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Review

Natural Compounds and Neuroprotection: Mechanisms of Action and Novel Delivery Systems

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Abstract. *Neurodegeneration characterizes pathologic conditions, ranging from Alzheimer's disease to glaucoma, with devastating social and economic effects. It is a complex process implicating a series of molecular and cellular events, such as oxidative stress, mitochondrial dysfunction, protein misfolding, excitotoxicity and inflammation. Natural compounds, because of their broad spectrum of pharmacological and biological activities, could be possible candidates for the management of such multifactorial morbidities. However, their therapeutic potential against neurodegenerative diseases has been hampered by their poor bioavailability and subsequent insufficient delivery to the brain. This article provides an overview of the molecular mechanisms through which natural compounds exert their neuroprotective effects, as well as the development of novel natural compound-loaded delivery systems that could improve their neuroavailability.*

Neurodegenerative diseases are characterized by progressive loss of structure or function of neurons and include a broad range of conditions, from Parkinson's (PD), Alzheimer's (AD), Huntington's disease (HD) to glaucoma (1). They represent rapidly growing causes of disability and even death, having profound social and economic implications. Neurodegeneration is the result of a complex cascade of pathological events, including oxidative stress, mitochondrial dysfunction, inflammation and protein aggregation (2, 3). The increasing knowledge of the cellular and molecular events underlying the degenerative process has greatly stimulated research for identifying compounds capable of stopping or, at least, slowing the progress of neural deterioration.

Natural compounds are complex chemical multiple-target molecules found mainly in plants and microorganisms (4). These agents have been extensively studied regarding their antioxidant activities. However, in addition to their ability to prevent damage caused by oxidative stress, they have been shown to modulate multiple signal transduction pathways through direct effects on enzymes, such as kinases, regulatory proteins and receptors (4, 5). Furthermore, it has been suggested that many polyphenols exert some of their beneficial biological effects *via* chromatin remodeling and epigenetic modifications (6). This broad spectrum of pharmacological or biological activities has made them suitable candidates for the treatment of multifactorial diseases, such as cancer and neurodegenerative diseases (7-9). Indeed, there are studies suggesting a correlation between consumption of flavonoids and low population rates of dementia (10). However, their physicochemical properties are not drug-like and a number of challenges, concerning their stability and neuroavailability, need to be overcome in order to be established as effective therapeutics.

This review focuses on the neuroprotective role that natural compounds have through different molecular mechanisms on the biological processes involved in neurodegenerative diseases. Furthermore, the development of novel delivery systems, that could improve the neuroavailability and subsequently the neuroprotective activity of the natural compounds, is discussed.

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Neuroprotective Targets of Natural Compounds

Mitochondrial Dysfunction

Neurons are heavily dependent on mitochondria for survival because of their high energy requirement. Mitochondria are important in various essential cellular functions, including apoptosis, metabolism and calcium homeostasis. Regarding oxidative stress, they are both an important source of reactive oxygen species (ROS) production and a major target for ROS-induced cellular injury. Given the role of mitochondria as key regulators of cellular death and life, it is expected that alterations in their biology have implications in a wide array of diseases, such as neurodegenerative ones (11-13). A direct link between mitochondrial dysfunction and neurotoxic manifestations of anticancer drugs has also been established (14).

SIRT1, a sirtuin protein family member, is a nicotinamide adenine dinucleotide (NAD)(+)-dependent histone and protein deacetylase. A large number of studies have reported that activation and overexpression of SIRT1 are neuroprotective in both acute central nervous system (CNS) injuries and chronic neurodegenerative diseases (15). AMP-activated protein kinase (AMPK) enhances SIRT activity by increasing cellular NAD+ levels leading to the deacetylation and modulation of the activity of downstream SIRT1 targets like peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) (16), a master regulator of mitochondrial biogenesis (17). Therefore, the AMPK/SIRT1/ PGC-1α axis is strongly related to the orchestration of mitochondrial function and energy/redox status in mammalian cells.

Nature has been a major source of substances that can improve mitochondrial function (18). Among them polyphenols, such as luteolin, myricitrin, quercetin (QCT) and epigallocatechin gallate (EGCG) have been extensively studied regarding their beneficial effects on mitochondrial function both *in vitro* and *in vivo* (19-22). In addition to these, proanthocyanidins, a group of polyphenolic bioflavonoids, ameliorate the hydrogen peroxide-induced mitochondrial dysfunction *via* stimulating the mitochondrial membrane potential (MMP) and respiratory chain complex IV, while moderating the mitochondrial free radical production, ROS and mitochondrial superoxide (23). Also, hesperidin has been reported to enhance the mitochondrial complex I-IV enzymatic potential (22). On the other hand, resveratrol (RSV) may act directly or indirectly on the mitochondria with subsequent beneficial effects (reviewed by de Oliveira *et al*. (24)). The mechanism by which RSV modulates mitochondrial function is through regulation of cell signaling pathways and genes involved in mitochondrial biogenesis, endogenous antioxidant defense and oxidative phosphorylation (25, 26). In particular, RSV regulates the gene expression of antioxidant enzymes, such as manganese-dependent superoxide dismutase (*Mn-SOD*) and modulates uncoupling protein 2 (UCP2) protein levels in mitochondrial membranes, both important in the redox maintenance of the organelle, possibly through SIRT1 activation (24, 27). It has also been shown in different *in vivo* and *in vitro* experimental models that the AMPK–SIRT1 pathway plays a pivot role in RSV-induced neuroprotection (28-30). Furthermore, co-administration of EGCG and RSV reversed the severe impairment of mitochondrial bioenergetics and biogenesis in hippocampal progenitor cells from a Down syndrome mouse model *via* activation of the AMPK/Sirt1/PGC-1α axis as well (31). Finally, the neuroprotective role of viniferin, a stilbene RSV dimer, in an HD model was shown to be mediated through the AMPK/SIRT3 pathway (32).

Concerning anti-neoplastic agent-induced neurotoxicity, natural compounds have also been studied. Co-administration of curcumin (CUR) and QCT mitigated peripheral neurotoxicity induced by oxaliplatin through the restoration of glutathione S-transferase (GST), glutathione peroxidase (GPx) and MnSOD activity (11, 14, 33).

Neurodegeneration, as a complication of diabetes, it is known to be associated with dicarbonyl glycation and methylglyoxal (MGO), a major precursor of advanced glycation end products (AGEs), which target mainly mitochondrial proteins. Several *in vivo* and *in vitro* studies have pointed out that flavonoids could inhibit the formation of AGEs and prevent diabetic neurodegeneration (34, 35). Moreover, myricitrin was shown to alleviate MGO-induced mitochondrial dysfunction, possibly through modulation of the AGEs/Receptor for AGEs (RAGE)/Nuclear factor kappa B (NF-kappaB) pathway (36).

Apoptosis

Apoptotic neuronal death is a common feature in the brain of patients suffering from many neurodegenerative diseases and either intrinsic (mitochondrial-mediated) or extrinsic (death receptor-mediated) (37) is controlled by several proteins (38). The Bcl-2 protein family plays an essential role in the regulation of the intrinsic pathway *via* monitoring mitochondrial membrane permeability and the release of the pro-apoptotic factor, cytochrome c, which promotes the caspase-9 activation (39, 40). Bcl-2 proteins include members that inhibit apoptosis (such as Bcl-2, Bcl-w, Bcl-xL, Mcl-1) or promote apoptosis (such as Bak, Bad, Bax, Bcl-rambo). It is the balance between these members that determines whether or not a cell will undergo apoptosis. On the other hand, the caspase cascade may be initiated at the endoplasmic reticulum (ER) as well (40) by stress conditions, which affect the folding of proteins in ER lumen (41, 42). Finally, in addition to ER-resident proteins and mitochondria, several stress-sensing transcription factors are stimulated and implicated in AD pathogenesis (43).

Many natural compounds with neuroprotective effects have been shown to act by directly affecting programmed cell death pathways. Bilobalide, the main terpenoid of Ginkgo biloba leaves, showed potent protective effects on neurons and Schwann cells (44), prevented ROS-induced apoptosis in early stages and attenuated the elevation of Bax, p53 and caspase-3 in PC12 cells (43, 45). Furthermore, bilobalide modified mitochondrial function through up-regulation of cytochrome c oxidase subunit I (46). Huperzine A, a sesquiterpene alkaloid, has been shown to inhibit apoptotic factors, such as caspase-3, Bax and p53 (47). Finally, ER stress-induced apoptosis was impeded by the bioflavonoid apigenin, through suppression of ROS accumulation, inhibition of caspase-12 and -3 activation and cleavage of poly (ADP-ribose) polymerase (PARP).

Excitotoxicity

Glutamate is a main excitatory neuro-transmitter in the CNS, including the retina (48). It is released in the presynaptic terminals for very brief periods of time and binds to a variety of receptor-linked channels in the postsynaptic membrane, resulting in the influx of Ca^{++} and the initiation of the action potential (49). There are three classes of glutamate-gated ion channels, known as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and N-methyl-D aspartate (NMDA) receptors. Glutamate presence in excessive amounts or for excessive periods of time can literally excite cells to apoptotic cell death, mainly due to high Ca^{++} level in the cytosol (50, 51). Furthermore, the disruption of energy metabolism during acute and chronic neurodegenerative disorders may lead to inefficient glutamate clearance or even inappropriate release, which cause elevated levels of glutamate and increased concentrations of cytosolic Ca^{++} (52). Finally, excitotoxicity can arise even with normal levels of glutamate, if NMDA receptor is activated (53).

Glutamate receptor-mediated excitotoxicity has been associated with several diseases of the brain, whereas *in vivo* and *in vitro* studies have shown that blocking the NMDA and the non-NMDA receptors simultaneously results in maximum protection against ischemic neurodegeneration (54). (–)-kaitocephalin, a natural compound isolated from the fungus *Eupenicillium shearii*, has been shown to be a potent antagonist of particular subtypes of glutamate receptors (AMPA and NMDA, but not kainate) and to protect CNS neurons from excitotoxicity (55). Furthermore, myricetin inhibited glutamate-induced excitotoxicity in neurons; specifically, it affected NMDAR receptor (NMDAR) phosphorylation, which had, as a result, reduction of intracellular Ca^{++} overload. Myricetin also inhibited the glutamate-induced ROS production and the activity of caspase-3 by interacting with it. (56). On the other hand, acacetin has been shown to effectively prevent kainic acid-induced *in vivo* excitotoxicity by inhibiting glutamate release from rat hippocampal synaptosomes *via* attenuation of voltage-dependent Ca^{++} entry (57).

Inflammation

Chronic inflammation in the CNS has been shown to be related to neuronal injury and death in neurodegenerative diseases (58). Activated microglia, the resident immune cells of the CNS, are one of the prime participants in neuroinflammation (59) and thought to contribute to neuronal death through the production of reactive nitrogen species (RNS) and ROS (60). The fibrillar β-amyloid peptide (Aβ) deposits also play a crucial role in tissue neuroinflammation (61).

NF-kappa B/Rel proteins are dimeric, sequence-specific transcription factors involved in the activation of a remarkably large number of genes, in response to tumor necrosis factor α (TNF-α), lipopolysaccharide (LPS) and other stressful stimuli that require rapid reprogramming of gene expression (62). NF-kappa B is sequestered and inactive in the cytoplasm bound to inhibitory I-kappa B proteins in unstimulated cells. Induction results in phosphorylation, ubiquitinylation and, ultimately, proteolytic degradation of Ikappa B and subsequent release and translocation of NF-kappa B to the nucleus where it activates the transcription of specific target genes (62). NF-kappaB induces production of various mediators, such as nitric oxide (NO), and regulates a number of inflammation- and oxidative stress-related genes, such as cyclooxygenase 2 (*COX-2*) (43, 63). The activation of NF-kappaB, particularly in the CNS, has been shown to trigger multicellular responses, including transactivation of inflammatory molecules and production of free radicals in glial cells, which are intricately associated with the initiation and progression of neurodegenerative diseases. (63). However, the final effect of NF-kappa B stimulation on neuronal survival and death potentially depends on parameters, such as cell type, developmental stages of cells, type of signal and the nature of activated NF-kappaB dimers (64-66).

Based on the fact that inflammation contributes to the continued loss of CNS neurons, even if in some cases it is not the primary causative process, the use of anti-inflammatory compounds has been proposed for diminishing the cumulative effects of inflammation in the brain (67). Flavonoids have been reported to exert their anti-inflammatory effect through intervention in a broad range of molecular pathways related to inflammation (68, 69), such as the release of pro-inflammatory cytokines and microglia activation (70). Daidzein and possibly other isoflavones as well have been reported to be neuroprotective due to their ability to dampen the induction of microglial activation and

subsequent release of soluble pro-inflammatory factors by inhibiting the oxidative induction of the p38 mitogen-activated protein kinase (MAPK)-NFkappa B pathway (71).

Moreover, flavonoids, including EGCG, have been reported to modulate T cell response partially through inhibition of NF-kappa B signaling (72-74). In addition, a transgenic mouse model of amyotrophic lateral sclerosis treated with EGCG displayed increased neuron survival and diminished microglial activation (75).

Several studies have shown that NF-kappa B signal transduction is down-regulated by flavonoids (68) through activation of extracellular signal-related kinase 1,2 (ERK1/2) or inhibition of the IkappaB kinase activity (76). Since COX-2 is synthesized through an NF-kappa B-mediated pathway, another important target of flavonoids accounting for their anti-inflammatory effect could be COX-2 at the expression level. Indeed, many flavonoids were reported to be efficient COX inhibitors (68). On the other hand, polyphenols, such as CUR, RSV and catechins, have been reported to affect nuclear NF-kappaB expression and chromatin remodeling through modulation of histone deacetylase (HDACs) and DNA methyl transferase (DNMTs) activities (6). Interestingly, regarding CUR, it has been shown that it can also inhibit NF-kappaB signaling by acting as an agonist of the peroxisome proliferator-activated receptor γ (PPAR-γ) (77, 78).

Additionally, flavonoids have been shown to inhibit LPS-induced production of inflammatory cytokines in human monocytes (79) and astrocytes (80). Moreover, they have been demonstrated to inhibit the activity of kinases, such as protein kinase C (PKC), p38 MAPK and Jun N-terminal kinase/stress-activated protein kinase, that are important partners in inflammatory signal transduction pathways (81, 82).

Oxidative Stress

Oxidative stress is recognized as an essential factor in a variety of neurodegenerative diseases as a mechanism for age-related degenerative processes and as a mediator of the adverse effects of neurotoxicants (83). Oxidative stress causes damage to proteins, lipids, DNA and occurs when ROS accumulate in cells, from either excessive production or insufficient neutralization, due to an imbalance between antioxidant defense systems and production of ROS (84). Production of ROS and RNS may lead to irreversible deleterious modification of macromolecules like proteins and neuronal cell death. The brain is sensitive to accumulation of these reactive species due to its inadequate ability to neutralize their effects (85). In specific, it retains high concentration of transition metals, high aerobic metabolism and increased levels of ascorbic acid, all of them contributing to production of ROS/RNS and oxidized products (86), whereas it does not have a competent antioxidant defense system characterized by moderate activity of antioxidant enzymes, such as superoxide dismutases (SODs) and catalase, as well as low levels of glutathione (87). Finally, many neurotransmitters are autoxidized to generate ROS and RNS like NO (86). In addition to these, another contributing factor to oxidative stress in neurodegenerative disorders is inflammation caused by activated microglia (86, 88).

The nuclear factor E2-related factor 2 (Nrf2) signaling pathway is primarily responsible for cellular defense against oxidative stress (89). Nrf2 is a fundamental transcription factor implicated in transcriptional activation of phase II detoxifying enzymes through antioxidant response element (ARE) (90, 91). It has also been reported that Nrf2 activation, in macrophages and microglia, down-regulates the NF-kappa B-related inflammatory responses (92, 93).

Natural compounds have received much attention as potent antioxidants and polyphenols have been the most investigated (94). Phenolic compounds, such as flavonoids, rosmarinic acid, ferulic, caffeic, chlorogenic, vanillic, p-hydroxybenzoic acid, protocatechuic acid and p-coumaric acid, were identified to contribute to the antioxidant potential by various scavenging assays (83, 86). Besides enhancing the efficiency of antioxidant gene regulation, natural antioxidants also exert their effects through additional mechanisms of action, including hydrogen atom transfer, electron donation, direct radical scavenging, metal chelation, restoration of endogenous antioxidant levels, activation of antioxidant enzymes, singlet oxygen quenching and activation of Nrf2 pathway (reviewed by Fraubberger *et al.* (95)).

Protein Misfolding

Most neurodegenerative disorders share a common feature. A protein accumulates in an insoluble form in the affected tissue (96). The identity of the proteins and the site of the deposits are distinguishing for each particular disorder (97). However, the majority of the affected proteins or protein fragments are, at least, partially unfolded under physiological conditions (96, 98) and all of them share a typical intramolecular cross-beta sheet conformation that leads to the formation of insoluble fibrillar structures (96). The mechanism of amyloid formation in protein misfolding disorders follows a process of seeded polymerization similar to one-dimensional crystal growth (96). Large fibrillar aggregates are formed by aggregates of a certain size or conformation, which stabilize and catalyze the addition of monomers (96, 99). Products of an alternative proteolytic processing of the amyloid precursor protein (APP) forms the extracellular protein deposits in AD (96), whereas intraneuronal deposits in the form of neurofibrillary tangles are formed by the microtubule-associated highly phosphorylated protein tau (96, 100-102). The other frequent protein misfolding disease, PD, is characterized by deposits

located in dopaminergic neurons of the substantia nigra, which primarily contain the alpha-synuclein protein (αS) but have also tau and Aβ as secondary components (96, 103).

Polyphenolic extract has been shown to decrease the formation of amyloid deposits (104, 105) and to significantly attenuate cognitive deterioration in a mouse model of AD (106) through its antioxidant activity (107) and the promotion of APP degradation into non-amyloidogenic peptides (108-110). It has also been reported that EGCG prevents the fibrillization of several proteins that are implicated in protein misfolding disorders by binding directly to them (96, 111). Moreover, it promotes the formation of spherical, stable, not cytotoxic aggregates, which have a lower β-sheet content than fibrils, and do not catalyze fibril formation (96). Derivatives of orcein have been reported not only to accelerate fibril formation of the AD-related Aβ peptide but also to deplete oligomeric and protofibrillar forms of the peptide (96). The phenylethanoid oleuropein aglycone (OLE), which arises from deglycosylation of oleuropein, found in the leaves and drupes of *Olea europaea*, was able to abolish the formation of toxic oligomers during the *in vitro* amyloid aggregation of the Aβ peptide, as well as promote fibril and plaque disaggregation, in various model organisms with subsequent relief of AD-like symptoms (112-115). OLE is also active against tau and human islet amyloid polypeptide (hIAPP) aggregation *in vitro* (116, 117). Finally, RSV derivatives significantly inhibited Aβ aggregation, disaggregated fibrils generated by self- and Cu(II)-induced Aβ aggregation and displayed antioxidant effect (118).

Neurotrophic Activity

Neurotrophins, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3) and neurotrophin 4 (NT4), play essential roles in development, maintenance, repair and survival of particular neuronal populations (119), whereas the diminished function of neurotrophins and their receptors can result in neuronal damage, contributing in that way to the pathogenesis of neurodegenerative disorders (120).

Neurotrophins interact with two receptor types: neurotrophin receptor p75 (p75NTR) and the tropomyosin receptor kinase (Trk) receptors (TrkA, B and C) (121). The Trk receptors are dimerized upon neurotrophins binding and are activated by transphosphorylation of the cytoplasmic domain kinases, an event leading to the stimulation of the downstream signaling effectors MAPK, phoshpatidyloinositol-3-kinase (PI3K)/Akt and phospholipase C-γ1 (121, 122).

Several studies have shown that various polyphenols, including flavonoids and acetylated flavonoid glycosides from *Scoparia dulcis*, are capable of enhancing the activity of NGF (123), whereas the stilbenoid compound RSV produced neurotrophic effects on cultured dopamine neurons through promoting neurotrophic factors release (124).

A few polyphenolic compounds act as Trk receptors agonists, whereas many others activate downstream effectors, leading to a neurotrophic effect (120). 7,8-Dihydroxyflavone (7,8-DHF) triggers TrkB dimerization and tyrosine phosphorylation and stimulates downstream effectors (125). The flavonoid epicatechin has been reported to restore TrkA phosphorylation in diabetic animal models and to reduce diabetes-related neuronal cell death (120, 126). The diterpenes, kansuinin A, D, E, isolated from the roots of *Euphorbia kansui*, promoted the survival of TrkA- or TrkA- and B-expressing fibroblasts (127). The quinic acid metabolite (–)-3,5-dicaffeoyl-muco-quinic acid has been shown to enhance neurite outgrowth in PC12 cells through activation of signaling pathways similar to NGF, thus suggesting that this secondary metabolite specifically activates TrkA (128). Interestingly, a compound isolated from the fungus *Penicillium fellutanum*, fellutamide B, has been reported to possess unique neurotrophic activity through inhibition of the proteasome and increase in the production and secretion of NGF (129, 130). Many polyphenolic compounds, including flavonoids, have also been shown to increase the expression of NGF, glial cell line-derived neurotrophic factor (GDNF), BDNF, TrkA or TrkB, in various *in vivo* animal models (120) *via* activation of ERK-CREB-BDNF pathway, Nrf2/ARE signaling pathway or Akt/ Glycogen synthase kinase 3β (GSK-3β) signaling pathway (reviewed by Moosavi *et al*. (120)). Finally, the neuroprotective potency of natural compounds could be a consequence of less studied mechanisms, such as modulation of action of Na+/K+/2Cl co-transporter (NKCC1) or A2A receptor (131).

Neuronal Survival Signaling Pathways

Modulation of neuronal survival signal transduction pathways may be an attractive approach to the treatment of CNS diseases.

Wnt signaling contributes to normal neural development, neuronal homeostasis, axonogenesis, synaptic plasticity and the establishment of brain polarity (43, 132). GSK-3β inhibition by CUR has been demonstrated to lead to Wnt/β-catenin signaling activation and subsequent reduced Aβ production (133-135).

ERK pathway, a part of MAPKs, has been involved in many neuronal functions, such as proliferation, differentiation, survival and regulation of neuronal response to various growth factors (120). ERK1/2 activation by several polyphenolic compounds like luteolin promoted survival in various cell lines, enhanced neurite outgrowth and neuronal differentiation (136, 137). Moreover, liquiritin, icaritin and rutin have shown favorable effects against Aβ-

induced neurotoxicity *in vivo* through activation of MAPK and BDNF (120).

A number of studies have also reported that PI3K and its downstream effector Akt may be responsible for neuronal survival, increased neurite outgrowth, as well as other polyphenols-mediated neurotrophic actions (120). The PI3K/Akt pathway, for instance, has been implicated in the neuroprotective effect of CUR in a rat model of Aβ-induced cognitive impairment (138). Puerarin similarly, *via* stimulation of the ERK1/2 and PI3K/Akt pathways, potentiated NGF-induced neuritogenesis in PC12 cells and protected dopaminergic cells (139). Finally, activation of the MAPK/ERK and PI3K/Akt pathways, both downstream signaling effectors of BDN, have been shown to account for the astilbin-induced improvement of depressive-like behaviors in mice models of depression (120).

CREB is a transcription regulator that recognizes Cyclic AMP response element (CRE) sequence and, once activated, up-regulates the expression of genes responsible for survival, growth, synaptic plasticity, dendritic spine formation, differentiation and long-term memory (120, 140). CUR, nobiletin and hesperetin have all been shown to induce CREB phosphorylation in PC12 cells, while green tea catechins and several flavonoids have been shown to activate CREB in various *in vivo* neurodegenerative models (120).

Autophagy

Autophagy is a multistep process implicating the formation of the autophagosomes, double- membrane structures, which fuse with lysosomes, (141) and their content (cellular metabolic waste, misfolded proteins) is degraded by hydrolytic enzymes. Autophagy is also crucial for mitochondrial turnover under physiological conditions, in a process known as mitophagy (142). Normal basal autophagy plays a fundamental role in the integrity of the CNS (141, 143). Therefore, stimulation of autophagy in the CNS would lead to neuroprotection and that could be the case for the beneficial effects of various compounds, including RSV (144). QCT-induced autophagy has been shown to alleviate Schwann cells' damage caused by high glucose (145). OLE was also found to induce autophagy and to reduce inflammation in a mouse model of Aß deposition (115). Furthermore, RSV was shown recently to affect mitochondrial fission and mitophagy as well (24).

Epigenetics

Epigenetic mechanisms, such as DNA methylation, genomic imprinting, histone modification and regulation by microRNA, are important for normal development and maintenance of adult life and their dysregulation may also contribute to the susceptibility and complexity of neurodegenerative diseases (146). Indeed, DNA methylation is involved in AD-related molecular mechanisms (147) (reviewed by Mastroeni *et al*. (148)).

Natural compounds, including polyphenols, alkaloids, terpenoids and organosulfur compounds, may play an essential role in modulating these epigenetic modifications (6, 28) and several of them have been reported to be able to alter DNA methylation and histone modifications leading to gene activation or silencing (6). Many polyphenols display their neuroprotective effects through activation of HDACs, whereas polyphenols with anti-inflammatory properties, such as catechins, RSV and CUR, were reported to modify NF-kappaB expression and chromatin remodeling through modulation of both HDACs and DNMTs activities (6).

Other Targets

It has been shown that AD is related to a reduction of cholinergic neurons' activity (149). Galantamine, an alkaloid used for the symptomatic treatment of AD, shows neuroprotective effect through activation of muscarinic acetylcholine receptors (150). Finally, flavonoids, as well as other natural compounds, have been reported to inhibit monoamine oxidases (MAO) (151), mitochondrial bound enzymes, which have been implicated in various processes leading to neurodegeneration, such as oxidative stress, neuroinflammation, triggering of apoptosis and glial activation (152).

Bioavailability Issues and Development of Novel Delivery Systems

Natural compounds usually target multiple signaling pathways and regulate gene expression broadly leading to a wide-ranging spectrum of activities, such as anti-inflammatory and antioxidant. These multi-targeting properties of natural compounds make them attractive candidates for the treatment of disorders, where a multitude of pathophysiological pathways is affected, like neurodegenerative diseases (7-9).

However, their physicochemical properties are not drug-like. Several natural compounds show limited stability as they are sensitive to degradation or are metabolized to inactive derivatives in circulation (153, 154). Indeed, tea catechins undergo extensive methylation, glucuronidation and sulfation (155). Also, RSV and CUR have low bioavailability due to their rapid metabolism and elimination (156, 157). Compound solubility might be an additional issue, since most of them show limited solubility in water (153). Moreover, restricted passage across the blood brain barrier (BBB) (158) and subsequent limited distribution to brain tissue contribute to poor bioavailability (153). But even when the compound reaches the brain and passes the BBB, it will be diluted and cleared in cerebrospinal fluid before

distributed into the brain parenchyma (159). Therefore, the properties of the compound delivery system are crucial for efficient biodistribution (159). Finally, relatively high local compound concentrations are required for a desirable effect because of the modest potency of natural therapeutic agents.

Given the rapid progression in the field of nanomedicine, research has now concentrated on shifting from microsystems to nanocarriers for the treatment of neurodegenerative disorders. The incorporation of nanoparticles with the specific formulation and physicochemical properties aims to improve the bioavailability, as well as the targeting and the controlled-release profiles of natural products (160).

In order to overcome solubility issues of natural compounds for *in vivo* application, the liposomal formulation has been applied as a broadly used strategy (153). Encapsulating highly lipophilic compounds, such as EGCG, RSV and CUR, which dissolve poorly in the bloodstream, can increase their water solubility and efficiency. It has been reported, that EGCG nanolipids' oral bioavailability was higher than free EGCG (161) and lipid core nanocapsules loaded with RSV increased RSV concentration in brain tissue, compared to free RSV. Several drug delivery systems have been tested for improved targeting of CUR, such as liposomes, solid lipid nanoparticles (SLNs), polymeric nanoparticles (poly(lactic-co-glycolic acid -PLGA), nanogels, micelles and complexes with dendrimer/dimer (43). SLN of CUR showed a great recovery in membrane lipids, as well as acetylcholinesterase (AChE) activity, in aluminium chloride -treated mice, an effect that was comparable to rivastigmine (43, 162) Recently, SLN-encapsulated QCT showed a better neuroprotective effect, indicating improved penetration *via* BBB (163). According to another study, QCT-loaded β-cyclodextrin dodecylcarbonate nanoparticles decreased inflammatory mediators in a neuronal cell line (164). Incorporating the flavone apigenin into a carbon nanopowder, solid distribution improved its low lipid and water solubility, whereas self-nanoemulsifying QCT also showed increased bioavailability, compared to free QCT. (165, 166).

Polymeric nanoparticles have been broadly tested in combination with natural products and polymers, such as poly(vinyl alcohol (PVA), polyethylene glycol (PEG) and polylactide (PLA), have been utilized to improve the bioavailability of EGCG, luteolin, silibinin and tea polyphenols. (166). Berberine–loaded nanoemulsion formulation also increased its bioavailability (167) Finally, polysaccharides, which have recently been demonstrated to form amorphous solid dispersions in nanoparticle form, significantly enhanced the solubility and bioavailability of natural compounds, including CUR, ellagic acid, naringenin, QCT and RSV(168-170).

The route of delivery is also a great effector of a compound's bioavailability. Oral delivery is beneficial because of high patient compliance. However, systemic drug delivery relies on drugs to be targeted to brain tissue by employing cell-penetrating peptides or attaching targeting ligands to the nanocarriers' surface. The nasal pathway *via* the olfactory mucosa has also been explored for the delivery of macromolecules, small molecule drugs, enzymes and genetic material (171, 172).

The application of nanoparticles for natural compounds delivery offers further the opportunity to target specifically the desired tissues or organs. In that way, drug bioavailability is improved and toxic side effects are reduced. Targeting approaches include either attachment of a targeting ligand to the nanoparticle surface (active targeting) or application of nanoparticles without specific chemical modifications, whose physical transport and targeting relies upon their intrinsic properties, such as size, shape and surface charge (passive targeting) (166, 173). For example, one strategy for targeting the brain is to manipulate the lipophilicity of the nanoparticles, since the BBB favors crossing over of lipophilic molecules. Monoclonal antibodies conjugated onto nanoparticles are promising candidates for targeting the BBB, although there are no data regarding their use with natural compounds. (166, 174). A known amyloid-binding compound, benzothiazole aniline (BTA), has been reported to inhibit beta-amyloid protein aggregations (175). A BTA-based nanoparticle could potentially be modified to improve the delivery of neuroprotective natural compounds for the treatment of AD (166). Targeting can also be achieved using external forces, like magnetic fields. Magnetic-guided nanoparticles can be employed during magnetic resonance imaging (MRI) for targeted drug or gene delivery, tissue engineering applications and cell tracking within the brain tissue (176). Finally focused ultrasound (FU), as an approach to induce BBB permeability, has been analyzed, employing two-photon microscopy that resulted in temporary, focused alterations of BBB (177).

Application of nanoparticles for delivering natural compounds could also enable a controlled release of the drug. A variety of factors, such as the size and the type of the particle, the type and amount of the encapsulated natural compound and the microenvironment, define the amount and rate at which a compound is released from a nanoformulation (166, 178). Compound release from nanoparticles, for instance, can be triggered using environmental changes, such as ultrasound and light (179, 180). Nanoparticles, made with a new, based on the quinonemethide system, light-sensitive polymer, released an encapsulated drug after exposure to a particular light wavelength(s) (179). This approach could be beneficial for the treatment of ocular degenerative disorders due to the transparency of the optical media.

However, optimal application of neuroprotective agents still presents a pivotal challenge for treating neurodegenerative diseases. First, degenerative diseases are characterized by a neuronal compensated dysfunction for a prolonged period of time prior to cell loss that is amenable

to therapeutic intervention (181). Then, innovative strategies are needed to optimally deliver a drug to specific regions within the brain (181, 182). Finally, several issues arise from the development of these new formulations for the delivery of natural compounds. For example, higher BBB permeability conditions, which result in increased amount of the compound reaching the CNS parenchyma, may elevate the risk of neurotoxicity (94). Increased concentration, for instance, of a single antioxidant polyphenol might be harmful to human health (183). Furthermore, there are reports regarding discrepancies of a compound's effect on particular signaling pathways among different experimental settings, such as anti- or pro-oxidant function and stimulatory or inhibitory role on specific kinases activity (24, 86). This is probably due to the particular physiology of the different cells tested, as well as other parameters, such as concentration and incubation time with the compound. Further studies are also needed to investigate how targeted, but also not targeted, cells will be affected by the rise in compound availability due to nanotechnology-related strategies. Therefore, it is becoming clear that availability must be tightly controlled. In addition, the lack of knowledge concerning the interactions of nanomaterials with biological membranes, as well as the fate of the nanoparticles after they are administrated and distributed *in vivo* (184), the scarcity of adequate *in vitro* models to replicate the BBB (181) and the lack of technological platforms to screen large quantities of nanoparticles (166), are some of the issues that need to be elucidated before clinical application takes place.

The design and the development of novel compound formulation and delivery technologies based on nanomaterials in combination with a deep understanding of the targeted biological systems seems to be a favorable approach, in order for natural therapeutics agents to be used in the clinical practice against neurodegenerative diseases.

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