CHAPTER 17

Prominent Medicinal Plants for the Treatment of Neurodegenerative Disorders

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SUMMARY

The phrase "neurodegenerative diseases" refers to conditions that cause a major loss of neurons, both structurally and functionally. Neurodegenerative diseases are serious life-threatening in which neural cells in the brain stop working or die. One of the most recently discovered pathogenic processes in the genesis of neurological illnesses is mitochondrial dysfunction. Mitochondria play a significant role in various cellular processes such as the production of ATP, intracellular calcium, and generation of reactive oxygen species and improper function leads to diseases. Oxidative stress and aging are two other prevalent etiologies of neurological diseases. Several side effects have emerged as a result of current treatment methods and the progressive nature of illnesses, prompting patients to switch to other medications. The helpful impact of medicinal plants in these situations has been attributed to their demonstration through several cellular and molecular processes. Traditional plants have a few neuroprotective mechanisms: they reduce inflammatory responses, regulate pro-inflammatory cytokines' functional aspects such as tumor growth, and enhance antioxidant qualities. Plant prevention strategies for these diseases heavily rely on variations in transcription and transduction pathways. Some of the therapeutic herbs for preventing neurological disorders are *Panax ginseng, Curcuma longa, Zingiber officinale, Ginkgo bilob*a, and *Utrica diocia,* etc., have shown antioxidant as well as anti-inflammatory effects and also show a promising tool for treating neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, multiple sclerosis, and epilepsy. Medicinal plants contain various phytochemical constituents that improve oxidative stress, reduce mitochondrial damage, and protect against brain damage. In short, use of whole plants or parts of medicinal plants from roots to seeds extracted chemicals are used to prevent neurodegenerative illnesses.

INTRODUCTION

Neurons are the basic building blocks of the neurological system that make up the brain and spinal cord. There are 100 billion neurons in the human brain. These neurons play a part in several areas including smelling, visualizing, thinking, and listening. Every organ of the body is linked to the brain by these neurons and responds to the signals the brain receives to function. Since neurons often do not duplicate themselves, when they die or are injured, the body is unable to replace them (Luthra & Roy 2022). The disorder known as neurodegeneration is characterized by the increasing malfunction and death of neurons. Neurodegeneration occurs due to aging, unusual ecological factors, accumulation of proteins in neurons, and mitochondrial defects. The most common pathology involved in ND is protein deposition. Numerous neurodegenerative diseases are caused by various pathological compliance such as aggregation of synuclein Parkinson's disease (PD), accumulation of amyloid-β in Alzheimer's disease (AD), buildup of huntingtin proteins in Huntington's disease (HD), formation of TDP-43 in frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (Devi et al., 2021).

According to a report by the World Health Organization, it is assumed that in the next 20 years, neurodegenerative diseases will rank second in terms of the frequency of deaths. WHO has reported that ND affects billions of people each year and ranges from seizures to Alzheimer's. 50 million of the 1 billion affected individuals globally have epilepsy. Due to neurodegenerative

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conditions, almost 6.8 million people die each year. There are over 50 million dementia patients worldwide. Globally, Parkinson's disease has affected 6.1 million in 2016 compared to 2 million in 1990. Alzheimer's disease afflicted 36 million people worldwide in 2014, up from 26.6 million in 2006, of which 5.1 million are Americans and 20,000 of whom are under 65 years old (Adams et al., 2020).

NEURODEGENERATIVE DISORDERS

PARKINSON DISEASE

Parkinson's disease (PD) is the most prevalent neurodegenerative disorder distingue by the depletion of neurons involving dopamine as a neurotransmitter. It is caused by the combination of various environmental factors and genetic variants. The underlying cause of PD is the malfunctioning/loss of dopamine-generating cells (Vázquez-Vélez & Zoghbi 2021). Areas in the anterior part of the brain and Meynert's nucleus basalis over the septum exhibit pathological neuronal deprivation along with accumulations of neurofilament protein and ubiquitinated-synuclein in neuronal cytoplasms such as Lewy bodies (LB) and lewy neuritis [LN (Chu et al., 2022)].

Epidemiology and risk factors

Epidemiological studies have shown that the prevalence of PD is between 0.5 and 1% among adults between the ages of 65 and 69, and between 1 and 3 percent for those 80 years of age or older (Luthra & Roy 2022). Male gender carries a moderate risk, but age is the main risk factor for the condition. Some chemicals and rural life have been related to an increased risk of developing PD. It is interesting to note that several drugs, like annonacin and 1-methyl-4-phenyl tetrahydropyridine (MPTP), can result in the death of nigrostriatal cells and a specific type of atypical parkinsonism (Balestrino & Schapira 2020). Manganese, trichloroethylene, carbon monoxide, and β2-adrenoreceptor antagonists have all been related to an increased risk of PD whereas β2-adrenergic receptor agonists diminish the risk (Hopfner et al., 2019). Contrarily, there is evidence that the use of nonsteroidal anti-inflammatory medicines (NSAIDs) is inversely linked to the risk of PD, calcium channel blockers (CCBs), statins, coffee consumption, gout, and uric acid levels (Belvisi et al. 2020).

Pathophysiology of PD

The major event that causes disease outbreak is the pathway alongside with Lewy body in addition to numerous biochemical processes including mitochondrial dysfunction, lysosomal deterioration, oxidative stress, and misfolding during protein synthesis. As a result, there is a loss of motor function, cognitive deterioration, and the development of non-motor symptoms. On a clinical basis, postural impermanence, bradykinesia, stiffness, and resting juddering are all signs of Parkinsonism. It has been demonstrated that Lewy bodies are characteristically found in the inferior portion of the brain stem and the olfactory region. As the disease progresses, LB also appears in the midbrain, forebrain, and neocortex region. Furthermore, it has been demonstrated that the widespread distribution of Lewy bodies causes a change in some neurons (Borghammer et al., 2021). It has been studied that abnormal aggregates of alpha-syn trigger selective and neuronal death through several biochemical processes and are involved in initiating neurodegeneration in PD (Calabresi et al., 2023). Levodopa is the main drug of the current treatments for Parkinson's disease (PD), which can slow the progression of the condition but also comes with several side effects. There is still a need to identify any medication that can treat or exacerbate the sickness. Because both redox stabilization and mitochondrial refilling activities are crucial for the optimal functioning of neurons are seem to be the main remedial options in the case of Parkinson's disease (Luthra & Roy 2022).

ALZHEIMER DISEASE

Alzheimer's disease (AD) is a broadly well-recognized type of dementia. Amyloid peptides and intracellular neurofibrillary tangles are the two main pathogenesis-related features of the disease. Despite substantial investment in neurological research, the precise molecular process behind AD progression is still not entirely understood.

Epidemiology and risk factors

It is mostly observed in people over 60 years of age and older. In AD, there is a gradual decline in the mental capacity of people, and sustaining a normal life turns out to be too challenging for them. At the end stage, as AD persists to increase the patients become dependent on family members for survival. The prevalence of AD in persons aged 65-74 years is about 3%, about 19% in persons aged between 75-84 years, and those aged over 84 years have an incidence rate of 47% (Uwishema et al., 2022).

Pathophysiology of AD

According to studies oxidative damage, energy metabolism, and severe mitochondrial failure are all present in AD pathogenesis. The oxidative damage occurs before the formation of Aβ in APP (amyloid precursor protein). Numerous pathways have been revealed demonstrating the part played by mitochondrial dysfunction in the pathophysiology of AD (Jurcău et al., 2022). According to a study, transgenic APP mutant mice models with insufficient levels of the mitochondrial antioxidant enzyme have elevated levels of Aβ in

their brains (Li et al., 2022). In several studies, synaptic collapse and deterioration of mitochondria have been associated with the development of AD.

EPILEPSY

Epilepsy is a neurodegenerative disease indicated by seizures that last more than 30 minutes or repeated seizures. Seizures itself occur as a result of neuronal dysfunction. The unneeded discharge of brain neurons from grey matter causes seizures. In epilepsy, malfunctioning sodium and calcium channels with unnecessary glutamate-mediated neurotransmission start a chain of cellular-death-inducing events. Refractory status epilepticus (RSE) is a term used to describe acute, critical, and severe patients whose seizure duration exceeds an hour when second-line medications are unsuccessful (Wu et al., 2022).

Epidemiology and risk factors

Epilepsy affects about 50 million people of both sexes and all ages on a global scale. Males are more susceptible to epilepsy than women because of incidence of stroke, neurological disorders, and tumors is higher in this group and the peak of epilepsy is higher in old age. Focal seizures are more common in adults and young children in contrast to generalized seizures. The etiology of epilepsy diverges according to the social and demographic nature of the affected populations and the intensity of the work, but in approximately 50% of cases in high-income countries, the cause is still unknown (Beghi, 2020).

Pathophysiology of epilepsy

The pathophysiology of epilepsy involves the interaction of mitochondrial malfunction, oxidative stress, and ROS (reactive oxygen species) production. Neurological damage was reportedly caused by convulsions brought on by homocysteic acid in mice; however, this impact was reportedly mitigated by management with free radical spin traps that diminish oxidative stress. Rats treated with homocysteic acid also demonstrated mitochondrial malfunction, with a notable reduction in complex-1 action in the mitochondria of the cerebral cortex (Falco-Walter, 2020).

DEPRESSION

Depression is a likely lethal condition due to which millions of people have been affected. It can start at any age ranging from early life to old age. It is extremely expensive for society because it produces considerable suffering and disturbance in daily life and even can be fatal if not treated. Low or depressed mood and low energy or exhaustion make up the psychopathological state's triadic set of symptoms. Additionally, more common symptoms that a person experiences are gastrointestinal and autonomic issues, sleep and psychomotor issues, guilt-related sentiments, low confidence, and death instinct (Brigitta, 2022).

Epidemiology and risk factors

Globally, 34% of adolescents between the ages of 10 and 19 are at risk of having clinical depression, which is higher than the percentage reported for the ages of 18 and 25. About 3.8% of the population with 5% of adults and 5.7% of persons over the age of 60 is considered to suffer from depression. According to the World Health Organization (WHO), 280 million people with depression in the world. About 50% more women suffer from depression. Globally, more than 10% of pregnant mothers and new mothers suffer from depression. Every year, suicide kills more than 700,000 people. Suicide is the fourth leading cause of death among 15 to 29-year-olds (Shorey et al., 2022).

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a neurological disease characterized by degeneration of axons, demyelination, and inflammation. It is a disorder of CNS in which there is an inflammation in the myelin sheath of axons. Mitochondrial dysfunctioning is associated with the pathogenesis of MS which has been revealed in recent research (Cheng et al., 2023).

Epidemiology and risk factors of multiple sclerosis

MS development has been linked to smoking, stress, obesity, and low intake of vitamin D. The gut microbiome, infections, vaccinations, heavy metal exposure, and pesticide exposure are also risk factors for MS (Costantini et al., 2022).

ROLE OF MITOCHONDRIA IN NEURODEGENERATIVE DISORDERS

Mitochondrial dysfunction plays an important role in the development and progression of age-related neurodegenerative diseases such as Parkinson's disease (PD), epilepsy, Huntington's disease (HD), neuropathic pain, Amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), multiple sclerosis (MS), and schizophrenia Fig 1. Nearly 20% of the body's total oxygen needs are met by the human brain, which is extremely dependent on adequate oxygenation. To restore the resting membrane potential in excitatory cells, Na^+/K^+-ATPase consumes the brain's energy partially which is supplied by the central nervous system's (CNS) abundant mitochondria (Zhang et al., 2022).

In addition, the cellular function of the brain depends on adenosine triphosphate (ATP) which is abundantly produced as a result of oxidative pathways by mitochondria that include the Krebs cycle, oxidative phosphorylation, and glycolysis for the

oxidation of fatty acids and carbohydrates. The mitochondria perform a variety of household tasks such as producing energy from the metabolism of nutrients, oxidation of metabolites via the Krebs cycle, and oxidation of fatty acids, oxidative phosphorylation (OXPHOS). It also maintains calcium homeostasis, produces scavenging-free ions, and regulates cell differentiation and cell death (Bamshad et al., 2023).

NEUROPROTECTIVE PLANTS

Numerous plants are used in treating neurodegenerative disorders [Fig 2., (Li et al., 2021)]. Different plant sections are being utilized to extract chemicals, and occasionally the entire plant is used to extract biochemicals for the protection of the nervous system. The important medicinal plants with their therapeutic action in neurodegenerative disorders are mentioned in Tab. 1.

Artemisia dracunculus

The perennial herb *Artemisia dracunculus* also known as *A. dracunculus* has strong free radical scavenging and antioxidant properties. The bioactive components contain flavonoids, phenylpropanoids, coumarins, tannins, and essential oils. The antioxidant property of *A. dracunculus* is due to flavonoids and phenolic compounds. According to findings from peripheral blood mononuclear cells (PBMC), the aqueous extract of *A. dracunculus* shows anti-inflammatory activity by the suppression of nuclear factor-kB (NF-kB) signaling and decreased release of IFN and IL-6 (Bisht et al., 2021).

Curcuma longa

The polyphenols obtained from Curcuma longa are curcumin, dimethoxycurcumin, and bisdemethoxycurcumin which function as antioxidants and protect the brain against a variety of oxidative stress (Pavlovic et al., 2023). They also have neuroprotective and anti-aging properties due to their ability to hunt down superoxide anions (Costantini et al., 2022). The rhizome of C. longa is well-known as turmeric which is used in cooking food. Curcumin which is a main source of C. longa has antioxidant and anti-inflammatory potential and also maintains mind balance that's why used to treat AD and has shown antidepressant action in mice (He et al., 2022).

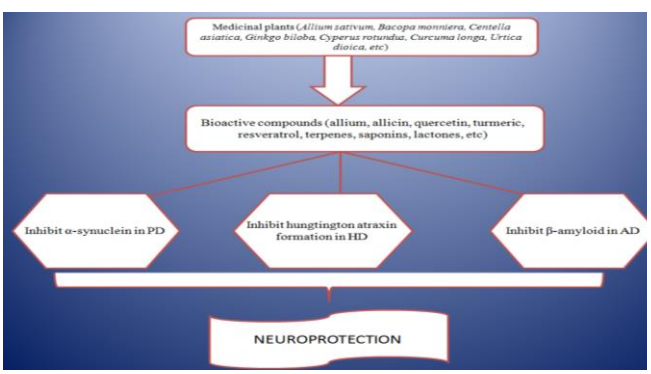

Fig 2. Actions of medicinal plants in neurodegenerative disorders.

Nuclear factor kappa beta (NF-kβ) transcription controls a large number of genes that are connected to the induction of immunological responses as well as acute and inflammatory responses. Curcumin prevents NF-kβ activation which has captivating therapeutic potential for neurological diseases and causes a down-regulation of particular inflammatory genes (Gachpazan et al., 2021).

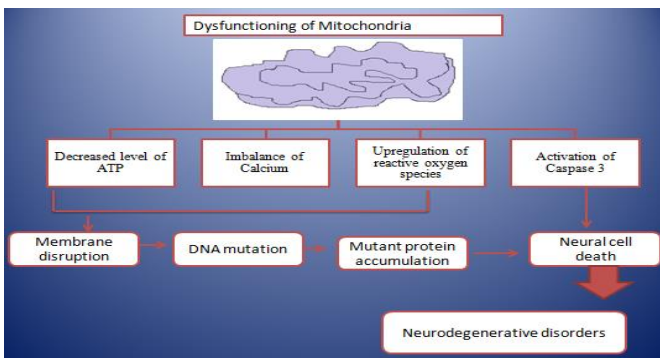

Fig 1. Action of mitochondrial dysfunction in neurodegenerative disorder.

Zingiber officinale

The root of Z. officinale is mostly employed in traditional medicine as an antioxidant and anti-inflammation. Due to bioactive compounds such as ginger, and gingerol, it exerts anti-inflammatory, antioxidant, and immunomodulatory effects and is used to treat ND (Rotimi et al., 2022). The immune responses related to Th-1, Th-2, Th-9, Th-17, Th-22, and Treg cells are regulated by ginger and its constituents. Ginger regulates immune responses related to β-cells, and modulates macrophages. It also increases inflammatory mediator production and expression of adhesion molecules. Gingerol which is the main bioactive of ginger disrupts Toll-like receptors (TLR) related signaling pathways and suppresses inflammasomes, and oxidative stress (Alolga et al., 2022).

Hypericum perforatum

Hypericum perforatum (*H. perforatum*) is beneficial for the treatment of disorders related to inflammation, neurodegenerative disorders, and cancer. Anti-inflammatory, antioxidant, and anti-apoptotic activities are shown by phenolic compounds, hypericin, phloroglucinols, pseudo hypericin, naphthodianthrones, and flavonoids present in extract (Fumia et al., 2022).

Tab 1. Medicinal plants in neurodegenerative disorders.

Botanical names	Therapeutic action	Therapeutic uses	References
Allium sativum	Suppress Aβ induced neurotoxicity, reduces oxidative stress and damage to brain cells Active compound: Allium, allicin	Antioxidant, and neuroprotective properties in AD, PD	Rakshit et al., 2023
Celastrus regelii	Inhibit nitric oxide synthase (NOS) Active compound: Celastrol	Neuroprotective activity in AD, and PD	Morén et al., 2022
Centella asiatica	Decrease mitochondrial viability and electron transport activity. Active compound: Triterpenoid, brahminoside, asiaticoside, and Asiatic acid	Antioxidant, and neuroprotective properties in HD	Hambali et al., 2021
Curcuma longa	Improves oxidative stress, increases dopamine neurons, restores mitochondrial membrane, and ATP production, and prevents a-synuclein fibrillization. Active compound: curcumin	Anti-inflammatory, antioxidant, AD	He et al., 2022
Ginkgo biloba	Improve memory by stabilizing mitochondrial function like ATP and interacting with the electron transport chain (ETC), also improve ROS. Increase dopamine neuron level. Active compound: Trilactonic diterpenes (ginkgolide A-C, ginkgolide J-M), Trilactonic sesquiterpene, quercetin, and isorhamnetin	Antioxidant, AD, PD, and dementia	Xie et al., 2022
Glycyrrhiza glabra	Reduce oxidative stress and protect against brain damage. Active compound: Triterpene saponin (glycyrrhizin) and phenol, Triterpenoid saponins, Glycyrrhizin, and glycyrrhetinic acid	Anti-inflammatory, antioxidant, and neuroprotection in AD, PD, and dementia	John et al., 2022
Panax ginseng	Suppress mitochondrial dysfunction and increase glutamate level, reduce calcium influx and free radical generation Active compound: Ginseng, Ginsenosides	Neuroprotection in AD	Ratan et al., 2021
Sesamum indicum	Reduce inactive nitric oxide synthase expression and neuroinflammation Active compound: sesamin, sesamolin, sesamol, sesaminol, sesamolin	Antioxidant, and neuroprotective property in AD	Beheshtimanesh & Rajaei 2023
Withania somnifera.	Improves acetylcholinesterase enzyme activity and improves cognitive function. Active compound: Steroidal lactones (withaferin A, withanolide A)	Antioxidant, and neuroprotective properties in HD	Afewerky et al., 2022

Panax ginseng

Ginseng is a Chinese and Korean curative plant. It has therapeutic effects against diseases like cancer, hypertension, neurodegenerative disorders, and diabetes. Its effectiveness against neurodegenerative disorders is due to the neuroprotective influence of ginsenosides (Rb3 and Rg1). It hinders the upsurge of the nigral iron level and reduces divalent metal transporter-1 as well as levitation ferroportin-1 expression in PD (Ratan et al., 2021).

Rosmarinus officinalis

Rosemary plants comprise compounds that exhibit anti-inflammatory and antioxidant activities. The antioxidant potential shown by antioxidants such as ferulic acid and carnosic acid is better as compared to butylated hydroxyl toluene (BHT) and butylated hydroxyl anisole (BHA). It also possesses COX-2 inhibitors such as eugenol, carvacrol, ursolic acid, and oleanolic acid. These COX-2 inhibitors are used in the prevention of AD (Abhishek et al., 2022).

Matricaria chamomila

It is also known as Chamomile. It tranquilities the nerves helps in digestion, the immune system, and sleeplessness, excites the brain, and dismisses lethargy. It also has an anxiolytic effect (Shabir et al., 2022).

Utrica diocia

Generally, it is known as stinging nettle. It encompasses 5-hydroxy tryptamine, histamine, acetylcholine, and proteins (Taheri et al., 2022). It also has the potential for the treatment of hay fever and further allergy indications. Certain biological anti-inflammatory compounds are also present in this plant. Boron present in this plant helps to enhance estrogen levels in the body which is helpful for short-term memory. In Alzheimer's patients, it also uplifts the mood (Shabir et al., 2022).

Glycyrrhiza glabra

The active constituents present in glycyrrhiza are glycyrrhizic, glycyrrhizin, and glycyrrhetinic acid. AD is because of the presence of senile plaques and loss of neurons. The basic constituent of these plaques is Amyloid-β peptide. That's why it has an encouraging effect against Aβ fragments that cause apoptotic death of nerve cells (John et al., 2022).

Lavandula officinalis

Generally, it is known as lavender. The extract of the lavender plant contains borneol, aflapin, valerianic acid, luteolin flavonoids cineol, geraniol, linalool, linalyl acetate, camphor, ursolic acid, and butyric acid (Patel et al., 2022). GABA receptors assisted soothing effects of this plant on CNS are due to these compounds. The oil of this plant declines neurologic deficit, carbonyl species, level of MDA, ROS, and stroke volume in rats. A robust neuroprotective effect is shown by this plant. Amplified consumption of antioxidants progresses spatial learning in mice that are affected by Alzheimer's disease (Teleanu et al., 2022).

Ginkgo biloba

Steroids such as sesquiterpene lactones, diterpenic lactones, and ginkgolides A, B, C, J, and M are the main components of this plant. It is helpful in the improvement of memory through the elimination of free radicals as well as by raising the supply of oxygen (Adebayo et al., 2022). Hereafter; it is used for the treatment of Alzheimer's disease (AD) as a neuroprotective agent and reduced toxicity produced by nitric oxide (NO). The main flavonoids, like quercetin and isorhamnetin, are present in *G. biloba* (Xie et al., 2022).

Bacopa monniera

Bacopa monniera is sometimes known as 'Brahmi' and has been used in traditional Ayurvedic medicines. *B. monniera* is used for memory enhancement, stress relief for nervousness, and wisdom. The main bioactive ingredients of *B. monniera* are bacosides, bacopa saponins, betulinic acid, and stigmastanol that help to repair impede neurons, restore synaptic activity, conduct nerve impulse, and kinase activity (Sangeet et al., 2022).

Centella asiatica

Centella asiatica commonly known as Asiatic pennywort contains active compounds such as brahminoside, brahmoside, thankunoside, asiaticoside, isothankunoside, and brahminoside. The leaf of *C. asiatica* is used to strengthen and regenerate nervous function. It is also used to improve memory and to prevent and restore dementia (memory loss). It halts the death of β-amyloid, so used to treat AD and prevent toxicity of β-amyloid. In addition, it is used against depression, mental weakness, and epilepsy (Hambali et al., 2021).

Cassia obtusifolia

Isorubrofusarin, and rubrofusarin are active compounds of *C. obtusifolia*. It protects against dopaminergic neuronal degeneration in the substantia nigra and striatum in MPTP-induced PD in rat models. The supplementation of *C. obtusifolia* attenuates cellular damage, depolarization of the mitochondrial membrane, and diminished ROS generation (Rizqiyah et al., 2022).

CONCLUSION

Neurodegenerative diseases are serious life-threatening in which neural cells in the brain stop working or die. Mitochondrial dysfunction has been a major risk factor in the progression of neurodegenerative disorders. Mitochondria play a significant role in various cellular processes such as the production of ATP, intracellular calcium, and generation of reactive oxygen species (ROS), and improper function leads to diseases. It also plays a role in the development of the brain, neural activity, and differentiation. The use of medicinal plants has gained attention for centuries to treat many diseases. The medicinal plants and their phytochemicals protect against mitochondrial dysfunction-associated neurodegenerative diseases. Various biochemical extracts are developed from parts of the plant such as leaves, root, stem, rhizome, bark, stem, seeds, and flowers as well as the whole plant, and are useful in treating NDs. These plants have shown antioxidant as well as anti-inflammatory effects and also show a promising tool for treating neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, multiple sclerosis, and epilepsy.

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