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Review

Plant-derived compounds and neurodegenerative diseases: Different mechanisms of action with therapeutic potential☆

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ABSTRACT

Neurodegenerative diseases are a group of disorders characterized by progressive degeneration of discrete groups of neurons causing severe disability. The main risk factor is age, hence their incidence is rapidly increasing worldwide due to the rise in life expectancy. Although the causes of the disease are not identified in about 90% of the cases, in the last decades there has been great progress in understanding the basis for neurodegeneration. Different pathological mechanisms including oxidative stress, mitochondrial dysfunction, alteration in proteostasis and inflammation have been addressed as important contributors to neuronal death. Despite our better understanding of the pathophysiology of these diseases, there is still no cure and available therapies only provide symptomatic relief. In an effort to discover new therapeutic approaches, natural products have aroused interest among researchers given their structural diversity and wide range of biological activities. In this review, we focus on three plant-derived compounds with promising neuroprotective potential that have been traditionally used by folk medicine: the flavonoid quercetin (QCT), the phytocannabinoid cannabidiol (CBD)and the tryptamine *N,N*-dimethyltryptamine (DMT).

These compounds exert neuroprotective effects through different mechanisms of action, some overlapping, but each demonstrating a principal biological activity: QCT as an antioxidant, CBD as an anti-inflammatory, and DMT as a promoter of neuroplasticity. This review summarizes current knowledge on these activities, potential therapeutic benefits of these compounds and their limitations as candidates for neuroprotective therapies. We envision that treatments with QCT, CBD, and DMT could be effective either when combined or when targeting different stages of these diseases.

Introduction

Neurodegenerative diseases (NDs) are a heterogeneous group of complex disorders characterized by progressive degeneration of vulnerable neuronal populations in the central nervous system (CNS). Examples of NDs include Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and many others, each differing in their clinical and neuropathological characteristics. AD is the most prevalent ND, characterized by memory loss and other cognitive impairments associated with the degeneration of hippocampal and cortical regions. The presence of amyloid-β peptide (Aβ) deposits and neurofibrillary tangles of hyperphosphorylated Tau protein are the histological hallmarks of this disease (Erkkinen et al., 2018). On the other hand, PD, the second most common neurodegenerative disease, is distinguished by motor symptoms resulting from the degeneration of dopaminergic neurons in the Substantia Nigra (SN) that project to the striatum. In this case, the distinctive feature is the presence of intracellular inclusions enriched in the protein α-synuclein called Lewy bodies (Erkkinen et al., 2018). MS is an autoimmune demyelinating disease that can affect different regions of the CNS, with diverse symptoms depending on the affected area (Dobson and Giovannoni, 2019).

Although some NDs are associated with genetic alterations as monogenic causes, most cases are sporadic forms, and the exact pathogenesis remains unclear. It has been proposed that in sporadic cases, the

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disease results from a complex multifactorial interaction among genetic, epigenetic, and environmental factors. At the cellular level, several common pathological mechanisms in NDs are known to participate in the cascade of events leading to neuronal death, including metabolic processes and mitochondrial dysfunction, increased oxidative damage, defects in the proteasome system, changes in iron and calcium metabolism, loss of synaptic connections, excitotoxicity, and inflammation (Sanghai and Tranmer, 2023).

NDs represent a significant health problem worldwide, affecting millions of people (Erkkinen et al., 2018). The prevalence and incidence of these diseases rise dramatically with age, and their burden on society is expected to grow substantially in the coming years as the population's lifespan continues to increase (Hou et al., 2019). For example, the World Alzheimer Report estimated that in 2019, there were 50 million people living with dementia (with an estimated 70 % of these cases being AD), with this number projected to increase to 152 million by 2050 (Alzheimer's Disease International World Alzheimer Report, 2019). On top of this, no effective therapeutics have been developed for NDs (Erkkinen et al., 2018). Current therapies aim to alleviate symptoms and/or provide palliative care rather than cure, halt, or slow the progression of the disease. Furthermore, many approved treatments suffer from severe side effects and/or are not accessible to the broader society (Hussain et al., 2018). Therefore, there is an urgent need to develop effective alternative treatments to manage NDs.

Over the last few decades, the therapeutic properties of numerous compounds capable of increasing neuron survival have been investigated, potentially serving as a basis for developing novel neuroprotective interventions. In this context, natural products, mainly derived from plants, have emerged as valuable structures in the search for new neuroprotective drugs due to their diverse mechanisms of action that could impact the various cellular processes involved in neurodegeneration. Historically, natural products have played a key role in drug discovery, with about 50 % of medications approved from 1981 to 2019 having natural origins (i.e. semi-synthetic, mimics of natural compounds and natural entities and derivatives) (Newman and Cragg, 2020). Natural products are structurally "optimized" by evolution to fulfill particular biological functions, including regulating endogenous defense mechanisms and interacting (often competing) with other organisms. Additionally, knowledge related to traditional medicine has been a major input in the investigation of medicinal plants and the production of pharmaceuticals. About 80 % of plant-based medicines are consistent with their original ethnopharmacological functions (Dias et al., 2012). Diverse plant-derived compounds have been reported to exhibit antioxidant, anti-inflammatory, anti-aggregation, anti-cholinesterase, and anti-apoptotic properties, all of which are important in preserving the structure and function of the nervous system (Shoaib et al., 2023). Therefore, the diverse mechanisms of action and the potential of plant-derived compounds to mitigate neurodegenerative processes make them strong candidates for developing neuroprotective therapies. In this review, we will focus on three natural products derived from plants traditionally used in folk medicine and belonging to different classes, with promising biomedical applications: the flavonoid quercetin (QCT), the cannabinoid cannabidiol (CBD), and the psychedelic *N,N*-dimethyltryptamine (DMT) (Fig. 1). These compounds, like other natural products, exhibit a wide variety of pharmacological properties. They exert neuroprotective effects through distinct mechanisms of action, some overlapping, but each demonstrating a principal biological activity: antioxidant for QCT, anti-inflammatory for CBD, and neuroplastic for DMT. We will discuss these actions in the context on NDs and the challenges for their translation of these compounds to the clinic. We envision that treatments with QCT, CBD, and DMT could be effective either when combined or when targeting different stages of these diseases.

QCT antioxidative stress properties in NDs

Several mechanisms have been proposed to contribute to the pathology associated with NDs (Sanghai and Tranmer, 2023). Among these, oxidative stress (OS) is considered one of the leading causes of neuronal damage (Morén et al., 2022). OS occurs when reactive oxygen and nitrogen species (ROS and RNS, respectively) accumulate in cells due to an imbalance between their production and the ability of cellular systems to detoxify these reactive products. OS causes damage to proteins, lipids and DNA, affecting cellular homeostasis and eventually leading to cell death (Valko et al., 2007).

The brain is especially vulnerable to OS due to several factors (Cobley et al., 2018). For instance, it consumes about 20 % of the body's oxygen despite accounting for only about 2 % of the body's weight. This high oxygen demand, needed to support ATP production for brain metabolism, is associated with the generation of ROS as byproducts of oxidative phosphorylation. Additionally, the brain contains high levels of transition metals like iron and copper, which can catalyze the production of ROS through Fenton and Haber-Weiss reactions. Some aspects inherent to the nervous system's function, like the use of calcium transients to release neurotransmitters and the metabolism of some neurotransmitters (e.g., dopamine), are also associated with the generation of free radicals. Compared to other organs, the brain produces more free radicals and has relatively low levels of antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). It also possesses high amounts of polyunsaturated fatty acids that are particularly susceptible to free radical-mediated oxidative damage (Ng et al., 2022).

Moreover, other pathological mechanisms that participate in neurodegenerative diseases, such as mitochondrial damage, neuroinflammation and altered proteostasis, are induced by and promote oxidative stress. All these processes lead to neuronal damage and loss of connectivity (Jellinger, 2010).

Given this, it is not surprising that several lines of evidence indicate that OS is a key contributor to neuronal death in NDs. Compounds capable of counteracting the production of free radicals are proposed as potential neuroprotectants (Morén et al., 2022).

QCT (3,3́,4́,5,7-pentahydroxyflavone) (Fig. 1) belongs to the group of flavonoids, a family of polyphenolic compounds produced by plants as secondary metabolites, serving diverse functions such as pigmentation, UV protection, defense against microorganisms and predators, and signaling between plants, among others (Santos et al., 2017; Mathesius,

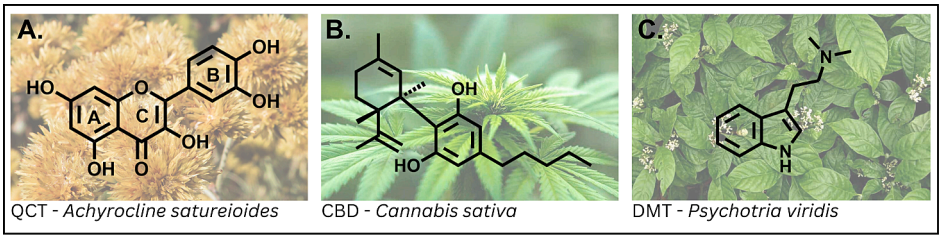

Fig. 1. Molecular structure of Quercetin (QCT) as found in *Achyrocline satureioides* (**A**), of Cannabidiol (CBD) as found in *Cannabis sativa* (**B**) and of *N,N*-dimethyltryptamine (DMT) as found in *Psychotria viridis* (**C**).

2018). Today more than 10,000 flavonoids have been identified, among which, QCT is the most studied. QCT is found in several fruits and vegetables (Sultana and Anwar, 2008) in its glycosylated form (glycone) and has attracted attention because of its potent antioxidant activity (Xu et al., 2019; Zhang et al., 2011), and its ant-iviral (Di Petrillo et al., 2022), anti-cancer (Reyes-Farias and Carrasco-Pozo, 2019); anti-inflammatory (Chiang et al., 2023), and immunomodulatory (Manjunath and Thimmulappa, 2022) properties. Interestingly, in the South American native species of Marcela (*Achyrocline satureioides*), a plant widely used in traditional medicine, QCT is present in high amounts in its free form (aglycone). This particularity has been associated with Marcelás neuroprotective properties in cellular models (Arredondo et al., 2004; Bianchi et al., 2023).

Numerous studies have demonstrated QCT́s neuroprotective actions in the CNS (Dajas et al., 2015). For example, it improved memory deficits and cognitive impairments, and reduced Aβ and Tau pathology in AD models (Zhang et al., 2020; Qi et al., 2020; Yu et al., 2020; Wang et al., 2022). QCT also ameliorated motor behavior alterations and nigrostriatal degeneration in PD́s models (de Oliveira Vian et al., 2024) and reduced demyelination, increased remyelination, and improved locomotor activity in experimental models of MS (Javanbakht et al., 2023). The neuroprotective properties of QCT in rodents were observed when administered in different formulations, routes, treatment schedules, and concentrations (de Oliveira Vian et al., 2024).

As previously stated, QCT has multiple biological activities, but its beneficial properties are mainly attributed to its capacity to counteract OS. Several reports show the ability of QCT to restrict the production of free radicals, reduce the oxidation of biomolecules and increase/restore the levels of antioxidant enzymes, both in experimental cellular paradigms of neurodegeneration (Zhang et al., 2020; Yu et al., 2020; Ansari et al., 2009; Suematsu et al., 2011; Echeverry et al., 2015; Chen et al., 2016; Ho et al., 2022) and in *in vivo* models of NDs (Kanter et al., 2016; Bahar et al., 2017; Li et al., 2019; Madiha et al., 2021; Alaqeel et al., 2022).

QCT does not bind to any specific receptor at the cellular surface, but its lipophilic properties allow the molecule to rapidly internalize into the cytoplasm and nucleus (Arredondo et al., 2010), where it can modulate OS by direct and indirect mechanisms. Structure-activity studies have shown that QCT presents optimal molecular characteristics that make this compound a potent direct scavenger of free radicals: it presents two antioxidant pharmacophores within the molecule, i.e., the catechol group in the B ring and the OH group at position 3 of the AC ring (Fig. 1). In fact, QCT is the most potent direct antioxidant within the flavonoid family and presents a higher free radical scavenger capacity than the standard antioxidants trolox and ascorbic acid (Kim et al., 2002). In the process of scavenging free radicals, QCT oxidizes into products like semiquinone radicals and quinones that have potential pro-oxidant activities (Boots et al., 2008). Such compounds might be involved in another important antioxidant effect of QCT, the activation of the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway (Fig. 2). This pathway is activated upon mild OS, resulting in the translocation of the transcription factor Nrf2 to the nucleus, where it binds to *cis*-acting antioxidant response elements (ARE) and promotes the transcription of over 250 genes involved in diverse processes of cytoprotection (Dodson et al., 2019). Among them, key antioxidant proteins are regulated, including gamma-glutamate-cysteine ligase catalytic subunit,

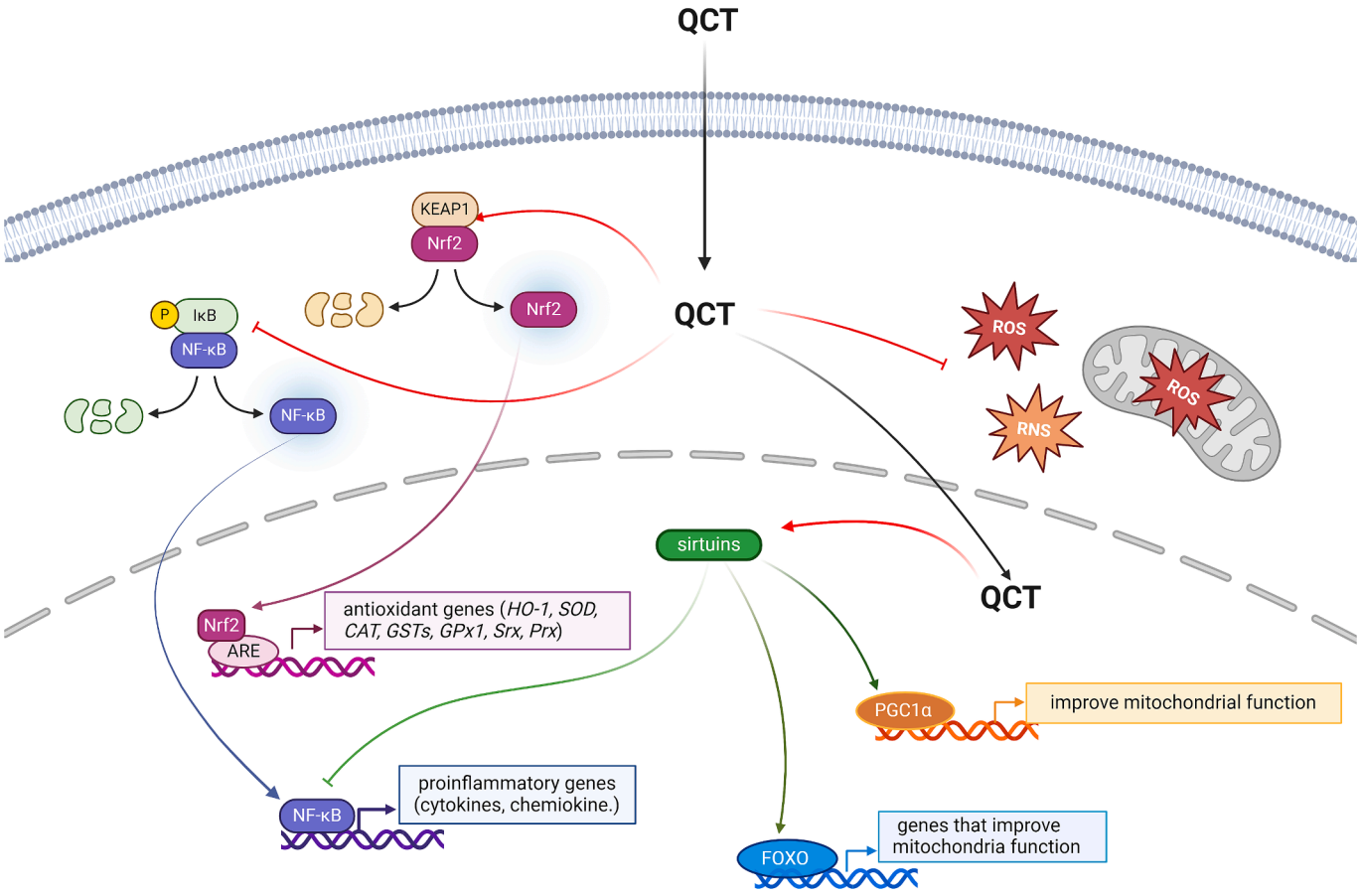

Fig. 2. Schematic representation of the main pathways involved in Quercetin's (QCT) antioxidant properties. ARE, antioxidant response element; CAT, catalase; FOXO, Forkhead box O; GST, glutathione S-transferases; GPx1, glutathione peroxidase-1; HO-1, heme-oxygenase 1; IκB, inhibitor of κB; KEAP, Kelch ECH associating protein 1; NF-κB, Nuclear factor kappa B; Nrf2, Nuclear factor (erythroid-derived 2)-like 2; PGC1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; Prx, peroxiredoxins; ROS, reactive oxygen species; RNS, reactive nitrogen species; SOD, superoxide dismutase; Srx, sulfiredoxin. Created with BioRender.com.

glutathione S-transferases, GPx, heme oxygenase-1, SOD, CAT, sulfiredoxin, and thioredoxin (Saha et al., 2020) (Fig. 2). QCT also modulates other intracellular signaling pathways that might indirectly contribute to its antioxidant properties. For example, it inhibits the activity of nuclear factor kappa B (NF-κB), a potent pro-inflammatory transcription factor (Shi et al., 2013) (Fig. 2). Given that neuroinflammation promotes the generation of ROS and RNS, QCT antiinflammatory action results in reduced OS (Bordt and Polster, 2014). Finally, another target of QCT that has been associated with its antioxidant effects are sirtuins (SIRTs), a family of proteins with histone deacetylase activity that are key regulators of cellular metabolism (Ungurianu et al., 2024). Activation of SIRT1 and 6 by QCT deacetylates certain key cellular effectors like Forkhead box O (FOXO) factors and peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC1α), which potentiate several cellular antioxidant defense mechanisms indirectly, including the induction of the antioxidant enzymes SOD2 and CAT, the improvement of mitochondrial function, the activation of the Nrf2 pathway, and the inhibition of NF-κB (Ungurianu et al., 2024; Singh et al., 2018) (Fig. 2).

Several studies have associated the modulation of these pathways with the beneficial effects of QCT in preclinical models of NDs. For example, in cellular models of neurodegeneration, QCT prevented ROS production, stimulated SIRT1 and Nrf2 pathways, increased the levels of glutathione (GSH) and antioxidant enzymes, and reduced the levels of NF-κB (Yu et al., 2020.; Bahar et al., 2017; Arredondo et al., 2010; Yammine et al., 2020; Mrvová et al., 2015; Han et al., 2021). In *in vivo* studies, QCT neuroprotective effects were associated to the reduction in OS, activation of SIRT1 and Nrf2 pathways and the attenuation of the NF-κB activation (Li et al., 2019; Josiah et al., 2022; Lazo-Gomez and Tapia, 2017; Lin et al., 2022).

In summary, QCT exerts neuroprotective effects by targeting OS through several mechanisms (Fig. 2), and thus, it could be a promising compound for the treatment of NDs.

CBD's anti-inflammatory properties in NDs

Emerging evidence also suggests that inflammation is one of the main factors contributing significantly to NDs progression. Microglial cells play an important role in the healthy brain by serving as the first responders to injury or disease, and they are key mediators in the inflammatory process. (Wendimu and Hooks, 2022). Traditionally, these cells were simply classified into two opposing phenotypes, M1 (pro-inflammatory) and M2 (anti-inflamatory), although today it is known that there is a great diversity of phenotypes (Wang et al., 2023). Generally, microglial cells activate to induce an inflammatory process to clear the threats. In this process, an interplay between pro- and anti-inflammatory factors is key. Under pathological conditions due to persistent stress exposure, exacerbated by the aging process, the pro-inflammatory microglia phenotype predominates leading to long lasting neuroinflammation (Wendimu and Hooks, 2022). This process is at the core of NDs.

Microglia recognizes damage- or pathogen-associated molecular patterns (DAMPs or PAMPs, respectively) through specific receptors such as toll-like receptors (TLRs), scavenger receptors and the cytosolic

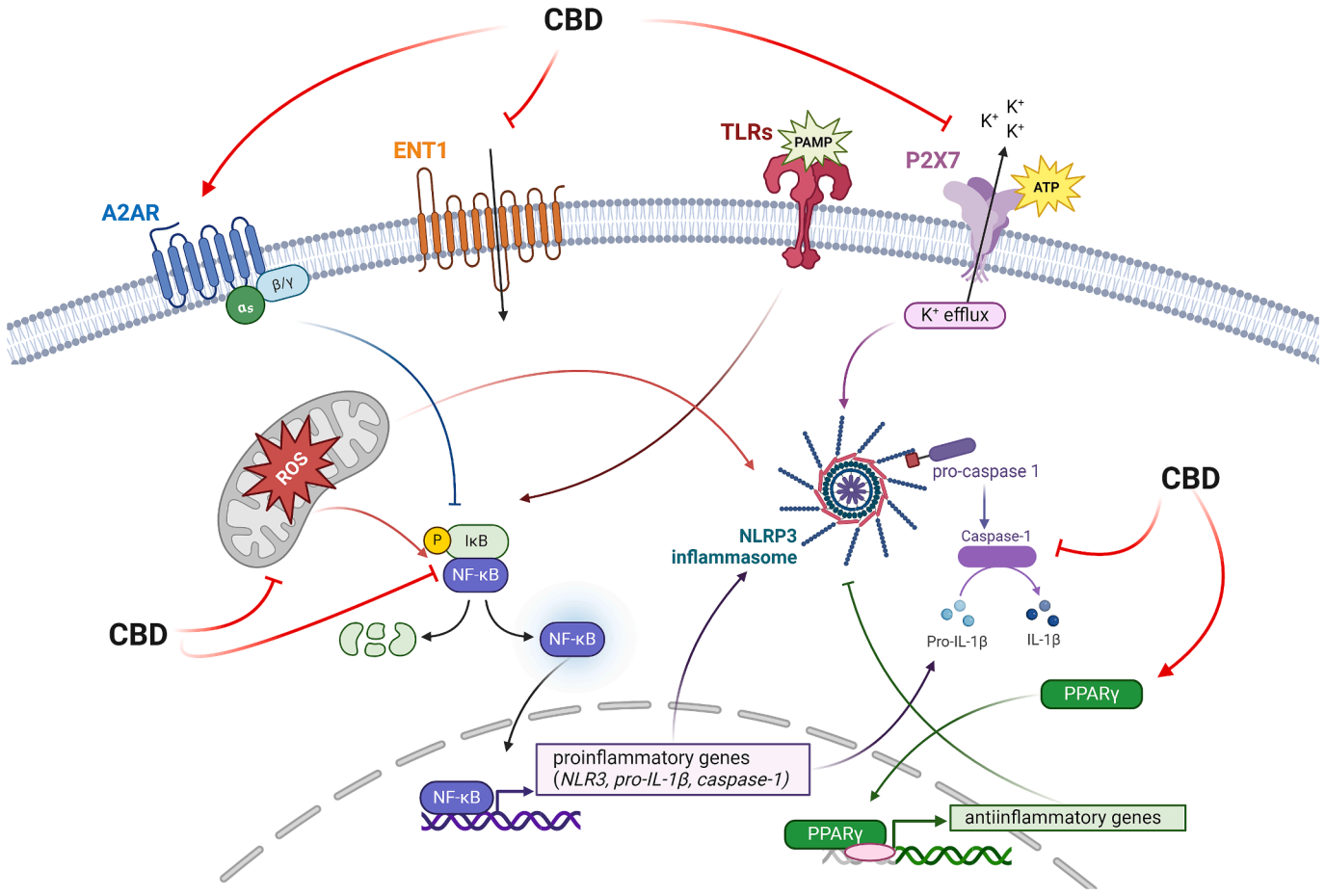

Fig. 3. Schematic representation of the main pathways involved in Cannaidiol's (CBD) anti-inflammatory properties. A2AR, adenosine receptor 2A; ATP, adenosine triphosphate; ENT1, adenosine transporter 1; IκB, inhibitor of κB; IL-1β, interleukin 1 beta; NRLP3, NLR family pyrin domain containing 3; NF-κB, Nuclear factor kappa B; P2X7, purinergic receptor P2X7; PAMP, pathogen-associated molecular patterns; PPARγ, peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; TLRs, toll-like receptors. Created with BioRender.com.

NOD-like receptors (NLRs). TLRs are the most studied but, in the last decades the NLRs, particularly the NLRP3 (NLR family pyrin domain containing 3), have achieved a lot of interest (Chen et al., 2023). NLRP3 is the sensor protein that gives name to the NLRP3 inflammasome, a multiprotein complex that plays a key role in the amplification of the inflammatory response. Its activation is unique in the sense that it involves a two-step process (Fig. 3). The first step implies the activation of the transcription factor NF-κB leading to the upregulation of several anti-inflammatory genes including NLRP3 inflammasome-related ones (i.e. pro-IL-1β, caspase-1, NLRP3) (Yang et al., 2019). This is followed by a second step of activation triggered by DAMPs that induces the oligomerization and activation of the NLRP3 inflammasome. This results in the production and release of the pro-inflammatory cytokines interleukin (IL) −1β and IL-18 by caspase-1, the proteolytic unit of the inflammasome (Chen et al., 2023; Yang et al., 2019). High levels of IL-1β and IL-18 amplifies the inflammatory response by recruiting and activating microglia and astrocytes, which in turn release these and other pro-inflammatory mediators like tumor necrosis factor alpha (TNF-α), IL-6, nitric oxide (NO), and proteases (Kwon and Koh, 2020). These activated cells can be detected in many neurodegenerative conditions and are considered to be crucial for the establishment of a chronic inflammatory environment, leading to neuronal dysfunction and eventually neurodegeneration (Kempuraj et al., 2016; Kwon and Koh, 2020). The central role of NLRP3 inflammasomes in neuroinflammatory response makes it an attractive drug target for NDs.

CBD (2-[(1*R*,6*R*)-6-Isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol) is a primary non-psychotropic terpenophenolic compound isolated from the plant *Cannabis sativa* (ElSohly and Slade, 2005; Echeverry et al., 2021) (Fig. 1). The experience of humanity with this plant has been meaningful and diverse, with evidence of its use dating back to around 1700 BCE (Pisanti and Bifulco, 2019). The plant, originated in Central Asia, was introduced to Latin America in the 16th century, where it has been used for medicinal and recreational purposes. Due to its psychotropic effect, the use of *Cannabis sativa* has been restricted since the 19th century in Latin America, but currently, the policies regarding its use (mainly for medicinal purposes) have become more permissive.

The therapeutic potential of CBD for a wide variety of conditions has been under clinical investigation for several years (Fernández-Ruiz et al., 2013; Campos et al., 2016; Singh et al., 2023; Peres et al., 2018). Regarding NDs, most of the evidence related to its neuroprotective actions has been investigated at the preclinical level (Bhunia et al., 2022; Calapai et al., 2019). For example, CBD has shown to be neuroprotective in several cellular and *in vivo* experimental models of AD, PD and MS (Echeverry et al., 2021; Bhunia et al., 2022; Cassano et al., 2020; Iuvone et al., 2004; Jones and Vlachou, 2020; Mecha et al., 2013; de Viana et al.., 2022; Rieder, 2020; Echeverry et al., 2024). Many of these studies suggest that the effects of CBD arise from the modulation of various signaling molecules, including the endocannabinoid system (ECS) (Ibeas Bih et al., 2015; Echeverry et al., 2023). The ECS is a neuromodulatory system that plays important roles in CNS development, synaptic plasticity, and the response to endogenous and environmental insults. Endocannabinoids exert these actions through the two cannabinoid receptors CB1 and CB2. Most studies have indicated that, although CBD has low affinity for CB1 and CB2 receptors (Pertwee, 2008), it can activate them indirectly by modulating the levels of the endocannabinoids (McPartland et al., 2015). In addition, it has been reported that CBD modulates multiple targets, including transient receptor potential (TRP) channels, adenosine receptors, serotonin receptors (5-HTR) and peroxisome proliferator activated receptors (PPARs) (Ibeas Bih et al., 2015; Echeverry et al., 2023). Particularly, one of the main actions of CBD is its anti-inflammatory property (Leonard and Aricioglu, 2023; Robaina Cabrera et al., 2021), which is proposed to be crucial in CBDs neuroprotective effect. The first report on the potential effect of CBD in neuroinflammation is dated in 2003 and addressed its ability to modulate microglial cell migration *in vitro* (Walter et al., 2003). Several subsequent studies have shown that CBD is capable of restoring neuroinflammatory markers in different *in vivo* models of NDs. For example, CBD decreased neuroinflammation induced by injection of Aβ through downregulating IL-1β, IL-6 and inducible NO-synthase (iNOS) levels in mice (Esposito et al., 2007; Martín-Moreno et al., 2011). In a PD mice model, CBD increased the levels of the anti-inflammatory cytokine IL-10, and decreased the levels of TNF-α, IL-1β and IL-6 and NLRP3 inflammasome components (Wang et al., 2022). In a model of MS, CBD ameliorated motor deficits and reduced microglial activation and pro-inflammatory cytokine production. These effects were partially attributed to the adenosine A2A receptors (A2AR) (Mecha et al., 2013). In this regard, it has been suggested that CBD may modulate A2A receptors through the inhibition of the adenosine transporter 1 (ENT1) which results in the accumulation of adenosine (Carrier et al., 2006).

Regarding the intracellular molecular mechanisms that underlie CBD anti-inflammatory actions, the NF-κB pathway is key. In this sense, CBD decreased the production and release of pro-inflammatory cytokines and other inflammatory mediators from activated glial cells by reducing the activity of the NF-kB pathway (Kozela et al., 2010; Juknat et al., 2016; dos-Santos-Pereira et al., 2020). In line with this, the activation of peroxisome proliferator-activated receptor gamma (PPARγ) by CBD prevents the NF-kB signaling pathway, thus inhibiting the transcription of pro-inflammatory genes and cytokines such as TNFα, IL-1 β and IL-6 (O'Sullivan, 2016; Sonego et al., 2021). Other studies have indicated that CBD also interferes with the second step of the NLRP3 inflammasome activation by attenuating DAMPs levels (Hartmann et al., 2023). For example, it has been proposed that CBD has antioxidant properties (directly or through Nrf2 activation) reducing free radicals levels (Atalay Ekiner et al., 2022). Besides, it can attenuate the signal of damage mediated by adenosine triphosphate (ATP) by inhibiting the purinergic receptors P2X7 (Liu et al., 2020). Finally, CBD can directly inhibit caspase-1, downregulating the production of pro-inflammatory cytokines (Liu et al., 2021) (Fig. 3).

The preclinical findings previously exposed suggest that CBD could provide neuroprotection through attenuation of pro-inflammatory cascades.

DMT's neuroplastic properties in NDs

In recent years, it has been proposed that impaired neuroplasticity is a critical pathological mechanism underlying NDs (Yuan et al., 2020). The term neuroplasticity refers to the brain's ability to change constantly throughout an individual's life, regulating functions like learning, memory, perception, understanding or self-awareness (Arendt, 2004; Toricelli et al., 2021). The cellular events that underlie these adaptive behaviors are morphological or functional changes in neurons and synapses. The main molecular events that drive neuroplasticity are the expression of synaptic proteins and trophic factors, like Brain Derived Neurotrophic Factor (BDNF), which impact at a cellular level by regulating synaptic strength, neurite sprouting (neuritogenesis) and the generation of new nerve cells (neurogenesis) or synapses (synaptogenesis).

Along with non-pathological aging, cognitive functions tend to decline and this can be attributed, at least in part, to changes in neuronal connectivity due to loss of spine density and dendritic branches as well as progressive neuronal loss. However, in NDs these events are exacerbated (Burke and Barnes, 2006; Castelli et al., 2019). Evidence is accumulating that in these diseases, the disruption of neuronal connectivity and loss of synapses may precede the death of neurons (Knight and Verkhratsky, 2010; Taoufik et al., 2018; Wareham et al., 2022). For instance, synaptic deficits in the hippocampus and neocortex is considered an early change and the major structural correlate of cognitive dysfunction in AD, preceding Aβ deposits formation and brain atrophy (Arendt, 2004; Sciaccaluga et al., 2021).

In this context, compounds capable of modulating such neuroplasticity-related events arise as a promising strategy for novel

therapies at early stages of NDs (Yuan et al., 2020; Toricelli et al., 2021; Colavitta and Barrantes, 2023; Smith, 2013).

DMT (2-(1*H*-Indol-3-yl)-*N*,*N*-dimethylethanamine) (Fig. 1) is a tertiary indolealkylamine naturally produced by many plants and animals, including humans (Cameron and Olson, 2018; Dean et al., 2019). It is the psychedelic component of a variety of teas, snuffs and decoctions that have been used for centuries with cultural, religious and medicinal purposes in Latin America (Dobkin de Rios, 1992). Such is the case of Ayahuasca, the ancient beverage traditionally used by indigenous peoples in the Amazon, which in recent years has gained scientific interest given the increasing evidence of its potential therapeutic applications to treat mental disorders (de Osório et al., 2015; Domínguez-Clavé et al., 2022; Palhano-Fontes et al., 2019; Sanches et al., 2016; Zeifman et al., 2021; González et al., 2019; Lafrance et al., 2017; Apud, 2021; Apud, 2020; Barbosa et al., 2018; Fábregas et al., 2010).

Additionally to its subjective psychedelic effects on conscious experience, DMT has shown other effects in the CNS such as antidepressant-like activity (Cameron and Olson, 2018; Cameron et al., 2019), anti-hypoxic/anti-ischemic actions, (Nardai et al., 2019; Szabo et al., 2016; Szabó et al., 2021) and neuroprotective effects (Cheng et al., 2024) evidenced in preclinical models.

The mechanisms that mediate these effects are still not fully understood, but recent evidence links DMT's ability to promote neuronal plasticity-related events to its beneficial effects on brain health. In this regard, Ly et al. reported in 2018 for the first time the neuroplasticity-promoting effects of DMT evidenced by an increased number and length of dendrites in cortical cultures and an increased density in dendritic spines of pyramidal neurons in rats (Ly et al., 2018). They evaluated possible mediators of this effect and found that the tyrosine receptor kinase B (TrkB; the BDNF receptor), the 5-HT_{2A}R and the mammalian target of rapamycin (mTOR) pathway are key (Ly et al., 2018) (Fig. 4).

TrkB stimulation activates at least one of its main intracellular cascades that can modulate neuroplasticity: the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) pathway, or the activation of the phospholipase C gamma (PLCγ) pathway (Chao, 2003; Reichardt, 2006) (Fig. 4). The PI3K/Akt pathway has many downstream targets, one of which is mTOR (Reichardt, 2006; Kumar et al., 2005), a protein kinase that plays a major role in cell growth and synaptogenesis (Hoeffer and Klann, 2010) and upregulates TrkB (Hou et al., 2017). In turn, the Erk could affect neuroplasticity through activation of the transcription factor cyclic AMP response-binding protein (CREB), promoting the expression of genes that are essential for neuronal differentiation and survival (Park and Poo, 2013). Finally, PLCγ pathway leads to CREB activation and calcium signaling through the generation of inositol-1,4,5-triphosphate (IP3) and diacylglycerol (DAG) (Reichardt, 2006).

It is still not clear how DMT modulates TrkB receptor or mTOR pathway, but it has been reported that some psychedelics may be able to directly agonize TrkB, though this has not been addressed for DMT specifically (Moliner et al., 2023).

On the other hand, the 5-HT_{2A}R has been considered central in psychedelic research since the hallucinogenic effect of "classical psychedelics" like DMT has been attributed to this agonistic action (Duan et al., 2024; Nichols, 2004; Nichols, 2016). However, the role of 5-

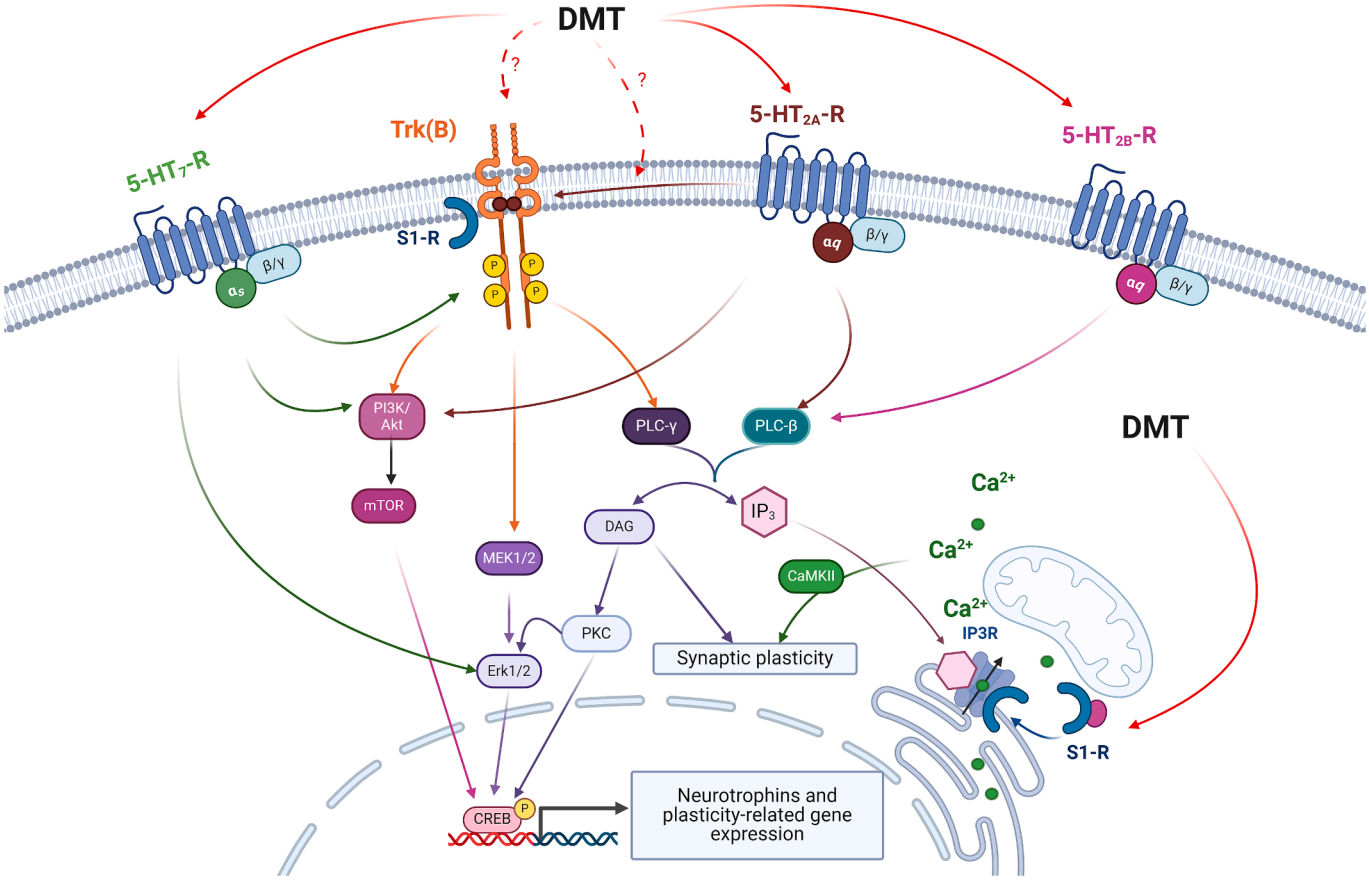

Fig. 4. Schematic representation of the main pathways involved in *N*,*N*-dimethyltryptamine (DMT) neuroplasticity promoting properties. 5-HT_{2A} -R/5-HT_{2B} -R/5-HT_7 -R, serotonin receptors 2A, 2B and 7, respectively; CaMKII, calcium/calmodulin-dependent protein kinase II; CREB, cyclic AMP response-binding protein; DAG, diacylglycerol; Erk1/2, extracellular signal-regulated kinase 1/2; IP3, inositol-1,4,5-triphosphate; IP3R, inositol-1,4,5-triphosphate receptor; MEK1/2, mitogen activated protein kinase kinases 1/2; mTOR, mammalian target of rapamycin; PI3K/Akt, phosphatidylinositol 3-kinase/Akt; PKC, protein kinase C; PLCβ/PLCγ, phospholipase C beta and gamma, respectively; S1R, sigma 1 receptor; TrkB, tyrosine receptor kinase B. Created with BioRender.com.

$HT_{2A}R$ extends to numerous physiological and pathological processes, including learning and memory. The 5-$HT_{2A}R$ could mediate neuroplastic changes through the activation of Akt/mTOR signaling pathway (Kumar et al., 2005; Schmid and Bohn, 2010) and, via phospholipase C beta (PLCβ), through the activation of the Erk/CREB pathway and calcium signaling (Jaggar and Vaidya, 2018; Ueda et al., 1996). In addition, 5-$HT_{2A}R$ activation may upregulate BDNF, and under certain conditions, allosterically modulate TrkB (Chao, 2003; Di Liberto et al., September 2018; Ilchibaeva et al., 2022) (Fig. 4).

Regarding other targets of DMT relevant to neuroplasticity, this psychedelic compound has the ability to agonize the sigma-1 receptor (S1R) (Fontanilla et al., 2009). S1Rs regulate calcium signaling between the endoplasmic reticulum and mitochondria, where it mostly resides, by modulating the IP3 receptor (IP3R) (Fig. 4) and play important roles in brain plasticity (Crouzier et al., 2020; Ishima et al., 2008; Nishimura et al., 2008; Takebayashi et al., 2002; Terada et al., 2018; Moriguchi et al., 2013; Sha et al., 2013). Indeed it has been reported that DMT, through its action on S1R, promotes adult neurogenesis both *in vitro* and *in vivo* (Morales-Garcia et al., 2020). Finally, though no reports were found specifically for DMT, some S1-R agonists upregulate TrkB receptor signaling (Cobos et al., 2009; Ryskamp et al., 2019) and it has been reported that S1-R directly interacts with the TrkB receptor mediating neuronal differentiation of cerebellar granule neurons (Kimura et al., 2013). This provides an additional mechanism by which DMT could modulate neuroplasticity (Fig. 4).

Considering DMT's pharmacology, it is worth mentioning its agonistic action on the 5-$HT_{2B}R$ and 5-HT_7R which could also contribute to its neuroplastic effects. The 5-$HT_{2B}R$ can activate PLCβ, whereas 5-HT_7-R can activate Erk, Akt and TrkB, which have shown to be relevant in neuroplasticity, as previously mentioned (Quintero-Villegas and Valdés-Ferrer, 2022; Wang et al., 2021). Moreover, 5-HT_7-R is highly expressed in the hippocampal neurons, making it an interesting pharmacological target for AD (Quintero-Villegas and Valdés-Ferrer, 2022; Thomas and Hagan, 2004) (Fig. 4).

In spite of the evidence exposed so far regarding DMT and its neuroplasticity-promoting actions, it has been reported that in an AD mouse model DMT impaired neurogenesis (Borbély et al., 2022). On the other hand, DMT has shown S1R-dependent neuroprotective action in a different mouse model of AD (Cheng et al., 2024). As it can be noticed, the research around DMT, its neuroplasticity-related effects and the molecular mechanisms involved is new and growing consistently. Hence it should not surprise us to find results that seem contradictory or not fully explicable, yet. This clearly shows the richness of psychedelic research today as well as the need to dig deeper into their fascinating effects on the CNS and their therapeutic potential for NDs.

Translational challenges in the use of QCT, CBD and DMT for the treatment of NDs

As stated previously, there is extensive preclinical evidence indicating the therapeutic potential of QCT, CBD and DMT. However, further studies are required to evaluate its effectiveness for the treatment of NDs.

QCT is not approved as a drug for medical use, but several dietary supplements containing this compound are available in the market (Vida et al., 2019). QCT supplements are consumed for various reasons, including boosting the immune system, reducing blood pressure, and preventing cardiovascular diseases and cancer. However, data supporting the safety of long term usage of these supplements is still lacking (Andres et al., 2018). On the other hand, the first CBD-based products were approved in 2018 by the U. S. Food and Drug Administration (FDA), indicated for the treatment of refractory seizure conditions (Devinsky et al., 2017). Other products of CBD in combination with THC are indicated for managing spasticity and pain in MS (Haddad et al., 2022). Many countries including Uruguay, have approved similar products for these diseases. CBD oils or supplements are available in the market and consumed to help with conditions such as chronic pain, inflammation, migraines, epilepsy, autoimmune diseases, depression, and anxiety (https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd). However, in many South American countries, including Uruguay, this kind of products are strictly regulated (https://ircca.gub.uy/marco-normativo). The situation is quite different for DMT, a compound classified as a Schedule I drug under the United Nations 1971 Convention on Psychotropic Substances (https://www.un-ilibrary.org/content/books/9789210555845s003-c001). This means that DMT is closely monitored and its use restricted to scientific research worldwide. However, natural materials containing DMT, like Ayahuasca, are not included in this Convention and hence, some countries, particularly in Latin America, have laws specifically addressing its possession or use. For example, in Peru, Ayahuasca is considered cultural heritage and therefore is legal, whereas in Uruguay there are legal vacuums or subtleties (Scuro and Apud, 2015).

Regarding clinical trials assessing QCT, CBD and DMT in NDs, a search in the National Institutes of Health database (ClinicalTrials.gov) showed very different situations for the three compounds. In the case of QCT, there are five clinical trials listed related to AD (NCT04063124, NCT04785300, NCT06470061, NCT05422885 and NCT04685590). In all these trials, QCT is administered in combination with other drug(s) and are in phase I or phase II. For CBD, there are three clinical trial related to PD (NCT02818777, NCT03582137, NCT05106504), four related to AD (NCT05822362, NCT06014424, NCT04075435, NCT06570928) and one related to Huntington's disease (NCT01502046). Most of them are in phase II. Regarding DMT, there are still no trials ongoing for NDs. However, there are several clinical trials registered in phase I, evaluating dosage and safety of DMT in healthy patients (NCT04353024, NCT0453023, NCT05384678, NCT05573568, NCT05695495, NCT059001012), which could set the bases for the potential use of DMT in NDs.

The transition of these compounds to clinical applications is promising but faces numerous obstacles, including low bioavailability, elucidation of complex mechanisms of action, drug interactions, dosage standardization, limited clinical evidence and, in the case of CBD and DMT, legal regulation considerations. One of the main challenges facing the clinical use of QCT for NDs is its poor bioavailability and low solubility in water. Even though QCT crosses the blood brain barrier, studies in rats and pigs have shown very low QCT levels in the brain after its administration, most probably due to extensive metabolization (Nardai et al., 2019; Dajas et al., 2003; de Boer et al., 2005). Strategies such as the use of different formulations like nanoencapsulation, mucoadhesive nanoemulsions, gels and other improved delivery systems have been proposed to overcome this limitation, but robust clinical validation is still required (Xu et al., 2019; de Oliveira Vian et al., 2024). Regarding CBD, even though its high liposolubility results in its accumulation in the brian (an important characteristic for the treatment of NDs) (Calapai et al., 2020), CBD presents poor bioavailability (6–19 %) upon oral administration mainly due to its extensive first-pass metabolism. (Chayasirisobhon, 2021; Huestis, 2005). Like for QCT, several techniques have been developed to improve the CBD's bioavailability. Some examples are polymer-based CBD inclusion complexes, lipid-based formulations, and/or nanoformulations administered via different routes (Hossain et al., 2023). Finally, the clinical application of DMT for NDs still has a long way ahead. Among other translational obstacles, DMT does not reach the brain when administered orally due to its metabolic degradation in the liver (Carbonaro and Gatch, 2016; Strassman, 1996). This bioavailability issue can be solved by changing the administration route to injected or inhaled, which shows as an additional advantage the short acute duration of its psychedelic effect (Timmermann et al., 2024). Development of DMT analogues that retain its neuroprotective or neuroplastic properties without inducing psychedelic effects could be a promising avenue, but this requires extensive research and a deeper understanding of the underlying mechanisms (Dunlap et al., 2020).

Besides, it is controversial whether the subjective effect is needed for the therapeutic outcome, as participants frequently rate their psychedelic experiences as among the most meaningful of their entire lives (further reading on this matter in Yaden and Griffiths, 2021). In all, DMT's therapeutic potential, though promising, still needs further investigation of its molecular mechanisms and, as for other psychedelics, the development of proper and safe environments for its medical application.

Another aspect to consider when incorporating these compounds into therapies for NDs is their different mechanisms of action that mainly target certain pathophysiological processes and the particularities of each disease. Thus, combination therapies might yield better results than using the isolated compounds. Additionally, it is possible that one compound may perform better for a particular stage of a disease. For example, given that MS is an autoimmune NDs, immunomodulators are the standard therapeutic approach. However, other therapeutic strategies that consider the evolution of the disease could be of interest. In MS, after the initial autoimmune phase that destroys the myelin, an important oxidative response is triggered. Thus, the combination of immunomodulators like CBD with antioxidants like QCT could be an innovative approach. Furthermore, the incorporation of a neuroplasticity-promoting compound like DMT could contribute to stimulating neural tissue repair and connectivity. Better mapping of the molecular mechanisms involved in the onset and progression of each NDs could be a valuable tool to design more successful treatments.

Conclusions and perspectives

While QCT, CBD and DMT offer promising prospects for the treatment of NDs, translating these compounds from the laboratory to the clinic presents significant challenges. Improving bioavailability, optimizing formulations and routes of administration, standardizing doses and administration regimens, evaluating drug interactions and overcoming ethical barriers are crucial aspects that must be addressed through multidisciplinary research and rigorous clinical trials. Overall, compared to QCT and CBD, clinical research on DMT is still in its early stages, and its application for NDs has a longer way to go.

CRediT authorship contribution statement

Carolina Echeverry: Writing – review & editing, Writing – original draft, Conceptualization. **Mariana Pazos:** Writing – review & editing, Writing – original draft, Conceptualization. **Maximiliano Torres-Pérez:** Writing – review & editing, Writing – original draft. **Giselle Prunell:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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