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Targeting Ubiquitin-Proteasome Pathway by Natural Products: Novel Therapeutic Strategy for Treatment of Neurodegenerative Diseases

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Misfolded proteins are the main common feature of neurodegenerative diseases, thereby, normal proteostasis is an important mechanism to regulate the neural survival and the central nervous system functionality. The ubiquitin-proteasome system (UPS) is a non-lysosomal proteolytic pathway involved in numerous normal functions of the nervous system, modulation of neurotransmitter release, synaptic plasticity, and recycling of membrane receptors or degradation of damaged and regulatory intracellular proteins. Aberrant accumulation of intracellular ubiquitin-positive inclusions has been implicated to a variety of neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease (HD), Amyotrophic Lateral Sclerosis (ALS), and Multiple Myeloma (MM). Genetic mutation in deubiquitinating enzyme could disrupt UPS and results in destructive effects on neuron survival. To date, various agents were characterized with proteasome-inhibitory potential. Proteins of the ubiquitin-proteasome system, and in particular, E3 ubiquitin ligases, may be promising molecular targets for neurodegenerative drug discovery. Phytochemicals, specifically polyphenols (PPs), were reported to act as proteasome-inhibitors or may modulate the proteasome activity. PPs modify the UPS by means of accumulation of ubiquitinated proteins, suppression of neuronal apoptosis, reduction of neurotoxicity, and improvement of synaptic plasticity and transmission. This is the first comprehensive review on the effect of PPs on UPS. Here, we review the recent findings describing various aspects of UPS dysregulation in neurodegenerative disorders. This review attempts to summarize the latest reports on the neuroprotective properties involved in the proper functioning

of natural polyphenolic compounds with implication for targeting ubiquitin-proteasome pathway in the neurodegenerative diseases. We highlight the evidence suggesting that polyphenolic compounds have a dose and disorder dependent effects in improving neurological dysfunctions, and so their mechanism of action could stimulate the UPS, induce the protein degradation or inhibit UPS and reduce protein degradation. Future studies should focus on molecular mechanisms by which PPs can interfere this complex regulatory system at specific stages of the disease development and progression.

Keywords: ubiquitin-proteasome pathway, neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, Huntington disease, Amyotrophic lateral sclerosis, Multiple myeloma, polyphenols

GRAPHICAL ABSTRACT | Polyphenols can act as proteasome-inhibitors or may modulate the proteasome activity, thereby improving neurodegenerative disorders by means of accumulation of ubiquitinated proteins, suppression of neuronal apoptosis, reduction of neurotoxicity, and improvement of synaptic plasticity and transmission.
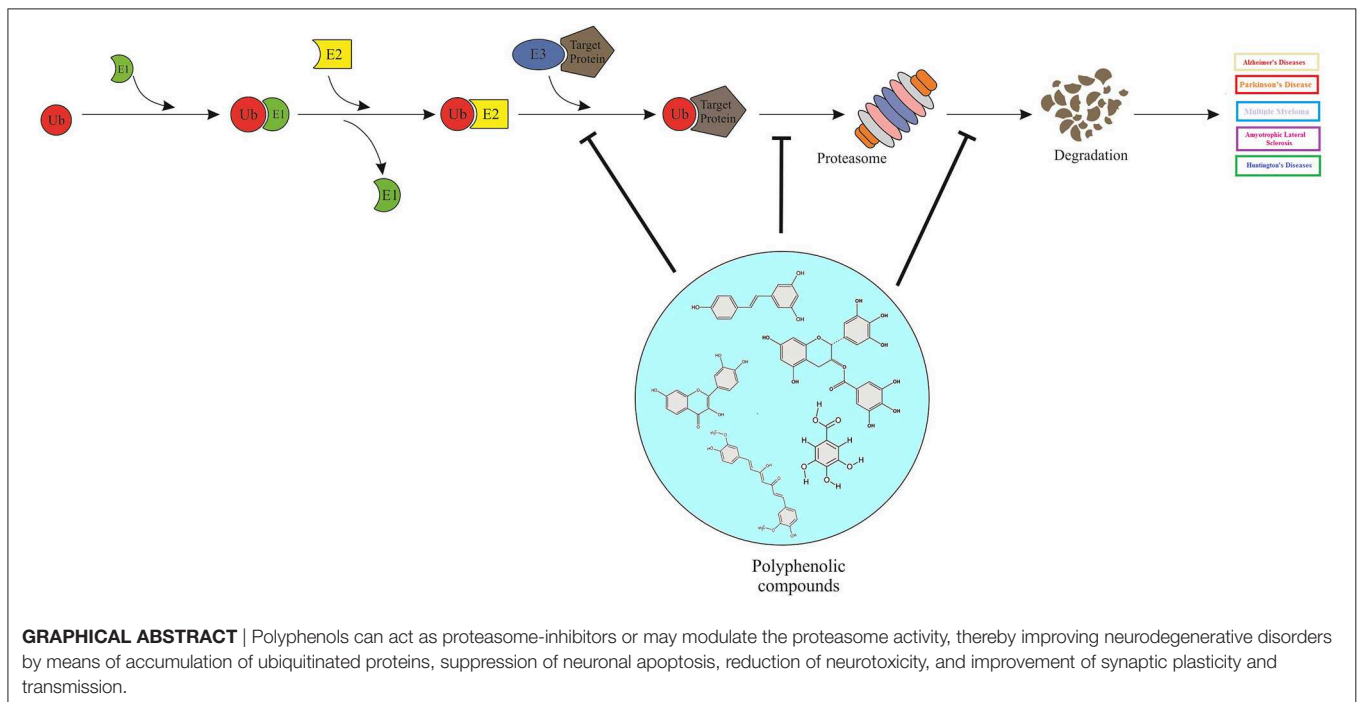
HIGHLIGHTS

- Aberrant accumulation of intracellular ubiquitin-positive inclusions associated to neurodegenerative disorders.
- Polyphenols, can act as proteasome-inhibitors or may modulate the proteasome activity.
- Polyphenols can manage neurodegenerative impairments by targeting the ubiquitin-proteasome system (UPS).
- Polyphenols exert UPS inhibitory activity, resulting in the accumulation of ubiquitinated proteins, suppression of neuronal apoptosis, reduction of neurotoxicity, and improvement of synaptic plasticity and transmission.

INTRODUCTION

Proper production and degradation of proteins are vital for both cellular homeostasis and neuronal function. Approximately, the majority of cellular proteins are degraded by UPS,

highlighting its regulatory effect on cell cycle, proliferation, and survival procedures. Generally, UPS modulates the procedure of proteolysis in neurons. In this manner, an evolutionarily conserved small protein named ubiquitin attached to the substrates (misfolded proteins); under precisely controlled conditions, via the sequential participation of several ubiquitinating and deubiquitinating enzymes, tagging them for degradation by a multi-subunit complex called the proteasome (Hegde and van Leeuwen, 2017). Later, the 26S proteasome binds to the polyubiquitinated proteins and efficiently degrades them (Grice and Nathan, 2016). In addition, proteolysis by UPS has great importance in regulation of many physiological processes, from gene transcription to posttranslational modification of proteins (Hegde and van Leeuwen, 2017).

Emerging data revealed that UPS plays an undeniable role in several neurodegenerative diseases, although, UPS impairment has been reported during the process of neurodegeneration. The

proper function of proteasome and UPS are essential factors for specific function of neurons (Jara et al., 2013). The deposition of protein aggregates and the formation of inclusion bodies are common features of most neurodegenerative diseases, since, the majority of intracellular inclusions contain ubiquitin. For instance, mutant α-synuclein (SACN) protein in PD, Amyloid-β (Aβ) and tau protein in AD, expanded polyglutamine tracts in HD and misfolded prion protein in Prion disorders (Zheng et al., 2016); besides, UPS dysregulation results in increased endoplasmic reticulum stress, and cell death in neuronal cells (Jara et al., 2013). In addition, current pharmacological standard treatments for neurodegenerative diseases, such as cholinesterase inhibitors licensed to treat AD; dopaminergic treatments for PD; antidepressants, neuroleptics, and tetrabenazine for HD; glutamate blockers to treat ALS; elicit a wide range of side effects. In this context, identification and characterization of compounds that selectively inhibit UPS and/or proteasome functions, or the substrates capable of triggering deubiquitinases, gained much attention, particularly in line of drug discovery for neurodegenerative diseases and various cancers.

Accordingly, herbal based interventions, predominantly PPs, seems to be an alternative adjuvant therapeutic approach to delay the onset of neurodegeneration and to reduce the burden of symptoms, to maximize the function and optimize the quality of patient's life. Mechanistic studies on the neuroprotective/neuroregenerative effects of PPs, exhibited that these compounds persuasively act as anti-inflammatory agents and antioxidants, either by quenching free radical species or by inhibiting pro-oxidant enzymes. PPs also function as modulators of the anti-apoptotic factors expression; intracellular neuronal signaling and metabolism; cell survival/death genes; protein aggregation and degradation pathways; and have mitochondrial function either directly or by regulating the mitochondrial signaling pathways (Mandel et al., 2011; Branquinho Andrade et al., 2016; Nabavi et al., 2018b).

Recently, both scientific and public interests shifted toward dietary regimens and nutraceuticals associated with reduced risk of neurodegenerative diseases, in a way to find molecules exploitable for prevention of the onset, progression, and severity of such impairments. Reliable evidence supports the beneficial effects of natural phytochemicals, in particular polyphenolic compounds in attenuating neurological deterioration by means of protein clearance machineries. Among these systems, UPS plays a crucial role in degradation of misfolded protein aggregates. Thereby, the scope of this review is to introduce the UPS in neurodegenerative diseases, to assess the favorable effects of PPs in UPS inhibition, and to discuss their potential application in clinical trials to target neurodegeneration pathologies in the quest for a disease modifying therapy.

UBIQUITIN-PROTEASOME SYSTEM

The ubiquitin proteasome system (UPS), a 76-amino acid complex, is a key regulator of protein catabolism in the mammalian nucleus and cytosol. The UPS is essential for the regulation of almost all vital processes including, organelles biogenesis, cell cycle, differentiation and development, immune response and inflammation, neural and muscular degeneration, as well as response to stress and extracellular modulators. Under extremely controlled conditions, UPS affects a wide variety of cellular substrates and molecular pathways; furthermore, UPS defects could result in the pathogenesis of numerous devastating human diseases (Leestemaker and Ovaa, 2017).

Protein degradation via UPS involves two separate and consecutive phases named conjugation and degradation. Throughout the conjugation phase, the substrate protein is tagged by the covalent attachment of multiple ubiquitin molecules, thereafter, 26S proteasome (composed of the catalytic 20S core and the regulatory 19S part) degrades the tagged protein, such process is called the degradation phase. This conventional function of UPS is usually associated with antigenic peptide generation, regulation of protein turnover, and housekeeping functions. Recently, it has been shown that protein modification by UPS also has unconventional (non-degradative) functions that is dictated by the number of ubiquitin units covalently tagged to proteins (poly vs. mono-ubiquitination), and by the type of ubiquitin chain linkage that is present (Akutsu et al., 2016). Ubiquitin is tagged to the ε-amine of lysine residues of target proteins via a series of ATP-dependent enzymatic steps named; E1 (ubiquitin activating), E2 (ubiquitin conjugating), and E3 (ubiquitin ligating) enzymes. Moreover, the C-terminal Gly75-Gly76 residues of ubiquitin are the key residues that play critical roles in the diverse chemistry of ubiquitin reactions. Ubiquitin could be conjugated to itself through particular lysine residues (K6, K11, K27, K29, K33, K48, or K63), resulting in various types of chain linkages. The isopeptide binds to a target protein and ubiquitin, thereby; specific deubiquitinating enzymes (DUBs) can reverse the linkages between several ubiquitins in a chain. Recent studies have revealed that many DUBs are parts of ubiquitin ligase complexes, which enables DUBs to regulate the activity and abundance of both the ligase and the substrate (Stolz and Dikic, 2018).

Substantial evidence has clarified the determinative role of UPS dysfunction in neurodegenerative disorders, involving abnormal accumulation of inclusion bodies or insoluble protein aggregates in neurons. Furthermore, dysregulation of UPS could impede the degradation of aberrant or misfolded proteins and negatively upset synaptic transmission (Zheng et al., 2014). Eventually, unsuccessful removal of damaged proteins could result in the aggregation of these proteins and neuronal apoptosis (Hyttinen et al., 2014). On the other hand, in neurodegenerative disorders, defectiveness in synaptic plasticity is attributed to dysregulation of ubiquitin-mediated proteolysis (Selkoe, 2002).

DEUBIQUITATION

DUBs play pivotal roles in hemostasis of biological processes such as cell cycle, proliferation, programmed cell death apoptosis, and DNA repair mechanisms. Ubiquitin-specific-proteasome-7 is a DUB enzyme. Its overexpression has been detected in numerous types of cancers (Hu et al., 2002; Li et al., 2004; Nicholson et al., 2007), in particular, stabilization of

MDM-2 (murine double minute). USP7 deubiquinates MDM2, therefore, maintaining the tumor suppressor p53 ubiquitinated, it also degraded by proteasome under normal condition (Everett et al., 1997; Cummins et al., 2004). In MM patients, deletion or mutation in p53 was detected, thereby; the inhibition of USP7 could be a useful therapeutic target for accumulation of functional p53.

Both USP14 ubiquitin-specific-protease and the ubiquitin C-terminal hydrolyase (UCHL5) are cysteine proteases. DUBs are associated with 19S proteasome regulatory subunit; hence, they may modulate the capability of proteasome for target proteins to be degraded (Borodovsky et al., 2001; Al-Shami et al., 2010; Lee et al., 2010). They are able to regulate the signaling pathways such as nuclear factor (NF)-κB (Al-Shami et al., 2010), transforming growth factor (TGF)-β (Wicks et al., 2005), and CXCR4 chemotaxis (Mines et al., 2009). USP14 and UCHL5 expression levels are upregulated in different types of tumors such as colorectal cancer (Shinji et al., 2006), ovarian cancer and MM (Tian et al., 2013). Selective USP14 and UCHL5 inhibitor b-AP15, induced apoptosis in MM cell lines and in primary MM cells via downregulation of cell division cycle 25C (CDC25C), CDC2, and cyclin-B1, as well as the activation of caspases and unfolded protein response pathways (p-IREα, p-eIF2α, and CHOP) (Tian et al., 2013). VLX1570 is another USP14 inhibitor, which induced apoptosis in MM cells (Wang et al., 2016).

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is recognized as a highly common neurodegenerative disease with visual-spatial confusion and loss of short-term memory. It is known that memory loss exacerbates over time, leading to cognitive dysfunction and reduced intellectual capacity in AD patients. The pathology of AD is related to misfolded-protein aggregation, inflammatory changes, and oxidative damage, resulting in neuronal loss (Querfurth and LaFerla, 2010). In an AD brain, the most important pathognomonic lesions include the intracellular neurofibrillary tangles (NFTs) and extracellular senile plaques (ESPs). Senile or neuritic plaques [composed of Aβ containing 39 to 42 amino-acid peptides, a product of the sequential cleavage of the β-amyloid precursor protein (APP)] and neurofibrillary tangles (filamentous bundles comprised of hyperphosphorylated tau proteins) are typical characteristic lesions in affected tissues (Haass and Selkoe, 2007). To date, two types of medications including cholinesterase inhibitors (Donepezil, Rivastigmine, Galantamine), and N-methyl-D-aspartate (NMDA) receptor antagonist (memantine) were approved by the U.S. Food and Drug Administration (FDA) to treat moderate to severe AD symptoms (Briggs et al., 2016).

Although the major cause of AD remains unknown, the familial type of autosomal dominant inheritance is involved in nearly 0.1% of cases. Mutations in genes encoding presenilin 1 (PS1), PS2, and amyloid precursor protein (APP), are incorporated to this type of AD (Waring and Rosenberg, 2008). Nearly 95% of all AD patients suffer from sporadic AD, which is associated with the late onset of symptoms (above 65 years)

(Minati et al., 2009). According to a recent investigation, UPS either is damaged or appears inadequate in some regions of the brain of young mice (Liu et al., 2014). In this regard, the interaction of ubiquitin C with different AD factors was reported by a proteomic study; accordingly, UPS dysregulation was introduced as a mechanism underlying AD (Manavalan et al., 2013). UPS dysregulation can prevent calmodulin degradation and block Ca^{2+}/calmodulin-dependent signaling pathways in AD (Esteras et al., 2012). Some UPS and AD-related proteins, such as C-terminus of Hsc70-interacting protein (CHIP) and ubiquitin carboxyl terminal esterase L1 (UCHL1), may be expressed aberrantly. These proteins along with a mutant form of ubiquitin, can inhibit the UPS and cause proteasomal dysfunction in AD patients (Oddo, 2008; Bilguvar et al., 2013).

Ubiquitin-Proteasome System and Amyloid Beta

Aβ is identified as a peptide from APP, cleaved by β- and γ-secretases. Following cleavage of APP in its ectodomain by β -secretase 1 (BACE1), γ-secretase splits the transmembrane domain of carboxy-terminal fragments and discharges Aβ peptides into the extracellular environment (Wang et al., 2018). Overexpression of APP increased the activity of UPS in the frontal cortex of transgenic AD mice model (Seo and Isacson, 2010). According to the literature, Lysine (Lys)-203 and Lys-382 are indispensable to proteasomal degradation of BACE1 (Wang et al., 2012). On the other hand, BACE1 proteasomal degradation is accelerated by ubiquitin carboxylterminal hydrolase L1 (UCHL1) (Zhang et al., 2012). It was shown that due to the accumulation of Aβ in neurons, the activities of proteasomes and the deubiquitinating enzymes reduced (Almeida et al., 2006). Clearance of Aβ can significantly diminish the early pathogenesis of tau (Budd Haeberlein et al., 2017). However, Aβ accumulation may damage proteasome function and promote tau accumulation (Tseng et al., 2008). In addition, mutant or wild-type APP in neural cells is known to affect downstream protease inhibition (Cecarini et al., 2014).

Ubiquitin-Proteasome System and Tau

Tau, which is described as a soluble protein in neurons, is concentrated in axons and stabilizes the microtubule network (Lee et al., 2013). In adult human brain, six tau isoforms are expressed. Although, the mechanism of tau fibrillization is still indefinite in pathological disorders, formation of paired helical filaments (PHFs) is triggered by hexapeptide motifs. Overall, diverse posttranslational modifications such as glycosylation, ubiquitination, hyperphosphorylation, and proteolysis could occur in tau (Hernandez and Avila, 2007; Martin et al., 2011). Besides, tau hexapeptide motifs, ubiquitin and apolipoprotein E are among other NFT components. Stepwise fragmentation happens in tau to generate cleaved molecules with proaggregation features, such as neurodegeneration (Wang et al., 2010). In a study by Dolan and Johnson, the autophagy system removed truncated tau, while UPS was not involved (Dolan and Johnson, 2010). On the other hand, Grune et al. (2010) reported that ATP/ubiquitin-independent 20S proteasome catalyzed tau degradation. Valosin-containing proteins (part of UPS; the

machinery that degrades damaged, misshapen, and excess proteins within cells) in AD synapses are negatively correlated with the buildup of hyperphosphorylated tau oligomers, and UPS dysfunction may progress concomitantly with tau hyperphosphorylation (Tai et al., 2012).

Ubiquitin-Proteasome System and Ubiquitin Carboxyl Terminal Esterase L1

UCHL1 enzyme attributed to the removal of ubiquitin from unfolded proteins and disassembly of polyubiquitin chains for recycling of ubiquitin. The enzyme is also capable of eliminating abnormal proteins, as it stabilizes monoubiquitinated proteins (Setsuie and Wada, 2007). In a model of APP/PS1 mice, UCHL1 transduction restored normal cognition and synaptic function in hippocampal slices treated with Aβ (Gong et al., 2006). The direct correlation of neuronal UPS with sporadic AD has been proven (Oddo et al., 2006). In a study on Chinese Han patients, AD was associated with serine-to-tyrosine substitution at codon 18 in exon 3 of UCHL1 gene; the genotypes were also more resistant in females (Xue and Jia, 2006). According to a recent study by Poon et al., UCHL1 was recognized vital for the regulation of neurotrophin receptors and supporting retrograde transport. It is also known that Aβ downregulates the UCHL1 in AD, thereby, compromising synaptic plasticity, as well as neuronal survival (Poon et al., 2013).

Ubiquitin-Proteasome System and Ubiquilin-1

Polyubiquitinated proteins are delivered to proteasomes for degradation by several proteins, including ubiquilin-1 with ubiquitin-like domains. The increased risk of AD is associated with the ubiquilin-1 gene (*UBQLN1*) allelic variant (Li et al., 2017). In a study by Stieren et al., reduction of ubiquilin-1 activity, led to the production of APP fragments, along with neuronal cell death (Stieren et al., 2011). Ubiquilin-1 seems to also contribute to the pathogenesis of other neurodegenerative disorders (Safren et al., 2015).

Ubiquitin-Proteasome System and Sequestosome 1 (p62)

Most NFTs contain p62, which is a UPS-related protein (Morawe et al., 2012). P62 serves as a receptor to bind ubiquitinated proteins and to shuttle proteins to proteasome for the purpose of degradation (Zaffagnini et al., 2018). Similarly, p62 shuttles polyubiquitinated tau to proteasome. In AD, p62 is detected in neuronal inclusion bodies, containing aggregates of ubiquitinated protein (Salminen et al., 2012).

PARKINSON DISEASES

PD is associated with severe motor symptoms, attributing to dopaminergic neuron death in the substantia nigra (Kaur et al., 2018). A number of medications have been approved to treat PD symptoms, of which Levodopa is the most effective pharmacologic treatment for severe motor symptoms, moreover, monoamine oxidase type B (MAO-B) inhibitors,

dopamine agonists (i.e., Bromocriptine, Pergolide, Pramipexole, Ropinirole) are effective for patients with mild symptoms at a younger age (Jankovic and Poewe, 2012). Of course, patients using such drugs are facing a verity of complicated adverse effects. Aside from reduced function of UPS, oxidative stress, and mitochondrial metabolism impairment seem to be involved in PD pathogenesis (Winklhofer and Haass, 2010). PD is associated with 10 different mutations, some of which is correlated with UPS, such as alpha-synuclein (α-SNCA), protein deglycase DJ-1 (or PARK7), UCHL1, PTEN-induced kinase 1 (PINK1), and PD protein 2 (PARK2 or parkin). Overall, parkin, PINK1, and DJ-1 mutations are involved in the autosomal recessive familial type of PD (Lunati et al., 2018; Zeng et al., 2018).

Ubiquitin-Proteasome System and α-synuclein

α-SNCA is described as the major constituent of Lewy bodies (LBs) in the brain of PD patients. LBs contain ubiquitinated proteins, such as α-SNCA. The LB protofibrils exert inhibitory effects against the degradation of 26S proteasome-mediated proteins (Chen et al., 2006; Zhang et al., 2008). α-SNCA is encoded by SNCA gene. Several mutations in SNCA at A53T, and A30P are directly linked to the familial form of PD and α-SNCAopathies (Kaur et al., 2018). It was shown that proteasome inhibitors cause α-SNCA aggregation and formation of LBs (Banerjee et al., 2014). Moreover, rats exposed to proteasome inhibitors displayed PD-like behavior and damage to the central nervous system similar to that observed in PD patients (Lorenc-Koci et al., 2011). Meanwhile, the α-SNCA aggregations may in turn selectively bind to the 6S subunit of the 26S proteasome to inhibit the proteasome activity, and to further induce neurons cytotoxicity, including mitochondrial damage and apoptosis (Tanaka et al., 2001; Snyder et al., 2003). Therefore, proteasome inhibition and α-SNCA may reciprocally regulate a feed forward mechanism and exacerbate the development of PD (Xie and Wu, 2016).

Ubiquitin-Proteasome System and Protein Deglycase DJ-1

Although DJ-1 protein is majorly expressed in the cytosol, it can also be detected in the nucleus. According to a study by Khasnavis et al., astrocytes produce DJ-1 in mice brain (Khasnavis and Pahan, 2014). Similarly, in a normal human brain, the astrocytes express DJ-1 (van Horssen et al., 2010). As suggested in literature, patients with sporadic PD have reduced levels of DJ-1 protein in the substantia nigra (Nural et al., 2009; Cookson and Bandmann, 2010). Familial forms of PD is associated with DJ-1 mutations (Giguere et al., 2018). In a study by Xiong et al., DJ-1 deficiency reduced parkin ubiquitination and improved aggregation of misfolded parkin substrates (Xiong et al., 2009). Nonetheless, to maintain the mitochondrial function, DJ-1 acts along with the PINK1/parkin pathway. Therefore, the association between DJ-1 and PINK1/parkin should be confirmed in further studies. Moreover, DJ-1 is described as a substrate for small ubiquitin-like modifier-1 (SUMO-1) conjugation, and its simulation is crucial (Shinbo et al., 2006).

Ubiquitin-Proteasome System and PTEN-Induced Kinase 1

PINK1 is expressed in different brain regions, including the hippocampus and substantia nigra (Blackinton et al., 2007; Heeman et al., 2011). Degradation of heat-induced misfolded proteins, mediated by parkin, is increased by the PINK1 expression. On the contrary, parkin and PINK1 mutations in PD, are less potent in promoting parkin substrate degradation. In fact, PINK1 leads to the clearance of aberrant proteins via proteasomal degradation (Clements et al., 2006). PINK1 mutations are involved in some cases of autosomal recessive and sporadic PD (Blackinton et al., 2007). The symptoms of PINK1 knockout mice, including mitochondrial dysfunction and reduced corticostriatal synaptic plasticity in dopaminergic neurons, are similar to PD patients (Kitada et al., 2007, 2009). Liu and colleagues reported that PINK1 deficiency interrupts proteasome activity and leads to α-SNCA aggregation. They also suggested a relationship between PINK1 and UPS in PD (Liu et al., 2009).

Ubiquitin-Proteasome System and Parkin

Considering the direct correlation between UPS and PD, the parkin gene mutations have been suggested to be involved. The amino acid sequence of parkin contains an ubiquitin-like domain at the N-terminus, as well as a RING box at the C-terminus with E3 ubiquitin-ligase activity (Kaur et al., 2018). Respecting T240R mutations in parkin gene, the association between autosomal recessive familial PD and parkin was identified. In addition, parkin can be found in PD-affected brain regions. Parkin exhibits neuroprotective functions in PD, which can be attributed to its E3 ubiquitin-ligase activity (Song et al., 2009). Wild-type α-SNCA is the most important target of ubiquitin degradation (Li et al., 2018). Research on the possible association of parkin with neurodegeneration reveals that parkin can regulate the aggresome-autophagy pathway (Lim et al., 2006). In addition, parkin triggers ubiquitination, as well as polyglutamine-expanded ataxin-3 degradation, resulting in reduced toxicity in cells (Kumar et al., 2012; Zheng et al., 2014). The deubiquitinating enzyme activity of ataxin-3, as a deubiquitinating enzyme, is improved through ubiquitination (Todi et al., 2009). To eliminate misfolded proteins, ataxin-3 and parkin contribute to aggresome formation (Olzmann et al., 2008). Parkin gene mutations lead to abnormal toxic substrate aggregation due to UPS dysfunction. Parkin might also be associated with the pathogenesis of PD, considering its role in mitochondrial functioning (Kumar et al., 2012). In addition, many mitochondrial processes in PD, involving parkin, are interrupted.

MULTIPLE MYELOMA

Multiple myeloma (MM) is a hematologic malignancy of bone marrow characterized by the accumulation and infiltration of mature plasma cells in the bone marrow (cells that produce high level of antibodies) (Morgan et al., 2012). The cancer incidence is low around 1, in every 132 individuals (0.76%). According to American cancer society, around 30,770 new cases will be diagnosed (16,400 in men and 14,370 in women) with MM and around 12,770 deaths will be expected (6,830 in men and 5,940 in women).

The offered treatment regimens for MM patients mainly include chemotherapy with a response range of 40 to 70%. Unfortunately, most patients suffer from relapsing due to the recurrence of the disease. Bone marrow transplantation combined with chemotherapy (Attal et al., 1996) is another regimen; still patients suffer from the recurrence of the cancer (Attal et al., 1996; Mitsiades et al., 2002). The urine and serum of patients contains high level of monocolonal immunoglobulins called M-protein or paraprotein, which is consisted of a heavy (most often IgG or IgA but also IgM, IgD, or IgE) and a light chain of kappa or lambda. In some patients, the plasma cells only produce light chain immunoglobulins, which dose not bind to the heavy chain. The light chain immunoglobulins are normally excreted in the urine, although their levels in the urineare considered as a prognostic marker for the MM patient.

Proteasome in Multiple Myeloma

Production of high amount of immunoglobulins require functional endoplasmic reticulum (ER) and ER quality control system (Ibba and Söll, 1999; Wickner et al., 1999), which prevents the processing of misfolded proteins and their translocation to its distinct location. Unfolded proteins induce the activation of unfolded protein response (UPR) pathway, leading to inhibition of further protein synthesis, and the expression of chaperones and enzymes required for folding proteins. Once, proteins cannot be refolded, misfolded proteins will be tagged for proteasome degradation by 26S proteasome (Ellgaard et al., 1999), however, unfolded protein stress is intolerable and unfixable, the cells will undergo apoptosis (Zinszner et al., 1998; Brewer and Diehl, 2000). Consequently, inhibition of UPR is a chemotherapeutic target in MM cells.

It was found that MM cells and the primary cells from MM patients express high level of UPR genes (i.e., chaperones glucose-regulated protein 78/binding-immunoglobulin protein (GRP78/Bip) and GRP94/gp96) (Obeng et al., 2006). Proteasome 26S is playing a vital role in maintaining cellular hemostasis via degradation of misfolded proteins, regulation of stress responses, cell cycle, DNA repair pathway, and apoptosis (Ciechanover, 2005). Proteasome 20S is a multi-catalytic enzyme with multi subunits. Each subunit performs one of the classical proteolytic activities; either chymotrypsin-like (ChT-L) activity localized in β5 subunit, trypsin-like (T-L) in β2 subunit, or peptidylglutamyl-peptide hydrolyzing (PGPH) activity in β1 subunit (Orlowski and Wilk, 2000).

There are two isoforms of proteasome, constitutive and immunoproteasome. The constitutive proteasome is distributed in most cells, while the immunoproteasome is expressed in cells of lymphoid organs. Immuoproteasome has great importance in antigen presentation by major histocompatibility class I (Rock et al., 1994, 2002), and also in proteolysis of proteins (Rivett and Hearn, 2004). The level of circulating proteasome was examined in 50 patients with MM, which showed a positive correlation with the advanced stages of the disease (Jakob et al., 2007);

representative of chemotherapeutic potential of proteasome in MM. The NFκB signaling pathway plays a major role in hemostasis of B-cells progenitor, where it inhibits the assembly of Igκ gene in prematured B-lymphocytes (Scherer et al., 1996), protects B cell lymphoma from apoptosis (Wu et al., 1996), induces the stimulus-dependent proliferation (William et al., 1995), and B cell receptor (BCR) responses (Bendall et al., 1999).

The cancer cells are characterized by high proliferative rate coupled with high levels of misfolded proteins, DNA damage and stress in comparison with normal cells, thus, cancer cells highly require a functional proteasome system. Bortezomib is a proteasomal inhibitor of MM, approved by FDA (Richardson et al., 2003). Bortezomib suppresses the NFκB signaling pathway through inhibition of proteasome degradation of iκB, which can maintain the NFκB sequestered and latent in the cytoplasm (Brockman et al., 1995; Hideshima et al., 2001; Russo et al., 2001; Sunwoo et al., 2001; Ma et al., 2003), activation of p53-mediated apoptosis, cell cycle arrest, and induction of both intrinsic and extrinsic apoptotic pathways. It also activates apoptosis via the c-Jun amino-terminal kinase (JNK)-dependent induction of mitochondrial release of second mitochondria-derived activator of caspase (SMAC) (Chauhan et al., 2003). The resistance of MM cells toward bortezomib, initiates an urgent need for either alternative or combinatorial therapy for MM patients (**Figure 1**).

Ubiquitin in Multiple Myeloma

CRL4 (Cullin-RING ubiquitin ligase) is an E3 ubiquitin ligase, composed of three subunits DDB1, cullin 4 (CUL4), and regulator of cullins 1 (RBX1/ROC1). This enzyme has great importance in ubiquitination of different cellular proteins such as c-MYC, interferon regulatory factor 4 (IRF4), Ikaros (IKZF1), and Aiolos (IKZF3) transcription factors. Lenalidomide treatment led to targeted degradation of IKZF1 and IKZF3 in different MM cell lines and primary cells from patients, via inhibition of CLR4 E3 ligase enzyme (Krönke et al., 2013).

Cereblon is a substrate recognizing subunit in E3 ligase enzyme, which binds to the DNA damage binding protein-1 (DDB1), CUL4, and Roc1 to form a functional enzyme complex (Fischer et al., 2014; Sang et al., 2015). Cereblon (442 amino acid protein) is ubiquity expressed in plants, rats, mice as well as humans, and is known to be responsible for memory and intelligence in humans (Higgins et al., 2010). Deletion of C-terminal of cereblon due to a non-sense mutation at amino acid 419 (R419X), resulted in intellectual disability syndrome. Cereblon binds to potassium (Higgins et al., 2008) and chloride channels in the brain and retina (Jo et al., 2005; Hohberger and Enz, 2009; Aizawa et al., 2011), respectively. It also inhibited the activation of adenosine monophosphate (AMP) kinase via binding to its subunit α1 (Lee et al., 2011) (**Figure 2**). Cereblon was found to be a selective target for thalidomide PS-341 (Ito et al., 2010) and lenalidomide (Krönke et al., 2013) activities in MM, leading to the degradation of IKZF3 and IKZF1. The degradation of IKZF3 transcription factor by lenalidomide led to reduction in mRNA and protein levels of IRF4 in multiple myeloma cells. IRF4 is a transcription factor required for the activation of lymphocytes (Mittrücker et al., 1997) and the plasma cells differentiation and maturation (immunoglobulin producing cells) (Klein et al., 2006; Sciammas et al., 2006). Shaffer et al.

(2008) showed that IRF4 is not genetically altered in myeloma cells, but it is addicted for the maturation and activation of B cells. Such data highlighted the role of CRL4 and Cereblon in regulating the pathogenesis of MM and could be used as further objects for MM treatment.
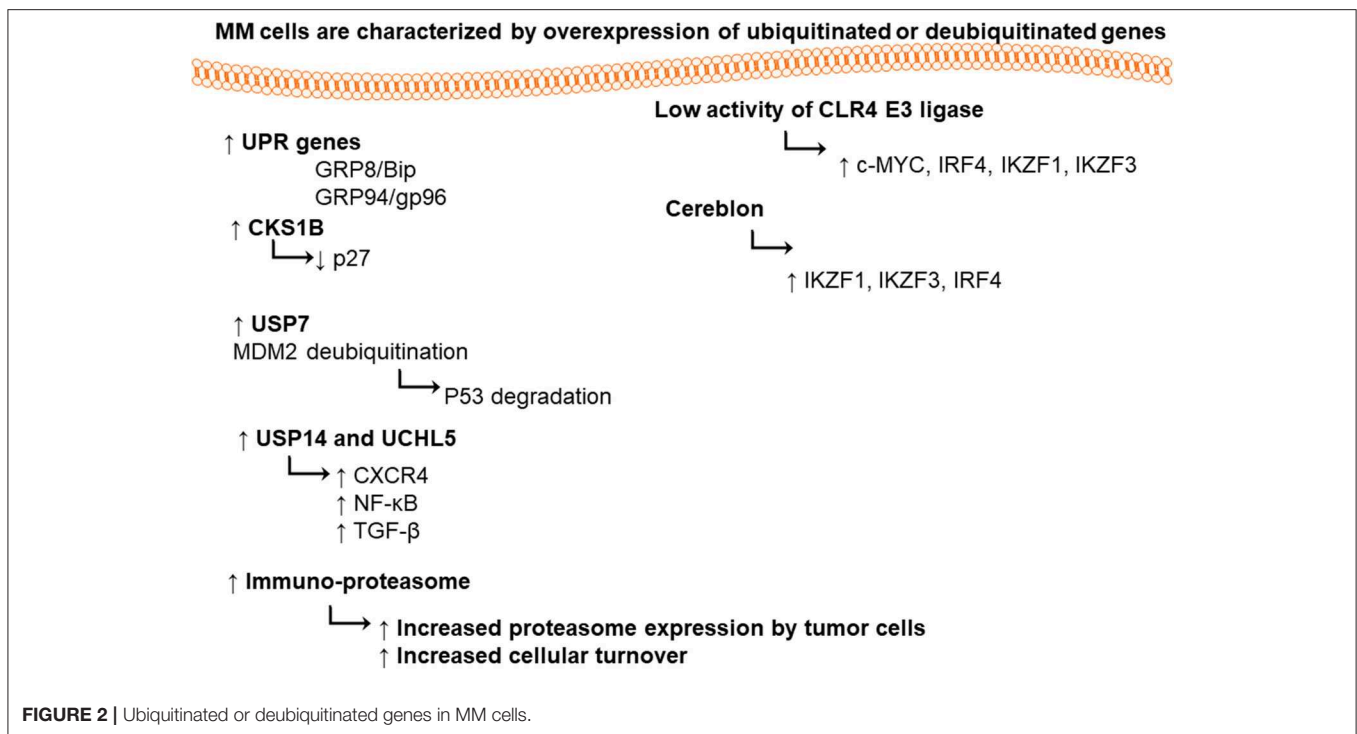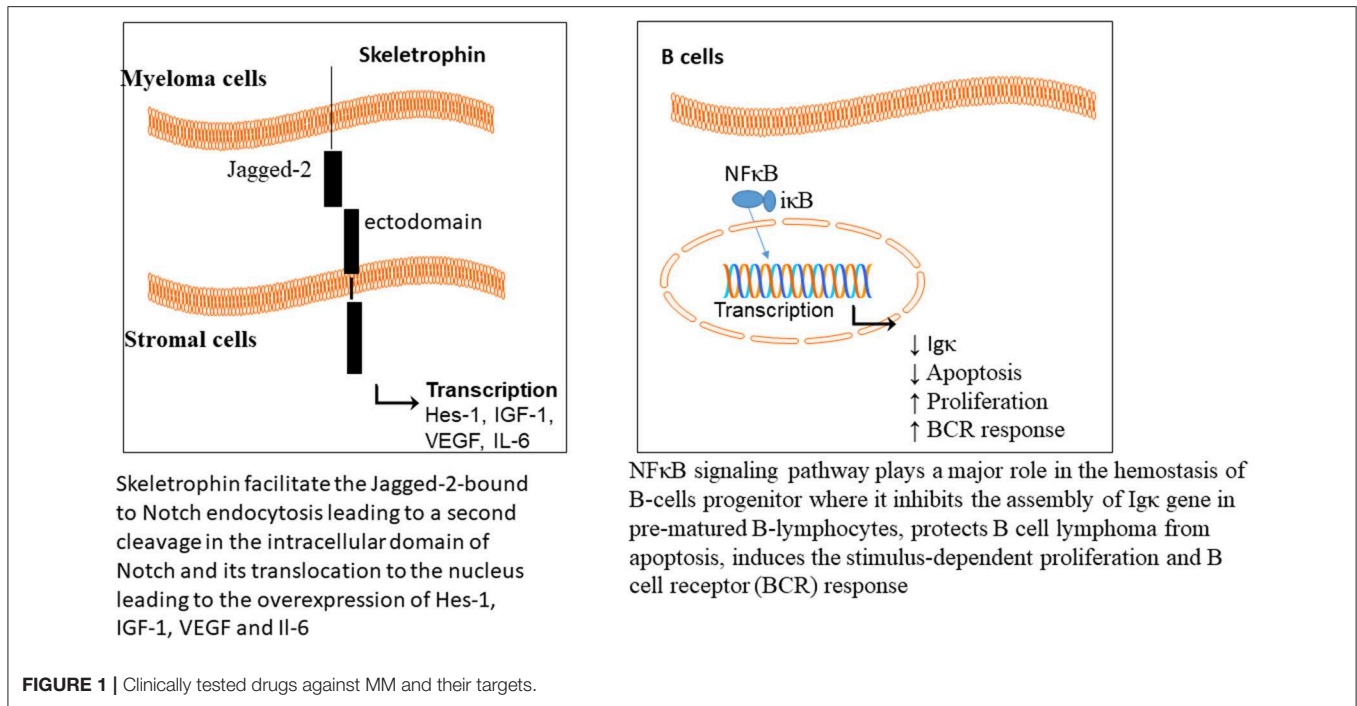
Skeletrophin is an E3 ligase, required for Notch signaling pathway activation (Saurin et al., 1996; Freemont, 2000). The Notch extracellular domains are composed of epidermal growth factor (EGF) repeats (29-36), Lin-12/Notch repeat (LIN), linker to the transmembrane and an intracellular domain. The Notch ligands are the transmembrane proteins and divided into two classes, Delta or Delta-like (Dll) and Serrate (Jagged-1 and Jagged-2 in mammals). Upon binding of the ligand to the Notch, a mechanical force leads to the cleavage of the Notch ectodomain, which is followed by endocytosis. Skeletrophin facilitates the Jagged-2-bound to Notch endocytosis, leading to a second cleavage in the intracellular domain of Notch and its translocation to the nucleus (**Figure 3**).

T-cell acute lymphoblastic leukemia (T-ALL) is characterized by chromosomal translocation, resulting in expression of truncated Notch characterized by constitutive Notch signaling activation. Moreover, myeloma cells as well as primary MM cells express high levels of Jagged-1 and−2, and play a role in the interaction between stromal and myeloma cells (Houde et al., 2004; Jundt et al., 2004). Such data introduce a new ubiquitin ligase, favorable for MM treatment.

CKS1B (Cyclin-Dependent Kinases Regulatory Subunit 1) is an accessory protein in SCF SKP2. F-box (40 amino acids motif)-containing protein S-phase kinase-associated protein 2 (SKP2) is one of the four subunits of ubiquitin ligase complex [SCF (Skp1, Cullin 1, F-box protein)]. SKP2 potentially regulates the transition of cells from G1 to S phase, through a phosphorylation-dependent degradation of cell cycle inhibitor p27 (Cyclin-dependent kinase inhibitor 1B) (Tsvetkov et al., 1999), which is considered as an oncoprotein. The inhibitor p27 downregulation, led to the inhibition of p21 (Yu et al., 1998), p27 (Tsvetkov et al., 1999), and p57 (Kamura et al., 2003) degradation, and prevention of other tumor suppressors such as c-MYC (Kim et al., 2003; Von Der Lehr et al., 2003; Song et al., 2008), transducer of ERBB2, 1 (Tob 1) (Hiramatsu et al., 2006), and Forkhead transcription factors FOXO1 (Huang et al., 2005). The P27 cell cycle inhibitor is also downregulated in numerous cancers including MM (Filipits et al., 2003). In the same time, the CKS1B is overexpressed in oral, gastric, breast and colon cancers, spectating the possible role of CKS1B in regulating the p27 degradation. (Zhan et al., 2007) showed that the silencing of CKS1B led to stabilization of p27 in 4 different MM cell lines.

AMYOTROPHIC LATERAL SCLEROSIS

ALS is a neurodegenerative disorder, sporadic in most cases, involved in progressive motor neuron degeneration in the brain and spinal cord, associated with muscle weakness (Zheng et al., 2014). ALS characterized by paralysis and death within 3 to 5 years from day of appearance of symptoms due to the impairment

FIGURE 1 | Clinically tested drugs against MM and their targets.

Skeletrophin facilitate the Jagged-2-bound to Notch endocytosis leading to a second cleavage in the intracellular domain of Notch and its translocation to the nucleus leading to the overexpression of Hes-1, IGF-1, VEGF and Il-6

NFκB signaling pathway plays a major role in the hemostasis of B-cells progenitor where it inhibits the assembly of Igκ gene in pre-matured B-lymphocytes, protects B cell lymphoma from apoptosis, induces the stimulus-dependent proliferation and B cell receptor (BCR) response

FIGURE 2 | Ubiquitinated or deubiquitinated genes in MM cells.

of respiratory systems (Hardiman et al., 2011). The loss of bulbar and limb function are the main features of ALS. According to Logroscino et al. (2010) study, the incidence rate in the Europe continent is 2.16/100,000 per year. The incidence rate was higher in men than women. Around 10% of patients inherited the disease (autosomal dominant) and 90% of patients have no family history of ALS (FALS), although they still show the pathologic features of FALS. Until now, there is no effective treatment for ALS, so the survival rate is low for the affected patients (Kim et al., 2009). In this context, only 2 drugs have FDA approval; Riluzole (glutamate inhibitor) and Edaravone (free radical and peroxynitrite scavenger with anti-inflammatory

Clinically –tested drugs against MM and their targets

Bortezomib (PS-341, Velcade®)
- P53-dependent apoptosis
- Cell cycle arrest
- Activation of both intrinsic and extrinsic apoptotic pathways
- Activation of JNK-dependent induction of SMAC
- Inhibition of NFκB via inhibition of proteasomal degradation of iκB

Lenalidomide
- Modulation of CLR4 E3 ligase activity
- Degradation of IKZF1 and IKZF3

Thalidomide
- Modulation of cereblon
- Degradation of IKZF1 and IKZF3
- Down regulation of IRF4

b-AP15
- Inhibition of USP14 and UCHL5
- Down regulation of cell division cycle 25C (CDC25C), CDC2 and cyclin-B1
- Activation of caspases
- Activation of unfolded protein response pathway (p-IREα, p-eIF2α and CHOP)

VLX1570
- Inhibition of USP14
- Activation of ER stress and oxidative stress
- Activation of apoptosis (caspase 3)
- Down regulation of CXCR4
- Accumulation of K48-linked ubiquitin chains

FIGURE 3 | Signaling pathways involved in MM.

properties), although they might cause side effects such as bruising, gait disturbance, hives, dizziness, gastrointestinal, and liver dysfunctions, as well as allergic reactions (Jaiswal, 2018). Although the cause of ALS is unknown in most cases, several mutations are related to familial ALS, including superoxide dismutase 1 (SOD1), ubiquilin 2 (UBQLN2), and RNA-binding protein fused in sarcoma (FUS) protein (Kwiatkowski et al., 2009; Vance et al., 2009; Deng et al., 2011). Twenty percentage of the familial ALS is linked to a genetic modification in chromosome 21 long arm q (Rosen et al., 1993).

Amyotrophic Lateral Sclerosis and Superoxide Dismutase 1

Based on several studies, UPS is associated with superoxide dismutase 1 (SOD1) turnover; however, the exact mechanism remains unclear. UPS degrades mutant SOD1 proteins faster than wild-type SOD1, and the proteasome inhibition improves the SOD1 stability (Bendotti et al., 2012). ALS-like pathologies are found in mice with conditional knockout of proteasome subunit, Rpt3 (Tashiro et al., 2012). ALS is also related to the induction of immunoproteasome subunits (Bendotti et al., 2012). In a study using a mutant SOD1-G93A model, pyrrolidine dithiocarbamate treatment reduced the survival of ALS (Ahtoniemi et al., 2007), therefore, the immunoproteasome expression may increase the coping of the nervous system with SOD1 mutations- induced ALS (Rao et al., 2015). In ALS, the function of SOD1 does not decrease, and mice with increased or decreased levels of SOD1 do not show ALS-like pathologies. On the other hand,

SOD1 mutation is known to trigger a toxic gain of function, causing SOD1 aggregation. Moreover, in some cases of sporadic ALS, wild-type SOD1 aggregates support the gain of function (Bosco et al., 2010). Mutant SOD1 can transfer the misfolded SOD1, which is followed by degradation (Crippa et al., 2010). In this regard, an increase was reported in the expression level of immunoproteasome (Cheroni et al., 2008). However, according to the literature, autophagy has greater significance in SOD1 turnover, compared to UPS (Dennissen et al., 2012).

In FALS, virtually 11 missense mutations in cytosolic Cu/Zn SOD1 linked to the accumulation of free radicals to the neurodegenerative diseases, where it leads to a damage in the mitochondrial hemostasis, axon transport, and glutamate transporter function (Rosen et al., 1993). It was found that the mutated form of SOD 1 inhibits the chymotrypsin-like activity of proteasome in Neuro2A cells and depresses the induction of motor neuron death in the transgenic mouse model (Urushitani et al., 2002). Kabashi et al. (2004) found that the mutant SOD 1 caused inhibition in chymotrypsin-like, caspase-like and trypsin-like activities of proteasome, without decreasing its level in lumbar spinal cord of the transgenic mice. These data indicated the importance of functional proteasome system in preventing the ALS development.

Amyotrophic Lateral Sclerosis and Fused in Sarcoma Protein

It was evidenced that genetic modifications such as angiogenin 3 (*ANG*), transactive response (TAR) DNA-binding protein

TDP-43 (*TARDP*), sarcoma/translated in liposarcoma and optineurin (OPTN) are linked to FALS. Ubiquitination of misfolded proteins is a pre-step in degradation by proteasome system. The accumulation of misfolded proteins in the hippocampus, neocortex and spinal cord is a pathologic feature of neurodegenerative diseases, TDP-43 protein is composed of glycine-rich C-terminal with two RNA-recognition motifs and it is the main pathologic manifestation for ALS (Wang et al., 2004). Its phosphorylation, ubiquitination and cleavage into two peptide fragments have been linked to the poor prognosis of ALS patients (Leigh et al., 1991; Okamoto et al., 1991; Neumann et al., 2006). It was found that ubiquilin 1 (UBQLN) (proteasome targeting cochaperone factor) binds to the ubiquitinylated TDP-43 aggregates and targets them either to autophagy or proteasomal degradation. The binding of the mutated form of TDP-34 (D169G) to UBQLN was greatly decreased in comparison with the wild-type TDP-43. More studies are required to confirm such hypothesis in the pathogenesis of ALS.

ALS has major similarities to the frontotemporal dementia (FTD) spectrum. FUS and TAR DNA- TDP-43 inclusions are detected in sporadic ALS (Deng et al., 2010). According to the literature, inclusions co-localize with ubiquitin similar to FTD. Moreover, VCP/P97, C9ORF72, and optineurin polymorphisms can produce FALS (Johnson et al., 2010; Maruyama et al., 2010; Deng et al., 2011; Renton et al., 2011). *TARDP* is localized in chromosome 1p36.2. The mutations in *TARDP* gene (p.Gly290Ala and p.Gly298Ser mutations) were found to be linked to the sporadic and FALS (Kabashi et al., 2008). The mutation either leads to gain- or loss-of-function in TDP-43, and may be essential in binding to hnRNPs (heterogeneous nuclear riboproteins) (Van Deerlin et al., 2008). However, the main molecular mechanism of ALS remains undetermined.

Amyotrophic Lateral Sclerosis and Ubiquilin-2

UBQLN2 disorders involved in the pathogenesis of different neurodegenerative disorders, as this protein regulates ubiquitinated protein degradation. Besides, UBQLN-2 mutations result in FALS, and UBQLN-2 accumulation co-localizes with skein-like inclusions (Deng et al., 2011). UBQLN-2 proteins contribute to the transfer of ubiquitinated proteins to proteasomes. The UBQLN-2 overexpression reduces PS1 and PS2 ubiquitination (Massey et al., 2004). The influence of ALS on lysosomal degradation has been confirmed in a previous study, as UBQLN proteins can increase the binding of early autophagosomes to the lysosomes (N'Diaye et al., 2009).

Amyotrophic Lateral Sclerosis and Optineurin

Optineurin (*OPTN*) was found to have three different types of mutations in familial and sporadic ALS. The heterozygous Glu478Gly missense mutation ubiquitin-binding region, homozygous Gln398X non-sense mutation and a homozygous deletion of exon 5 (Maruyama et al., 2010). Both missense and non-sense mutations prevented the inhibition of NF-κB

(Wagner et al., 2008; Maruyama et al., 2010). Glu478Gly missense mutation induces the accumulation of the mutated protein in the neurons and modulates the formation of inclusion bodies, resulting in a disturbance in the cell biological functions (Maruyama et al., 2010).

Amyotrophic Lateral Sclerosis and Cyclin F

Williams et al. (2016) performed exome-sequencing for locus chromosome 16p13.3 in order to discover new leads related to ALS pathogenesis. The authors discovered a missense mutation in *CCNF* gene (nucleotide A replaced by G, resulted in amino acid substitution Ser621Gly), which encodes the cyclin F in neuronal cells. Cyclin F (786 amino acid protein) contains F-box motif that recognizes and binds to SKP1 and CUL1 in order to form SCF E3 ligase complex (SKP1-CUL1-F-box protein) (D'Angiolella et al., 2013; Williams et al., 2016). The mutated cyclin F leads to abnormal ubiquitination and aggregation of ubiquitinated proteins such as TDP-43, forming ubiquitinated inclusion (Williams et al., 2016).

Amyotrophic Lateral Sclerosis and Neural-Precursor-Cell-Expressed-Developmentally-Down-Regulated-8

Ubiquitin-like protein Neural-precursor-cell-expressed-developmentally-down-regulated-8 (NEDD8) has a structure similar to ubiquitins and called Ub-like proteins. Ub-like proteins are classified into two groups according to the manner of protein conjugation; type 1 Ub-like proteins conjugate with the target protein in a way similar but not totally identical to the known ubiquitination mechanism such as NEDD8 and small Ub-related modifier (SUMO1), while type 2 Ub-like proteins have Ub-like protein structure with broad biological functions such Elongin B (subunit of the transcription factor B), Rad23 (Radiation sensitive), and Parkin (Parkinson Protein 2 E3 Ubiquitin Protein Ligase) (Tanaka et al., 1998).

NEDD8 immuno-reactivity was detected in different neurodegenerative diseases such as Parkinson disease (in LBs and Lewy neurites), multiple system atrophy (in ubiquitinated inclusions and oligodendroglial inclusions), AD (in neurofibrillary tangles), motor neuron disease (in ubiquitinated inclusions), and in triplet repeat diseases (in intranuclear inclusions) (Mori et al., 2005). Moreover, its immune-reactivity was also detected in other diseases such as alcoholic liver disease and astrocytoma (in Rosenthal fibers) (Dil Kuazi et al., 2003).

Signaling proteins and phosphoprotein array study in muscles of 36 ALS patients revealed that there are 17 differentially expressed proteins and phosphoprteins in ALS compared to normal muscle cells. In between, heat shock protein 90 (HSP90) (chaperone), and phospho-retinonlastoma (tumor suppressor, p-Rb at Ser780) were overexpressed, while cyclin-dependent kinase 4 (CDK4) and p-p53 at Ser392 were downregulated (Yin et al., 2012). The accumulation of P53 was detected in the nucleus of lumbar spinal cord of ALS patients. Moreover, the study showed that the immuostaining for p53 was also

positive for cell cycle regulators (pRb and E2F-1) and apoptotic proteins (Bax, caspase 8 and caspase 3). P53 stabilization is regulated by MDM2 via ubiquitin-proteasome machinery. ALS is characterized by dysfunction in ubiquitin-proteasome system and this may explain the stabilization of p53 and its translocation into the nucleus of the lumbar spinal cord. P53-MDM2 interaction could be a therapeutic target for improving the survival of ALS patients.

HUNTINGTON DISEASES

HD is a progressive hereditary neurodegenerative disorder caused by an autosomal dominant defective gene on chromosome 4 that encodes the huntingtin (HTT) protein, containing a repeating sequence of CAG at the N-terminus of HTT, a protein with an abnormally long polyglutamine (polyQ) sequence. In addition, amyloidogenic mutant huntingtin (mHTT) aggregates were implicated in progression of HD (Popovic et al., 2014). Generally, these neuronal aggregates containing N-terminal fragments of polyQ HTT are located in the striatum and in the cortex of HD patients; either in nuclear or in cytoplasmic regions of affected neurons (DiFiglia et al., 1997). Cognitive decline, behavioral abnormalities and involuntary movements accounted as marked hallmarks of HD; probably caused by both neuronal dysfunction and neuronal cell death; leading to a progressive decline in functional capacity, and ultimately death. Several factors have been associated with HD including alterations in calcium level, IGF signaling, vesicle transport, endoplasmic reticulum maintenance, and autophagy (Martin et al., 2015). Yet, there is no definite cure for HD, although several medications are prescribed to treat movement difficulties (Chorea Huntington) such as monoamine depletors (i.e., Tetrabenazine); or those targeting the atypical behavioral aspects of HD such as antidepressants [i.e., serotonin reuptake inhibitor (SSRI)] and antipsychotic drugs (i.e., Olanzapine) (Chen et al., 2012).

Various *in vitro* and *in vivo* studies ratified that dysfunction in ubiquitin metabolism contributes to the pathogenesis of HD, leading to the accumulation and aggregation of insoluble ubiquitin-containing mHTT (Bennett et al., 2007). Typically, HTT is ubiquitinated at amino acids K6, K9, and K15, resulting in its degradation and decreasing the toxicity of mHTT (Kalchman et al., 1996). The accumulation of K48-, K11-, and K63-linked ubiquitin chains in HD mouse models, and the brains from HD patients was shown to be a common feature of HD (Zucchelli et al., 2011). The fact that mHTT aggregates are abnormally enriched for ubiquitin and contain ubiquitin E3 ligases, confirms that the ubiquitination is a key factor in aggregate formation. Global changes in UPS, alike the accumulation of Lys48-, Lys63-, and Lys11-linked polyubiquitin chains associated with HD pathology (Bennett et al., 2007).

Ubiquitin-Proteasome System and Tumor Necrosis Factor Receptor Associated Factor 6

Tumor necrosis factor receptor associated factor 6 (TRAF6) is an E3 ubiquitin ligase and was found to be overexpressed in postmortem brains of HD patients. *In vitro* cultured cells, TRAF6 promoted the aggregate formation through mediating atypical ubiquitination of Lys6-, Lys27-, and Lys29-linked chains related to HTT. Both mHTT and TRAF6 were localized to insoluble protein fraction.

POLYPHENOLS IN NEURODEGENERATIVE DISORDERS

Various pharmacological agents have been studied and used to find suitable therapeutic interventions in neurodegenerative diseases; however, some defects have always been associated with such treatments, since the pathophysiology of such impairments is yet to be elucidated. A wide range of phytopharmaceuticals are being explored to improve the effects of commonly used drugs in the treatment of neurogenic disorders (Farzaei et al., 2018a), both via prophylactic and disease controlling approaches (Gorji et al., 2018). Natural products can also provide templates for the development of other drug compounds and to design new effective complex molecules (Babitha et al., 2014). Phytochemicals proven to possess potential neuroprotective effects and are able to protect the central nervous system (CNS) against neuronal injury (Kumar, 2006); hence people who consumed higher amounts of natural functional foods were found to show a lower risk for diseases caused by neuronal damage (Lobo et al., 2010).

PPs are the most abundant natural phytochemicals, capable of protecting neuronal cells in different *in vivo* and *in vitro* models through diverse intracellular targets. Various epidemiological and preclinical investigations confirmed the favorable effects of PPs in neurodegenerative diseases, primarily due to their antioxidant properties and their influence on stress response, mainly through nuclear factor erythroid 2-related factor (Nrf2) signaling, triggering the antioxidant defense machinery (Pandareesh et al., 2015; Farzaei et al., 2018b). In addition, polyphenolic compounds may exert neuroprotective effects involving phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/glycogen synthase kinase-3β (GSK-3β) (PI3K/Akt/GSK3β) neuronal survival pathway, through the N-methyl-D-aspartate (NMDA) receptors and by downstream signaling in hippocampus and cognitive deficits through tyrosine receptor kinase β (Trkβ) and brain-derived neurotrophic factor (BDNF) in hippocampus (Srivastava et al., 2018). Generally, natural compounds have shown inhibitory or therapeutic effects on neurodegerative disorders via biological effects such as antioxidant, anti-inflammatory, calcium antagonization, anti-apoptosis, and neurofunctional regulation (Choudhary et al., 2013).

Beside their free radical scavenger properties, the mechanisms by which polyphenolic compounds are able to counteract and prevent neurodegenerative diseases include: (1) anti-inflammatory activity through chromatin remodeling (modulation of both DNA methyl transferase and histone deacetylase activities) and alteration in the expression of related transcription factors such as NF-kB (Rahman and Chung, 2010), and dampening of microgliosis, astrogliosis, and glia-derived pro-inflammatory cytokines (Sundaram and Gowtham, 2012; Peña-Altamira et al., 2017; Sarubbo et al., 2017); (2)

improvement of mitochondrial function through stimulating the mitochondrial membrane potential and respiratory chain complex IV, enhancing the mitochondrial complex I–IV enzymatic potential, moderating the mitochondrial free radical production, and increasing endogenous antioxidant defense (Fiorani et al., 2010; Davinelli et al., 2013; Cai et al., 2015; de Oliveira et al., 2015) as well as mitochondrial biogenesis through activation of the AMPK/Sirt1/PGC-1α axis (Ayissi et al., 2014; Cao et al., 2014; de Oliveira et al., 2016; Valenti et al., 2016); (3) antioxidant activity through activation of Nrf2/ARE signaling pathway, increasing the expression of nerve growth factor, glial cell line-derived neurotrophic factor, BDNF, TrkA/B, activation of ERK1/2-CREB-BDNF and Akt/Glycogen synthase kinase 3β signaling pathways (Lin et al., 2010; Bagli et al., 2016; Moosavi et al., 2016; Martínez-Huélamo et al., 2017; Sanadgol et al., 2017).

Anthocyanins (Orhan et al., 2015), proanthocyanidins (Strathearn et al., 2014), stilbenes (Braidy et al., 2016), isoflavons (Devi et al., 2017), and curcumin (Hu et al., 2015), are among the most studied dietary phenolic compounds demonstrating protective effects against AD and PD, while there are also studies showing the potential of S-allylcysteine as organosulfur compounds (Farooqui and Farooqui, 2018) and isothiocyanates such as 6-methylsulfinylhexyl isothiocyanate (6-HITC) and sulforaphane (Giacoppo et al., 2015) to be active as neuroprotective dietary phytochemicals.

These herbal constituents seem to create their neuroprotective effects through mechanisms involving the activation of cellular antioxidant responses including activation of the Nrf2-mediated antioxidant response, stimulation of PGC-1α-mediated mitochondrial biogenesis, and alleviating neuroinflammation evoked by the activation of glial cells (de Rus Jacquet et al., 2017a). Several flovonoids like hesperidin, kaempferol, naringin, and epigallocatechin gallate (EGCG) have also been reported to show efficacy against 3-NP-induced neurotoxicity, which is an extensively used animal model for HD (Dey and De, 2015). Onjisaponin B and trehalose enhanced autophagy as one of therapeutic approach against toxic intracytosolic aggregate-prone mHtt protein in HD (Dey and De, 2015).

A number of PPs can modulate neural toxicity or loss by means of their antioxidant properties. For example, it was shown that a synthesized mitochondria-targeted curcumin (MTC), triphenylphosphonium cation-curcumin, reduced free radicals-induced neurotoxicity and mitochondrial impairments *in vivo* and *in vitro* (Hasan et al., 2019a). Similarly, curcumin and MTC showed protective effects against oxidative damage and cerebellar toxicity induced by rotenone *in vivo*, mainly through decrease of lipid peroxidation, and nitric oxide levels, and reduction of glutathione, SOD, and catalase activities, while enhancing the acetylcholine esterase activity (Hasan et al., 2019b).

Beside flavonoids, various non-flavonoid antioxidant phytochemicals like α-mangostin, curcumin, lycopene, and melatonin, have been reported as effective natural compounds in different HD models (Choudhary et al., 2013). Considering the role of oxidative stress and chronic inflammation in the ALS pathophysiology, natural compounds targeting such stressors are supposed to be effective alone or in combination with other natural/chemical substances to find new therapeutic approach for ALS management (Nabavi et al., 2015).

EGCG, quercetin, quercitrin, and curcumin have been found to be effective in ALS models (Koh et al., 2006; Ip et al., 2017). A 12-month, double-blind, randomized, placebo-controlled study on ALS patients, demonstrated that nanocurcumin combined with riluzole improved survival rate during the trial (Ahmadi et al., 2018).

Polyphenols, Ubiquitin–Proteasome, and Neurodegenerative Diseases

PPs directly or indirectly interfere with the cellular protein degradation systems including the chaperone-mediated autophagy; the ubiquitin–proteasome degradation pathway; and the lysosome-autophagy system, by eliminating the misfolded and damaged proteins. The accumulation of insoluble protein aggregates is a common mark of neurodegenerative diseases, making PPs a great interest for therapeutic strategies (Hajieva, 2017). On one hand, proteasomal inhibition by PPs would be undesirable in neurodegenerative disorders, and in the other hand, proteasome stimulation and reduction of protein degradation by proteasome inhibitors have shown beneficial consequences and were found to be presumably neuroprotective (del Rosario Campos-Esparza and Adriana Torres-Ramos, 2010; de Rus Jacquet et al., 2017b).

PPs and their derivatives have been shown to inhibit UPS (Nabavi et al., 2018a), yet, a number of limitations have impeded their clinical applications. PPs may target various components of this system through mechanisms involving proteasome inhibition, deubiquitinase activity and/or the activities of E1, E2, or E3, thereby, physiologically affecting the essential proteins and/or by effect on the protein substrates, leading to the imbalanced coordinated intracellular protein homeostasis and the consequent off-target effects (del Rosario Campos-Esparza and Adriana Torres-Ramos, 2010; Liu et al., 2015).

Aforementioned, several PPs were reported to act as proteasome-inhibitors, mainly through chymotrypsin-like activity (on both intracellular 26S and purified 20S proteasome) (Nam et al., 2001; Smith et al., 2002; Kazi et al., 2003; Marambaud et al., 2005; Chen et al., 2007a,b; Chang et al., 2015; Ding et al., 2018). Structure activity relationship studies showed that flavonoids with a hydroxylated B ring and/or unsaturated C ring are potent proteasome inhibitors, of which the carbonyl carbon on the C ring could be the site of nucleophilic attack on the proteasome β5 subunit (Chen et al., 2007a). Anthocyanins and anthocyanidins were reported to possess proteasome inhibitory effects, contributing to their neuroprotective activities (Dreiseitel et al., 2008). Several studies demonstrated that the proteasome inhibitory activities of green tea PPs, are responsible for its anticancer and neuroprotective assets (del Rosario Campos-Esparza and Adriana Torres-Ramos, 2010), for instance, EGCG and its analogs were shown to inhibit the chymotrypsin-like activity of the purified 20S proteasome *in vitro* (Nam et al., 2001; Smith et al., 2002). As an exception, curcumin exhibits a binary

function against proteasome. Curcumin at low concentrations activates the proteasome (Jana et al., 2004), while at high doses, the compound suppresses the proteasome activity by enhancing the accumulation of ubiquitinated proteins. In neuro 2a and Hela cells, curcumin inhibited the chymotrypsin, trypsin, and post-glutamyl peptidyl-like protease activity of the proteasome, decreased the free ubiquitin levels and increased the protein polyubiquitination (Jana et al., 2004). The neuroprotective effect of curcumin could also be explained by deubiquitination enzymes that specifically regulate the protein polyubiquitination, through cleavage of ubiquitin from ubiquitin-conjugated protein substrates, preventing molecular aggregation (Reyes-Turcu et al., 2009). Curcumin treatment reduced the activities of deubiquitination enzymes in HeLa cells (Si et al., 2007), also curcumin inhibited the ubiquitin isopeptidase activity (Mullally and Fitzpatrick, 2002). In a recent *in vitro* study, myricetin modulated endogenous levels of quality control E3 ubiquitin ligase E6-AP and reduced the misfolded proteins inclusions, resulting in the maintenance of proteostasis (Joshi et al., 2019).

A polyphenol-rich extract from elderflower was shown to suppress neurotoxicity elicited by PD-related symptoms in cortical astrocytes via Nrf2 stabilization and inhibition of Nrf2 degradation mediated by the ubiquitin proteasome pathway. Another way, down-regulation of UPS by elderflower polyphenols induces the Nrf2 activation through up-regulation of macroautophagy pathway (also called the lysosome–autophagy protein degradation pathway), leading to the Nrf2 stabilization (de Rus Jacquet et al., 2017b). Nrf2 is a transcription factor involved in regulating the expression of cellular antioxidant enzymes and the genes encoding cytoprotective proteins (Tambe, 2015). Up-regulation of the Nrf2-mediated cellular antioxidant response (i.e., increase in glutathione synthesis and glutathione metabolites levels), results in alleviation of neurodegeneration in PD (de Rus Jacquet et al., 2017b). Quercetin was shown to induce the expression of proteasome subunits by a similar mechanism (Kwak et al., 2003).

In AD brains, Aβ neurotoxicity has been shown to have an inhibitory impact on the activity of UPS (Tseng et al., 2008), compelling a decrease in proteasome activity. In HEK293 and neuro 2a cells transfected with human APP695, resveratrol promoted the intracellular degradation of Aβ in a way that total activity of the proteasome did not increase. This was proved where several proteasome inhibitors such as lactacystin, Z-GPFL-CHO, and YU101 significantly prevented the resveratrol-induced inhibition of Aβ activity, and the siRNA-directed silencing of the proteasome β5 subunit (Marambaud et al., 2005). In mouse model of early PD, an extract of mulberry fruits, rich in phenolic contents (i.e., flavonoids, anthocyanins, and arotenoids), down-regulated the expression of components such as α-SNCA and ubiquitin, also reduced neuronal toxicity; representing that the neuroprotective effect of this plant might be partially mediated by inhibition of the LBs formation in the brain. LBs is thought to trigger dopaminergic neurodegeneration in PD (Gu et al., 2017) (**Figure 4**).

Polyphenols/Ubiquitin-Proteasome System Interactions, Clinical Trials

Pharmacological activities of several phytochemicals in neurodegenerative diseases are extensively supported by preclinical and epidemiological studies, which some have shown the mechanistic potential of these compounds as the UP pathway inhibitors (Murakami, 2013). Previously stated, a variety of phenolic compounds have been characterized with their proteasome-inhibitory activity such as resveratrol, EGCG, curcumin, quercetin, chrysin, genistein, kampferol, myrycetin, luteolin, apigenin, gallic acid, ellagic acid, and tannic acid. However, few clinical trials were carried out on a limited basis. Up to date, curcumin and resveratrol are the most studied compounds followed by EGCG and genistein, alone or in combination with other conventional drugs.

Curcumin

Currently, 6 clinical trials related to the effects of curcumin on AD is being conducted (http://clinicaltrials.gov/ct2/results?term=alzheimer\pmand\pmcurcumin), of which 3 have been completed (4, 5, 6) and 2 studies are still in progress, whereas 1 study has unknown status (**Table 1**). In a pilot randomized clinical trial in China, 34 patients with a diagnosis of probable or possible AD were investigated in 3 subgroups including 4, 1 (compared with 3 g placebo), or 0 g curcumin (compared with 4 g placebo) once daily. They additionally received the standardized extract of gingko leaf (120 mg/day). Compared with the placebo, there was not any significant difference in cognitive function (as secondary outcome) or plasma isoprostanes iPF2α-III and plasma Aβ40 levels (as primary outcome) between 0, 1, and 6 months. Curcumin seemed to cause no major side effects in AD patients in this study (Baum et al., 2008).

In a double-blinded, placebo-controlled trial in the United States, a mixture of curcumin derivatives (2 and 4 g/day), consisting of curcuminoids, demethoxycurcumin, and bisdemethoxycurcumin was prescribed to the patients with mild-to-moderate AD for 24 weeks and an open-label extension to 48 weeks. No significant differences in cognitive function and in plasma or cerebrospinal fluid (CSF) biomarkers of AD (including Aβ40 and Aβ42 levels, and total tau and p-tau) were observed between curcumin and the placebo groups (Ringman et al., 2012).

A double-blind, randomized, placebo-controlled trial in Iran was designed to evaluate the safety and efficacy of nanocurcumin in ALS adults. Subjects with a definite or probable ALS diagnosis were received either nanocurcumin (80 mg/day) or placebo for 12 months. The primary outcomes were considered to be survival/death and any mechanical ventilation dependency. The authors found a considerable difference between the study groups survival. No major adverse events or drug adverse effects and death were reported (Ahmadi et al., 2018).

Another pilot randomized trial was carried out in Italy to investigate the efficacy of the higher dose of oral curcumin (600 mg/day, Brainoil) on clinical parameters and biochemical markers, in 42 ALS patients. The first 3 months of the study

FIGURE 4 | Polyphenols, ubiquitin–proteasome system and neurodegenerative diseases.
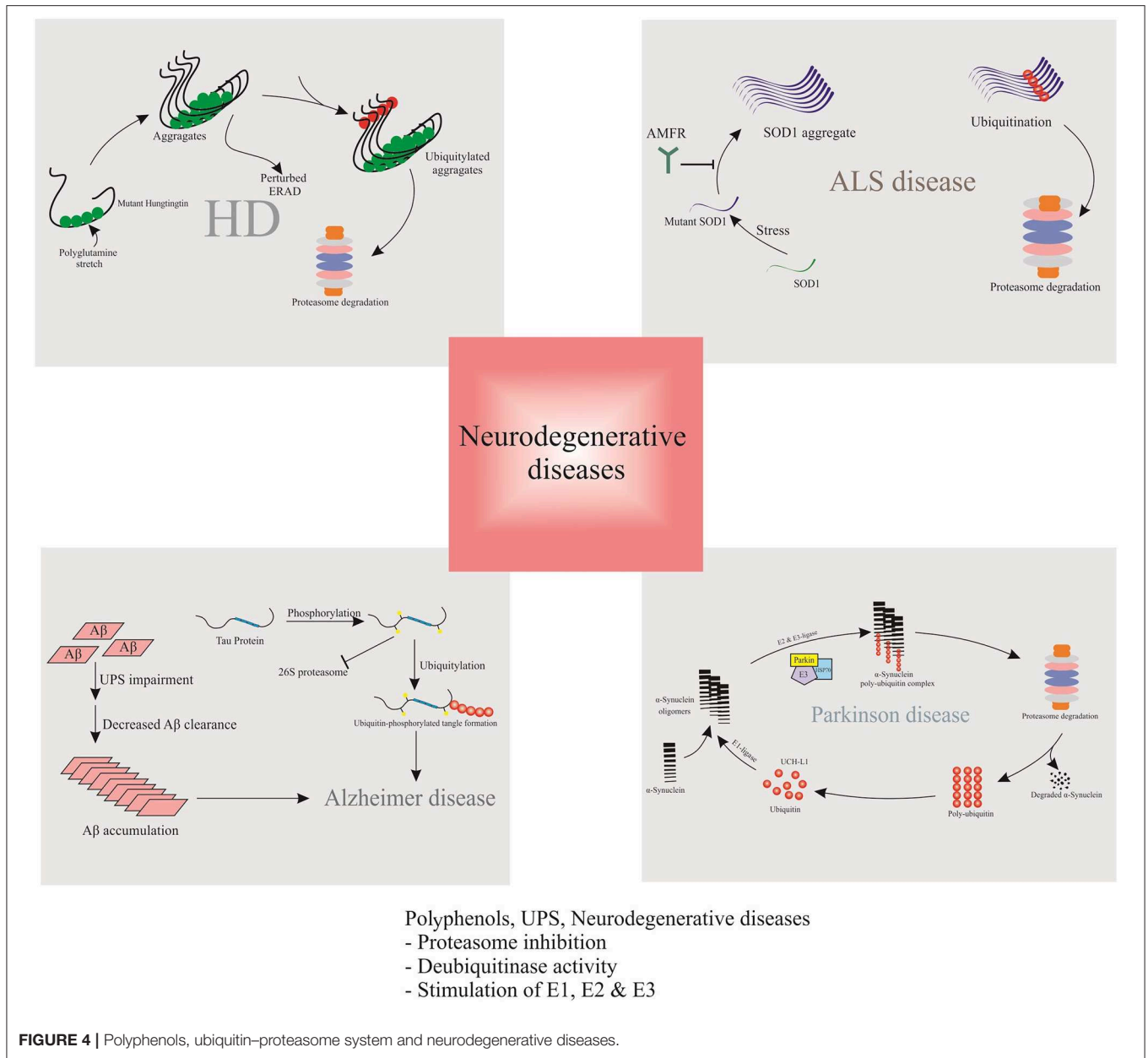
was double blind and the last 3 months were open-label. Clinical criteria were consisted of ALS Functional Rating Scale Revised (ALS-FRS-r), BMI, Medical Research Council (MRC) scale, and Maximum Handgrip Force (MHF) scale; and the plasma metabolic biomarkers (i.e., plasma values of Advanced Oxidative Protein Products (AOPPs), ferric reducing ability (FRAP), total thiols (T-SH) groups and lactate). Data were not significant, however, the authors concluded further studies is required due to disparity of results (Chico et al., 2018).

Resveratrol

There are 5 recorded clinical trials related to the effects of resveratrol on AD (http://clinicaltrials.gov/ct2/results?term$=$alzheimer\pmand\pmresveratrol), 3 studies have been

completed, 1 has been withdrawn and 1 is still active. Two clinical trials have reported that resveratrol altered several AD specific biomarkers with no major adverse effects in AD patients (Turner et al., 2015; Moussa et al., 2017). A phase 2 randomized, double-blind, placebo-controlled trial was performed in the United States, mainly to determine the safety, tolerability and pharmacokinetics of synthetic resveratrol (500 mg orally, once daily, increasing at 13 weeks intervals to a maximum of 1 g) in 119 individuals with mild to moderate AD for 52-weeks. They found that resveratrol was able to penetrate into the blood–brain barrier; likewise, the compound changed the AD biomarkers (Aβ40, Aβ42, tau, and phospho-tau) in the plasma and CSF. Plasma Aβ40 and CSF Aβ40 levels were found to be stabilized by resveratrol compared with a decrease in the

TABLE 1 | Clinical trials relevant to the phytochemicals with UPS inhibitory activity.

ID number (www.ClinicalTrials.gov)	Phase	Medication and dose	Duration	Number of subjects/Condition	Status	Country
NCT00164749	Phase 1,2	Curcumin 1 or 4 g/day (standardized ginkgo extract 120 mg/day)	6 months	34 Probable or possible AD	Published	China
NCT00099710	Phase 2	Curcumin C3 Complex® 2 or 4 g/day (1.9 or 3.8 g/day curcuminoids) [a]	24 weeks with an open-label extension to 48 weeks	36 Mild-to-moderate AD	Published	USA
NCT00595582	–	Curcumin 5.4 g/day (bioperine)	24 months	10 MCI or mild AD	Completed Results not available	USA
NCT01001637	Phase 2	Longvida® 4 or 6 g/day	2 months	26 Probable AD	Unknown	India
NCT01383161	Phase 2	Theracurmin[TM] 2.79 g/day (180 mg/day curcumin)	18 months	132 MCI	Active, not recruiting	USA
NCT01811381	Phase 2	Longvida Curcumin® (800 mg/day of curcumin)	12 months	80 MCI	Recruiting	USA
NCT01504854	Phase 2	Resveratrol 500 mg/day with dose excalation by 500 mg increments ending with 2 g/day	52 weeks	119 Mild-to-moderate AD	Published	USA
NCT00743743	Phase 3	Longevinex brand resveratrol supplement (resveratrol 215 mg/day)	52 weeks	50 Mild-to-moderate AD	Withdrawn	USA
NCT00678431	Phase 3	Resveratrol with glucose and malate	12 months	27 Mild-to-moderate AD	Completed Result not available	USA
NCT01126229	Phase 1	Resveratrol 300 mg/day or 1,000 mg/day	12 weeks	32 ≥65 years old	Completed Result not available	USA
NCT01219244	Phase 4	Resveratrol or omega-3 supplementation or caloric restriction	6 months	330 MCI	Recruiting	Germany
NCT01766180	-	ResVida (resveratrol 150 mg/day) alone or associated with Fruitflow [a]-II 150 mg/day	3 months	80 Subjects with memory impairment	Recruiting	USA
NCT02621554	Phase 2/Phase 3	Resveratrol (dose not reported)	12 months	60 ≥50 years Healthy or with subjective memory complaints	Recruiting	Germany
NCT02502253	Phase 1	Bioactive Dietary Polyphenol Preparation (BDPP) at low, moderate, and high dose	4 months	48 MCI	Recruiting	USA
NCT01982578	-	Genistein (60 mg BID)	180 days	50 AD	Unknown	Spain
NCT00205179	Phase 2	Soy isoflavones 100 mg/day; Novasoy®; (85% daidzin and genistin, as glycosides)	6 month	59 AD	Published	USA
NCT00951834	Phase 2, 3	Epigallocatechin-gallate (EGCG) with increasing doses (in months 1–3: 200 mg EGCG, months 4–6: 400 mg, months 7–9: 600 mg and months 10–18: 800 mg EGCG).	18 month	21 subjects in the early stages of AD	Completed Results not available	Germany
NCT01699711	Phase 2	9 mg/kg of EGCG, (in green tea extract standardized for EGCG)	12 month	84 DS	Published	Spain
NCT01662414	Phase 4	Soy protein (as placebo) vs. HMS 90® (whey protein) by the dose of 1 sachet (10 g) 2 times/day as add-on (adjuvant) therapy.	6 month	32 Idiopathic PD	Published	Thailand

(Continued)

TABLE 1 | Continued

ID number (www.ClinicalTrials.gov)	Phase	Medication and dose	Duration	Number of subjects/Condition	Status	Country
NCT02336633	–	Resveratrol (80 mg/j = 4 capsules/day)	12 month	120 HD	Recruiting	France
Not available	Pilot	Curcumin (600 mg/day, Brainoil) (for the first 3 months), followed by an open-label phase (for the last 3 months)	6 month	42 ALS	Published	Italy
Not available	–	Nanocurcumin (80 mg daily)	12 month	54 Subjects with definite or probable ALS	Published	Iran

AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington disease; DS, Down syndrome; ALS, Amyotrophic Lateral Sclerosis.

placebo group; it also stabilized CSF Aβ42 in the subset of patients with biomarker-confirmed AD (baseline Aβ42 < 600 ng/ml). Additionally, the brain volume loss was increased in resveratrol treated group (3 vs. 1%), probably due to anti-inflammatory activity of resveratrol. Totally, the results were not interpretable due to the study limitations; furthermore, no significant effects were found on clinical (secondary) outcomes. Resveratrol was found safe and well-tolerated with minor side effects such as nausea, diarrhea and weight loss (Turner et al., 2015).

Moussa et al., suggested that resveratrol treatment could preserve the integrity of the blood-brain barrier in AD patients with CSF Aβ42 < 600 ng/ml, declined the level of CSF MMP9 (matrix metallopeptidase 9), and elevated macrophage-derived chemokine (MDC), interleukin (IL)-4, and the fibroblast growth factor (FGF)-2 (Moussa et al., 2017).

Moreover, resveratrol enhanced the plasma MMP10 and decreased the pro-inflammatory makers including IL-1R4, IL-12P40, IL-12P70, TNF-α, and RANTES compared to the baseline values. It also attenuated the accumulation of Aβs in the brain with no alterations in CSF tau and p-tau. From clinical point of view, resveratrol improved cognitive and functional decline (mini-mental state examination (MMSE) and activities of daily living) during 12-months study. The authors concluded that resveratrol reduced CSF MMP9, modified neuro-inflammatory factors, and caused adaptive immunity (Moussa et al., 2017).

Another randomized, double-blind phase 3 study has been carried out on 27 participants with mild-to-moderate AD. The treatment group received resveratrol (unknown dose) with glucose and malate, delivered in grape juice. Cognitive measurements (the ADAS-Cog scale and Clinical Global Impression of Change (CGIC) scale) were used at follow up visits at months 3, 6, 9, and 12 months. Although this study was completed, results are unpublished to date (Zhu et al., 2018).

One randomized double-blind placebo controlled trial is already running to investigate the effect of resveratrol on 102 early affected HD patients in France (5≤UHDRS≤40). Subjects received either resveratrol at 80 mg or placebo for 1 year. Clinical outcomes and biological tolerance evaluated every 3 months. The primary measure is the rate of caudate atrophy after 1-year treatment.

Genistein

Despite promising pre-clinical data, there is no clinical trials on the applications of genistein for AD treatment. Up to our knowledge, only one trial was conducted. Genistein (60 mg) administration for 180 days changed the Aβ level in CSF of AD patients, besides, improved MMSE, ADAS-cog and the memory alteration test at determined intervals. Although, the study has passed its completion date, but the results are not available (Yassa et al., 2009).

Soy Isoflavones

There is a pilot randomized clinical trial examining the effect of soy isoflavones on cognitive function in old men and women over the age of 60 diagnosed with AD. Sixty-five participants were randomized to treatment for 6 months by soy isoflavone (100 mg/day; 85% daidzin and genistin as glycosides), or matching placebo capsules. No significant differences were observed between isoflavones treated group and placebo group or between the genders in terms of cognition outcomes, and self-report of mood symptoms. Besides, it was found that cognitive functions (speed dexterity and verbal fluency) were associated with equal levels (Gleason et al., 2015). A double-blind, placebo-controlled, Phase IV trial was designed in Thailand to compare HMS 90® (an immune system stimulant) vs. soy protein (as placebo), by the dose of 1 sachet (10 g) 2 times/day as adjuvant therapy in 38 individuals with idiopathic PD. No significant clinical outcomes were observed in biomarkers of oxidative stress (glutathione), plasma amino acids, and the brain function in both groups (Tosukhowong et al., 2016).

Epigallocatechin Gallate

The normalization of tyrosine phosphorylation regulated kinase 1A gene (Dyrk1A) and APP functions as therapeutic approaches for cognition improvement and slowing AD progression was investigated in a phase 2 randomized clinical study. Down syndrome (DS) patients received a daily oral dose of 9 mg/kg of EGCG, (in green tea extract standardized for EGCG) for 12 months. EGCG caused significant improvement in the adaptive behavior and brain-related changes in young adults with DS (de la Torre et al., 2016). In a phase 2 randomized placebo-controlled clinical trial, 21 patients over the age of 60 and in the early stages of AD received EGCG in an increasing manner

(in months 1–3: 200 mg EGCG, months 4–6: 400 mg, months 7–9: 600 mg, and months 10–18: 800 mg EGCG). ADAS-COG score, MMSE score, safety and tolerability, and the brain atrophy were assessed, although the study is completed but data are not available (https://clinicaltrials.gov/ct2/show/NCT00951834).

CONCLUSION AND FUTURE PROSPECTS

The unique involvement of UPS in malfunction of the nervous system encloses a broad range from drug abuse to neuroinflammation, making UPS an emerging topic in neurodegeneration and an important target for drug discovery. Since, UPS function is downregulated in vulnerable degenerating neurons in neurodegenerative diseases, thus, normal function of UPS assures a balanced regulation of misfolded protein degradation, which contributes to eliminate abnormal protein aggregates and to maintain the cellular protein homeostasis in the brain and neural network.

So far, a number of UPS regulators were developed. For example, cAMP phosphodiesterases inhibitors and UCHL1 that can modulate the brain cAMP-dependent protein kinase A (PKA)-cAMP response element binding protein (CREB) PKA-pCREB levels in AD subjects, resulting in enhanced protein degradation and synaptic functions (Cao et al., 2019). According to the collected data, a number of PPs are able to exert UPS inhibitory activity, mainly through chymotrypsin-like activity on both intracellular 26S and purified 20S proteasome. PPs interfere in many steps of degradation processes by means of proteasome inhibition, deubiquitinase activity, and stimulation of E1, E2, or E3, resulting in reduction of neurotoxicity, improvement of synaptic plasticity, and transmission, as well as enhanced neuronal survival. In this context, few clinical trials were carried out, mostly on a limited basis, however, the results are inconclusive and in most cases statistically insignificant. However, concerning PPs and their probable interaction with UPS, two hypotheses can be speculated; either their proteasomal inhibitory effects or their proteasomal stimulatory functions. PPs can induce ubiquitination which results in accelerating the elimination of damaged soluble proteins and degradation of short-lived regulatory proteins. Another way, inhibition of proteasomal activity by proteasome inhibitors i.e., PPs has been linked to synaptic plasticity.

Considering PPs and their roles in neuroprotection, curcumin, and resveratrol are the most studied polyphenolic compounds followed by EGCG and genistein, alone or in combination with other conventional drugs. Recently, it was proposed that UPS dysregulation, aberrant mRNA splicing, mitochondrial dysfunction, and excessive oxidative stress directly interplay with the process of neurodegeneration, thereby, future design of biomarkers and the drug development plans have to focus on concurrent targeting of multiple components and steps of neurodegenerative diseases (Tan et al., 2019). It is plausible that a combination of PPs and current drugs may improve the PPs therapeutic application for neuronal related destruction disorders. In this way, PPs offers considerable opportunity for development of specific therapeutics approaches via UPS, for particular groups of misfolded proteins. However, direct links and molecular mechanisms remain elusive and require to be addressed.

This is important to have a clear understanding of PPs molecular mechanism of action and their possible interplay with UPS. In addition, the upstream regulators or downstream targets of UPS have to be characterized, empowering researches to develop treatment strategies with more specificity and efficacy. Another question that has to be responded is whether the inhibition of UPS by PPs is more favorable for the neurodegenerative diseases or the stimulation of this system? Concerning neurodegeneration, further clinical interventions with greater sample size, proper duration, applicable formulations, and/or dosages should be designed to assess the potential efficacy of natural bioactive compounds as UPS inhibitors/regulators.

AUTHOR CONTRIBUTIONS

ZM, FE-S, NS, FG, MK, and AA contributed to the collection and/or assembly of data and interpretation, and the writing of the manuscript. SM, MA, and MF contributed to the provision of study material, conception and design, and final approval of manuscript. All authors have read and approved the manuscript.

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