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Review

Potential therapeutic role of phytochemicals to mitigate mitochondrial dysfunctions in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a decline in cognitive function with neuronal damage. Although the precise pathobiology of AD is still elusive, accumulating evidences suggest that mitochondrial dysfunction is one of the underlying causes of AD. Mutations of mitochondrial or nuclear DNA that encode mitochondrial constituents may cause mitochondrial dysfunctions. In particular, dysfunction of electron transport chain complexes along with interactions of mitochondrial pathological proteins are associated with mitochondrial dysfunctions in AD. Mitochondrial dysfunction causes an imbalance in reactive oxygen species, leading to oxidative stress (OS) and vice-versa. Neuroinflammation is another potential contributory factor to induce mitochondrial dysfunction. Phytochemicals or other natural compounds have the potential to scavenge oxygen free radicals and enhance cellular antioxidant defense system, and thereby protect against OS-mediated cellular damage. Phytochemicals can also modulate other cellular processes, including autophagy and mitochondrial biogenesis. Pharmacological intervention through neuroprotective phytochemicals can, therefore, be a potential strategy to combat mitochondrial dysfunctions as well as AD. This review focuses on the role of phytochemicals to mitigate mitochondrial dysfunction in the therapy of AD pathogenesis.

Keywords: Alzheimer's disease; mitochondrial dysfunctions; phytochemicals; reactive oxygen species (ROS); autophagy.

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1. Introduction

Several evidences have been revealed that dysfunction of mitochondria leads to several neurodegenerative diseases, including Alzheimer's disease (AD) [1-3]. AD shows common symptoms like insanity and leads to morbid state and death in the aged peoples [4]. In both familial and sporadic patterns, AD is characterized by dual unique medical hallmarks: amyloid-β (Aβ) peptide extracellular accumulation in the senile plaques and neurofibrillary tangles (NFTs) intracellular deposition formed through hyperphosphorylation of tau proteins [5,6]. These phenomena are accompanied by both pre- and postsynaptic and neuronal casualty [4,7], although AD pathogenesis is still questionable. Along with, multiple documentations prove the axonal transports (AT) alterations are the precise culprit to the development of neurodevelopmental disease like AD [8]. In fact, AD in mammalian has been noticed that involvement of atypical decomposition of several abnormal organelles like mitochondria, resulting degeneration of senile plaques along with abnormal neuronal expansion resulting decline neurites [9]. Phytochemicals or plants derived chemical compounds are usually used to define the compounds that are currently under research with unestablished health benefits [10]. Phytochemicals have been revealed to show multiple beneficial action in dysfunction of mitochondria [11], although there is not enough investigations have done yet for the clinical application.

A wide range of literatures have been demonstrated that numerous bioactive phytochemicals and other organic compounds may improve treatment of AD [12]. It has been found that phytochemicals incuding polyphenolic compounds which have widely been existed in numerous plant origins reported to employ several essential properties such as anti-inflammatory potential, DNA repairing, autophagy, and antioxidant activities [13]. In AD patients brains as well as transgenic AD mouse models, APP and Aβ have been found to present in mitochondrial membranes which interrupt mitochondrial electron transport system [14]. Potential therapeutic actions of these phytochemicals effects on antioxidant and anti-inflammatory actvities via modulating Aβ toxicity. It has been revealed that mitochondrian dysfunction discharge excessive quantities of H_2O_2 which ultimately effect on irreversible cellular dysfunction and damage in the brain [15]. Aggregated Aβ peptides, H_2O_2 induced hydroxyl radical, and APP damaged mitochondria dysfunction in AD may restrain in addition to pharmacological approaches using phytochemicals which preserve mitochondrial dynamics [16]. Due to therapeutic capabilities, phytobioactive compounds have been progressively

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deliberated as favorable beneficial agents for AD and age-related diseases [17]. Therefore, the current review is proposed to confer the major dysfunction of mitochondria in the pathogenesis of AD and discussing about how phytochemicals may mitigate this mitochondrion dysfunctions.

2. Mitochondrial dysfunction in AD through ROS production

Oxidative stress (OS) has been typified by the asymmetric occurrence between the reactive oxygen species (ROS) generation and the cellular antioxidant competence. OS stands for excess quantities of ROS production that incur damage to nucleic acids, small molecules like protein or lipids. OS can lead to neuronal, specifically neurodegenerative diseases and cellular ageing process [18]. Restrained ROS productions have their physiological roles particularly in controlling cellular redox equilibrium and the regulation of intracellular signal transduction [19,20]. ROS (collectively, H_2O_2, OH, and $O_2^{\cdot -}$) imply to be the causative factor in the defect of mitochondrial respiration and also in developing processes of the human brain that escort by augmented ROS generation as well necessarily contributes to dynamic changes in the brain in an active manner during Ad and ageing progression (Figure 1).

The primary origins of ROS production in brain under functional circumstances as well as in pathological processes (e.g., neurological diseases) are deliberate to complex I and complex III of the respiratory chain. Complex I discharges superoxide ($O_2^{\cdot -}$) to the intermembrane space like 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 the enzyme called superoxide dismutase and along with it can pass through by the inner membranes and can be the origin of extremely reactive hydroxyl radical ($^{\cdot}OH$). In physiological conditions, both the immensity of proton movements and the respiratory state of mitochondria produced H_2O_2 and O_2^- from the electron transport chain (ETC) [21]. On the contradictory, complex IV also enhances the generation of ROS whereas, complex III and V generate a minimal amount of ROS [22]. Apart from these, physically distorted production and detoxification of ROS are critically involved in mitochondrial dysfunctions [23]. In the aging progression, a high amount of ROS is generated due to defective mitochondria; likewise, a decline in antioxidant enzyme activities ensued leading to increased ROS production [23,24]. Excess ROS production has adverse sequelae on the ETC; complexes I, III and IV appear to be the most affected, while complex II remains undisturbed [23,25].

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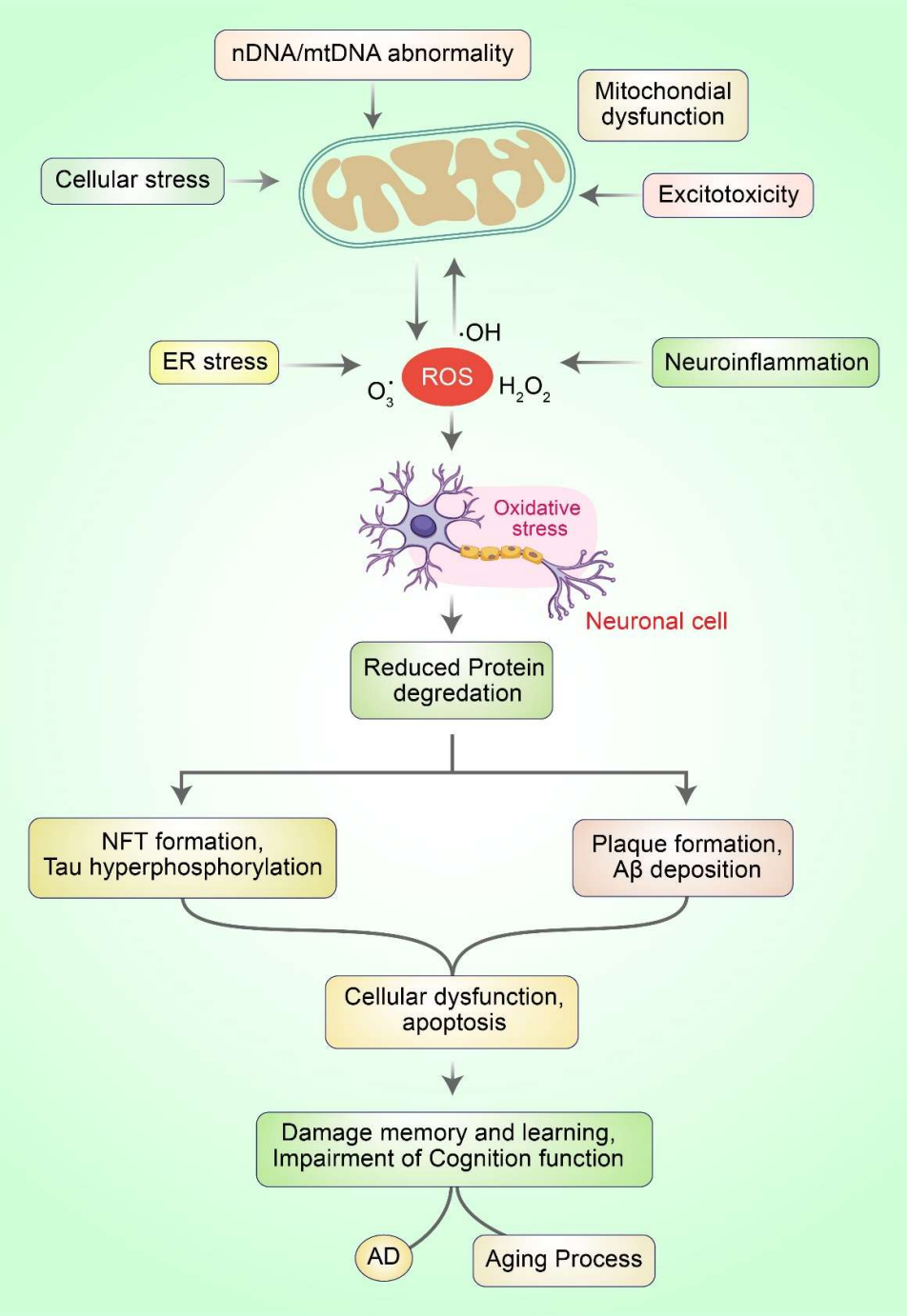

Figure 1: Mitochondrial dysfunction and oxidative stress in neuron leads to produce AD. Generally, ROS become produced via numerous actions such as ER stress, mitochondrial dysfunction, neuroinflammation, and excitotoxicity. Excessive ROS generation lead to cause oxidative stress (OS) which are responsible for mitochondrial dysfunction. OS prevent degradation of protein molecules and impair misfolded protein clearance which subsequently deposit protein aggregation leading to cause neuronal death and AD.

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3. Mitochondrial deformity as an outcome of AD pathologic progression

A large body of research has stated that metabolic alterations play a pivotal role in AD pathologic progression mediated by several pathogenic factors such as ROS, mitochondrial deformity, Aβ load, and so forth [26]. Extensive research has shown that ROS formation mediated by Aβ and calcium imbalance causes mitochondrial injuries (Figure 2), which are known as the secondary mitochondrial failure. Hippocampal expressions of mutant APP and Aβ in mouse HT22 cell lines induced impaired mitochondrial dynamics, alterations of mitochondrial structure as well as action in neurons [27]. Amyloid precursor proteins (APP) can overexpress in mitochondrial protein import channels of AD sensitive brain regions, leading to mitochondrial malfunction [28]. Alternatively, several studies evidenced that Aβ precisely disorganizes mitochondrial action and dynamics and hinders critical enzymatic functions. Lustbader *et al.* announced that Aβ-binding alcohol dehydrogenase (ABAD) directly interacts with Aβ and generates Aβ-linked apoptosis, mitochondrial toxicity and free-radical formation in neuronal cells [29]. Furthermore, voltage-dependent anion-selective channel 1 protein (VDAC1) excessively expressed in AD-vulnerable brains, which combines with phosphorylated tau as well as Aβ to arrest 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 all facts leads to AD pathologic progression. Nevertheless, the originator of mitochondrial impaired dynamics in AD pathogenesis remains elusive.

4. Phytochemicals prevent mitochondrial dysfunction and improve biogenesis

It has been reported that 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 growth signaling. In this section, we discuss recently explored phytochemicals that have been shown to protect neurons from mitochondrial dysfunctions in AD by stimulating numerous signaling pathways. Molecular targets, experimental model, research outcomes, and molecular signaling system of these phytochemicals are summarized in Table 1.

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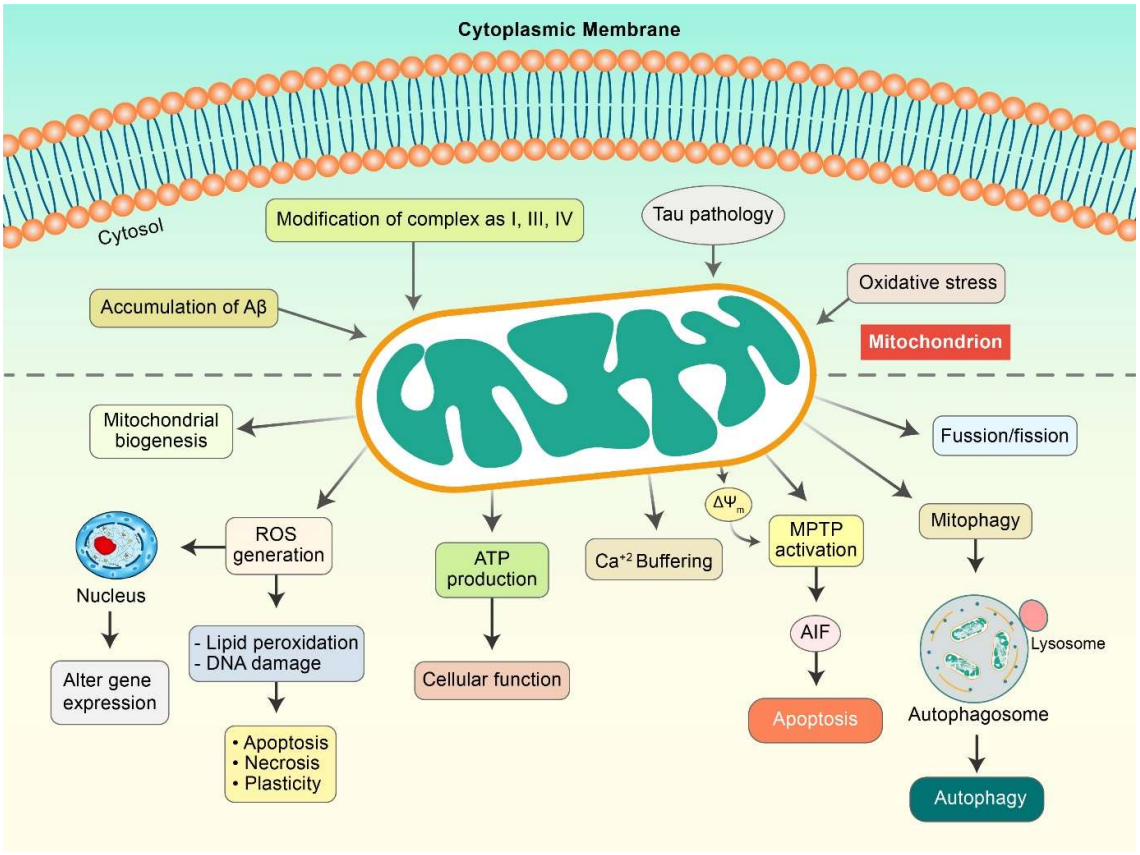

Figure 2: Mitochondrial dysfunctions in AD pathogenesis. Aβ and Tau initiates to cause mitochondrial dysfunctions which can result in modulation of several factors. ROS was generated which cause lipid peroxidation and DNA damage to initiate apoptosis. Damage mitochondria stimulates to decrease mitochondrial membrane potential (ΔΨm) as a results of activation of mitochondrial permeability transition pores (mPTPs) which release cytochrome c and apoptosis inducing factor (AIF) and consequently initiates apoptosis pathway. Aβ and pTau cause to improve mitochondrial fission and mitophagy.

Anthocyanins controlled mitochondrial fission/fusion pathways and prevented complex I APP Swedish K670N/M671L double mutation (APPswe) and stimulate mitochondrial dynamics [32]. Numerous phenolic compounds have been described to show neuroprotective actions against AD and other neurodegenerative disease models. Sulfuretin, a well-known flavonoid glycoside derived from *Albizia julibrissin*, has been protected primary hippocampal neuronal cells and SH-SY5Y neuroblastoma cells from Aβ-mediated neurotoxicity [33]. Polyphenol resveratrol, derived from grapes and black barriers, protected HT22 and PC12 cells against Aβ toxicity through activating PI3K/Akt/Nrf2 pathway [34]. In addition, resveratrol prevented cell death and repressed ROS production induced by Aβ toxicity via enhancing PI3K/Akt

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phosphorylation, SOD, HO-1, as well as GSH protein levels, and Nrf2 nuclear translocation [35]. Quercetin, a hydroxytryrosol derived from olives, prompted mitochondrial biogenesis and enhances muscle mtDNA in adult men [36]. Tea polyphenols (TPs) mitigate OS in H_2O_2-induced human neuroblastoma SH-SY5Y cells via Keap1-Nrf2 signaling initiation and decreased H_2O_2-mediated cell death as well as ROS and H_2O_2 levels to protect mitochondrial dysfunction [37]. Liquiritigenin prompted mitochondrial fusion as well as prevented mitochondrial cytotoxicity in addition to fragmentation prompted through Aβ in SK-N-MC cells [38]. Besides, EGCG and resveratrol have been found to increase Sirt-1 as well as AMPK and increase mitochondrial biogenesis through PGC-1α, thereby protected neuronal cells [39].

Conversely, kaempferol, resveratrol luteolin, wogonin, quercetin, theaflavins, EGCG, curcumin, and baicalein opened the mPTP which activated apoptosis pathway in cancer cells via Bcl-2 and Bcl-xL inhibition along with oligomerization of Bax induction in addition to downregulate NF-κB signaling [40]. Curcumin protected mitochondrial apoptosis by mitigating autophagic pathway via mediating PI3K/Akt/mTOR pathway in ischemia/reperfusion-induced rat model [41].

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	[32]
Resveratrol	Aβ-induced cytotoxicity in PC12 cells	Oxidative stress	Neuroprotection, Reduction of memory impairment	Reduced ROS, Induced SOD, PI3K, Akt	[42]
Tea polyphenols	SH-SY5Y cells	Oxidative stress	Neuroprotection	Keap1-Nrf2 signaling initiation	[37]
Sulfuretin	Aβ neurotoxicity in primary	Oxidative stress	Neuroprotection	Activate Nrf2/HO-1 and PI3K/Akt	[33]

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	hippocampal neurons and SH-SY5Y cells				
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.	[43,44]
Liquiritigenin	Aβ-induced SK-N-MC cells	Mitochondrial fragmentation	Inhibited mitochondrial fragmentation and cytotoxicity	Mediated by Mfn1, Mfn2, and Opa1 signaling	[38]
Kaempferol	Porcine embryos	Oxidative stress	Prevented mitochondrial membrane potential and ROS generation.	Induced autophagy	[45]
Curcumin	Sprague Dawley male rats	Cerebral Ischemia	Neuroprotection	Autophagy and PI3K/Akt/mTOR pathway	[41]
Epigallocatechin-3-gallate (EGCG)	Rat primary cortical neuron	Pathological tau species	Enhanced tau degradation in an Nrf2-dependent manner	Increase autophagy, tau clearance	[46]
Quercetin	H_2O_2-induced neurotoxicity in Sprague-Dawley rat	Oxidative stress	Neuroprotection	Increased Aβ clearance	[47]

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Phytochemical intervention of molecular signaling pathways related to mitochondrial dysfunctions in AD

Accumulated evidences have indicated that a large number of phytochemicals are capable of showing numerous benefits against mitochondrial dysfunctions in AD pathogenesis through 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 radical, terminate radical chain reactions, and upregulate several protective genes that encode for extracellular signal-related kinase 1/2 (ERK1/2), heat shock protein 70, and heme oxygenase-1 (HO-1) [11]. Several *in vivo* and *in vitro* studies have revealed that curcumin can prevent mitochondrial dysfunctions in AD by scavenging hydroxyl radical, hydrogen peroxide, and peroxynitrite and attenuating lipid peroxidation [48]. Flavonoids exhibited antioxidant activity and protected neurons through modulation of cellular signaling pathways in addition to the induction of several gene expression [49]. Flavonoids can also increase ROS-eliminating enzymes such as catalase, SOD, and glutathione reductase through the activation of Keap1/Nrf2/ARE-mediated signaling pathway [50]. Polyphenols such as catechin, apigenin, luteolin, kaempferol, curcumin, and quercetin were shown to inhibit ROS-generating xanthine oxidase (XO), NADPH oxidase (NOX), and MAO [51,52].

Flavonoids have been displayed to employ neuronal effects through several lipid kinase and protein kinase signaling, for instance, the protein kinase C, MAPK tyrosine kinase, PI3K/Akt signaling pathways and NF-κB pathway [53]. The stimulatory or inhibitory properties of these pathways can significantly modulate gene expression by altering the phosphorylation state as well as affect neuronal property and function of target molecules. As a result, this might cause synaptic protein synthesis, morphological variations, and plasticity involved in neurodegenerative processes in AD. A serine/threonine kinases signaling known as MAPK, mitogen-activated kinases, regulate numerous cellular functions through extracellular signal transduction pathway into intracellular downstream signal [54]. 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) [55]. These results might lead to alterations in memory function and synaptic plasticity via upregulation of neuroprotective pathways in AD.

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Blueberry supplementation rich in anthocyanins and flavonols increased memory performance in rats via CREB activation and promoting pro- and mature BDNF levels in hippocampus [56]. 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 hippocampus of aged animals [56]. This might promote morphology and spine density in neuronal cells and thereby enhance learning and memory function. Besides, treatment of green tea catechins ameliorated memory impairments and promoted spatial learning function through diminishing oligomers of Aβ (1-42) in senescence-accelerated mouse via augmenting PKA/CREB pathway in hippocampus [57]. Furthermore, EGCG encouraged ERK and PI3K-mediated phosphorylation of CREB as well as stimulated GluR2 levels and modulated synaptogenesis, neurotransmission activity, and plasticity in cortical neurons [58]. Also, flavonoids modulate PI3K via direct interactions with its ATP binding site [59]. Hesperetin has been revealed as an activator of Akt/PKB pathways in cortical neurons. In contrast, quercetin inhibited prosurvival of Akt/PKB pathways through preventing the activity of PI3K [60].

Flavonoids have been shown beneficial effects through preventing certain activities of CDK5/p25 and GSK-3β that contribute to hyperphosphorylation of Tau and neurofibrillary tangles accumulation in AD pathogenesis [55]. Indirubins have been found to prevent CDK5/p25 and GSK-3β and inhibit abnormal phosphorylation of tau in AD pathogenesis [61]. Likewise, GSK-3β activity was inhibited by flavonoid morin [62]. Morin can prevent GSK-3β-mediated phosphorylation of tau *in vitro*, decrease Aβ induced phosphorylation of tau and protect against Aβ cytotoxicity of human SH-SY5Y neuroblastoma cells [62]. Furthermore, morin has been found to reduce hyperphosphorylation of tau in 3xTg-AD mice hippocampal neurons [62]. Luteolin reduced soluble Aβ, interrupted PS1-APP association, and diminished GSK-3 activity in AD mouse model of Tg2576 and rescued cognitive impairments [63].

Phytochemicals inhibit AD specific protein aggregation

Neuropathological characteristics of AD involves accumulation of amyloid-β plaques and neurofibrillary tangles and neuronal loss in limbic neocortical brain regions [64]. Pathobiology of AD encompasses oxidative stress, mitochondrial dysfunction, neuroinflammation, apoptosis, reduced neurotrophic factors and neurogenesis, loss of cholinergic system, autophagy dysfunction, and glutamatergic excitotoxicity [65,66]. Various phytochemicals, anti-inflammatory medications, and antioxidants have been found to prevent amyloidogenic

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monomer synthesis, fibrillar aggregates, and oligomeric formation [67]. Phytochemicals also stimulated nontoxic aggregate formation and proteolytic system activation to ameliorate neuronal mitochondrial dysfunction triggered by Aβ [68]. It has been well-known that amyloidogenic Aβ 40-42 are produced via consecutive APP cleavage through β-secretase (BACE1) as well as γ-secretase enzymes [69]. Tannic acid, genistein, ferulic acid, nobiletin, galangin, sinensetin, and tangeretin were shown to inhibit β-secretase in addition to increasing behavioral enhancement in AD animal models [11]. Also, resveratrol, EGCG, icariin, quercetin, luteolin, 7,8-dihydroxyflavine, rutin, and curcumin decreased β-secretase expression and protected neurons [70]. Furthermore, curcumin, oleuropein, genistein, and EGCG promoted APP cleavage through α-secretase, producing nontoxic N-terminal soluble APPα product and C-terminal α fragment [71]. Phytochemicals promoted α-secretase or prevent β-secretase activity and inhibit fibril and toxic oligomer production [60]. Curcumin as well as other polyphenolic compounds have been changed to mature Aβ aggregation which make nontoxic molecules as well.

Many phytochemicals have been found to inhibit mTOR signaling, thereby inducing autophagy pathway [6,72]. Polyphenols have also been revealed to inhibit oligomer synthesis and formation in addition to prevent tau hyperphosphorylation and aggregation reduction *in vitro* and *in vivo* [73]. Soluble Aβ oligomers along with profibrillar species are produced via the action of rosmarinic acid, myricetin, and curcumin which reduced the toxic oligomers as well as fibrils [74,75]. Aβ aggregation was inhibited by honokiol, myricetin, and luteolin when bound to the hydrophobic site of the amyloid pentamer [76]. Numerous phytochemicals intervening AD pathogenesis are indicated in Figure 3. Another potential benefit of phytochemicals in AD may include their potential role in tau phosphorylation. Tau oligomer is a toxic form and causes synaptic dysfunction in AD. Several findings have raveled that hyperphosphorylation of tau can be inhibited via the treatment of caffeic acid, altenusin, EGCG, curcumin, and resveratrol [77,78]. Moreover, EGCG inhibited formation of tau aggregate into toxic oligomers [79]. Also, emodin and daunorubicin repressed tau aggregation and dissolved paired helical filaments *in vitro* [80]. In another study, epicatechin-5-gallate and myrecetin were shown to hinder heparin-mediated tau formation and EGCG administration in AD transgenic mice model leads to control sarkosyl-soluble tau isoforms phosphorylation [81,82].

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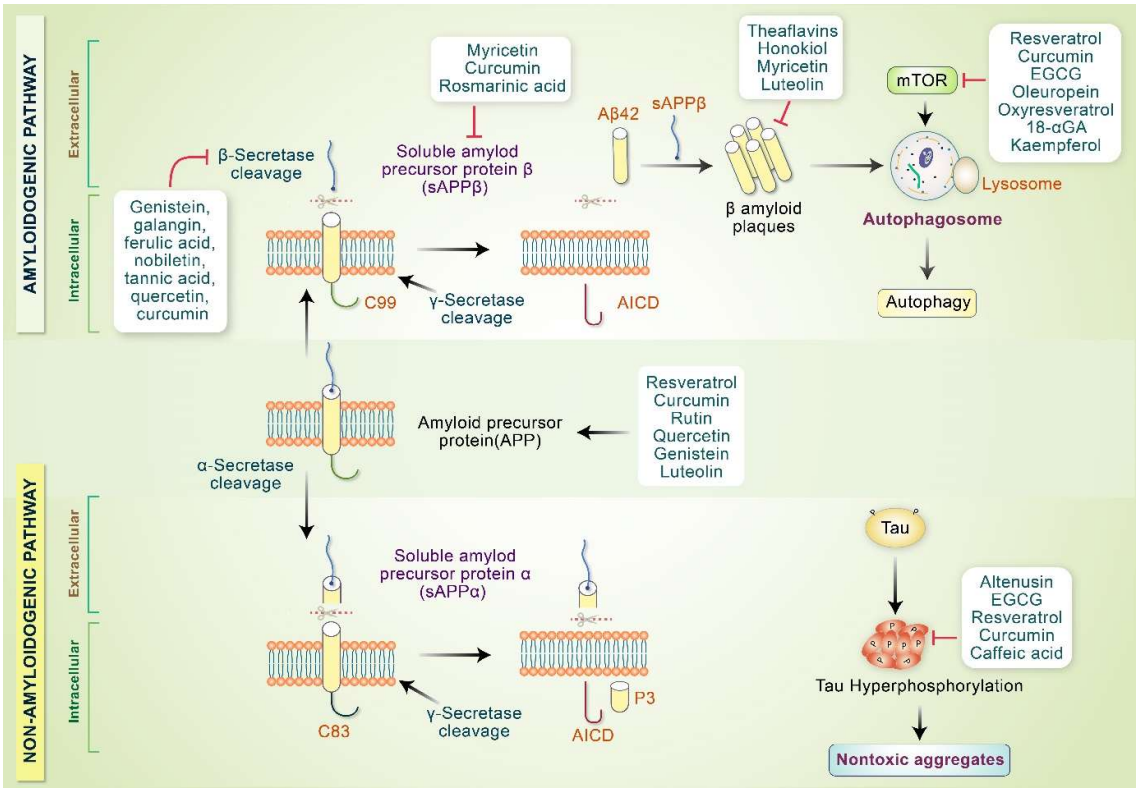

Figure 3: Phytochemicals modulate AD pathogenesis. Phytochemicals stimulate α-secretase or may hinder β-secretase activity which inhibits toxic oligomer production. Polyphenols and other compounds modify Aβ aggregates and turn into nontoxic oligomers. Some phytochemicals inactivate mTOR and initiate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

5. Therapeutic applications of phytochemicals in mitochondrial dysfunctions in AD

Many studies reported that antioxidants and mitochondria-targeting agents such as vitamin C, vitamin E, carnitine and alpha-lipoic acid show an effective therapeutic potential in AD [83]. The coenzyme Q10, piracetam, simvastatin, curcumin, ginkgo biloba, piracetam and the omega-3 polyunsaturated fatty acids also show effective therapeutic potential [84]. An effective therapeutic strategy can be developed against AD by targeting the mitochondrial proteins. By using these strategies, various types of mitochondria-targeted antioxidants have been manufactured. The alteration of mitochondrial movement shows a negative impact on mitochondrial function, thereby contributing critically to the pathogenesis of AD [85]. Consequently, approaches to modify the defective mitochondrial movement and transportation may constitute an effective therapeutic innovation for the treatment of AD. Therapeutics that possess its role to decrease the activation of the mitochondrial fission proteins such as Drp1, pTau and Aβ can rescue the neurons from the toxic distresses of those agents and their

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interconnection. A diversity of phytochemicals available in numerous plant sources have been described for various pharmacological properties, including neuroprotection [86,87], apoptosis induction [88-95], autophagy activation [72,96-98], antioxidant [99] and anti-inflammatory action [100], and DNA repairing function [13]. Due to these capabilities, phytochemicals are progressively considered as a favorable therapeutic candidate for AD therapy [10] (Figure 4).

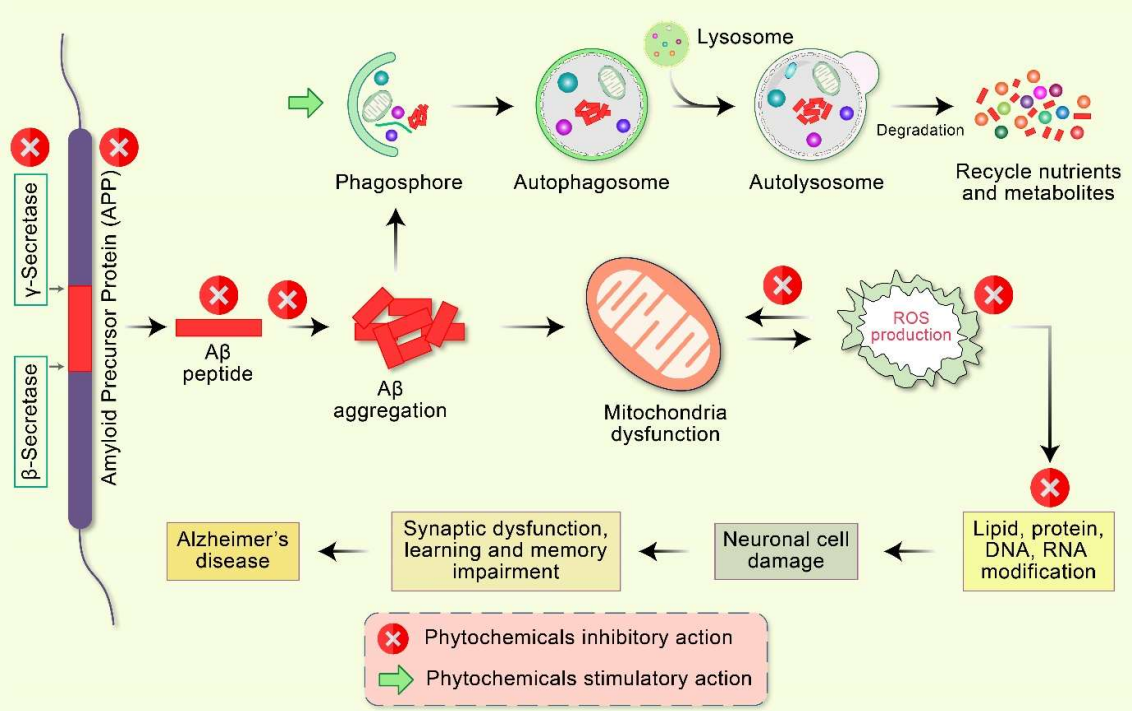

Figure 4: Emergeing potential therapeutic targets of phytochemicals in mitochondrial dysfunctions and AD pathogenesis. Abnormal amyloid precursor protein (APP) was proteolyticlly cleaved by β- as well as γ-secretase which make to store accumulation of extracellular amyloid-β (Aβ). Deficient clearance of Aβ, or Aβ production increased aggregation which consequences accumulation of diversity of Aβ assemblies. Accumulation of Aβ directly interrelated with mitochondrian as well as ROS generation with different intracellular pathways. These oxidative stress reactions cause neuronal impairment of synapses and dendrites function with multifactorial mechanisms in addition to cause neurological degeneration and synaptic function dysregulation in the brain regions which has been implicated in learning as well as memory impairment in AD. Additionally, Aβ aggregation has been degradated by autophagy mechanism through stimulatory action of phytochemicals.

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The therapeutic possibilities of curcumin were considered in various aging-related pathological disorders, including type 2 diabetes, ocular diseases cancer, atherosclerosis, osteoporosis, rheumatoid arthritis, chronic kidney disorders, hypertension, cardiovascular, and neurodegenerative disorders [101]. The neuroprotective action of curcumin in AD has been well-known. Curcumin was revealed to protect Aβ-mediated mitochondrial dysfunction and synaptic toxicities in SH-SY5Y human neuroblastoma cells [102]. However, the effects of curcumin in placebo-controlled, double-blinded clinical trial with AD patients were moderately inadequate [103]. Low solubility might be a potential cause. Recently, several preclinical investigations claimed anti-AD potential of quercetin [104]. Treatment with quercetin exhibited improvement of mitochondrial dysfunction through returning mitochondrial membrane potential which led to reduce ROS production in addition to restore ATP synthesis [105]. Meanwhile, this treatment furthermore initiated significant enhancement of AMPK expression, decreased scattered senile plaques formation as well as abandoned learning and memory impairment [105]. More recently, in triple transgenic AD mouse model, the long-term oral administration of quercetin led to reduced tauopathy, astrogliosis, microgliosis, and β-amyloidosis in amygdale and hippocampus which improved cognitive functional retrieval and performance on learning and spatial memory function [106,107]. Different phytochemicals and other chemicals used in mitochondrial-targeted AD treatments in preclinical and clinical studies have been listed in Table 2.

Genistein, a soy isoflavonoid, was shown to have a potential therapeutic implication in many aging-related mitochondrial dysfunctions in pathological conditions, including neuroinflammation, oxidative stress, and aggregation of Aβ in AD. This therapeutic possibilities of genistein were due to its ability to improve function impairments induced by Aβ aggregates in mitochondrial dysfunctions [108]. However, genistein pretreatment in a primary astrocyte culture prevented Aβ-mediated pro-inflammatory mediators' production [109]. Recently, in streptozotocin-induced rat model, a higher dose of genistein (150 mg/kg/day) was revealed to activate autophagy in AD sporadic form [44]. Additionally, genistein treatment resulted in completely degrade tau hyperphosphorylation and Aβ proteins in the brain of mitochondrial dysfunctions. Currently, it has been innovated the designs in nanocomposites with genistein-loaded which has confirmed to develop the oral delivery system in addition to overcome the toxic effects isoflavonoid [110].

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Table 2: Phytochemicals and other chemicals used in mitochondrial-targeted therapies in AD models in preclinical and clinical studies

Phytochemical/ Drug candidate	AD model	Mitochondrial effect	References
Melatonin	HEK293-APPswe AD model	Increase mitochondrial biogenesis and mitochondrial membrane potential, Decrease APP processing	[111]
Coenzyme Q10	TgP301S mice, M17 cell line treated with $A\beta_{1-42}$ peptide, HUVEC cell line $A\beta_{25-35}$ peptide-treated	Decrease ROS, Reduce accumulation of Aβ peptide, mtΔΨ protection, Promote ETC	[112,113]
Astaxanthin	Mouse hippocampal neurons treated by $A\beta_{1-42}$ oligomers	Reduction of mitochondrial H_2O_2 production	[114]
Resveratrol	APP/PSEN1 mice	Activation of mitophagy, Reduce ROS accumulation	[115]
Pioglitazone	APP/PSEN1 mice	Reduce Aβ1-42 level, Restore mitochondrial function	[116]
Dimebon	Mild-to-moderate AD patients	Improve cognition and memory function	[117]
Oxaloacetate (OAA)	AD cultured cells and mice	Activate mitochondrial biogenesis	[118]
2-deoxyglucose	Adult rats treated with Aβ peptides	Increase mitochondrial biogenesis, Reduction of mitochondrial stress	[119]
Curcumin	APP/PSEN1 mice, APP751SL mice	ROS reduction, Increase synaptic function	[102]
Epigallocatechin-3-gallate (EGCG)	APP/PSEN1 mice	Restore mitochondria respiratory rates, Reduction of ROS and Aβ	[120]
Catalase	MCAT/APP mice	Reduce oxidative damage, Aβ, BACE1 activity, and APP processing	[121]
α-lipoic acid	AD patients	Increase cognition function, Protect Aβ toxicity	[122]

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N-Acetyl-cysteine (NAC)	A double-blind AD patient	Improved cognitive and behavioral functions	[123]
Quercetin	APP/PSEN1 mice	Improvement of ΔΨ, Prevent intrinsic apoptosis	[47]
G. biloba	Older adults and AD patients	Prevention of cognition and memory decline	[124]
SkQ1	OXYS rats	ROS reduction, COX increase	[125]
SS31	APP mouse model (Tg2576)	Decrease Aβ production and dysfunction, Stimulates mitochondrial biogenesis and	[126]
Ketones	3xTgAD)	Mitochondrial functions and dynamics enhancement	[127,128]
Rapamycin	Aβ treated PC12 cell line	Increases mitophagy	[129]
Red ginseng (RG)	5XFAD mice	Ameliorate Aβ deposition, Increase mitochondrial biogenesis	[130]
Thiosemicarbazones	AD model of SK-N-MC neuroepithelioma cells	Inhibit Aβ deposition, Reduce ROS	[131]

Plant polyphenols have been shown to stimulate mitochondrial biogenesis as well as diminish mitochondrial dysfunction in AD [132]. Resveratrol was found to repress cAMP phosphodiesterases and augmented cAMP through cAMP/CaMK/AMPA activation pathway [133]. Additionally, mitochondrial dynamics, biogenesis, and function have been activated by resveratrol via the activation of AMPK, protein kinase C epsilon (PKCε), as well as improved NAD^+ levels [134]. In contrast, EGCG encouraged biogenesis of mitochondrial function in Ad model with Down's syndrome through the Sirt1/PGC-1α signaling pathway via the upregulation of TFAM and Nrf1 in addition to mtDNA content [135]. Several flavones such as wogonin, quercetin, and baicalein improved biogenesis of mitochondrial activities through improved Sirt1/AMPA/PGC-1α expression *in vitro* and *in vivo* [136]. Extra virgin olive oil contains oleuropein has augmented mtDNA, PGC-1α, complex II and IV expression, and controlled mitogenesis, mitochondrial biogenesis function in AD, diminishing oxidative stress [137]. Therefore, pharmacological intervention through polyphenols has been anticipated as a promising therapeutic approach for mitochondrial dysfunction-associated neurodegenerative disorders.

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6. Concluding Remarks and Future Directions

Although the prevalence of AD is growing tremendously, still there is no specific therapeutic strategy to cure, or even slow down or prevent AD [138]. Mitochondrial dysfunction is thought to play a crucial role in the pathogenesis of AD. However, the elusive mechanism of AD pathobiology further complicates treatment strategies. In this perspective, ongoing research is dedicated to underscoring the precise pathomechanism of AD as well as exploring the possibility of alternative treatment strategies. In light of current discussion, pharmacological intervention through natural products, particularly phytochemicals, is one of the promising strategies to combat AD-associated pathological factors, including mitochondrial dysfunction. Phytochemicals and other natural compounds can prevent mitochondrial dysfunction by regulating several signaling pathways, including those associated with cellular antioxidant defense, anti-inflammation, autophagy and other quality control systems, mitochondrial biogenesis, and cell survival system. Although several phytochemicals have shown promise against AD, they are still far from their clinical application. Since the therapeutic applications of many phytochemicals are limited by their poor pharmacokinetic properties, strategies like nanoparticle synthesis may potentially improve their drug-likeness. Moreover, clinical evidences are far smaller than preclinical data. Therefore, further human trials are necessary to translate the existing findings into clinical use. Understanding the advanced pathobiology of AD and the pharmacological mechanism of phytochemical-based therapy may offer an emerging novel neuroprotective approach for AD in the future.

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