stimulates the activation and proliferation of astrocytes, leading to astrocyte hyperplasia, which is a typical response to brain injury. Thus, IL-1β is considered one of the most potent proinflammatory cytokines in ischemic strokes.[61,70]

Another cytokine considered extremely important is IL-6, whose elevation due to ischemia and hypoxia, oxidative stress, vascular occlusion, and inflammation leads to the production of acute phase proteins in the liver, stimulating the recruitment of leukocytes and causing thrombosis, which leads to numerous cardiocerebrovascular diseases, most notably ischemic strokes.[76] Therefore, IL-6 is being studied as a high-yield marker of poststroke inflammation. When elevated, it is mainly secreted by neurons, microglia, astrocytes, and endothelial cells in the ischemic hemisphere, but is considered a predictive factor for the prognosis of ischemic stroke. High serum levels of IL-6 are consequently associated with a higher risk of ischemic stroke.[77,78]

In addition to the ischemic stroke studies, there is the cytokine IL-10, which has been extensively studied as an anti-inflammatory cytokine, evidencing significant effects on patients, with its inhibitory effect on immune cells playing an essential role in the damage caused by ischemic stroke and helping to protect against cerebral ischemia, as its action reduces inflammation and limits apoptosis through association with IL-10 receptors. Therefore, lower levels of IL-10 are associated with poor stroke outcomes.[79–81]

TNF-α, a proinflammatory cytokine, is one of the cytokines being investigated and researched in ischemic stroke studies. In stroke patients, activated microglia and astrocytes release high levels of TNF-α, which is considered toxic because it negatively affects synaptic transmission and plasticity in learning and memory processes, which is the central symptom of these patients. Elevated TNF-α levels are therefore associated with greater neurological deficits and poorer outcomes in the treatment of patients with ischemic stroke, suggesting another risk factor marker in these patients as well as a biomarker for survival.[82–84]

Regarding oxidative damage, free radicals, including ROS/RNS, play a crucial role in reperfusion injury and cerebral ischemia. The brain is considered the largest producer of free radicals in the entire body, as it consumes more oxygen than any other organ, namely, 20% of the entire body's oxygen consumption. Increased production of ROS and RNS by brain tissue leads to the activation of cell signaling cascades that contributes to increased BBB permeability, cerebral edema, hemorrhage, inflammation, and neuronal death.[17,85]

The most important and damaging ROS include the superoxide anion (O_2^-), hydroxyl radicals (OH^-), and hydrogen peroxide (H_2O_2). The excess production of ROS in the initial phase of ischemic stroke originates mainly from the mitochondrial respiratory chain but may also originate from other metabolic pathways. When the blood flows back, a lot of oxygen arrives, which accelerates oxidative damage. It is also known that oxidative stress can activate proapoptotic signaling pathways such as the cytochrome c pathway, leading to DNA damage, changes in protein structure and function, and lipid peroxidation during I/R.[50,86–90]

Hemorrhagic transformation, which is strongly related to the integrity of the BBB, and cerebral edema are the main complications caused by revascularization, and the damage caused by oxidative stress is closely related to these complications. Therefore, neuroprotection is considered a common strategy for the treatment of ischemic stroke, and the development of a neuroprotective and anti-inflammatory agent is currently the focus of many studies. Furthermore, the mechanisms of the ischemic cascade induce peripheral immunosuppression with deleterious effects on the individual.[5,91–93]

There is increasing evidence that the CNS and the immune system are two closely linked systems.[97–99] Such functional interaction may be a pathway for the occurrence of immunological manifestations as a consequence of CNS injury and vice versa.[100,103] Similarly, the occurrence of systemic infection following acute brain injury may be a symptom of reduced CNS-mediated immunocompetence, as has been described in people with brain tumors, epilepsy or traumatic brain injury.[95,101,102]

In this sense, inhibition of immunity, which is considered a major infection cause in individuals after ischemic stroke, is characterized by lymphopenia and impaired monocyte function, leaving the individual susceptible to a variety of pathogens.[94,96] Pre-clinical and clinical studies show that monocytes, dendritic cells, and regulatory T cells increase the secretion of IL-10 after stroke, blocking the proinflammatory response.[104]

In addition to the altered mechanisms of immune cells, the sympathetic nervous system (SNS) is also involved in immunosuppression after an ischemic stroke.[104] Hyperactivation of adrenergic nerve endings is considered a mechanism of poststroke immunosuppression, which triggers activation of the SNS and leads to secretion of catecholamines by the adrenal gland and nerve endings in peripheral organs.[105] Catecholamines act on immune cells *via* β-adrenergic receptors, lowering TNF-α and increasing IL-10.[36] Furthermore, stimulation of D1 and D2 receptors by increased dopamine after ischemic stroke leads to a decrease in the expression of nuclear factor kappa B (NF-κB) and consequently to a decrease in the production of proinflammatory cytokines.[106] Such stimulation alters NF-κB activation in a time-dependent manner.[107]

Regarding the hypothalamic-pituitary-adrenal axis and the involvement of its activation in poststroke immunosuppression, it is known that the production of proinflammatory cytokines can be recognized by the hypothalamus, leading to excessive secretion of glucocorticoids after ischemic stroke.[108] Glucocorticoids may impair the functionality of T cells (reducing the production of IFN-γ and inducing apoptosis) and monocytes (promoting the secretion of IL-10). These effects may explain the lymphocyte apoptosis and lymphopenia observed after ischemic stroke.[109]

Another important immunosuppression mechanism is the stimulation of the vagus nerve in the modulation of cerebral and systemic inflammation through the release of noradrenaline and the activation of the cholinergic anti-inflammatory pathway.[110] This stimulus occurs through the action of the efferent vagus nerve on the α7 nicotinic acetylcholine receptor (nAChRα7), which is stimulated after ischemic stroke.[111] In this sense, alveolar macrophages and alveolar epithelial cells express α7nAChR,[112] and this peripheral immunological stimulus can alter the immune response in lung tissue.[113]

It is also known that in stroke, cells in the hypoperfused area become necrotic, release DAMPs such as High Mobility Group Box 1 (HMGB1), induce the expansion of a subpopulation of monocytes with an M2 profile, and contribute to the immunosuppressive state in the subacute phase of ischemic stroke, predisposing individuals to pneumonia.[114,115] Genetic or pharmacological blockade of signaling through the receptor for advanced glycation end products, one of the HMGB1 receptors, reversed cellular immunosuppression and restored lymphocyte activation in the subacute phase after ischemic stroke, according to an experimental study.[65] It has also been postulated that ischemic stroke-induced immunosuppression may be an adaptive response to acute brain injury, as systemic immunosuppression may limit inflammation in the brain or reduce the occurrence of autoimmune responses against neuroantigens.[116]

Finally, the susceptibility to infections after a stroke could be due to an impairment of the gut-brain axis. The intestinal microbiome develops an important role in pulmonary infections pathogenesis after ischemic stroke. In an experimental mouse model of stroke, pulmonary inflammation occurred in mice free of specific pathogens. Ischemic intestinal permeability and barrier dysfunction were shown to precede the dissemination of bacteria into peripheral tissues that were orally inoculated.[117] Mice with antibiotic-induced depletion of the gut microbiota exhibit increased bacterial proliferation, inflammation, and mortality, and their alveolar macrophages show a reduced ability to clear pathogens from the lungs.[118] Given the countless possibilities of infections and complications after a stroke, it is necessary to develop therapies that have a positive effect on the entire ischemic cascade. In addition, the endocannabinoid system (ECS) has been increasingly researched and unprecedented discoveries have been made in this field.[119–121]

The ECS and Its Role in Neuroinflammation

The ECS is characterized by a complex biological and molecular system, which was discovered in 1988 by scientists Allyn Howlett and W.A. Devane. However, this system was only discovered and researched because in 1964 the scientist Raphael Mechoulam succeeded in determining the structure of tetrahydrocannabinol (THC), the most important psychoactive phytocannabinoid. Only after this discovery the

impetus for studying and researching this ECS raised up.[122,123]

The ECS is an intercellular communication system that plays a fundamental role in the regulation of numerous physiological processes, such as memory, inflammation, nociception, synaptic transmission, appetite, thermoregulation, and others. Consequently, this system and the elements that make it up, such as receptors, endogenous ligands, and synthesis and degradation enzymes, promote a fundamental role in neurotransmission, the endocrine and neurological systems.[124,125]

Cannabinoids can be divided into three categories, namely, endocannabinoids, phytocannabinoids, and synthetic cannabinoids.[126] The ECS refers to the cannabinoid receptors CB1 and CB2. These receptors are activated by endogenously produced cannabinoid ligands, so-called endocannabinoids, and their biosynthetic and degradative enzymes. Endocannabinoids consist mainly of arachidonoylethanamide or anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Biosynthetic and metabolic enzymes include fatty acid amide hydrolase and monoacylglycerol lipase. The receptors are also activated by phytocannabinoids and synthetic cannabinoids.[122,127–129] It is important to emphasize that most ECS components are multifunctional. Therefore, it is not a discrete and isolated system, but the ECS influences many other signaling pathways and it is influenced by them.[130,131]

CB1 receptors (CB1Rs) mediate the cannabimetic effects of THC and are highly expressed in presynaptic neurons in the CNS where they modulate the release of neurotransmitters, in addition they are also expressed in glial cells.[132] CB2 receptors (CB2Rs) are mainly expressed in immune cells, but also by CNS cells such as microglia, astrocytes, and oligodendrocytes. And it has recently been discovered that CB2 is also present at high levels in the brain, just as CB1 is also present in the periphery. Both can be stimulated even when they are not activated.[125,133]

This class of cannabinoid ligands, the endogenous cannabinoid system, acts mainly to modulate pain. In chronic pain, such as in patients with fibromyalgia, there is involvement of the ECS, which has been reported preclinically and clinically, and for which cannabis and cannabis-based medications show promising effects, although more in-depth studies are needed.[134]

Studies show that CB1R inhibition exerts a neuroprotective effect in animal models ischemic stroke such as middle cerebral artery occlusion (MCAO), just as CB1-deficient animals show a reduction in neuronal death. Conversely, CB2R agonism has also been shown to exert a neuroprotective effect in MCAO and to contribute to the reduction of infarct volume in stroke. Its antagonism causes the opposite of the neuroprotective effect by reducing the number of neurons and leading to a sensorimotor deficit.[135]

Under physiological conditions, the expression of CB1 in the brain is low, but under pathological conditions, such as ischemic stroke, this expression is positively regulated at the brain level. ECS is present in the cerebral microvascular endothelium. Likewise, expression of CB1 and CB2 is found in microvascular endothelial cells, by that it is involved in the regulation of the BBB. Among the various functions of ECS, its effect on the CNS stands out, including the modulation of synaptic plasticity, pain transmission, and regulation of neurotransmission in neurons.[136,140] The presence of cannabinoid receptors in astrocytes and oligodendrocytes has also been demonstrated. Like other CNS cells, astrocytes and oligodendrocytes undergo significant morphological, molecular, and functional changes after an ischemic event and can be shaped and regulated by the activation of cannabinoid receptors.[152,153]

Microglia consists of robust ECS, CB2Rs are also more abundant in microglia and there is an increase in these cells in inflammatory conditions. In addition to the studies in animals, treatment with reserpine in an animal model of Parkinson's disease (PD) resulted in reduced expression of CB1R in the striatum.[129,141] In a sepsis model in rats administered *N*-oleoyl-dopamine, an endocannabinoid agonist of the transient vanilloid receptor potential - TRPV, it induced an anti-inflammatory response and reduced proinflammatory responses.[142] Administration of the CB1 receptor inhibitor AM251 was shown to reduce the number of damaged neurons in the acute phase of an animal model of epilepsy.[143]

In a model of CNS injury induced by endothelin-1A and endotoxemia, pretreatment with the CB2R agonist HU308 showed a significant reduction in the extent of brain injury compared with untreated animals.[145] Other pre-clinical studies have investigated the link between CNS injury amelioration and the role of cannabinoid receptors, which show neuroprotective and anti-inflammatory effects upon CB2R activation.[137–139]

ECS modulation may have beneficial effects in both early and late poststroke phases, just as ECS may be

involved in the immunological consequences following CNS injury.[146] In a model of hypoxia-ischemia (HI) in neonatal rats, the use of URB447, a synthetic cannabinoid, was shown to reduce HI-induced brain damage.[147] In an MCAO model designed to study the interaction between CB2R and brain inflammation, animals were pretreated with the CB2R agonist AM1241, which resulted in a decrease in brain inflammation and infarct size and a positive effect on neurological deficits, although delayed treatment has not been shown to be sufficient to achieve such results.[148,149]

On the contrary, there are several risk factors for ischemic stroke that are related to endocannabinoid signaling. In insulin-resistant obesity, an inflammatory insult associated with the occurrence of ischemic stroke, AEA and 2-AG levels are elevated in obese individuals compared with normal weight individuals, and obese women have higher AEA and 2-AG levels compared with their control groups.[144]

Use of Phytocannabinoids in Therapy for Ischemic Stroke

In recent years, many studies have been conducted to explore the therapeutic principles of *Cannabis sativa* in various experimental systems and in several clinical trials.[154,155] Although cannabis is rich in diverse and interesting phytochemicals, it was largely ignored by researchers in the past because it was classified as a narcotic and access for research purposes was restricted. However, it was not until after the 1990s, when the ECS was discovered and the signaling pathways responsible for physiological homeostasis were demonstrated, that researchers began to gain incentive and acceptance for the subject.[156]

Recent changes in cannabis regulations around the world have sparked renewed interest in the plant for medicinal purposes. Numerous clinical trials are being conducted to investigate its therapeutic potential. Even the cannabis being known for many years, it is only recently that studies on this plant have gained the prominence it deserves in the scientific and medical community due to its positive potential. Its active compounds have a variety of effects on the CNS, making them promising alternatives for psychopharmacological use in the treatment of many neuropsychiatric disorders.[150,151,157–160]

To improve and better understand the *Cannabis sativa* plant, there are more than 550 chemical compounds in it, with more than 140 phytocannabinoids (cannabinoids found in the *cannabis* plant) identified. *Cannabis sativa* also contains aromatic terpenes, of which more than 100 have been identified. Cannabis and its constituents have been shown to be therapeutic agents in numerous conditions, such as pain, anxiety, epilepsy, nausea and vomiting, post-traumatic stress disorder, and numerous neurodegenerative disorders, including ischemic stroke.[6,155,156,161–163] However, the role and importance of most compounds in disease is not yet fully understood. Research to date has focused on the two main cannabinoids in cannabis, THC and CBD.[155,164,165]

THC is the main psychoactive constituent of the plant, and these effects result from THC's activity as a partial agonist of the CB1 receptor. Its effects affect behavior, nociception, and appetite, and it also has anti-inflammatory, antitumor, and antiemetic properties. This substance is also responsible for psychotropic effects and addictive properties.[166,167]

CBD is an abundant component of the *Cannabis sativa* plant. It makes up around 40% of the plant's active substances and is the most important nonpsychotropic active ingredient. CBD has been extensively studied for its anti-inflammatory, immunomodulatory, and analgesic properties, sometimes dependent on the activation of CB1 and CB2 receptors, but also independent of the activation of these receptors.[126,168,169]

Treatment with cannabinoids has been suggested in some studies as a possible way to positively influence changes after ischemic stroke and improve neuroinflammation and other neuropathologies. Activation of CB1 and CB2 receptors attenuates BBB rupture, reduces cerebral edema and infarcted tissue volume, and improves cerebral microcirculation, thereby improving neurological function.[135,161,170–172] The potent anti-inflammatory profile of cannabinoids appears to be one of the most consistent mechanisms leading to injury reduction and neuroprotective and neuroreparative effects, through actions acting on resident, vascular, and peripheral cells.[173,174] Another advantage of cannabinoid treatment is its ability to be a highly lipophilic drug and to pass quickly through the BBB.[175]

By having a broad profile of action, with activities not only within the endocannabinoid neuromodulatory system, but at multiple molecular sites with potential targets for cannabinoids, such as in all major cellular elements related to the control of neuronal survival (e.g., neurons, astrocytes, resting and reactive

microglia, oligodendrocytes and oligodendrocyte progenitor cells, and neural progenitor cells) and also in key brain structures such as the BBB, cannabinoids have neuroprotective benefits, and this multiplicity of molecular sites enables that a single cannabinoid (or a combination of cannabinoids with different profiles) may reduce excitotoxicity by acting *via* CB1R, reduce the toxic impact of reactive microgliosis by acting *via* CB2R, or increase trophic and metabolic support of neurons by acting *via* CB1 or CB2.[172,176–178] These effects may also include effects through mechanisms that do not involve cannabinoid receptors/enzymes, but interactions with transcription factors, for example, Nrf-2 and NF-κB.[172]

Thus, these compounds exert their biological effects in different ways and by interacting with a variety of receptors, such as those already described, but also with a number of other non-cannabinoid receptors, including peroxisome proliferator-activated receptors, G protein-coupled receptors (GPR55, GPR3), and ion channels. The ability of phytocannabinoids to bind to these types of orphan G protein-coupled receptors has been suggested as an important pathway for cannabis in the context of its use as an alternative treatment for a number of diseases, including chronic pain, nausea, epilepsy, anxiety, multiple sclerosis (MS), Alzheimer's disease (AD), and PD.[179] In AD, a reduction in astrocytic reactivity, neuroinflammation, memory loss, and cognitive scores has already been observed in pre-clinical studies, while in PD a reduction in cell death of dopaminergic neurons and neuroinflammation associated with recovery has been observed. In addition, studies in MS also describe a reduction in neuroinflammation as well as a decrease in lymphocyte infiltration in the CNS and the severity of spasticity.[180]

Furthermore, phytocannabinoids also have effects that reduce oxidative stress and attenuate inflammatory effects. In this sense, CBD seems to be the main player, considering that although many studies have shown the beneficial effects of THC in various conditions, including aging, the adverse symptoms mainly related to the euphoric effects of THC have drawn a significant amount of research and attention to CBD.[181]

CBD has been shown to affect the redox balance by altering the level and activity of oxidants and antioxidants. Like other antioxidants, CBD interrupts free radical chain reactions by scavenging them or converting them into less active forms. The free radicals generated in these reactions are characterized by numerous resonance structures in which unpaired electrons are mainly found in the phenolic structure, suggesting that the hydroxyl groups of the phenolic ring are mainly responsible for the antioxidant effect of CBD.[182]

In a comprehensive meta-analysis, cannabinoids have been proposed as promising neuroprotective agents for the treatment of stroke, reducing infarct volume and increasing cerebral blood flow.[183] The main advantage of cannabinoids in neuroprotection is their broad spectrum of action on multiple cellular and molecular mechanisms involving not only the ECS itself but also the immune system. Cannabinoids can limit excitotoxicity, oxidative stress, and neuroinflammation and increase trophic and metabolic neurons support by acting through specific signaling pathways mediated by cannabinoid receptors or by direct interactions with transcription factors.[184,185]

The cannabinoids that had a positive effect in these models included phytocannabinoids such as Δ9-THC, which binds not only to CB1R and CB2R but also to CBD, which has no affinity for these receptors but is highly effective against cerebral ischemia. In most cases, the benefits of these cannabinoid-related compounds administered after the cytotoxic insult included improvement in neurological performance, reduction in infarct size, edema, BBB dysfunction, inflammation and gliosis, and control of immunomodulatory responses, and included activation of CB1R and/or CB2R.[172] Similarly, cannabidivarin and cannabigerol, two phytocannabinoids, have recently been shown to protect against oxygen and glucose deprivation/reoxygenation (OGD/R) in human endothelial cells, astrocytes, and pericytes, the various cells that form the BBB. Overall, the evidence to date suggests that modulation of astrocyte function/reactivity with cannabinoids could be used as a possible therapeutic approach to limit/interrupt neurotoxic processes or promote recovery mechanisms in ischemic stroke.[124]

In a pre-clinical study, treatment with CBD in ischemic mice was shown to prevent cognitive and emotional deficits, in addition to reducing neurodegeneration in the hippocampus, white matter injury, and glial response, which simultaneously increased brain-derived neurotrophic factor (BDNF).[187] It was noted that the neuroprotective effects of CBD after stroke may be a consequence of inhibition of N-methyl-D-aspartate (NMDA) receptor activity by antagonist-

like activity at the sigma-1 receptor to reduce the cellular effects of excessive glutamatergic activity.[188] CBD increased cerebral blood flow during the ischemic period. In addition, CBD was shown to suppress a decrease in cerebral blood flow due to cerebral microcirculatory failure for 1 h after reperfusion. CBD has been shown to have neuroprotective properties when administered long after cerebral ischemia. Thus, repeated treatment with CBD from the first or third day after stroke onset improved functional deficits, survival rates, and ischemic damage. The neuroprotective effect of CBD depended, at least in part, on the activation of the TRPV2 channel.[189]

Interestingly, it was found that after OGD, TRPV2 channel expression in CA1 pyramidal neurons decreased significantly and CBD prevented this effect, whereas THC did not. However, qualitative analyzes showed that OGD increased TRPV2 channel expression in microglial cells, which changed their morphology and became activated phagocytic and rod-shaped microglia. CBD prevented all these effects, whereas THC did not.[190]

In a recent study in which CBD was used to treat ischemic strokes in rats, it was shown that the treatment could reduce infarct volume and alter the levels of many enzymes such as catalase, superoxide dismutase and lipid peroxidation, and apoptosis.[191] CBD also was able to reduce brain damage after a stroke, with the neuroprotective effect of CBD being maintained in the long term. The treatment resulted to functional recovery in the motor and sensory areas.[192] In an animal model of bilateral common carotid artery occlusion, CBD was able to reduce microglial and astroglial cell-mediated inflammatory responses.[187,194] In addition, another recent study using MCAO model of ischemic stroke has shown that CBD is able to exert a protective effect in the subacute phase and enhance its potent anti-inflammatory property (Fig. 1).[195]

However, when it comes to research on cannabinoids and stroke, studies are sparse and often inconclusive, thereby this article is a promising and important piece of research for the current scientific community. Furthermore, it is important to consider different dosages, routes of administration, and formulations as part of the treatment before denying the effect of CBD and other phytocannabinoids on any pathology. Elucidating the mechanisms involved with these compounds in various pathologies opens the door for future therapeutic interventions. In-depth studies are needed to understand how phytocannabinoids work as part of a treatment for a specific disease and to find a promising future application.

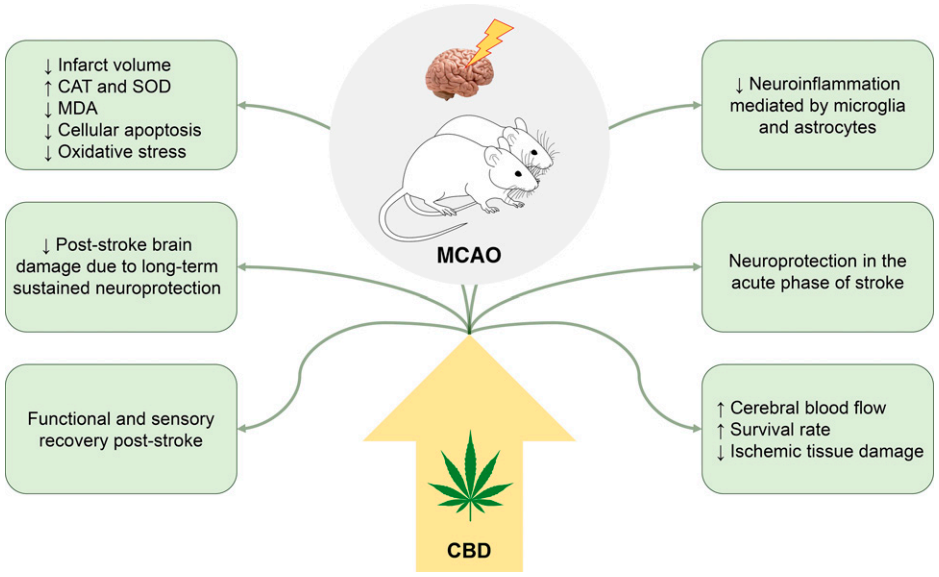

FIG. 1. Cannabidiol (CBD) showed neuroprotective properties as measured by oxidative parameters. CBD treatment after stroke led to an improvement in functional deficits, survival rates, and ischemic damage.

Conclusions

Given the high rate of hospitalization and death in patients who suffer an ischemic stroke, and despite tremendous progress in understanding the consequences of this inflammatory ischemic cascade, existing therapies are still limited and often unsuccessful in the short and long term. Considering this, understanding new pathways that intervene in the inflammatory process and improve the neurological condition of these patients is becoming increasingly important and relevant from a scientific perspective. Thus, cannabinoid therapy has the potential to improve patients overall, accompanied by results that could help to reduce mortality and the consequences of stroke.

There is ample evidence for the involvement of the ECS in the pathophysiology of ischemic stroke. However, although many studies have investigated the beneficial effects of THC or CBD, few have focused on the effects of the full-spectrum cannabis plant (full-spectrum extract). Since this plant produces a broad spectrum of cannabinoids, terpenes, flavonoids, and other bioactive molecules that likely contribute to the various biological effects, the presence of all these bioactive molecules in cannabis extracts for experimentation is a great interest for current research *in vivo*.[196,197]

Therefore, cannabinoid-based drugs could serve as a new therapy capable of halting neurodegeneration in acute and chronic neurodegenerative conditions, as they are able to normalize glutamate homeostasis, reduce oxidative damage, and attenuate local inflammatory processes.[184],187

In this sense, it is extremely important to provide a review of the involvement of a therapeutic agent in brain alterations in neurodegenerative diseases, especially after ischemic stroke. Given the fact that brain changes and secondary changes in patients who have suffered an ischemic stroke remain a fundamental unanswered question. Thereby, this promising article is to be considered in relation to the use of cannabinoids and their effects, by that new clinical and preclinical research can emerge in the scientific world.

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Authors' Contributions

S.d.S.S.: Concentration, methodology, and writing of the article. R.S.M.: Resources. F.P.: Supervision and administration. All other authors commented on previous versions of the article. All authors read and approved the final article.

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Abbreviations Used

2-AG = 2-arachidonoylglycerol
AD = Alzheimer's disease
AEA = anandamide
ATP = adenosine triphosphate
BBB = blood brain barrier
BDNF = brain-derived neurotrophic factor
CAT = catalase
CBD = cannabidiol
CB1Rs = CB1 receptors
CB2Rs = CB2 receptors
CCR = chemokine receptor
CNS = central nervous system
DAMPs = damage-associated molecular patterns
DAYLY = disability-adjusted life years
ECS = endocannabinoid system
GDP = Gross Domestic Product
GPR = G protein-coupled receptors
HI = hypoxia- ischemia
HMGB1 = high mobility group box 1
IFN-γ = interferon gamma
IL = interleukin
IP-10 = interferon-gamma inducible protein-10
I/R = ischemia and reperfusion
MCAO = middle cerebral artery occlusion
MCP-1 = monocyte chemoattractant protein -1
MDA = malondialdehyde
MIP-2 = macrophage inflammatory protein-2
MS = multiple sclerosis
nAChRα7 = α7 nicotinic acetylcholine receptor
NF-κB = nuclear factor-kappa B
NMDA = N-methyl-D-aspartate
Nrf2 = nuclear factor erythroid-derived 2-like 2
OGD/R = oxygen and glucose deprivation/reoxygenation
PD = Parkinson's disease
SOD = superoxide dismutase
SNS = sympathetic nervous system
RNS = reactive nitrogen species
ROS = reactive oxygen species
THC = tetrahydrocannabinol
TNF-α = tumor necrosis factor alpha
TRPV = transient receptor potential vanilloid
WHO = World Health Organization