EGCG for NDs Treatment

Subjects: Pathology

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Neurodegenerative diseases (NDs) are common chronic diseases typically characterized by a progressive loss of function and death of neurons in the brain or peripheral nervous system. NDs are among the most widespread health problems, affecting millions of people worldwide. The potential to treat NDs of the major bioactive compound of green tea, epigallocatechin-3-gallate (EGCG), is well documented. Numerous findings now suggest that EGCG targets protein misfolding and aggregation, a common cause and pathological mechanism in many NDs.

Keywords: green tea ; catechins ; epigallocatechin-3-gallate ; natural products ; neuroprotective ; neurodegenerative diseases ; Alzheimer's disease ; Parkinson's disease

1. Neurodegenerative Diseases

NDs are among the most widespread health problems, affecting millions of people worldwide [1]. Moreover, the number of individuals living with NDs such as Alzheimer's disease (AD) and Parkinson's disease (PD) is increasing, negatively affecting families, communities, and healthcare systems worldwide [2][3]. These disorders are becoming highly prevalent, in part due to global increases in human life expectancy, since NDs are age-dependent disorders [4][5]. Indeed, aging is the primary risk factor for most NDs [6]. The impact of these diseases will further increase in the coming decades as humans live longer lives [5].

NDs are common chronic diseases typically characterized by a progressive loss of function and death of neurons in the brain or peripheral nervous system [7]. Although NDs differ in their clinical presentation, they do share several common pathological mechanisms, which are characterized by multiple targets. The underlying pathobiological processes are largely shared, with most involving the formation of abnormal protein deposits at their onset and all exhibiting a common and characteristic pattern of neuronal degeneration in anatomically or functionally related regions [8]. This idea that diverse NDs have a common cause and pathological mechanism supports that a common therapeutic strategy for these devastating disorders might be possible [9].

AD, PD, amyotrophic lateral sclerosis (ALS), and Huntington’s disease (HD) are just a few examples of NDs that share similar biochemical reactions that lead to neurodegeneration [10][1][11]. Extensive evidence shows that misfolded proteins such as amyloid-beta peptide (Aβ) and tau in AD, alfa-synuclein (α-syn) in PD, and TAR DNA-binding protein 43 (TDP-43) in ALS participate in the formation, accumulation, and deposition of toxic misfolded aggregates [12][13][14]. Furthermore, protein misfolding (Table 1) is one of the principal causes of the onset and progression of NDs [10][15].

Table 1. Protein misfolding disorders affecting the nervous system [16].

Disease	Misfolded Protein(s)	Cell Types Primarily Affected	Clinical Feature(s)
Alzheimer’s disease (AD)	Aβ, tau	Hippocampal neurons	Dementia
Parkinson’s disease (PD)	α-syn	Substantia nigra Dopaminergic neuron	Parkinsonism
Multiple system atrophy (MSA)	α-syn	Basal ganglia and/or cerebellar oligodendrocytes	Parkinsonism and/or ataxia
Dementia with Lewy bodies (DLB)	α-syn	Cortical and/or hippocampal and/or striatal neurons	Dementia and/or parkinsonism
Huntington disease (HD)	huntingtin	Striatal neurons	Dementia
Spinocerebellar ataxia	Ataxin	Cerebellar neurons	Cerebellar ataxia
Amyotrophic lateral sclerosis (ALS)	Ataxin, FUS, TDP43, C9orf72 or superoxide dismutase 1 (SOD1)	Motor neurons	Muscular atrophy

Disease	Misfolded Protein(s)	Cell Types Primarily Affected	Clinical Feature(s)
Frontotemporal dementia	FUS, TDP43, C9orf72 or SOD1	Cortical neurons	Dementia
Gerstmann–Sträussler–Scheinker syndrome (GSS)	Prion protein	Cerebellar neurons	Ataxia
Fatal familial insomnia	Prion protein	Thalamic neurons	Insomnia
Creutzfeldt–Jakob disease (CJD)	Prion protein	Cortical neurons	Dementia

It has also been proposed that the overproduction of reactive oxygen species may have a complex role in promoting disease development [17][18]. In such cases, neurodegeneration results from the excessive production of free radicals induced by fragments of insoluble and/or overproduced misfolded proteins due to functional alterations in the mitochondria, inadequate energy supply, production of inflammatory mediators, and alteration of antioxidant defenses. Oxidative stress is, therefore, considered to be a common key player in the etiology and progression of these NDs [18][19].

Protein misfolding events can promote an excessive immune response causing neuroinflammation, which is also a common feature of NDs [20]. It is hypothesized that release of protein aggregates from neurons activates microglia triggering an inflammatory response characterized by liberation of inflammatory mediators, which contribute to disease progression and severity. For instance, in AD, the glial activation is followed by nuclear factor NF-kβ activation, synthesis, and release of proinflammatory cytokines including tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-12 that affect neuronal receptors with an overactivation of protein kinases [20].

Neurodegeneration can, therefore, be seen as a consequence of several detrimental processes, including protein aggregation, oxidative stress, and neuroinflammation, which finally lead to the loss of neuronal functions and cognitive impairments [10][18][20]. Since NDs are multifactorial diseases related to complex pathophysiological characteristics and complicated interactions with a large number of genes and proteins, there is still no effective drug treatment of these conditions [21][22].

1.1. Alzheimer’s Disease

AD is the most common ND worldwide and also the most common cause of dementia in elderly patients [3][23]. To date, only five drugs (tacrine, donepezil, rivastigmine, galantamine, and memantine) have been approved by the FDA to treat AD. The disease is currently incurable, with the available drugs only managing the symptoms and exhibiting severe side effects [21][24][25]. These drugs are based on a single-target strategy and focus on restoring neurotransmitter homeostasis. Finding disease-modifying AD therapies remains an urgent and unmet clinical need [26][27].

AD is a multifactorial disease characterized by the progressive accumulation of Aβ fibrils and abnormal tau proteins in extracellular spaces and in neurons, respectively, with associated neuron and synapse loss in multiple brain regions, especially in the frontal cortex and hippocampus [28][29]. The Aβ ($A\beta_{40}$ and $A\beta_{42}$ with 40 and 42 amino acids) and tau proteins (352 to 421 amino acids) have been clearly identified as the key misfolded proteins in AD [30][31].

At the microscopic level, the brains of AD patients are characterized by the concurrent presence of two classes of abnormal structures: extracellular amyloid plaques and intraneuronal neurofibrillary tangles (NFTs). Both structures are made of highly insoluble, densely packed filaments. These structures are formed by distinct soluble building blocks: Aβ peptides for plaques and tau for NFTs [30].

The senile plaques and NFTs are recognized as the two major neuropathological hallmarks of AD [32][33][34]. As the major component of senile plaques, the Aβ peptide is considered to be a crucial factor that underlies neuronal and synaptic dysfunction in AD progression [35]. Hence, the amyloid hypothesis proposes Aβ as the principal cause of AD, suggesting that clinical symptoms such as memory loss and cognitive decline are caused by misfolding of the extracellular Aβ protein accumulates in senile plaques and also by intracellular deposition of misfolded tau protein [35][36][37].

1.2. Parkinson’s Disease

PD is s considered to be the second most frequent ND in the world after AD [2][38]. PD is a progressive ND characterized by the selective loss of dopaminergic neurons in the substantia nigra pars compacta, located in the basal ganglia of the brain, resulting in the lack of dopamine in this organ [39][40][41]. Dopaminergic cell loss causes clinical signs and symptoms such as bradykinesia, rigidity, postural instability, and tremors [42].

So far, no cure has been available to treat PD, with pharmacological treatments mainly consisting of dopaminergic drugs, which are only therapies to reduce symptoms that are still limited by several side effects [43]. The majority of current drugs were approved for clinical use in the second half of the twentieth century, with the development of new drugs proceeding slowly since the FDA approval of levodopa in 1970. Levodopa remains the most effective drug therapy for the motor symptoms of PD, despite its long-term complications [44][45][46].

The pathological hallmark of PD is the presence of Lewy bodies within dopaminergic neurons in the brains of affected patients, and misfolded α-syn is known to be the principal component of Lewy bodies [47][48][49][50].

1.3. Natural Products against NDs

Many medicinal plants and their NPs have been reported as being able to alleviate the symptoms of NDs, including AD and PD [51][52][53][54][55][56]. Historically, NPs that are the most important sources of drugs may also hold promise for treating NDs [57][58].

A number of medicinal plants contain active components that are known to possess antioxidant action [59][60]. Abundant data in the literature suggests that dietary NPs found in fruits and vegetables are powerful antioxidants that offer health benefits against several oxidative stress-induced NDs, including AD [61][62]. Most of these NPs have remarkable antioxidant properties and act mainly by scavenging free radical species [60][63].

Since oxidative stress has long been associated with neurodegeneration, there has been a significant increase of interest in finding natural and synthetic compounds with antioxidant and anti-inflammatory effects as promising drug candidates for treating NDs [64]. In recent years, several natural antioxidants have been exploited for their actual or supposed beneficial effect against oxidative stress, including flavonoids and polyphenols [65][66]. Likewise, plant-derived antioxidant polyphenols have come under the research spotlight due to their potential to prevent oxidative stress [60][63].

Several dietary phytochemicals with known antioxidant properties and anti-amyloidogenic effects have been investigated for their potential beneficial effects, including curcumin, resveratrol, and green tea catechins like EGCG [62]. In particular, green tea catechins have been highlighted as having potential protective effects against NDs due to their diverse array of physiological actions, which include potent antioxidant effects [67][68].

Notably, because of their broad spectrum of pharmacological and biological activities, NPs are considered promising alternatives for treating neurodegeneration as they might play a role in ND drug development and discovery [69][70][71][72]. NPs remain a promising pool for discovering scaffolds with high structural diversity and various bioactivities that can be directly developed or used as starting points for optimization into novel drugs [73]. Many of these NPs are known as multi-targeted compounds as they alter multiple pathways at the molecular level, making them ideal therapeutic options for multifactorial and complex diseases such as NDs [74].

NPs have, therefore, emerged as potential multi-targeted agents for treating NDs. The major mechanisms through which NPs exert their neuroprotective effects include antioxidant, anti-inflammatory, antithrombotic, antiapoptotic, and neurotrophic activities, as well as acetylcholinesterase and monoamine oxidase inhibition [75]. Among neuroprotective NPs, phenolic molecules are of particular interest since most can target both amyloid aggregation and oxidative stress, as confirmed by numerous studies with phenolic compounds such as EGCG, curcumin, resveratrol, quercetin, and oleuropein [75][76][77][78].

2. EGCG for Treating Neurodegenerative Diseases

In light of the major potential of using green tea in ND treatment, green tea catechins have been extensively studied, including in vitro and in vivo studies and clinical trials [79][68]. The therapeutic potential of EGCG, the major bioactive compound of green tea, is now well known in ND research [80]. Over the last 20 years, EGCG has been shown to counteract oxidative stress and improves AD- and PD-like phenotypes in different in vitro and in vivo models (Table 2 and Table 3).

Table 2. Selected evidence of EGCG effectiveness on in vitro neurotoxicity models.

Experimental Models	Cell Line	Outcomes
Aβ-induced neurotoxicity model	**Primary culture**	**Elevates cell survival and decreases the levels of malondialdehyde (MDA) and caspase activity [81]**
Paraquat-induced PD model	**PC12 cells**	**Protects against paraquat-induced apoptosis via modulating mitochondrial function [82]**

Experimental Models	Cell Line	Outcomes
$A\beta_{1-42}$-exposure neuronal cells	Primary culture	Suppresses Aβ-induced BACE-1 upregulation [83]
6-OHDA-induced PD model	SH-SY5Y cells	Protects against cell death through STAT3 activation [84]
Aβ-induced oxidative and nitrosative cell death	BV2 microglia	Fortifies cellular antioxidant glutathione pool via elevated expression of γ-glutamylcysteine ligase [85]
Human neuronal cells	MC65 cells (overexpressing APP)	Suppresses Aβ -induced neurotoxicity by inhibiting c-Abl/FE65 nuclear translocation and GSK3β activation [86]
ROT-injured murine brain cultures	Primary mesencephalic cell cultures	No influence on the survival of dopaminergic neurons in mesencephalic cultures [87]
DDT-induced cell death	SH-SY5Y cells	Activates endogenous neuroprotective mechanism(s) that can protect against cell death [88]
Fibril-induced neurotoxicity	HEK-293 cells(overexpressing α-syn)7PA2 cells(overexpressing APP)PC12 cells	Remodels mature α-syn and amyloid-β fibrils and reduces cellular toxicity [89]
MPP+-induced PD model	PC12 cells	Suppresses oxidative stress via the SIRT1/PGC-1α signaling pathway [90]
6-OHDA-induced PD model	N27 cells	Pretreatment with EGCG protected against neurotoxicity by regulating genes and proteins involved in brain iron homeostasis, especially modulating hepcidin levels [91]
Microglia-mediated neuroinflammation	EOC 13.31	Attenuates Aβ-induced inflammation and neurotoxicity [92]
α-syn induced neurotoxicity	α-syn transduced-PC12 cells	Protects cells against α-syn-induced damage by inhibiting the overexpression and fibrillation of α-syn in the cells [93]
Cu(II)-mediated toxicity	α-syn transduced-PC12 cells	Inhibits the overexpression and fibrillation of α-syn and reduces Cu(II)-induced oxidative stress [94]

BACE-1: Beta-secretase-1; BV2: Murine brain microglial cell line; DDT: Dichlorodiphenyltrichloroethane; EOC 13.31: Mouse immortalized microglia cell line; GSK3β: Glycogen synthase kinase 3β; HEK-293: Human kidney (embryonic) cell line; 6-OHDA: 6-hydroxydopamine; 7PA2: CHO cells overexpressing APP; MC65: Human neuroblastoma cell line (MC65) that conditionally expresses a C-terminal derivative of APP; MPP+: 1-methyl-4-phenylpyridinium (ion); N27: Rat mesencephalic dopaminergic neuronal cell line; PD: Parkinson´s disease; PC12: Rat adrenal phaeochromocytoma cell line; ROT: Rotenone; SH-SY5Y: Human neuroblastoma cell line; SIRT1/PGC-1α: Sirtuin 1/peroxisome proliferator-activated receptor gamma coactivator 1-α; STAT3: Signal transducer and activator of transcription-3.

Table 3. Main evidence of the neuroprotective effects of EGCG in animal models.

Alzheimer's Disease		
Experimental Models	**Animal Strain**	**Outcomes**
Transgenic mice overproducing Aβ	Tg APPsw (line 2576)	Decreases Aβ levels and plaque associated with promotion of the nonamyloidogenic α-secretase proteolytic pathway [95]
Stereotaxic surgery lesion	Wistar rats	Restores β-amyloid-induced behavioral derangements relating to coordination and memory abilities [96]
Transgenic mice overproducing Aβ	Tg APPsw (line 2576)	Provides cognitive benefit and modulates tau pathology [97]
Transgenic mice overproducing Aβ	Tg APPsw (line 2576)	Inhibits GSK3β activation and c-Abl/Fe65 complex nuclear translocation [86].
LPS-induced AD model	ICR mice	Inhibition of Aβ generation through the inhibition of β- and γ-secretase activity [98]
Aβ-induced AD model	ICR mice	Downregulates β- and γ-secretase activities and eventually decreases toxic Aβ levels in the cortex and hippocampus [99]
D-gal-induced AD model	Kunming mice	Increases the activities of antioxidant enzymes and reduces the activation of caspase-3 [100]

Alzheimer's Disease		
Experimental Models	**Animal Strain**	**Outcomes**
LPS-induced AD model	ICR mice	Prevents activation of astrocytes and elevation of proinflammatory cytokines including TNF-α, as well as the increase of inflammatory proteins such as inducible nitric oxide synthase (iNOS) andcyclooxygenase-2 (COX-2) [101]
Streptozotocin-induced AD model	Wistar rats	Neuroprotective effects through reversion of oxidative stress and decreased acetylcholinesterase activity [102]
Transgenic mice overproducing Aβ	Tg CRND8 mice	Ameliorates some behavioral manifestations and cognitive impairments [103]
Senescence-accelerated mouse (SAM)	SAMP8	Attenuates cognitive deterioration by upregulating neprilysin expression [104]
Senescence-accelerated mouse (SAM)	SAMP8	Oral consumption of EGCG ameliorates memory impairment and reduces the levels of $A\beta_{1-42}$ and BACE-1 [105]
Aluminum-induced AD model	Wistar rats	Oral administration of EGCG nanoparticles attenuates neurobehavioral deficits and Aβ and Tau pathology [106]
Transgenic mice expressing mutant human APP and presenilin 1	APP/PS1 mice	Inhibition of endoplasmic reticulum stress-associated neuronal apoptosis [107]
Transgenic mice expressing mutant human APP and presenilin 1	APP/PS1 mice	Combination of EGCG with ferulic acid improves behavioral deficits, ameliorating cerebral amyloidosis and reducing Aβ generation [108]
Transgenic mice producing abundant Aβ plaques	APPswe/PS1dE9 mice	Oral administration of EGCG/ascorbic acid nanoparticles reduces Aβ plaque burden, $A\beta_{42}$ peptide levels, and neuroinflammation while enhancing synaptogenesis, memory, and the learning process [109]
Transgenic mice producing abundant Aβ plaques fed with a high-fat diet (mixed model of familial AD and T2DM)	APPswe/PS1dE9 mice	Decreases brain Aβ production and plaque burden by increasing the levels of α-secretase and reduces neuroinflammation by the decrease in astrocyte reactivity and toll-like receptor 4 (TLR4) levels [110]
Transgenic mice expressing mutant human APP and presenilin 1	APP/PS1 mice	Reduces Aβ plaques in the brain [111]
Parkinson's disease		
Experimental models	**Animal strain**	**Outcomes**
MPTP-induced PD model	C57/BL mice	Alleviates dopamine neuron loss in the substantia nigra and tyrosine hydroxylase (TH) protein level depletion [112]
MPTP-induced PD model	C57B6 mice	Decreases expressions of nitric oxide synthase in the substantia nigra [113]
6-OHDA-induced PD model	Wistar rats	Reverses the striatal oxidative stress and immunohistochemistry alterations [114]
MPTP-induced PD model	C57BL/6J mice	Regulates the iron-export protein ferroportin in substantia nigra, reduces oxidative stress, and exerts a neurorescue effect [115]
MPTP-induced PD model	C57BL/6J mice	May exert neuroprotective effects by modulating peripheral immune response [116]
ROT-induced PD model	*Drosophila melanogaster*	Ameliorates neuronal and behavioral defects by remodeling gut microbiota and turandot M (TotM) expression [117]
ROT-induced PD model	Wistar rats	Reduces NO level and lipid peroxidation production, increases the levels of catecholamines in the striatum, and reduces the levels of neuroinflammatory and apoptotic markers [118]
Amyotrophic lateral sclerosis		
Experimental models	**Animal strain**	**Outcomes**

Alzheimer's Disease		
Experimental Models	**Animal Strain**	**Outcomes**
Transgenic mice carrying a human SOD1 with a G93A mutation	**B6SJL Tg (SOD1-G93A)**	**Increases the number of motor neurons and reduces the concentration of NF-kB caspase-3 and iNOS [119]**
Transgenic mice carrying a human SOD1 with a G93A mutation	**B6SJL Tg (SOD1-G93A)**	**Prolongs symptom onset and life span, preserving more survival signals and attenuating death signals [120]**
	Huntington's disease	
Experimental models	**Animal strain**	**Outcomes**
Transgenic flies expressing mutant huntingtin fragments with 93 glutamines	***Drosophila melanogaster***	**Modulates early events in huntingtin misfolding and reduces toxicity [121]**
3-nitropropionic acid induced cognitive dysfunction and glutathione depletion	**Wistar rats**	**Improves memory and restores glutathione system functioning [122]**
	Familial amyloidotic polyneuropathy (FAP)	
Experimental models	**Animal strain**	**Outcomes**
Transgenic mice for human TTR	**Tg hTTR V30M mice**	**Decreases non-fibrillar TTR deposition and disaggregation of amyloid deposits [123]**

APP/PS1 or PS1dE9: Double transgenic mice expressing a chimeric mouse/human amyloid precursor protein (Mo/HuAPP695swe) and a mutant human presenilin 1 (PS1-dE9); B6SJL Tg: Transgenic mice expressing a G93A mutant form of human SOD1; 6-OHDA: 6-hydroxydopamine; iNOS: Inducible nitric oxide synthase; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; ROT: Rotenone; SAMP8: Senescence-accelerated mouse prone; Tg APPsw (line 2576): Overexpresses a mutant form of APP (isoform 695) with the Swedish mutation (KM670/671NL), resulting in elevated levels of Aβ and ultimately amyloid plaques; Tg hTTR V30M mice: Transgenic mice expressing human transthyretin (TTR) with the V30M point mutation.

In addition to displaying well-demonstrated neuroprotective effects, EGCG has emerged as a promising modulator of amyloid aggregation that can prevent the toxicity of misfolded protein aggregates in a range of experimental models of NDs. A wealth of evidence is now available to support EGCG as a potent anti-amyloidogenic agent that interacts with a set of amyloidogenic proteins, such as Aβ in the case of AD and α-syn in the case of PD (Table 4).

Table 4. Main evidence that EGCG targets toxic misfolded aggregates in neurodegenerative diseases.

Protein	Main Outcome	Experimental Techniques
Huntingtin	**Modulates misfolding and oligomerization [121]**	**Dot-blot and AFM**
$A\beta_{42}$ α-syn	**Redirects aggregation cascades and thus prevents the formation of toxic, β-sheet–rich aggregation products [124]**	**ThT fluorescence, TEM, CD, and dot-blot**
$A\beta_{42}$ α-syn	**Binds to β-sheet-rich aggregates remodeling mature fibrils [89]**	**ThT fluorescence, TEM, AFM, and CD**
α-syn	**Inhibits and disaggregates oligomers [125]**	**Confocal single-particle fluorescence spectroscopy**
$A\beta_{40}$	**Induces the formation of nontoxic well-structured oligomers [126]**	**Solid-state NMR and MTT assay**
$A\beta_{40}$	**The amyloid remodeling activity is dependent on auto-oxidation of the EGCG [127]**	**ThT fluorescence, congo red assay, EM, AFM, CD, and MTT assay**
$A\beta_{42}$ $PrP_{106–126}$	**Reduces the number of fibrils [128]**	**NMR, TEM, and CD**
α-syn	**Inhibits oligomer toxicity, moderately reduces membrane binding, and immobilizing the oligomer -terminal tail [129]**	**Calcein release assay, LSCM, NMR, TEM, CD, DLS, SAXS, MTT assay, and ITC**
Tau	**Prevents aggregation and toxicity [130]**	**ThT fluorescence, AFM, and MTT assay**

Protein	Main Outcome	Experimental Techniques
α-syn	Inhibits fibrillation and disaggregates amyloid fibrils [83]	ThT fluorescence, CD, NMR, AFM, and TEM
α-syn	Aggregates showed small fibrillar length, and less toxicity correlates with reduction of exposed hydrophobic surface [131]	ThT fluorescence, CD, FTIR, ANS fluorescence, TEM, NMR, SPR, and MTT assay
α-syn	Protects against membrane disruption and cytotoxicity caused by oligomers [132]	ThT fluorescence, tyrosine intrinsic fluorescence, TEM, CD, DLS, FTIR, AFM, and MTT assay
$A\beta_{40}$	Remodels toxic oligomers to nontoxic aggregates [133]	DEST, NMR, ANS fluorescence, DLS, and TEM
$A\beta_{42}$	Remodels soluble Aβ assemblies into less toxic species with less exposed hydrophobic sites [134]	Comparative analysis of N-R2 and DEST NMR combined with WAXD, TEM, DLS, and extrinsic fluorescence
$A\beta_{42}$	Higher EGCG-to-$A\beta_{42}$ ratios promote the rate of aggregation, while lower EGCG-to-$A\beta_{42}$ ratios inhibit the aggregation rate [135]	ThT fluorescence, TEM and EPR
Aβ40	Alleviates aggregation induced by metal ions [111]	ThT fluorescence, TEM, ICP-MS, UV–Vis spectroscopy
Tau	Dual effect on aggregation inhibition and disassembly of full-length Tau [136]	ThT fluorescence, MALDI-TOF analysis, and ITC
α-syn	EGCG microparticles reduce the cytotoxic effects of oligomers; besides, they increase the activity of other antiamyloidogenic compounds when used together [137]	ThT fluorescence, CD, DLS, TEM, and cell viability assay

ANS: 8-anilino-1-naphthalenesulfonic acid ammonium salt; AFM: Atomic force microscopy; CD: Circular dichroism; DEST: ^{15}N-dark state exchange saturation transfer; DLS: Dynamic light scattering; EPR: Electron paramagnetic resonance; FTIR: Fourier-transform infrared; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; ICP-MS: Inductively coupled plasma-mass spectrometry; ITC: Isothermal titration calorimetry; LSCM: Laser scanning confocal microscopy; MALDI-TOF: Matrix-assisted laser desorption ionization time-of-flight mass spectrometry; NMR: Nuclear magnetic resonance; SAXS: Small-angle x-ray scattering; SPR: Surface plasmon resonance; TEM; Transmission electron microscopy; ThT: Thioflavin T; UV–Vis: Ultraviolet-visible; WAXD: Wide-angle X-ray diffraction.

2.1. Evidence from In Vitro Neurotoxicity Models

In the 1990s, studies with the Aβ-induced neurotoxicity model showed that the presence of $A\beta_{1-42}$ leads to neurotoxicity and increased protein oxidation and, as a result, oxidative stress [138][139][140]. The neurotoxicity of the Aβ protein is mediated through oxygen-free radicals and can be attenuated by antioxidants and free radical scavengers. The attenuation of oxidative stress by antioxidant compounds can, therefore, be a potential therapeutic strategy for treating AD. In the early 2000s, the potent antioxidant properties of the green tea polyphenol EGCG were investigated in an Aβ-induced neurotoxicity model using cultured hippocampal neurons, with the results suggesting that EGCG has protective effects against Aβ-induced neuronal apoptosis from scavenging reactive oxygen species. This was one of the first reports on the benefits of EGCG for preventing AD [81].

Subsequently, the molecular mechanism underlying the neuroprotective effect of EGCG in the Aβ-induced neurotoxicity model was investigated with a focus on the cellular metabolism of reduced glutathione with antioxidant properties. The results indicated that EGCG treatment fortified the cellular glutathione pool via elevated expression of γ-glutamylcysteine ligase [85].

Oxidative stress has also been shown to induce BACE-1 protein upregulation in neuronal cells, which is the rate-limiting enzyme in APP processing and Aβ generation, as well as being a therapeutic target for AD [141][142]. Although exposure of $A\beta_{1-42}$ to neuronal culture increased BACE-1 protein levels, EGCG treatment significantly attenuated the Aβ-induced production of radical oxygen and β-sheet structure formation [83].

In the early 2010s, it was known that EGCG inhibits Aβ and α-syn fibrillogenesis in cell-free assays; researchers then investigated whether EGCG can remodel insoluble Aβ and α-syn aggregates in a cell model system [89]. This research showed that EGCG can reduce cellular toxicity of mature Aβ and α-syn fibrils by remodeling their structure. The EGCG-mediated remodeling of β-sheet-rich amyloid structures leads to the appearance of smaller amorphous protein aggregates that are nontoxic to mammalian cells [89].

In 2017, the employment of α-syn-transduced PC12 cells was performed to investigate the protective effects of EGCG, providing evidence that EGCG can protect these cells against α-syn-induced damage by inhibiting the overexpression and fibrillation of α-syn in the cells [93].

A more recent study reported that EGCG can interfere with Cu(II)-induced fibrillation of α-syn and protect cell viability. The researchers demonstrated that EGCG inhibits the generation of Cu(II)-induced reactive oxygen species (ROS), leading to reduced overexpression and fibrillation of α-syn in the cells. Moreover, the combination of Cu and EGCG exhibited better cryoprotection than EGCG alone. Here, it is worth noting that Cu(II) is an oxidant that also accelerates fibrillation and protein aggregation [94].

There are also pieces of evidence of neuroprotective effects of EGCG in neurotoxicity models of PD Parkinsonian neurotoxins include compounds like 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone (ROT), and paraquat. EGCG has demonstrated remarkable neuronal protection against paraquat, 6-OHDA, and MPP+ neurotoxicity, though not against ROT [82][84][87][90][91].

In an evaluation of the neuroprotective effects of EGCG on ROT-treated dissociated mesencephalic cultures and organotypic striatal cultures, EGCG partially counteracted the effects of ROT in striatal slice cultures through the reduction of nitric oxide (NO) but did not dissociate cells against ROT toxicity [87]. Although the latter study did not demonstrate that EGCG protects against ROT-induced neurotoxicity in cell models, it was recently reported that EGCG had a neuroprotective effect in vivo on ROT-induced PD models [117][118]. Together, these results from in vitro neurotoxicity models support the notion that EGCG can be used as a neuroprotective agent to treat NDs.

2.2. Evidence from Animal Models

Because of its broad spectrum of pharmacological activities, EGCG displayed therapeutic potential on various in vivo models of NDs, including AD, PD, HD, and ALS (Table 2). The therapeutic potential of EGCG in an animal model of AD was first reported in 2005 using Swedish mutant APP-overexpressing mice (Tg APPsw). The researchers demonstrated that intraperitoneal (i.p.) injection (20 mg/kg) of EGCG significantly decreased both Aβ levels and Aβ plaques in the brain [95].

Moreover, EGCG similarly reduced Aβ deposition in Tg APPsw when administered orally in drinking water (50 mg/kg), as observed in a study conducted in 2008. The results further indicated that EGCG provides cognitive benefits and modulates tau hyperphosphorylation in these AD transgenic mice [97]. Another study involving Tg APPsw mice focused on the molecular mechanism of neuroprotective action of EGCG. EGCG was found to reduce Aβ-induced neurotoxicity by inhibiting glycogen synthase kinase-3β (GSK-3β) activation and c-Ab/FE65 complex nuclear translocation in these transgenic mice [86]. In addition to transgenic mouse models of human AD pathology, toxin-induced models are also considered to be suitable for exploring the therapeutic treatments of NDs. The neuroprotective effects of EGCG have been reported in toxin-induced AD models such as Aβ-induced, LPS-induced, D-galactose (D-gal)-induced, streptozotocin-induced, and aluminum chloride ($AlCl_3$)-induced AD models [143].

Two studies from the 2000s and early 2010s used the LPS-induced AD model with orally administered EGCG (1.5 or 3 mg/kg). They demonstrated that EGCG prevents apoptotic cell death by preventing elevated levels of Aβ via the inhibition of β- and γ-secretases. The findings also showed that EGCG prevents memory impairment and amyloidogenesis by inhibiting neuroinflammatory-related cytokines released from astrocytes [98][101].

The oral administration of EGCG (1.5 or 3 mg/kg) has also been shown to protect against Aβ-induced memory and coordination impairment in Aβ-induced AD rats, while intragastrical (i.g.) administration of EGCG (2 or 6 mg/kg) had potent neuroprotective effects on aging mice induced by D-gal, acting via antioxidative and antiapoptotic mechanisms [99][100]. Furthermore, additional evidence from toxin-induced models confirms the potential of EGCG to improve oxidative stress with streptozotocin-induced and $AlCl_3$-induced models. These studies showed that EGCG can reduce oxidative stress in peripheral and brain tissue and that it may suppress behavioral changes related to toxin-induced cognitive deficits in these animal models [102][106].

The senescence-accelerated mouse prone (SAMP8), a spontaneous animal model of accelerated aging, has also been used in studies with EGCG. This animal model is considered a robust model for studying the pathology of sporadic AD [144]. Studies have demonstrated the ability of EGCG to attenuate cognitive deterioration and memory deficits in these mice via i.g administration of low (5 mg/kg) and high doses (15 mg/kg) [104][105].

Returning to the transgenic mice model, in the late 2010s, studies with APP/PS1 mice provide additional evidence for the in vivo neuroprotective properties of EGCG. One study investigated the effect of EGCG on neuronal apoptosis induced by endoplasmic reticulum (ER) stress, revealing that EGCG treatment inhibited ER-stress-induced apoptosis in the cerebral

cortex of APP/PS1 mice [107].

It has also been suggested that therapies combining EGCG and ferulic acid in aged APP/PS1 mice confer additional benefits over single treatments in terms of improving behavioral deficits, ameliorating cerebral amyloidosis, and reducing Aβ generation [108]. There is also evidence that dual-drug loaded nanoparticles of EGCG/ascorbic acid enhance the therapeutic efficacy of EGCG in APPswe/PS1 transgenic mice [109]. Recently, a study with a well-established preclinical mixed model of familial AD and type 2 diabetes mellitus (T2DM) using transgenic APP/PS1 mice fed with a high-fat diet revealed that EGCG improves cognitive deficits aggravated by an obesogenic diet through modulation of the unfolded protein response [110].

EGCG has also been widely studied in toxin-induced animal models of PD, including the classical 6-OHDA and MPTP, which are the two most extensively used neurotoxins for in vivo PD models [145]. The neuroprotective effect of EGCG on the MPTP-induced PD model was first reported in the early 2000s. Oral administration of EGCG (2 and 10 mg/kg), as well as green tea extract (0.5 and 1 mg/kg) containing high levels of EGCG, clearly alleviated dopamine neuron loss in the substantia nigra [112]. Another study tested whether EGCG attenuates MPTP-induced PD in mice by inhibiting neuronal NO synthase (nNOS) expression. The outcomes revealed that both green tea extract and EGCG decreased expressions of nNOS in the substantia nigra [113].

In the 2010s, additional studies using the MPTP-induced PD model confirmed the neuroprotective effect of EGCG against MPTP neurotoxicity [115][116]. EGCG was shown to regulate the iron-export protein ferroportin in substantia nigra, reducing oxidative stress and exerting a neurorescue effect against MPTP-induced functional and neurochemical deficits in mice [115].

A 2018 study with an MPTP-induced mouse model of PD focused on the effects of EGCG on the peripheral immune system. The outcomes revealed that EGCG treatment protects dopaminergic neurons from MPTP-induced degeneration, restoring the movement behavior of these mice. In addition, EGCG inhibited the expression of neuroinflammatory cytokines and reversed the T cell dysfunction in the peripheral immune system of MPTP mice [116].

An in vivo study with a 6-OHDA-induced PD rat model showed that EGCG administered by gavage (10 mg/kg) reverts the striatal oxidative stress and immunohistochemistry alterations. Furthermore, EGCG treatment attenuated the behavioral changes, indicating neuroprotection manifested as decreased rotational behavior, increased locomotor activity, anti-depressive effects, and improvement of cognitive dysfunction [114].

Recently, another study with a PD rat model focused on the effects of EGCG on ROT-induced motor and neurochemical dysfunctions. This study demonstrated that the possible neuroprotective effects of EGCG (100 or 300 mg/kg i.p.) against ROT-induced motor and neurochemical dysfunctions in rats are associated with its antioxidant effects, prevention of mitochondrial dysfunction, prevention of neurochemical deficiency, anti-neuroinflammatory effects, and anti-apoptotic effects [118].

EGCG supplementation was recently shown to result in profound changes in gut microbial compositions in an invertebrate PD model, restoring the abundance of a set of bacteria [117]. The study with PTEN induced putative kinase 1 (PINK1) mutant flies showed that EGCG ameliorates neuronal and behavioral defects by remodeling gut microbiota [117]. In PD animal models, gut microbiota regulates motor deficits and neuroinflammation [146]. Interestingly, emerging evidence suggests that EGCG remodels the architecture of human gut microbiota [147][148].

The wealth of evidence from studies with animal AD and PD models suggests that EGCG may be useful for treating AD and PD. However, the available evidence of EGCG neuroprotective effects is not just limited to studies with AD and PD animal models. EGCG has also demonstrated in vivo potential in preventing other NDs in studies published since the 2000s, including transgenic mouse models of ALS and FAP, a *Drosophila* model of HD, and a 3-nitropropionic acid-induced rat model of HD [121][119][120][122][123]. Taken together, these preclinical animal studies suggest that EGCG has considerable potential as a drug candidate for neurodegenerative drug discovery.

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