We Are What We Eat: Ubiquitin–Proteasome System (UPS) Modulation Through Dietary Products

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Abstract

During lifetime, the molecular mechanisms that are responsible for cellular defense against adverse conditions such as oxidative and heat stress tend to be less efficient, thus gradually leading to the natural phenomenon of aging. Aging is linked to increased oxidative stress and is characterized by the accumulation of damaged macromolecules. The accumulation of oxidized and misfolded proteins is also accusable for various neurodegenerative pathologies that are linked to aging. Among self-defense mechanisms of cells, proteostasis network is responsible for the proper biogenesis/folding/trafficking of proteins and their elimination through proteolysis. The ubiquitin-proteasome system (UPS) is the major proteolytic mechanism that has attracted the interest of many researchers as an antiaging target. Interestingly, many natural compounds have been identified as potent UPS activators. Given that diet is a manageable environmental factor that affects aging, consumption of natural dietary products that may potentially enhance the UPS function, would contribute to increased health span and delayed onset or progression of age-related disorders. Herein, we summarize natural compounds and extracts derived from edible products that have exhibited antiaging and anti-aggregation properties and the beneficial properties have been linked to the UPS modulation.

Keywords

Ubiquitin–proteasome system (UPS) · Proteasome modulation · Aging · Age-related diseases · Dietary compounds

Abbreviations

Aβ	Amyloid β
AD	Alzheimer's disease
ALP	Autophagy-lysosome pathway
APP	Amyloid precursor protein
C-L	Caspase-like
CP	Core proteasome
CT-L	Chymotrypsin-like
DUB	Deubiquitinating enzymes/ deubiquitinases
D3T	3H-1,2dithiole-3-thione
EVOO	Extra virgin olive oil
GHE	Guarana hydroalcoholic extract
HD	Huntington's disease
HGPS	Hutchinson-Gilford progeria syndrome

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HSP	Heat shock protein
HTT	Huntingtin
NHDF	Normal human dermal fibroblasts
Nrf2	Nuclear factor (erythroid-derived 2)-like 2
PD	Parkinson's disease
PDMs	Polyphenol digested metabolites
PKA	Protein kinase A
PolyQ	Polyglutamine
RP	Regulated particle
UPS	Ubiquitin-proteasome system
T-L	Trypsin-like
6-OHDA	6-hydroxydopamine
18α-GA	18α-glycyrrhetinic acid

15.1 Introduction

Protein integrity is vital for the normal function of all cell types. To maintain a healthy proteome, cells have developed a protein quality control system which is crucial for cell metabolism and stress adaptation. The proteostasis network is responsible for: (a) protein synthesis, stabilization, folding mostly by chaperons of the heat shock protein (HSP) family and trafficking, and (b) protein degradation mainly through the ubiquitin–proteasome system (UPS) and the autophagy–lysosome pathway (ALP) [1, 2]. Molecular chaperons recognize misfolded protein species and if the repair is impossible, they cooperate with the proteolytic systems favoring the degradation of these proteins [3, 4]. Attenuation of proteostasis mechanisms is linked to aging and is considered as one of the hallmarks of aging [5, 6]. Moreover, impaired function of proteostasis has also been reported in various age-related disorders such as Alzheimer's (AD), Parkinson's (PD) and Huntington's (HD) diseases which are characterized by chronic expression of misfolded or aggregated proteins [7].

The average life expectancy has progressively elevated in the last decades. Subsequently, the development of age-related disorders has ensued this rapid increase. Aging and age-related neurodegeneration have been associated with increased oxidative stress but also with nutrients and their metabolites that may alleviate these toxic processes, playing a pivotal role in the battle against organismal time decline [8]. For example, a plethora of studies gives prominence to the antiaging properties of polyphenolic compounds (phenolic acids, flavonoids, stilbenes, lignans) [9]. Given that these substances mainly contribute to plant protection from adverse environmental conditions through their antioxidant activities, it is possible to be effective as antiaging factors in mammalian cells as well [10]. These compounds can be easily isolated from plants and are included in daily nutritional products like fruits, vegetables, and cereals.

Among the proteostasis mechanisms, the UPS system has been extensively investigated for its involvement in aging and age-related disorders [11]. Due to its capacity to degrade prone-to-aggregation proteins and oxidatively damaged proteins, UPS activation by natural or synthetic substances consists a desirable strategy against aging and aggregation-related disorders [12–14].

Herein, we review natural compounds that have been shown to positively affect the UPS and to exert beneficial properties against aging and age-related disorders. The reported substances can be found in edible natural products that we daily consume in the context of a normal nutrition or in dietary supplements.

15.2 The UPS System

The UPS is a key player for the degradation of short-lived, misfolded, and damaged proteins and under normal conditions it is involved in cell cycle progression, apoptosis, and cell proliferation, among others [15]. The proteasome is a large multi-subunit enzymatic complex that is the core of the UPS system catalyzing the ATP/ubiquitin-dependent and independent proteolysis (Fig. 15.1) [16, 17].

Ubiquitin is a conserved protein that modifies and tags proteins for degradation through the

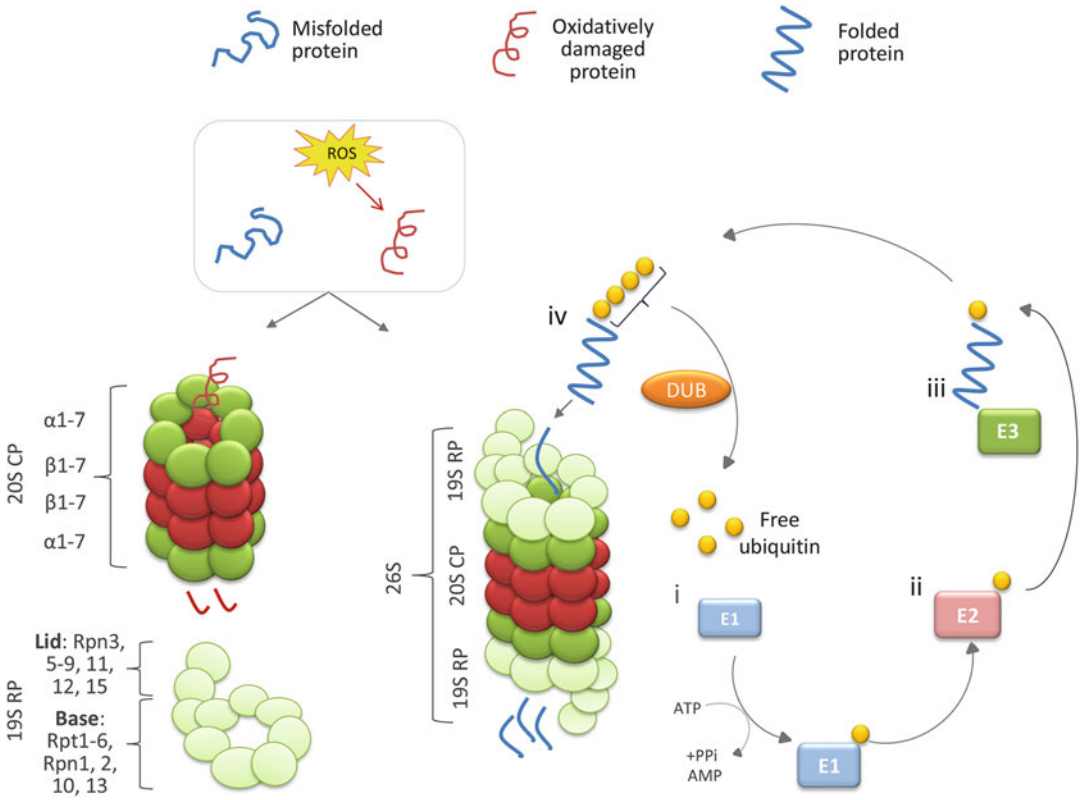


Fig. 15.1 The UPS system. Misfolded, oxidatively damaged or normally folded proteins are degraded in an ATP/ubiquitin-dependent or independent manner by the 26S and 20S proteasomes, respectively

ubiquitination process which includes three steps. (i) The E1 ubiquitin-activating enzyme activates the ubiquitin which (ii) is transferred to E2 ubiquitin-conjugating enzyme. Subsequently, the ubiquitin-charged E2 binds to (iii) the E3 ubiquitin-ligase enzyme which catalyzes the final step of ubiquitination. E3 ligase carries the substrate for degradation and thus ubiquitin is transferred to the substrate. This cycle is repeated and results in the poly-ubiquitination of the target protein which in turn (iv) is recognized and degraded by the 26S proteasome followed by the release of the ubiquitin molecules (through the action of deubiquitinases) to be reused [17].

The 26S/30S (referred to 26S proteasome hereafter) proteasome is formed following the capping of the 20S core proteasome (CP) by one (26S) or two (30S) 19S regulated particles (RP) and is mostly responsible for the degradation of ubiquitinated proteins. The 20S proteasome is composed of 28 subunits (14-α type and 14-β type). The 20S subunits form four rings with seven subunits of the same type per two rings in a barrel-like structure. The two inner rings are formed by β subunits (β1-7) and exert proteolysis through β1 (caspase-like/C-L), β2 (trypsin-like/T-L), and β5 (chymotrypsin-like/CT-L) subunits. The two outer rings are formed by α-type subunits and create a gated channel through which the protein substrate reaches the three catalytic centers [18]. The 19S RP consists of two sub-complexes: the lid that consists of nine subunits (Rpn3, Rpn 5-Rpn9, Rpn11, Rpn12, and Rpn15) and the base, which interacts directly with the 20S core and is composed of hexameric AAA-ATPases (Rpt1-6) and tetrameric non-ATP-ases namely Rpn1, Rpn2, Rpn10, and Rpn13. Rpn11 subunit possesses deubiquitination activity while Rpn3 and Rpn10

Table 15.1 Human genes that encode the 26S/30S and 20S proteasome subunits

20S CP				19S RP			
α subunits	Gene	β subunits	Gene	Base subunits	Gene	Lid subunits	Gene
α6	PSMA1	β1	PSMB6	Rpt1	PSMC2	Rpn3	PSMD3
α2	PSMA2	β2	PSMB7	Rpt2	PSMC1	Rpn5	PSMD12
α7	PSMA3	β3	PSMB3	Rpt3	PSMC4	Rpn6	PSMD11
α3	PSMA4	β4	PSMB2	Rpt4	PSMC6	Rpn7	PSMD6
α5	PSMA5	β5	PSMB5	Rpt5	PSMC3	Rpn8	PSMD7
α1	PSMA6	β6	PSMB1	Rpt6	PSMC5	Rpn9	PSMD13
α4	PSMA7	β7	PSMB4	Rpn1	PSMD2	Rpn11	PSMD14
				Rpn2	PSMD1	Rpn12	PSMD8
				Rpn10	PSMD4	Rpn15	SEM1
				Rpn13	ADRM1		

serve as ubiquitin receptors [19, 20] (Table 15.1). In the 26S proteasome ubiquitin-ATP-dependent proteolysis, proteins tagged with ubiquitin are recognized by Rpn3 and Rpn10 receptors and deubiquitinating enzymes (DUB) like Rpn11, USP14, and UCH37 remove the ubiquitin tag [21]. Subsequently, the base of the 19S complex unfolds the protein and promotes it to the catalytic centers for degradation [22]. On the other hand, the 20S proteasome has been suggested to promote the degradation of unfolded and oxidized proteins in an ATP-independent manner and does not require poly-ubiquitination of target proteins and 19S-mediated protein unfolding [16] (Fig. 15.1).

15.3 Proteasome Activation

Proteasome activation is feasible through genetic manipulation, post-translational modifications of specific proteasome subunits, or conformational alterations of the 20S core structure [14]. Treatment with specific compounds (including some that are part of our diet) can also modulate the expression and/or the function of the proteasome and they will be further presented below (Fig. 15.2).

The transcription factor Nrf2 (Nuclear factor (erythroid-derived 2)-like 2) is the key response factor against oxidative stress that regulates the induction of the expression of various antioxidant enzymes [23]. A cross talk between Nrf2 and the proteasome has been reported and several studies have shown that Nrf2 is able to modulate the 20S and 19S gene expression following oxidative stress or dietary Nrf2 modulation [24, 25]. Apart from Nrf2, Rpn4 is another transcription factor in yeast that has been shown to regulate proteasome biogenesis. Under normal conditions, Rpn4 is short lived and rapidly degraded by the proteasome. However, upon proteasome inhibition following proteotoxic stress, Rpn4 is stabilized to upregulate the expression of proteasome genes. With regard to genetic manipulation of the proteasome, we have previously demonstrated that stable overexpression of the β5 catalytic subunit or the hUPM1/POMP chaperone in human fibroblasts may induce all three proteasomal activities [26, 27], while PSMD11 (RPN-6 in *C. elegans*) has also been shown to be correlated with increased proteasome assembly and activity [123, 124].

Proteasome activation has also been succeeded through post-translational modifications such as phosphorylation. 26S upregulation has been achieved through cAMP-dependent protein kinase A (PKA) phosphorylation of the Rpt6 proteasome subunit [28]. Moreover, PKA-mediated phosphorylation of Rpn6 has been shown to enhance the degradation of ubiquitinated proteins [29]. Additionally, inhibition of the proteasome deubiquitinases such as USP14 and UCH37 resulted in elevated proteasome activities [30]. Finally, various peptides and compounds have been shown to favor proteasome function through conformational alterations that mainly affect the α-gated channel of the 20S core. Molecules that modulate 20S and/or 26S proteasome function are known as gate-openers or stimulators [14].

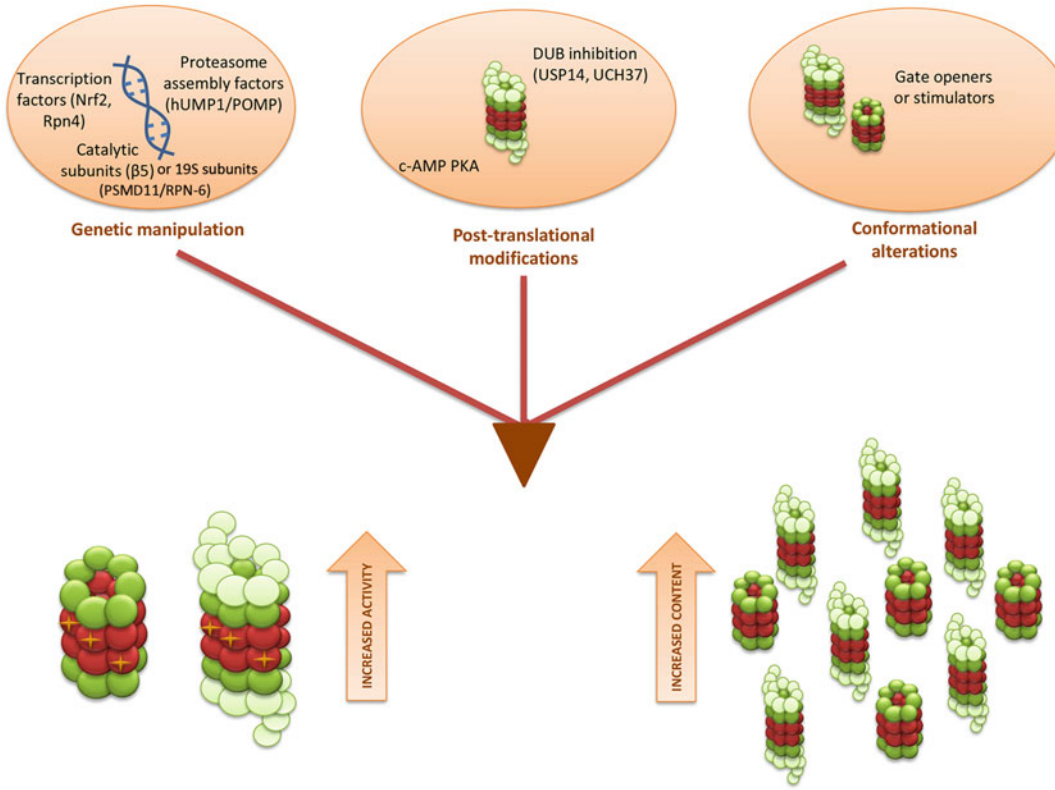


Fig. 15.2 Proteasome activation. Increased proteasome activity or content may occur through genetic manipulation, post-translational modifications, and conformational alterations. Natural or synthetic compounds can modulate proteasome activity and function either directly as stimulators or through modulation of molecules responsible for proteasome activation

15.4 UPS Modulation in Aging and Neurodegenerative Diseases

Aging is a natural decline of the organism and its function during lifetime affects, in several rhythms, almost whole animal and plant kingdoms. This natural process is characterized by the attenuation of self-defense mechanisms and the decline of homeostatic mechanisms. Impairment of proteostasis has been associated with aging and results in reduced capacity of cells to repair misfolded or damaged proteins or to remove them through degradation pathways [31]. Proteasome activation has been shown to decelerate aging in vivo and in vitro [32]. The accumulation of misfolded proteins also characterizes many neurodegenerative disorders that are linked to aging such as AD, HD, PD, and Hutchinson–Gilford progeria syndrome (HGPS).

AD is the most common cause of dementia and is characterized by loss of synaptic connections and brain atrophy. The accumulation of amyloid β (Aβ) plaques and hyper-phosphorylated Tau protein in neurofibrillary tangles are distinctive AD features [33]. Aβ is formed by the Amyloid Precursor Protein (APP) when the latter is cleaved by β- and γ-secretases. The proteasome is one of the major agents for Aβ metabolism, albeit the Aβ aggregates lead to proteasome impairment resulting in accumulation of aggregates in a vicious cycle [34]. Additionally, the E3 ubiquitin ligase HRD1 and the deubiquitinase UCHL-1 are downregulated during AD further highlighting the importance of UPS restoration in this disorder [35, 36].

Huntingtin (HTT) is the most involved protein in HD pathogenesis. Mutations in *HTT* gene are related to expansion of the CAG triplet resulting in a polyglutamine (polyQ) tract in the N-terminus of the HTT protein [37]. Like in other proteinopathies, there is evidence of the UPS implication in HD. Mutations in ubiquitin UBB^{+1}, PARKIN, NHLRC1 (an E3 ubiquitin ligase), and reduction of E1 and E2 ubiquitin enzyme activities along with 26S proteasome inhibition by HTT are characteristic alterations that lead to the UPS impairment in HD [38, 39].

PD is characterized by the accumulation of Lewy bodies (eosinophilic intracytoplasmic inclusions); α-synuclein is the main component [40]. α-synuclein has been shown to impede both the 20S and 26S proteasome function [41]. Moreover PARKIN, an E3 ligase, is the second most involved protein in PD pathology. PARKIN has been shown to enhance the interaction between 19S proteasome subunits underlining the importance of this ligase on the 26S proteasome activation [42]. PARKIN is affected by Lewy bodies that along with PARKIN mutations result in the degradation impairment observed in PD [43, 44].

Finally, progeroid syndromes are genetic conditions characterized by premature aging. Given that aging is accompanied by impairment of proteostatic mechanisms subsequently the UPS may also affect this type of syndromes. HGPS is a genetic condition in which a point mutation in the *LMNA* gene is observed. There are not many studies referring to UPS implication in HGPS; however, the downregulation of β5 and β7 proteasome subunits and reduction of CT-L proteasome activity have been reported [45]. Therefore, the UPS also appears as an attractive target against HGPS.

15.5 UPS and Diet

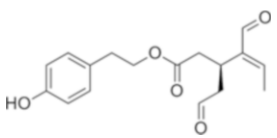
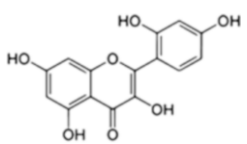
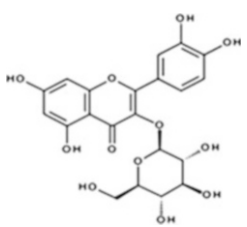
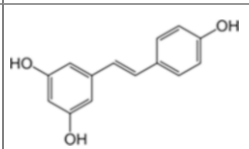
Several compounds have been shown to induce the UPS expression and/or function and thus to affect the progression of aging and age-related disorders. These compounds are summarized in the following sections and in Table 15.2.

15.5.1 Aggregation-Related Disorders

Well known for its stimulant activity on the central nervous system, **guarana** (*Paullinia cupana)* is consumed widely in Brazil in high-energy drinks and dietary supplements. Guarana compounds such as polyphenols, caffeine, and other methylxanthines have been associated with its beneficial biological properties which include antioxidant, antimicrobial, and chemophylactic activities in carcinogenesis [75]. Moreover, guarana powder has been shown to prevent Aβ aggregation in human neuronal-like cells while guarana water extract reduced the formation of polyQ aggregates expressed in *C. elegans*, suggesting a beneficial effect in AD and HD, respectively [76, 77]. According to a recent study, treatment with guarana hydroalcoholic extract (GHE) increased proteasomal and lysosomal activities and reduced intracellular ROS in *C. elegans*. It was also demonstrated that GHE eliminated the toxic phenotypes associated with protein misfolding and accumulation in nematode models of HD and AD. All the data above suggest the contribution of protein degradation mechanisms in GHE-mediated protection against polyQ protein aggregation and Aβ-induced toxicity [46].

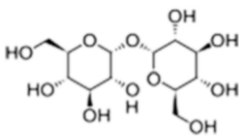
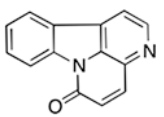
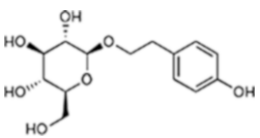
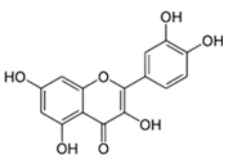
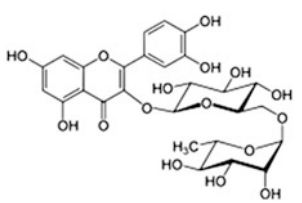
Numerous studies have extensively investigated the pivotal role of the Mediterranean Diet in the prevention of a wide range of age-related pathological conditions [78]. The extra virgin olive oil (EVOO) is one of the most characteristic components of the Mediterranean Diet and it has attracted the interest of many researchers due to its antioxidant and antiaging properties while many of EVOO's ingredients have been proposed as nutraceuticals against AD disease [79, 80]. **Oleocanthal** is one of the EVOO's phenols responsible for its bitter and pungent taste. Many studies demonstrated the potential neuroprotective and anti-aggregation effects of oleocanthal [81–83]. According to a recent study, oleocanthal upregulated the expression of *PSMD1* and *PSMB4* subunits in neuron-like SH-SY5Y cells under stress and normal conditions, suggesting the involvement of oleocanthal in the degradation of misfolded proteins rather than oxidized ones. Moreover, oleocanthal increased

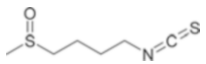
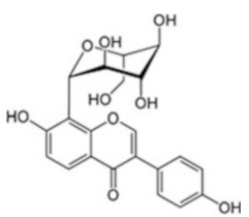
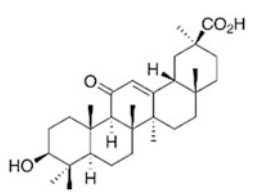
Table 15.2 Natural compounds/extracts that trigger UPS activation and affect aging and/or age-related disorders

Natural compound/ extract	Structure	Source	UPS target	Model	Disorder	References
Guarana hydroalcoholic extract (GHE)[a]		*Paullinia cupana*	CT-L activity	*C. elegans* (CL2006, CL4176, AM141)	AD/HD	[46]
Oleocanthal		Extra virgin olive oil (EVOO)	*PSMD1, PSMB4*	SH-SY5Y cells	AD	[47]
Morin		Leaves of *Psidium guajava* (guava tea), white mulberry and red wine	26S proteasome	APP695-transfected SH-SY5Y cells	AD	[48]
Isoquercitrin		*Mangifera indica* (mango), leaves of *Annona squamosa* and *Camellia sinensis*	26S proteasome	APP695-transfected SH-SY5Y cells	AD	[48]
Resveratrol		Blueberries, raspberries, peanuts, the skin of grapes, red wine, cocoa and various other herbs	Aβ proteasome-dependent reduction	APP695-transfected HEK293 cells	AD	[49–51]
			CT-L activity, UBA-1	*C. elegans* (CL2006)		
			T-L activity	Mouse (3xTg-AD) (cerebral cortex)		

(continued)

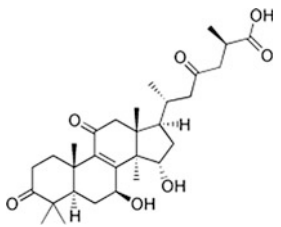
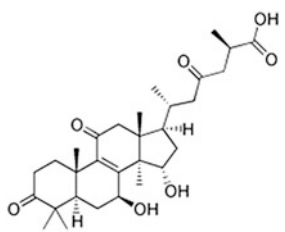
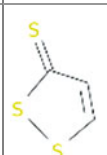
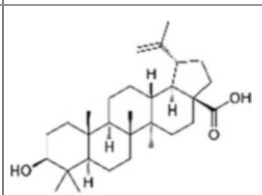
Table 15.2 (continued)

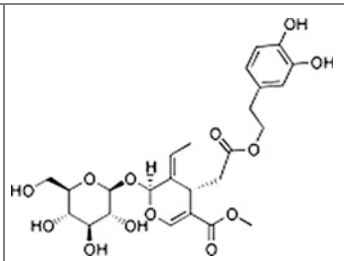
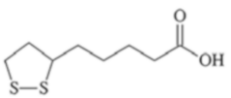
Natural compound/ extract	Structure	Source	UPS target	Model	Disorder	References
Trehalose		Honey, mushrooms, lobsters, shrimps, wine	CT-L activity	Glial cultures from R6/1 mouse model of HD	HD	[52]
			CT-L activity	HD human fibroblasts		[53]
Canthin-6-one		Extract of many plants including *Zanthoxylum chiloperone*, *Eurycoma longifolia* and *Aerva lanata*	CT-L activity, *Psmd1*	PC12 cells	PD	[54]
Salidroside		*Rhodiola rosea*	PARKIN, UCH-L1, CT-L activity	A30P α-synuclein-transfected SH-SYS5 cells	PD	[55]
Quercetin		Variety of widely consumed products including green tea, honey, red wine, and onions	*uba-1*, *ubq-1*, CT-L activity	*C. elegans* (CL2006)	AD	[56]
			CT-L activity	APP695-transfected SH-SY5Y cells		[57]
			CT-L activity	HFL-1 cells	Aging	[58]
			CT-L activity	mHTT-transfected Neuro2a cells	HD	[59]
Rutin		Variety of plants including citrus fruits	CT-L activity	APP695-transfected SH-SY5Y cells	AD	[57]

Sulforaphane		Cruciferous vegetables	CT-L activity, T-L activity, C-L activity	mHTT-transfected HEK293 cells	HD	[60]
			CT-L activity, PSMC2	Fibroblasts from patients with HGPS	HGPS	[61]
			CT-L activity	hESCs (human embryonic stem cells)	Aging	[62]
Polyphenol digested metabolites (PDMs) from leaves and fruits of *Arbutus uneda*		*Arbutus unedo* (strawberry tree)	HRD-1, proteasome function	Yeast cells transformed with α-synuclein	PD	[63]
Ginkgo biloba extract EGb761		Ginkgo biloba	*PSMB6, PSMB6, PSMB7*	mHTT-transfected HEK293 cells	HD	[64]
Puerarin		*Pueraria lobata*	CT-L activity	MPP^+-treated SH-SY5Y cells	PD	[65]
18α-glycyrrhetinic acid (18α-GA)		*Glycyrrhiza radix*	CT-L activity	*C. elegans* (CL2006, CL4176, CL2331)	AD	[66]
			CT-L	SH-SY5Y cells exposed to 7PA2-conditioned medium		
			CT-L activity, T-L activity, PBS-5, PAS-1-7, RPT-6	*C. elegans*	Aging	[66, 67]
			CT-L activity, T-L activity, C-L activity	HFL-1 cells		

(continued)

Table 15.2 (continued)

Natural compound/ extract	Structure	Source	UPS target	Model	Disorder	References
Ganoderic acid DM		Ganoderma mushrooms	Proteasome function	T-REx293 expressing Aβ42-EGFP	AD	[68]
Polysaccharide 5		*Rubia cordifolia* L.	Proteasome function	T-REx293 expressing Aβ42-EGFP	AD	[68]
3H-1,2dithiole-3-thione (D3T)[a]		Cruciferous vegetables	CT-L activity, T-L activity, C-L activity, PSMA1, PSMA4, PSMB3, PSMB5, PSMB6	Mouse	AD	[69]
Betulinic acid[a]		Many plants including *Betula pubescens*, *Ziziphus mauritiana* and *Prunella vulgaris*	CT-L activity	Purified proteasome	AD	[70]

Oleuropein		Green olives, olive leaves and EVOO	CT-L activity, T-L activity, C-L activity	IMR90, W138 cells	Aging	[71]
Lipoic acid		Broccoli, spinach, tomatoes and brussels sprouts	CT-L activity, PSMB5	NHDF cells	Aging	[72]
Bee pollen extract		Bee pollen	CT-L activity	HFL-1 cells	Aging	[73]
Zinc		Plethora of natural edible products	CT-L activity	Humans (population study)	Aging	[74]

[a]Compounds that have demonstrated anti-aggregation properties, but the association, if there is any, between their potency to act as proteasome activators and their contribution in protection against age-related disorders has not been studied yet

HSP90 levels, a chaperone that is essential for proteasome integrity and function [47, 84, 85].

Morin is a flavonol present in guava leaf tea (*Psidium guajava*), white mulberry (*Morus Alba L.*), and red wine. It is known for its antioxidant activity as well for its antiapoptotic and neuroprotective properties [86, 87]. Regarding its neuroprotective effects in AD, morin restricted β- and γ-secretase activities to impede Aβ aggregation as well as to disaggregate preformed fibrils and to act against H_2O_2-induced stress in APP695-transfected SH-SY5Y cells. In the same cell line, morin positively affected the 26S proteasome activity under H_2O_2 stress conditions. The same results were also produced by another flavonoid namely **isoquercitrin** [48].

The potential therapeutic properties of **resveratrol** including life span extension, neuroprotection, and cytoprotection, foreshadow the potential contribution of this polyphenol in age-related disorders [88, 89]. Resveratrol's effects on neurodegenerative disorders have been studied both in cellular and organismal level in models of AD; the effects on UPS among their positive outcomes have also been investigated [90]. For instance, in APP695-transfected HEK293 cell line, resveratrol reduced Aβ levels through proteasomal degradation [49]. The same phenotype was reported in *C. elegans*; treatment with resveratrol reduced Aβ aggregates in CL2006 strain which expresses the human Aβ1-42 and paralyzes as Aβ aggregates accumulate [91]. Reduced Aβ aggregates have also been linked to proteostasis factors including UBA-1 (the only ubiquitin-activating enzyme in *C. elegans*) and enhanced proteasome activity [50]. Resveratrol was also shown to activate the brain proteasome function in the 3xTg-AD mouse model. Moreover, resveratrol administration enhanced the levels of neprilysin, an amyloid-degrading enzyme and diminished the levels of the amyloidogenic secretase BACE-1 [51]. On top of these effects, the already known effect of resveratrol on deacetylase SIRT1 [92] seems to dictate a preferential degradation of phosphorylated-Tau through enhanced deacetylation of Tau [51]. The abovementioned biochemical alterations led to ameliorated cognitive behavior and function. Natural sources of resveratrol are blueberries, raspberries, peanuts, the skin of grapes, red wine, cocoa and various other herbs [93].

Trehalose is a disaccharide that is characterized as an autophagy enhancer [94]. During the last decades, many studies have reported the longevity effects of trehalose and its neuroprotective properties against HD [95]. In vivo experiments with mouse models of HD showed that trehalose administration reversed many aspects of pathological phenotype caused by polyQ aggregates [96]. In HD human fibroblasts, trehalose increased proteasome activities and decreased HTT protein levels [53]. Similar results were observed in glial cultures from R6/1 mice [52]. Trehalose is found naturally in honey, mushrooms, lobsters, shrimps, wine, and other edible products.

Canthin-6-one is a natural derived alkaloid that can be isolated by many herbs including the edible plant *Aerva lanata*. In PD cellular models (PC12 cells), canthin-6-one promoted α-synuclein degradation through the UPS. Specifically, this alkaloid promoted the expression of *Psmd1* gene by activating PKA, subsequently favoring the UPS activation [54].

Salidroside is a glycoside with antiaging, antioxidant, and neuroprotective properties. In SH-SY5Y cells treated with 6-hydroxydopamine (6-OHDA), salidroside alleviated pSer129-α-synuclein burden. Additionally, in the same PD model salidroside elevated the protein levels of PARKIN and UCH-L1 which are two of the most involved constituents of UPS in PD. Free ubiquitin protein levels were also increased due to salidroside treatment along with the 20S proteasome activity (CT-L activity). Moreover, treatment with salidroside enhanced 20S proteasome activity in SH-SY5Y cells transfected with A30P α-synuclein [55]. The herb *Rhodiola rosea* is the main source of salidroside. *Rhodiola rosea* is consumed in the form of tea, made from the roots of the plant and it has been used as an antiaging herb in traditional Chinese medicine.

Quercetin is a flavonoid found in many edible products like green tea, onions, and red wine.

Many studies reveal the positive outcome of quercetin in AD in vivo and in vitro [56]. In CL2006 transgenic strain of *C. elegans*, quercetin was able to reduce Aβ aggregates and the downstream paralysis phenotype. Among the defense mechanisms, quercetin promoted the UPS activation. Restriction of *uba-1* and *ubq-1* expression hindered the protective effects of quercetin against paralysis. The same research group observed enhanced proteasome activity in CL2006 animals treated with quercetin [56]. Proteasome activation by quercetin was also observed in APP695-transfected SH-SY5Y cells [57]. The same action was also revealed for **rutin**, a flavonoid mostly derived from citrus fruits that has the potential to prevent Aβ aggregation [97]. Both quercetin and rutin target agents related to proteasome activation, like Nrf2 [98]. Finally, in an HD cell line model, quercetin eliminated mHTT aggregates through proteasome activity enhancement [59].

Sulforaphane is an organic compound mainly found in many dietary products like onions, broccoli, cherries, and red grapes as well as in edible products like green tea and red wine. Through its strong antioxidant activity, sulforaphane exerts protective effects against neurodegenerative diseases [99, 100]. In murine neuroblastoma cells, sulforaphane enhanced proteasome activity via the Nrf2 transcription factor leading to elevated expression of proteasome subunits and thus to resistance against oxidative stress [25]. In an HD cellular model (mHTT-transfected HEK293 cells) treatment with sulforaphane enhanced mHTT degradation by the proteasome [60]. Additionally, sulforaphane was also able to induce proteasome activation in fibroblasts derived from patients with HGPS and improved the growth rate of these cells. In the same study, increased levels of HSP27 protein were also reported; sulforaphane has been shown to enhance proteasome activity through upregulation of HSP27 [61, 101].

As mentioned above polyphenols exhibit antioxidant and anti-aggregation activities. Interestingly, a recent study revealed the implication of **polyphenol digested metabolites** (PDMs) in PD [63]. PDMs from leaves and fruits of *Arbutus unedo* limited α-synuclein aggregates in a yeast model of PD through proteostasis network modulation, including proteasome elevated activity. Moreover, PDMs influenced the transcription levels of HRD-1, an ubiquitin ligase which is induced by unfolded protein response (UPR). HRD-1 recognizes and ubiquitinates misfolded proteins in ER favoring their degradation through the proteasome indicating a cross talk between the UPR and the UPS in the clearance of α-synuclein by PDMs.

Many phenolic acids and flavonoid compounds such as myricetin, quercetin, and kaempferol along with terpenes attribute to **Ginkgo biloba extract** strong antioxidant properties [102]. Treatment of mHTT-transfected HEK293 cells with Ginkgo biloba extract EGb761 was able to decrease the amount of poly-Q proteins. Accordingly, it was reported that EGb761 promotes proteasome activation and elevated transcript levels of *PSMB5*, *PSMB6*, and *PSMB7* subunits [64].

Puerarin is mainly isolated from *Pueraria lobata* and belongs to the isoflavone family. Beverages made by roots of *Pueraria lobata* contain a small number of isoflavones including puerarin. Many studies reveal the positive effects of puerarin in neuronal survival and cytoprotection in PD organismal and cellular models [103, 104]. In 1-methyl-4-phenylpyridinium (MMP^+)-treated SH-SY5Y cells, treatment with puerarin increased CT-L activity and lowered the amount of α-synuclein and ubiquitin-conjugated proteins, suggesting the implication of the UPS in puerarin positive results in PD [65].

18α-glycyrrhetinic acid (18α-GA) is a triterpenoid isolated from *Glycyrrhiza radix*. We have shown that 18α-GA enhanced proteasome activity and function through elevated protein expression of PBS-5, PAS-1-7 and RPT-6 subunits that are orthologs of PSMB5, α-subunits and Rpt-6 proteasome subunits, respectively in *C. elegans*. In the same study, 18α-GA was able to promote deceleration of the paralysis phenotype in a proteasome-dependent manner in nematode models of AD [66]. 18α-GA has been shown to enhance

proteasome activity through the induction of Nrf2 transcription factor in human primary cells or its ortholog, namely SKN-1, in *C. elegans* [66, 67]. Finally, in the same study 18α-GA reduced Aβ toxicity in SH-SY5Y cells while parallel proteasome inhibition abolished this effect.

Ganoderic acid and **polysaccharide 5** isolated from Ganoderma mushrooms and the plant *Rubia cordifolia L.*, respectively, were shown to induce Aβ clearance through the proteasome in T-REx293 embryonic kidney cell line expressing Aβ42-EGFP [68].

Finally, there are two natural compounds that were shown to possess anti-aggregation properties and have also been shown to modulate the UPS, but the association, if there is any, between their potency to act as proteasome activators and their contribution in protection against aggregate accumulation has not been studied yet. **3H-1,2dithiole-3-thione** (D3T) can be found in cruciferous vegetables. In a recent study, treatment of a mouse model of AD (Tg2576) with D3T markedly decreased the levels of insoluble Aβ40-42 and enhanced the expression of Nrf2 [105]. Interestingly, D3T has been previously revealed to elevate the 26S proteasome activation and increase the expression of multiple proteasomal subunits in an Nrf2-dependent manner [69]. Whether the Nrf2-mediated proteasome activation is responsible for the protection against Aβ-toxicity remains to be elucidated. Last but not least, **betulinic acid** is a triterpenoid present in a plethora of plants and has been studied for its neuroprotective effects [106]. Betulinic acid has been reported as stimulator that enhances 20S proteasome activity [70]; the link between betulinic acid action as proteasome stimulator and the neuroprotection that it exerts is still not investigated.

15.5.2 Aging

Oleuropein is a phenolic compound found in high amounts in green olives, olive leaves, and EVOO. Oleuropein effectively exerted antiaging activity and enhanced proteasome function suggesting for the first time that proteasome activators are interesting targets for the development of antiaging agents. More specifically oleuropein extended the life span of IMR90 and W138 human primary embryonic fibroblasts and increased CT-L, C-L, and T-L activities. Potential conformational changes of the proteasome structure by oleuropein were suggested to be responsible for the observed proteasome enhancement [71].

Quercetin is not only efficient against age-related disorders, but it positively affects the process of aging. Quercetin has been shown to prolong the life span of *S. cerevisiae* and *C. elegans* [107]. Constant treatment of HFL-1 cells with quercetin increased CT-L proteasome activity and proteasome quantity and delayed the senescence phenotype [58].

Lipoic acid is an organosulfur compound that is naturally synthesized by animals and is an essential cofactor in oxidative metabolism [108]. Nevertheless, lipoic acid can also be found in common ingredients of our diet like broccoli, spinach, tomatoes, and brussels sprouts. Lipoic acid is a strong antioxidant acting as a radical scavenger. With regard to its antiaging properties, α-lipoic acid has been shown to increase life span in *C. elegans* and *D. melanogaster* [109–111]. In normal human dermal fibroblasts (NHDF), treatment with lipoic acid positively affected the 20S proteasome activity and upregulated the protein levels of PSMB5 subunit leading to attenuation of oxidative damage and enhanced cell proliferation [72].

Sulforaphane is an isothiocyanate and its protective effects against neurodegeneration and aging have attracted the interest of many researchers [112]. Sulforaphane exerts its protective effects through interaction with the Nrf2 pathway [113–115]. Sulforaphane treatment maintained self-renewal and polypotency and delayed differentiation of human embryonic stem cells through Nrf2 activation and elevated proteasome activity [62].

Bee pollen is widely used and consumed by humans since ancient times [116]. Due to its composition (mixture of polyphenolic compounds) bee pollen has been shown to protect cells through antioxidant and anti-inflammatory

mechanisms [117, 118]. Treatment of HFL-1 cells with bee pollen was shown to trigger the proteasome activity and to elevate protein expression levels of β2 and β5 subunits [73].

18α-GA has been shown to extend the life span of treated human fibroblasts and to positively affect proteasome activity in an Nrf2-dependent process [67]. Furthermore, increased life span and enhanced CT-L and T-L activities were also observed in wild-type *C. elegans* upon 18α-GA administration [66].

Finally, it is known that **zinc** is an essential trace element involved in the maintenance of many homeostatic mechanisms and its deficiency has been associated with aging [119, 120]. In a population study, zinc administration to the elderly increased CT-L proteasome activity and reduced proteotoxicity [74].

15.6 Conclusions

Aging is a natural, unavoidable process that affects almost all organisms. UPS dysfunction is considered as one of the hallmarks of aging and is reported in many age-related pathologies [121]. An important number of investigations reveals the contribution of diet on aging. Diets that are high in fish, fresh fruit and vegetable consumption, like the Mediterranean-type Diet, have been suggested to favor healthy aging and to lower the risk of age-related pathologies. The abovementioned dietary products are rich in phytochemicals which are known for their antioxidant properties and their positive effects on aging and many pathologies including neurodegeneration [122]. Nevertheless, clinical trials and populational studies are missing for most of these compounds. Another pitfall is the fact that all experimental procedures are performed using isolated compounds usually in the μM range. Nevertheless, these concentrations are often unreachable through diet. On top of that, other constituents of dietary extracts may also have adverse effects that can dampen the beneficial properties of a single compound. Therefore, more detailed studies are needed. Given that the life span and the population of older adults have been elevated, along with the incidence of age-related disorders, consumption of dietary products with potent UPS activation properties may represent a promising strategy for health span extension and improvement.

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