Supplemental Substances Derived from Foods as Adjunctive Therapeutic Agents for Treatment of Neurodegenerative Diseases and Disorders[1,2]

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ABSTRACT

Neurodegenerative disorders and diseases (NDDs) that are either chronically acquired or triggered by a singular detrimental event are a rapidly growing cause of disability and/or death. In recent times, there have been major advancements in our understanding of various neurodegenerative disease states that have revealed common pathologic features or mechanisms. The many mechanistic parallels discovered between various neurodegenerative diseases suggest that a single therapeutic approach may be used to treat multiple disease conditions. Of late, natural compounds and supplemental substances have become an increasingly attractive option to treat NDDs because there is growing evidence that these nutritional constituents have potential adjunctive therapeutic effects (be it protective or restorative) on various neurodegenerative diseases. Here we review relevant experimental and clinical data on supplemental substances (i.e., curcuminoids, rosmarinic acid, resveratrol, acetyl-L-carnitine, and ω-3 (n–3) polyunsaturated fatty acids) that have demonstrated encouraging therapeutic effects on chronic diseases, such as Alzheimer's disease and neurodegeneration resulting from acute adverse events, such as traumatic brain injury. *Adv. Nutr. 5: 394–403, 2014.*

Introduction

Neurodegenerative disorders and diseases (NDDs)[5] are a rapidly growing cause of disability and death, characterized by progressive pathology and dysfunction. Manifestations of disease states can be chronically acquired in an indiscriminate manner or incited by an acute/singular event. For example, physiologic and functional deficits in chronic neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease, are evident, with these deficits having both primary (intrinsic/hereditary) and secondary (sporadic/nongenetic) components. Similarly, traumatic brain injury (TBI), particularly moderate to severe, initiates a number of biochemical cascades resulting in prolonged and continual neurodegeneration and long-term neurologic deficits associated with cognitive disorders and dementia (1,2), sensorimotor disability, and mortality (3). As such, a single moderate-to-severe TBI represents the beginnings of a chronic disease process. Although the increasing prevalence of cognitive decline and dementia, mainly associated with AD, is emerging as a pervasive health threat to the growing aging population (4,5), TBI represents an increasing cause of chronic disability and mortality in the young (2,6). Thus, NDDs represent a considerable public health concern and socioeconomic burden that necessitates more research to advance our understanding of potential treatment strategies.

Major advancements in our understanding of NDDs revealed several common pathologic features or mechanisms, including oxidative stress and immune-mediated inflammation (5,7). The burden of these biologic mechanisms on degenerative pathophysiology are mutable, influenced by environmental factors and behavioral determinants, such as diet and exercise (8). In fact, there is growing evidence that certain dietary compounds have potential therapeutic applications for numerous neurodegenerative diseases. Research showed that certain polyphenols and endogenous compounds have considerable positive effects on oxidative and inflammatory mechanisms associated with NDDs (4,9) and are capable of countering metabolic abnormalities associated with these disorders (10,11). Here we review 5

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[5] Abbreviations used: AD, Alzheimer's disease; ALC, acetyl-L-carnitine; Aβ, β-amyloid; MCI, mild cognitive impairment; NDDs, neurodegenerative diseases and disorders; RA, rosmarinic acid; RCT, randomized placebo-controlled trial; TBI, traumatic brain injury.

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types of compounds: 3 dietary polyphenols [i.e., rosmarinic acid (RA), resveratrol, and curcuminoids] and 2 endogenous compounds [i.e., acetyl-L-carnitine (ALC) and ω-3 (n–3) PUFAs]. We selected these compounds to review because of epidemiologic evidence and promising clinical support. We subsequently include data on safety, tolerability, and efficacy when available and include emerging experimental (preclinical) evidence. Finally, we highlight the effect of these compounds in AD and/or TBI because they are emerging NDDs in aged and young populations, respectively. In summary, our underlying intention is to advance the discussion of "therapeutic intervention" in regards to supplemental substances derived from food as therapies for NDDs.

Polyphenol Compounds

RA. RA is the structural ester of caffeic acid and 3,4-dihydroxyphenyllactic acid and a predominant phenol in many well-known herbs in the *Lamiaceae* (mint) family (12), such as rosemary, sage, basil, mint, and thyme. Of the vast genus and species within the RA family, extracts from *Salvia officinalis* (sage), *Salvia lavandulaefolia* (Spanish sage), and *Rosmarinus officinalis* (rosemary) have demonstrated beneficial effects on functional outcome measures with a number of neurologic diseases. Several human studies investigated the potential effects of RA extracts on cognitive function (**Table 1**). Single-dose (25–150 μL) *S. lavandulaefolia* was able to elicit consistent improvements in several cognitive performance tasks and mood assessment in healthy young individuals (13–15), with similar results also observed in healthy aged (>65 y) individuals (16). Dose escalation in the aged study was greater (167–1332 mg) than in the studies involving young individuals, suggesting that the cognitive benefit observed with this sage extract is dose dependent in these distinct populations. Moreover, *S. officinalis* (uncertain dose) administered daily over 4 mo conferred improved cognitive and behavioral function in aged (65–80 y) individuals with clinically diagnosed moderate AD (17). A similar pilot trial of individuals with mild-to-moderate AD that administered dose-escalating *S. lavandulaefolia* (50–150 μL) over 6 wk proved tolerable and safe, and individuals showed improvement in memory and attention (18).

In addition, sage extracts were shown to inhibit acetylcholinesterase in vitro (19–21), long implicated in cholinergic deficits observed in the pathogenesis of AD. To our knowledge, there have been no explicit studies investigating RA and TBI (either clinical or experimental). However, RA was shown to be neuroprotective, attenuating oxidative stress and neuronal cell death in vitro (22–24) and reducing inflammatory responses in experimental models of ischemic stroke (25), all of which are common biologic processes associated with TBI pathology. These further demonstrate their potential as therapeutic agents that may target key pathologic features of NDDs and improve functional outcome measures.

Resveratrol. Resveratrol is the major nonflavonoid polyphenol found in a variety of berries, peanuts, and medicinal plants (26), with the most substantial source of dietary

TABLE 1 Randomized double-blind placebo-controlled trials of polyphenol compounds in cognitive neurodegenerative conditions[1]

Study Design	Location	Dose	Duration	Population	Status/Outcome	Miscellaneous	Reference
Rosmarinic acid							
T, R, TB, PC	Tehran, Iran	Unclear ("fixed" dose)	4 mo	Probable AD or mild-to-moderate dementia	Significantly improved outcome on cognitive function (ADAS-cog; CDR-SB)		16
pR, DB, PC	Newcastle upon Tyne, UK	25–150 μL	Single dose	Healthy young adults	≥50 μL improved immediate word recall		13
R, DB, PC	Newcastle upon Tyne, UK	25–50 μL	Single dose	Healthy young adults	25–50 μL improved acute cognition and mood		13
R, DB, PC, COA	Melbourne, Australia	167–1332 mg	Repeated dose escalation	Healthy aged adults	Dose-specific (333 mg) improvement in working memory		16
R, DB, PC, COA	Newcastle upon Tyne, UK	50 μL	Repeated single dose	Healthy young adults	Improved performance on secondary memory and attention		15
Resveratrol							
R, DB, PC, COA	Newcastle upon Tyne, UK	250–500 mg	Repeated single dose	Healthy young adults	Dose-dependent increase in cerebral blood flow during task performance		33
Curcumin							
T, R, DB, PC	Hong Kong, China	1 or 4 g/d	6 mo	Possible or probable AD	No significant difference in cognitive measures (MMSE) and plasma Aβ concentration	Plus *Gingko* (120 mg/d)	50
T, R, DB, PC	California	2 or 4 g/d	6 mo	Mild-to-moderate AD	No significant difference in cognitive function or plasma and CSF Aβ or τ concentrations		51

[1] AD, Alzheimer's disease; ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; Aβ, β-amyloid; CDR-SB, clinical dementia rating scale sum of boxes; COA, crossover assignment non-blinded; CSF, cerebrospinal fluid; DB, double blind; MMSE, mini-mental state examination; PC, placebo controlled; pR, partially blinded; R, randomized; T, treatment; TB, triple blind.

resveratrol being grapes and red wine (27). A wide range of biologic properties of resveratrol has been reported, including antioxidant, anti-inflammatory, and anticarcinogenic properties (28,29). Several investigations suggested considerable neuroprotective effects of resveratrol. Human (or clinical) trials investigating resveratrol effects on neurodegenerative disorders have been limited to this point. There were several reviews of clinical trials for resveratrol that investigated the biologic effects in humans by examining variables such as pharmacokinetics, metabolism, safety, tolerance, and bioavailability (27,30,31). These trials include conditions, such as cancer, cardiovascular disease, obesity, and diabetes. Reported studies highlight the relative safety of resveratrol over varying doses (25 mg to 5 g), in either a single dose or multiple doses, with minor or inconsistent side effects in short-term or acute studies. However, to date, there is no substantial data on the toxicity of chronic intake of resveratrol, although data from upcoming and ongoing trials may begin to address this (31,32). To our knowledge, and as currently reported by the NIH (32), there are several clinical trials in progress investigating the potential therapeutic effect of resveratrol on cognitive function and cerebral blood flow in the aging brain, with mild cognitive impairment (MCI) and AD, as well as injury (Table 1). One study reports data showing a dose-dependent (250–500 mg/d) increase in cerebral blood flow in the prefrontal cortex during cognitive tasks (33), illustrating the effect of resveratrol on cerebral hemodynamics. Because cerebral blood flow is pathologically affected in numerous disorders, including AD, this may be 1 area in which resveratrol may prove clinically beneficial.

In vitro, resveratrol was shown to protect neurons against β-amyloid (Aβ)-induced toxicity and cell death (34–36) and to destabilize Aβ fibrils (37,38). Importantly, anti-inflammatory and antioxidative effects of resveratrol were linked to suppressing the activation of NF-κB, sirtuin 1, and MAPK pathways. This was shown to attenuate the release of proinflammatory TNF-α, IL-1β, and NO specifically in microglia (39–41), highlighting a potential role in limiting neurodegenerative pathology. In vivo models of sporadic and transgenic AD and tauopathy demonstrated that resveratrol substantially attenuates oxidative stress, neurodegeneration, and cognitive impairment (42,43), with significant decreases in plaque burden in cortical, striatal, and hypothalamic regions (44). Resveratrol was also shown to reduce oxidative stress and lesion volume after experimental TBI (45) and in in vitro models of glutamate-mediated excitotoxic transmission (46) (a key feature of neuronal damage in TBI). Evidence from these studies and the demonstrated safety and tolerance in human trials should stimulate similar population-based trials directed at examining neurologic outcome measures and hasten the advancement of research into the therapeutic effects of adjunctive resveratrol in NDDs.

Curcuminoids. Curcuminoids are the main polyphenol constituents of turmeric (*Curcuma longa*) and have 3 chemical components, including curcumin (75–80%), demethoxycurcumin (15–20%), and bisdemethoxycurcumin (3–5%). Epidemiologic data suggest that dietary curcumin intake is positively related to cognitive function in healthy elderly individuals (47), with evidence that concentrations of Aβ and tau are lower in populations that consume large amounts of curcumin (48,49). To our knowledge, there are 7 clinical investigations of the safety, tolerance, pharmacokinetics, and treatment effects of curcumin in AD (NIH registry) (Table 1), although observations from 4 of these are still pending. Reported data thus far suggest that discernible differences in cognitive scores and/or biochemical features of AD were absent (50,51), but several limitations to these pilot studies should be mentioned. To properly evaluate clinical relevance, a much larger sample size, followed for a longer duration, will be necessary. Importantly, a better understanding of both effective dose and bioavailability will be fundamental for appropriate evaluation. In fact, evidence for tolerability of curcuminoid formulations of up to 12,000 mg was reported previously (52), and, in this regard, dose escalation studies far exceeding the reported 4 g would be pragmatic. Moreover, the hydrophobic nature of curcuminoids (53) has precipitated research into conjugated curcumin or curcumin-like analogs to increase bioavailability and potential effects and improvement in AD (54,55).

Moreover, a growing scientific literature reports potent antioxidative and anti-inflammatory effects of curcuminoids in neurodegenerative conditions, including AD (56–63) and focal TBI (64–70), accompanied by resultant cognitive improvements. In vitro models of AD show that curcuminoids are sufficient for recovery of Aβ-induced long-term potentiation impairment, and in vivo administration can enhance spatial memory in rodents displaying AD-like neuronal loss (71–73). These effects were linked to the antioxidative (56–60) and anti-inflammatory (61–63) properties of curcuminoids and their capabilities in reducing amyloid plaque burden and disaggregating preformed Aβ fibrils (37,60, 74–76), the pathologic hallmark of AD. Notwithstanding the compelling epidemiologic data, methodologically sound clinical studies are still necessary to accurately evaluate the treatment effect of supplemental curcuminoid administration.

Endogenous Compounds

ALC. ALC is a metabolic intermediate that functions as an important transmitochondrial membrane transporter of long-chain FAs for β-oxidation. ALC is produced through endogenous biosynthesis of lysine and methionine, primarily in the brain, liver, and kidneys, and can also be consumed through foods and supplementation (10,11). Mitochondrial dysfunction associated with metabolic and oxidative stress is a hallmark feature in a number of NDDs. ALC was proposed recently as neuroprotective because of its ability to confer improved mitochondrial function. There were a number of human trials on the use of ALC in mild dementia or MCI that were reviewed previously and well described (**Table 2**) (77,78). Of these studies, the duration varied from 3 mo to 1 y, with ALC dose ranges from 1.5 to 3 g/d. Although several studies report considerable benefits of ALC (vs. placebo) on

TABLE 2 Randomized double-blind, placebo-controlled trials of endogenous compounds in cognitive neurodegenerative conditions[1]

Study Design	Location	Dose	Duration	Population	Status/Outcome	Miscellaneous	Reference
Acetyl-L-carnitine							
R, DB, PC	Italy	2 g/d	6 mo	Probable AD	Improved cognitive performance		82
R, DB, PC	Italy	2 g/d	6 mo	Probable AD	Improved cognitive performance		83
R, DB, PC	Italy	3 g/d	6 mo	Mild dementia	Improved cognitive performance		84
R, DB, PC	Italy	3 g/d	12 wk	Probable AD	Improved cognitive performance		85
R, DB, PC	United Kingdom	2 g/d	6 mo	Mild dementia	Improved cognitive performance		86
R, DB, PC	Italy	2.5 or 3 g/d	6 mo	Mild dementia	Improved cognitive performance		87
R, DB, PC	Italy	3 g/d	6 mo	Mild dementia	Improved cognitive performance		88
R, DB, PC	United States	2.5 or 3g/d	6 mo	Probable AD	Improved cognitive performance		89
R, DB, PC	Italy	2 g/d	16 wk	Probable AD	Improved cognitive performance		90
NR, DB, PC	Pennsylvania	3 g/d	1 y	Probable AD	Improved cognitive performance		91
R, DB, PC	Germany	1.5 g/d	12 wk	Mild-to-moderate AD	Significant difference in ≥1 subgroups of clinical global impression		80
R, DB, PC	United Kingdom	2 g/d	6 mo	Mild-to-moderate AD	No significant difference in cognitive performance		92
R, DB, PC	Germany	3 g/d	1 y	Mild-to-moderate AD	Improved cognitive performance in both treatment and placebo		80
R, DB, PC	Wales	2 g/d	6 mo	Mild AD	Significant difference in ≥1 subgroups of clinical global impression		80
R, DB, PC	United Kingdom	2 g/d	6 mo	Mild AD	No significant difference in cognitive performance		93
R, DB, PC	United States	3 g/d	1 y	Probable AD	No significant difference in cognitive performance		94
R, DB, PC	United States	3 g/d	1 y	Probable AD	No significant difference in cognitive performance		95
R, DB, PC	United States	3 g/d	1 y	Probable AD (subset of younger patients)	Improved cognitive performance		96
ω-3 PUFAs							
R, DB, PC	United States	9 mg/d	6 mo	Healthy individuals with age-related cognitive decline	Improved learning and memory function		124
R, DB, PC	Stockholm, Sweden	1.7 g DHA plus 0.6 g EPA/d	6 mo	Diagnosed AD	Positive effects on cognition (MMSE) in mild AD only		125
R, DB, PC	Taipei, Taiwan	1.8 g/d	6 mo	Mild-to-moderate AD	Significant cognitive improvement (ADAS-cog) in mild AD only		126
R, DB, PC	Portland, Oregon	2 g/d	18 mo	Mild-to-moderate AD	No significant difference in cognitive performance		127
T, R, DB, PC	Portland, Oregon	675 mg DHA plus 975 mg EPA/d	1 y	Probable AD or MCI	Stabilization in cognitive performance (MMSE)	+/− ALA	129

[1] AD, Alzheimer's disease; ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; ALA, α-lipoic acid; DB, double blind; MCI, mild cognitive impairment; MMSE, mini-mental state examination; NR, nonrandomized; PC, placebo controlled; R, randomized; T, treatment.

clinical and psychometric assessment in study participants with probable AD and/or MCI (79–88), other studies including participants with diagnosed moderate AD progression were less conclusive (89–92) and may indicate a prospective "therapeutic window" in terms of extant disease progression. Additional studies and reviews showed that ALC can slow pathologic decline in young patients with AD, improve clinical features of AD (93,94), and, when administered as a component of a vitamin formula, can delay cognitive decline in both early- and late-stage AD (95,96). In general, although the efficacy of ALC in cognitive decline has not been fully delineated, this may in part reflect variability in study design, methodology, and assessment (77).

Growing preclinical evidence seems to support the aforementioned clinical observations. In rodent models, ALC supplementation improves synaptic transmission and learning capacity in aged rats (97,98) and attenuated age-related mitochondrial decay (99,100). Also, ALC was shown to directly affect the cholinergic system (101), which is substantially impaired in AD (102), and provide beneficial effects in experimental models of AD. In vitro analysis reveals that ALC is neuroprotective against Aβ-induced neurotoxicity (103,104). In genetic models of AD, treatment with ALC (500 mg reported in 1 study) was sufficient to reduce oxidative stress, decrease harmful alterations in mitochondrial structure, and attenuate both spatial and temporal memory and cognitive decline (105–107). This indicates that ALC may be beneficial in delaying the progression of AD-associated cognitive decline. Moreover, ALC treatment (100 mg/kg) was effective in reducing brain lesion volume, improving behavioral outcome after experimental TBI (108), and reducing oxidative stress and preserving mitochondrial membrane potential after glutamate-induced neurotoxicity (109), an established feature of TBI-induced neuronal death. Overall, these experiments support ALC as an effective and clinically applicable therapy.

ω-3 PUFAs. Dysregulated lipid metabolism and signaling are principal components of several NDDs (110,111). ω-3 Essential PUFAs, now well understood to be highly bioactive molecules, were shown to regulate a number of metabolic and inflammatory pathways and exert pleiotropic effects in various central nervous system pathologies. Specifically, DHA, found in high concentrations in the brain [~40% of neural plasma membrane phospholipids (9,112)], is suggested as valuable for underlying neuroprotection. Epidemiologic studies show decreases in DHA with cognitive decline in both healthy aged individuals (113,114) and patients with AD (115,116), as well as age-adjusted decreases in DHA in postmortem samples from AD brains (117). Moreover, in populations with higher dietary intake of DHA (118–120) and higher concentrations of plasma DHA (114,116), there is a lower associated risk of cognitive impairment or AD. As such, there were a substantial number of clinical investigations to evaluate the therapeutic efficacy of ω-3 FA treatment in AD (Table 2). In fact, there were several recent reviews that discussed study outcome in depth. Recent evidence reports that DHA (900 mg/d) administered for 6 mo was able to improve learning and memory function in age-related cognitive decline in healthy adults (121), and several additional human trials examining DHA supplementation (240 mg/d to 1.8 g/d) ranging from 3 to 12 mo report improvement or stabilization of memory and attention as assessed by mini-mental state examination and AD assessment scale (122–124) in individuals with MCI only but not individuals with extant AD. Similarly, a more recent report (125) using DHA (2 g/d) for 18 mo did not find a benefit for patients with diagnosed AD, supporting the previous opinion (126) that posits DHA may be a more beneficial therapy in MCI and may delay the onset of age-related cognitive decline, but not in individuals with already diagnosed AD progression. Interestingly, ω-3 FA treatment given as a component of a combination therapy (i.e., in combination with other dietary compounds or supplements, such as lipoic acid) showed encouraging results, stabilizing or improving memory scores in patients with mild AD (127,128), which may be promising in the application and design of future studies. Despite promising experimental evidence, to our knowledge, there are minimal human studies evaluating the effect of ω-3 FAs in TBI (129–131). One study reported that oral PUFA intake [both ω-3 and ω-6 (n–6) FAs] for 90 d improved cognitive dysfunction in a very small cohort of patients with chronic TBI (123). ω-3 FAs have the potential to target a number of mechanisms involved in secondary injury in TBI, and, because their safety and tolerance is well established (132–135), directed clinical evaluation is warranted.

DHA deficiency was shown to activate caspases in modeled AD (136) and exacerbate age-related decline in glutamatergic transmission in rats (137). Conversely, DHA supplementation was shown to attenuate oxidative stress, specifically lipid peroxidation, and protect against memory loss in various rat models of AD and aging (138–140), as well as reduce interneuronal Aβ and tau accumulation (141–143), hallmarks of AD pathology. Furthermore, several studies showed that animals fed ω-3 FA-enriched diets display substantially greater learning acquisition and memory performance (144–150), with these observations extending to aged animals (146,151,152). Finally, in animal models of TBI, DHA supplementation substantially reduces axonal injury, apoptosis, and memory deficits (153–155) and improves biochemical markers of synaptic transmission and learning ability (156), further reinforcing the concept of introducing DHA as an adjunctive therapy for NDDs.

Discussion and Perspective

There has been a broadening body of scientific evidence supporting the potential application and benefit of dietary and nutritional substances in a number of NDDs. Many of the compounds discussed here exert therapeutic effects by limiting pathologic progression associated with common metabolic, oxidative, and inflammatory processes and merit additional study to properly delineate their utility as a therapeutic intervention. Moreover, because a small number of studies suggested positive combination effects in various

conditions, emerging areas of study would benefit from investigating the efficacy of multi-therapeutic treatment in these NDDs. This would bring to light the possibility of synergistic effects on oxidative- and/or inflammatory-related pathology. Given the relative safety and tolerance of the compounds discussed, such advances are realistic and feasible.

Although the purpose of this review is to highlight some of the promising evidence emerging in this area, it would be remiss to omit that several caveats and limitations still remain. Several negative (or null) reports, beyond the few mentioned here, were described for most of the polyphenol and endogenous compounds and in a number of the conditions discussed. Extensive experimental data has not always translated to a singular or definitive clinical effect. Variability in doses, population demographics, study design, and testing measures all contributed to the inconsistencies observed. Furthermore, the purity/quality of the compounds also likely contributed to variability and is a valid concern that must be addressed.

As a final point, the inconsistencies observed may in part reflect shortcomings in research approaches being used in nutritional sciences. Although we focused on discussing evidence primarily from randomized placebo-controlled trials (RCTs), considered the gold standard of research design, there was recent discussion that aimed to reevaluate and advance the evidence-based model for nutritional research (157). In short, it has been debated that the central features of RCTs in evidence-based medicine are not appropriate in the nutritional context. Studies on drug therapy and/or medical interventions are designed to test a single dose–dependent effect in a short timeframe and must be compared with a control/placebo condition. Evaluation is based on a large curative effect on a disease that is not caused by the absence of the intervention. In contrast, the efficacy of nutrients is determined by their ability to prevent dysfunction or disease that is a direct result of their inadequate intake. In general, the effects of nutrients are primarily dependent on the intake amount, and, as such, a "true" placebo cannot be used because a "zero" or nutrient-deficient group is unethical to consider. These highlight the inherent limitations associated with extending the RCT paradigm to clinical nutritional science; therefore, a broader consideration of alternate and/or additional research strategies should be incorporated to evaluate the best available evidence.

In summary, the ability of dietary substances to confer therapeutic effects to neurodegenerative conditions still needs to be critically explored, warranting continued basic research to drive appropriate clinical assessment. Here, we aimed to highlight the importance of continued research in this promising area.

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