

Promising modulatory effects of autophagy on APP processing as a potential treatment for Alzheimer's disease

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Abstract

Autophagy refers to the degradation of cytoplasmic constituents by a lysosomal-mediated pathway, which plays a critical role in maintaining cellular homeostasis. Importantly, dysregulation of autophagy has been implicated in multiple neurodegenerative disorders. Previous studies reported that autophagy affects the processing of amyloid precursor protein (APP), thus stimulating β -amyloid ($A\beta$) production in Alzheimer's disease (AD) eventually. Although the mechanism of autophagy modulation on APP processing and its pathogenesis has not yet been fully elucidated at the molecular level, but modulation of autophagy has received considerable attention as a promising approach for the treatment of AD. In the early stage of AD, $A\beta$ may prompt autophagy to facilitate its removal via mTOR-independent as well as-dependent pathways. However, a recent study proposed that autophagy processes are not properly regulated as AD continues to progress, and consequently, the production of $A\beta$ tends to accumulate rapidly. Meanwhile, a number of autophagy-related genes (Atg) as well as APP genes are also thought to influence the development of AD, which may serve as a bi-directional link to autophagy and AD pathology. In this review, we summarized current observations related to autophagy regulation and APP processing, focusing on their dynamic modifications associated with the progression of AD. Recent findings together highlight the essential role of autophagy in the removal and clearance of APP and $A\beta$ deposition in the pathological condition of AD.

Keywords: Autophagy; Amyloid precursor protein (APP); β -amyloid ($A\beta$); mTOR; Alzheimer's disease (AD).

1. INTRODUCTION

Amyloid precursor protein (APP), a transmembrane glycoprotein (type-I), is a key molecular driver for Alzheimer's disease (AD) pathogenesis. An extracellular domain and a small cytosolic domain present in APP are generally accepted to be responsible for AD progression [1]. APP is ubiquitously present in the brain, and is involved in building synaptic network as well as regulating neurogenesis [2]. In addition, APP has a modulatory effect in cell surface receptors and axonal transport. However, the exact functionality of the APP still remain elusive [3]. In general, upon its synthesis on the endoplasmic reticulum, phosphorylation and glycosylation of APP take place and APP is finally transported into the Golgi apparatus. Additional processing of APP is also observed in the trans-Golgi-network (TGN), and the highest concentrations of APP are found in TGN under normal physiological conditions. Cleavage of APP by α -secretase produces a soluble molecule, sAPP α , within the A β domain [4], and APP goes inside the cargo by the process known as the endosomal/lysosomal degradation pathway. Lysosomal degradation is a clearance mechanism required to maintain a healthy state and to prevent the accumulation of undesirable cellular wastes materials. The generated peptide serves an important role in synaptic plasticity and neuronal survival in the healthy state [5]. However, the toxic amyloidogenic peptide is produced due to the mutations of genes encoding APP, presenilin-1 and presenilin-2, and the excessive cleavage of APP through β -secretase (BACE-1) and γ -secretase in place of α -secretase led to unwanted assembly and accretion of irregular A β peptides. The diffusible oligomers and insoluble senile plaque are formed due to abnormal presentation of A β peptides, thereby resulting in higher neurotoxicity. Moreover, a fibrillary plaque is found in the intracellular space due to the aggregation of abnormal A β oligomers [6]. Hyperphosphorylation of tau, the most common form of AD, is interrelated to its aggregation as well as the formation of neurofibrillary tangles (NFTs) and is considered as pathologically condition of AD [7]. Intracellularly, NFTs are formed which contain a microtubule binding protein known as phosphorylated tau [8]. However, genetic mutations affect the levels of A β -peptide, for example Presenilin 1 (PSEN1), Presenilin 2 (PSEN2), and APP which cause AD pathogenesis [9]. Collectively, the neurotoxic effect of NFTs and A β associated with the excessive accumulation of extracellular plaque in brain is a hallmark of AD pathogenesis [10].

Autophagy provides a widespread role in both physiological and multiple pathological conditions, including cancer and neuronal disorder [11], and has gained extensive linkage to the AD pathogenesis [12]. Autophagy, a self-digesting mechanism, is an intracellular cleansing process mediated by the removal of malformed proteins and damaged cellular organelles to membrane-bound vesicles known as autophagosome [11]. These autophagosomes subsequently fuse with the lysosome to form autophagolysosome that allows the degradation of its cargo, and acid hydrolysis mediates the lysosomal degradation of dysfunctional materials within the cell [13]. Autophagy is a complex and tightly regulated enzymatic process which is largely classified into two categories: mammalian target of rapamycin (mTOR)-independent and -dependent pathway. A defect in the autophagy lysosomal pathway harnessing pathological amyloids induces the formation of toxic A β aggregates, which causes cellular apoptosis as well as tissue and organ damages, culminating into clinical symptoms. In the beginning of AD, existence of A β may prompt autophagy to accelerate their removal process by employing both mTOR-independent and -dependent pathway. Progression of AD terminates the regular autophagy pathway, resulting in the continuous generation of A β , which exaggerates both autophagy malfunction and AD [14]. In addition, both oligonucleotides and proteins, such as miRNAs, transcription factors EB (TFEB), presenilin, Nrf2, and Beclin-1 are simultaneously convoluted in the regulation of autophagy, which are meticulously interrelated to the pathogenesis of AD [15]. Therefore, it is evident that the regulation of autophagy is crucial for APP cleansing and the elimination of AD pathogenesis. Abnormal autophagy is associated with AD pathogenesis; therefore, targeting autophagy may have a profound role in AD management [16].

2. AUTOPHAGIC PATHWAY

The autophagy pathway is initiated with the generation of the phagophore and ends the clearance of the autophagosome. Degradation of autophagosome mediates that recycling of the cargo [17]. The autophagy related gene Atg12-Atg5-Atg16 complex controls the autophagosome formation and microtubule-associated protein light chain 3 (LC3-I)-phospholipid conjugates (LC3-II). Both of LC3-I and II are used as a marker for double-membrane vesicle autophagosome. Furthermore, p62 is a marker for lysosomal degradation, which indicates autophagosome produced by

interaction with lysosome degrades its cargo. This state is known as the activation of the autophagic flux [18].

A starving condition in a cell initiates autophagy response, and a double-membraned structure, known as autophagosome, is produced by the sequestration of the cytoplasmic materials. Autophagosome fuses with lysosome, and acid hydrolysis degrades the cargo, which contributes to the mitochondrial quality control and cellular homeostasis [19]. Autophagy can be portioned into the following steps: the formation of isolated membrane (nucleation), membrane elongation, autophagosome maturation, docking and fusion between autophagosome with the endosome and finally the lysosome, and degradation of the internal materials inside the autolysosome [17] (Figure 1). Autophagy is controlled by numerous growth factors as well as nutrient signaling, such as mTOR complex 1 (mTORC1) and class I PI3K/Akt signaling pathway. Dysregulation of autophagy deposits unwanted debris within a cell rather than recycling; therefore, inhibition of autophagy is implicated in multiple pathophysiological processes, including neurodegenerative diseases like AD [11].

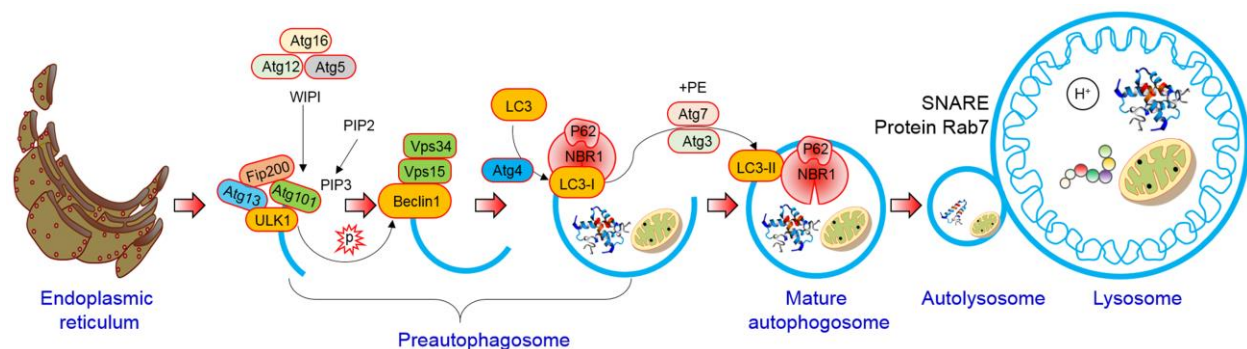


Figure 1: Schematic diagram of different phases of autophagy. Autophagy is initiated by inactivation of mTOR pathways and numerous autophagy related proteins. Pre-autophagosome synthesis comprises with coupling of LC3 in association with ULK1 and Vps34 protein. Autophagosome membrane along with formation of double membrane vesicles are sequestered material of cytoplasm which form mature autophagosome. Finally, fusion of mature autophagosomes and lysosomes discharge the products into the cytoplasm which may further used as nutrients.

2.1 Autophagy pathway: mTOR-dependent

Mammalian target of rapamycin (mTOR) is an essential serine-threonine protein kinase, comprising mTOR complex 1 (mTORC1) as well as mTOR complex 2 (mTORC2) [20]. mTOR is known as a classical regulator of autophagy and controls vital cellular functions, such as protein translation and cell growth [21,22]. The mTOR activity is closely associated with numerous factors, including chronic stress, starvation, and glucocorticoids. During starvation, mTORC1 activity is down-regulated, thereby initiating autophagy to recycle intracellular constituents and thus to generate a source of energy. Phosphoinositide 3-kinases (PI3K) as well as protein kinase B (Akt/PKB) are dual upstream mTOR molecules [20]. These two molecules interact with mTOR and modulate the PI3K/Akt/mTOR pathway that controls autophagy. However, blockage as well as inhibition of any molecules of this pathway triggers autophagy, thereby augmenting the clearance or removal of A β in AD [20]. Previous studies have been shown that the inhibition of mTORC1 during starvation or its pharmacological blockade with rapamycin, CCI-779, Torin1 or PP242 stimulates autophagy [23,24].

Furthermore, adenosine 5'-monophosphate-activated protein kinase (AMPK) elicits autophagy [22]. AMPK is an upstream regulator of mTOR. However, peroxisome proliferator-activated receptors- γ (PPAR γ) and mTOR organized PPAR γ /AMPK/mTOR also regulate the autophagy. In addition, dihydroceramide desaturase (Des1 and Des2) are the enzymes that catalyze the synthesis of dihydroceramide into ceramide, which can trigger the levels of mTORC1 and inhibition of autophagy (Figure 2). The findings from a study suggested that inhibiting Des1 activity might modulate autophagy and mTORC1 activity in neurons, thereby suppressing amyloid secretion in AD [25]. In addition, the transient receptor potential mucolipin-1 (TRPML1) is extensively articulated in cell lysosomes, which also serves as an autophagy regulator. Lacking the activity of TRPML1 PPAR γ /AMPK signaling pathway block mTOR signaling, triggering the accumulation of degraded cellular components via the inhibition of autophagy flux. A study using transgenic mice revealed that TRPML1 is a precursor for the progression of AD due to the blocking of autophagy machinery [26]. Besides, DNA damage, oxidative stress, hypoxia, and metabolic stress generate reactive oxygen species (ROS) which modulate autophagy via the Akt/mTOR pathway [27,28].

2.2 Autophagic pathway: mTOR-independent

An increase in AMPK-mediated phosphorylation activates autophagy machinery. Ca^{2+} -dependent protein kinase β (CaMKK β) is an upstream controller of AMPK, and the influx of Ca^{2+} through TRPM7 maintains basal autophagy via the CaMKK β /AMPK pathway. The aggregation of A β interferes with the homeostasis of Ca^{2+} levels that causes mitochondrial dysfunction, which is closely connected to the AD pathogenesis [29]. Generally, AMPK-mediated phosphorylation occurs in the serine-317/777 sites of autophagy initiation kinase, ULK1. In addition, AMPK, an upstream signaling molecule of Beclin-1, is related with pre-autophagosomal complex initiation and AMPK directly phosphorylates the serine-91/94 sites of Beclin-1, thereby initiating autophagy (Figure 2). Inflammatory response activates the microglia that increase the transportation of p-tau in neurons and assist the degradation of p-tau in lysosomes. This course of action increases autophagic flux in microglia and assists the clearance of cellular debris in a regular manner. ROS production by mitochondria causes an oxidative damage to mitochondrial proteins and triggers autophagy-mediated cell death via mTOR independent manner [30].

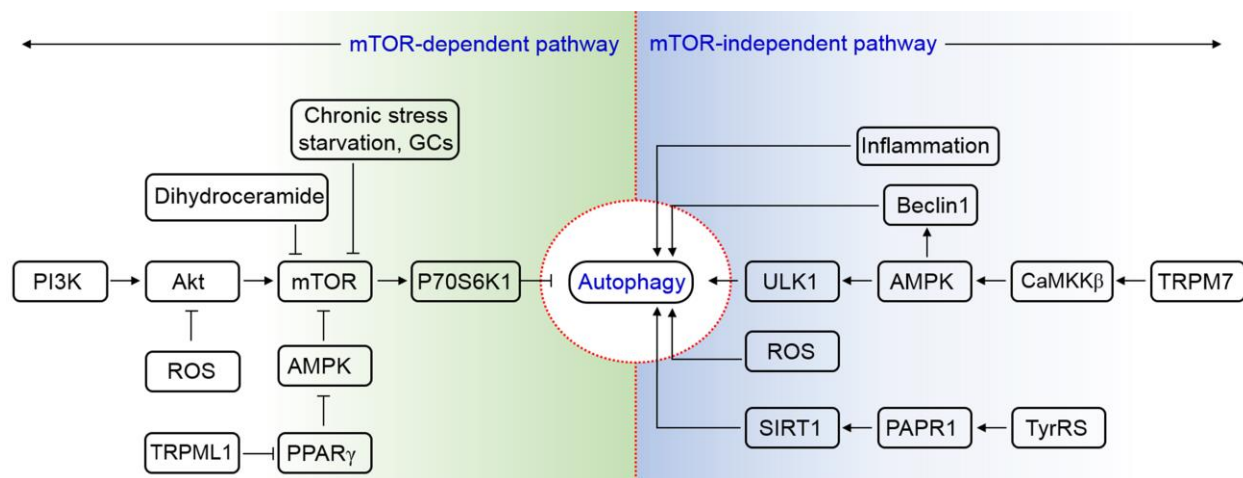


Figure 2: Autophagy regulates by mTOR signaling pathway. mTOR-dependent pathway as well as mTOR-independent pathway can be regulated the overall autophagy signaling. mTOR phosphorylation can lead to ribosomal P70S6K1 phosphorylate which is a mTOR substrate protein, therefore preventing autophagy initiation. Another physiological condition, autophagic pathway can additionally be stimulated over some other elements for example starvation, chronic stress, as well as GCs through mTOR inhibition. Furthermore, TRPML1/PPAR γ /AMPK/mTOR and

PI3K/Akt/mTOR are positive and negative autophagy regulator respectively, stimulation as well as prevention of these pathways may trigger autophagy. Also, dihydroceramide is a controller of mTOR-mediated autophagy induction. However, ROS stimulates autophagy via mTOR-dependent as well as mTOR-independent pathways. Besides, inflammatory stimulation of microglia similarly acting a role autophagy in initiating in some condition. TRPM7, CaMKK β , AMPK as well as TyrRS, PARP1, SIRT1 are most important positive pathways in autophagy regulation of mTOR-independent pathways.

3. NEURONAL ROLES OF APP

Although A β plays the fundamental role in the pathogenesis of AD, the evolutionary preservation of APP and the existence of APP isoforms that lack the APP gene sequence indicate that amyloid formation is not an intended physiological function of this family of proteins under normal circumstance. Current amassed evidence has shown that APP is vital for the generation, differentiation, and migration of neurons [31]. In dominant expression neuronal cells could rescue this phenotype significantly. In addition, APP also plays a significant role in *Drosophila melanogaster*, and the suppression of APPL gene causes an alteration of chemotactic behavior [32]. Interestingly, high levels of APPL are associated with the neuronal regeneration in the brain injury model of *Drosophila* increased mortality. APPL is positively correlated with the increased protrusions of dendritic neurites, and the potential role of APP in axonal growth after a traumatic brain injury was reported previously [33]. Moreover, overexpression of APP promotes synaptic differentiation, and APPL mutants reduce the number of synaptic lobes in the *Drosophila* neuromuscular junction [34].

APP is omnipresent in mammalian cells and shown to have a multifunctional role in cellular functions, such as cell adhesion, differentiation of neuronal cells, nerve migration, synapse formation, and neurite growth. APP immunoreactivity was reported to increase after a brain injury in mice, which is consistent with a traumatic injury of the brain. APP-deficient mice showed weight loss, balance and muscle weakness, impaired behavior and long-term potentiation [35]. Evidence from other animal models of APP deficiency has demonstrated the potential role of APP in the generation, differentiation, and migration of neurons. The potentially important role of APP as part of a complex mechanism involved in several neurological functions, such as nerve

development [36]. Growing evidence suggests that soluble sAPP α plays a neuroprotective role and functions similar to growth factors, and it has been shown that the APP intracellular domain (AICD) interacts with numerous proteins involved in the regulation of transcription and axonal transport [37].

4. APP PROTEOLYTIC PROCESSING IN ALZHEIMER'S DISEASE

APP is proteolytically cleaved into several fragments during intracellular transport, and these metabolites of APP mediate multiple cellular functions, some of which are harmful. Thus, the net effect of the full-length APP on the activity of cells may be due to the combination of different metabolite roles that mainly depend on the percentage of each APP metabolite level. APP may undergo non-amyloidogenic or amyloidogenic excision by several secretases [38,39]. APP amyloidogenic processing, which is first mediated by β -secretase, leads to the production of a large APP (sAPP β) and AICD containing a carboxy-terminal fragment (CTF99) [39]. In the brain, β -site cleavage enzyme of APP (BACE1) is considered as a primary β secretase [40]. APP also undergoes proteolytic processing by an γ -secretase complex containing presenilin, which is known as a non-amyloidogenic pathway [41]. In this process, A β sequence is cleaved from inside, resulting in the formation of A β [42]. The non-amyloidogenic processing produces a carboxy-terminal fragment (CTF83) and a soluble fragment (sAPP α) which is thought to play a neuroprotective role in contrast to A β [43]. The CTF83 and CTF99 fragments are consecutively cut in the transmembrane domain by the action of γ -secretase, producing AICD and A β , respectively [44,45]. Induced levels of β -secretase were reported to increase the level of CTF99 and A β as well as the reduction in CTF83 and AICD levels *in vitro*. In contrast, higher levels of α -secretase drive to increase AICD43 generation [46]. The details of APP processing by the amyloidogenic and non-amyloidogenic process are demonstrated in Figure 3. Collectively, the cleavage of APP by α -secretase and β -secretase may have different effects on the subsequent release of AICD [40].

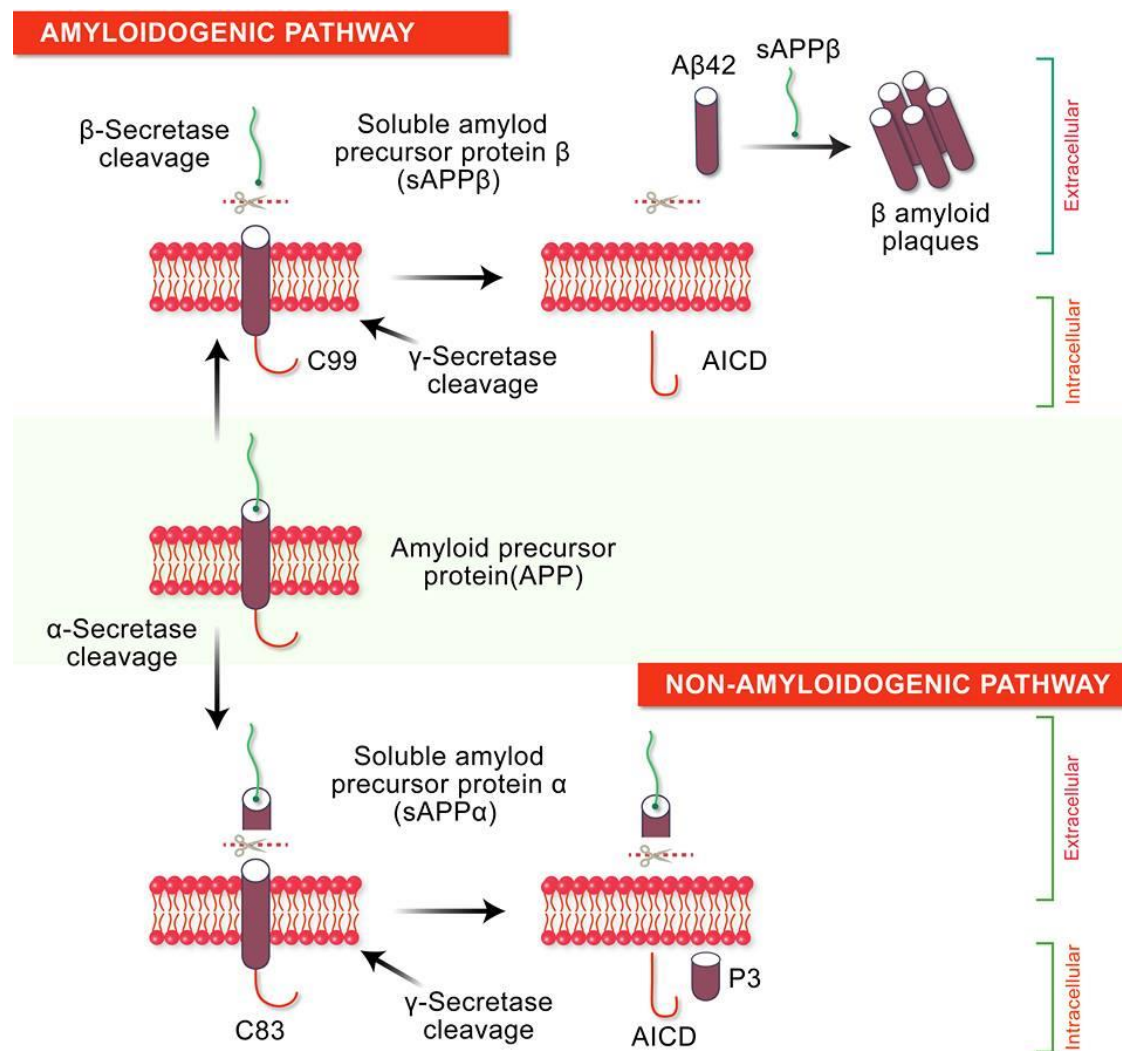


Figure 3: The non-amyloidogenic pathway cleavages APP through α -secretase to form two fragments, intracellular C-terminal fragment, C83, and soluble amyloid precursor protein α , sAPP α , extracellular fragment. Cleavage of C83 fragment via γ -secretase yields a P3 peptide short fragment and APP intracellular domain (AICD) fragment. The amyloidogenic stores pathway neurotoxic A β . Extracellular sAPP β releases by β -Secretase in addition to large N-terminal soluble amyloid precursor protein C99 fragment. C99 fragment Cleavage by γ -secretase produces the A β peptide.

5. PATHOGENESIS OF APP

Under a regular condition, APP is cleaved inside the A β domain by the action of α -secretase [1]. The peptides produced are non-amyloidogenic and can have an advantageous consequence on

synaptic flexibility as well as neuronal survival at the physiological level. In contrast, mutations in the APP, presenilin-1 and presenilin-2 genes were reported to facilitate the excision of APP by the action of β -secretase (BACE-1) and γ -secretase in place of α -secretase, which resulted in excessive generation and accumulation of A β peptide [47]. The A β peptides exhibit high neurotoxicity by forming insoluble senile plaque and diffusible oligomers. The A β oligomers are also combined to form a fibrillar structure in the intracellular space that accumulates and deposits on the plaques. In addition, A β oligomers enhance phosphorylation and aggregation of tau proteins, although its mechanism is still unknown at the molecular level. Evidence also suggests that the suppression of the tau protein decreases the production of A β and inhibits the toxicity induced by the feedback mechanism [10]. On the other hand, phosphorylated tau causes the destabilization of the microtubules, the degeneration of the cell membrane, and the intracellular aggregation of NFT, which eventually leads to cell death [8]. In addition, it has been also proposed that A β accumulation and aggregation of p-tau cause ER stress and contribute to synaptic dysfunction as well as neurodegeneration in AD [10]. The ER compartment regulates protein folding, modification, and quality control, and mild stress in ER causes the denaturation of misfolded and aggregated proteins in the ER lumen and prompts an unfolded protein response (UPR) to restore the homeostasis of proteins. However, excessive stress promotes UPR reports to proapoptotic programs and causes cell death [48] (Figure 4).

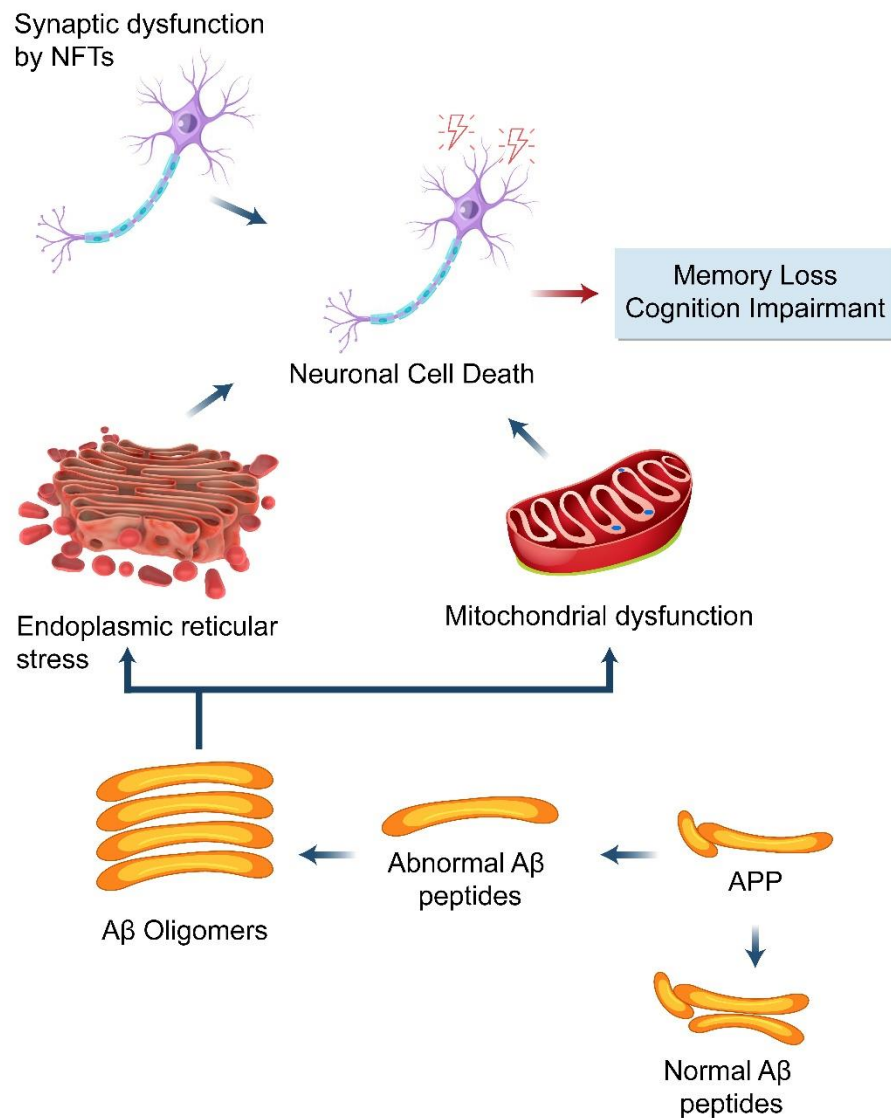


Figure 4: Schematic representing AD pathogenesis modulation by APP. AD pathogenesis initiates from accumulation of abnormal A β peptides derived from APP proteolytic cleavage through γ -secretase and β -secretase. A β oligomers stimulates ER stress and trigger mitochondrial injury which lead to initiate neuronal death in addition to cognition impairment during AD progression. In addition, synaptic dysfunction is also initiated by phosphorylation of tau which lead to form NFTs which cause the loss of neurons in AD.

6. AMYLOID PRECURSOR PROTEIN (APP) PROCESSING IN AUTOPHAGIC PATHWAY

Autophagy is a cellular process that removes the unnecessary substances from the cell by acid hydrolases within the lysosomes [11]. Increasing evidences show that autophagy process is impaired in various neurodegenerative diseases, including AD. Aging process is also involved in the interruption of autophagy process which ultimately leads to AD pathogenesis [49]. The activation of autophagy is associated with the reduction of A β deposition and improves memory deficits in AD mice. Autophagy is a main signaling for altering APP as well as intracellular A β peptides production. Autophagy vacuoles (AVs) contain immunoreactive A β and its precursor proteins in AD models [50]. In addition, the levels of APP in AVs are constant, implying that the cleavage of APP arises in the AVs [51]. This is supported by the data that those AVs contain secretase accountable for producing CTF [16]. In addition, AV fractions encompass notable levels of presenilin-1 in addition to nicastrin, demonstrating that AVs are the slot for abnormal APP cleavage [50] (Figure 5).

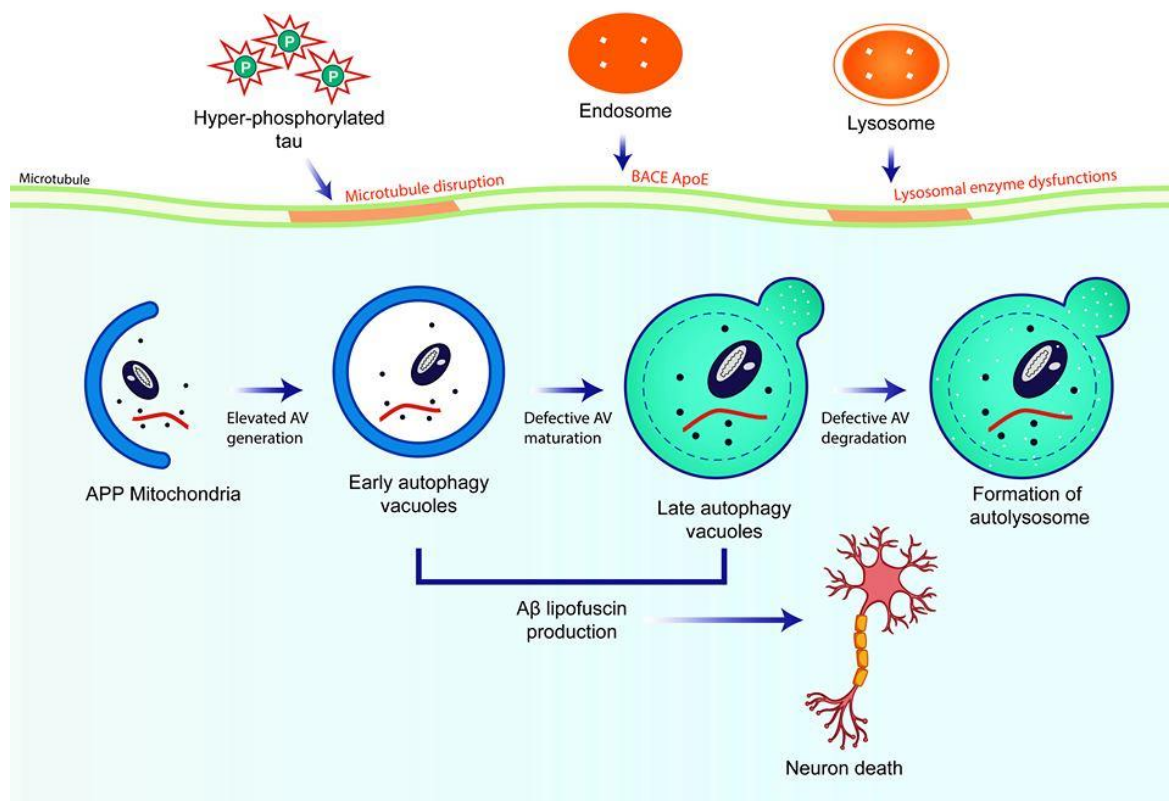


Figure 5: Related molecules such as ApoE, BACE, and APP are dealing with autophagy in initial period of AD, autophagy vacuoles (AVs) are augmented via the stress of mutant APP which ultimately damaged mitochondria. During late stage of AD, maturation as well as degradation of autophagosomes are blocked as a result of disruption of microtubule affected via hyperphosphorylation of tau. Tau hyperphosphorylation may effect on microtubule assembly inhibition and could be disrupted the preassembled microtubules *in vitro* [52]. Eventually, dysfunction of lysosome enzyme interferes autophagosome-lysosome fusion in AD. Entirely these defects of autophagy contribute to AVs accumulation along with AD-related others molecule which increases the intracellular A β deposition as well as lipofuscin causing neuronal cell degeneration and death.

6.1 Autophagy and A β processing

APP is cleaved by β -secretase (BACE1) and γ -secretase to yield A β [40,47]. Acceleration of AD progression was observed when there was an enhanced activities of BACE1 as well as γ -secretase, which increases APP processing and the formation of A β [53]. Autophagy exhibits a critical role in the processing of APP [54]. In animal model of AD, triggering of Atg5-dependent autophagy stimulates early degradation of APP, and thus, inhibits A β accumulation [55]. Sirtuin1 (SIRT1), a positive regulator of autophagy, increases the expressions of Atg5, beclin-1, as well as LC3-II and accelerates clearance of A β [56]. Inhibition of mTOR stimulates autophagy and decreases the levels of BACE1 expression in an APP/PS1 transgenic mouse model of AD [57]. In addition, PPAR α -mediated activation of autophagy facilitated the clearance of APP and decreased A β pathology in APP/PS1 mice [58]. Treatment of PPAR α agonists also decreased A β levels in the hippocampus and cortex, and improved autophagosome biogenesis. These observations together suggest that PPAR α is a critical player for autophagy involved in the A β processing [59]. The mutant APP was reported to impair energy metabolism in mitochondria in AD neurons. In addition, dysfunction of autophagy activates γ -secretase, and stimulates APP cleavage leading to the formation of A β . 3-Methyladenine (3-MA), an autophagy inhibitor, enhances γ -secretase to boost its activity and stimulate A β production [60]. It is also reported that the unfamiliar autophagy activate APP cleavage which leads to the production of A β . All of these evidences indicate that APP is an autophagy substrate in the early stage of A β production [50], and therefore, maintaining a regular function of autophagy is important for the removal and clearance of APP [61]. Still now,

however, the molecular mechanism of how APP serves as a substrate for autophagy remains unclear.

6.2 Dysfunctional autophagy and A β processing

In the initial phase of AD, autophagy can be activated by A β formation, and the A β is likely to be degraded by autophagosome-lysosomal system [61]. Evidences suggest that A β was expressed in the abnormal autophagic vesicles which could be a source of A β extracellular plaque formation in a *Drosophila* model [62]. Autophagy may contribute to A β secretion through a secretory pathway or a secretory lysosomal pathway; likewise, neuronal autophagy absence might reduce A β secretion. For this reason, autophagy is suggested to play a bi-directional role in A β degradation as well as secretion, and therefore, additional study on the dual character of autophagy in the clearance and secretion of A β in pathogenesis of AD is needed [63]. In the later stage of AD, the continuous addition of A β induces abnormal autophagy, which leads to neuronal dysfunction and accelerates AD symptoms. The toxic form of A β , A β -derived diffusible ligands (ADLLs), is involved in AD development and regulates autophagy [64]. The exposure of ADLLs to neuronal cells decreased phosphorylated p70S6K1, indicating that mTOR inhibition causes an intricate outcome in ADLLs-mediated abnormal autophagy [64]. A β increases ROS generation and the hyperactivation of autophagy via NOX4 upregulation, leading to neuronal cell death [28]. Interestingly, reduction of NOX4 as well as ROS levels can prevent autophagy from over-activation as well as neuronal cell death. RAGE, receptor of advanced glycation end-products, is a main receptor in facilitating the toxicity of A β [65], and A β 1-42 mediates abnormal autophagy through the RAGE-associated pathway [65]. The treatment with A β peptide induces autophagy dysfunction in astrocytes where p62 was aggregated and LC3-I/LC3-II transformation was decreased [66]. The mitochondrial abnormalities caused by A β -mediated dysfunction of the voltage-dependent anion channel 1 protein (VDAC1) as well as dynamin-related protein 1 (Drp1) [67]. Mitophagy promotes the removal of injured mitochondria, where PTEN-induced putative kinase 1 (PINK1) plays a vital role in regulating mitochondrial function [68]. The lower levels of PINK1 were linked to the pathology of A β . In AD, PINK1-mediated pathology of A β with mitophagy promoting to the cognitive and synaptic dysfunction [69]. Interestingly, overexpression of PINK1 enhanced the removal of injured mitochondria through upholding mitophagy in AD. In

an AD mouse model, the hippocampal A β decreases PINK1 expression, which reduces mitophagy and causes cognitive decay [5].

7. THERAPEUTIC ACTION OF APP TRIGGERING BY AUTOPHAGY

AD incidence has posed a global health burden on elderly people, and is predicted to increase significantly worldwide. A considerable effort to develop drugs for the treatment of AD has been devoted, focusing on drug structures, and potential molecular mechanisms of AD. An example of generally accepted hypotheses is that the reduced levels of acetylcholine cause AD in neurons. However, drugs targeting acetylcholine so called “cholinesterase inhibitors” could poorly improve AD [70,71]. Therefore, targeting other drugs which comprise potential autophagy regulators that have a greater possibility for the treatment of AD.

7.1 Use of small molecules to modulate autophagy in AD

Another hallmark regarding the pathogenesis of AD is the accumulation of amyloid beta proteins and hyperphosphorylated tau which are considered toxic to neurons [72]. Dysregulated or insufficient autophagy might be causative factors behind the development and progression of AD [14], and therefore, the discovery of drugs targeting autophagy-related signaling pathways might be an attractive approach for the treatment and management of AD [11]. The potential candidates of small molecules which is likely to be involved in the regulation of autophagy pathways and their implication on AD therapy is summarized in Figure 6.

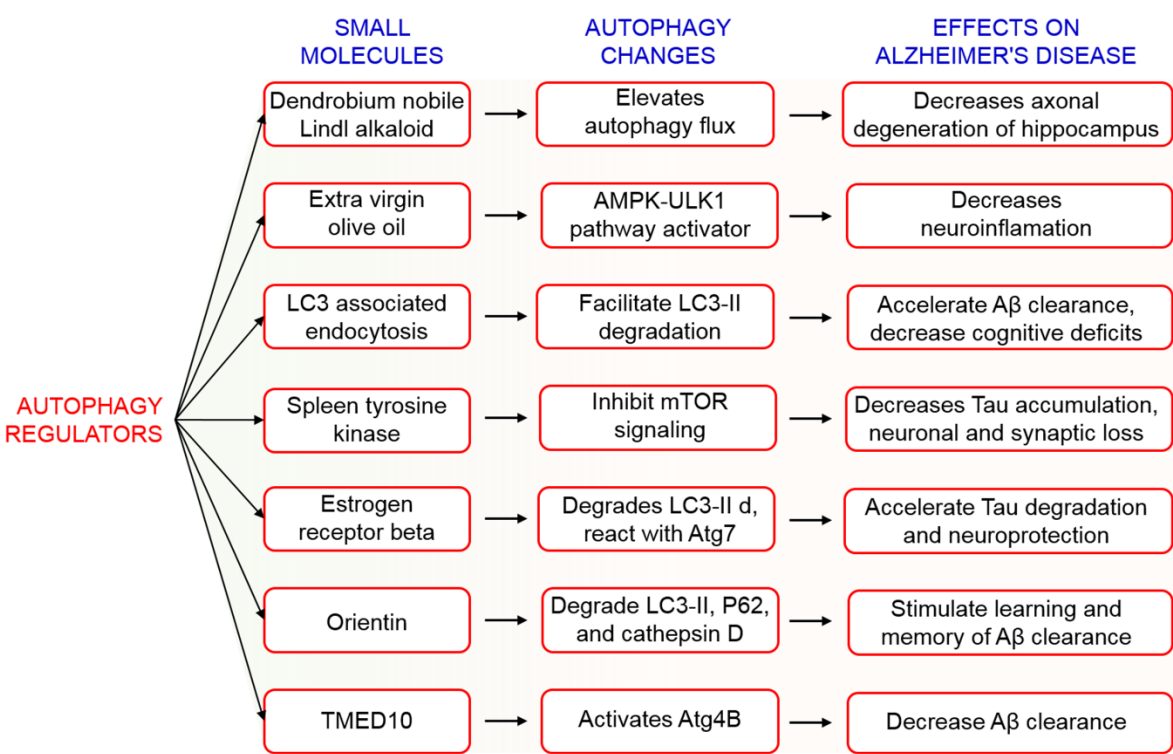


Figure 6: Implication of several small molecules to modulate autophagy and their action in AD treatments.

7.2 Use of natural compound to modulate autophagy in AD

Natural products and herbal medicine may be used for the management of neurodegeneration, cancer, and apoptosis [73-80] as well as autophagy inducer [81]. Recent studies revealed that active compounds in natural products exhibit curative effects against AD via a variety of mechanisms, including anti-cholinesterase activity, anti-apoptosis, and neuroprotective effects via anti-oxidation through targeting autophagy [82,83]. Emerging evidence suggests that the natural compounds are attractive sources of autophagy regulators [82,84]. Integrating reports demonstrate that the active compounds regulating autophagy process pave a new therapeutic way for neurodegenerative diseases [85,86]. Examples of plant-derived active components ameliorating the symptoms of AD via targeting autophagy are summarized in Table 1.

Alkaloids are important examples of active compounds isolated from plants and show anti-cholinesterase and modulatory effects on autophagy implicated in the treatment of neurodegenerative diseases. For instance, alkaloids can modulate autophagy in AD [87], and

Dendrobium nobile Lindl extracts possess alkaloids components that are capable of hindering axonal degeneration [88]. Plant alkaloid berberine ameliorated learning and memory functions, and accelerated A β clearance in an AD mouse model [89]. Berberine can also promote autophagy processes in the brain [90], and has a neuroprotective activity [91]. An oxindole alkaloid called Corynoxine obtained from *Uncaria rhynchophylla* (Miq.) is another example of autophagy enhancers [92]. Moreover, an isomer of Corynoxine, corynoxine B, was shown to promote autophagy and reduced the accumulation of A β levels by facilitating the degradation of APP [93].

Table 1: Modulation of autophagy by natural products, and their therapeutic implication in Alzheimer's disease

Natural products	AD Model	Activities/ Effects	Molecular mechanism	References
Ginsenoside Rg2	5 \times FAD transgenic mice	Removal of A β aggregation	AMPK/ULK1-mediated autophagy induction	[94]
Protopanaxadiol derivative DDPU	APP/PS1 mice model	Stimulate the clearance of A β	Inhibition of PI3K/mTOR-mediated autophagy induction	[95]
Berberine	3 \times Tg-AD mice	Promote the clearance of A β	Activate Bcl2/Beclin1-mediated autophagy induction	[96]
Flavonoids Silibinin	A β 1–42-induced rat model	Attenuate neuronal damage	Inhibit autophagy	[97]
Corynoxine B	Tg2567 mice, N2a-SwedAPP cell model	Augment APP and A β degradation	Unclear pathway to induce autophagy	[93]
Gypenoside XVII	APP/PS1 transgenic mice	Prevent A β accumulation	Promote TFEB to induce autophagy	[98]
<i>Ginkgo biloba</i> extract	TgCRND8 mice	Improve cognitive function	Induce autophagy	[99]
<i>Radix polygalae</i> extract	Cell model of CHO-APP/BACE1	A β 1–40 decrease	Activate AMPK/mTOR and promote autophagy	[100]
Madecassoside	D-galactose-induced	Autophagy inhibition	Rise Bcl-2 and decrease Beclin-1	[101]

	mouse model			
Hesperetin	N2a cell model	Increase A β -damaged	Autophagy inhibition	[102]
<i>Morus alba</i> extract	SH-SY5Y cell	Autophagy induction	mTOR dependent autophagy pathway	[74,82]
Wogonin	SH-SY5Y-APP primary cortical astrocytes	Enhance A β removal	Activate ULK1/mTOR and induce autophagy	[103]
Curcumin	APP/PS1 transgenic mice	Prevent A β deposition	Inhibit PI3K/mTOR and induce autophagy	[104]
Resveratrol	N2a-APP cell, HEK293-APP cell	Decrease A β production and aggregation	Induce autophagy by activating AMPK/mTOR signaling	[105,106]
Sulforaphane	AD model	Nrf2 signaling	Induce autophagy	[107]
Carnosic acid	A β 25–35-induced SHSY5Y cell	Inhibition of A β 1–42 aggregation	Activate AMPK/mTOR and induce autophagy	[108]
Tripchlorolide	5 \times FAD transgenic mice	Reduce cerebral A β deposits	Activate PI3K/mTOR pathway	[109]
β -asarone	APP/PS1 transgenic mice	Decrease A β level	Activate PI3K/mTOR and inhibit autophagy	[110]
Oxyresveratrol	SH-SY5Y cell model	Stimulate autophagy	Atg5/7, Beclin-1, and LC-3 induction	[24]
18 α -Glycyrrhetic acid	SH-SY5Y cell model	Induction of autophagy flux	mTOR dependent autophagy induction	[23]
Gintonin	Mouse cortical Astrocytes	Autophagic flux induction	Beclin-1, Atg5/7, LAMP-1 induction	[22]
Emodin	APP/PS1 mice	Autophagy inhibition	Activate Bcl-2/Beclin-1/PIK3C3 pathway	[93]

Many studies demonstrated that active components of flavonoids can affect autophagy in various diseases. *Silybum marianum* possessed plant flavonoid Silibinin ameliorated A β 1–42-induced depression in rats, and it alleviated damage of neurons in the hippocampus via inhibiting autophagy [97]. Another flavonoid component wogonin isolated from *Scutellaria baicalensis* enhances A β clearance in cortical astrocytes and reduces A β deposition via modulating autophagy signaling

pathway [103]. Moreover, hesperetin and its glycoside hesperidin is implicated in the protection of neuron cells via decreasing A β -mediated autophagy [102].

A variety of products isolated from *Panax Ginseng* have also been shown to provide neuroprotection and to ameliorate memory function in dementia [111]. For example, Rg2 ginseng triggers autophagy [94], accelerates the clearance of aggregated proteins, increases the accumulation of cerebral A β , and ameliorates cognitive functions via autophagy in a mouse model of AD [93]. Protopanaxadiol is associated with axonal outgrowth in neuronal degeneration, and it can ameliorate memory disorders of AD mice [95]. DDPU was implicated in the development of AD behavior in associated with autophagy [95]. Another alkaloid gypenoside XVII found in ginseng *Panax notoginseng* enhanced the removal of amyloid deposition in the hippocampus and cortex of mice, and Gypenoside XVII also exert a neuroprotective effect on AD via triggering autophagy [98]. Madecassoside, a triterpenoid saponin compound, inhibits autophagy through increasing the levels of Bcl-2 and decreasing Beclin-1 in neuronal cells [101]. It has also been observed that madecassoside improves cognitive function and synaptic plasticity in the AD mice model [112]. However, O-GlcNAcylation modulation has been regulated autophagy in astrocytes and control antidepressant-like phenotype in neurons [113,114]. Gintonin has been used for the treatment or prevention of AD through elevation of hippocampal neurogenesis in APP^{swe}/PSEN-1 double Tg mouse model of AD [115], and it is demonstrated that gintonin-mediated treatment is nontoxic and possibly beneficial in cognitively impaired elderly in AD [116].

Curcumin relieves cognitive impairment and inhibits A β formation by blocking autophagy through PI3K/Akt/mTOR downregulation pathway [104]. A polyphenol resveratrol is being considered widely because of its use in AD model [117]. Recently, it has been found that decreasing the production of A β hinders the development of AD. The synthesis of A β was declined in the cells via influencing the signaling pathways such as triggering AMPK as well as preventing mTOR to activate autophagy. It was also reported that oral administration of resveratrol suppressed A β accumulation in the cortex [118]. One of the primal bioactive components, tetrahydroxystilbene-2-O-glycoside of *Radix Polygoni multiflori*, decreases APP expression and enhances the cognitive activity in transgenic AD mice via reducing Beclin-1 as well as LC3-II expression through autophagy [93]. Emodin, obtained from *Rheum palmatum* L., has been involved to treat in AD by reducing LC3-II expression; however, it increases Bcl-2 expression [93]. The polyphenolic

Carnosic acid of *Rosemarinus officinalis* is involved in the reduction of neurotoxicity induced by amyloid deposition, and decreases the accumulation of amyloid aggregates and hyperphosphorylation of tau [108]. The consumption of Ginkgo biloba extract enhanced the cognitive and synaptic function AD mice model through partially activating the autophagy [99]. Besides, some compounds having special structural features, such as arctigenin, triphenylolide and β -asarone were shown to improve memory by modulating autophagy-related signaling pathways. The significant levels of arctigenin were observed in the brain, indicating that it might not cross the blood-brain barrier [119]. Therefore, natural products might be considered as the therapeutic target for the management of AD.

7.3 Use of FDA-approved drugs to modulate autophagy in AD

Clomipramine, an FDA-approved drug used for the treatment of psychiatric disorders, was shown to block the fusion of autophagosome and lysosome, thus interfering with autophagic flux [120]. Benzoporphyrin derivative, another FDA-approved drug known as verteporfin, is likely to inhibit formation of autophagosome in presence of chloroquine (CQ), a lysosomal inhibitor [121]. APP 5' UTR-directed drugs decreased APP in SH-SY5Y neuroblastoma cells [122]. In figure 7, we represented that lower levels of A β peptide was achieved by FDA-preapproved drugs that lowered intracellular APP holoprotein levels in the SH-SY5Y cell model [123]. The pharmacological action of DMP, DFO, paroxetine, phenserine, and tetrathiomobdylate to decrease the levels of APP and A β peptide is described in Figure 7. Azithromycin dramatically changed the processing of APP [124]. Thus, it has been described that a subsection of drugs that have been selected to stimulate APP 5' UTR-mediated translation are furthermore as a coactivators of nonamyloidogenic pathway of APP processing.

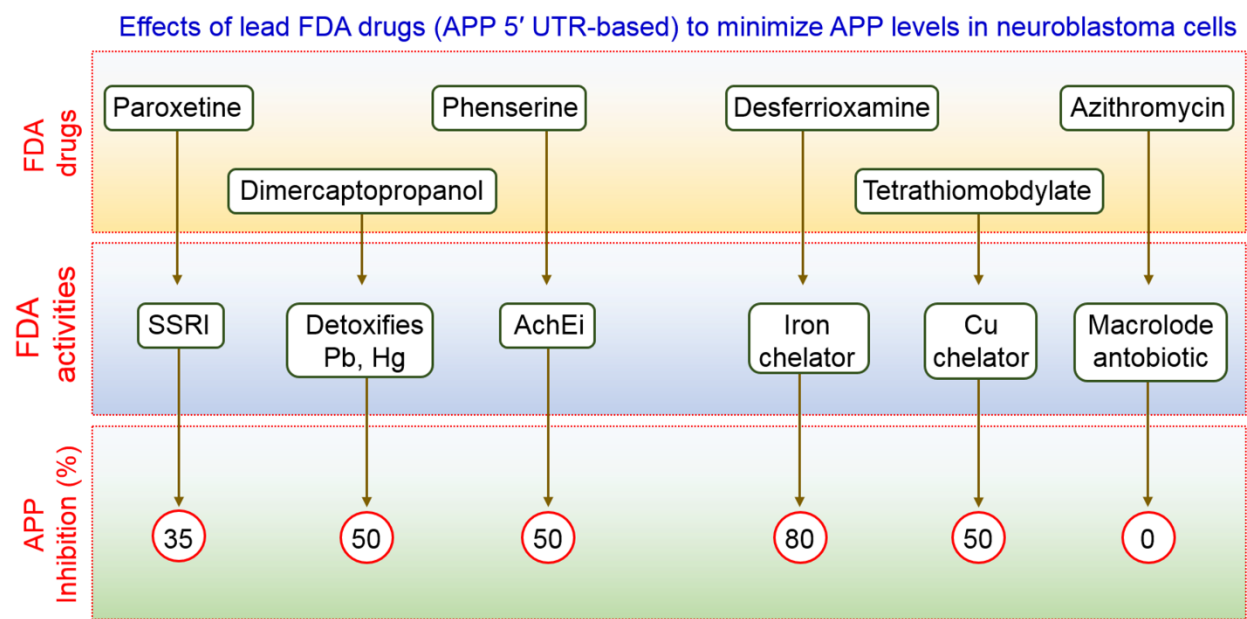


Figure 7: Effects on FDA-approved drug used for the treatment of AD-associated disorders.

8. Conclusion

From the above discussion, it has been implicated that autophagy is an important cellular process in AD pathogenesis, which regulates the production and degradation of primary pathological proteins, such as A β and p-tau. While autophagy shows a dual role in the case of AD, systematic research with new evidence will provide information on the modulation of autophagy process in AD treatment. Taken together, recent studies demonstrate that a variety of bioactive components from medicinal herbs, small molecules, and FDA drugs are likely to improve AD via the modulation of autophagy pathway.

Authors' Contributions

This collaboration work was carried out among all authors. MAR designed the outline and wrote the draft. MSR prepared the figures. MR, MRR, MJU and ANMMR wrote some part of the manuscript. MGP reviewed the manuscript. HR proposed the original idea of this manuscript. HH reviewed the scientific contents of the manuscript. All authors read and approved the final version of this manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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