Dietary polyphenols in metabolic diseases and neurodegeneration: Molecular targets on autophagy and biological effects

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ABSTRACT (100 words)

Polyphenols represent a group of secondary metabolites of plants which have been analyzed as potent regulators of multiple biological processes, including cell proliferation, apoptosis and autophagy, among others. These natural compounds exhibit beneficial effects and protection against inflammation, oxidative stress and related injuries including metabolic diseases, such as cardiovascular damage, obesity and diabetes and neurodegeneration. In the present review, we report the main biological effects in relationship to autophagy regulation in response to different dietary polyphenols and its impact on metabolic and neurodegenerative diseases.
Keywords: polyphenols; autophagy; mechanisms; oxidative stress; inflammation; disease models

Abbreviations: Aβ, Amyloid beta; AD, Alzheimer’s disease; AMPK, adenosine monophosphate (AMP)-activated protein kinase; APP, amyloid precursor protein; Atg, autophagy related; CMA, chaperone-mediated autophagy; ER, endoplasmic reticulum; LC3, Microtubule-associated protein 1A/1B-light chain 3; LB, Lewy bodies; miRNA, microRNA; mTORC1, mammalian/mechanistic target of rapamycin complex 1; PD, Parkinson’s disease; T2DM, type 2 diabetes; TSC, tuberous sclerosis complex; UPR, unfolded protein response; UPS, ubiquitin-proteasome system; Ub, ubiquitin.
1. Introduction

One of the consequences of the normal function in living organisms is the intracellular production of free radicals in significant amounts. Cytosol, mitochondria, lysosomes, peroxisomes and epithelial membranes are the main locations where free radicals reactions take place.

The antioxidant defenses which are usually present in different tissues are responsible of counteracting the oxidative stress caused by the accumulation of the reactive molecules derived from extracellular or intracellular factors. Thus, redox homeostasis can be considered as the cumulative action of all free radical reactions (mainly oxygen and nitrogen centered) and the antioxidant defenses at cellular level, which provide suitable conditions for life.

When the antioxidant defenses are not able to counteract an extensive free radical production, oxidative stress is caused through the reaction with several molecule types within the cell: lipids, proteins, nucleotides, sugars, etc. Free radicals are able to activate several pathways by signal transduction such as mitochondrial kinases, protein kinase A, protein kinase B/Akt, protein kinase C (PKC), extracellular signal-regulated protein kinase, c-Jun N-terminal kinase or p38 nitrogen activated kinase, among others, which are the final responsible of the cell damage. Therefore, signal transduction is the mechanism that converts a cellular mechanical or chemical stimulus into a specific cellular response: it starts with a signal to a cell membrane receptor and ends with a change in cell behavior.

Apoptosis is a highly regulated programmed cell death pathway that contributes to tissues homeostasis. Uncontrolled apoptosis is the main response to intense oxidative stress with consequent tissue damage (1). This process runs through several steps, starting with the nucleus condensation and fragmentation which causes changes in the cell form and structure, leading to the separation from other cells; a swelling of the mitochondria and destruction of the endoplasmic reticulum (ER) structure are then observed, together with the vacuolization in the cytosol and the disappearance of the microvilli in the plasmatic
membrane. All these changes finally cause cell contraction and death, without any immune reaction.

Main systems of cellular protein degradation are the ubiquitin (Ub)-proteasome system (UPS) and the autophagy machinery. The UPS system involves the activity of enzymes including E1 (Ub-activating enzyme), E2 (Ub-carrier or conjugating proteins) and E3 (Ub-protein ligase). These enzymes label proteins with Ub to mark them for the recognition by the 26S proteasome which degrades ubiquitinated proteins to small peptides (2). In addition, UPS dysfunction leads to the accumulation of misfolded proteins in the ER, triggering ER stress.

Autophagy is a physiological recycling process highly conserved in eukaryotic cells, which confers an alternative pathway to the UPS for clearing out cytoplasmic long-lived proteins and different cellular organelles within the lysosome (3). In this context, autophagy functions to degrade polyubiquitinated protein aggregates induced by proteasome inhibitors or UPS suppression alleviating ER stress (4).

Antioxidants are endogenous or exogenous compounds which are able to counteract the free radicals production by cell metabolism. Antioxidants act by giving their own electrons to free radicals so that the later will no longer attack the cell, breaking the chain reaction of oxidation. By definition, when an antioxidant donates an electron it becomes a free radical itself; nonetheless, antioxidants have the ability to accommodate the changes in the number of electrons without becoming reactive.

Oxidative stress and depletion of intracellular antioxidants (enzymatic and non-enzymatic defenses) make it necessary to have an additional exogenous source of counteracting systems providing small antioxidant molecules such as fat-soluble vitamin E, beta-carotene, coenzyme Q and water-soluble vitamin C, mainly provided by fruits, vegetables, seeds, nuts, meats and oils.

Polyphenols constitute one of the main groups of secondary metabolites from plants. Their role in the vegetal cell metabolism is generally involved in the cellular defense against
ultraviolet radiation or aggression by pathogens, whereas they contribute to the bitterness, astringency, colour, flavour, odour and oxidative stability.

Polyphenolic compounds are synthesized in plants from phenylalanine or shikimic acid, primarily in conjugated forms, with one or more sugar residues linked to hydroxyl groups or to an aromatic carbon. More than 8,000 polyphenolic compounds have been identified in the Plant kingdom which can be classified into several groups depending on the number of phenol rings that they contain and the structural elements that bind these rings one to another. The main four classes are phenolic acids, flavonoids, stilbenes and lignans (Figure 1).

Figure 1. Basic chemical structures of the main classes of polyphenolic compounds from plants.
Phenolic compounds demonstrated a potent antioxidant activity mainly due to their redox properties which allow them to act as chelating agents of metal ions, hydrogen donors, or reducing agents. This antioxidant ability leads to several beneficial actions such as antiinflammatory, antimutagenic and antitumoral effects (5,6). For instance, caffeic and ferulic acids, which are hydroxycinnamic acids, bind a sugar moiety for increasing stability; preventing peroxidation mediated by UVR by inhibiting the chain reaction of lipid peroxidation and scavenging nitrogen oxides. Moreover, ferulic acid, together with caffeic acid, strongly absorb UV-photons; protecting human skin from UVB-induced erythema, which justifies their inclusion in the formulation of several topical solutions and sunscreens (7).

In humans, most polyphenols are ingested from the diet (fruits - especially red berries-, vegetables, cereals and beverages) in the form of glycosides, which are bound to one or more sugar molecules. After ingestion, glycosides are hydrolyzed by intestinal hydrolases of gut microflora and the released aglycones are then absorbed by the intestinal cells and converted into their respective metabolites in intestinal and hepatic cells. Metabolites are then transported by the blood to various cells and/or excreted in the urine.

The oral bioavailability of dietary polyphenols is low due to several characteristics of their metabolism: poor absorption, rapid excretion, and extensive biotransformation and conjugation that occur during their absorption from the intestine and in the liver (8).

Epidemiological data suggested that long term consumption of a polyphenol-rich diet was associated with lower risk of certain cancers and coronary heart diseases, a decrease in arterial pressure and plasma concentration of lipids, as well as a protection against development of diabetes, osteoporosis and even neurodegenerative diseases. Nonetheless, overconsumption of some type of food has been associated with the induction of oxidative stress and the consequent development of pathological transformations (9).

The aim of this review is to contribute to the knowledge of the main mechanisms of action of dietary polyphenols in relation to autophagy regulation and their impact on several
metabolic diseases in order to allow the development of new effective drugs for the treatment of oxidative-stress related diseases.

2. Molecular mechanisms of autophagic process and its regulation

Autophagy plays an important role in cytoplasmic quality control through the elimination of cytosolic protein aggregates, damaged organelles and invasive microbes, reducing ER stress, and thus, maintaining cellular homeostasis and enhancing cell survival, which contribute to health and longevity (10,11). Moreover, this catabolic process is upregulated under a wide range of extracellular and intracellular stresses such as nutrient starvation including growth factor and insulin deprivation, hypoxia, infections, ER stress and oxidative stress, and the resulting macromolecular constituents are then recycled. In this context, activation of autophagy allows metabolic adaptation during starvation by providing an alternative source of energy and nutrients (12) and it also participates in cellular defense against infections (13,14).

Molecular mechanisms of autophagy involved the activities of proteins encoded by autophagy-related (ATG) genes and it could be a nonselective process degrading non-specific cargoes and ubiquitinated proteins (also referred as “bulk autophagy”), or highly specific, eliminating distinct cargoes including lipids (termed lipophagy), peroxisomes (pexophagy), mitochondria (mitophagy), nucleus (nucleophagy), ribosomes (ribophagy), ER (reticulophagy), and microbes (xenophagy), among others.

In mammalian cells, there are three primary types of autophagy based on how the cargo is delivered to the lysosome – macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) (15).

Macroautophagy (hereafter referred to as autophagy) initiates with the formation of a cytosolic double-membrane cistern called the phagophore upon the induction and the
assembly of the Atg1/ULK1 (unc-51-like kinase) complex. This phagophore comes from the plasma membrane, ER, mitochondria or the Golgi apparatus. This initiation process also depends on the assembly of ATG9 and the class III phosphatidylinositol 3-kinase (PI3K-III) complex composed by ATG14, the vacuolar sorting-protein-34 (VPS34), VPS15 and beclin-1 (BECN1) which acts at the stage of the formation of the phagophore assembly site (PAS) and the generation of phosphatidylinositol 3-phosphate, facilitating initiation of autophagy. For the vesicle nucleation and the elongation of the phagophore to form a spherical vesicle termed autophagosome, it is required the recruitment of the ubiquitin-like conjugation systems: the ATG5/ATG12/ATG16L complex and the ATG8 family proteins, which are both catalyzed by ATG7 (E1-like enzyme). ATG8 proteins can be subdivided into the microtubule-associated protein 1A/1B-light chain 3 (LC3) and GABA type A receptor-associated protein (GABARAP) families. The ATG8/LC3 has three different isoforms (LC3A, LC3B, LC3C) which can be conjugated to phosphatidylethanolamine (PE) to form LC3-PE (a membrane-bound form of LC3 also referred to as LC3-II) by sequential activation of ATG7, ATG3 (E2-like enzyme), and the ATG12 complex (E3-like enzymes). The level of the lipidated form of LC3 (LC3-II) has been widely used to monitor the number of autophagosomes and autophagic activity. Another important protein involved in this process is p62/sequestosome 1 (SQSTM1), which links the autophagy pathway and the UPS by binding the ubiquitinated proteins with the LC3 proteins for autophagic degradation. Finally, autophagosomes fuse with the membrane of lysosomes or endosomes to form autolysosomes or amphisomes, respectively. Within autolysosomes, the autophagic cargo are degraded by lysosomal acid hydrolases (16-18). The main autophagic pathway is schemed in figure 2.
Figure 2. The different phases of autophagic process.

On the other hand, microautophagy is mediated by lysosomal membrane invagination which directly engulfs the cytoplasmic cargo (15).

Finally, the mechanism of chaperone-mediated autophagy (CMA) is highly specific. In CMA, the heat shock 70 kDa protein 8 (HSPA8/HSC70) and other chaperones recognize target proteins containing a KFERQ-like peptide motif and translocate them to the lysosomal membrane, where the LAMP2A (lysosomal-associated membrane protein 2A) receptor is localized and it translocates the target proteins from the cytosol to the lysosomal lumen.

Autophagic process is tightly regulated depending on nutrient status by different signaling pathways that include the mammalian target of rapamycin complex 1 (mTORC1), AMP-activated kinase (AMPK), and Sirtuin-1 (SIRT1) pathways. Autophagy is negatively regulated by the mTORC1 pathway, which also regulates several important and essential processes including cell growth and protein synthesis (19). Under nutrient rich conditions, mTORC1 is activated and phosphorylates ULK1, thereby preventing its activation by AMP-activated protein kinase (AMPK), a key activator or autophagy (20). Moreover, mTORC1
phosphorylates and inhibits the nuclear translocation of the transcription factor TFEB, which drives the expression of genes for lysosomal biogenesis and the autophagy machinery (19). Conversely, mTORC1 is inhibited following nutrient starvation or energy deprivation, and thus, AMPK which is a key energy sensor is activated and autophagy is induced (20). When AMPK is activated, it phosphorylates and activates the tuberous sclerosis complex (TSC) which is composed of the TSC1 (hamartin), TSC2 (tuberin) and TBC1D7 proteins. The TSC complex is an essential inhibitor of mTORC1 activity through the activation of its GAP (GTPase-activating protein) activity towards the small G-protein Rheb (Ras homologue enriched in brain) (21). Inactivation of mTORC1 activity by the TSC complex occurs via lysosomal recruitment of cytosolic TSC complex, where mTORC1 is located (22).

In addition, AMPK activation stimulates the activity of the nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase SIRT1, by elevating the intracellular levels of its co-substrate, NAD+ and inducing lifespan extension (23). In this sense, the polyphenol resveratrol (2,3,4′-trihydroxystilbene), which is a caloric restriction mimetic (CRM), stimulates in vivo SIRT1, inducing the kinase activity of liver kinase B1 (LKB1), leading to AMPK activation and increased mitochondrial biogenesis and function (24). Regarding post-translational modifications, the acetylation status of histones as well as cytoplasmic proteins is related with the regulation of autophagic flux (25,26). In this sense, growing evidence indicate that the activity of sirtuins, deacetylation protein status and activation of autophagic flux decline with age (27).

Upon starvation, hypoxia, mitochondrial dysfunction and under several circumstances in which there is high intracellular levels of reactive oxygen/nitrogen species (ROS/RSN), the c-Jun N-terminal kinase (JNK), or stress-activated protein kinase, is activated. JNK activation mediates the phosphorylation of B-cell lymphoma 2 (BCL2) protein to induce apoptosis. On the contrary, when JNK is not activated, dephosphorylated BCL2 interacts with beclin-1, which is a BCL2-interacting protein, mediating the inhibition of beclin-1 dependent autophagy. This mechanism represents the crosstalk between autophagy and apoptosis (28).
Mitochondrial quality control mechanisms involved the activity of the phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1) and an ubiquitin E3 ligase known as Parkin. PINK1 protein acts as a molecular sensor of damaged mitochondria and promotes the recruitment of Parkin on the outer mitochondrial membrane (OMM) resulting in the ubiquitination of numerous OMM proteins, which in turn recruits other proteins to mitochondria to initiate mitophagy.

It is well known that an alteration of this mitophagy and/or autophagy pathways leads to the accumulation of altered proteins and damaged organelles contributing to metabolic and aging-associated disorders.

3. Dietary polyphenols and type 2 diabetes

The mechanism of action of different polyphenols in the control of several metabolic diseases, including obesity and type 2 diabetes mellitus (T2DM) in relation with autophagy modulation has been reported. It is well known that polyphenols are a group of molecules with positive effects in the modulation of aging; in fact, all these groups of diseases present a higher prevalence with aging. T2DM is a very complex disease and it is considered epidemic worldwide. T2DM is the resultant from multiple factors in a progressive manner, being insulin resistance and pancreatic β cell dysfunction the most relevant. T2DM is associated with increased levels of glucose and lipids that could contribute to β cell death. T2DM is characterized by two different phases. During the first one, which main event is the existence of insulin resistance with normal levels of glycemia, pancreatic β cells increase their mass, by hyperplasia or hypertrophy, with a concomitant insulin and amylin secretion (29). The duration of this phase depends on the patient and can be extended for years. At the final stage, pancreatic β cells fail, and then, hypoinsulinemia appears. In addition to that, amylin deposition occurs in almost 90% of T2DM patients. During the progression to T2DM, our group and many others have detected a chronic activation of mTORC1 signaling pathway. Although this activation is necessary during the first phase of the disease, for insulin resistance compensation by pancreatic β cells, its chronic effect is deleterious for
these cells (30), (31). Importantly, this maintained activation of mTORC1 generates a blockade in autophagic flux, which it is essential for a correct elimination of damaged organelles or protein aggregates. These effects generate a continuous stimulation of the unfolded protein response (UPR), which up-regulates ER protein chaperones promoting protein folding. However, when the ER protein folding capacity is overwhelmed, cells undergo a condition of chronic ER stress, triggering the activation of apoptosis (32,33). Nowadays, T2DM is considered a disease affecting folding capacity of pancreatic β cells. In fact, the expression of different endogenous ER chaperones such as the 78-kDa glucose-regulated protein (GRP78) or BiP protein and protein disulfide isomerase, or chemical chaperones, such as taurine-conjugated derivative from ursodeoxycholic acid (TUDCA) or 4-phenyl butyric acid (4-PBA), diminished β cell failure and facilitates the correct folding, avoiding protein aggregation and apoptosis (34). In this regard, azoramide, a small molecule which modulates UPR activity, has a very potent action as antidiabetic (35,36). In addition to all the changes mentioned before through the progression to T2DM, it is well known the presence of mitochondrial dysfunction. In general terms, mitochondrial dysfunction occurs as the natural history of aging (37). However, during T2DM progression these effects have been observed with a concomitant defect in the mitochondrial clearance or mitophagy, promoting an accumulation of aberrant and dysfunctional mitochondria, which cannot be eliminated by mitophagy (38). In this regard, our group has demonstrated that a chronic activation of mTORC1 in pancreatic β cells inhibits both general autophagy as well as mitophagy, with a higher production of oxidized mitochondrial proteins and an accumulation of mitochondria with an altered membrane potential, which are not degraded by mitophagy (39). One of the mechanisms that could explain this failure in mitophagy is the reduction in the levels of PINK1, which is an essential component in the recognition of mitochondria with an altered membrane potential observed in fibroblasts with mTORC1 hyperactivation (40). In addition to that, our group has described that the overexpression of human amylin in pancreatic β cells, impairs both bulk autophagy as well as mitophagy (41). More importantly, these defects have been observed in prediabetic’s states as well as in T2DM patients (42).
One of the most characterized and studied polyphenols with respect to its effects in diabetes, is resveratrol. Apart from its protective effects in diabetes, resveratrol can be a positive treatment in diabetes-related pathologies such as diabetic cardiomyopathy (43). In fact, positive effects of resveratrol in the reduction of oxidative stress (44) as well as an increased in insulin sensitivity (45) with a concomitant decrease in lipid levels have been assessed (46). In addition to all of these actions, it has been proposed that resveratrol can modulate the expression of both pro-apoptotic as well as anti-apoptotic factors (47). Furthermore, polyphenol stilbenes can stimulate an important antioxidant defense such as the transcription factor called nuclear factor-erythroid-2-related factor-2 (Nrf2). Nrf2 is involved in the control of the transcription of different antioxidants in response to inflammation and oxidative stress (48). Polyphenol stilbenes are involved in the activation of autophagy as well, through the modulation of p62 protein levels and SIRT1 activity (49). An essential role of SIRT1 has been proposed for the induction of autophagy in response to hypoxia in a T2DM rat model (50). Resveratrol stimulates autophagic flux, improving diabetic cardiomyopathy in a diabetic mouse model. This protective effect was mediated by a decrease in p62 protein levels and facilitating SIRT1 activity. Moreover, it has been proposed a potential therapeutic pathway SIRT1/FOXO/Rab7 mediating the effects of resveratrol on autophagic flux, ameliorating dysfunctional autophagy in diabetic cardiomyopathy (51). Resveratrol can modulate autophagy by alternative indirect mechanisms which involve transcriptional regulation of microRNA’s (miRNA’s for short). miRNA-18a-5p is one of the miRNA whose expression is enhanced in a diabetic mouse model after treatment with resveratrol (52).

Another polyphenol with a variety of protective action in diabetes is curcumin and its analogues. These groups of molecules are able to down-regulate the chronic stimulation of ER stress, reducing apoptosis (53). There are multiple evidences indicating a pro-autophagic role of curcumin in order to moderate the negative effects of T2DM (54). For instance, curcumin can modulate several proteins involved in autophagy including LC3, p62 and beclin1, among others. These effects have been described in a diabetic mice model treated with curcumin, preventing podocyte apoptosis during diabetic nephropathy (55).
Another polyphenol with a significant effect in autophagy modulation is (-)-epigallocatechin-3-gallate (EGCG), which has been isolated from green tea. EGCG is able to regulate autophagy at different levels alleviating part of the deleterious effects observed in diabetic patients. For example, it can avoid lipid accumulation in vascular endothelial cells increasing the degradation of lipids by lipophagy, facilitating a better recognition between LC3B, located in the autophagosomes, with lipid droplets for degradation (56). This polyphenol can alter mitochondrial dysfunction as well as aberrant autophagy found in the heart of diabetic rats associated with T2DM (57); (58).

Finally, punicalagin, one of the main polyphenolic components of pomegranate, protects liver dysregulation in response to T2DM. In fact, this molecule has been proposed very recently as an autophagy inducer, by the modulation of different protein markers such as LC3B and p62, restoring autophagy again (59). Oleuropein, another polyphenolic compound has been related with an induction of autophagy as part of its way of action (60). Oleuropein, together with hydroxytyrosol, are involved in the induction of autophagy through the regulation of AMPK/mTORC1 signaling pathway (61); (62).

4. Dietary polyphenols and neurodegeneration

Dysfunction of autophagy contributes to the formation of protein misfolding and aggregation which underlies the pathogenesis of human proteinopathies such as Alzheimer (AD), Parkinson (PD) and Huntington diseases (63). Protein homeostasis is essential for maintenance in all the cells but, it is especially relevant in postmitotic neurons, which has a limited regenerative potential. Then, in these cells, all the mechanisms involved in the elimination of damaged organelles or protein aggregates are crucial for preserving cell survival (64). Although the mechanisms that control these three diseases are different, they share a common feature, which is the accumulation of different protein aggregates in neurons, leading to cell toxicity and neurodegeneration. As happened with diabetes, neurodegenerative diseases increase during aging process. It is well known that all the
systems involved in protein quality control including UPS and autophagy-lysosome system fail within aging, promoting the accumulation of aggregates not shown in younger states.

In the case of Alzheimer’s patients there is an accumulation of amyloid β (Aβ) and an intracellular accumulation of an hyperphosphorylated form of Tau protein, forming a structure called neurofibrillary tangles. Although there is a part of the patients which inherit a mutation in one of the genes involved in the disease, including presenilins 1 and 2 or amyloid precursor protein (APP), they represent less than 1% of all the cases of the disease. In contrast, the rest of patients (around 90%) are called sporadic and depends on both genetic and environmental determinants (65). Aβ oligomers and tau produce several alterations in neurons including inhibition of proteasome and autophagy-lysosome degradation system, which contributes to a higher accumulation of these proteins (66). In addition, it has been shown that Aβ can accumulate lysosomes inside, altering their membrane permeability (67). Tau protein is involved in microtubule assembly as well as stability, depending on its phosphorylation degree, which is the result of the activity of kinases as well as phosphatases. Microtubule stability is associated with an unphosphorylated form of tau protein (68); (69). In contrast, hyperphosphorylation of tau provokes a microtubule instability, which generates an alteration in the polymerization of microtubules, altering the correct transport and movement of different organelles, which is an essential process in the regulation of synapsis (70).

With respect to PD, another protein known as α-synuclein, is involved. This protein can assemble into aggregates forming deposits known as Lewy bodies (LB), mainly in dopaminergic neurons (71). In the same line with AD, different mutations related to the increased capacity of this protein to aggregate, have been found in PD. This aggregation alters normal cellular physiology and organelles, including endoplasmic reticulum as well as mitochondria, which in the end contributes to cell death (72); (73). There are multiple genes associated with the disease such as LRRK2, SNCA, LAMP3, ATP13A2 and others. Although, SNCA, which encodes α-synuclein, is the major genetic alteration related with the
pathology, there are others genetic mutations in other genes, involved in the mitochondrial quality control mechanisms. These other genes are PINK1 and protein deglycase (DJ-1).

However, other mechanisms have been found to be altered as a consequence of α-synuclein aggregation, including vesicular trafficking between compartments such as ER-Golgi transport and Golgi apparatus fragmentation (74); (75). In addition, several posttranslational modifications such as phosphorylation, ubiquitination, acetylation and others, with the structure of α-synuclein and the correct function and its aggregation capacity have been described (76). Very interestingly, an hyperphosphorylation state of α-synuclein has been related with a change in the subcellular localization of the protein, leading to an interaction with histones and an inhibition of its activity, inducing neurotoxicity and cellular apoptosis (77); (78); (79). This phosphorylation could be mediated by different kinases in cells. Although the exact mechanism remains unknown, polo-like kinases (PLK) could be responsible for regulating this phosphorylation event in the serine 129 (80). Apart from phosphorylation, lysine acetylation status of α-synuclein has been involved in the pathogenesis of the disease as well (81). In addition, this modification of the protein impairs mitophagy in fibroblasts obtained from Parkinson’s disease patients (82).

Autophagy modulation is a key avenue for the treatment of neurodegenerative diseases as it has been very recently reviewed in (83). In this regard, different polyphenols have been proposed as protective in different neurodegenerative diseases such as AD and PD. For instance, curcumin can modulate autophagic machinery in order to restore the defects observed in the neurons of patients affected with these diseases (84). In addition, it has been demonstrated a direct interaction of curcumin with α-synuclein avoiding its aggregation and hence its toxicity (85). This effect on aggregation reduces synaptic toxicity in response, not only to curcumin but to other phenolic compounds such as myricetin, rosmarinic acid, norhydroguaiaretic acid and ferulic acid (86). In addition, a synthetic form of curcumin, called C1 is able to activate autophagy by inducing TFEB, a master transcription factor for lysosomal biogenesis as well as autophagy machinery (87). Another mode of action of polyphenols is through the effect on stem cells. For instance, in AD, polyphenols can stimulate neurogenesis in order to counteract the disease. Then, it is suggested that
Polyphenols could have a therapeutic potential for stem cell therapy (88). In general terms, polyphenolic neuroprotection occurs at different levels, including modulation of antiapoptotic proteins, stimulation of different signaling pathways inside the cells, inhibition of pro-oxidant enzymes and alteration of mitochondrial function. Furthermore, polyphenols have an active role in quenching free radical species and chelate metal ions. Furthermore, these compounds have the capacity to regulate the major degradative pathways of proteins as it has been reviewed in (89). Oleuropein has been involved in alleviating oxidative stress as well as an induction in autophagic flux (90). In this regard, it has been involved in the profound reduction of β-amyloid deposits, with a concomitant increase in autophagy activation. In parallel, there was a great reduction in mTORC1 signaling pathway in response to oleuropein (91). Resveratrol and other compounds called sirtuin activating compounds or STACS, have been described as potent inducers of SIRT1 (92). For instance, SIRT1 inhibits c-Jun by deacetylation, decreasing the transcriptional activity of the activator protein-1 (AP1), involved in the expression of several inflammatory and stress genes (93); (94). The essential role of SIRT1 as autophagy regulator derives from a seminal paper published some time ago by Toren Finkel’s lab, which demonstrated that SIRT1 is able to bind to an ATG protein regulating its activity by deacetylation and hence, autophagy (95). Figure 3 depicts the main molecular targets of some polyphenols and their beneficial effects on metabolic and neurodegenerative diseases.
Figure 3. Main molecular mechanisms involved in the antioxidant activity and the beneficial effects of dietary polyphenols in metabolic and neurodegenerative diseases.

6. Conclusions

Natural products and dietary polyphenols among them have emerged as a promising group of potential agents in health promotion, supported by their structure and results from molecular studies. Polyphenols may act on multiple molecular targets in relation to autophagic flux activation with potential effects on metabolic diseases such as T2DM and neurodegeneration. In this review, different protein targets and signaling pathways modulated by these natural products have been shown.

Since years, the positive effects of a variety of plant extracts and dietary polyphenols including resveratrol, curcumin, epigallocatechin-3-gallate, punicalagin, oleuropein, myricetin and rosmarinic, norhydroguaiaretic and ferulic acids have been reported. These compounds are CR mimetics and anti-aging molecules which may activate AMPK and SIRT1 activities by increasing intracellular levels of AMP and NAD⁺, this leading to mitochondrial function improvement and autophagy stimulation. Activation of autophagy removes protein aggregates, lipid droplets and damaged organelles, stimulates antioxidant...
defenses and alleviates ER-stress and oxidative stress mediated by mTORC1 hyperactivation resulting in an enhancement of cell survival.

In conclusion, in view of their potential beneficial effects, polyphenols represent a promising chemical group for which further studies, including clinical trials, should be conducted for their in-depth knowledge which would likely help for translational outcomes.

**Author Contributions**

AG-A, OPR-P, MB and CGV wrote the paper. All the authors have read, contributed, approved the final manuscript and agreed to its publication in Antioxidants.

**Conflict of Interest**

The authors declare no financial or commercial conflicts of interest.
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