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Article *in* Pharmacological Research · July 2018

DOI: 10.1016/j.phrs.2018.07.004

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PII: S1043-6618(18)30531-0
DOI: https://doi.org/10.1016/j.phrs.2018.07.004
Reference: YPHRS 3941

To appear in: *Pharmacological Research*

Received date: 15-4-2018
Revised date: 3-7-2018
Accepted date: 5-7-2018

Please cite this article as: Shirooie S, Nabavi SF, Dehpour AR, Belwal T, Habtemariam S, Argüelles S, Sureda A, Daglia M, Tomczyk M, Sobarzo-Sanchez E, Xu S, Nabavi SM, Targeting mTORs by omega-3 fatty acids: a possible novel therapeutic strategy for neurodegeneration?, *Pharmacological Research* (2018), https://doi.org/10.1016/j.phrs.2018.07.004

Targeting mTORs by omega-3 fatty acids: a possible novel therapeutic strategy for neurodegeneration?

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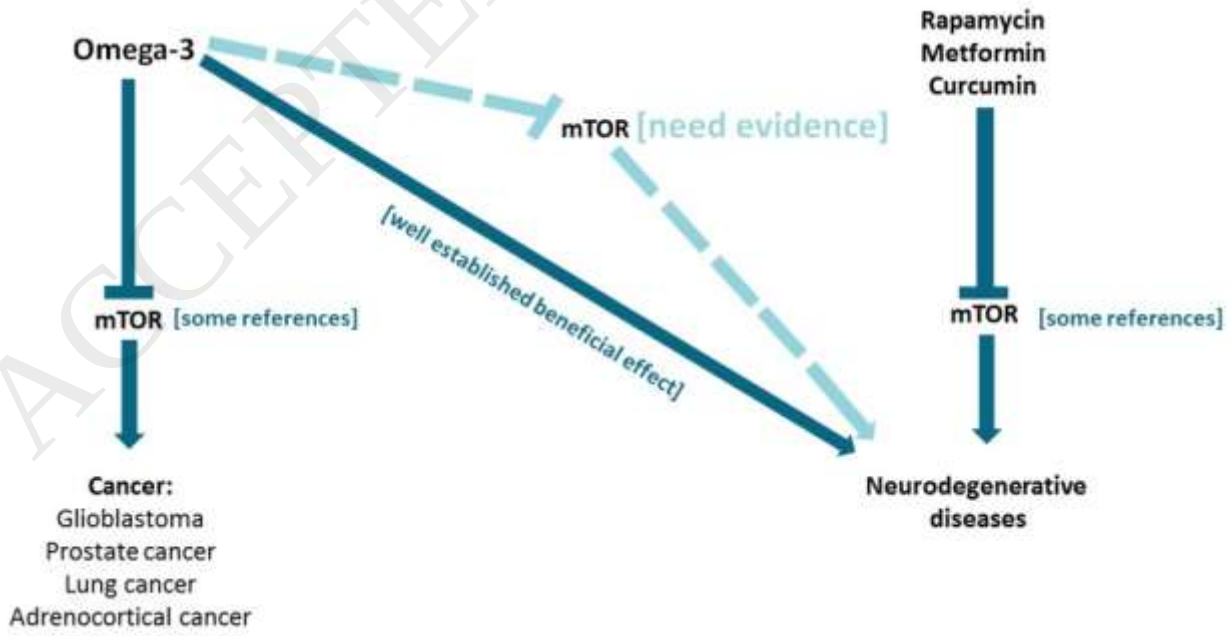
Graphical abstract



Abstract

Neurodegenerative diseases (NDs) such as Parkinson's (PD), Alzheimer's (AD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) cause significant world-wide morbidity and mortality. To date, there is no drug of cure for these, mostly age-related diseases, although approaches in delaying the pathology and/or giving patients some symptomatic relief have been adopted for the last few decades. Various studies in recent years have shown the beneficial effects of omega-3 poly unsaturated fatty acids (PUFAs) through diverse mechanisms including anti-inflammatory effects. This review now assesses the potential of this class of compounds in NDs therapy through specific action against the mammalian target of rapamycin (mTOR) signaling pathway. The role of mTOR in neurodegenerative diseases and targeted therapies by PUFAs are discussed.

Keywords: Neurodegenerative diseases, mTOR, omega-3, docosahexaenoic acid, eicosapentaenoic acid.

1. Introduction

The progressive neuronal cell functional losses that arise from some kind of abnormal biochemical and structural changes or cell death is called neurodegeneration; while the disease associated with the processes are known as neurodegenerative diseases (NDs). The classical examples of the NDs are Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) and that occur through the progressive neuronal degeneration accumulated over a period of time. Extensive researches in recent decades have been devoted to understanding the pathophysiological changes and risk factors of these chronic NDs [1]. One of the common risk factors is age and, in fact, these group of diseases are called age-relate neurodegenerative pathologies. Taking into account recent reports suggesting a significant increase in life expectancy in the very near future [2], a higher incidence of chronic NDs together with a lack of effective therapy would be a real concern.

Even though the molecular mechanisms responsible for NDs are not fully elucidated, dysregulation of several signal transduction pathways such as autophagy and endosomal-lysosomal [3], AMPK [4], p53 [5], P38 MAPK [6], JAK/STAT [7], PI3K/AKT [8], mTOR [9] etc., have been shown to be associated with these disorders. Within these pathways, mammalian target of rapamycin (mTOR), has been extensively studied in the context of aging and age-related NDs. The mTOR has a key role in important cellular processes including cell survival, protein synthesis, mitochondrial biogenesis, proliferation, apoptosis, autophagy, etc. [10,11], and whose dysregulation can promote the initiation and progression of NDs. Since classical NDs has special features of accumulating abnormal misfolded or toxic proteins which regulates autophagy and cell fate, targeting mTOR may have important consequences on therapy against NDs. mTOR pathway in normal conditions inhibits autophagic mechanisms, which are necessary to degrade

and eliminate abnormal or aggregated proteins [71]. Therefore, mTOR inhibitors may represent an interesting therapy for this kind of diseases by inducing autophagy or regulating apoptotic processes (Bove et al., 2011). In fact, classic mTOR inhibitors such as rapamycin or metformin have been reported to improve the neuronal damage in human and animal models of NDs [12]. Another important approach to fight against NDs are the use of natural products/compound including antioxidants [13], flavonoids [14], polyphenols [15], and polyunsaturated fatty acids (PUFAs) [16]. The omega-3 PUFAs represent a wide-range of unsaturated fatty acids which are often claimed to have numerous health benefits [17]. The best studied omega-3 FAs are docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and α-Linolenic acid (ALA). Structurally, the omega-3 group of FAs (Fig 1, drawn following the gguidelines for preparing color figures [18] is characterized by having the first double bond at position 3 of the terminal carbon or methyl group which is designated as omega (ω or n). However, the most common nomenclature of these compounds is the numbering starting from the carbonyl acid carbon assigned as carbon-1 and as shown in Fig. 1. Omega-3 FAs differ from each other by the total number of carbon groups in the molecule and amount and position where double bonds are formed. The essential oils of the higher plants are the main source of ALA while fish oils and other marine animal fats are the main sources of DHA and EPA. Hence, the Mediterranean dietary pattern, rich in vegetables and fish oils/products along with algae as the primary producers of EPA and DHA, have been advocated as a healthy diet option in recent years [19,20].

Omega-3 PUFAs have a central role in the maintenance of cerebral functions and brain development contributing to neurogenesis and neuroplasticity. Moreover, these PUFAs also exert significant protective effects against inflammatory damage to the neurons and glial cells. Among

the omega-3 fatty acids, the EPA has been reported to show the best promising effects as antidepressant agent [21,22]. Omega-3 PUFAs also have beneficial effects on cardiovascular diseases, as lipid lowering [23], antihypertensive [24] and antiinflammatory effect *via* modulation of cytokines and adhesion molecules expression [25]. These antiinflammatory properties have been well demonstrated in various animal models [26-29]. Moreover, omega-3 PUFAs reduce the risk or incidence of autoimmune diseases such as type 1 diabetes [30], multiple sclerosis [31], lupus erythematosus [32], psoriasis [33] and rheumatoid arthritis [34,35]. Mounting evidence has shown that omega-3 PUFAs can improve mental disorders such as schizophrenia and bipolar disorder [36]. The negative correlation between omega-3 PUFAs consumption and risk for cancer including pancreatic [37], colon [38], breast cancer [39] have been documented. Previous review articles also showed the potential of omega-3 PUFAs in diabetes retinopathy and other pathologies [40,41]. Omega-3 PUFAs, particularly DHA, have protective role in retina [42]. In addition, to the modulation of cytokine and adhesion molecules, the antiiflamatory effects of omega-3 PUFAs are associated to their incorporation in cell membrane phospholipids, contributing to the decrease in the production of proinflammatory omega-6 mediators [43]. Omega-3 PUFA are also important for the generation of anti-inflammatory factors, such as neuroprotection D1 (NPD1) [44]. Recent evidences reported that omega-3 PUFAs can act as negative regulators of PI3K/Akt pathway which, in turn, results in mTORC1 inhibition [45]. In this sense omega-3 PUFAs could be interesting agents to prevent the initiation and progression of NDs.

The aim of this review is to overview the potential of omega-3 PUFAs as therapy for NDs through a possible specific action against the mTOR signaling pathway. Here, we summarize the

main concepts of neurodegeneration, the role of mTOR in ND, and therapeutic implications of targeting mTOR pathway with omega-3 PUFAs.

2. Hallmark of Neurodegeneration: Protein misfolding and precipitation.

Neurodegenerative diseases (NDs) such as PD, AD, HD, and ALS cause significant world-wide morbidity and mortality. Hence, accumulation of deleterious changes through aging process is the main factor associated with many NDs [46]. The most common form of NDs is AD, which is characterized by a loss of memory in the older age group and account to over 60% of all forms of dementia cases [47]. As with many other NDs, protein misfolding and precipitation are the hallmark of AD, the key player being the amyloid β (Aβ) peptides [48]. In addition to the presence of extracellular amyloid plaques composed of aggregated peptides, AD is characterized by intracellular neurofibrillary tangles comprising the microtubule-associated protein tau [49]. Aβ peptides derive from the proteolytic cleavage of the amyloid precursor protein (APP) by aspartyl-proteases and secretases [50]. The link between Aβ peptides aggregation and inflammation and oxidative stress in the Alzheimer's brain has been established [51-54]. The main group affected in AD appear to be those of the cholinergic type that are closely linked to memory storage and retrieval [55,56]. PD is a cognitive and motor dysfunction characterized by the degeneration or loss of dopaminergic neurons [57,58]. The key pathological hallmark of PD is the appearance of Lewy bodies which derive from the progressive deposition of protein inclusions of α-synuclein and ubiquitin leading to cell death (apoptosis or necrosis). ALS is a complex disorder which has the special feature of degenerated motor neurons, followed by muscle weakness, paralysis, and finally, death [59]. The basis of ALS is multifactorial and comprises genetic mutations with more than 20 genes involved, and epigenetic and

environmental risk factors. The misfolding of the antioxidant enzyme, superoxide dismutase (SOD), has also been linked to ALS [60,61] while prion proteins are known to be involved in a range of spongiform encephalopathy diseases [62,63]. HD is a progressive neurodegenerative disease which has a wide variety of symptoms including movement, cognition and behavior [64]. The disorder is an autosomal-dominant neurodegenerative consequence of a genetic mutation in the *HTT* gene leading to ubiquitous expression of mutant huntingtin protein [65]. The NDs could also arise from a range of other acute (e.g., accident or direct form of physical injury to the CNS) or chronic diseases. A number of cardiovascular disease such as hypertension could also lead to stroke and results in significant neuronal changes and/or death [66]. The common pathology of NDs involve oxidative stress and inflammatory cascades through orchestrated cell-cell interaction including the immune cells in the central nervous system, such as the microglia [67].

3. The mTOR signaling pathway

Mammalian target of rapamycin (mTOR) has been shown to be a master regulator of cell proliferation as well as cellular metabolism. mTOR can be found in two multi-protein complexes: mTORC1 and mTORC2 [10]. The mTORC1 core complex contains mTOR, regulatory associated protein of TOR (raptor), DEP-domain containing mTOR interacting protein (DEPTOR), proline–rich Akt substrate 40kDa (PRAS40), and mammalian lethal with sec-13 protein 8 (mLST8). On the other hand, mTORC2 contains mTOR, mLST8, DEPTOR, rapamycin insensitive companion of mTOR (rictor), protein observed with rictor (Protor), and stress-activated protein kinase-interacting protein 1 (mSin1) [68]. Rapamycin, which was found to exert immunosuppressive and anti-proliferative activities can inhibit the activation of mTORC1 by binding to FK506-binding protein 1A, 12 kDa (FKBP12), and prevent mTORC1

formation [69,10]. The important upstream molecules of mTORC1 are PI3K/AKT and Ras/Erk, which are activated by growth factors like insulin. These pathways can activate mTORC1 by phosphorylation-dependent inhibition of TSC1/TSC2 complex. The TSC1/TSC2 complex has inhibitory effect on GTPase Rheb, which activates mTORC1. The AKT also inhibits the PRAS40 by phosphorylation, which negatively regulates mTORC1 [70]. The IκB kinase β (IKKβ) in response to pro-inflammatory cytokines like tumor necrosis factor-α (TNFα), can phosphorylate TSC1 at Ser487 and Ser511, thus attenuates its inhibitory effect on mTORC1 [68]. Other signals that affect mTORC1 activity are hypoxia and low energy stress. AMP-activated protein kinase (AMPK) which is activated in low energy stress, phosphorylates TSC1 and promotes its inhibitory effect on Rheb, thus inhibiting mTORC1 activity. Also, AMPK can phosphorylate raptor, and inhibit the pathway [71].

The most important downstream effectors of mTORC1 are S6 kinase 1 (S6K1) and eukaryotic inhibition factor eIF4E binding protein 1 (4E-BP1). The mTORC1 phosphorylates S6K1 at mRNAs translation with a 5'-terminal oligopolypyrimidine (5'-TOP). Phosphorylation of S6K1 by mTORC1 promotes the phosphorylation of eIF4B and S6, which are components of the translation initiation complex [69,70], as well as phosphorylation of EF2K, which through phosphorylating elongation factor-2 (eEF2) can regulate the translation of elongation step [72]. Another important effect of mTORC1 is the capability to inhibit mTORC2 and insulin receptor substrate (IRS). Recently, Cano and colleagues summarized other important downstream targets of S6K1 such as eIF4B, EF2K, BAD1, RafB/PKCe, MDM2, hnRNPs, Rictor or SKAR, as well as molecular mechanisms associated with S6K1 dysregulation have notable implication in aging and age-related diseases [73]. In addition to the mTORC1, the serine/threonine kinase p70S6K1 can also be activated by PDK1, MAPK and SAPK. The second main target of mTORC1 target is

4EBP1 which binds to eukaryotic translation initiation factor 4E (eIF4E) and inhibits its activity. mTORC1-mediated phosphorylation of 4EBP1 increases the dissociation of 4EBP1/ eIF4E complex and leads to the initiation of translation.

As concern mTORC2, growth factors can activate it via the PI3K signaling pathway, increasing the association between mTORC2 and ribosomes. Some of the mTORC2 targets are PKC-α, AKT and the GTPases Rac and Rho. The mTORC2 is involved in cellular metabolism and cell shape such as actin by PKC-α and Rho GTPase and in cellular proliferation by regulation of AKT. mTORC2 phosphorylates AKT at position Ser473, which promotes PDK1-mediated phosphorylation of AKT at The308, thus leading to full activation of AKT. Phosphorylation of AKT by mTORC2 is necessary to act on some of its targets such as forkhead box O1/3a (FoxO1/3a), while for others like TSC2 and GSK3-β, phosphorylation is not needed. The FoxO1/3a is also phosphorylated by SGK1, which is activated by mTORC2 [74]. The mTORC2 pathway is generally less clear than the mTORC1 [10,70].

3.1. mTOR and autophagy process

Another important function of mTOR is its ability to modulate autophagy via different signaling pathways (Fig 2). Autophagy is a cellular digestion mechanism that recycles components in the cytoplasm to eliminate damaged molecules and non-functional organelles [75]. In this process proteins and organelles are delivered to autophagosomes that fuse with lysosomes for degradation [70]. It has been evidenced that inhibition of mTORC1 increases autophagy, while stimulation of mTORC1 decreases the process [76]. On the contrary, mTORC2 seems to indirectly suppress autophagy via phosphorylation of Akt resulting in Akt/mTORC1 signaling activation [77]. Diverse investigations reported that mTORC1 inhibits the autophagy-initiating

UNC-5 like autophagy activating kinase (ULK) complex formation by promoting the phosphorylation of complex component ULK1/2. Activated ULK1/2, then, phosphorylates ATG13 (autophagy-related gene 13) and FIP200 (focal adhesion kinase family-interacting protein of 200 kDa) leading to the suppression this kinase complex essential to initiate autophagic process [78-80]. In addition, it was also reported that mTORC1 indirectly inhibits autophagy by preventing the ubiquitination of ULK1 through phosphorylating autophagy / Beclin-1 regulator 1 (AMBRA1) [81]. mTORC1 also inhibits autophagosome formation through phosphorylation of ATG14L in the VPS34 complex, a class III PI3K, which reduces the kinase activity of VPS34 [82]. Another mechanism responsible for mTORC1 mediated autophagy regulation is at transcriptional level through phosphorylating and inhibiting the activity of the transcription factor EB (TFEB), which is a principal regulator of lysosomal biogenesis and autophagic processes [83].

3.2. mTOR and chronic diseases

Several studies have been evidenced a relation between mTOR and diverse diseases. In this sense, a role of mTOR and their downstream targets has been found in cancers [84,85]. Over activity in PI3K and mutation in TSC1/2, LKB1 and PTEN genes, which are tumor suppressor genes, affect mTOR signaling pathway in cancers [68]. Obesity, an important risk factor for diabetes and many cancers like endometrial, has been shown to be linked to excessive activity of AKT/mTOR signaling pathway. Metformin, a common anti-diabetic therapeutic agent, has inhibitory effect on cancer cells by activation of AMPK through LKB1 signaling pathway leading to mTOR suppression [86]. In addition, metformin was also capable to inhibit mTOR and cell-cycle arrest via REDD1, independent of AMPK [87]. Chronic activation of mTOR due

to high level of nutrients, results in non-alcoholic fatty liver disease [88]. The mTORC1 has also positive role on the size and function of pancreatic β-cell, but chronic activity of mTORC1 has negative effect on insulin receptor substrate 1& 2 and leads to apoptosis in pancreatic β-cell [86,10]. Moreover, since mTORC1 is negative regulator of autophagy, which is one of the pathways to degrade misfolded proteins and defective autophagy is associated with multiple neurodegenerative diseases [89,90], studies have shown that mTORC1 inhibitors such as rapamycin increase autophagy and clearance of toxic proteins involved in NDs [10,91].

4. Role of mTOR in neurodegenerative diseases

The common feature of neurodegenerative disorders, such as PD, AD and HD, is the accumulation of toxic proteins in neurons which causes neural damage and cell death. Autophagy is necessary for clearance of misfolded proteins to decrease their aggregated load and, consequently, can reduce the neurodegeneration associated consequences. Taking into account that mTORC1 negatively regulates autophagy that inhibits the degradation of misfolded proteins accumulating in neuronal cells, over activity of mTORC1 can lead to neural damage. Hence, mTOR inhibitors may have a protective role against NDs [10,91]. Upregulation of autophagy is a potential therapeutic strategy against several neurodegenerative diseases [92-95]. However, hyperactivation results in complete stoppage of autophagy and leads to accumulation of toxic proteins such as tau and Aβ, which is the major cause of NDs, as seen in the development of epilepsy or epileptogenesis [96]. The mTOR signaling is important for memory reconsolidation [97] as it regulate protein synthesis in neurons and also played critical role in maintaining synaptic plasticity underlying memory formation. The mTOR inhibition for long time may however cause complications, as mTOR control several cellular processes [98,99].

Thus, the regulatory role of mTOR signaling pathway is important for preventing major NDs as is shown in Table 1. Furthermore, the inhibition of mTOR could exert a protective effect on brain against inflammation. A study performed by Dasuri et al. indicated that Donepezil, an acetylcholinesterase inhibitor, decreases mTOR phosphorylation as well as the phosphorylation of its downstream targets, such as p-p70S6K, in the brain tissues of mice administrated high fat diet and has a protective effect against neuroinflammation [184].

4.1. Alzheimer's diseases

AD is a progressive cognitive neurodegenerative disease linked to accumulation of extracellular Aβ plaques and hyperphophorylated tau protein leading to the formation of intracellular neurofibrillary tangles [100,101]. Excessive activity of mTOR increases the activity of β- and γ-secretase, which leads to the generation of Aβ plaques from APP (amyloid precursor protein). Diverse studies using humans and animal models evidenced that mTOR activation is related to the malfunction of Aβ elimination from the brain since mTOR-mediated inhibition of autophagy favors the accumulation of Aβ [102-104]. In addition, a relationship has been observed between the immaturity of the autofagolysosomes and the accumulation of autophagic vacuoles (AV) that can contribute to the generation of Aβ. In this sense, activation of mTOR alters the autophagic process leading to the accumulation of immature forms of AVs [105]. mTOR also regulates tau phosphorylation, which leads to the development of intracellular filaments. In accordance with this effects, inhibition of mTOR by rapamycin could in a transgenic mouse model alleviate cognitive impairments as well as reducing the alterations associated with amyloid plaques accumulation and neurofibrillary tangles via autophagy activation [106,107].

Extensive studies have shown that in AD, functional impairments of synaptic plasticity normally develops before neurodegeneration resulting in neuronal damage and/or lost [108,109]. mTOR integrates multiple inputs associated with nutrients, growth factors and the cellular energy status that result in its activation or inhibition being a crucial regulator between anabolic and catabolic processes [110,111]. Diverse investigations have evidenced that soluble oligomers of Aβ, derived from APP, are able to inhibit long-term potentiation (LTP) and cause deficits in learning and memory [112-114]. Ma and colleagues studied the association of mTOR signaling pathway with Aβ-induced synaptic dysfunction. The authors reported that in the hippocampus of animal models of AD, the activity of mTOR was decreased, and when mTOR signaling was activated, the inhibition of LTP associated with Aβ was recovered. In 3xTg mice model of AD without evidence of amyloid plaques and tangles, the mTOR-induction of autophagy with rapamycin have been reported to ameliorate cognitive deficits [115]. The chronic treatment with rapamycin reduced the progression of AD and increased autophagy which, in turn, reduced Aβ levels in the mouse model of the human amyloid precursor protein (PDAPP) [116]. Thus, mTOR pathway regulates Aβ-related synaptic dysfunction in AD [113]. Other studies also reported that mTOR activation induces tau hyperphosphorylation contributing to the progress of AD [117,118]. Rapamycin treatment reduces the phosphorylation of tau (at Ser214) via regulating cAMP-dependent kinase. Also, autophagy induction could improve the clearance of the hyperphosphorylated tau [119,120].

4.2. Down syndrome (DS)

DS is regarded as a frequently-occurring chromosomal abnormality which leads to intellectual disorder or disability [121,122]. The neurophysiology of AD with respect to DS is multifaceted

and includes impaired functions of mitochondria [123], defects in neurogenesis [124], high generation of oxidative species [125], impaired autophagy networks and proteostasis [126] due to triplication of chromosome 21. Gene products at Chromosome 21 are recognized as principal neuropathogenic moieties in the development of DS [127,128]. Moreover, DS after age 40-50 has considerable AD-like neuropathology and individuals present notable signs of dementia. Thus, two principal biomarkers of the etiology of AD (senile plaques that are mostly composed of fibrillar Aß peptides and hyperphosphorylated tau protein) appear to operate through the mTOR signaling system. Moreover, it has been reported that inhibition of mTOR decreases the tau pathology [106].

4.3. Parkinson's disease

In PD, the pathology is associated with deletion of dopaminergic cells in central and peripheral neurons, associated to the presence of lewy bodies formation with the major toxic protein component of α-synuclein (α-syn), that is phosphorylated in serine residue at position 129 [129]. *In vitro* studies have shown that metformin reduces phospho-Ser129 α-syn through activation of the AMPK which inhibits mTOR activity and decreases the levels of phosphorylated forms of mTOR downstream targets including p-S6K [69]. Inhibition of mTOR leads to PP2A activation, a neuroprotective protein phosphatase, which dephosphorylates phospho-Ser129 α-syn. Rapamycin has also shown to display similar effect to metformin reducing the formation of lewy bodies [130]. In animal models of PD, rapamycin mediated inhibition of mTOR also exerts neuroprotection through blockade of expression of stress response protein RTP801 and survival-promoting kinase Akt [131].

Moreover, it has been observed that the mTOR pathway showed central role in dopaminergic neurons activity in PD [132,133] [134]. There is increasing evidence to suggest that activation of PI3K/Akt/mTOR pathway can regulate neuronal development, survival and differentiation, and it also played a crucial role in synaptic plasticity [9,135]. Nakasoand colleagues observed in a cellular model of PD that the neuroprotective effect of caffeine was caused by the activation of the PI3K/Akt pathway [136,134]. Additionally, administration of MPP^+ (1-methyl-4-phenylpyridinium) decreased the phosphorylation of mTOR and its canonical substrate, p70S6K, in control and G2019S LRRK2-mutant skin fibroblasts [137,134]. The PI3K/Akt/mTOR genes in the SH-SY5Y dopaminergic cells also provide a reference gene framework for researchers working in PD. The expression pattern will further offer useful clues about the function of the signaling pathway during PD pathogenesis and possible neuroprotection options [138,134,139]. However, mTOR has a controversial sort of role as various results presented neuroprotective as well as neurotoxic effects in different studies. For instance, rotenone, a known PD toxin, caused downstream regulation of mTOR and decreased cell viability in different PD models [140,141]. Lysosomal dysfunction appears to contributes to rotenone's neurotoxicity [142,143] and could be antagonized by pretreatment with rosuvastatin [144]. On the other hand, there are evidences suggesting that upstream regulation of mTOR causes partial prevention in neuronal cell loss provoked by PD toxin [145,146]. Therefore, future studies are warranted to explore the exact role of mTOR signaling pathway in PD.

4.4. Huntington's disease (HD)

HD is an autosomal dominant neurodegenerative disease, which is characterized by neurodegeneration of the basal ganglia and cortex linked to the aggregation of huntingtin protein.

Mutant huntingtin protein has expansion of CAG (cytosine-adenine-guanine) triplet repeats, which is not cleared from cells and leads to neural death. *In vivo* studies has indicated that rapamycin mediated inhibition of mTOR can relieve the symptoms of HD by increasing autophagy and clearance of mutant huntingtin [147,91]. Evidence also supports that mTOR inhibitors have protective roles in neurodegenerative diseases in animal models, but more studies are needed using mTOR inhibitors.

4.5. Amyotrophic lateral sclerosis (ALS)

ALS is associated to the progressive loss of functional motor neurons, and to the formation of misfolded protein inclusions in neurons [148]. Diverse studies using SOD1G93A mice (which mimics the most usual familial cause of ALS), evidenced that the treatment with rapamycin failed to protect against the disease progression even aggravated motor neuron loss [149,150]. Similar results were obtained using rapamycin in a mouse model of ALS induced by mutant valosin protein [151]. On the contrary, the treatment with trehalose, an mTOR-independent activator of autophagy prolonged motor neuron survival and reduced the autophagic flux defect in a SOD1G93A mouse model of ALS [152]. Taking together these results suggest that in ALS mTOR seems not to be an adequate target.

5. Omega-3 fatty acids and neurodegeneration

The broad protective effects of omega-3 PUFAs in the CNS function have been well recognized (Table 2 and Table 3). As described above, AD is a devastating neurodegenerative disease with over-expression of Aβ peptide, extensive inflammation and neuronal cell death [153,154]. Omega-3 PUFAs have been shown to improve mental health and cognition including in

Alzheimer's disease [155]. They also attenuates the symptoms of attention-deficit/hyperactivity disorder (ADHD) and improve attention and the ability to complete tasks in children [156]. Multiple reports have clearly demonstrated that omega-3 PUFA can prevent or treat psychopathologies such as "emotional depression," "bipolar disorder," "schizophrenia," and AD [36].

The DHA and EPA treatment have significant anti-inflammatory effects in AD [157]. The EPA showed effect through BDNF over expression while DHA caused down regulation of TNF-α [158,159] leading to phagocytosis and anti-inflammatory effects. The potential role of PUFAs in immunoregulation has also been reported in patients with AD suplemented with omega-3 PUFAs [160,161].

Both Aβ and *tau* aggregates results in increasing neuronal death, stress and defects in neuronal pathways, and leads to neurodegenerative disease. Omega-3 was found to attenuate the disease condition and enhances neuroprotection by increasing the expression of BDNF and also high affinity BDNF receptor (TrkB). During neurodegeneration disease such as AD and PD, the omega-3 concentration were shown to decrease in the brain and resulted in more serious consequences. In an experiment where three transgenic AD animal model were used to evaluate the impact of omega-3 on neurological disorders, adding omega-3 in diet was found to revert the condition via inhibitory accumulation of Aβ, hyperphosphorylation of tau and improve the cognitive deficits [162].

Aβ accumulation is the major cause of AD causing oxidative damage, inflammation of neurons and also phosphorylating tau protein, [163]. In a study, a transgenic animal model of memory loss and Aβ depletion (Tg 2576 mouse) exposed to PUFA (1g/kg/day), dietary intake for 16-20 months, reduces the Aβ accumulation [162,164] and exert neuroprotective activity. DHA

treatment (0.98g/kg/day) for 6 to 10 months in transgenic animal model (APPs we/PSIdE9) decreases Aβ accumulation [165]. In similar study, the intraneuronal Aβ concentration along with tau accumulation and phosphorylation decreases, when DHA incorporated to the diet (2.3g/kg/day) was given for 9 months in the 3xTg-AD mouse model [166]. Also, NPDI derived from omega-3 was found to protect neurons from Aβ direct apoptosis in HN culture cells [167,168].

Kusat and colleagues studied the effect of omega-3 along with betaine for possible protection against alcohol induced neurodegeneration [169]. In their study, female rats in the prenatal and postnatal stages were exposed to high alcohol concentrations (25-75 mL ethanol) that cause fetal alcohol syndrome (FAS) [170-172]. When omega-3 PUFAs in modified diet were administered during pregnancy and after delivery, they provoked a significant reduction in brain necrosis induced by excessive ethanol intake. It is already known that neonatal rat brain is highly sensitive to ethanol and necrosis is regard as the primary death caused after acute neonatal head injury [173], which was also noted in histopathalogical studies [174].

Various studies have confirmed the role of omega-3 in preventing neurodegeneration [175-177], along with clinical trials proven its effectiveness [178-181]. A mechanistic activity of omega-3 PUFA in protecting NDs has been shown in Figure 3.

PUFAs have been shown to have critical role in cerebral functions and brain development. For example, DHA in the brain contributes in gene expression, neurogenesis, neuroplasticity, neuron differentiation, survival, oxidative metabolism, learning and memory process [155,182]. The EPA and DHA diet in rats during post-natal development, can increase SOD [183].The EPA can also inhibit JNK activation, which phosphorylate and inhibit the antiapoptotic bcl-2 protein by proliferator activating receptors (PPAR- Aα) [184]. The DHA decreases the production and

aggregation of Aβ from amyloid precursor protein. The DHA diet for 8-10 months in Aged 3×Tg-AD mice also improved cognition and prevent the pathological effect of mpp^{+}onnigral cells and striatum. Ethyl-EPA diet in MPTP-probencid mouse model of PD can also prevent some of the PD symptoms such as hypokinesia but it failed to prevent the decreation of nigrostriatal dopamine [185]. In mouse model of HD, oral administration of PUFAs can prevent motor deficits [182]. The Rthyl-EPA in YAC128 HD mice has also been shown to decrease motor deficits [182]. On the other hand, DHA-enriched diet can increase the number of dendrite spine in hippocampus of animals. Moreover, there is a negative association between homocyteine levels and DHA in plasma. Homocysteine can act as a glutamate agonist on NMDARs and has excitotoxicity effect and neurodegeneration [186].

6. mTOR as a new omega-3 target in NDs therapies?

As reported above, in section 4, mTOR seems to be an interesting candidate for some types of NDs, such as AD, SD, PD and HD. In scientific literature, as described in section 5, the omega-3 PUFAs role as neuroprotective agent is well recognized. Some references reported mTOR as an omega-3 target in different pathological conditions, but in NDs there aren't studies that prove mTOR as an omega-3 target. Nevertheless, considering the promising evidence regarding the involvement of mTOR in other chronical pathologies, studies on the omega-3 beneficial activity in NDs through mTOR inhibition are strongly needed.

6.1. Omega-3 mechanism of action in NDs

Omega-3 PUFAs protect neurons and related disorders through mTOR signaling pathway. Upstream of mTOR, *i.e.,* PI3K/Akt pathway was activated by omega-3 PUFAs which is central

for cell survival. Accordingly, omega-3 PUFAs supplementation facilitates Akt translocation to the membrane for activation and this process is blocked under serine-depleted conditions, suggesting that omega-3 PUFAs-derived phosphatidylserine (PS) is necessary for this effect [187]. Omega-3 PUFAs are suggested to be the best substrate for PS synthesis which prevents normal cell death and is one of the potent neuroprotective agents. The serine/theonine Akt kinase is an important enzyme in cell survival [188] and it played important role in mediating the protective effect of omega3 in neuronal cells [189,190]. The reduction in activity of Akt kinase pathway leads to the apoptotic death, which can be prevented by omega-3 via phosphorylation/ activation of Akt kinase. The PS is also involved in signaling event of kinases such as protein kinase C, Raf-1 kinase [187] and Akt [190] . In addition to the effects via mTOR, diverse evidenced showed that the omega-3 also form neuroprotectin D1 (NPD1), a new DHA-derived 10,17S-docosatriene, which prevents the Aβ secretion and, consequently, represses Aβ triggered activation of proinflammatory genes and activation of antiapoptosis genes [191]. In AD mouse model and human neuroglial (HNG) cells cultured with Aβ protein, the role of omega-3 derived NPD1 was also investigated [192]. The results showed that NPD1 treatment prevented the Aβ driven expression of proinflammatory enzymes (COX-2 and B-94), downregulated apoptosis and reduced neuronal cell death. However, diverse studies using human retinal pigment epithelium cells reported that NPD1 leads to cell survival after challenged with oxidative stress, at least in part, via activating the PI3K/Akt and mTOR/p70S6K pathways [193,194]. Similar protective effects of omega-3 were recorded by Ma and coworkers in the survival in cultured hippocampal neurons by upregulating the expression genes with anti-apoptotic functions, repressed pro-inflammatory genes and inhibit the phosphorylation of IRS-1 by different pathways including PI3K/Akt/mTOR and tau by Aβ [195].

The mechanism of omega-3 was studied in some of experiments. For instance, omega-3 enriched diet which has direct effect on signaling pathway (PI3K/Akt/mTOR), increased the neurotrophin levels like NGF (Nerve growth factor) and BDNF and thus, improved cognition function [196]. These neurotrophins regulate/stimulate the transcription and release of the vascular endothelial growth factor (VEGF) [197]. VEGF represents a major pro-angiogenesis protein [198]. VEGF is regulated by HIF-1 alpha levels which, in turn, depend on PI3K/Akt/m+TOR pathway. Activation of mTOR pathway by BDNF and NGF neurotrophins, phosphorylates the two downstream effectors P7056K and 4E-BP1, which regulate and promote angiogenesis [199].

Autophagy is an important part of cell cycle and has a role in preventing cellular damage by elimination of toxic protein aggregates, which causes cell death. In case of neuronal death, these toxic proteins result in increased Aβ and *tau* concentration. The mTOR signaling pathway mainly regulates autophagic process, which is regulated by growth factors, cellular stress and nutritive deficiency. The PI3K/Akt pathway modulates the mTOR signaling pathway and thus played role in modulating the disorders. In one way, this pathway enhances the autophagic events of Aβ, on the other side hyperactivation of pathway will also leads to neuronal death. Thus, the regulation of this process is important and omega-3 PUFAs play a crucial role as proved by several studies.

6.2. Targeting mTOR by omega-3 in pathological conditions

Some studies showed that mTOR inhibition represent one major mechanisms whereby omega-3 PUFAs exert beneficial effects towards different types of pathologies.

Both *in vitro* and *in vivo* studies, have reported mTOR as an omega-3 target in different chronical pathological conditions, such as glioblastoma [200], prostate cancer [173], lung cancer

[201], adrenocortical cancer [202]. Moreover, omega-3 PUFAs trough mTOR inhibition resulted to be active in renal ischemia reperfusion injury attenuation [183], in the protection against systemic inflammation and insulin resistance through the inhibiting the activation of NLRP3 inflammasome, as well as subsequent caspase-1 activation, and the secretion of cleaved IL-1β [203].

Previous study has shown that AMPK and TSC1/2 knockdown by siRNA slightly decrease the inhibitory effect of DHA on mTORC1. The DHA can stabilize the mTOR-raptor complex and decrease its activity. The omega-3 PUFAs decrease the IGF1R and increase PTEN levels, negative regulator of PI3K/Akt pathway which activates mTORC1 [204]. In an *in vitro* study performed on isolated $CD4^+$ T cells from spleen tissues from NOD mice, while, omega-3 PUFAs treatment inhibited the differentiation of CD4+ T cells into Th1 cells by inhibiting TORC1, thus having beneficial effects in autoimmune diseases such as type 1 diabetes [205]. In one study, DHA has been shown to increase the level of intracellular ROS. It was proposed that ROS inactivate AKT/mTOR signaling and, consequently, both autophagy and apoptosis are activated in cancer cells [206]. The LKB1 gene expression and its activity are also stimulated by DHA. In mammary epithelial cells expressing LKB1, the treatment with for 24h evidenced increased AMPK phosphorylation which leads to the inhibition of the mTOR pathway [84].

Recently, diets rich in EPA and DHA have shown beneficial effects in muscular activity when studied in older American citizens causing over expression of muscle mTOR and p70s6k phosphorylation [207] and strongly support memory loss in AD [208]. Hence, evidence suggest that omega-3 PUFAs reduce the over activity of mTOR, but additional clinical trials would be more helpful to investigate the involvement of mTOR pathway and mTOR inhibitors like n-3 PUFAs on patients with neurodegenerative disorders.

The mTOR can be a useful mechanistic pathway for targeting drug resistance in anticancer therapy [209]. The mTOR inhibitor showed marked reduction in the growth of melanoma cells, support apoptosis and prevent necrosis [210,209]. DHA increases autophagy in metastatic adenocarcinoma cell lines (human PC3 and DU145) by mitochondrial ROS accumulation [206,184,211]. An *in vitro* observation on MCF7 cells showed that DHA elevated the expression and the activity of LKB1, and this increase also phosphorylated and activated AMPK, a negative regulator of mTOR. As in LKB1 knockdown MCF7 cells, pS6 expression, a downstream target of mTOR, did not alter beside the control [212]. Corticosteroids elicited muscular atrophy by hitting the proteasomal and lysosomal systems [213,214] and mediating through molecular regulation of muscular trophysm, such as through the IGF-1/PI-3K/Akt/mTOR [215]. Polyunsaturated fatty acids caused significant renal protection through various mechanisms including autophagy. In fat-1 mice, omega-3 accumulation evoked renal protection and better kidney functioning possibly acting through activation of AMPK which causes downstream regulation of mTOR singling pathway [216].

7. Conclusion

In conclusion, NDs, such as AD, PD and HD, remain major age-related disorders with significant world-wide morbidity and mortality. The lack of effective therapy for these diseases require adopting new strategies for the search of new drugs including those from natural sources that act through novel biological targets.

In this regard, the careful analysis of scientific literature carried out in this review showed that:

1) The identification of mTOR as significant regulator of cell cycle and cancer has been extended in recent years to NDs. In fact, growing evidences suggest the possible role of

mTOR inhibitors as a new interesting therapy for NDs, due to their ability to induce apoptotic processes, which are necessary to degrade and eliminate abnormal or aggregated proteins;

2) It is well known that omega-3 PUFAs exert a protective role on central nervous system against numerous pathologies;
3) Both *in vitro* and *in vivo* studies have reported mTOR as an omega-3 target in different chronic and systemic pathological conditions.

Therefore, omega-3 PUFAs which are recognized as mTOR inhibitors in different chronic pathologies, might be also considered as mTOR inhibitory agents to develop new therapeutic strategies for NDs. This hypothesis should induce the researchers to deepen the study of the mechanism through which omega-3 PUFAs exert their protective action in NDs, focusing their attention on mTOR.

These studies as well as our knowledge on the mTOR signaling pathway regulation are however still in their infant stage and further studies and clinical trials on these promising dietary constituents should be strongly encouraged in the future. Thus, additional studies are needed to underline the omega-3 inhibitory activity on mTOR in NDs (Figure 4).

Conflict of interests

All Authors declared no conflict of interests.

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Figures legends:

Figure 1. Structures of some common Omega-3 PUFAs

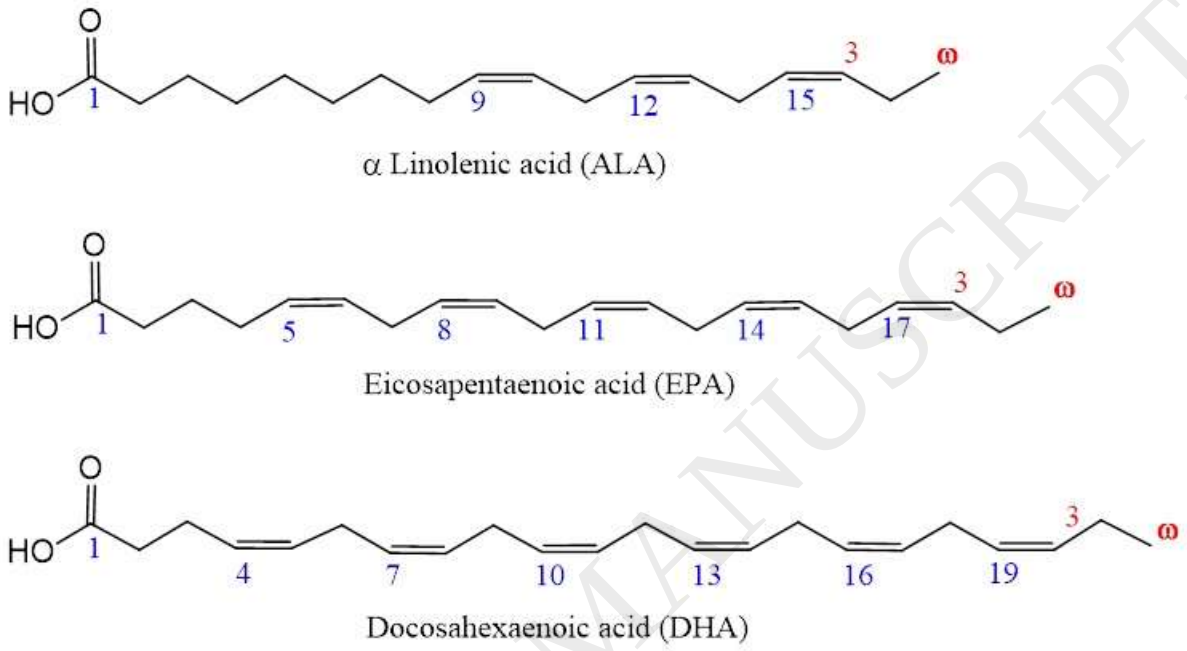


Figure 2: Role and regulation of mTOR signaling pathway. mTOR is a major modulator of autophagy and it receives inputs from different signaling pathways. The kinase mTOR is a downstream target of PI3K and kinase AKT pathway, which is activated by receptors of neurotrophins and growth factors, and promotes cell growth, differentiation and survival, while downregulating apoptotic signals. AKT also promotes mTOR activity by suppressing the repressive action of TSC by phosphorylating TSC2. TSC2 phosphorylation promotes activation of Rheb and stimulation of mTOR activity. Rag A/B is also activated by the presence of RagGTPase, which further regulates mTOR signaling. Activation of mTOR leads to regulation of many target proteins including FoxO3, Aβ, autophagy, synaptic plasticity, cell growth,

differentiation and survival. This figure has been prepared according to the guidelines as published in [217].

mTOR (mammalian target of rapamycin), PI3K (phosphatidylinositol 3 kinase), TSC (tuberous sclerosis complex), Rheb (Ras homolog enriched in brain), Rag (recombination activating gene), Aβ (amyloid beta), ATG (autophagy related protein), ULK (serine/threonine protein kinase ULK), FoxO3 (forkhead box O3)

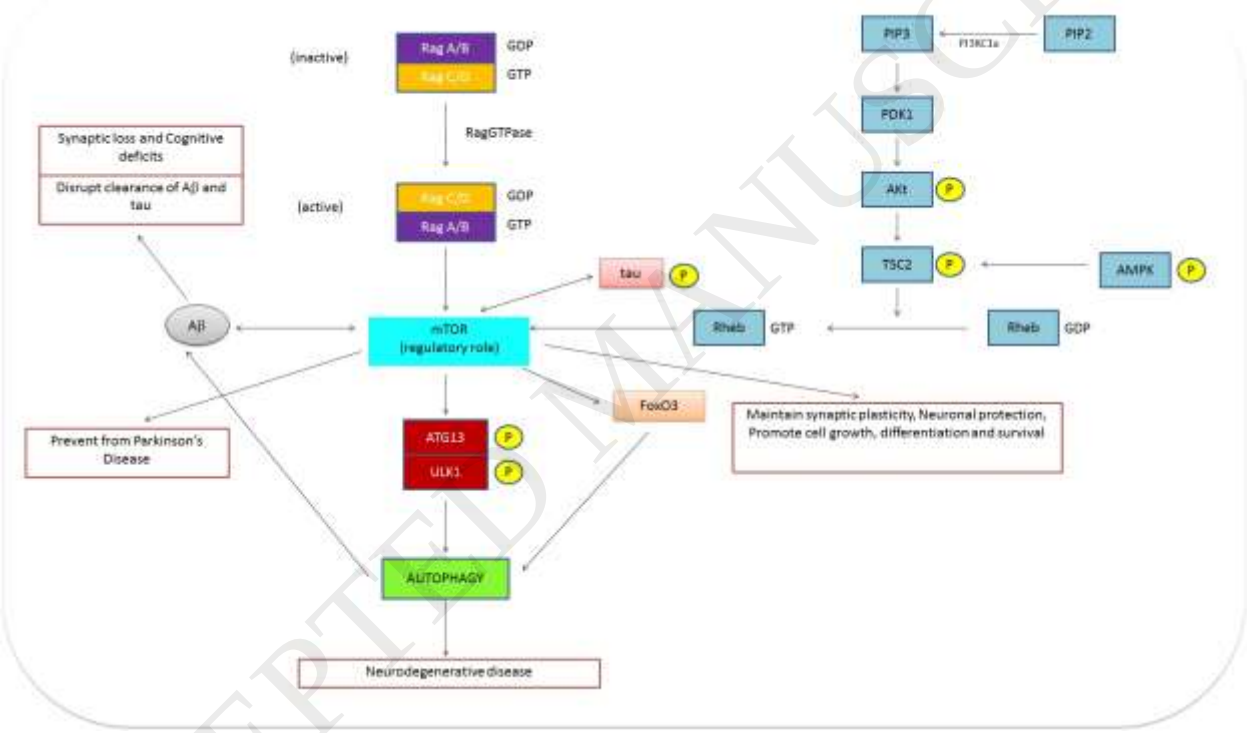


Figure 3. Potential of omega-3 in neurodegenerative diseases therapy through inhibition of mammalian target of rapamycin (mTOR) signaling pathway. Aging, stress and inflammation are common risk factor for neurodegenerative diseases such as Alzheimer's (**AD**), Parkinson's (**PD**), amyotrophic lateral sclerosis (**ALS**), and Huntington's disease (**HD**), in which defects in autophagy cause accumulation of toxic proteins in neurons which leads to neural damage and death. The mTOR has a key role in important cellular process such as cell survival, protein synthesis, mitochondrial biogenesis, proliferation, apoptosis, and is negative regulator of

autophagy. The mTOR signaling can be activated by PI3K/AKT and inhibited by AMPK. Omega-3 can inhibits mTOR activity through a mechanism involving activation of PTEN and AMPK. Eicosapentaenoic acid (**EPA**), docosahexaenoic acid (**DHA**) and α-Linolenic acid (**ALA**), adenosine monophosphate-activated protein kinase (**AMPK**), tuberous sclerosis complex (**TSC**), ribosomal protein S6 kinase (**S6K**), initiation factor 4E-binding protein (**4E-BP**), eukaryotic initiation factor 4E (**eIF4E**), eukaryotic initiation factor 4B (**eIF4B**).

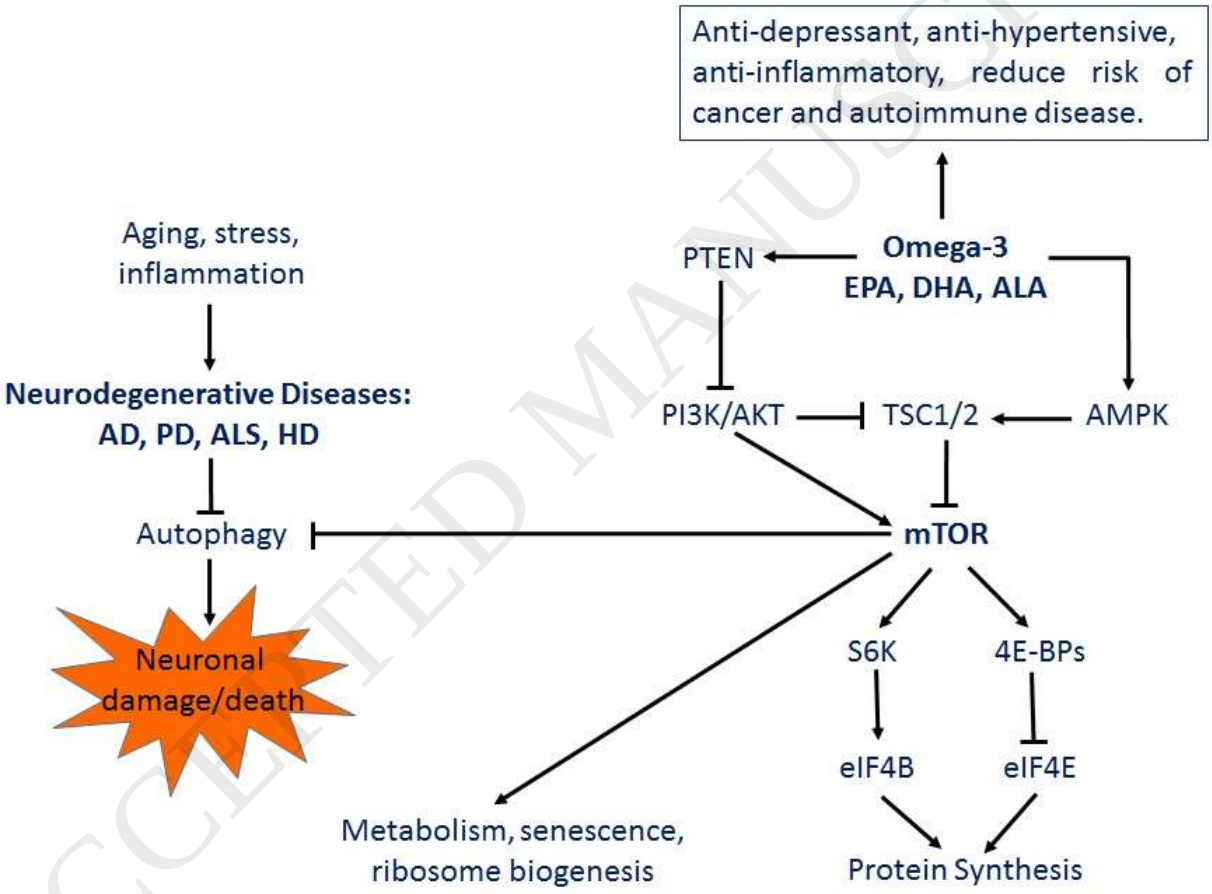
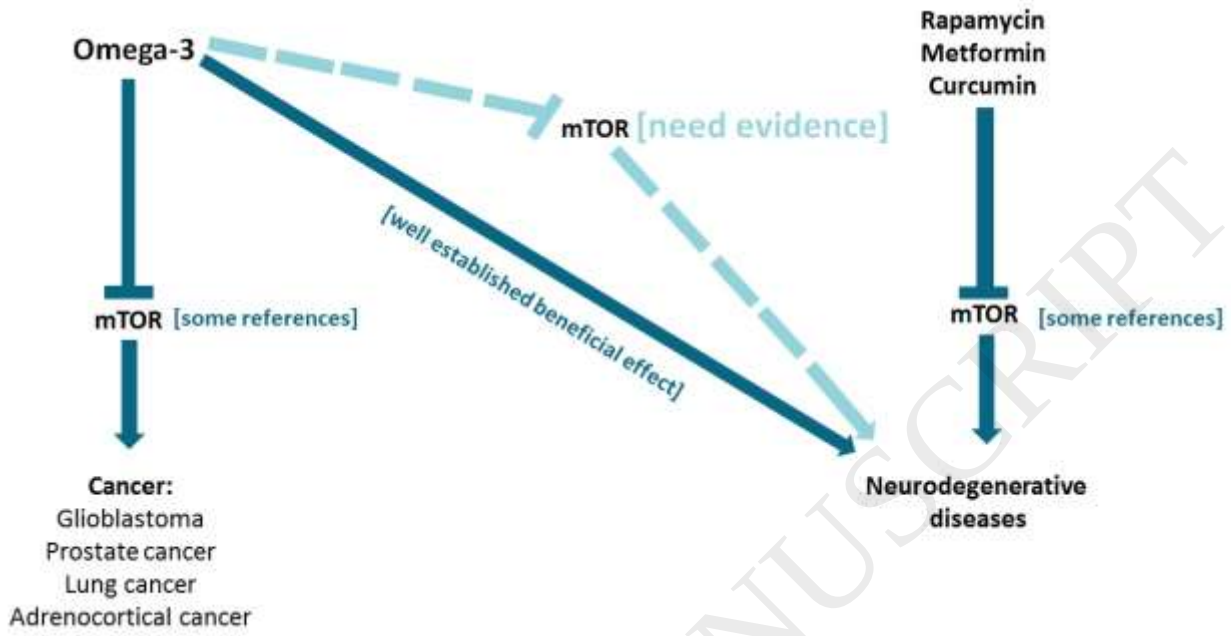


Figure 4. Schematic report on literature evidence suggesting omega-3 as mTOR inhibitor in neurodegenerative diseases. Omega-3 PUFAs which are recognized as mTOR inhibitors in different chronic pathologies, might be also considered as mTOR inhibitory agents to develop

new therapeutic strategies for NDs.



Table

Table 1. mTOR inhibitors used in the context of neurodegenerative diseases.

Compounds	Type of NDs	Reference
Rapamycin	Seizures, tuberous sclerosis complex, Alzheimer disease, Parkinson disease and Huntington disease, neurofibromatosis, fragile X syndrome, epilepsy, traumatic brain injury	[218,108,219-221]
Metformin	Seizure, schizophrenia	[222-224]
Curcumin	PD, epilepsy, Huntington disease	[225-227]

Table 2. Omega-3 treatment effects on neurodegenerative diseases models

Omega-3	Type of NDs	Effect	Reference
n-3 PUFAs	AD	Slow down cognitive decline and prevent neuropsychological disorder in AD	[228]
DHA	AD	Modulate hippocampal lipid homeostasis	[229]
DHA	AD	Reduce the formation of both Aβ plaques and prefibrillar Aβ oligomers	[230]
Omega-3 fatty acids	AD	increase the unfolded protein response and improve amyloid-β phagocytosis by macrophages	[231]
α-linolenic acid	PD	Suppresses the dopaminergic neurodegeneration and movement disorder	[232]
DHA	Schizophrenia	Neuroprotective properties, especially at early stages	[233]
DHA	Spinocerebellar ataxia	an improvement of clinical symptoms and cerebellar hypometabolism	[234]
TG-DHA	autoimmune encephalomyelitis	Modulate neuroinflammatory processes	[235]
n3-PUFAs	cognitive function	enhances expression of soluble epoxide hydrolase in murine brain	[236]

Table 3. Clinical trials omega-3 in the context of neurodegenerative diseases

Type of NDs	No of patients	Effect	Reference
AD	384	Brain amyloid pathology may limit the delivery of DHA to the brain in AD	[2367]
Huntington's disease	290	Ethyl-EPA was not beneficial in patients with HD during 6 months of placebo-controlled evaluation	[238]
AD	174	Improved cognitive function in the omega-3 study	[239]
AD	201	The findings in this open-label extension study warrant further investigation toward the long-term safety and efficacy of Souvenaid	[240]
AD	26	Souvenaid™ therapy for the treatment of behavioral disturbances and social cognition skills in behavioral variant of frontotemporal dementia.	[241]
Schizophrenia	79	supportive effects on vascular immune response	[242]