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Review

Biopharmaceutical Monotargeting versus 'Universal Targeting' of Late-Onset Alzheimer's Disease Using Mixtures of Pleiotropic Natural Compounds

Howard Friel*
Universal Targeting, Northampton, MA, USA

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Abstract. A five-year close reading of the scientific literature on late-onset Alzheimer's disease (AD) has prompted the invention of a novel therapeutic method that biomechanistically targets the targetable disease-process targets of AD with one or another mixture of non-toxic pleiotropic natural compounds. The featured mixture herein is comprised of curcumin, resveratrol, and EGCG. The mixture's targets include central pathological elements of AD (including amyloid, tau, synaptic dysfunction, oxidative stress, mitochondrial dysfunction, and aberrant neuroinflammation), modifiable risk factors, comorbidities, and epigenetic elements. The featured mixture and other such mixtures are suitable for long-term use, and may be applied to any stage of AD, including primary and secondary prevention. Such mixtures also would be amenable for use as pre-treatment, co-treatment, and post-treatment applications with certain biopharmaceutical agents. The targeting focus here is the major credible hypotheses of AD. The focus of future such articles will include other AD-related targets, modifiable risk factors and comorbidities, *APOE4*, epigenetic factors, bioavailability, dose response, and implications for clinical testing. The "universal targeting" method described herein—that is, "targeting the targetable targets" of AD using certain mixtures of natural compounds—is reprogrammable and thus is applicable to other chronic neurological conditions, including Parkinson's disease, vascular dementia, ischemic-stroke prevention and recovery, and sports-related head injuries and sequelae leading to chronic traumatic encephalopathy.

Keywords: Alzheimer's disease, amyloid hypothesis, curcumin, epigallocatechin gallate (EGCG), mitochondrial dysfunction, neuroinflammation, oxidative stress, resveratrol, synaptic dysfunction, tau

INTRODUCTION

The thesis of this article is that biomechanistically targeting the targetable targets of late-onset Alzheimer's disease (AD) with mixtures of non-toxic pleiotropic natural compounds represents a novel and potentially superior method for the prevention and treatment of AD. Such mixtures would be variously comprised of any number of the following compounds: curcumin and other curcuminoids, resveratrol, grape-seed extract, other grape polyphenols, red wine polyphenols, quercetin, isoquercitrin, quercetin-3-O-rutinoside (rutin), epigallocatechin gallate (EGCG) and other green

*Correspondence to: Howard Friel, Universal Targeting, Northampton, MA, USA. Tel.: +1 413 687 1991; E-mail: howard friel@gmail.com.

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tea catechins, oleocanthal, oleuropein, hydroxytyrosol, blueberry extracts, pterostilbene, fisetin, punicalagin, lycopene, lutein, zeaxanthin, bilberry, berberine, genistein, diosmin, hesperidin, schizandra, sulforaphane, silymarin, apigenin, caffeic acid, ellagic acid, ferulic acid, luteolin, myricetin, naringenin, nordihydroguaiaretic acid, rosmarinic acid, cannabidiol, tetrahydrocannabinol, magnesium, vitamin A, folic acid, vitamin B6, vitamin B12, thiamine, benfotiamine, inositol, choline, vitamin C, vitamin D, vitamin E tocopherols and tocotrienols, alpha-lipoic acid, R-lipoic acid, coenzyme q10, taurine, melatonin, docosahexaenoic acid, eicosapentaenoic acid, and other natural compounds. The ability to target the targetable targets of AD using mixtures of such compounds is referred to herein as the "universal targeting" of AD.

While each of these compounds is highly pleiotropic and thus capable of targeting multiple disease-process factors of AD, to my knowledge no single such compound is capable of targeting all disease-process factors (targets). Thus, to arrive at a biomechanistic capability to target the targetable targets of AD, it was necessary to invent a method of therapeutic design involving mixtures of natural compounds, such that the combined partial targeting capabilities of each compound embodied a mutually advantageous conjunction of targeting capabilities, resulting in each mixture possessing the capability to biomechanistically target the known targetable targets of AD. It is also apparent that the same method of targeting targetable targets, by definition of the method, can be applied to other well-studied neurological conditions and other major chronic diseases, including the most common cancers.

In contrast, the laboratory-made molecules that have been developed and deployed to date in clinical trials by the biopharmaceutical industry to prevent and treat AD—including monoclonal antibodies targeting amyloid-β (Aβ), cleavage proteases targeting amyloid-β protein precursor (AβPP), and tau-targeting drugs—possess few if any therapeutically significant pleiotropic capabilities, and are often designed to preferentially engage or "monotarget" a single target. While the capability to target the targetable targets of AD rests exclusively with the combined targeting effects of certain natural compounds, it may be useful in some cases to combine certain monotargeting pharmaceutical products with certain mixtures of pleiotropic natural compounds, and thus convert traditional monotargeting to a universal-targeting combination therapy. The odd-couple combination of monotargeting with high-affinity biopharmaceutical agents and universal targeting with pleiotropic natural compounds in some cases may maximize clinical effectiveness while reducing adverse effects.

DISCOVERY OF UNIVERSAL TARGETING

My initial encounters leading to the idea that it might be possible to target the targetable targets of AD with mixtures of natural compounds involved the proteolytic cleavage of AβPP. It is thought that the AβPP-related first-cut cleavage activity of α-secretase (ADAM10) may help prevent and treat AD, while the competing first- and second-cut cleavage activity, respectively, of β-secretase (BACE1) and γ-secretase (presenilin1), may be among the early steps leading to AD. Meanwhile, it had been shown that EGCG, a green tea catechin and a highly pleiotropic phytochemical, was capable of upregulating α-secretase activity [1, 2] while also generating the neuroprotective cleavage product, soluble AβPPα [3, 4], but that curcumin, which also is highly pleiotropic, by itself was possibly incapable of these effects on α-secretase [5]. Conversely, it had been shown that curcumin (and demethoxycurcumin and bisdemethoxycurcumin) was capable of inhibiting the cleavage activity of β-secretase [6–8] and γ-secretase [9, 10], and that the capabilities of EGCG as applied to β-secretase and γ-secretase were less clear [11, 12].

It had thus occurred to me that a combination of EGCG and curcuminoids, but possibly not one or the other, appeared to be capable of upregulating α-secretase while also inhibiting both β-secretase and γ-secretase. This exercise had thus realized in a sense the total targetable targeting of non-amyloidogenic AβPP processing with a simple two-compound mixture of natural compounds. In contrast, each of the pharmaceutical cleavage proteases that had targeted AβPP processing was limited to inhibiting or modulating the cleavage activity of *either* β-secretase *or* γ-secretase, with no apparent industry focus on α-secretase.

This was the first instance of targeting a full set of targetable targets of AD versus biopharmaceutical monotargeting among the same set of AD-related targets. The pharmaceutical effort toward AβPP processing in at least one instance also had led to serious toxicity among AD patients in clinical trials [13].

FROM AβPP PROCESSING TO Aβ

Knowing that the limitations of pharmaceutical monotargeting that applied to AβPP processing also was characteristic of the monoclonal antibodies that had been designed for use against AD, since each of the antibodies that had been developed and tested preferentially targeted one or another species of soluble or insoluble $A\beta_{42}$, I then devised a three-compound mixture of natural compounds—curcuminoids and EGCG plus resveratrol—to inhibit $A\beta_{42}$ peptide aggregation [14, 15] including oligomeric [16, 17], fibrillar [18, 19], and plaque formation [20–22], to enhance neprilysin-related amyloid-degrading activity [23, 24], to enhance $A\beta_{42}$ clearance from the brain [25, 26], to reduce $A\beta_{42}$ neurotoxicity [27, 28], and to protect synaptic function [29, 30].

Given the total targeting of AβPP processing and of the soluble and insoluble species of $A\beta_{42}$ as indicated above, thus including in a fundamental sense a capability to reduce production while enhancing clearance of $A\beta_{42}$, the three-compound mixture of curcuminoids and EGCG plus resveratrol seems potentially capable of achieving homeostasis between the production and clearance of Aβ. This is a long-standing therapeutic objective of the amyloid hypothesis of AD that the research community had long-identified, but that the pharmaceutical industry clearly has not achieved.

The idea of targeting targetable sets of targets within the amyloid hypothesis of AD with mixtures of natural pleiotropic compounds expanded to the targeting of other sets of targets of other credible hypotheses of AD, including those involving tau, synaptic dysfunction, oxidative stress, mitochondrial dysfunction, and neuroinflammation, as indicated below. The idea expanded further to all targetable targets of the AD-related disease-process with such mixtures of compounds, as exhibited in a 998-page technical manual that I have submitted to the editors of the *Journal of Alzheimer's Disease Reports*. This includes the capability to target major modifiable risk factors and comorbidities of AD. This vast targeting capability is exhibited by the mixture of curcuminoids, resveratrol, and EGCG in the aforementioned technical manual.

The research further showed that the universal targeting approach, involving the use of mixtures of well-studied non-toxic natural compounds, which humans have consumed safely throughout the past few thousand years, for example, as tea and wine drinkers, fruit and vegetable eaters, spice enthusiasts, and olive oil cultivators, also seemed capable of targeting the targetable disease-process targets of other neurological conditions and major chronic diseases with similarly designed mixtures of pleiotropic natural compounds.

STATUS OF THE AMYLOID HYPOTHESIS

One problem, perhaps, with testing the amyloid hypothesis of AD is that the underlying disease process as described in the hypothesis has never been sufficiently targeted in clinical trials. Thus, the modest clinical-trial results involving amyloid-related targets do not necessarily demonstrate that targeting amyloid-related targets should be abandoned, or that "innovative" AD-related pharmaceutical drug development henceforth simply means monotargeting a multitude of non-amyloid targets. The scientific findings and targeting theories that have informed the research and development of the monoclonal antibodies and cleavage proteases reflect key insights into the pathogenic process of AD. As such, the underlying science of the amyloid hypothesis has been incorporated into the scheme of therapeutic design that is asserted here. Thus, the non-amyloidogenic processing of AβPP and the targeting of soluble and insoluble species of $A\beta_{42}$ likely remain necessary, if not sufficient, pieces of what must be targeted to successfully prevent and treat the disease.

TARGET AGNOSTICISM

Given the puzzle-pieces of credible hypotheses that together portray an intricate and complex disease process, the likelihood seems small that any one piece of the puzzle is dispositive as a full representation of the puzzle. It is imprudent, however, to discard a credible hypothesis of the AD-related disease process, when an aggregation of such hypotheses likely provides a fuller disease-process picture, which then may be universally targeted as suggested above. And if somehow it should be discovered that one such credible hypothesis by itself and by decree credibly holds the keys to prevent and treat AD, then the universal targeting model, having incorporated the targetable targets of several credible hypotheses of AD, likely would be capable of targeting the targetable targets of that one hypothesis. The universal targeting method of AD therapeutics then, as a tenet of therapeutic design,

and to facilitate the formulation and implementation of the method and associated mixtures, is formally agnostic about the therapeutic validity of any one credible hypothesis of AD.

ON COMPLEXITY AND TARGETABILITY

In addition to the amyloid hypothesis of AD, the tau hypothesis reflects a credible description of the AD-related disease process, including as articulated below in selections from the scientific literature. The overall effects of these selections, which also involve synaptic dysfunction, oxidative stress, mitochondrial dysfunction, and neuroinflammation, in addition to amyloid and tau, paint a complex, multifactorial, interactive picture of the AD-related disease process, with no scientific consensus as to its etiology or progression. This medical enigma seems potentially conquerable by a therapeutic approach that is capable of mechanistically and non-toxically targeting the targetable complexity of the disease.

The universal targeting model thereby uniquely solves multiple problems from the perspective of AD therapeutics, since it is designed to attend to any level of complexity at any stage of the disease involving any or all credible hypotheses of AD. Whereas the absence of a consensus on the causes and progression of the disease heretofore has posed serious challenges to the design of AD-related therapeutic agents, the thesis asserted here is that a model of mechanistic targeting that incorporates numerous credible hypotheses and their associated targets represents a potentially superior therapeutic approach.

TAU HYPOTHESIS

The verbatim selections below on tau were selected from the basic-science side of the literature, and briefly present key AD-related tau targets. This is followed by verbatim selections from the applied side of the literature, which exhibit the tau-related targeting capabilities of the natural compounds—curcumin, resveratrol, and EGCG—that comprise the featured mixture. The patterned use of the basic-science side followed by the applied-science side also is featured in the verbatim selections below on synaptic dysfunction, oxidative stress, mitochondrial dysfunction, and neuroinflammation.

This narrative device authoritatively and conveniently reveals the complexity and interactivity of the disease-process elements of AD, as well as the remarkable extent of the targeting capabilities of the three compounds that comprise the featured mixture. Together with the amyloid-associated targets that are listed above, the presentations below, beginning with tau-related targets, function as a brief primer to six key dimensions of AD pathophysiology and by extension the universal targeting method summarized above.

Tau summarized

"Tau is a microtubule-associated protein thought to help modulate the stability of neuronal microtubules. In tauopathies, including Alzheimer's disease and several frontotemporal dementias, tau is abnormally modified and misfolded resulting in its disassociation from microtubules and the generation of pathological lesions characteristic for each disease" [31].

"Tau can be compared to railroad ties that stabilize a train track that brain cells use to transport food, messages and other vital cargo throughout neurons... In Alzheimer's, changes in the tau protein cause the tracks to become unstable in neurons of the hippocampus, the center of memory. The abnormal tau builds up in neurons, which eventually leads to the death of these neurons. Evidence suggests that abnormal tau then spreads from cell to cell, disseminating pathological tau in the brain's cortex" [32].

"Recent studies have suggested that abnormal hyperphosphorylation of tau in the brain plays a vital role in the molecular pathogenesis of AD and in neurodegeneration" [33].

"For a long time, research has focused on neurofibrillary tangles (NFTs) and other large metastable inclusions composed of aggregated hyperphosphorylated tau protein... Lately, the significance and toxicity of NFTs have been challenged and a new aggregated tau entity has emerged as the true pathogenic species in tauopathies and a possible mediator of Aβ toxicity in AD; specifically, aggregates of a size intermediate between monomers and NFTs, the so-called tau oligomers" [34].

In addition, scientists reported in 2014 as follows: "Neurofibrillary pathology, which is made up from abnormally hyperphosphorylated microtubule-associated protein tau, is both a hallmark and key lesion of AD and related tauopathies"; "the density

of neurofibrillary pathology in the cerebral cortex correlates with the degree of dementia"; "both experimental and transgenic animal studies have consistently shown that abnormal hyperphosphorylation of tau causes cognitive impairment"; "the bulk of studies have shown that abnormal hyperphosphorylation [of tau] is the key gain of toxic function step"; and "aggregated tau can lead to neurodegeneration." The scientists concluded, "in our opinion, inhibition of abnormal hyperphosphorylation of tau is the most rational therapeutic target" in AD [35].

Whereas the mixture of curcuminoids and EGCG plus resveratrol appears to be capable of targeting the broad set of disease-process factors involved in the amyloid hypothesis of AD, the same mixture appears to be capable of targeting hyperphosphorylated tau, tau oligomers, and tau neurofibrillary tangles, including as described by research scientists below.

Tau targeted

"[P]retreatment of PC12 cells with 10 microg/ml curcumin for 1 h significantly reversed the effect of Abeta [amyloid-beta], by decreasing the oxidative stress, and DNA damage induced by Abeta, as well as attenuating the elevation of intracellular calcium levels and tau hyperphosphorylation induced by Abeta. Taken together, these data indicate that curcumin protected PC12 cells against Abeta-induced neurotoxicity through the inhibition of oxidative damage, intracellular calcium influx, and tau hyperphosphorylation" [36].

"The dynamic light scattering analysis and atomic force microscopic images revealed that curcumin inhibits the oligomerization of tau. Curcumin also disintegrated preformed tau oligomers. Using Far-UV circular dichroism, curcumin was found to inhibit the β-sheets formation in tau indicating that curcumin inhibits an initial step of tau aggregation. In addition, curcumin inhibited tau fibril formation. Furthermore, the effect of curcumin on the preformed tau filaments was analyzed by atomic force microscopy, transmission electron microscopy, and 90° light scattering. Curcumin treatment disintegrated preformed tau filaments. The results indicated that curcumin inhibited the oligomerization of tau and could disaggregate tau filaments" [37].

"We generated a fragment of tau (HisK18ΔK280) that forms stable, toxic, oligomeric tau aggregates *in vitro*. We show that (-) epigallocatechin gallate (EGCG), a green tea polyphenol that was previously found to reduce Aβ aggregation, inhibits the aggregation of tau K18ΔK280 into toxic oligomers at ten- to hundredfold substoichiometric concentrations, thereby rescuing toxicity in neuronal model cells" [38].

"Histopathological assessment of the cortex and hippocampus of AlCl3 [aluminum chloride]-induced rat brains showed the presence of both neuritic plaques and neurofibrillary [tau] tangles. In nanoEGCG-treated rats this pathology was absent" [39].

"We found that long-term dietary resveratrol activates AMPK pathways and pro-survival routes such as SIRT1 in [SAMP8 mice]. It also reduces cognitive impairment and has a neuroprotective role, decreasing the amyloid burden and reducing tau hyperphosphorylation" [40].

"In summary, these findings provide evidence that Res[veratrol] protects N2a cells from FA [formaldehyde]-induced damages and suggests that inhibition of GSK-3β and CaMKII and the activation of PP2A by Res protect against the hyperphosphorylation and/or mediates the dephosphorylation of tau protein, respectively. These possible mechanisms underlying the neuroprotective effects of Res against FA-induced damages provide another perspective on AD treatment via inhibition of tau protein hyperphosphorylation" [41].

SYNAPTIC DYSFUNCTION

In ways that are involved with both AD-related Aβ and tau, synaptic dysfunction plays a major pathophysiological role in AD, as indicated below.

Synaptic dysfunction summarized

"In its earliest clinical phase, Alzheimer's disease characteristically produces a remarkably pure impairment of memory. Mounting evidence suggests that this syndrome begins with subtle alterations of hippocampal synaptic efficacy prior to frank neuronal degeneration, and that the synaptic dysfunction is caused by diffusible oligomeric assemblies of the amyloid β protein" [42].

"Insoluble amyloid plaque cores from Alzheimer's disease cortex did not impair LTP [long-term potentiation] unless they were first solubilized to release Abeta dimers, suggesting that plaque cores are largely inactive but sequester Abeta dimers that are synap-

totoxic. We conclude that soluble Abeta oligomers extracted from Alzheimer's disease brains potently impair synapse structure and function and that dimers are the smallest synaptotoxic species" [43].

"Amyloid beta and tau form fibrillar lesions that are the classical hallmarks of AD. Recent data indicate that both molecules may have normal roles at the synapse, and that the accumulation of soluble toxic forms of the proteins at the synapse may be on the critical path to neurodegeneration. Further, the march of neurofibrillary tangles through brain circuits appears to take advantage of recently described mechanisms of trans-synaptic spread of pathological forms of tau. These two key phenomena, synapse loss and the spread of pathology through the brain via synapses, make it critical to understand the physiological and pathological roles of amyloid beta and tau at the synapse" [44].

"Synapses are the principal sites for chemical communication between neurons and are essential for performing the dynamic functions of the brain. In Alzheimer's disease and related tauopathies, synapses are exposed to disease modified protein tau, which may cause the loss of synaptic contacts that culminate in dementia. In recent decades, structural, transcriptomic and proteomic studies suggest that Alzheimer's disease represents a synaptic disorder. Tau neurofibrillary pathology and synaptic loss correlate well with cognitive impairment in these disorders. Moreover, regional distribution and the load of neurofibrillary lesions parallel the distribution of the synaptic loss. Several transgenic models of tauopathy expressing various forms of tau protein exhibit structural synaptic deficits. The pathological tau proteins cause the dysregulation of synaptic proteome and lead to the functional abnormalities of synaptic transmission. A large body of evidence suggests that tau protein plays a key role in the synaptic impairment of human tauopathies" [45].

"The cornerstone of the two-decade-old hypothetical amyloid cascade model is that amyloid pathologies precede tau pathologies. Although the premise of Aβ-tau pathway remains valid, the model keeps evolving as new signaling events are discovered that lead to functional deficits and neurodegeneration... Although still elusive, many novel upstream and downstream signaling molecules have been found to modulate tau mislocalization and tau hyperphosphorylation. Here we will discuss the mechanistic interactions between [amyloid-beta prion protein (C)]-mediated neurotoxicity and tau-mediated synaptic deficits in an updated amyloid cascade model with calcium and tau as the central mediators" [46].

Whereas the mixture of curcuminoids and EGCG plus resveratrol appears to be capable of targeting the disease-process factors involved in the amyloid and tau hypotheses of AD, the same mixture also targets synaptic function in AD models, including as follows.

Synaptic dysfunction targeted

"To investigate the effects of curcumin on synapses, APPswe/PS1dE9 double transgenic mice were used, and the ultra-structures of synapses and synapse-associated proteins were observed. Six months after administration, few abnormal synapses were observed upon electron microscopy in the hippocampal CA1 areas of the APPswe/PS1dE9 double transgenic mice. The treatment of the mice with curcumin resulted in improvements in the quantity and structure of the synapses. Immunohistochemistry and western blot analyses revealed that the expressions of PSD95 [post-synaptic density protein 95] and Shank1 were reduced in the hippocampal CA1 areas of the APPswe/PS1dE9 double transgenic mice, but curcumin treatment increased the expressions of these proteins. Our findings suggest that curcumin improved the structure and function of the synapses by regulating the synapse-related proteins PSD95 and Shank1" [47].

"Organotypic hippocampal slice cultures exposed to Aβ1-42 were used to study the neuroprotective effects of curcumin through a spectral analysis of multi-electrode array (MEA) recordings of spontaneous neuronal activity. Curcumin counteracted both deleterious effects of Aβ; the initial synaptic dysfunction and the later neuronal death... Curcumin-mediated attenuation of Aβ-induced synaptic dysfunction involved regulation of synaptic proteins, namely phospho-CaMKII and phospho-synapsin I. Taken together, our results expand the neuroprotective role of curcumin to a synaptic level" [48].

"We investigated the effects of natural phenolic compounds, such as myricetin (Myr), rosmarinic acid (RA), ferulic acid (FA), curcumin (Cur) and nordihydroguaiaretic acid (NDGA) on the aggregation of amyloid β-protein (Aβ), using *in vitro* and *in vivo* models of cerebral Aβ amyloidosis. The *in vitro* studies revealed that these phenolic compounds efficiently inhibit oligomerization as well as fibril formation of Aβ through differential binding, whilst reducing Aβ oligomer-induced synaptic and neuronal

toxicity. Furthermore, a transgenic mouse model fed orally with such phenolic compounds showed significant reduction of soluble Aβ oligomers as well as of insoluble Aβ deposition in the brain" [49].

"In the present study, we used a hippocampal injection model in rats to investigate the effects of resveratrol on Aβ1-42-induced impairment of spatial learning, memory and synaptic plasticity as well as on alterations of SIRT1 expression and CREB phosphorylation. We found that resveratrol significantly reversed the water maze behavioral impairment and the attenuation of long-term potentiation (LTP) in area CA1 that were induced by hippocampal injection of Aβ1-42. Interestingly, resveratrol also prevented the Aβ1-42-induced reductions in SIRT1 expression and CREB phosphorylation in rat hippocampus. In conclusion, in rats, resveratrol protects neurons against Aβ1-42-induced disruption of spatial learning, memory and hippocampal LTP" [50].

"[C]hronic 0.05% or 0.1% GTC [green tea catechin] consumption prevented the reductions of three representative proteins of synaptic function and synaptic structure, including brain-derived neurotrophic factor (BDNF), post-synaptic density protein-95 (PSD95) and Ca(2+)/calmodulin-dependent protein kinase II (CaMKII). These results demonstrated that long-term 0.05% or 0.1% green tea catechin administration may prevent spatial learning and memory decline of SAMP8 mice by decreasing Abeta(1–42) oligomers and upregulating synaptic plasticity-related proteins in the hippocampus" [51].

OXIDATIVE STRESS

Other research scientists have conveyed a highly credible model of oxidative stress and AD, including as follows.

Oxidative stress summarized

"Since 1999, oxidative damage to RNA molecules has been described in several neurological diseases including Alzheimer's disease, Parkinson's disease, Down syndrome, [and] dementia with Lewy bodies... An early involvement of RNA oxidation of vulnerable neuronal population in the neurodegenerative diseases has been demonstrated, which is strongly supported by a recent observation of increased RNA oxidation in brains of subjects with mild cognitive impairment" [52].

"[M]ore prominent levels of neuronal RNA oxidation compared to normal aging have been described in neurodegenerative disorders including Alzheimer disease, Parkinson disease, dementia with Lewy bodies, and amyotrophic lateral sclerosis... Of particular interest, the accumulating evidence obtained from studies on either human samples or experimental models coincidentally suggests that RNA oxidation is a feature in neurons of aging brain and more prominently observed in vulnerable neurons at early-stages of age-associated neurodegenerative disorders, indicating that RNA oxidation actively contributes to the background, the onset, and the development of the disorders" [53].

"A considerable amount of evidence points to oxidative damage to mitochondrial DNA (mtDNA) as a determinant event that occurs during aging, which may cause or potentiate mitochondrial dysfunction favoring neurodegenerative events... The accumulation of oxidized mtDNA bases during aging increases the risk of sporadic AD, an event that is much less relevant in the familial forms of the disease" [54].

"The post-mortem evidence of oxidative damage in the brain of Alzheimer's disease patients is overwhelming, which is also supported by the similar changes in transgenic mice models of this disease... [T]he review suggests that the oxidative stress could be an early event in the disease process and may trigger various adaptive responses such as the alterations of amyloid beta metabolism and the activation of stress responsive kinases which can subsequently lead to neuronal degeneration and AD pathology" [55].

"Evidence indicates the critical role of Aβ metabolism in prompting the oxidative stress observed in AD patients. However, it has also been proposed that oxidative damage precedes the onset of clinical and pathological AD symptoms, including amyloid-β deposition, neurofibrillary tangle formation, vascular malfunction, metabolic syndrome, and cognitive decline" [56].

As with amyloid, tau, and synaptic dysfunction, evidence indicates that the same mixture of curcuminoids and EGCG plus resveratrol is capable of targeting the effects of oxidative stress on the aging brain and AD, including as follows.

Oxidative stress targeted

"[C]urcumin inhibited early DNA/RNA oxidation as indicated by immunocytochemistry and increased nuclear Nrf2 protein by inducing nuclear accumulation of Nrf2. These findings suggest that curcumin

activates the expression of thioredoxin, an antioxidant protein in the Nrf2 pathway, and protects neurons from death caused by oxygen-glucose deprivation in an *in vitro* model of ischemia/reperfusion" [57].

"Calorie restriction and resveratrol supplementation prevent age-related DNA and RNA oxidative damage in a non-human primate" [58].

"[C]urcumin strongly induced modulator effects on oxidative stress, intracellular Ca(2+) levels, and the caspase-3 and –9 values in an experimental oxidative stress model in SH-SY5Y cells" [59].

"Resveratrol reduced apoptosis, decreased oxidative status and alleviated mitochondrial damage in Aβ1-42-treated PC12 cells" [60].

"Our studies showed that pretreatment with resveratrol could reduce Aβ1-42-induced oxidative stress in PC12 cells by inhibiting the generation of MDA [malondialdehyde] and ROS [reactive oxygen species] and increasing the production of SOD [superoxide dismutase] and GSH [glutathione]" [61].

ABERRANT NEUROINFLAMMATION

Scientists also have reported a highly credible model of neuroinflammation and AD, including as follows.

Neuroinflammation summarized

"In the AD brain, microglial cells are found in close association with amyloid β (Aβ) deposits. Histological examination of AD brains as well as cell culture studies have shown that the interaction of microglia with fibrillar Aβ leads to their phenotypic activation. The conversion of these cells into a classically "activated" phenotype results in production of chemokines, neurotoxic cytokines and reactive oxygen and nitrogen species that are deleterious to the CNS [central nervous system]" [62].

"Activated microglia are associated with the progression of Alzheimer's disease, as well as many other neurodegenerative diseases of aging. Microglia are therefore key targets for therapeutic intervention. β-amyloid (Aβ) deposits activate the complement system, which, in turn, stimulates microglia to release neurotoxic materials. Research has focused primarily on antiinflammatory agents to temper this toxic effect" [63].

"Brain inflammation, characterized by increased microglia and astrocyte activation, increases during aging and is a key feature of neurodegenerative diseases, such as Alzheimer's disease (AD). In AD, neuronal death and synaptic impairment, induced by amyloid-β (Aβ) peptide, are at least in part mediated by microglia and astrocyte activation. Glial activation results in the sustained production of proinflammatory cytokines and reactive oxygen species, giving rise to a chronic inflammatory process" [64].

"Increasing evidence suggests that Alzheimer's disease pathogenesis is not restricted to the neuronal compartment, but includes strong interactions with immunological mechanisms in the brain. Misfolded and aggregated proteins bind to pattern recognition receptors on microglia and astroglia, and trigger an innate immune response characterised by release of inflammatory mediators, which contribute to disease progression and severity" [65].

"Aβ itself, an inducer of microglia activation and neuroinflammation, has been considered as an underlying and unifying factor in the development of AD. A vicious cycle of inflammation has been formed between Aβ accumulation, activated microglia, and microglial inflammatory mediators, which enhance Aβ deposition and neuroinflammation. Thus, inhibiting the vicious cycle seems to be a promising treatment to restrain further development of AD. With increasing research efforts on microglia in AD, intervention of microglia activation and neuroinflammation in AD may provide a potential target for AD therapy in spite of the provisional failure of nonsteroidal antiinflammatory drugs in clinical trials" [66].

As with amyloid, tau, synaptic dysfunction, and oxidative stress, evidence indicates that the same mixture of curcuminoids and EGCG plus resveratrol is capable of targeting the disease-process factors of neuroinflammation in the aging brain and AD, as follows.

Neuroinflammation targeted

"[U]sing both APP/PS1 transgenic mice and beta-amyloid-induced neuroinflammation in mixed neuronal/glial cultures, we showed that curcumin significantly alleviated spatial memory deficits in APP/PS1 mice and promoted cholinergic neuronal function *in vivo* and *in vitro*. Curcumin also reduced the activation of microglia and astrocytes, as well as cytokine production and inhibited nuclear factor kappa B (NF-κB) signaling pathway, suggesting the beneficial effects of curcumin on AD are attributable to the suppression of neuroinflammation" [67].

"In the present study, we found that curcumin improved microglial viability against Aβ42 in a

time- and dose-dependent manner and remarkably suppressed Aβ42-induced CD68 expression. Moreover, curcumin concentration-dependently abolished Aβ42-induced interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) production in mRNA and protein levels in microglia. Besides, curcumin exerted an inhibitory effect on phosphorylation of ERK1/2 and p38 in Aβ42-activated microglia. Further experiments indicated that blockage of ERK1/2 and p38 pathways reduced inflammatory cytokines production from microglia. These results show that curcumin suppresses ERK1/2 and p38 signaling, thus attenuating inflammatory responses of brain microglia" [68].

"Our results indicated that EGCG significantly suppressed the expression of tumor necrosis factor α (TNFα), interleukin-1β, interleukin-6, and inducible nitric oxide synthase (iNOS) in Aβ-stimulated EOC 13.31 microglia. EGCG also restored the levels of intracellular antioxidants nuclear erythroid-2 related factor 2 (Nrf2) and heme oxygenase-1 (HO-1), thus inhibiting reactive oxygen species-induced nuclear factor-κB (NF-κB) activation after Aβ treatment. Furthermore, EGCG effectively protected neuro-2a neuronal cells from Aβ-mediated, microglia-induced cytotoxicity by inhibiting mitogen-activated protein kinase-dependent, Aβ-induced release of TNFα" [69].

"[W]e found that EGCG prevented LPS-induced activation of astrocytes and elevation of cytokines including tumor necrosis factor-α, interleukin (IL)-1β, macrophage colony-stimulating factor, soluble intercellular adhesion molecule-1 and IL-16, and the increase of inflammatory proteins, such as inducible nitric oxide synthase and cyclooxygenase-2, which are known factors responsible for not only activation of astrocytes but also amyloidogenesis. In the cultured astrocytes, EGCG also inhibited LPS-induced cytokine release and amyloidogenesis" [70].

"The results of the present study demonstrated that resveratrol inhibited the proliferation of [oligomeric] Aβ-induced microglia and the production of pro-inflammatory factors, including ROS [reactive oxygen species], NO [nitric oxide], TNF-α and IL1β. Subsequent mechanistic investigations demonstrated that resveratrol inhibited the oAβ-induced mRNA and protein expression levels of p47phox and gp91phox" [71].

"Stimulation of microglia with Abeta increased acetylation of RelA/p65 at lysine 310, which regulates the NF-kappaB pathway. Overexpression of SIRT1 deacetylase and the addition of the SIRT1 agonist resveratrol markedly reduced NF-kappaB signaling stimulated by Abeta and had strong neuroprotective effects. Our results support a glial loop hypothesis by demonstrating a critical role for microglial NF-kappaB signaling in Abeta-dependent neurodegeneration. They also implicate SIRT1 in this pathway and highlight the therapeutic potential of resveratrol and other sirtuin-activating compounds in Alzheimer disease" [72].

MITOCHONDRIAL DYSFUNCTION

In addition to the amyloid, tau, synaptic dysfunction, oxidative stress, and aberrant neuroinflammation hypotheses of AD, another highly credible hypothesis of AD centrally involves mitochondrial dysfunction, including as described below.

Mitochondrial dysfunction summarized

"Mitochondrial dysfunction is a major feature of Alzheimer's pathology, which might be one of the early events that trigger downstream principal events" [73].

"Mitochondrial dysfunction is elevated in very early stages of Alzheimer's disease and exacerbates oxidative stress, which contributes to disease pathology" [74].

"Mitochondria are well-known cellular organelles that play a vital role in cellular bioenergetics, heme biosynthesis, thermogenesis, calcium homeostasis, lipid catabolism, and other metabolic activities. Given the extensive role of mitochondria in cell function, mitochondrial dysfunction plays a part in many diseases, including diabetes and Alzheimer's disease (AD). In most cases, there is overwhelming evidence that impaired mitochondrial function is a causative factor in these diseases" [75].

"[W]e describe mainly the bioenergetic properties of mitochondria, such as those found in the ETC [electron transport chain] that may be altered in Alzheimer's disease (AD). Increasing evidence points to several mitochondrial functions that are affected in AD. Furthermore, it is becoming apparent that mitochondria are a potential target for treatment in early-stage AD. With growing interest in the mitochondria as a target for AD, it has been hypothesized that deficit in this organelle may be at the heart of the progression of AD itself" [76].

"Mitochondrial abnormalities are one of the earliest and prominent features in AD patient brains. Amyloid-β (Aβ) and tau both trigger mitochon-

drial alterations. Accumulating evidence suggests that mitochondrial perturbation acts as a key factor that is involved in synaptic failure and degeneration in AD. The importance of mitochondria in supporting synaptic function has made them a promising target of new therapeutic strategies for AD" [77].

"Despite the complexity of the etiology of [Alzheimer's disease], synaptic failure is the pathological basis of cognitive impairment, the cardinal sign of AD. Decreased synaptic density, compromised synaptic transmission, and defected synaptic plasticity are hallmark synaptic pathologies accompanying AD. However, the mechanisms by which synapses are injured in AD-related conditions have not been fully elucidated. Mitochondria are a critical organelle in neurons. The pivotal role of mitochondria in supporting synaptic function and the concomitant occurrence of mitochondrial dysfunction with synaptic stress in postmortem AD brains as well as AD animal models seem to lend the credibility to the hypothesis that mitochondrial defects underlie synaptic failure in AD" [78].

"Peroxisomal and mitochondrial malfunction, which are highly intertwined through redox regulation, in combination with defective proteostasis, are hallmarks of the most prevalent multifactorial neurodegenerative diseases—including Alzheimer's (AD) and Parkinson's disease (PD) and of the aging process—and are also found in inherited conditions" [79].

As with amyloid, tau, oxidative stress, synaptic dysfunction, and neuroinflammation, evidence indicates that the same mixture of curcuminoids and EGCG plus resveratrol is capable of mechanistically targeting the disease-process factors of mitochondrial dysfunction in the aging brain and AD, as follows.

Mitochondrial dysfunction targeted

"Treatment of SAMP8 mice with curcumin improved MMP [mitochondrial membrane potential] and ATP and restored mitochondrial fusion, probably by up-regulating nuclear factor PGC1α protein expression. In conclusion, SAMP8 compared to SAMR1 mice are a suitable model to study age-dependent changes in mitochondrial function and curcumin emerges as a promising nutraceutical for the prevention of neurodegenerative diseases that are accompanied or caused by mitochondrial dysfunction" [80].

"Using human neuroblastoma (SHSY5Y) cells, curcumin and Aβ, we studied the protective effects of curcumin against Aβ... Aβ was found to impair mitochondrial dynamics, reduce mitochondrial biogenesis and decrease synaptic activity and mitochondrial function. In contrast, curcumin enhanced mitochondrial fusion activity and reduced fission machinery, and increased biogenesis and synaptic proteins. Mitochondrial function and cell viability were elevated in curcumin treated cells. Interestingly, curcumin pre- and post-treated cells incubated with Aβ showed reduced mitochondrial dysfunction, and maintained cell viability and mitochondrial dynamics, mitochondrial biogenesis and synaptic activity. Further, the protective effects of curcumin were stronger in pretreated SHSY5Y cells than in post-treated cells, indicating that curcumin works better in prevention than treatment in AD-like neurons" [81].

"To identify flavonoids and other natural products that may correct amyloid-induced mitochondrial dysfunction, 25 natural products were screened for their ability to restore altered mitochondrial membrane potential (MMP), reactive oxygen species (ROS) production, or ATP levels in neuroblastoma cells expressing mutant amyloid-β protein precursor (AβPP). Epigallocatechin-3-gallate (EGCG) and luteolin were identified as the top two mitochondrial restorative compounds from the *in vitro* screen. EGCG was further tested *in vivo* to determine its effects on brain mitochondrial function in an AβPP/PS-1 double mutant transgenic mouse model of AD. EGCG treatment restored mitochondrial respiratory rates, MMP, ROS production, and ATP levels by 50 to 85% in mitochondria isolated from the hippocampus, cortex, and striatum" [82].

"Metabolic stress induced by high-fat (HF) diet leads to cognitive dysfunction and aging, but the physiological mechanisms are not fully understood. Senescence-accelerated prone mouse (SAMP8) models were conducted under metabolic stress conditions by feeding HF for 15 weeks, and the preventive effect of resveratrol was studied. This dietary strategy demonstrates cognitive impairment in SAMP8-HF and significant preventive effect by resveratrol-treated animals. Hippocampal changes in the proteins involved in mitochondrial dynamics optic atrophy-1 protein (OPA1) and mitofusin 2 (MFN2) comprised a differential feature found in SAMP8-HF that was prevented by resveratrol" [83].

"Resveratrol has been viewed as an antioxidant, anti-inflammatory, anti-apoptotic, and anticancer agent. Moreover, it has been reported that resveratrol modulates mitochondrial function, redox biology,

and dynamics in both *in vitro* and *in vivo* experimental models. Resveratrol also attenuates mitochondrial impairment induced by certain stressors. Resveratrol upregulates, for example, mitochondria-located antioxidant enzymes, decreasing the production of reactive species by these organelles. Resveratrol also triggers mitochondrial biogenesis, ameliorating the mitochondria-related bioenergetics status in mammalian cells" [84].

CONCLUSION

Mixtures of certain pleiotropic natural compounds, including one such mixture of curcuminoids and EGCG plus resveratrol, are capable of non-toxically (and inexpensively) targeting the disease-process targets of at least six major hypotheses of AD that feature Aβ, tau, synaptic dysfunction, oxidative stress, mitochondrial dysfunction, and aberrant neuroinflammation. This mixture and others are biomechanistically capable of targeting AD beyond what has been shown here. Alternative embodiments of the "targeting the targetable targets" method with mixtures of certain pleiotropic natural compounds include Parkinson's disease, other neurodegenerative disorders, and other major chronic conditions.

CONFLICT OF INTEREST

Howard Friel's method of targeting the targetable targets of Alzheimer's disease and other chronic conditions using mixtures of pleiotropic natural compounds is patent pending.

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