Phytochemicals mitigate AD mitochondrial dysfunctions

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a decline in cognitive function and neuronal damage. Although the precise pathobiology of AD remains elusive, accumulating evidence suggests that mitochondrial dysfunction is one of the underlying causes of AD. Mutations in mitochondrial or nuclear DNA that encode mitochondrial components may cause mitochondrial dysfunction. In particular, the dysfunction of electron transport chain complexes, along with the interactions of mitochondrial pathological proteins are associated with mitochondrial dysfunction in AD. Mitochondrial dysfunction causes an imbalance in the production of reactive oxygen species, leading to oxidative stress (OS) and vice versa. Neuroin-flammation is another potential contributory factor that induces mitochondrial dysfunction. Phy-tochemicals or other natural compounds have the potential to scavenge oxygen free radicals and enhance cellular antioxidant defense systems, thereby protecting against OS-mediated cellular damage. Phytochemicals can also modulate other cellular processes, including autophagy and mitochondrial biogenesis.

Keywords: Alzheimer's disease ; mitochondrial dysfunctions ; phytochemicals

1. Introduction

Several studies have demonstrated that mitochondrial dysfunction leads to several neurodegenerative diseases, including Alzheimer's disease (AD) [1][2][3]. AD shows common symptoms such as insanity and leads to a morbid state and death in the aged population [4]. In both familial and sporadic patterns, AD is characterized by dual unique medical hallmarks: senile plaques formed via the extracellular accumulation of amyloid-β (Aβ) peptide and intracellular deposition of neurofibrillary tangles (NFTs) formed via hyperphosphorylation of tau proteins [5][6]. These phenomena are accompanied by both pre- and postsynaptic and neuronal casualty [7]; however, the pathogenesis of AD pathogenesis is still unclear. In addition, multiple reports demonstrate that the alterations in axonal transport (AT) are the precise culprit for the development of neurodevelopmental diseases such as AD [8]. AD in mammals involves the atypical decomposition of several abnormal organelles like mitochondria, resulting in the degeneration of senile plaques along with abnormal neuronal expansion leading to a decline in neurites [9]. Phytochemicals or plant-derived chemical compounds are currently under research with unestablished health benefits [10]. Phytochemicals show multiple beneficial effects on mitochondrial dysfunction [11]; however, enough investigations have not been performed yet examining their clinical application.

A wide range of studies have demonstrated that numerous bioactive phytochemicals and other organic compounds may improve the treatment of AD [12]. Phytochemicals, including polyphenolic compounds that are present in numerous plants exhibit several essential properties such as anti-inflammatory potential, DNA repair, autophagy, and antioxidant activities [13]. In the brains of AD patients as well as transgenic AD mouse models, APP and Aβ are present in mitochondrial membranes, interrupting the mitochondrial electron transport system [14]. Potential therapeutic effects of these phytochemicals include antioxidant and anti-inflammatory activities via modulation of Aβ toxicity. Mitochondrial dysfunction discharges excessive quantities of H_2O_2, which ultimately leads to irreversible cellular dysfunction and damage in the brain [15]. Aggregated Aβ peptides, H_2O_2-induced hydroxyl radical, and mitochondrial dysfunction caused by APP in AD may restrain in addition to pharmacological approaches using phytochemicals that preserve mitochondrial dynamics [16]. Owing to their therapeutic capabilities, phytobioactive compounds have been deliberated as favorable beneficial agents for AD and age-related diseases [17].

2. Mitochondrial Dysfunction in AD via ROS Production

Oxidative stress (OS) occurs owing to the imbalance between the generation of reactive oxygen species (ROS) and cellular antioxidant potential. OS stands for excess quantities of ROS production that incur damage to nucleic acids and small molecules such as proteins or lipids. OS can lead to neuronal, specifically causing neurodegenerative diseases and

cellular aging processes [18]. Restrained ROS production has physiological roles, particularly in controlling cellular redox equilibrium and regulating intracellular signal transduction [19][20]. ROS (collectively, H_2O_2, OH, and $O_2)^{\cdot -}$) may be the causative factor leading to defects in mitochondrial respiration and the development processes of the human brain that are accompanied by augmented ROS generation. They also contribute to dynamic changes in the brain during AD and aging progression (Figure 1).

The primary origins of ROS production in the brain under functional circumstances as well as in pathological processes (e.g., neurological diseases) are complex I and complex III of the respiratory chain. Complex I discharge superoxide ($O_2^{\cdot -}$) into the intermembrane space such as the matrix, and complex III liberates $O_2^{\cdot -}$ to both sides of the electron transport chain (ETC) or inner mitochondrial membrane. Hydrogen peroxide (H_2O_2) can be generated from $O_2^{\cdot -}$ by an enzyme called superoxide dismutase. Both molecules can cross the inner membranes and can produce extremely reactive hydroxyl radical (·OH). Under physiological conditions, the proton movements and the respiratory state of mitochondria produce H_2O_2 and O_2^- from the electron transport chain (ETC) [21]. Complex IV also enhances the generation of ROS, whereas complexes III and V generate a minimal amount of ROS [22]. Apart from these, defective production and detoxification of ROS are critically involved in mitochondrial dysfunction [23]. During the aging process, a high amount of ROS is generated due to defective mitochondria. Likewise, a decline in antioxidant enzyme activities ensues, leading to increased ROS production[23][24]. Excess ROS production adversely affects the ETC; complexes I, III, and IV appear to be the most affected, while complex II remains undisturbed [23][25].

Figure 1. Mitochondrial dysfunction and oxidative stress in neurons lead to the development of AD. Typically, ROS are produced via numerous mechanisms such as ER stress, mitochondrial dysfunction, neuroinflammation, and excitotoxicity. Excessive ROS generation leads to oxidative stress (OS), which is responsible for mitochondrial dysfunction. OS prevents the degradation of protein molecules and impairs the clearance of misfolded proteins, which subsequently leads to protein aggregation causing neuronal death and AD.

3. Mitochondrial Deformity as an Outcome of AD Progression

Accumulating evidence has demonstrated that metabolic alterations play a pivotal role in AD progression mediated by several pathogenic factors such as ROS, mitochondrial deformity, and Aβ load [26]. Extensive research has shown that ROS formation mediated by Aβ and calcium imbalance leads to mitochondrial injuries (Figure 2), which are categorized as a secondary mitochondrial failure. Hippocampal expression of mutant APP and Aβ in mouse HT22 cell lines led to impaired mitochondrial dynamics, alterations of mitochondrial structure, and action in neurons [27]. Amyloid precursor proteins (APP) can lead to the overexpression of mitochondrial protein import channels in AD sensitive brain regions, leading to mitochondrial malfunction [28]. Alternatively, several studies have shown that Aβ precisely disorganizes mitochondrial dynamics and hinders critical enzymatic functions. Lustbader et al. reported that Aβ-binding alcohol dehydrogenase (ABAD) directly interacts with Aβ and leads to Aβ-linked apoptosis, mitochondrial toxicity, and free-radical formation in neuronal cells [29]. Furthermore, voltage-dependent anion-selective channel 1 protein (VDAC1) is excessively expressed in AD-vulnerable brains, which combines with phosphorylated tau and Aβ to block mitochondrial intramembranous pores, accelerating mitochondrial impairment [30]. A distinct number of in vitro analysis proposed a connection among augmented Aβ levels, mitochondrial abnormal function, and oxidative burden, collectively leading to AD progression. Nevertheless, the origin of the impairment of mitochondrial dynamics in AD pathogenesis remains elusive.

4. Phytochemicals Prevent Mitochondrial Dysfunction and Improve Biogenesis

Several phytochemicals function to neutralize ROS and activate cellular antioxidant mechanisms. Phytochemicals also enhance mitochondrial biogenesis and protect neurons from toxic damage [31]. Additionally, phytochemicals can stimulate cell survival pathways by triggering many growths signaling pathways. In this section, we discuss recently explored phytochemicals that have been shown to protect neurons from mitochondrial dysfunction in AD by stimulating numerous signaling pathways. Molecular targets, experimental model, research outcomes, and molecular signaling systems of these phytochemicals are summarized in Table 1. Additionally, epidemiological as well as clinical interventions have been displayed that dietary phytochemicals, for example Mediterranean diet, exhibit beneficial properties in dementia patients, AD, PD, depressive disorders, and mild cognitive impairment [32]. Secondary metabolites of phytochemicals from Mediterranean diet contain ω-3 polyunsaturated fatty acids which has been described to maintain cognitive function in human studies [33].

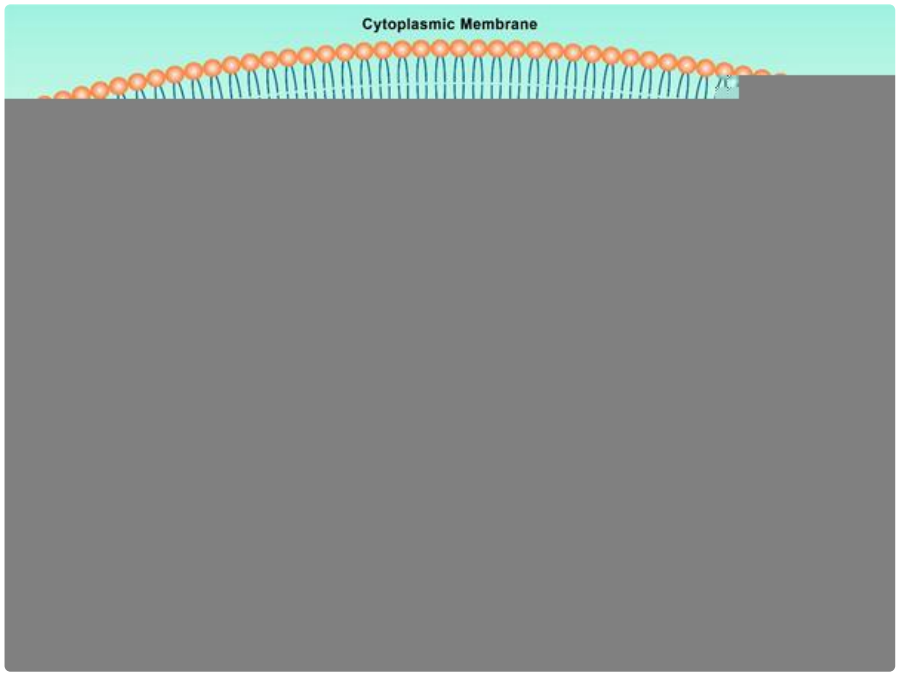

Figure 2. Mitochondrial dysfunction in AD pathogenesis. Aβ and Tau initiate mitochondrial dysfunctions that can result in the modulation of several factors. ROS is generated, which causes lipid peroxidation and DNA damage to initiate apoptosis. Damaged mitochondria demonstrate a decrease in mitochondrial membrane potential (ΔΨm) as a result of the activation of mitochondrial permeability transition pores (mPTPs), which release cytochrome c and apoptosis-inducing factor (AIF), and consequently, initiate apoptosis pathway. Aβ and pTau improve mitochondrial fission and mitophagy.

Anthocyanins control mitochondrial fission/fusion pathways, prevent complex I APP Swedish K670N/M671L double mutation (APPswe), and promote normal mitochondrial dynamics [34]. Numerous phenolic compounds exert neuroprotective effects in AD and other neurodegenerative diseases and. Sulfuretin, a well-known flavonoid glycoside derived from *Albizia julibrissin*, protects primary hippocampal neuronal cells and SH-SY5Y neuroblastoma cells from Aβ-mediated neurotoxicity [35]. Dietary (poly)phenols have been found to cross blood-brain barrier (BBB) in endothelial cells and shown neuroprotective potential [36]. Polyphenol resveratrol, derived from grapes and black barriers, protects HT22 and PC12 cells against Aβ toxicity by activating the PI3K/Akt/Nrf2 pathway [37]. In addition, resveratrol prevents cell death and represses ROS production induced by Aβ toxicity by enhancing PI3K/Akt phosphorylation, the protein levels of SOD, HO-1, and GSH, and Nrf2 nuclear translocation [38]. Resveratrol also found to cross BBB [39]. Quercetin, a hydroxytyrosol derived from olives, prompts mitochondrial biogenesis and enhances muscle mtDNA in adult men [40]. Tea polyphenols (TPs) mitigate OS in H_2O_2-induced human neuroblastoma SH-SY5Y cells via Keap1-Nrf2 signaling initiation and decrease in H_2O_2-mediated cell death, as well as ROS and H_2O_2 levels to protect against mitochondrial dysfunction [41]. Liquiritigenin prompts mitochondrial fusion and prevents mitochondrial cytotoxicity, in addition to the fragmentation induced by Aβ in SK-N-MC cells [42]. In addition, EGCG and resveratrol increase the levels of Sirt-1 and AMPK along with mitochondrial biogenesis via PGC-1α, thereby protecting the neuronal cells [43]. Conversely, kaempferol, resveratrol luteolin, wogonin, quercetin, theaflavins, EGCG, curcumin, and baicalein open the mPTP, which activates the apoptosis pathway in cancer cells via Bcl-2 and Bcl-xL inhibition along with oligomerization of Bax, in addition to the downregulation of NF-κB signaling pathway [44]. Additionally, curcumin has been found to cross BBB to enter brain tissue and considerable exhibited neuro-protective as well as anti-cancer properties [45]. A previous study showed that curcumin protected against mitochondrial degeneration by mitigating the autophagic pathway via modulation of the PI3K/Akt/mTOR pathway in the ischemia/reperfusion-induced rat model [46]. Kaempferol passed to penetrate BBB and attenuates neuroinflammation as well as BBB dysfunction in cerebral ischemia/reperfusion rats in addition to improve neurological deficits [47]. A ginseng-derived exogenous lysophosphatidic acid receptor ligand, gintonin, improves blood-brain barrier permeability in primary human brain microvascular endothelial cells (HBMECs) [48].

Table 1. Different phytochemicals mitigating mitochondrial dysfunctions in AD pathology.

Phytochemicals	Experimental model	Pathobiology	Research outcomes	Molecular signaling	References

Anthocyanins	APP Swedish K670N/M671L double mutation (APPswe)	Mitochondrial dysfunction and oxidative stress	Ameliorate mitochondrial dysfunction	Increased NADH levels	[34]
Resveratrol	Aβ-induced cytotoxicity in PC12 cells	Oxidative stress	Neuroprotection, Reduction of memory impairment	Reduced ROS, Induced SOD, PI3K, Akt	[49]
Tea polyphenols	SH-SY5Y cells	Oxidative stress	Neuroprotection	Keap1-Nrf2 signaling initiation	[41]
Sulfuretin	Aβ neurotoxicity in primary hippocampal neurons and SH-SY5Y cells	Oxidative stress	Neuroprotection	Activation of Nrf2/HO-1 and PI3K/Akt	[35]
Genistein	Transgenic APP/PS1 rat model of sporadic AD	Impairment of cognition, Increased β-amyloid and hyperphosphorylated tau protein	Improved learning and memory recognition, Inhibition of apoptosis and antioxidant functions	PPARγ-mediated increased release of ApoE, Autophagy activation and reduction in protein aggregates.	[50][51]
Liquiritigenin	Aβ-induced SK-N-MC cells	Mitochondrial fragmentation	Inhibited mitochondrial fragmentation and cytotoxicity	Mediated by Mfn1, Mfn2, and Opa1 signaling	[42]
Kaempferol	Porcine embryos	Oxidative stress	Prevented mitochondrial membrane potential and ROS generation.	Induced autophagy	[52]
Curcumin	Sprague Dawley male rats	Cerebral Ischemia	Neuroprotection	Autophagy and PI3K/Akt/mTOR pathway	[46]
Epigallocatechin-3-gallate (EGCG)	Rat primary cortical neuron	Pathological tau species	Enhanced tau degradation in an Nrf2-dependent manner	Increase autophagy, tau clearance	[53]

Quercetin	H_2O_2-induced neurotoxicity in Sprague-Dawley rat	Oxidative stress	Neuroprotection	Increased Aβ clearance	[54]

4.1. Phytochemical Intervention of Molecular Signaling Pathways Related to Mitochondrial Dysfunctions in AD

Accumulating evidence has indicated that a large number of phytochemicals are capable of showing numerous benefits against mitochondrial dysfunction in AD pathogenesis by modulating molecular signaling pathways. Several polyphenols promote mitochondrial functions and biogenesis, particularly by regulating ETC activity, redox state modulation, and apoptosis inhibition. Phenolic acids can scavenge peroxynitrite, superoxide, and hydroxyl radicals, terminate radical chain reactions, and upregulate several protective genes that encode extracellular signal-related kinase 1/2 (ERK1/2), heat shock protein 70, and heme oxygenase-1 (HO-1). Several in vivo and in vitro studies have revealed that curcumin can prevent mitochondrial dysfunction in AD by scavenging hydroxyl radicals, hydrogen peroxide, and peroxynitrite and attenuating lipid peroxidation [55]. Flavonoids exhibit antioxidant activity and protect neurons via modulation of cellular signaling pathways, in addition to the induction of expression of several genes [56]. Flavonoids can also increase the expression of ROS-eliminating enzymes such as catalase, SOD, and glutathione reductase via the activation of the Keap1/Nrf2/ARE-mediated signaling pathway [57]. Polyphenols such as catechin, apigenin, luteolin, kaempferol, curcumin, and quercetin can inhibit ROS-generating xanthine oxidase (XO), NADPH oxidase (NOX), and MAO [58][59].

Flavonoids exert neuronal effects via several lipid kinase and protein kinase signaling pathways, such as the protein kinase C, MAPK tyrosine kinase, PI3K/Akt signaling pathways, and NF-κB pathway [60]. The stimulatory or inhibitory properties of these pathways can significantly modulate gene expression by altering the phosphorylation state as well as affecting the neuronal properties and function of target molecules. As a result, this might lead to synaptic protein synthesis, morphological variations, and plasticity involved in neurodegenerative processes in AD. Serine/threonine kinases, known as MAPK and mitogen-activated kinases, regulate numerous cellular functions via extracellular signal transduction pathways, generating intracellular downstream signals [61]. Flavonoids have selectively interacted with MAPK kinases, including ERK, MEK1, and MEK2 signaling, resulting in the activation of downstream cAMP response element-binding protein (CREB) [62]. These results might lead to alterations in memory function and synaptic plasticity via the upregulation of neuroprotective pathways in AD.

Blueberry supplementation rich in anthocyanins and flavonols increased memory performance in rats via CREB activation and promoting pro-BDNF and mature BDNF levels in the hippocampus [63]. In another study, 12 weeks of blueberry supplementation activated Akt phosphorylation, mTOR downstream activation, and enhanced activity-regulated cytoskeletal-associated protein (Arc/Arg3.1) expression in the hippocampus of aged animals [63]. This might promote morphology and spine density in neuronal cells, thereby enhancing learning and memory function. In addition, treatment with green tea catechins ameliorated memory impairments and promoted spatial learning function by diminishing the oligomers of Aβ (1–42) in senescence-accelerated mice by augmenting the expression of the PKA/CREB pathway in the hippocampus [64]. Furthermore, EGCG promoted ERK and PI3K-mediated phosphorylation of CREB as well as stimulated GluR2 levels and modulated synaptogenesis, neurotransmission activity, and plasticity in cortical neurons [65]. In addition, flavonoids modulate the activity of PI3K via direct interactions with its ATP binding site [66]. Hesperetin is an activator of the Akt/PKB pathway in cortical neurons. In contrast, quercetin inhibits the prosurvival Akt/PKB pathways by preventing the activity of PI3K [67].

Flavonoids prevent certain activities of CDK5/p25 and GSK-3β, which contribute to the hyperphosphorylation of Tau and accumulation of neurofibrillary tangles in AD pathogenesis [62]. Indirubins prevent CDK5/p25 and GSK-3β and inhibit abnormal phosphorylation of tau in AD pathogenesis [68]. Likewise, GSK-3β activity is inhibited by flavonoid morin [69]. Morin can prevent GSK-3β-mediated phosphorylation of tau in vitro, decrease Aβ-induced tau phosphorylation, and protect against Aβ cytotoxicity in human SH-SY5Y neuroblastoma cells [69]. Furthermore, morin reduces the hyperphosphorylation of tau in the hippocampal neurons of 3xTg-AD mice [69]. Luteolin reduces soluble Aβ, interrupted the PS1-APP association, and diminished GSK-3 activity in an AD mouse model of Tg2576, and rescued cognitive impairments [70].

4.2. Phytochemicals Inhibit AD Specific Protein Aggregation

Neuropathological characteristics of AD involve the accumulation of amyloid-β plaques, neurofibrillary tangles, and neuronal loss in the limbic neocortical brain regions [71]. Pathobiology of AD encompasses oxidative stress, mitochondrial dysfunction, neuroinflammation, apoptosis, reduced neurotrophic factors and neurogenesis, loss of the cholinergic system, autophagy dysfunction, and glutamatergic excitotoxicity [72][73]. Various phytochemicals, anti-inflammatory medications, and antioxidants prevent amyloidogenic monomer synthesis, fibrillar aggregates, and oligomeric formation [74]. Phytochemicals also stimulate nontoxic aggregate formation and proteolytic system activation to ameliorate neuronal mitochondrial dysfunction triggered by Aβ [75]. It is well known that amyloidogenic Aβ 40–42 is produced via consecutive APP cleavage mediated by β-secretase (BACE1) and γ-secretase enzymes [76]. Tannic acid, genistein, ferulic acid, nobiletin, galangin, sinensetin, and tangeretin inhibit β-secretase activity, in addition to behavioral enhancement in AD animal models. In addition, resveratrol, EGCG, icariin, quercetin, luteolin, 7,8-dihydroxyflavine, rutin, and curcumin decrease β-secretase expression and protect neurons [77]. Furthermore, curcumin, oleuropein, genistein, and EGCG promote APP cleavage via α-secretase, producing nontoxic N-terminal soluble APPα product and C-terminal α fragment [78]. Phytochemicals promote α-secretase or prevent β-secretase activity and inhibit fibril and toxic oligomer production. Curcumin as well as other polyphenolic compounds have been changed to mature Aβ aggregates, which make nontoxic molecules as well.

Many phytochemicals inhibit mTOR signaling, thereby inducing the autophagy pathway [79]. Polyphenols inhibit oligomer synthesis and formation, in addition to preventing tau hyperphosphorylation and aggregation reduction under in vitro and in vivo conditions [80]. Soluble Aβ oligomers along with profibrillar species are produced via the action of rosmarinic acid, myricetin, and curcumin, which reduce the number of toxic oligomers and fibrils [81][82]. Aβ aggregation is inhibited by honokiol, myricetin, and luteolin upon binding to the hydrophobic site of the amyloid pentamer and employed the most prominent Aβ1-42 aggregate inhibition in PC12 cells to protect anti-aggregative properties as well as neuronal toxicity [83]. Numerous phytochemicals involved in the pathogenesis of AD are indicated in Figure 3. Another potential benefit of phytochemicals in AD may include their potential role in tau phosphorylation. Tau oligomers are toxic and cause synaptic dysfunction in AD. Several findings have revealed that hyperphosphorylation of tau can be inhibited by treatment with caffeic acid, altenusin, EGCG, curcumin, and resveratrol [84][85]. Moreover, EGCG inhibits the conversion of tau aggregates into toxic oligomers [86]. In addition, emodin and daunorubicin repress tau aggregation and dissolve paired helical filaments under in vitro conditions [87]. In another study, epicatechin-5-gallate and myrecetin were shown to hinder heparin-mediated tau formation, and EGCG administration in an AD transgenic mouse model controlled the phosphorylation of sarkosyl-soluble tau isoform [88][89].

Figure 3. Phytochemicals modulate AD pathogenesis. Phytochemicals stimulate α-secretase activity or may hinder β-secretase activity that inhibits toxic oligomer production. Polyphenols and other compounds modify Aβ aggregates and convert them into nontoxic oligomers. Some phytochemicals inactivate mTOR and initiate the autophagy pathway. Polyphenols and other compounds prevent tau hyperphosphorylation and convert tau aggregates into nontoxic aggregates.

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