Chapter 3

Polyphenols as Potential Therapeutic Drugs in Neurodegeneration

Patrizia Polverino de Laureto, Luana Palazzi and Laura Acquasaliente

Abstract

Several therapeutic approaches have been suggested so far for the treatment of neurodegenerative diseases, but to date, there are no approved therapies. The available ones are only symptomatic; they are employed to mitigate the disease manifestations and to improve the patient life quality. These diseases are characterized by the accumulation and aggregation of misfolded proteins in the nervous system, with different specific hallmarks. The onset mechanisms are not completely elucidated. Some promising approaches are focused on the inhibition of the amyloid aggregation of the proteins involved in the etiopathology of the disease, such as Aβ peptide, Tau, and α-synuclein, or on the increase of their clearance in order to avoid their aberrant accumulation. Here, we summarize traditional and new therapeutic approaches proposed for Alzheimer's and Parkinson's diseases and the recent technologies for brain delivery.

Keywords: Alzheimer's disease, Parkinson's disease, amyloidosis, protein fibrils and oligomers, polyphenols, brain delivery technologies

1. Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative disorders. They are multifactorial, progressive, age-related, and influenced by genetic and environmental factors. Despite being public health problems and widely studied, there are no effective treatments. The therapies in use at the moment are only symptomatic and focused to ameliorate patients' life quality. Moreover, there are no diagnostic methods for the early detection of these diseases that, especially at the onset, share some pathological hallmarks. There are specific proteins associated with the diseases, but it is still unclear when and how they lose their functionality and become toxic. Several pathways of cellular dysfunction have been described to explain the toxicity associated with the disease, but the pathological role of proteins involved still remains controversial. Currently, the most promising therapeutic approaches are focused on personalized treatments and targeted drugs.

Here, we summarize some relevant features of the new proposed therapies for AD and PD. In the last decade, renewed interest rises toward alternative pharmacological treatments and products of natural origin, especially those associated

with the Mediterranean diet, such as polyphenols. The unexpected benefits and the wide-range properties of polyphenols suggest deepening the study of these molecules for a more comprehensive understanding of their mechanism of action in order to use them in effective therapies.

2. Molecular aspects of Alzheimer's and Parkinson's diseases

2.1 Brief introduction to AD and PD

AD is characterized by the gradual decline in the cognitive function, memory loss, and behavior changes [1]. Typical features of the disease are a synaptic deficit in the neocortex and the limbic system, neuronal loss, white matter loss, astrogliosis, microglial cell proliferation, and oxidative stress [2]. The major areas of the human brain affected by AD are schematically represented in **Figure 1**. The pathological hallmarks of AD are the presence of intracellular flame-shaped neurofibrillary tangles and extracellular plaques in the brain. The tangles are especially present in the perinuclear cytoplasm and are prevalently formed by the Tau protein, in a hyperphosphorylated form. The plaques derive from the progressive accumulation of amyloid β-peptide (Aβ) in a filamentous form [3]. The neuritic plaques have a diameter ranging from 10 to more than 120 μm [2]. The methods used for the diagnosis of the pathology have been standardized. They refer to the density and the grade of compactness of the neuritis amyloid plaques and neurofibrillary tangles [4]. AD aggregates can be classified into positive and negative lesions as a function of their localization and level of progression [5]. Typical positive lesions are represented by amyloid plaques and neurofibrillary tangles, neuropil threads, and dystrophic neurites, essentially formed by hyperphosphorylated Tau [6]. The negative lesions provide loss of neurons and neuropil threads [7].

Clinically, PD typically manifests with motor symptoms, such as bradykinesia, rigidity, tremor at rest, and instability. Since there is no definitive test for the diagnosis of PD, the appearance of these clinical manifestations is important for the early treatment of the disease [8]. PD is characterized by the loss of dopaminergic neurons in the *Substantia nigra pars compacta* (**Figure 1**) and by the deposition of

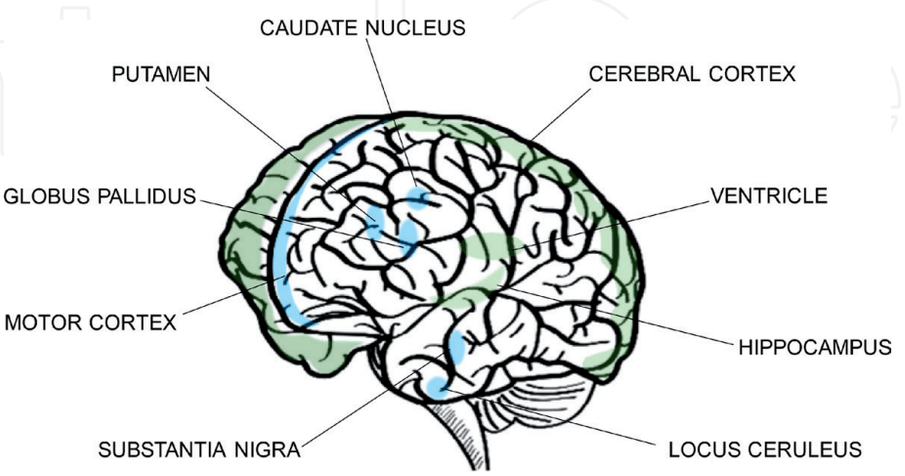

Figure 1.
Affected brain regions in AD and PD. Cross-section of human brain showing the principal districts affected by AD (green) and PD (blue). AD typically involves parts of the brain involved in memory, like hippocampus and ventricles, and the cerebral cortex responsible for language. In PD nerve cells of the motor cortex and in part of the basal ganglia (composed by substantia nigra, putamen, caudate nucleus, globus pallidus, and locus coeruleus) degenerate. As a result, the basal ganglia cannot control muscle movement as it normally does, leading to tremor, bradykinesia, and hypokinesia.

intraneuronal proteinaceous aggregates, mainly composed by α -synuclein (Syn), named Lewy bodies and Lewy neurites [9]. Syn was also found in the pathological inclusions of Lewy body variant of both AD and multiple system atrophy. Furthermore, Syn inclusions characterize other neurodegenerative diseases, defined as α-synucleinopathies, including Down's syndrome, progressive autonomic failure, and familial and sporadic AD [10]. In a very recent study, Shahmoradian and coll. have reported that Lewy bodies are not only formed by Syn deposit but also by clusters of lipid vesicles [11]. These important findings further correlate Syn-lipid interaction with neurodegeneration [12, 13].

AD and PD are generally sporadic and occur in individuals between ages 60 and 70, but the ~20% of patients have a genetically linked familial form. The onset of these forms occurs earlier, and it is associated with mutations in several genes [14]. The main mutations are listed in **Table 1**. The proteins involved in such neurodegenerative diseases, Aβ, tau, and Syn, are completely distinct in terms of structure and putative functions, most of which are not completely clarified. However, the formation of aggregated structures is a common feature among these macromolecules. Fibrils, which originate from the association of monomeric forms of the proteins, pass through intermediate species such as oligomers (**Figure 2**). Generally, they can cross the membrane and spread throughout the brain. Several evidences

Disease	Mutated protein	Phenotype	Notes	Refs
AD	APP	Abnormal production of Aβ	www.molgen.ua.ac.be/ADMutations	[15]
	ApoE	Increase of the density of Ab plaques High risk of AD, late onset of AD and Down syndrome	www.molgen.ua.ac.be/ADMutations	[16]
	Presenilin1	Increased the Aβ42/Aβ40, and reduced γ-secretase activity	>200 mutations	[17, 18]
	Presenilin2	Increased the Aβ42/Aβ40, and reduced γ-secretase activity	Rare, <40 mutations	[19]
PD	Syn	Familiar and early onset PD	A53T; A30P, E46K, G51D, H50Q, gene duplication and triplication	[20–25]
	Leucine-rich repeat kinase 2 (LRRK2)	Autosomal dominant PD; mid-to-late onset and slow progress	>20 mutations	[26, 27]
	E3 ubiquitin ligase Parkin	Early-onset PD and parkinsonism	>150 mutations, deletions, insertions	[28]
	PINK1	Sporadic early-onset Parkinsonism	>60 mutations	[29]
	DJ-1	Autosomal recessive PD	>10 mutation, deletions	[30]

Table 1.
Main mutations involved in familiar forms of AD and PD.

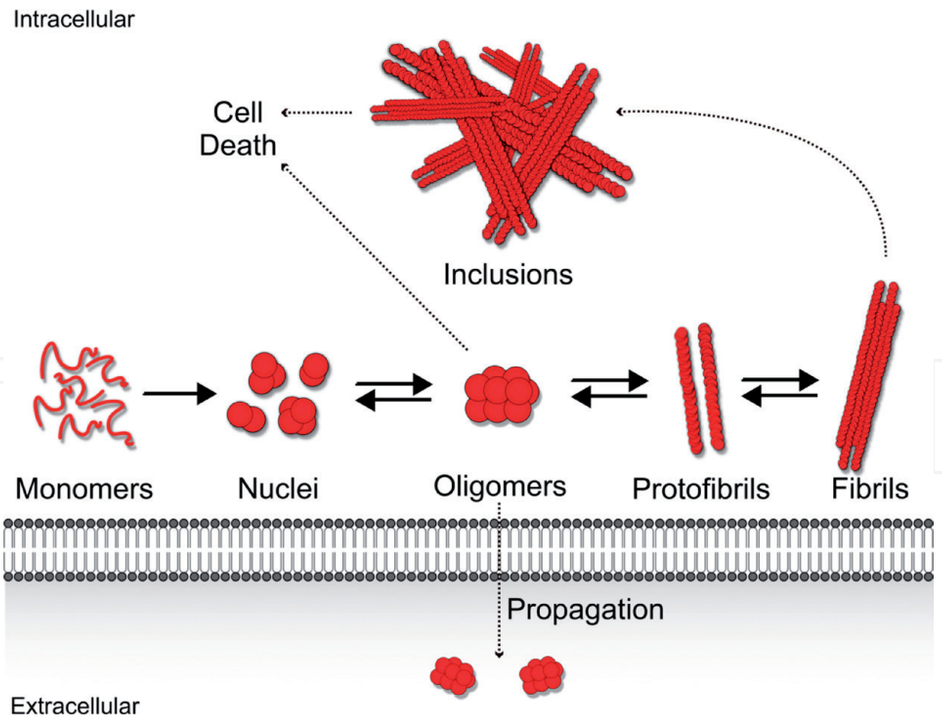

Figure 2.
Scheme of the aggregation process of amyloid proteins. The formation of fibrils occurs through a nucleation-dependent pathway starting from the monomeric form of the protein and leading to fibril elongation through intermediates (oligomers and protofibrils). The formation of the nucleus is the rate limiting step, and at this stage, the protein has acquired an aggregation-prone conformation. Fibrils are composed of a β-sheet structure in which hydrogen bonding occurs along the length of the fibril, and the β-strands run perpendicular to the fibril axis.

suggest that oligomers are the species responsible for the cytotoxicity. There are many proofs in support of this hypothesis, but unfortunately, due to the extreme heterogeneity in oligomer structures and their transient nature, a conclusive view has not been obtained yet [31–33]. The atomic structure of fibrils has been studied by several biophysical techniques. A quite accepted hypothesis agrees with the presence of a common molecular organization independent from the original structure of the involved protein: repetitive β-sheet units parallel to the fibril axis with their strands perpendicular to it [34, 35]. Amyloid fibrils can self-assemble *in vitro* from many structurally different proteins and peptides, not necessarily involved in diseases. It has been postulated that the cross-β structure represents a generic conformation, which represents another folding state for proteins [36, 37]. In addition to these characteristics, there are also some common aspects in the onset of the diseases. Several studies suggest possible interplays and synergistic activities between the involved proteins. Clinton et al. [38] provided evidence that Aβ, tau, and Syn could interact *in vivo* to promote their self-aggregation, thus accelerating the cognitive dysfunction [38]. High levels of Syn were found in patients suffering from AD [39]. Aβ stimulates Syn fibril formation in the transgenic mouse model through a seed mechanism [40]. In another study, Syn seems to inhibit the deposition of Aβ into the amyloid plaques [41].

2.2 Key proteins in neurodegeneration

2.2.1 Aβ peptide

The Aβ peptide was found in the amyloid plaques in 1984 [3]. Aβ represents a group of peptides constituted by 37–49 residues (**Figure 3A**), derived from the proteolytic processing of the amyloid precursor protein (APP) [42, 43] (**Figure 4**).

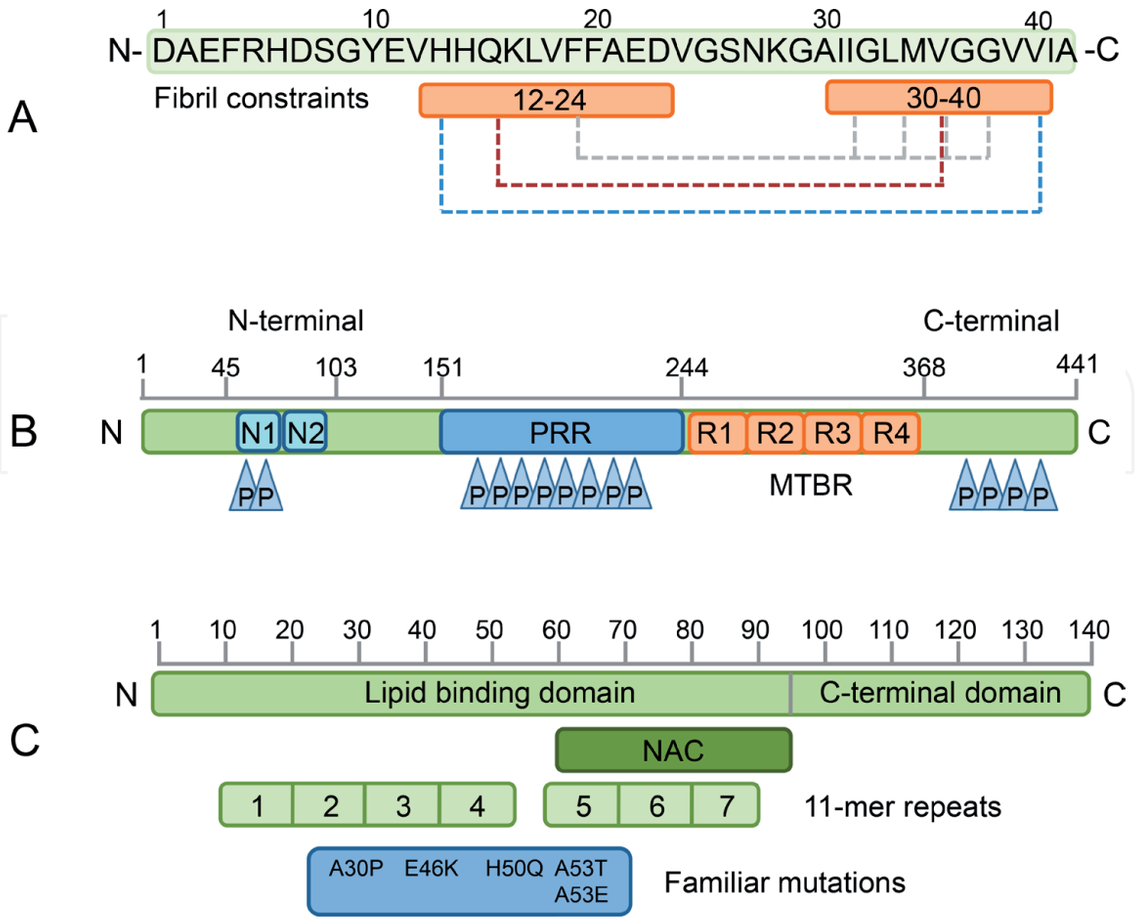

Figure 3.
Sequence and structural domain organization for Aβ (A), tau (B), and Syn (C). For Aβ, the residues 12–24 and 30–40 involved in the formation of a cross-β fibril structure are highlighted and connected by dashed lines. In (B), the longest isoform (441 residues) of tau is shown, where N indicates the possible N-terminal insertion defining other isoform, PRR, the proline-rich region, target of phosphorylation (P), and MTBR, the microtubule binding region that can contain three or four repeats (R), and other phosphorylations (P) occur at the C-terminal. In the case of Syn (C), the N- and C-terminals and NAC domains are shown, as well as the position of the mutations responsible for familiar form of PD. Residues 1–95 form the lipid-binding region.

APP is a single membrane-spanning domain protein, containing a large extracellular glycosylated N-terminus and a shorter cytoplasmic C-terminus. The enzymatic processes responsible for the release of Aβ from APP are to date well elucidated [2]. Specifically, APP undergoes several proteolytic cleavages. The processing by α-secretase results in the release of the large fragment sAPPα in the lumen, and the C-terminal fragment (CTF83) remains in the membrane. Two membrane endoproteases β- and γ-secretase sequentially hydrolyze APP. Firstly, APP releases sAPPβ by the action of β-secretase in the extracellular space. A fragment of 99 amino acids, CTFβ, remains bound to the membrane. CTFβ is successively and rapidly processed by γ-secretase generating Aβ. A precise cleavage site was not defined; therefore, Aβ is characterized by heterogeneity at the C-terminal and the peptide can end at position 40 (Aβ40) with a high frequency of occurrence (~80–90%) or at position 42 (Aβ42, ~5–10%). It is well established that Aβ42 generally generates fibrils more quickly than Aβ40 [44]. The production of Aβ is a normal metabolic event; in fact, these species are found in the cerebrospinal fluid and the plasma in healthy subjects [45]. Their abnormal accumulation, deriving from an imbalance between the production and clearance of these peptides, is associated with the pathogenesis of AD. Monomer, oligomer, and fibril forms of Aβ are differently involved in the onset of AD. The most common hypothesis is the Aβ-amyloid cascade [46]. The overproduction or the reduced clearance of Aβ leads to the deposition of fibrillar Aβ in the

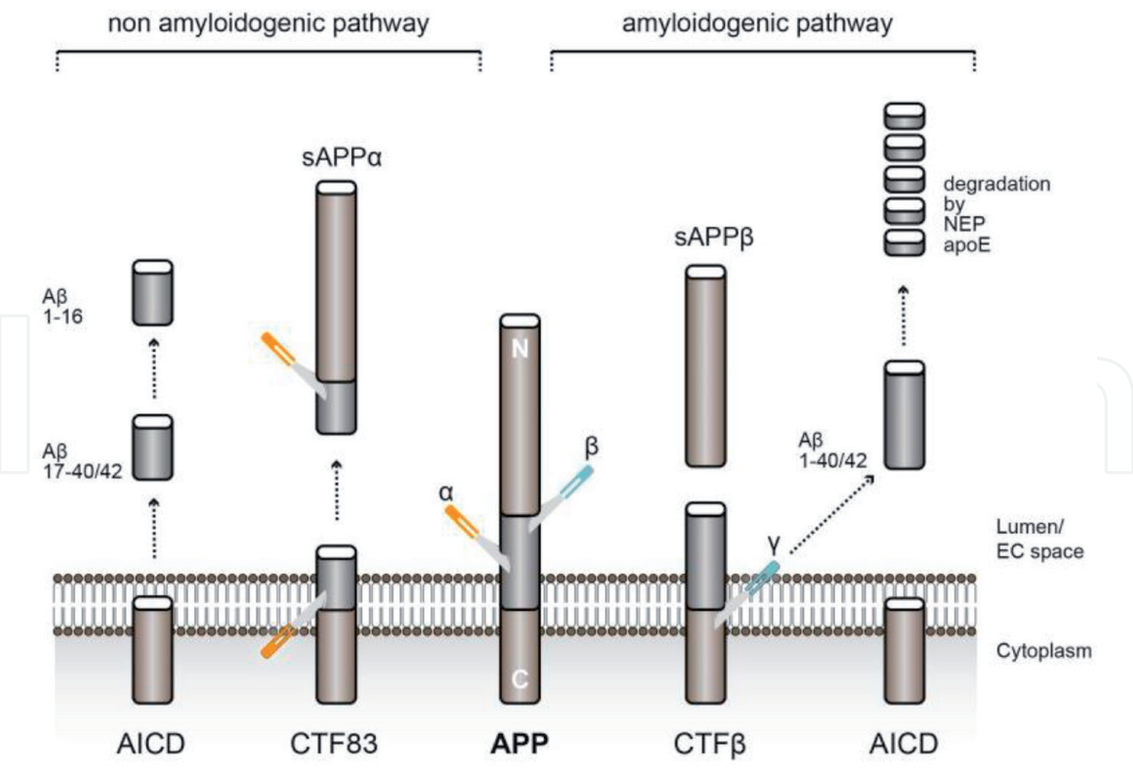

Figure 4.
Scheme of metabolism of APP and accumulation of the Aβ peptide. Aβ1–40/42 peptides are released from APP by the action of two membrane endoprotease β- and γ-secretases. Firstly, APP releases sAPPβ by the action of β-secretase in the extracellular space, and a fragment of 99 amino acids, CTFβ, remains bound to the membrane. CTFβ is successively and rapidly processed by γ-secretase generating Aβ peptides. Under physiological conditions, Aβ1–40/42 are degraded by enzymatic clearance processes. The proteolytic pathway mediated by α-secretase is also shown.

brain, determining synaptic and neuronal toxicity and thus neurodegeneration. There are many evidences in support of the so-called Aβ-amyloid oligomer hypothesis [31]. The proteolytic degradation of Aβ is a major route of clearance. Neprilysin (NEP) is considered one of the most important endopeptidase for the control of cerebral Aβ levels [47, 48] and for the degradation of some vasoactive peptides including natriuretic peptides and neuropeptides. Aβ clearance is mediated by other proteolytic enzymes such as apolipoprotein E (apoE) [49] and by autophagy [50]. Reduced activity of the clearance enzymes, which could be caused by aging, can contribute to AD development by promoting Aβ accumulation.

The secondary and tertiary structure of Aβ in solution has been studied by several biophysical techniques. These conformational studies are difficult for the protein high tendency to aggregate in solution. However, Aβ seems to populate distinct states in solution and to adopt a collapsed-coil structure, as deduced by NMR studies [51, 52]. Aβ preferentially binds to negatively charged lipids and acquires α-helical structure in the presence of membranes, membrane-like systems, and fluorinated alcohols [53, 54]. In the presence of phospholipids, Aβ undergoes conformational transition and forms β-sheets [55, 56]. Oligomeric Aβ binds to membranes with high affinity. Upon interaction, a membrane damage can occur as causative of the cellular toxicity [57]. It seems that especially oligomeric Aβ can disrupt the membrane bilayer by a detergent mechanism [58].

2.2.2 Tau

Tau is a neuronal protein associated with the microtubules [59]. Six Tau isoforms, which differ only in their primary structure, were detected in the human

brain and central nervous system (**Figure 3B**), while in the peripheral nervous system other Tau isoforms were also found [60]. The longest isoform contains 441 residues and the shortest 352 residues [61]. Depending on the isoform, the N-terminal can contain 0, 1, or 2 inserts (N). The protein appears largely post-translational modified, especially in terms of phosphorylation (P). Other modifications are acetylation, deamidation, methylation, glycosylation, or ubiquitination [59]. Tau proteins are also subjected to proteolytic degradation that seems to be correlated with AD [62]. The region PRR (proline-rich region) contains the main sites of phosphorylation. Although all the post-translational modifications seem to contribute to the physiological and pathological properties of Tau, the signaling cascades and the effect on protein kinases and phosphatases are not completely clarified yet. The region 244–369 (microtubule binding region, MTBR) is responsible for the binding to the microtubule and contains three or four repeats (R1-R4). Physiologically, Tau stabilizes the microtubule through MTBR, and such binding is modulated by the coordinated actions of kinases and phosphatases. Structurally, Tau belongs to the intrinsically disordered proteins, lacking a well-defined secondary and tertiary structure [59] and can interact with several other proteins. Upon aggregation, Tau can form dimers, oligomers, and larger polymers. In such aggregates, cysteine residues may play an important role [63]. Similarly, to other proteins involved in neurodegeneration, the oligomeric forms have a cytotoxic effect and might be involved in the Tau-related pathogeneses [64]. In neurofibrillary tangles, Tau forms the so-called paired helical filaments (PHFs) and straight filaments (SFs) [65, 66]. In PHF, Tau is ~three to four-fold more hyperphosphorylated than in the normal brain. The Tau filaments exhibit the typical cross-β structure found in other types of fibrils [67].

2.2.3 α-Synuclein (Syn)

Syn is a small protein (14.4 kDa) mainly expressed in pre-synaptic nerve terminals of the central nervous system and very abundant in erythrocytes and platelets [68]. Despite the intensive investigation and the discovery that the protein plays a central role in synaptic transmission and vesicle recycling [69], the complete Syn biological function remains still elusive. Syn may control the neurotransmitter release, promoting the formation and assembly of the SNARE complex [70, 71]. Syn structure could be divided into three main domains: N-, central, and C-terminals (**Figure 3C**). The N-terminal region (amino acids 1–60) contains seven imperfect repeats, with a hexameric consensus motif (KTKGEV). All the known missense mutations of Syn, responsible for the familiar forms of PD, are located in this region (**Table 1**). The central hydrophobic domain (amino acids 61–95) is known as the non-amyloid-β component of AD amyloid plaques (NAC). It is responsible for Syn amyloid aggregation [72]. N-terminal and NAC domains together (amino acids 1–95) mediate the interaction of Syn with lipids, membranes, and fatty acids [73]. The C-terminal domain (amino acids 96–140) is an acidic, negatively charged, highly soluble, and disordered tail, target of post-translational modifications. This region plays a series of important roles, modulates Syn binding to membrane and metals, Syn aggregation and its protein-protein interaction properties. The deletion of this domain increases the aggregation rate of Syn *in vitro* and in cells [74].

Syn is the prototype of the natively unfolded proteins, but adopts a stable secondary structure as a function of the environment [75]. Multiple studies have demonstrated that Syn is more compact than expected for a random coil due to long-range interactions between the C-terminal tail and the NAC domain as well as electrostatic interactions between the N terminus and the C terminus [76]. Syn is supposed to populate different conformers in solution and can undergo conformational transition as a function of the environment and/or upon binding. The extreme Syn conformational

flexibility is responsible for its multifunctional properties, its capability to adopt different conformations, and to interact with different systems and other proteins [77]. For example, the interaction of Syn with negatively charged membranes, vesicles, bilayers, and lipids in general has important physiological consequences [78, 79], corroborating the hypothesis that Syn functions are correlated with lipids [80].

3. Overview of recent therapeutic approaches in Alzheimer's and Parkinson's diseases

3.1 Traditional ongoing therapies

Current pharmacological therapies (**Table 2**) for neurodegenerative diseases focus to ameliorate the life conditions of patients and are generally only palliative. Since in many cases, the aberrant deposition of the protein strongly contributes to the toxicity associated with the diseases, some treatments are currently thought to target such specific proteins (i.e., Syn and Aβ) in order to restore their correct physiological levels *in vivo.* Given the complexity in the onset and progression of these diseases, treatments should be customized and tailored to the individual needs of the patients.

In the case of AD, a therapy based on the use of cholinesterase inhibitors (ChEIs) and the N-methyl-d-aspartate (NMDA) antagonist is currently available and Food and Drug Administration (FDA)-approved. In particular, three ChEIs are used: donepezil, rivastigmine, and galantamine [81]. The aim is to increase the levels of acetylcholine, a neurotransmitter responsible for memory and cognitive function, by reducing its enzymatic breakdown. Another class is represented by NMDA receptor antagonists, such as memantine, a noncompetitive antagonist, capable to block the effects of the excitatory neurotransmitter glutamate [82]. There are

DISEASE	CLASS	DRUG	MECHANISM of ACTION
AD	cholinesterase inhibitors	donepezil	selective reversible non-competitive inhibitor
		rivastigmine	pseudo irreversible inhibitor
		galantamine	reversible inhibitor
	NMDA antagonist	memantine dimebolin	non-competitive antagonists
	antidepressants	escitalopram	selective serotonin reuptake inhibitor
		mirtazapine	antihistamine, α2-antagonist
	anticonvulsants	carbamazepine	Na^+Ca^{2+}channels inhibitor, adenosine receptor antagonist
		levetiracetam	Ca^{2+}channel inhibitor, binder of synaptic vesicle glycoprotein SV2A
	mood stabilizer	lithium	Na^+K^+ATPasi inhibitor, neurotransmitter modulator
	stimulant	methylphenidate	norepinephrine and dopamine reuptake inhibitor
PD	dopaminergic drugs	levodopa	dopamine precursor
	dopamine agonists	ropinirole	non-ergoline agonist
		rotigotine	
	monoamino oxidase B inhibitors	rasagiline	irreversible inhibitor
		selegiline	
	catechol-O methyl-transferase inhibitors	entacapone	reversible inhibitor

Table 2.
Current available drugs for the treatment of AD and PD.

a series of molecules under study referred to as "disease-modifying" drugs. They should interfere with key steps in AD development, including the deposition of Aβ plaques and neurofibrillary tangle formation, inflammation, oxidative damage, iron deregulation, and cholesterol metabolism. Many drugs are proposed for their ability to alleviate behavioral symptoms of AD. A few examples include antidepressants, such as escitalopram and mirtazapine, anticonvulsants, that is, carbamazepine and levetiracetam, mood stabilizers, and stimulants, such as methylphenidate [83]. The treatments for PD are still based on dopaminergic drugs, such as levodopa, the precursor of dopamine [84]. Long-term use of levodopa determines the development of motor problems. In association with levodopa, a decarboxylase inhibitor is administered to prevent some side effects. PD therapy involves the use of dopamine agonists, such as ropinirole or rotigotine, monoamino oxidase B inhibitors, such as rasagiline and selegiline, and catechol-O-methyltransferase (COMT) inhibitors, which can reduce the metabolism of endogenous dopamine.

3.2 New generation therapies

Novel experimental approaches are under investigation and the most promising have as a target the protein involved in the diseases. The stages of intervention could be at the level of the protein synthesis or clearance and at the level of protein aggregation or propagation of the toxic species or their precursors (**Figure 5**).

1. *Control of the protein concentration in vivo*. To reduce the production of Aβ, Tau, and Syn, the RNA interference approach is to date quite attractive [85–87]. It is based on the idea to inhibit specific protein expression by activating a sequence-specific RNA degradation process. This technology results useful to study gene function, investigate the mechanism of the disease, and validate drug targets. Of course, the suppression of the target protein might have

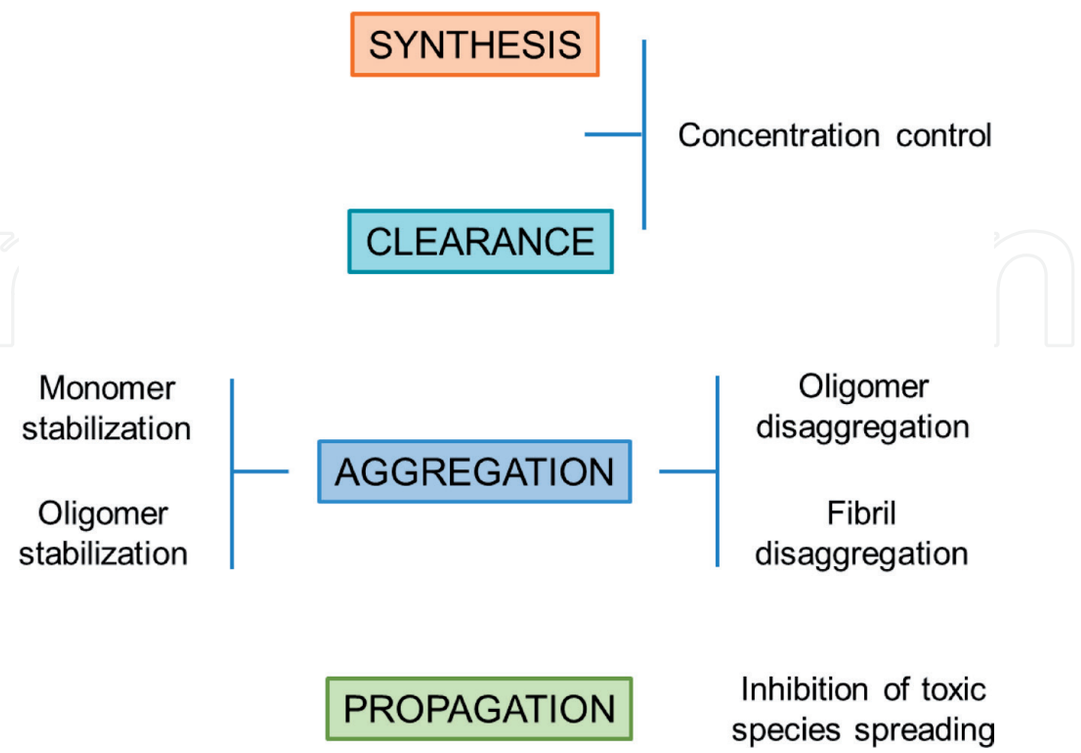

Figure 5.
New generation therapies in AD and PD. Potential levels of intervention to counteract the abnormal accumulation of the amyloidogenic proteins and restore their physiological concentration, which results from a balance between the rates of synthesis, clearance, aggregation, and propagation.

negative implications, due to the alteration of its physiological equilibrium. Additionally, the transcription of the gene can be reduced. Clenbuterol was shown to be efficient in reducing Syn expression by 35% in neuroblastoma cell lines [88]. Some AD therapies based on the modulation of AD gene expression are proposed on the basis of the important progresses made in the understanding of the transcriptional regulation of some enzymes such as beta-secretase 1 (BACE1), apolipoprotein E (apoE), APP amyloid precursor protein (APP), and presenilin (PSEN) promoters [89]. Alternatively, to reduce the level of the active protein *in vivo*, its clearance can be enhanced. This can be obtained by increasing the intracellular degradation *via* autophagy or *via* the ubiquitin system. This topic is excellently reviewed by Boland et al. [90].

2. *Protein aggregation inhibitors*. An attractive approach would be the use of small molecules able to bind the monomeric form of the protein preventing its assembly into potentially toxic aggregates. Unfortunately, it remains still unclear which conformation of these proteins must be targeted, since all of them are natively unfolded, and multiple and concurrent events contribute to their conversion in oligomers and fibrils [91]. In this ambit, the use of polyphenols is quite promising, and, as described below, these compounds exhibit in some cases the ability to disaggregate preformed oligomers and fibrils [92].

4. Effect of polyphenol compounds in neurodegeneration

4.1 Natural polyphenol products

Polyphenols are natural compounds, generally secondary metabolites, produced by plants and found mainly in fruits, vegetables, and cereals and in their derivatives. Some of them are synthetized during the normal development of the plant while others are produced in response to stress stimuli [93, 94]. They exert their function acting during the phase of development, reproduction, nutrition, growth, and communication with other plants, as well as in plant defense mechanisms like resistance to microbial pathogens, herbivore, insects, and protection to UV-light radiation [95]. More than 8.000 polyphenols have been identified in different plant species. They all derive from common precursors like phenylalanine and shikimic acid [96]. Often, they are linked with a sugar through the hydroxyl moiety, directly to the aromatic ring or conjugated with other compounds [97]. Polyphenols are characterized by a minimal hydroxyphenyl structure, and despite the multitude of existing polyphenols, they are grouped into different classes according to the number of phenol rings. The main groups are phenolic acids, flavonoids, stilbenes, and lignans [98] (**Figure 6**).

4.2 Potential therapeutic applications of polyphenols

Several epidemiological studies have been reported concerning the potentiality of polyphenols compounds in disease treatment and prevention [99, 100]. Polyphenols exert a positive role in cardiovascular disease [101–103], diabetes [104, 105], cancer [106, 107], aging, and neurodegeneration [108, 109]. One of the main activities of polyphenol resides is their antioxidant properties. Indeed, they are capable to protect cells and macromolecules from oxidative damage which in turn leads to degenerative age-associated diseases [110, 111]. Nevertheless, polyphenol function is also bound to its action on enzymes, immune defense, inflammation, cell signaling, and other pathways critical for the onset of the disease [112]. All these properties make the polyphenols potential drugs for preventing and treating neurodegenerative diseases, in particular

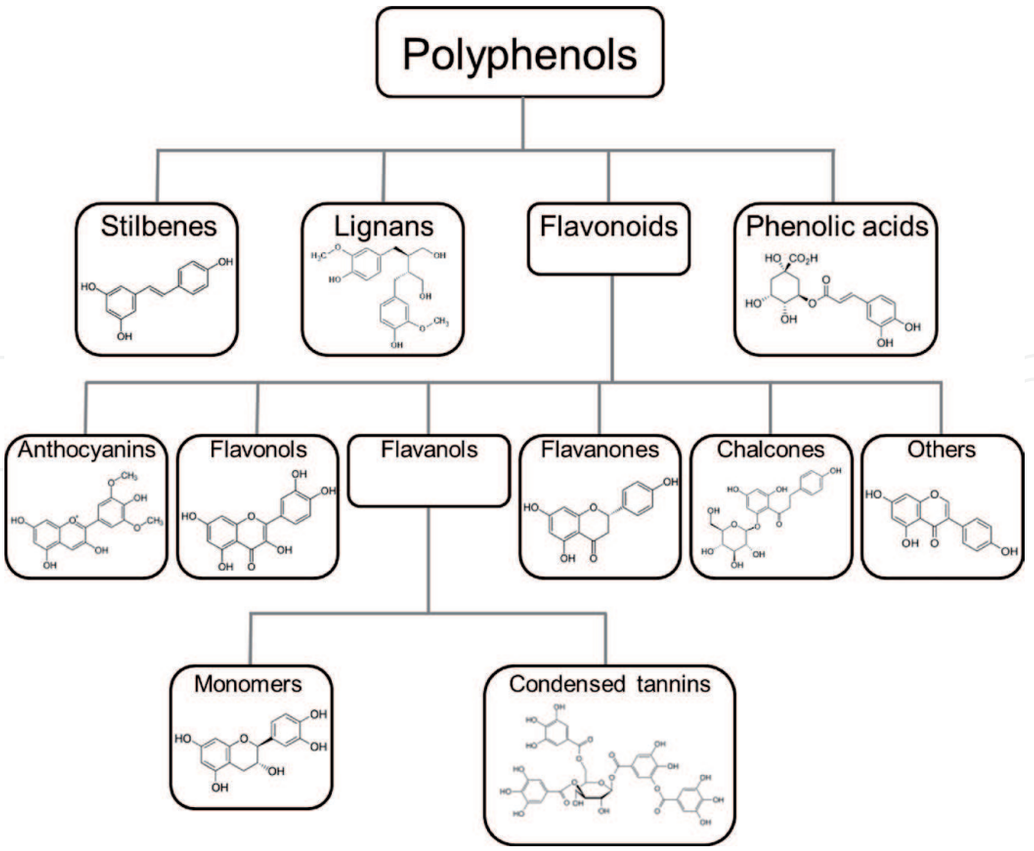

Figure 6.
Scheme of the main polyphenols and their chemical structures. Polyphenols are grouped into four principal classes: stilbenes, lignans, phenolic acids, and flavonoids. The last one is organized into six subclasses: anthocyanins, flavonols, flavanols, flavanones, chalcones, and others.

AD and PD. Actually, these compounds have shown to be effective in epidemiological, *in vitro*, and pre-clinical studies, but not in the early phase of the disease.

4.3 Polyphenols in Alzheimer's and Parkinson's disease

The effects of polyphenols on AD and PD can be divided into two main categories: the effects on nonamyloidogenic pathways (i.e., anti-oxidation pathway, interaction with cell signaling events, and interactions with enzymes) and the effects on amyloidogenic pathways. Below, the main beneficial effects shown by polyphenols on AD and PD are analyzed.

1. *Effects on memory*. One of the hallmarks of AD is the memory impairment. This can be due to deficiency of factors, such as the brain-derived neurotrophic factor (BDNF) and the accumulation of formaldehyde. Polyphenols have been shown to improve the long-term memory by increasing BDNF concentration *in vivo* and decreasing the accumulation of formaldehyde [113–115].

2. *Effects on inflammation pathway*. Inflammation plays an important role in the development of neurodegeneration. It is demonstrated that there is a correlation between the microglia activation and the neuroinflammatory response [116, 117]. Upon microglia activation, the transcription factor NF-kB (nuclear factor k-light-chain-enhancer of activated B cells) moves from cytoplasm to nucleus, inducing the expression of interleukins (i.e., IL-1β, IL-6, IL-12, and IL-23), other factors (i.e., TNF-α and iNOS), and cyclooxygenase 2 (COX-2). In this scenario, polyphenols can interact with certain types of kinases (including the mitogen-activated protein (MAP) kinase) preventing the activation of

proinflammatory mediators [118, 119]. Polyphenol compounds are able to protect cells from inflammation by acting on reactive oxygen species (ROS), decreasing the secretion of prostaglandin E2 [120–123] and increasing the amount of the regulatory enzyme sirtuin1 over sirtuin2, unbalanced after accumulation of Aβ [20]. Cell and PD-mouse model studies demonstrated that these compounds decrease the expression of NF-kB and other inflammatory factors [124–126].

3. *Effects on oxidative pathway, cell death and mitochondrial dysfunction*. In neurodegeneration, there is an uncontrolled production of free radicals and ROS that are not detoxified by the dedicated systems [127]. This leads to macromolecule damage and progressively to cell death [128]. Polyphenols lower the amount of ROS, increase the expression of enzymes, like glutathione, dedicated to scavenger the free radicals and prevent the disruption of mitochondrial membranes [129]. In addition, these compounds seem to prevent the lipid peroxidation [130]. These effects indirectly influence the fibrillation process of Syn, affected by some byproducts of lipid oxidation and peroxidation [131], as demonstrated in PD-animal model studies [132]. Moreover, polyphenols inhibit the cell death by acting on proteins involved in the apoptosis mechanism like Bcl/Bax, caspase 3, and protein kinases and by decreasing the accumulation of Aβ fibrils that exert cytotoxic effects [133, 134]. Another important scenario affected by polyphenols is the mitochondrial dysfunction (MD) that becomes increasingly important in the onset of PD [135]. Different factors play a pivotal role in MD: the presence of neurotoxin, Complex 1 deficiency (involved in mitochondrial electron transport), and penetration of mitochondrial membrane by amyloid aggregates [136, 137]. Polyphenol compounds exert their activity restoring membrane potential, increasing the expression and activity of the Complex 1 and scavenging the ROS, free radicals, and metals [138–141].

4. *Effects on acetylcholinesterase activity*. Nearly 30 years ago, dysfunction in the cholinergic system was found correlated with AD and cognitive impairment [142]. This dysfunction can be originated by a reduction in acetylcholine synthesis, reduced levels of choline acetyltransferase, reduced choline uptake, or cholinergic neurons degeneration [143]. The use of acetylcholinesterase inhibitors to restore the cholinergic pathway has proved to alleviate the cognitive dysfunction in neurodegenerative diseases [144]. Polyphenol compounds have shown to inhibit acetylcholinesterase, improving memory, learning, and cognitive functions [145].

5. *Effects on Aβ formation*. Polyphenol compounds act on the enzyme responsible for Aβ formation, decreasing the cleavage of APP into the peptide. They interact with and inhibit β-secretase [146]. In addition, they are able to restore the normal levels of γ-secretase, another enzyme involved in APP processing [147].

6. *Effects on the amyloidogenic pathways*. Polyphenols can act on Aβ monomer preventing its fibrillation, through the stabilization of the monomer and/or to the formation of an off-pathway oligomer. This can be due to the interaction of polyphenols with metal ions that promote the Aβ aggregation or to the non-covalent interaction with the peptide [148]. They are also able to disaggregate oligomers and fibrils, interacting with the β-sheet structure. This has been confirmed by *in vivo* studies where polyphenol intake reduces the amyloid deposit in the mouse brain [149, 150]. Polyphenols exert their anti-amyloidogenic action by interfering also with the aggregation of Tau [151–153], inhibiting Tau phosphorylation *in vitro* [154] and *in vivo* [155]. Several polyphenols have been tested for their anti-fibrillogenic properties *in vitro* and in PD-animal models.

Their main activity regards the interaction with Syn monomers leading to protein stabilization and fibrillation prevention [92]. Another factor concerns the formation of not toxic off-pathway oligomers that do not form fibrils nor interact with the membrane [156, 157]. Some polyphenols are also able to interact with oligomeric and fibrillar species, leading to their destabilization [65, 92]. The major effect of polyphenols is due to the noncovalent interaction with the Syn C-terminal domain. In addition, these compounds can chemically modify the lysine residues, present mainly in the N-terminal region, through Michael addition and Schiff-base formation [158]. This reduces the conformational plasticity of Syn and its tendency to be converted into fibrils. Moreover, structure-activity relationship studies indicate that the differences in polyphenols activities reside in the number and position of OH groups in the phenyl ring [159].

5. Polyphenols as a drug in the brain delivery system

5.1 Blood-brain barrier and neurodegeneration

The human brain comprises more than 600 km of blood vessels that guarantee oxygen, energy metabolites, and nutrients to brain cells and remove carbon dioxide and toxic metabolic products from the brain to the systemic circulation. A highly selective semipermeable border, called blood-brain barrier (BBB), separates the circulating blood from the central nervous system (CNS), regulating CNS homeostasis. Brain microvascular endothelia cells, neurons, astrocyte, pericytes, tight junctions, and basal membrane constitute tight brain capillaries in the BBB [160, 161]. It follows that BBB does not have fenestrations or other physical fissures for diffusion of small molecules. In fact, ions, solutes, and hormones can pass the BBB by passive diffusion through the paracellular pathway between adjacent cells. Hydrophilic biomolecules (i.e., proteins and peptides) can cross the BBB within specific and saturable receptor-mediated transport mechanisms [162]. The components of BBB constantly adapt in response to various physiological and pathological modifications into the brain [163, 164]. Loss of BBB integrity is correlated with vascular permeability increase, cerebral blood flow impairs, and hemodynamic response alteration [165]. In neurodegenerative disorders, endothelia degeneration leads to loss of tight junctions [166, 167], brain capillary leakages [168, 169], pericyte degeneration [170], endothelial cell remodeling [164], cellular infiltration [171, 172], and aberrant angiogenesis [173, 174]. All these BBB disruptions let different blood proteins (i.e., fibrinogen, plasminogen, and thrombin), water, and electrolytes to accumulate in different zones of CNS, enhancing the on progress of PD and AD [165]. Consequently, to project effective drugs for neurodegeneration, it is necessary to understand in detail BBB pathological aberrations.

Due to their safeness and tolerance [175–177], polyphenols are currently studied as neuroprotectors. It is important to point out that for exerting their action, polyphenols must accumulate in the brain in an active form and in sufficient concentration. The limiting step is choosing the right administration route. In most of the clinical studies, the oral administration is the preferred way, but recently the nasal delivery is taken into consideration for the easiness to bypass the BBB [178], the increased bioavailability, the decreased metabolism, and peripheral side effects [179, 180]. The major problem of oral administration relies on poor absorbance of the modified form of polyphenols (i.e., glycosides and ester polymers) in the upper portion of the gut leading to the passage in the colon in which polyphenols are converted by gut-microbiota in the aglycone form or other substances able to be better absorbed [181, 182]. Once absorbed, they can be further modified by enzymes and eliminated [183, 184] or adsorbed to plasmatic proteins (i.e., albumin) and then accumulated in different districts [185].

5.2 Nanotechnology-based delivery system: An innovative strategy

Nanotechnology is a new branch of science involving the formulation, synthesis, and characterization of small particles, with diameters ranging from 1 to 1000 nm [186], which become key players in innovative drug delivery and cell targeting. Recent studies suggest that nanoparticle-based delivery systems represent innovative and promising approaches to improve drug solubility, prevent acid-degradation, minimize toxic side effects, and increase blood availability [187, 188]. Considering the low bioavailability of polyphenols, different strategies have been developed in order to enhance their chemical stability, solubility, and cell-membrane permeability. These goals have been achieved by adding chemical agents to preserve the structure [189], enzyme inhibitors to contrast biotransformation [190], and lipids or proteins to increase the solubility [191]. Recently, nanoparticle-mediated delivery system is emerged as the most promising approach. Using biodegradable and biocompatible polymers, polyphenols can be encapsulated in different nanostructures and then possibly administrated *via* intravenous, transdermal, nasal, and oral route. As describe above, this aspect is fundamental in neurological diseases, in which polyphenols must cross the BBB, with the opportune grade of lipophilicity [162, 192, 193] and reach the brain tissue in sufficient quantities for therapeutic use. These new delivery systems are represented by nanospheres, nanocapsules, nanoemulsions, solid lipid nanoparticles, cyclodextrins, liposomes, and micelles (**Figure 7**).

Nanospheres (10–200 nm) [194] are homogeneous solid matrix particles characterized by a hydrophobic portion in the inner part and hydrophilic chains anchored on the surface. In nanospheres, the drug is dissolved, entrapped, encapsulated, or attached to the matrix of the polymer, so protected from chemical and enzymatic degradation. Various kinds of polymers are used to prepare nanospheres: polylactic acid (PLA), poly-glycolic acid (PGA), poly-lactic-co-glycolic acid (PLGA), polyethylene glycol (PEG), poly ε-caprolactone (PCL), and chitosan (CS) [195, 196].

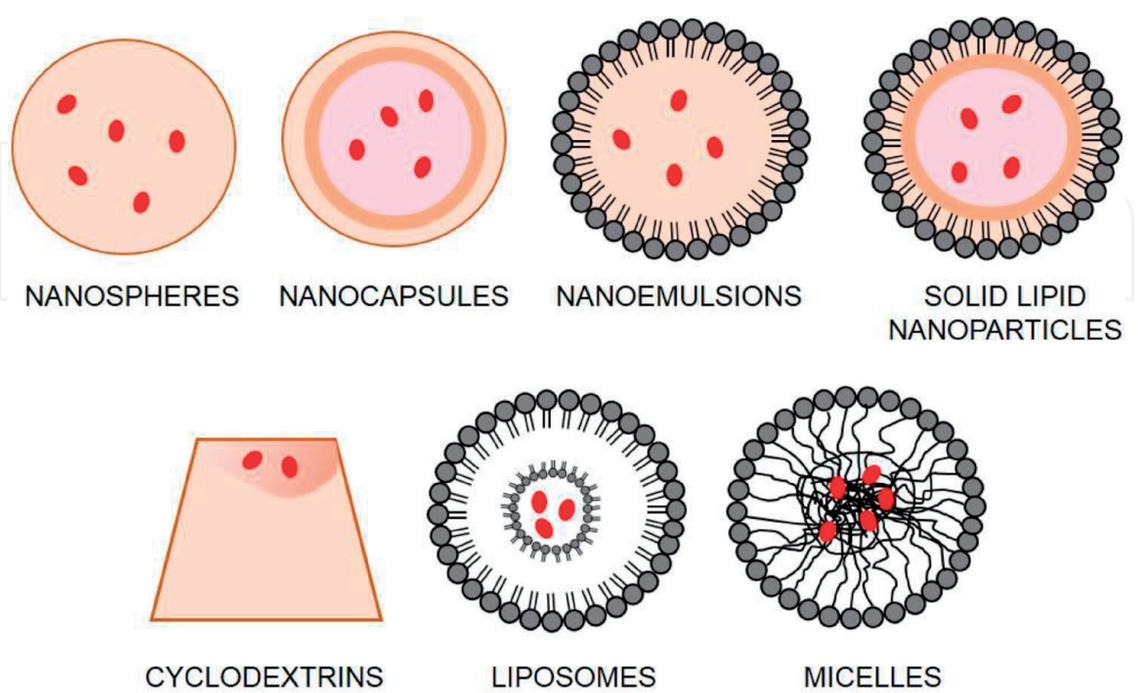

Figure 7.
Schematic representation of nanosized delivery systems for polyphenols. Nanoparticles can enhance polyphenol bioavailability, enhancing their adsorption across intestinal epithelium, increasing their concentration in the bloodstream, and improving their ability to cross the blood-brain barrier.

Nanocapsules (10–1000 nm) have a similar chemical composition but comprise an oily or aqueous core, which is surrounded by a thin polymer membrane [197, 198]. The cavity can contain the drug in liquid or solid form. Furthermore, the medication can be carried on nanovector surface or absorbed in the polymeric membrane [198–200].

Nanoemulsions are oil-in-water or water-in-oil emulsions stabilized by one or more surfactants (i.e., phosphatidylcholine, sodium deoxycholate, sorbitan monolaurate, poloxamers, sodium dodecyl sulfate, and poly(ethylene glycol)) delivered in droplets of small dimensions (100–300 nm) [191]. The strategy allows having a higher surface area and a long-term chemical and physical stability [201, 202]. Nanoemulsions represent an innovative formulation to deliver polyphenols directly into the brain through the intranasal route. In fact, mucoadesive polymers, such as CS, can be added to slow down nasal clearance [191].

Solid lipid nanoparticles (50–1000 nm) [194] are composed of high melting point lipid, organized in a solid core, coated by aqueous surfactants (i.e., sphingomyelins, bile salts, and sterols) [198]. Even though these nanoparticles present high biocompatibility, bioavailability and physical stability, the common undesirable disadvantages are particle growth, arbitrary gelation tendency, and unpredicted dynamic of polymorphic transitions [198].

Cyclodextrins (1–2 nm) [194] are a group of structurally related natural products formed from the bacterial digestion of cellulose. Cyclodextrins are cyclic oligosaccharides consisting of (α-1,4)-linked α-D-glucopyranose units with a lipophilic central cavity and a hydrophilic outer surface [203]. The hydroxyl functions are orientated to the exterior, while the central cavity is wrinkled by the skeletal carbons and ethereal oxygens of the glucose residues. Natural cyclodextrins are classified by the number of glucopyranose units in α-(six units), β-(seven units), and γ-(eight units) [204]. Recently, cyclodextrins containing from 9 to 13 glucopyranose units have been reported. These carriers are useful for increasing the solubility and the stability of poorly water-soluble drugs. Moreover, cyclodextrins can be derivatized with hydroxypropyl, methyl, and sulfobutyl-ether additives [203]. So, drugs can be allocated into the cavity *via* van der Waals forces, hydrophobic interactions, or hydrogen bonds [205].

Liposomes (30–2000 nm) [194] are phospholipid vesicles containing one or more concentric lipid bilayers enclosing an aqueous space. Liposomes can assemble spontaneously by hydration of lipid-derivate powder (i.e., cholesterol, glycolipids, sphingolipids, long chain fatty acids, and membrane proteins) in aqueous buffer [195]. Due to their ability to capture hydrophilic and lipophilic substances, in the aqueous space or into the lipid bilayer membrane, respectively, they can protect drugs from early inactivation, degradation, and loss [206].

Micelles (5–100 nm) are colloidal dispersions, consisting of amphiphilic copolymers (i.e., PEG, PLGA, and PCL) that assemble naturally in water at a specific concentration and temperature [207]. When polymer concentration is greater than the critical micelle concentration, micelles start to be assembled: hydrophobic fragments of amphiphilic reagents form the core, whereas hydrophilic portion form the shells [208]. Micelles are characterized by high stability, biocompatibility, and ability to keep in solution poorly soluble drugs.

5.3 Nanotechnology as an innovative delivery system of polyphenols

The use of biodegradable and biocompatible polymers allows rationalizing the design of innovative nanostructures able to encapsulate polyphenols that can cross the BBB, improving the limitations associated with conventional administrations. In this scenario, curcumin is the most studied drug candidate, due to the prominent results obtained in the animal model of neurodegenerative diseases [209–211].

In fact, the efficacy of curcumin is so far limited by the poor aqueous solubility, low adsorption in the gastrointestinal tract, and rapid metabolism. Nanosphere of PGLA containing curcumin can be the right strategy for crossing BBB. Recent studies indicated how curcumin-PGLA nanoparticles can interfere with Aβ aggregation and improve the brain self-repair mechanism, increasing the neural stem cell proliferation and neuronal differentiation [212]. In the same way, liposomes loaded with curcumin can efficiently inhibit the *in vitro* formation of Aβ fibrils and deposition in the brain [213]. Curcumin-solid lipid nanoparticles seem to be effective for MD and central oxidative stress [214]. In addition, curcumin and piperine co-loaded glycerol mono-oleate nanoparticles can interfere with Syn aggregation, reducing oxidative damage and apoptosis [215]. Curcumin was also taken in consideration for intranasal delivery to the central nervous system by nanoemulsions. In the presence of CS, nanoemulsions of curcumin (added in the oil phase) can effectively cross the mucosa without showing cytotoxicity [209].

Another good candidate is resveratrol. It is known for its ability to induce the degradation of APP and to remove Aβ [216]. But, due to its rapid and extensive metabolism, resveratrol is subjected to a *person-to-person* bioavailability. PEG-PCL and PGLA nanoparticles loaded with resveratrol let a controlled release profile of the drug, essential for prolonging its plasmatic level and the antioxidant activity [217, 218]. A promising approach is the oil-in-water nanoemulsion [219]. Adding Vitamin E and other surfactants, this formulation can reach the brain *via* the nasal route, with encouraging efficacy [220]. Furthermore, the co-encapsulation of curcumin and resveratrol (1:1 weight ratio) in mucoadhesive nanoemulsions protects the active substances from degradation and preserves their antioxidant properties. Notably, *in vivo* quantification in animal brain indicated an increase of the amount of the two polyphenols after 6 hours [221]. Unfortunately, these systems have not yet reached clinical trials, but the results accumulated so far encourage new original therapeutic approaches.

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Author details

Patrizia Polverino de Laureto*, Luana Palazzi and Laura Acquasaliente
Protein Chemistry Unit, Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Padova, Italy

*Address all correspondence to: patrizia.polverinodelaureto@unipd.it

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