Phytocannabinoids as Therapeutic Agents in Central Nervous System Disorders: A Review

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***Abstract*—Phyto cannabinoids are naturally occurring, biologically active compounds derived from the Cannabis sativa plant that exert their modulatory effects on the endocannabinoid system with associated molecular pathways that targets the central and peripheral nervous systems (CNS and PNS). Beyond the psychoactive delta-9-tetrahydrocannabinol (THC), non-intoxicating cannabinoids such as cannabidiol (CBD), cannabigerol (CBG), and delta-9-tetrahydrocannabivarin (THCV) also exhibit promising pharmacological properties across a spectrum of central and peripheral nervous system disorders as they have emerged as promising candidates for the treatment of epilepsy, neurodegenerative diseases, affective disorders, and chronic pain. This review synthesizes findings from preclinical models and clinical trials, focusing on the mechanisms of action, therapeutic efficacy of phytocannabinoids on the CNS. Their multitarget engagement—including CB1/CB2 receptors, TRP channels, 5-HT receptors, and immune modulators—offers a poly-pharmacological framework that supports further translational research and drug development.**

***Index Terms*—Phyto cannabinoids, Cannabidiol (CBD), delta-9-tetrahydrocannabivarin (THC), CB1 receptor, CB2 receptor, CNS & PNS disorders, TRP channels, Neurodegeneration, Delta-9-Tetrahydrocannabivarin (Δ⁹-THCV), Cannabigerol (CBG)**

I. INTRODUCTION

Phyto cannabinoids are plant-derived terpenophenolic compounds with structurally diverse scaffolds and receptor promiscuity. Their pharmacological profile extends beyond classical CB_1 and CB_2 receptor interactions, encompassing TRPV1, GPR55, PPARγ, and 5-HT_1A targets — positioning them as polypharmacological agents with broad therapeutic reach.

Unlike single-target drugs, phytocannabinoids exert pleiotropic effects through simultaneous modulation of neurotransmission, inflammatory cascades, and metabolic regulators. This multi-receptor engagement enables therapeutic intervention across disorders with complex etiologies, including neurodegeneration, epilepsy, affective dysregulation, and cachexia. Their ability to fine-tune homeostatic systems — from synaptic plasticity to immune signalling — underscores their translational relevance in modern pharmacotherapy.

II. BIOSYNTHESIS PATHWAY OF PHYTO CANNABINOIDS

Phytocannabinoids originate from geranyl pyrophosphate (GPP) and olivetolic acid, catalysed by CBGA synthase to form cannabigerolic acid (CBGA) — the central precursor.

- A [GPP + Olivetolic Acid] --> B[CBGA]
- B --> C [THCA via THCA synthase]
- B --> D [CBDA via CBDA synthase]
- B --> E [CBCA via CBCA synthase]

Decarboxylation (heat or time) converts acidic forms to active cannabinoids:

- THCA → Δ⁹-THC
- CBDA → CBD
- CBCA → CBC

III. STRUCTURAL VARIANTS AND SAR INSIGHTS

- Side chain length affects receptor affinity:

1. Pentyl (C_5) chains → higher CB_1 activity (e.g., THC)
2. Propyl (C_3) chains → altered psychoactivity (e.g., THCV)

- Ring aromatization (e.g., CBN) → reduced CB_1 potency, increased stability
- Hydroxylation patterns influence solubility and receptor selectivity

IV. CORE PHYTOCANNABINOIDS AND THEIR CHEMICAL STRUCTURES

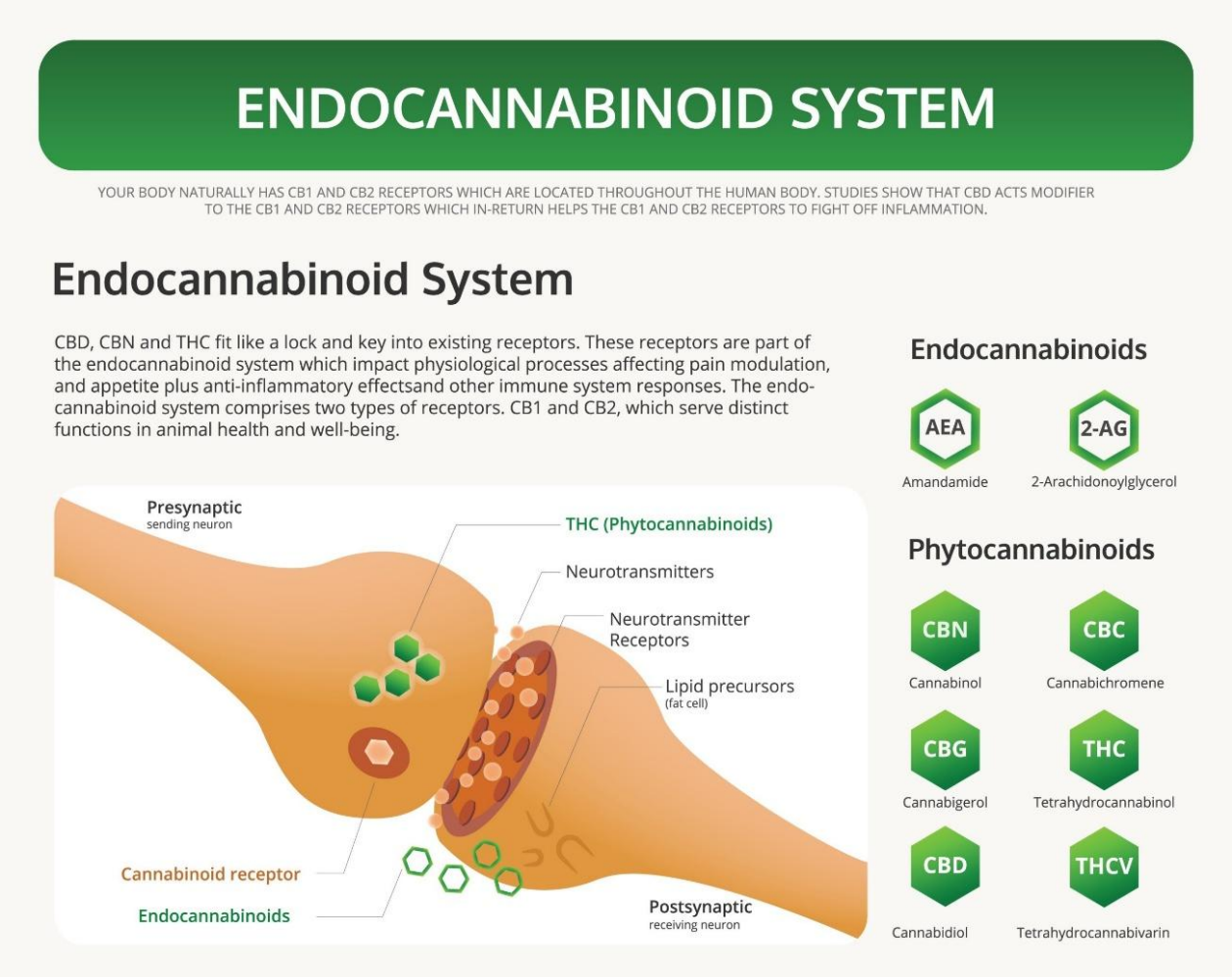
Compound	Structure Highlights	Molecular Formula	Psychoactivity	Key Receptor Targets
Δ^9-THC	Tricyclic ring, hydroxyl group	$C_{21}H_{30}O_2$	Yes	CB_1 (agonist), CB_2
CBD	Open-ring, two hydroxyls	$C_{21}H_{30}O_2$	No	TRPV1, 5-HT_1A, PPARγ
CBG	Linear precursor, hydroxyls	$C_{21}H_{32}O_2$	No	α_2-adrenergic, TRPM8
CBC	Cyclohexene ring	$C_{21}H_{30}O_2$	No	TRPA1, CB_2
CBN	Aromatized THC derivative	$C_{21}H_{26}O_2$	Mild	CB_1, CB_2
THCV	Propyl Side chain	$C_{19}H_{26}O_2$	Mild	CB_1 (antagonist), CB_2

V. RECEPTORS OVERVIEW

1. The Endocannabinoid System (ECS)

The ECS is the primary regulatory system with which phytocannabinoids interact, consisting of three main components: receptors, endogenous ligands, and metabolic enzymes.

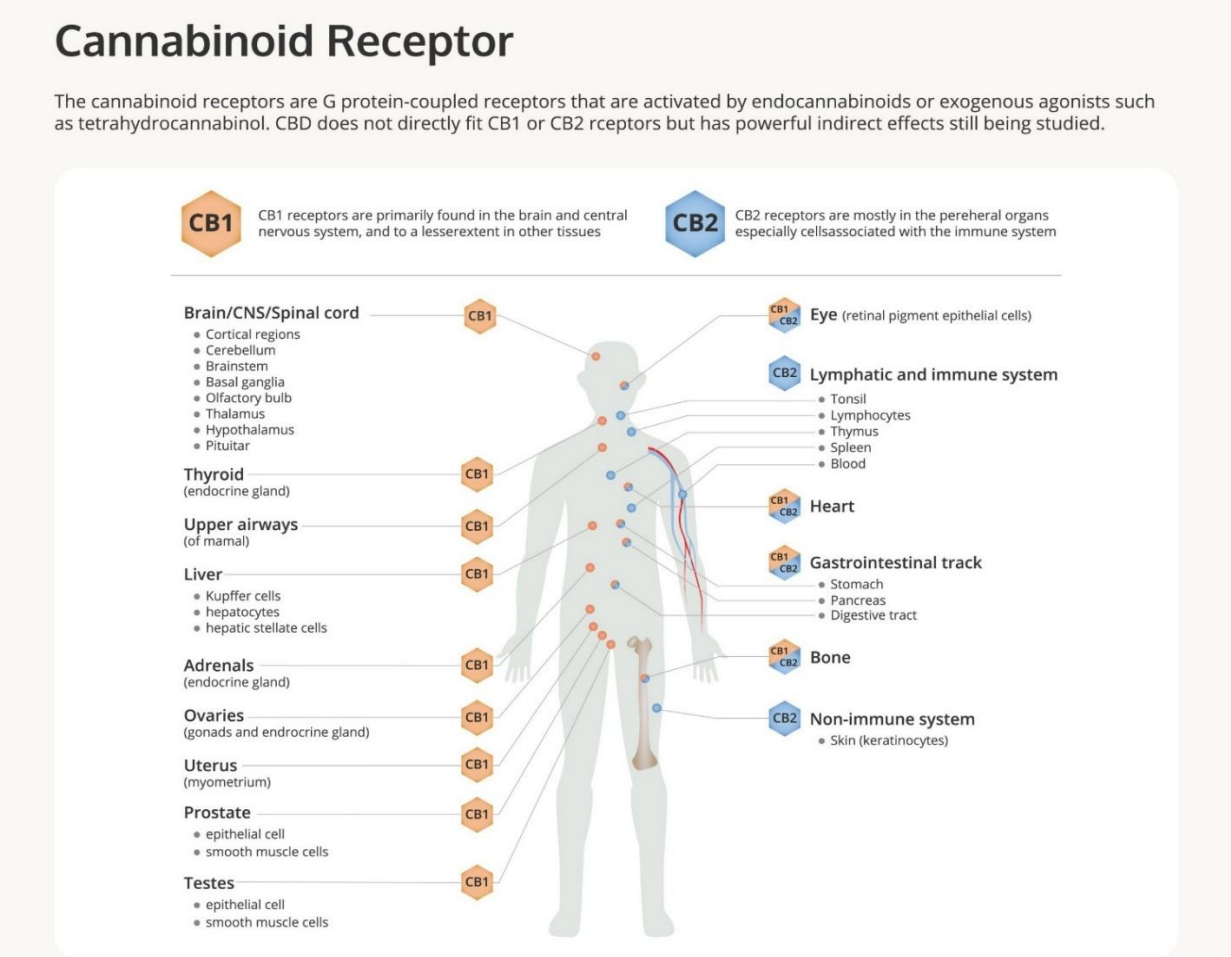
Component	Key Elements	Location & Primary Function
Receptors	CB1 Receptor	CNS (presynaptic terminals). Inhibits neurotransmitter release (retrograde signalling). Mediates psychoactivity.
	CB2 Receptor	Immune cells and activated microglia/astrocytes in the CNS. Mediates immunomodulation and anti-inflammation.
Endogenous Ligands	Anandamide (AEA)	Binds primarily to CB1. Involved in pain, memory, and appetite.
	2-Arachidonoyl-glycerol (2-AG)	Full agonist at both CB1 and CB2. Most abundant endocannabinoid.
Metabolic Enzymes	FAAH	Hydrolyzes (degrades) [AEA]
	MAGL	Hydrolyzes (degrades) [AG]



2. Cannabidiol (CBD)

CBD is a classic example of poly-pharmacology; it has low affinity for CB1 and CB2 but acts potently via other pathways:

Therapeutic Mechanism	Molecular Target	Clinical Relevance
Anticonvulsant	T-type Ca2+ Channels	Highly effective in reducing neuronal excitability in refractory epilepsy (Dravet Syndrome, LGS).
Anxiolytic/Antipsychotic	5-HT 1A Receptor Agonism	Contributes to its anti-anxiety and antidepressant effects; a key non-ECS target.
Neuroprotection	Antioxidant Activity & TRPV1 Modulation	Direct scavenging of free radicals and modulation of the TRPV1 receptor (involved in pain/inflammation).
Indirect ECS Modulation	FAAH/AEA Reuptake Inhibition	May increase endogenous Anandamide (AEA) levels, enhancing its protective effects.



3. Delta-9-Tetrahydrocannabivarin (Δ⁹-THCV)

Δ⁹-THCV stands out for its unique, dose-dependent activity:

- Low Dose: Functions as a CB1 Neutral Antagonist—a key mechanism for suppressing appetite (hypophoria), offering potential for anti-obesity or metabolic disorders.
- High Dose: Acts as a CB2 Partial Agonist—beneficial for anti-inflammatory and neuroprotective effects in NDDs.

4. Cannabigerol (CBG)

Often referred to as the "mother cannabinoid", CBG is the precursor from which Δ⁹-THC and CBD are synthesized. CBG is particularly noted for:

- Alpha2 Adrenoceptor Agonism: Implies potential anti-hypertensive and sedative effects.
- Antagonism at 5-HT1A Receptors: A different profile from CBD, highlighting the diverse biological roles among PCBs.

VI. DISEASES OVERVIEW

Neurodegenerative Disorders

1) Parkinson's Disease

Parkinson's Disease (PD) is a progressive neurodegenerative disorder primarily affecting motor function. It is characterized by tremors, bradykinesia, rigidity, and postural instability. Non-motor symptoms include cognitive decline, mood disturbances, and sleep disorders. PD predominantly affects individuals over the age of 60, with incidence increasing with age. The disease results from the degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to dopamine deficiency in the striatum.

➢ Pathophysiology

The hallmark of PD is the loss of tyrosine hydroxylase-positive (TH+) neurons and the presence of Lewy

bodies composed of α-synuclein aggregates. Neuroinflammation, oxidative stress, mitochondrial dysfunction, and excitotoxicity contribute to neuronal death. Environmental toxins (e.g., MPTP, pesticides), genetic mutations (e.g., SNCA, LRRK2), and aging are key causative factors. Parkinson's disease is primarily a movement disorder caused by degeneration of dopaminergic neurons in the substantia nigra pars compacta, a region of the midbrain. This leads to a significant reduction in dopamine levels within the nigrostriatal pathway, which is essential for regulating voluntary motor control.

Key Mechanisms:

- α-Synuclein Aggregation: Misfolded α-synuclein proteins accumulate to form Lewy bodies, disrupting neuronal function and triggering apoptosis.
- Mitochondrial Dysfunction: Impaired mitochondrial complex I activity leads to reduced ATP production and increased reactive oxygen species (ROS), contributing to oxidative stress.
- Neuroinflammation: Activated microglia release pro-inflammatory cytokines, exacerbating neuronal damage.
- Excitotoxicity: Excessive glutamate activity causes calcium overload and neuronal death.
- Genetic Factors: Mutations in genes such as SNCA, LRRK2, PINK1, DJ-1, and Parkin are implicated in familial PD.

➢ Phyto cannabinoid Therapeutic Potential

Phytocannabinoids such as cannabidiol (CBD) and Δ⁹-tetrahydrocannabivarin (Δ⁹-THCV) exhibit neuroprotective, anti-inflammatory, and antioxidant properties. Δ⁹-THCV acts as a CB1 antagonist and CB2 agonist, improving motor symptoms and reducing microglial activation in preclinical PD models.CBD has shown efficacy in reducing psychosis and improving quality of life in PD patient. These compounds modulate glutamate release, inhibit reactive oxygen species, and interact with TRPV1 and 5-HT1A receptors.

The dopamine deficit affects both the direct and indirect basal ganglia pathways, resulting in bradykinesia, rigidity, resting tremor, and postural instability. Non-motor symptoms like depression, sleep disturbances, and autonomic dysfunction are linked to degeneration beyond the substantia nigra. Overall, Phytocannabinoids offer a multi-targeted approach to PD management, addressing both motor and non-motor symptoms. Unlike traditional dopaminergic therapies, they exhibit fewer side effects and may slow disease progression. Their integration into modern therapeutics could complement existing treatments and improve patient outcomes.

2) Alzheimer's Disease

Alzheimer's Disease (AD) is the most prevalent form of dementia, affecting over 55 million people globally. It is characterized by progressive cognitive decline, memory loss, and behavioural changes. AD typically manifests after age 65, though early-onset cases also occur. The disease is marked by extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein.

➢ Pathophysiology

The amyloid cascade hypothesis posits that abnormal cleavage of amyloid precursor protein (APP) by β- and γ-secretases leads to accumulation of Aβ42 peptides, which aggregate into plaques. These plaques trigger neuroinflammation, oxidative stress, and synaptic dysfunction. NFTs result from tau hyperphosphorylation, disrupting microtubule stability and intracellular transport. Neuroinflammation, mediated by microglia and astrocytes, further exacerbates neuronal damage.

Key Mechanisms:

- Amyloid-β Plaques: Extracellular accumulation of Aβ peptides, derived from abnormal cleavage of amyloid precursor protein (APP), disrupts synaptic transmission and induces neurotoxicity.
- Tau Hyperphosphorylation: Intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein impair microtubule stability and axonal transport.
- Cholinergic Deficit: Loss of cholinergic neurons in the basal forebrain reduces acetylcholine levels, impairing memory and learning.

- Oxidative Stress & Mitochondrial Dysfunction: Increased ROS and impaired mitochondrial function accelerate neuronal death.
- Neuroinflammation: Chronic activation of microglia and astrocytes contributes to synaptic loss and disease progression.
- Genetic Susceptibility: Mutations in APP, PSEN1, PSEN2, and the presence of APOE ε4 allele increase risk and influence disease onset.

Clinical Correlation:
Early symptoms include memory impairment and disorientation, progressing to language deficits, executive dysfunction, and behavioural changes. The spread of tau pathology correlates with disease severity and cognitive decline.

➢ Phyto cannabinoid Therapeutic Potential

Phytocannabinoids such as CBD and THC exhibit neuroprotective, anti-inflammatory, and antioxidant effects relevant to AD pathology:

- CBD reduces Aβ-induced neurotoxicity, inhibits tau hyperphosphorylation, and promotes neurogenesis.
- It modulates PPARγ, TRPV1, and 5-HT1A receptors, reducing ROS and inflammatory cytokines like IL-1β and TNF-α.
- THC, at low doses, has shown to reduce Aβ aggregation and improve mitochondrial function.
- Multi-cannabinoid formulations (CBD + THC) may offer synergistic benefits via the "entourage effect".

In conclusion, Phytocannabinoids offer a multi-targeted approach to AD management, addressing amyloid pathology, tau aggregation, neuroinflammation, and oxidative stress. Unlike current symptomatic treatments (e.g., donepezil, memantine), they may modify disease progression and preserve cognitive function. While clinical trials are still emerging, their integration into therapeutic strategies could redefine AD care.

3) Huntington's Disease

Huntington's Disease (HD) is a rare, inherited neurodegenerative disorder characterized by progressive motor dysfunction, cognitive decline, and psychiatric disturbances. It follows an autosomal dominant inheritance pattern, meaning a single copy of the mutated gene is sufficient to cause the disease. The genetic defect lies in the HTT gene on chromosome 4, where an abnormal expansion of CAG trinucleotide repeats leads to the production of a toxic form of the huntingtin protein. HD typically manifests between the ages of 30 and 50, although juvenile onset (<20 years) and late-onset (>70 years) variants exist. The disease course spans 10–25 years, culminating in severe disability and death. The prevalence is estimated at 4–15 per 100,000 in populations of European descent.

➢ Pathophysiology

Mutant huntingtin protein (mHTT) undergoes abnormal proteolysis, producing toxic fragments that aggregate within neurons. These aggregates disrupt transcriptional regulation, impair proteostasis, and interfere with synaptic signalling. Striatal medium spiny neurons are particularly vulnerable due to excitotoxic glutamate signalling, mitochondrial dysfunction, and impaired energy metabolism. Neuroinflammation further accelerates neuronal death, while circuit-level disruption of basal ganglia pathways underlies motor and psychiatric symptoms.
Key Mechanisms:

- Neuronal Toxicity: mHTT accumulates in neurons, forming nuclear and cytoplasmic inclusions that impair transcription, axonal transport, and synaptic function.
- Genetic Basis: CAG repeat expansion (>36 repeats) in the HTT gene leads to a polyglutamine tract in the huntingtin protein, causing misfolding and aggregation.
- Selective Vulnerability: Medium spiny neurons (MSNs) in the striatum are particularly susceptible due to their high metabolic demand and glutamate sensitivity.
- Excitotoxicity: Dysregulated glutamate signalling leads to NMDA receptor overactivation, calcium influx, and mitochondrial damage.
- Mitochondrial Dysfunction: mHTT impairs oxidative phosphorylation, increases ROS production, and reduces ATP synthesis.
- Proteostasis Failure: Impaired autophagy and ubiquitin-proteasome systems result in accumulation of misfolded proteins.

- Neuroinflammation: Activated microglia and astrocytes release pro-inflammatory cytokines (IL-1β, TNF-α), exacerbating neuronal injury.

➢ Phyto cannabinoid Therapeutic Potential

Phytocannabinoids such as CBD and THC demonstrate neuroprotective and anti-excitotoxic properties relevant to HD pathology:

- CBD reduces glutamate-induced excitotoxicity, attenuates oxidative stress, and improves mitochondrial function.
- It modulates PPARγ and TRPV1 receptors, restoring neuronal homeostasis and reducing neuroinflammation.
- THC, via CB1 receptor modulation, may alleviate chorea and motor dysfunction, while CB2 agonism dampens microglial activation.
- Multi-cannabinoid formulations (CBD + THC) may synergistically improve motor coordination and psychiatric symptoms.

In conclusion, phytocannabinoids offer a multi-targeted approach to HD management, addressing excitotoxicity, mitochondrial dysfunction, and neuroinflammation. While clinical validation is limited, their integration into therapeutic strategies could complement existing treatments and improve quality of life.

4) Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a chronic, immune-mediated neurodegenerative disorder of the central nervous system that predominantly affects young adults, with a higher prevalence in women. Clinically, MS is characterized by relapsing-remitting episodes or progressive neurological decline, manifesting as motor weakness, sensory disturbances, visual impairment, and cognitive dysfunction. The disease is a leading cause of non-traumatic disability worldwide, with both genetic predisposition and environmental factors contributing to its onset.

➢ Pathophysiology

The hallmark of MS is immune-driven demyelination and axonal injury. Autoreactive T lymphocytes, particularly Th1 and Th17 subsets, cross the blood–brain barrier (BBB) and initiate inflammatory cascades against myelin antigens. B cells contribute by producing autoantibodies and presenting antigens, amplifying the immune response. Inflammatory cytokines such as TNF-α, IFN-γ, and IL-17 increase BBB permeability, allowing infiltration of macrophages and microglia. These immune cells strip myelin sheaths from axons, impairing saltatory conduction and exposing neurons to degeneration. Chronic inflammation leads to mitochondrial dysfunction, oxidative stress, and excitotoxicity, while astrocytic proliferation forms sclerotic plaques that hinder remyelination. Over time, irreversible axonal loss explains the progressive disability even in the absence of active demyelination.

Key Mechanisms:

Breakdown of the blood–brain barrier and immune cell infiltration

- Demyelination mediated by autoreactive T cells and B cells
- Axonal degeneration due to chronic inflammation and excitotoxicity
- Mitochondrial dysfunction and oxidative stress
- Astrocytic scarring and impaired remyelination

➢ Phyto cannabinoid Therapeutic Potential

Phytocannabinoids such as CBD and THC exhibit neuroprotective, anti-inflammatory, and antioxidant effects relevant to AD pathology:

- THC reduces spasticity and neuropathic pain via CB1 receptor modulation of neurotransmission.
- CBD attenuates oxidative stress, suppresses pro-inflammatory cytokines (IL-17, TNF-α), and enhances remyelination potential.
- CBG contributes analgesic and anti-inflammatory effects through α2-adrenergic and TRPM8 receptor activity.
- Nabiximols (THC: CBD spray) is clinically approved for MS-related spasticity, demonstrating translational efficacy

In conclusion, Phytocannabinoids offer a multi-targeted approach to AD management, addressing amyloid pathology, tau aggregation, neuroinflammation, and oxidative stress. Unlike current symptomatic treatments (e.g., donepezil, memantine), they may modify disease progression and preserve cognitive function. While clinical trials are

still emerging, their integration into therapeutic strategies could redefine AD care.

VII. CONCLUSION

Phytocannabinoids represent a polypharmacological class of agents with therapeutic potential across diverse neurodegenerative disorders. Their ability to modulate CB1/CB2 receptors, TRP channels, serotonin receptors, and immune pathways allows them to address the multifactorial nature of diseases such as Parkinson's, Alzheimer's, Huntington's, Multiple Sclerosis, ALS, and prion-related conditions. Unlike conventional single-target therapies, phytocannabinoids offer multi-target neuroprotection, combining antioxidant, anti-inflammatory, and anti-excitotoxic effects. Clinical translation remains limited, but emerging evidence highlights their role in symptom management (spasticity, pain, psychiatric disturbances) and possible disease-modifying effects.
In summary, phytocannabinoids hold promise as next-generation therapeutics for neurodegenerative disorders, bridging symptomatic relief with potential disease-modifying strategies. Their integration into modern pharmacotherapy could reshape the management of CNS and PNS disorders.

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