Polyphenols for the Prevention and Treatment of Cognitive Impairment

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Summary Epidemiological studies have suggested that diets rich in polyphenols/phenolic compounds are associated with reduced risk of cognitive impairment and Alzheimer’s disease (AD). Experimental studies have indicated that these compounds have specific effects on AD pathogenesis as well as anti-oxidant and anti-inflammatory effects. For clinical use, several compounds have been investigated by clinical trials to establish their efficacy for prevention and treatment of AD or cognitive impairment.

Key Words polyphenols, cognitive impairment, dementia, Alzheimer’s disease, prevention

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The number of people with dementia is rapidly growing in association with extreme population aging. Global efforts for prevention of dementia, especially Alzheimer’s disease (AD) which accounts for approximately two-thirds of all causes of dementia, are ongoing. Here, I review dietary polyphenols/phenolic compounds as preventive and therapeutic agents for cognitive impairment, dementia, and AD.

Epidemiological studies for cognitive impairment and diets rich in polyphenols

Epidemiological studies have suggested that diets rich in polyphenols or phenolic compounds are associated with a reduced risk of cognitive impairment, dementia or AD; these include vegetables, fruits, spice, derived products such as wine and non-alcoholic beverages (fruit and vegetable juices, green tea, and coffee), and traditional diets such the Mediterranean and Indian diets (1, 2). The Mediterranean diet, characterized by a high intake of vegetables, fruits, cereals, olive oil, and fish, in combination with a low intake of meat and poultry, has been well known to be associated with reduction of risk of dementia, mild cognitive impairment (MCI), and AD (3).

In our population-based cohort for dementia in Naka-jima, Nanao City, Ishikawa, Japan (the Nakajima study), we have performed a prospective, longitudinal study tracking cognitively normal residents aged 60 y or older at baseline. For the purpose of exploring protective factors of dementia, we have analyzed how lifestyle-related factors (diets/exercise and laboratory data) at baseline of normal cognition are related to future cognitive decline. We found that consumption of green tea, but not coffee or black tea, was associated with reduction of risk of cognitive impairment (onset of MCI or dementia) approximately 5 y after the baseline of normal cognition, after controlling confounding factors such as age, gender, lifestyle-related diseases, lifestyle-related factors, and apolipoprotein E (ApoE) E4 (4). AD accounted for 67% of all causes of dementia in this cohort. As green tea is rich in polyphenols, we considered that natural polyphenols may have preventive effects on the development of AD.

Effects of polyphenols on Alzheimer’s disease (AD) in AD models

Deposition of the amyloid β-protein (Aβ) is a central feature of AD. Cerebral Aβ deposition is associated with deposition of phosphorylated tau protein, followed by neurodegeneration. Oxidative stress and neuro-inflammation also play a role in the AD pathogenesis. Polyphenols/phenolic compounds have been well known to have anti-oxidant and anti-inflammatory properties. However, the remarkable effects of natural polyphenols/phenolic compounds on cognitive decline suggested in epidemiological studies indicate that they may have more specific effects on the pathways of AD pathophysiology in addition to anti-oxidant and anti-inflammatory effects.

It has been reported in AD models that dietary polyphenols/phenolic compounds have the following specific actions for AD (1, 2); modulation of amyloid precursor protein (APP) processing, inhibition of Aβ aggregation, destabilization of Aβ aggregates, promotion of Aβ clearance, alleviation of Aβ-induced oxidative stress/toxicity/synaptic dysfunction, and inhibition of tau phosphorylation and aggregation; such effects have been reported in various natural polyphenols/phenolic compounds: flavones such as baicalein, flavonols such as myricetin, querectin, and morin, isoflavones such as glycine and genistein, flavonoids such as curcumin, resveratrol, and curcuminoids such as curcumin (Cur), secoiridoids such as oleuropein, and others; in addition, extracts of natural products rich in polyphenol-
nols/phenolic compounds have been used for studies, including extracts of grape seeds, wine, berries, tea, cocoa, guarana, and Pueraria lobata.

Based on the results of our observational study in the Nakajima cohort (4), we investigated effects and action mechanisms of polyphenols/phenolic compounds using experimental AD models (1). The in vitro and ex vivo studies revealed that some polyphenols, such as RA and myricetin, efficiently inhibit oligomerization as well as fibril formation of Aβ through differential binding, whilst reducing Aβ oligomer-induced synaptic and neuronal toxicity (5–7). Furthermore, a transgenic mouse model fed orally with such compounds showed significant reduction of soluble Aβ oligomers as well as of insoluble Aβ deposition in the brain (8). In addition, RA, the best phenolic compound in our in vivo as well as in vitro studies, was found to suppress Aβ aggregation by increasing monoamine secretion, and tau phosphorylation by the JNK signaling pathway (9, 10). The data indicated that these compounds have specific anti-AD effects in addition to well-known anti-oxidant and anti-inflammatory effects.

**Clinical trials with polyphenols for cognitive impairment and Alzheimer’s disease**

For clinical use, several polyphenols or phenolic compounds have been investigated in clinical trials. Concerning Cur, seven clinical trials for AD patients or those who have risk for AD or cognitive decline have been posted on the website of the U.S. National Institutes of Health (NIH) (ClinicalTrials.gov), including multimodal interventions (other nutritional supplements, lifestyle changes, yoga, etc.) combined with Cur. The results of two randomized controlled trials (RCTs) for AD were published (NCT00164749, NCT00099710) (11, 12); they failed to demonstrate clinical or biomarker evidence of efficacy of a half-year oral Cur intake. In an RCT with non-demented adults (cognitively unimpaired or MCI), an 18-mo oral intake of a bioavailable form of curcumin improved memory and attention with decreases of amyloid and tau accumulation on positron emission tomography (PET) imaging (NCT01383161) (13).

Regarding resveratrol, the NIH website reports that five clinical trials for AD or MCI are active or completed; the results of two RCTs were published. A one-year oral intake of resveratrol (500 mg to 2 g/d or placebo) in AD patients was safe and well-tolerated, and resveratrol and its major metabolites penetrated the blood-brain barrier, although there was no clinical or biomarker evidence of efficacy (NCT01504854) (14); additional retrospective analysis with biomarker-confirmed AD cases in this study suggested that resveratrol decreased neuroinflammation and attenuated cognitive decline and change in activities of daily living (ADL) (15). Another RCT with a one-year intake of low-dose resveratrol (10 mg/d), glucose, and malate showed no statistically significant difference in clinical outcome (NCT00678431) (16). In addition, an RCT for AD in the Chinese registry (CTR20151780X) reported that a one-year oral intake of 500 mg trans-resveratrol daily showed significant reduction of Aβ40 and matrix metalloproteinase 9 in cerebrospinal fluid, which may suggest a neuroprotective effect (17).

Two clinical trials with EGCG for AD or subjective cognitive decline (SCD) have been posted on the NIH website. Prevention of cognitive decline in SCD individuals carrying the ApoE ε4 allele after the use of EGCG and a multimodal intervention in lifestyle has been under study (NCT03978052) (18). A six-month oral intake of soy isolavones (100 mg/d) did not benefit cognition in AD subjects (NCT00205179) (19).

As our experimental studies suggested potentials of RA as a therapeutic or preventive agent for AD, we proceeded to clinical trials with RA for prevention and treatment of AD/dementia. For clinical trials, we prepared capsules of Melissa officinalis (lemon balm) leaf extract rich in RA. A randomized-controlled trial in healthy individuals confirmed the safety, tolerability, and pharmacokinetics of the Melissa officinalis extract (UMIN-CTR: UMIN000004997) (20). Then, we performed an RCT with the RA-rich Melissa officinalis extract in patients with mild AD dementia, and found that the extract was safe and well-tolerated, and that the Neuropsychiatric Inventory Questionnaire (NPI-Q) score significantly improved in the Melissa officinalis group compared with worsening in the placebo (p=0.012), suggesting that the Melissa officinalis extract may improve neuropsychiatric symptoms (UMIN000007734) (21). Currently, an RCT to elucidate the effect of the Melissa officinalis extract for dementia prevention in non-demented subjects is ongoing (UMIN000021596).

In future clinical trials, several factors need to be carefully considered, including a larger number of participants, a longer duration of treatment, and better preparations of polyphenols/phenolic compounds with higher bioavailability and penetration to the brain.

**Conclusions**

Beneficial properties of dietary polyphenols/phenolic compounds for the prevention and treatment of AD or cognitive impairment/dementia have been suggested in epidemiological and experimental studies. For clinical use, several compounds have been investigated by clinical trials; however, preventive or therapeutic effects on AD or cognitive impairment/dementia have not been proved so far, requiring further clinical trials to establish their efficacy.

**Disclosure of state of COI**

No conflicts of interest to be declared.

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