Dietary Polyphenols to Target Alzheimer’s Disease

Subjects: Neurosciences | Biotechnology & Applied Microbiology

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Dietary polyphenols may provide various levels of protection for neuronal health. This entry extensively examines this topic tabulating the *in vivo* and *in vitro* studies that have been performed, the methods used, the doses and duration of treatments, and most importantly the outcomes. The entry can be particularly useful as a reference and for those embarking on studies to further exploit dietary polyphenols for protection against neurodegenerative diseases such as Alzheimer's Disease.

Keywords: Alzheimer’s Disease ; nutraceuticals ; pharmaceuticals

1. Introduction

Deaths due to Alzheimer’s Disease (AD) and other dementias are a major cause of mortality in the elderly worldwide, and the rate is increasing rapidly with a doubling time of 20 years [1]. AD is an age-related neurodegenerative disease that leads to cognitive impairment and death. Neuronal synapsis disruption, accumulation of amyloid plaques in brain, formation of neurofibrillary tangles in neuronal cells, loss of cellular homeostasis and accumulation of oxidative stress are major hallmarks of the disease [2]. However, mitochondrial dysfunction, loss of protein and lipid homeostasis, alterations in biometal distribution, cellular senescence, loss of nutrient sensing and accumulation of misfolded proteins are also associated with the AD [3]. Despite the efforts of more than three decades of research, the precise cause of AD has not been found. Many hypotheses have been made to address the major molecular events in the neuronal cells with AD (refer to **Figure 1**) [2]. Polyphenolic compounds have been reported to have multiple effects in cells including inducing antioxidant activity, induction of autophagy, restoration of lipid homeostasis, antiproliferative property, anti-proteinopathies, inhibition of choline esterases, anti-inflammatory activity, metal chelation, clearance of lipofuscin and others (refer to **Table 1**). This review details how polyphenols exert their neuroprotective role at the cellular level helping to prevent and possibly cure AD.

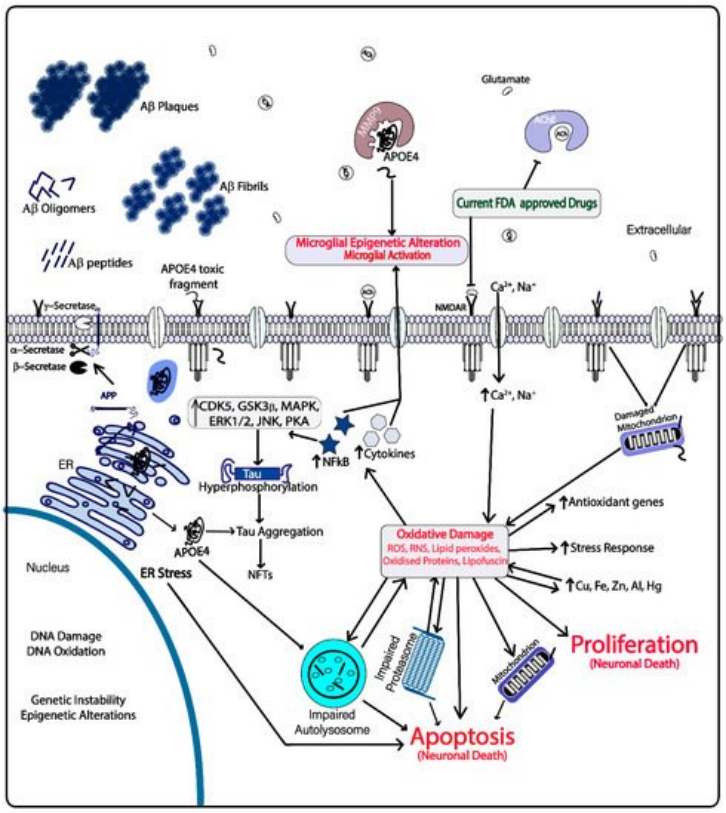

Figure 1. Current drug targets and molecular events occurring in the Alzheimer’s Disease (AD) brain microenvironment.

Table 1. Neuroprotective roles of some polyphenols for AD.

Polyphenol	Analytical System	EPC[a]/ROA[b]	Effects of Polyphenols at Cellular Level	Effects in Relation to AD	Reference
Quercetin	*In vitro*	NA	mTORC inhibitor	Induces autophagy, anti-amyloidogenic, inhibits proteasomal degradation, antioxidant, restores biometal distribution, antiproliferative and enhances neuronal synapsis	[4][5][6][7][8]
	ARPE 19 cells	2 µM	TFEB activation		
	APPswe cells	10 µM	Inhibits Aβ fibril formation		
	Rat neonatal cardiomyocytes	5 µM	Inhibits all the catalytic subunits of proteasome		
	In vitro	NA	Chelates iron		
	In vitro	NA	Reduces ROS and RNS		
	In silico and *in vitro*	NA	Inhibits acetyl choline esterase		
Resveratrol	Tg6799 mice	60 mg/kg/d for 60 d/oral administration	Reduces amyloid plaque formation	Induces autophagy, increases lysosomal biogenesis, restores lipid homeostasis, increases stress resistance, regulates cell cycle, antiproliferative, anti-apoptotic, increases longevity and anti-inflammatory	[9][10][11][12][13][14]
	Primary neuronal culture	30 µM	SIRT1 activation and NFκB inhibition		
	Obese healthy men clinical trial	150 mg/d for 30 d/oral administration	TFEB activation		
	Human aortic endothelial cells	50 µM	AMPK mediated LC3II activation		
	Human aortic endothelial cells	10 µM	Decreases ROS and RNS, increases SOD		
	LNCaP cells	20 µM	p53 regulation, PI3K/Akt/mTOR inhibition, induces FOXO transcriptional activity including cell cycle regulation and stress resistance		
Epigallocatechin gallate (EGCG)	Human bladder cancer cell line T24	20 µg/ml	Inhibits Beclin1 suppressors and PI3K/Akt/mTOR	Induces autophagy, restores lipid homeostasis, anti-amyloidogenic, increases antioxidant capacity, restores impaired autophagosomes and biometal distribution, increases cell survival	[15][16][17][18][19]
	Bovine aortic endothelial cells	10 µM	Increases LC3II formation and activates AMPK/ULK1		
	HepG2 cells	40 µM	Degrades lipid droplets through Ca^{2+}/CAMKKB AMPK dependent mechanism		
	In vitro	NA	Chelates zinc and copper		
	PC12 cells (rat pheochromocytoma	100 µg/mL	Interacts with Aβ40 and changes its conformation, inhibits lipofuscin formation		

Polyphenol	Analytical System	EPC[a]/ROA[b]	Effects of Polyphenols at Cellular Level	Effects in Relation to AD	Reference
Anthocyanin	Sprague–Dawley rats	100 mg/kg/d for 28 d/oral administration	Restores calcium homeostasis and activates Nrf2 subsequently activating phase II detoxifying genes	Activates autophagy, increases expression of anti-oxidant genes, reduces ROS and increases cell survival	[20][21][22][23]
	HT22 cells and primary cultures of hippocampal neurons	0.1 mg/mL	Induces AMPK		
	In vitro	0.005 mg/mL	ROS scavenging		
	HCC cell lines PLC/PRF/5 and HepG2 cells	0.2 mg/mL	Increase expression of Beclin1, LC3 II		
Kaempferol	SK-HEP-1 human hepatic cancer cell	75 µM	Increases the levels of p-AMPK, LC3-II, Atg 5, Atg 7, Atg 12 and beclin 1, inhibits PI3K/Akt/mTOR	Reduces mitochondrial dysfunction, anti-proliferative, increases autophagy, increases unfolded protein response, reduces APOE4 fragmentation and associated toxicity	[24][25][26][27]
	BALB/c nude mice	150 mg/kg/d for 31 d/intraperitoneal injection	Activates DNMT methyltransferase ubiquitination		
	SCC-4, human tongue squamous cell carcinoma cell	50 µM	Activates IRE1-JNK-CHOP signaling, downregulates ERK1/2 signaling which reduces MMP2		
Hydroxytyrosol	Male db/db (C57BL/6J) mice	10 mg/kg/d for 8 weeks/oral administration	Activates Nrf2 and SIRT1/AMPK/PGC-1, reduces protein oxidation, increases NMDAR1 and NGF mRNA expression	Enhances autophagy, increases stress resistance and longevity, antioxidant, anti-inflammatory, restores lipid homeostasis and improves cognition	[28][29][30][31][32][33]
	VECs cells	50 µM	Activates AMPK/FOXO3a		
	VECs cells	10 µM	Reduces ROS		
	VAFs from Sprague–Dawley rats	25 µM	Increases LC3II/LC3I, Bcl1 and SIRT1 expression		
	HepG2 and Huh7 cells	100 µM	Inhibits PI3K/Akt/mTOR, expression of IL1β & IL6, and NFκB DNA binding		
	Rat hepatocytes	25 µM	Inhibits Acetyl CoA carboxylase, HMG CoA reductase, diacylglycerol acyl transferase		

Polyphenol	Analytical System	EPC[a]/ROA[b]	Effects of Polyphenols at Cellular Level	Effects in Relation to AD	Reference
Oleuropein aglycone	Rat ventricular myocyte	100 μM	Increases Bcl1 and LC3II expression, TFEB nuclear localization, LAMP1 and p62 expression	Induces autophagy, increases lysosomal biogenesis and reduces oxidative damage	[33][34][35]
	Human SH-SY5Y neuroblastoma cells and rat RIN5F insulinoma cells	50 μM	Inhibits MAOA, induces AMPK/ULK1, inhibits mTOR		
	Rat hepatocytes	25 μM	Inhibits acetyl CoA carboxylase, HMG CoA reductase and diacylglycerol acyl transferase		
Curcumin	Male Sprague–Dawley rats	15 mg/kg/d for 4 weeks/subcutaneous injection	Activates AMPK and regulates lipid metabolism	Induces autophagy, restores lipid homeostasis, antioxidant, anti-amyloidogenic, anti-inflammatory, anti-apoptotic antiproliferative, increases lysosomal biogenesis and longevity	[36][37][38] [39][40][41] [42][43][44] [45]
	Adult male Wistar rats	30 mg/kg for 30 d/oral administration	Activates Nrf2, inhibits NFκB and mTOR		
	Adult Swiss male albino mice	80 mg/kg/d for 7 d/intraperitoneal injection	Inhibits MaoB and reduces ROS		
	APPswe Tg2576 transgenic mice (chronic 500 ppm curcumin diet)	Blood curcumin level ~2 μM for 1 h/injection in right carotid artery	Inhibits formation of Aβ, oligomers, fibrils and plaques		
	$Tsc2^{+/+}$, $Tsc2^{-/-}$ MEFs and HCT116 cells	10 μM	Activates TFEB, increases levels of LC3 and inhibits pAkt		
	Sprague–Dawley rats' primary cortical neurons	10 μM	Upregulates SIRT1 and inhibits Bax		
	APP/PS1 double transgenic mice	160 ppm for 6 months/oral administration	Inhibits PI3K/Akt/mTOR signaling, increases LC3I/II and Beclin1 expression		
Myricetin	HepG2 Cells	50 μM	Inhibits mTOR and increases LC3II expression	Induces autophagy, antiproliferative, increases stress resistance, longevity, antioxidant capacity and mitochondrial regeneration	[46][47][48]
	Adipocytes differentiated from C3H10T1/2 cells	10 μM	Activates SIRT1/SIRT3/SIRT5		
	Male ICR mice	50 mg/kg/d for 21 d/oral administration	Increases mitochondrial mass and increases PGC1α, SIRT1, TFAM, Nrf1 & FOXO1		

Polyphenol	Analytical System	EPC[a]/ROA[b]	Effects of Polyphenols at Cellular Level	Effects in Relation to AD	Reference
Urolithin A	C2C12 myoblasts	50 μM	Induces mitophagy, increases LC3I/LC3II and activates AMPK signaling	Increases mitophagy, and autophagy, antioxidant, increases lysosomal biogenesis, anti-inflammatory, anti-amyloidogenic, improves cognition and longevity	[49][50]
	Female APP/PS1 transgenic mice B6C3-Tg (APPswe, PS1dE9) 85Dbo/J and age-matched wild type mice	300 mg/kg/d for 14 d/oral administration	Activates AMPK, decreases NFκB/MAPK/BACE1 activities and APP levels		
Ferulic Acid	HeLa cells and mouse primary hepatocytes	1 mM	Increases LC3 II and inhibits mTOR	Anti-apoptotic, anti-amyloidogenic, antioxidant, anti-inflammatory and induces autophagy	[51][52][53][54]
	In vitro	NA	Inhibits Aβ aggregation and reduces ROS		
	(APP)swe/presenilin 1(PS1)dE9 (APP/PS1) mouse model	5.3 mg/kg/d for 6 months/oral administration	Reduces amyloid deposition and interleukin-1 beta (IL-1β) levels		
Acacetin	*Drosophila melanogaster*	100 μM	Inhibits BACE1	Anti-amyloidogenic, antioxidant, anti-inflammatory and induces autophagy	[55][56][57][58]
	C57BL/6J mice	~10 mg/kg/d for 14 d/oral administration (gavage)	Inhibits MAPK and PI3K/Akt pathways		
	ICR mice	100 mg/kg for 7 h/intraperitoneal injection	Increases LC3II, Atg5 and Atg7 expression, modulates TNF-α/IL-6 expression and suppresses TLR4 signaling		
Baicalein	SH-SY5Y human neuroblastoma cells	12.5 μM	Increases ROS scavenging and activates Nrf2	Anti-amyloidogenic, anti-apoptotic, antioxidant, anti-inflammatory, inhibits excitotoxicity, stimulates neurogenesis and neuronal differentiation	[59][60][61][62][63][64][65]
	In vitro	NA	Chelates iron		
	CHO/APPwt cells	5 μM	Induces α-secretase and inhibits Aβ formation		
	In vitro	30 μM	Dissociates amyloid aggregates, Aβ oligomerization and fibrillation		
	HeLa cells	100 μM	Inhibits NFκB activation		
	C57BL/6J APP/PS1 mice	80 mg/kg/d for 60 d/oral administration (drinking water)	Inhibits GSK3β mediated tau phosphorylation		
	Sprague-Dawley male rats	20 mg/kg 30 min before and 2/4 h after onset of ischemia/intraperitoneal injection	Induces Bcl-2/Bcl-xL associated phosphorylation		

Polyphenol	Analytical System	EPC[a]/ROA[b]	Effects of Polyphenols at Cellular Level	Effects in Relation to AD	Reference
Icariin	Primary cortical neurons prepared from E16-17 mouse embryos	1.2 μM	Activates SIRT1	Antioxidant, anti-amyloidogenic, reduces ER stress, increases synapsis and neuronal plasticity, inhibits tau hyperphosphorylation, increases cell viability, antiapoptotic and anti-inflammatory	[66][67][68][69][70][71][72][73]
	Wistar rats	60 mg/kg/d for 3 months/oral administration	Increases SOD activity		
	Tg2576 mouse model	60 mg/kg/d for 3 months/oral administration	Reduces expression of BACE1 and APP		
	Sprague-Dawley rats	120 mg/kg/d for 28 d/oral administration	Induces PSD95, BDNF, pTrkB, pAkt, and pCREB expression		
	SH-SY5Y cells	1 μM	Inhibits GSK3β activation		
	PC12 cells	10 μM	Inhibits JNK/p38, MAPK and p53 activity		
	HT29 and HCT116	20 μM	Inhibits NFκB signaling		
Nobiletin	Male 3XTg-AD mice	30 mg/kg/d for 3 months/intraperitoneal injection	Reduces Aβ levels and plaque formation in brain	Anti-amyloidogenic, increases stress resistance, neuronal synapsis and plasticity, antioxidant and anti-inflammatory	[74][75][76][77]
	Male Sprague-Dawley rats	25 mg/kg/d for 3d/intraperitoneal injection	Increases activity of Akt, CREB, BDNF and Bcl2, increases Nrf2, HO-1, SOD1 and GSH expression, reduces NFκB, MMP-9 and MDA expression		
Genistein	*In silico* and *in vitro*	NA	Inhibits chymotrypsin-like activity of proteasomes	Antioxidant, increases degradation of Aβ, increases apoptosis, enhances autophagy and inhibits proteasomal protein degradation	[78][79][80][81]
	LNCaP cells	100 μM	Increases Kip1 and reduces IκBα/Bax		
	Human dermal fibroblasts (HDFa)	30 μM	Increases TFEB expression		
	Human mammary gland tumor cells (MCF-7)	0.5 μM	Enhances antioxidant gene expression		
Luteolin	HT-29 cells	50 μM	Reduces ROS, NFκB signaling, Cox2 expression, blocks JAK/STAT signaling	Anti-inflammatory, antioxidant, modulates autophagy and apoptosis, increases survival	[82][83][84][85][86]
	Male Sprague-Dawley rat myocytes	8 μM	Downregulates Bax expression, upregulates PI3k/Akt signaling and Bcl-2 expression		
	Human HCC cell line SMMC-772	100 μM	Increases expression of LC3B-II, Bcl1 and caspase 8		

Polyphenol	Analytical System	EPC[a]/ROA[b]	Effects of Polyphenols at Cellular Level	Effects in Relation to AD	Reference
Mangiferin	Swiss albino male rats	15 mg/kg/d for 14 d/intraperitoneal injection	Increases ROS scavenging, activates Nrf2, inhibits NFκB signaling, increases GSH levels, decreases lipid peroxidation	Antioxidant, anti-apoptotic, chelates metals, increases stress resistance, autophagy, longevity, neuronal synapsis and plasticity	[87][88][89][90][91]
	In vitro	NA	Rescues mitochondrial respiration, chelates iron		
	Male Swiss albino mice	40 mg/kg/d for 21 d/oral administration	Reduces lipid peroxides and ROS/RNS induced by aluminum and restores regulation of BDNF and NGF		
	Human astroglioma U87MG, U373MG and CRT-MG cells	100 µM	Inhibits PI3K/Akt signaling, MAPK pathway, MMP9 gene expression		

Footnotes: NA, not applicable; [a] EPC, minimum concentration of the polyphenols that have significant neuroprotective effect; [b] ROA, route of administration of polyphenols in *in vivo* models.

2. Multiple Targets of Polyphenols against AD

Polyphenols are a class of compounds that are commonly found in many plants. Four major classes of polyphenols including flavonoids, stilbenes, phenolics and lignans are highly regarded as potential therapeutics for neurodegeneration, cardiovascular diseases, cancer and obesity. Many more polyphenolic compounds are yet to be studied for their potency in AD and other neurodegenerative diseases. Polyphenols are classified according to their structure (reviewed in [92]). Structures of some important polyphenols that are described in the text are depicted in **Figure 2**.

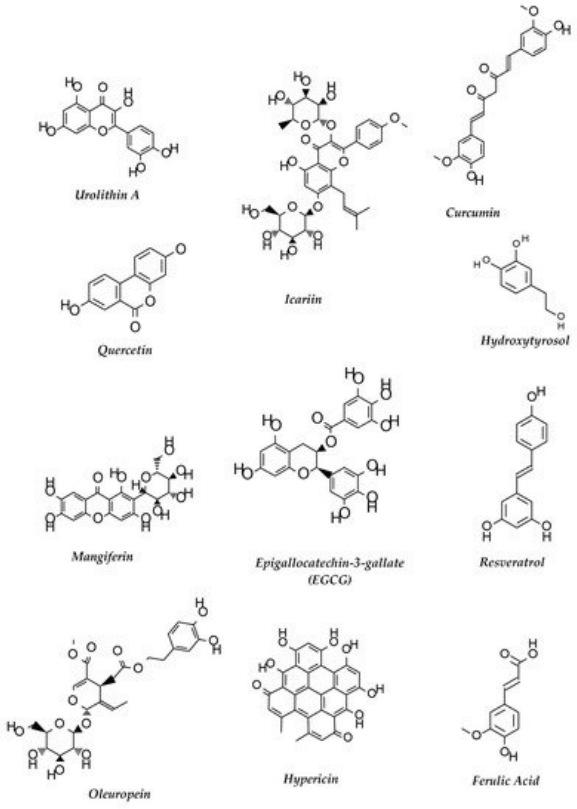

Figure 2. Structures of some polyphenols that show neuroprotective functions against AD.

Polyphenolic compounds abound in mushrooms and are one of their main antioxidants. They are mainly phenolic acids which can be divided into groups of either hydroxybenzoic acids and hydroxycinnamic acids derived from the non-phenolic molecules benzoic and cinnamic acid, respectively [93]. The most common benzoic acid derivatives present in mushrooms were reported as *p*-hydroxybenzoic, protocatechuic, gallic, gentisic, homogentisic, vanillic, 5-sulfosalicylic, syringic, ellagic and veratric acids as well as vanillin. Meanwhile, cinnamic acid derivatives mainly found in mushrooms were *p*-coumaric, *o*-coumaric, caffeic, ferulic, sinapic, 3-*o*-caffeoylquinic, 4-*o*-caffeoylquinic, 5-*o*-caffeoylquinic and tannic acids [93].

It is known that only plants synthesize flavonoids, while animals and fungi are not capable of it. However, accumulating studies indicate the presence of flavonoids in different edible mushrooms [94]. The presence of flavonoids in mushrooms could arise from absorption from the substrates where they grow or from neighboring plants by establishing symbiotic interactions via formation of mycorrhizae [95].

2.1. Polyphenols as Antioxidants

Naturally occurring polyphenols provide protection against neurodegeneration through their role as antioxidants [96]. Dietary polyphenols have direct ROS scavenging activity [97]. Several polyphenolic antioxidants identified in common edible mushrooms include protocatechuic acid, *p*-coumaric, and ellagic acid as well as gallic acid, pyrogallol, homogentisic acid, 5-sulfosalicylic acid, chlorogenic acid, caffeic acid, ferulic acid and quercetin [98][99]. Most of these polyphenols donate electrons to the free radicals thus neutralizing them, which ultimately reduces the levels of ROS within the cells. Polyphenols activate Nuclear factor erythroid 2-related factor 2 (Nrf2), a basic leucine zipper transcription factor. Nrf2 normally is complexed with Kelch-like ECH-associated protein 1 (Keap1) in the cellular environment inhibiting Nrf2′s nuclear translocation. Furthermore, Keap1 also facilitates ubiquitination and proteasomal degradation of Nrf2 [100]. The separation of Nrf2 from Keap1 leads to activation and nuclear translocation of Nrf2, where it complexes with musculoaponeurotic fibrosarcoma (Maf) proteins. This heteromeric Nrf2-Maf complex then binds with antioxidant response element (ARE) sequences located upstream to the phase II detoxifying genes upregulating their expression. Phase II antioxidant genes encode proteins, such as heme oxygenase 1, γ-glutamyl cysteine synthetase, peroxiredoxins, glutathione reductases, thioredoxin reductase, drug metabolizing and detoxification enzymes NAD(P)H quinone dehydrogenase 1, glutathione-*S*-transferase, uridine diphosphate-glucuronosyltransferase and regulators, transketolase, PPARγ-coactivator 1 β (PGC1-β), etc [101]. These proteins act in the cell as antioxidant proteins, having a major role in restoration of the redox imbalance and cellular signaling [102][103]. Additionally, polyphenols also elucidate their antioxidant property through inhibition of NADPH oxidase (NOX) activities [104]. NOX proteins are transmembrane proteins that signal the immune modulators through ROS generation [105]. Lower levels of ROS may be important for cellular signaling, however, at higher levels they can cause damage to the neuronal cells. These proteins, found to be involved in increasing Aβ-induced oxidative stress, could be potential therapeutic targets for AD [106].

Oxidative damage is more prominent when the damage is coupled with mitochondrial dysfunction. Enzymes such as monoamine oxidases (e.g., MaoB) increase the cellular stress by producing hydrogen peroxide [107]. In brains, monoamine oxidase activity of substrate neurotransmitters causes mitochondrial damage, while dietary polyphenols have been found to inhibit MaoB, thus decreasing the ROS generation and mitochondrial dysfunction [36]. Additionally, polyphenols also aid in regeneration of mitochondria in the cells through activation of the master regulator SIRT1 [108]. SIRT1 is a NAD^+-dependent histone deacetylase enzyme that has multiple targets for deacetylation. SIRT1′s involvement in reducing oxidative stress comes from deacetylation of its substrate PGC-1α, which activates nuclear respiratory factors (Nrf1 and Nrf2) and peroxisome proliferator-activated receptor (PPARα) [109]. Further downstream, these molecules enhance the expression of transcription factor A, mitochondrial (TFAM) that initiates the transcription and replication of mitochondrial DNA ultimately causing the regeneration of mitochondria [109]. The activation AMPK, either directly or indirectly (through SIRT1 activation) activates PGC-1α, thus helping in mitochondrial biogenesis.

Biometals such as iron and copper are the major contributors of ROS formation in defunct mitochondria [110]. Quercetin, baicalein, curcumin, etc., are found to provide a protective antioxidant property also through biometal chelation [4][111][112]. Furthermore, alterations in biometal distribution in the neuronal cells is also an important hallmark of AD. The mechanism through which polyphenols act as antioxidants in the cellular environment is schematically presented in **Figure 3**. Antioxidants can also act as pro-oxidants in certain sub-optimal concentrations and cause oxidative damage to the cells. Thus, their optimum concentration needs to be considered prior to their application.

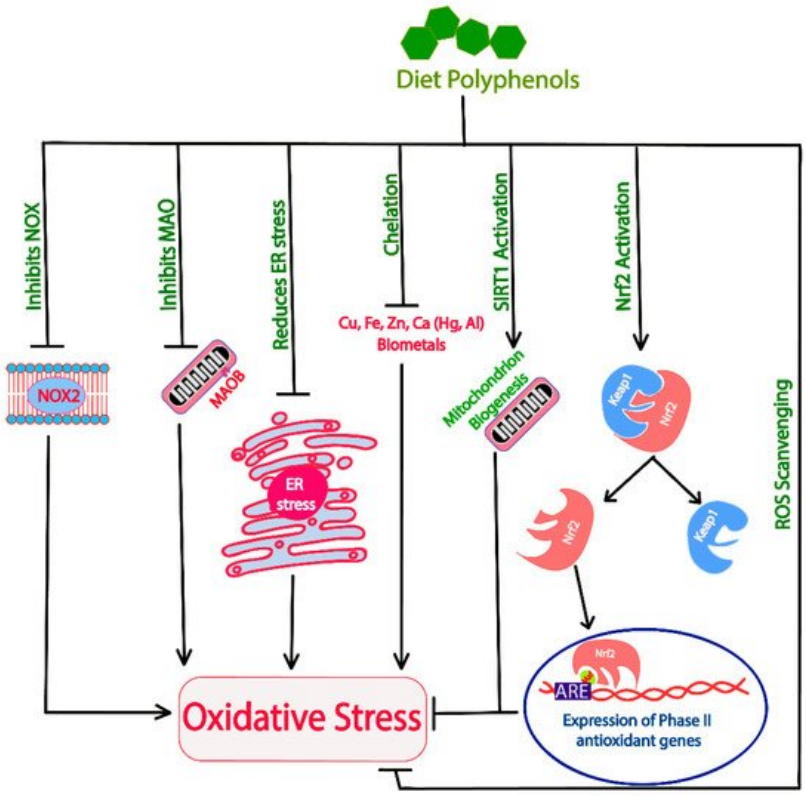

Figure 3. Schematic representation for showing molecular mechanisms by which polyphenols acts as antioxidants (adapted from [36][97][100][101][104][108][111]).

2.2. Modulation of Protein Homeostasis and Longevity with Polyphenols

Dietary polyphenols modulate the protein quality control mechanisms increasing the cellular efficiency to clear misfolded proteins. Apart from induction of autophagic clearance, the UPR and ubiquitin proteasome system are also modulated by dietary polyphenols [113][114][115]. The ability of polyphenols to activate lysosomal biogenesis and increase longevity make them an important class of neuroprotective compounds [5][34][37]. In addition, some of the polyphenols like EGCG and curcuminoids reduced the lipofuscin granules in cells, which normally are impossible to degrade or exocytose from the cell [15][116]. Reduction of lipofuscin in the cell can contribute to the restoration of the protein homeostasis by reducing the damage to autophagosomes and proteasomes.

Most of the polyphenolic compounds act through upregulation of the expression of the master regulator SIRT1 [117]. The SIRT1 protein has been found to have multiple targets that play a vital role in regulating major cellular processes (refer to **Figure 4**) [117]. The activation of AMPK/Unc-51 like autophagy activating kinase 1 (ULK1), transcription factor EB (TFEB), Fork head box O transcription factors (FOXO), deacetylation of p53 and inhibition of PI3K/Akt/mTOR, NFkB, MAPK and the c-Jun N-terminal kinases (c-JNK) pathway are important cellular processes that will induce autophagy through SIRT1 [118][119][120]. Most of these molecular targets are deacetylation substrates of SIRT1. Activation of transcription factors like TFEB reinforces the cellular autophagy by activating lysosomal biogenesis. TFEB itself is another master regulator for the coordinated lysosomal expression and regulation (CLEAR) network. The CLEAR network has important roles in various cellular processes. Energy metabolism, DNA metabolism, steroid biosynthesis, protein clearance, haemoglobin degradation, antigen presentation, phagocytosis and signal transduction are important events regulated by TFEB [121][122].

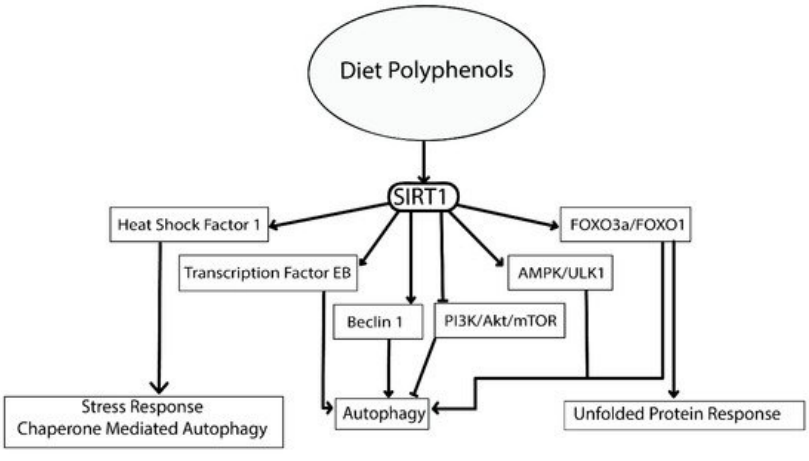

Figure 4. SIRT1 activation by polyphenols and its effect in protein degradation pathways in the intracellular environment (adapted from [37][117][118][119][120][123]).

Similarly, SIRT1 has a significant role in determining cellular fate via Fork head transcription factors (FOXO1 and FOXO3). The deacetylated form of these transcription factors are major contributors of autophagy activation, cell cycle arrest, stress resistance (expression of manganese superoxide dismutase) and immune modulation. Reduction in the levels of FOXO by ubiquitination and proteasomal degradation with the help of SIRT1 reduces the levels of acetylated forms. Reduction in acetylated FOXO's suppresses cell death caused by apoptosis driving cells towards survival and increasing longevity (refer to **Figure 5**) [119][123]. This is of particular interest for neurodegenerative diseases, where survival of neuronal cell after damage is crucial. It has been illustrated that polyphenols activate these master regulators of longevity (Nrf2, SIRT1 and AMPK) providing unprecedented protection against various disease [103][124][125]. However, limited bioavailability of these dietary polyphenols in human has limited their application. Polyphenols such as hydroxytyrosol, oleuropein aglycone, curcumin, resveratrol, rotenone, rutin, myricetin, urolithin A, epigallocatechin 3-gallate (EGCG), ferulic acid, genipin, etc. have been reported to induce autophagy. The olive oil polyphenol, hydroxytyrosol activates AMPK pathway and is reported to reduce Aβ levels in mouse models of AD [28][126]. Similarly, oleuropein aglycone has been reported to activate SIRT1/AMPK/mTOR and TFEB mediated autophagy [127][128].

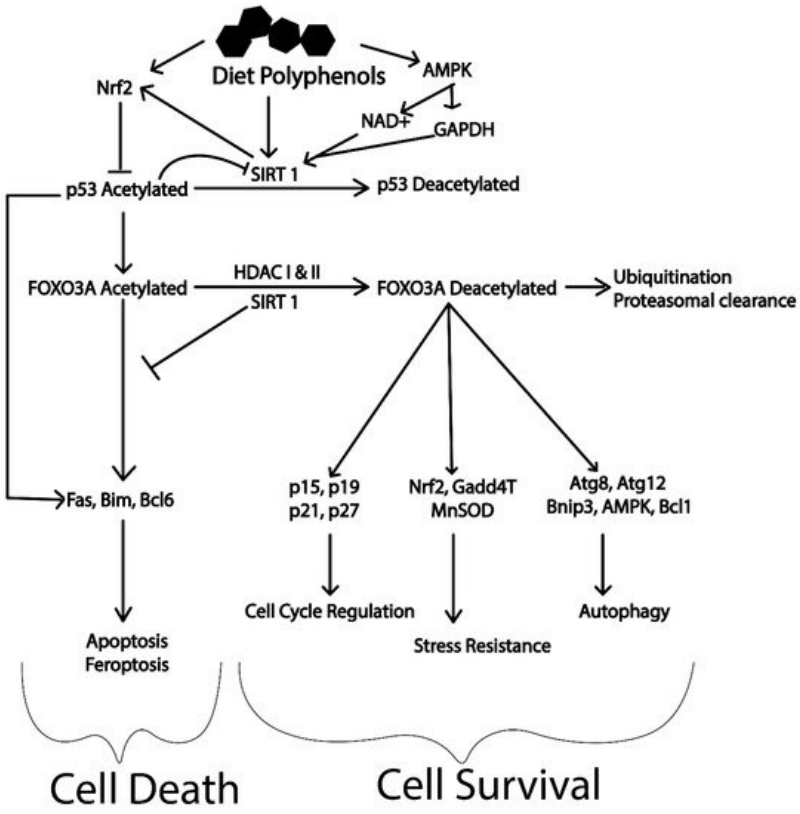

Figure 5. Modulation of longevity by the action of polyphenols through SIRT1 activation (adapted from [115][118][119][122][123][124][125]).

Curcumin, one of the most studied polyphenols, has multifactorial benefits in balancing the protein homeostasis by activation of AMPK/ULK1 and inhibition of PI3K/Akt/mTOR through activation of SIRT1 [38]. EGCG, a catechin family polyphenol, inhibits the suppressors (Bcl2 and Bcl-XL) of Beclin1. However, the activity of this polyphenol is also dependent on the concentration of the compound. A higher concentration of EGCG inhibits autophagy and induces apoptosis, whereas, lower concentrations induce autophagy that also degrade lipid droplets through a Ca^{2+}/CAMKKB/AMPK dependent mechanism. Thus, the concentration of polyphenols is a crucial factor before considering it as a therapeutic option. EGCG has also been reported to reduce the catalytic activity of 19S and 20S proteasomal proteins, deactivate NFkB pathway and enhance p53 tumour suppressor protein expression [129]. An important feature of EGCG also includes its ability to inhibit lipofuscin formation, which otherwise impairs autophagy and the proteasome during ageing [15].

Resveratrol is another important polyphenol frequently studied for its beneficial effect in increasing longevity and balances cellular protein homeostasis. The activation of SIRT1/AMPK and extracellular signal-regulated kinases (ERK1/2) is the molecular mechanism by which this polyphenol was found to be neuroprotective [9][130][131]. The metabolite of ellagitannin, urolithin A, extracted from pomegranate has been reported to activate autophagy through SIRT1 activation [132]. Furthermore, the natural compound was also found to increase mitophagy and longevity in a *Caenorhabditis elegans* (*C.*

elegans) model that has provided insight on human neurodegeneration [49]. Quercetin has shown multiple benefits in human health by enhancing autophagy through SIRT1activation, inhibiting proteasomal degradation (inhibition of all the catalytic subunits), reducing proliferation and activating apoptosis [133]. Apart from autophagy inducers, hesperitin and hesperidin have also been reported to have negative effects on Aβ-induced autophagy and glucose metabolism impairment [134][135].

2.3. Polyphenols and Cellular Lipid Balance

Polyphenols are also considered as potential therapeutic agents against obesity and other life-threatening conditions [136][137][138]. This property of polyphenols is associated with the activation of AMPK, which targets lipid metabolism as well [139]. Activation of AMPK decreases the activity of acetyl CoA carboxylase, HMG-CoA reductase and diacylglycerol acyl transferase, and thus avoids hepatic accumulation of lipids [140][141]. These actions of AMPK reduce the levels of free fatty acids as well as the complex lipids. Polyphenols are also found to inhibit the adipogenesis by inhibiting proteins like PPARγ [142][143]. Additionally, as explained in previous sections, polyphenols increase autophagic clearance. Induction of autophagy is not only limited to restoring the protein balance but is also associated with the degradation of lipids to meet the energy demands of the cells. Thus, polyphenols can also reduce lipid accumulation in the intracellular environment [144]. AD is also termed as Type III diabetes due to its similarity with diabetes. High levels of cholesterol have been found to be associated with AD brains [145]. Lowering the levels of cholesterol has been an important approach for the treatment of AD, despite limited success. Furthermore, studies support increased activity of γ-secretase and β-secretase with higher levels of lipids in the membrane environment that could contribute to increased Aβ levels in the brain [146]. Considering these facts, polyphenols are hypothesized to have their neuroprotective action in part through the restoration of lipid homeostasis.

2.4. Anti-inflammatory Activity of Polyphenols

ROS act as signaling molecules for induction and release of pro-inflammatory mediators including NFκB and cytokines. NFκB exists in an inactivated form bound to an inhibitor referred to as p65/p50 dimer in normal conditions [147]. When this complex gets activated by increased ROS, the p65/p50 dimer translocates to the nucleus upregulating expression of the inflammatory markers [148]. The expression of these inflammatory mediators inside the cells triggers the downstream process of inflammation. Deacetylation of NFκB through the action of SIRT1 at specific amino acid residues renders it inactivated and reduces the inflammatory response by reducing the expression of downstream genes [147]. Since polyphenols are antioxidants capable of lowering the ROS in the cells, they can downregulate the expression of proinflammatory mediators [149]. However, the highest anti-inflammatory activity of polyphenols is attributed to their ability to activate the master regulator SIRT1 [150]. Many polyphenols have been reported to have an anti-inflammatory effect which could provide the basis for protection against diseases with chronic neuroinflammation/inflammation.

2.5. Polyphenols as Anti-amyloid Agents

Oleuropein, an olive polyphenol, is found to increase α-secretase activity. Thus, it prevents cells from producing Aβ: instead such activity results in the formation of the Aα peptide [151]. Formation of Aα instead of Aβ is anti-amyloidogenic, which may be helpful in reducing the Aβ-associated toxicity. Some polyphenols (such as rutin) reduce the β-secretase activity [6]. Similarly, other polyphenols disaggregate the amyloid aggregates *in vitro* [6][152]. Furthermore, the ability of polyphenols to lower the cholesterol levels in cells also favors the reduced activity of β-secretase and γ-secretase [6][145]. Apart from the anti-amyloid functions, polyphenols also possess the ability to inhibit tau aggregation [153].

Through characterization of the cell-free extracts of different bacteria, fungi and yeast, Lee *et al*. (2007) identified the BACE1 inhibitory effects of different mushrooms [154]. Mushroom species having anti-BACE1 effects were *Flammulina velutipes*, *Pleurotus ostreatus*, *Grifola frondosa*, *Dictyophora echinovolvata*, *Fomitella fraxinea* and *Inonotus obliquus*. Hispidin, a polyphenolic compound found in abundance in the mushroom *Phellinus linteus* inhibits BACE1 non-competitively and scavenges free radicals [155]. BACE1's inhibitory effect of *Auricularia polytricha* has also been indicated to be hispidine mediated [156].

2.6. Polyphenols in Cognition and Synapsis

Polyphenolic compounds like α-isocubebenol, tacrine and their derivatives, 2′,4′-dihydroxy-6′methoxy-3′,5′-dimethyl-dihydrochalcone, tetrahydropyranodiquinolin-8-amines, quercetin and tiliroside have been shown to have neuroprotective properties attributed to their inhibiting activity against acetylcholine esterase [157][158][159][160]. In addition, some other polyphenols, including genistein, luteolin-7-O-rutinoside and silibinin, are reported to have a moderate effect on the butyrylcholine esterase [159]. Among the polyphenols, flavonoids are an important class of polyphenols that have anti-

choline esterase activity [161]. Flavonoids extracted from *Ginkgo biloba* have been reported to have inhibitory effects against acetyl choline esterase [162]. Molecular docking experiments revealed the mechanism of action of quercetin was through strong hydrogen bond formation with certain amino acids of AChE, thus leading to competitive inhibition of AChE. Similarly, macluraxanthone exhibited non-competitive type interference with the activity of acetyl choline esterase [161]. The combination of numerous hydrogen bonds with several amino acids and hydrophobic interaction may be responsible for how these polyphenols inhibit acetylcholine esterase activity [163].

Polyphenols exert neuroprotective effects in experimental systems but there is a need to translate this in guidelines for neuroprotection of aging populations. For translation of animal studies to human trials, dose accuracy plays a critical role. For example, consider resveratrol levels in **Table 1**: an effective dose in mice is 60 mg/kg/d by oral administration. In humans this translates to ~290 mg for a 60 kg person per day [164]. Such levels are rarely reached. In the case of resveratrol, the suggested daily intake is 200 mg/day and this is unlikely to be a protective level. In addition, alterations in polyphenol administration routes may reduce the amount of polyphenol to be used on daily basis, signifying the benefits of alternative administration strategy. However, long term uptake of the polyphenol could still have beneficial effects in lower doses. On the other hand, some nutraceutical products may contain the polyphenol at more than the optimal amount, which could have negative effects in brain health [165]. This bimodal activity of polyphenols should be highly considered before translating the beneficial effects of the polyphenols for human use.

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