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Mini Review



# Natural Products for the Therapy of Proteinopathies Underlying the Neurodegenerative Conditions: Protein Misfolding and Fibrillization in Alzheimer's Disease and Parkinson's Disease

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## Introduction

Significant progress has been made in our understanding of dysregulated proteostasis and protein misfolding which underlie the pathogenesis of such neurodegenerative diseases as Alzheimer's disease (AD) and Parkinson's disease (PD). In the 1990s the kinetics of β-amyloid (Aβ) fibrillization was well characterized [1,2]. Epidemiology had shown that mutations in amyloid precursor protein (APP) or the beta- and gamma-secretases which elevate the level of Aβ in the brain, as well as mutations which increase the propensity for Aβ to polymerize, are strongly associated with the development of Alzheimer's disease. Oligomers of Aβ are more neurotoxic than the monomers [3-5]. These observations suggested that molecules which would interfere with polymerization and fibrillization might slow the progression of AD. During the testing of natural compounds, Thioflavin-T (Th-T) was often used to monitor the state of Aβ polymerization [6].

The tendency for many proteins and peptides to convert from their native functional state into intractable amyloid aggregates was found to underlie multiple human disorders including Alzheimer and Parkinson diseases, type II diabetes, prion disease and several systemic amyloidosis (e.g. Aβ, αs, PrP, τ, IAPP, TDP-43, p53) [7-15]. Multiple therapeutic strategies have been employed to find disease-modifying agents against amyloidosis [16]. Some natural compounds found in the diet have anti-amyloid effects and may reduce the risk for AD and T2D [17,18]. Epidemiologic studies have suggested that diets with a high intake of flavonoids and polyphenolic compounds may have protective effects against AD, T2D and dementia [19-21]. Several polyphenols have progressed to clinical trials for the treatment of AD including resveratrol, curcumin, epigallocatechin-3-gallate (EGCG) and palm fruit bioactive [19,22,23].

**Abbreviations:** Aβ: Beta-Amyloid; αs: Alpha-Synuclein; τ: Tau Protein; PRP: Prion Protein; IAPP: Islet Amyloid Peptide; TDP-43: TAR DNA-Binding Protein 43; P53: Tumour Suppressor P53; T2D: Type 2 Diabetes Mellitus; AD: Alzheimer's Disease; PD: Parkinson's Disease; ALS: Amyotrophic Lateral Sclerosis

These polyphenols, demonstrating a range of anti-inflammatory, antioxidant and metal chelating bioactivities, have served as structural backbones in the computational design of novel drugs [24,25]. A PubMed literature review of natural compounds which modulate amyloid aggregation revealed 72 compounds, of which 44 are phenolic compounds including 16 flavonoids, 4 anthraquinones, 13 alkaloids (including 3 pyridines, 3 indoles, 2 porphyrins), steroids and terpenes [26].

Epidemiologic studies of diets have shown that the regular ingestion of curcumin, myricetin, EGCG, along with green tea polyphenols is associated with healthy cognitive function [19,27,28]. Cohort studies on the moderate consumption of red wine suggest that resveratrol reduces the risk of dementia, AD or cognitive decline associated with aging [21,29] Among the 72 anti-amyloid compounds identified in the PubMed search are many phenolic compounds which are found in brain-healthy diets associated with reduced risk of aging-associated amyloid pathologies [19,30,31]. These compounds include: EGCG and myricetin found in green tea; curcumin found in turmeric; caffeic acid and rosmarinic acid found in culinary herbs; oleuropein and oleocanthal found in olive

oil; resveratrol found in red wine and grapes; genistein found in legumes; and cinnamaldehyde found in cinnamon. Investigations into the mechanism of action by which these compounds inhibit amyloid aggregation show that some exert their effects through the formation of covalent bonds [32-39] and others exert their effects through non-covalent interactions [40-57].

The proteinopathies, involving protein misfolding and aggregation into toxic fibrillar deposits, are common to multiple neurodegenerative conditions including AD, PD, ALS, TDP-43, IAPP, prion diseases as well as to such systemic disorders of T2D and systemic amyloidosis [58-62]. Clinical trials aimed at reducing the level of toxic misfolded protein aggregates have not been successful over the past decade, perhaps due to a futile intervention following irreversible and irreparable cell and tissue damage. More promising is the potential for preventing the organ damage in the first place, through the regular intake of a diet rich in phenolics, which have dual activity as both amyloid aggregation inhibitors and as antioxidants.

Beta amyloid (Aβ) and tau (τ) aggregates are pathognomonic for AD [63]; alpha-synuclein (αs) deposits are seen in PD [64]; prion diseases and transmissible spongiform encephalopathies (TSE) present with misfolded prion protein (PrPSC) [65]; aggregates of superoxide dismutase 1 (SOD-1) and TAR DNA-binding protein 43 (TDP-43) characterize ALS [66-68]; and fronto-temporal dementia (FTD) also manifests aggregates of TDP-43 [69]; Huntington's disease manifests aggregation of glutamine-rich (polyQ) Huntingtin protein (htt) [70]. The toxic protein aggregates dysregulate the cellular metabolism and activate a complex cascade of events which may lead to acute inflammation or apoptosis. The amyloid aggregates may also block proteasomal activities and cause a marked disturbance in proteostasis. Beta-sheet-rich proteins jam the entry site to the catalytic core, thereby blocking the proteasome system [71-73]. Often the autophagy system seems impaired in these diseases with accumulation of autophagic vacuoles [74-76]. The toxic aggregates also disrupt permeability of cell membranes, impair mitochondrial function, increase reactive oxygen species, induce acute inflammation and disrupt proteostasis. The protein aggregates also expose hydrophobic portions which interact abnormally with other cellular proteins, which results in their sequestration and loss of normal function [61,77,78].

Epigallocatechin-3-gallate (EGCG) is a flavanol found in green tea leaves [79] EGCG has demonstrated neuroprotective, antioxidant, antibacterial and antitumor activity in vitro and in vivo [80,81] EGCG reduces the aggregation and toxicity of a wide range of proteins involved in proteinopathies. Some papers report that EGCG acts at an early stage of aggregation by binding with the proteins in a non-sequence specific manner [82]. Evidence suggests that it may bind to and stabilize unfolded conformations of Aβ and αs, thereby reducing fibrillation and re-directing the proteins from the aggregation cascade to off-pathway amorphous non-toxic aggregates.45 EGCG also binds to partially misfolded tau [83]. Through its multiple mechanisms of action on inhibiting amyloid aggregation suggests its potential use in preventive clinical trials on AD.

Curcumin is a biphenolic compound found in Curcuma longa, the Indian spice turmeric used in curry dishes, has strongly documented anti-inflammatory and antioxidant properties [84,85]. Based on its general activity inhibiting amyloid aggregation, Curcumin has shown beneficial effects in AD, PD, T2D and prion diseases [84,86,87] Clinical trials are underway for Curcumin for AD and T2D. Curcumin directly binds to Aβ and inhibits its aggregation in vitro [88] and in vivo [89]. Curcumin also disaggregates peptides from toxic aggregates.

Resveratrol is a natural phytoalexin stilbenoid polyphenolic compound found in grapes, berries, soybeans, peanuts and red wine. Resveratrol inhibits the aggregation of Aβ through selective transformation of the oligomers and shuttling them into off-pathway species which are unable to aggregate [90]. Resveratrol can bind multiple conformations of Aβ including Aβ42, Aβ40 and fibrillar Aβ [91]. Resveratrol is able to disaggregate Aβ from Aβ42 fibrils [92] In cell culture, resveratrol reduces the hyperphosphorylation of tau proteins [93]. In transgenic AD murine models, resveratrol has been shown to reduce amyloid plaque deposition without directly affecting the processing of APP [94,95].

In the transgenic murine AD models, resveratrol also:

1. Improves cognitive function [96,97],
2. Protects permeability of the blood-brain barrier [98],
3. Reduces acute inflammatory response through a decrease in microgliosis, and
4. Reduces the generation of reactive oxygen species (ROS) [99,100].

Botes and Sinskey have observed that Palm Fruit Bioactive, comprising a polyphenol-rich extract from the Elaeis guineensis, reduce the cytotoxicity of aggregated α-synuclein in a transgenic yeast rescue assay [101]. Other promising natural agents with potent anti-amyloid aggregation properties include: Apigenin, Fisetin, Kaempferol, Morin, Quercetin, Myricetin, Brazilin, Gallic acid, Oleocanthal, oleuropein, oleuropein aglycone, Orcein, Rosmarinic acid, Tanshinones, and Tannic acid. These natural compounds have been undergoing extensive investigation for their potential in preventing or reducing the proteinopathies, but a more detailed discussion of them is beyond the scope of this mini review.

## Conclusion

The clinical trials with these natural compounds over the past decade have been disappointing but this may be the result of attempting to overcome irreversible and irreparable damage to the brain. We must consider implementing a diet rich in these natural anti-amyloid compounds early in life to prevent the neurotoxicity of these amyloid aggregates and thus prevent the inception and progression of these devastating neurodegenerative conditions. The answer may be in the prevention rather than the cure of these conditions.

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