Natural Phenolic Compounds as Therapeutic and Preventive Agents for Cerebral Amyloidosis

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Masahito Yamada, Kenjiro Ono, Tsuyoshi Hamaguchi, and Moeko Noguchi-Shinohara

Abstract

Epidemiological studies have suggested that diets rich in phenolic compounds may have preventive effects on the development of dementia or Alzheimer's disease (AD). 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. These data, together with an updated review of the literature, indicate that natural phenolic compounds have anti-amyloidogenic effects on Aβ in addition to well-known anti-oxidative and anti-inflammatory effects, hence suggesting their potential as therapeutic and/or preventive agents for cerebral Aβ amyloidosis, including AD and cerebral amyloid angiopathy (CAA). Well-designed clinical trials or preventive interventions with natural phenolic compounds are necessary to establish their efficacy as disease-modifying agents.

Keywords

Alzheimer's disease • Amyloid β-protein • Amyloidosis • Polyphenols • Therapy

Abbreviations

Aβ	amyloid β-protein
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale

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αS	α-synuclein
ApoE	apolipoprotein E
APP	amyloid-β precursor protein
CAA	cerebral amyloid angiopathy
CD	circular dichroism
CSF	cerebrospinal fluid
Cur	curcumin
DLB	dementia with Lewy bodies
EGCG	(−)-epigallocatechin-3-galate
FA	ferulic acid
fAβ	Aβ fibrils
GSPE	grape seed polyphenolic extract
LTD	long-term depression
LTP	long-term potentiation
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide
Myr	myricetin
NDGA	nordihydroguaiaretic acid
NMR	nuclear magnetic resonance
PD	Parkinson's disease
PHF	paired helical filament
PICUP	photo-induced cross-linking of unmodified proteins
RA	rosmarinic acid

4.1 Epidemiological Studies Suggesting Preventive Effects of Phenol Compound-Rich Diets on Dementia or Alzheimer's Disease

Epidemiological studies have reported that diets rich in phenolic compounds or polyphenols may be associated with a reduced risk of dementia or Alzheimer's disease (AD). These include vegetables, fruits, spice, and derived products such as wine and non-alcoholic beverages.

The Mediterranean diet, characterized by a high intake of vegetables, fruits, cereals, olive oil, fish, in combination with a low intake of meat and poultry, was reported to be associated with a reduction in risk of dementia, mild cognitive impairment (MCI), and AD in prospective longitudinal studies (Scarmeas et al. 2006, 2009; Féart et al. 2009). In a randomized trial with nutritional intervention comparing two Mediterranean diets supplemented with either extra-virgin olive oil or nuts versus a low-fat control diet for 6.5 years, cognitive performance examined by Mini-Mental State Examination (MMSE) and Clock Drawing Test was significantly better in the group of Mediterranean diets than in a low-fat control group, after adjusting multiple confounding factors (Martínez-Lapiscina et al. 2013). Recent systematic reviews with meta-analysis indicate that a higher adherence to Mediterranean diet is associated with a reduced risk of MCI, dementia, and AD; nevertheless, further prospective cohort studies with longer follow-up and randomized controlled trials are necessary to unequivocally establish the effects of this type of diet on cognitive decline and AD (Psaltopoulou et al. 2013; Singh et al. 2014).

Traditional Indian diets and medicines contain spices such as yellow curry spice turmeric, curcumin. Frequency of AD in India is about one-quarter of that in the US (aged 70–79 years, 0.7 % vs 3.1 %; aged 80 years or older, 4.0 % vs 15.7 %), suggesting influence of ethnic differences in environmental, including dietary, apart from genetic factors (Ganguli et al. 2000). In a population-based cohort of non-demented elderly Asian subjects, more curry consumption was associated with better cognitive performance suggesting possible preventive effects of curry spice curcumin on cognitive decline, although further prospective cohort studies with long follow-up are required (Ng et al. 2006).

Several prospective cohort studies also reported that moderate intake of wine was associated with a reduced risk of dementia, AD, or cognitive decline (Orgogozo et al. 1997; Truelsen et al. 2002; Luchsinger et al. 2004; Solfrizzi et al. 2007; Mehlig et al. 2008; Arntzen et al. 2010). As this protective effect was not seen for alcoholic beverages other than wine (Truelsen et al. 2002; Luchsinger et al. 2004; Mehlig et al. 2008; Arntzen et al. 2010), it is suggested that

the association for wine may be attributable to components of wine other than ethanol itself. In a population-based prospective study, consumption of fruit and vegetable juices, containing a high concentration of polyphenols, decreased a risk of AD (Dai et al. 2006).

Coffee, black tea, and green tea are enriched in polyphenols, and may be protective against onset of dementia including AD. Several longitudinal studies (Lindsay et al. 2002; van Gelder et al. 2007; Ritchie et al. 2007; Eskelinen et al. 2009) have investigated the relationship between coffee consumption and dementia, AD, or cognitive decline, but findings from these studies are inconsistent. Longitudinal studies of black tea consumption have not found any association with reduced risks for dementia, AD, or cognitive decline (Laurin et al. 2004; Dai et al. 2006). One cross-sectional study has shown that higher green tea consumption is associated with lower prevalence of cognitive impairment (Kuriyama et al. 2006). To determine whether the consumption of green tea, coffee, or black tea influences the incidence of dementia and MCI in older people, we recently conducted a population-based prospective study with Japanese residents aged >60 years from Nakajima, Japan (the Nakajima Project) (Noguchi-Shinohara et al. 2014). Participants received an evaluation of cognitive function and blood tests. The consumption of green tea, coffee, and black tea was also evaluated at baseline. Of 723 participants with normal cognitive function at a baseline survey (2007–2008), 490 completed the follow up survey in 2011–2013. The incidence of dementia during the follow-up period (mean ± SD: 4.9 ± 0.9 years) was 5.3 %, and that of MCI was 13.1 %. To analyze the independent effects of green tea, coffee, and black tea consumption on the risk of developing dementia or MCI, multivariate logistic regression analysis was performed with adjustment for sex, age, history of hypertension, diabetes mellitus, and hyperlipidemia, formal education, apolipoprotein E (*ApoE*) phenotype status (*ApoE* E4+ or E4-), smoking status, alcohol consumption, green tea, coffee, and/or black tea consumption, physical activities and/or hobbies. The multiple-adjusted odds ratio for the incidence of overall cognitive decline (dementia or MCI) was 0.32 (95 % CI: 0.16–0.64) among individuals who consumed green tea every day and 0.47 (95 % CI: 0.25–0.86) among those who consumed green tea 1–6 days per week compared with individuals who did not consume green tea at all (Fig. 4.1). No association was found between coffee or black tea consumption and the incidence of dementia or MCI. Our results indicate that green tea consumption is significantly associated with reduced risk of cognitive decline, even after adjustment for possible confounding factors. This was the first prospective longitudinal study that examined the association between green tea consumption and incidence of dementia or cognitive decline.

Figure 4.2 shows components of green tea, black tea, and coffee with possible effects on cognitive decline. The major tea-related polyphenols present in green tea are catechins, especially (−)-epigallocatechin-3-galate (EGCG), whereas black tea mainly contains theaflavins (Peterson et al. 2005). In addition, green tea contains greater amounts of myricetin (Myr) compared with black tea (Peterson et al. 2005). Other tea-related polyphenols such as quercetin, kaempferol, apigenin, and luteolin, are also present in both green and black tea, but the amounts of these polyphenols are not significantly different between tea types (Peterson et al. 2005). The caffeine content is 40–57 mg/100 mL in coffee (Barone and Roberts 1996), 25.5 mg/100 mL in black tea, and only 15.3 mg/100 mL in green tea (Khokhar and Magnusdottir 2002). High intake of ascorbic acid was reported to be associated with lower risk of AD (Engelhart et al. 2002). The content of ascorbic acid is 6 mg/100 mL in green tea, which is the most common source of ascorbic acid in Japan (Ogawa et al. 2002); on the other hand, coffee and black tea do not contain ascorbic acid. As the serum levels of ascorbic acid were associated with the frequency of coffee consumption, but not green tea consumption in our study (Noguchi-Shinohara et al. 2014), it is unlikely that the effects of green tea on cognitive function could be explained as those of ascorbic acid. Taken together, phenolic compounds enriched in green

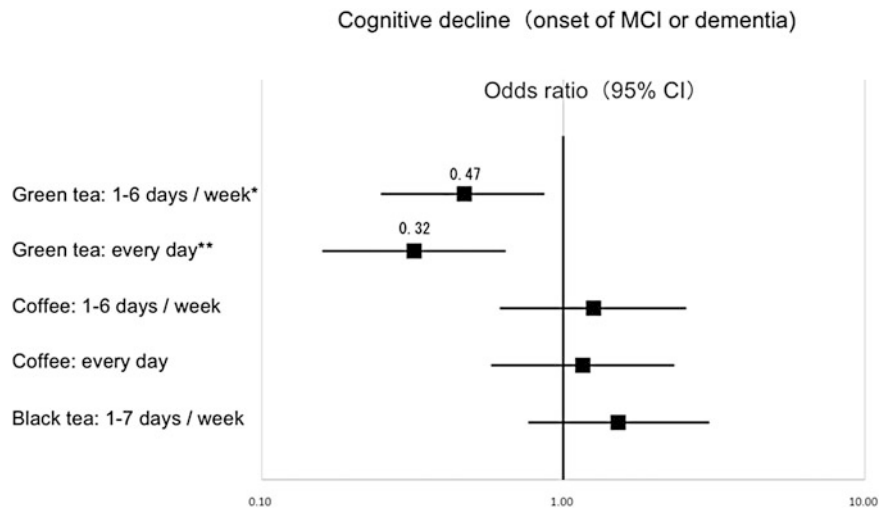

Fig. 4.1 Association between green tea, coffee, or black tea consumption and the incidence of cognitive decline [mild cognitive impairment (MCI) or dementia] in cognitively normal subjects (age > 60 years) ($n = 490$) during the follow-up period (mean ± SD: 4.9 ± 0.9 years). The multiple-adjusted odds ratio[#] for the incidence of cognitive decline (MCI or dementia) is shown compared with individuals who did not consume green tea, coffee, or black tea at all. Details were reported in the reference (Noguchi-Shinohara et al. 2014) [#]Multivariate logistic regression models were used to analyze the independent effects of green tea, coffee, and black tea consumption on the risk of developing dementia or MCI so that the lowest category (none) served as the reference group. Model was adjusted for sex, age, history of hypertension, diabetes mellitus, and hyperlipidemia, formal education, apolipoprotein E (*ApoE*) phenotype status (*ApoE* E4+ or E4-), smoking status, alcohol consumption, green tea, coffee and/or black tea consumption, physical activities and/or hobbies*P-value < 0.05, **P-value < 0.01

tea, such as EGCG and myricetin, would be candidates to exert preventive effects on cognitive decline (Fig. 4.2).

4.2 Effects of Natural Phenolic Compounds in Cerebral Amyloidosis Models

4.2.1 Studies Using *In Vitro* Models of Cerebral Amyloidosis

Natural phenolic compounds have been commonly reported as having anti-oxidant, anti-inflammatory, and other activities that may exert neuroprotective effects on AD and other dementias. However, the remarkable effects of such compounds on cognitive decline observed in epidemiological studies with older people suggest that they may have more specific effects on pathways involved in the pathophysiology of cerebral amyloidosis and other neurodegenerative disorders such as dementia with Lewy bodies (DLB).

Cerebral parenchymal deposition of the amyloid β-peptide (Aβ) is a central feature of AD. In addition, Aβ deposits in the cerebral vasculature of older subjects and AD, called cerebral amyloid angiopathy (CAA), cause cerebral hemorrhages and other cerebrovascular disorders. As amyloid deposition is considered to be the most upstream event in AD pathogenesis (amyloid cascade hypothesis), the process of Aβ deposition is the main target of drug development in AD. Although α-cleavage of amyloid-β precursor protein (APP) by α-secretase prevents production of Aβ, β- and γ-cleavages of APP by β- and γ-secretases produce Aβ; Aβ peptides subsequently aggregate from monomers to oligomers, protofibrils, and fibrils (Fig. 4.3). Moreover, tau protein is phosphorylated and aggregates forming intracellular neurofibrillary tangles composed of paired helical filaments. Finally, synaptic dysfunction and neuronal death occur. In DLB as well as Parkinson's

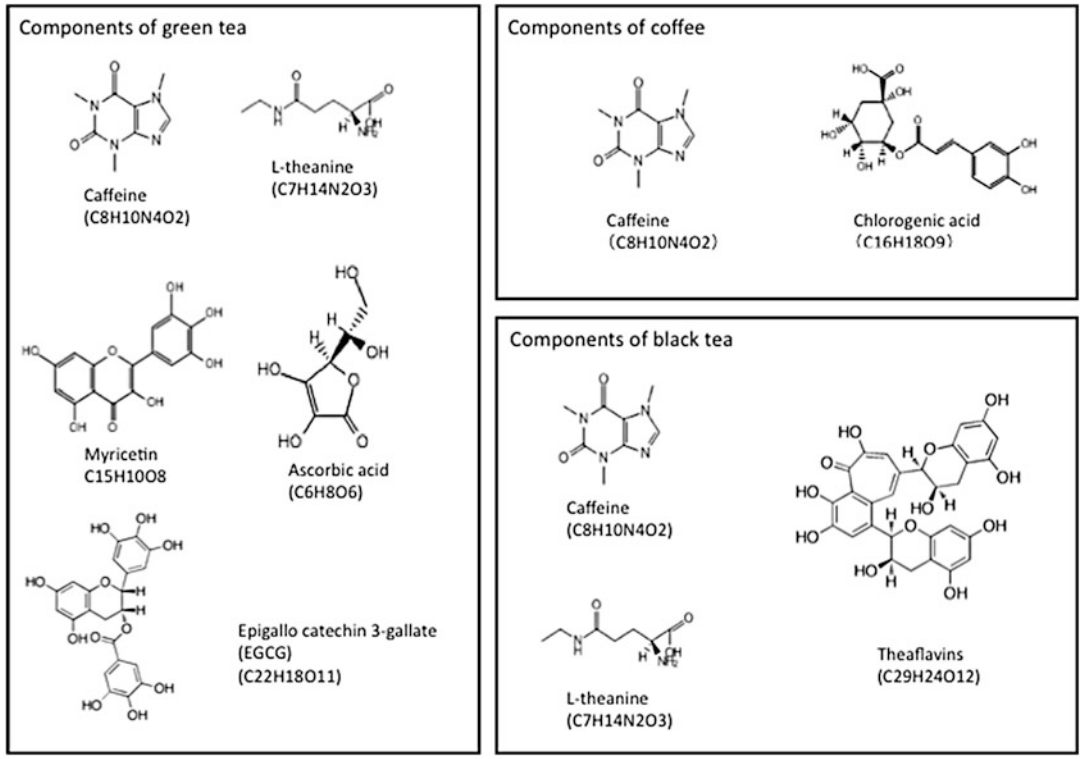

Fig. 4.2 Components of green tea, coffee, and black tea that may be implicated in preventive effects on cognitive decline

disease (PD), α-synuclein (αS) is aggregated in neuronal cell bodies and neurites (Lewy bodies and neurites) in the brain (α-synucleinopathies). Widespread tau aggregation is found in other neurodegenerative dementias than AD (non-AD tauopathies), such as Pick's disease, argyrophilic grain disease, and senile dementia of the neurofibrillary tangle type.

Recent studies have reported that natural phenolic compounds have the following specific actions: modulation of the processing of APP (Levites et al. 2003; Rezai-Zadeh et al. 2005; Obregon et al. 2006; Chakraborty et al. 2011; Kostomoiri et al. 2013; Yoshida et al. 2014; Zhang et al. 2013), inhibition of Aβ aggregation and remodeling and destabilization of aggregates (Ono et al. 2002, 2003, 2004a, b, 2005, 2008, 2012; Yang et al. 2005; Bastianetto et al. 2006; Rivière et al. 2007, 2009; Ehrnhoefer et al. 2008; Shoval et al. 2008; Wang et al. 2008, 2014; Bieschke et al. 2010; Grelle et al. 2011; Thapa et al. 2011; Rigacci et al. 2011; Hirohata et al. 2012; Ge et al. 2012; Cheng et al. 2013; Sinha et al. 2012; Rushworth et al. 2013; Palhano et al. 2013; Zhang et al. 2013; Ho et al. 2013; Cui et al. 2013; Richard et al. 2013; da Silva Bittencourt et al. 2014), promotion of Aβ degradation/clearance (Marambaud et al. 2005; Vingtdeux et al. 2010), alleviation of Aβ-induced oxidative stress/toxicity/synaptic dysfunction (Ono et al. 2003; Savaskan et al. 2003; Sultana et al. 2005; Bastianetto et al. 2006; Joshi et al. 2006; Feng et al. 2009, 2013; Bieschke et al. 2010; Choi et al. 2010; He et al. 2011; Fuentealba et al. 2011, 2012; Grelle et al. 2011; Rushworth et al. 2013; Ho et al. 2013; Wong et al. 2013; Cimini et al. 2013; Camilleri et al. 2013; da Silva Bittencourt et al. 2014), inhibition of αS aggregation (Ono and Yamada 2006; Masuda et al. 2006, 2009; Ehrnhoefer et al. 2008; Bieschke et al. 2010; Grelle et al. 2011; Marchiani et al. 2013), detoxification

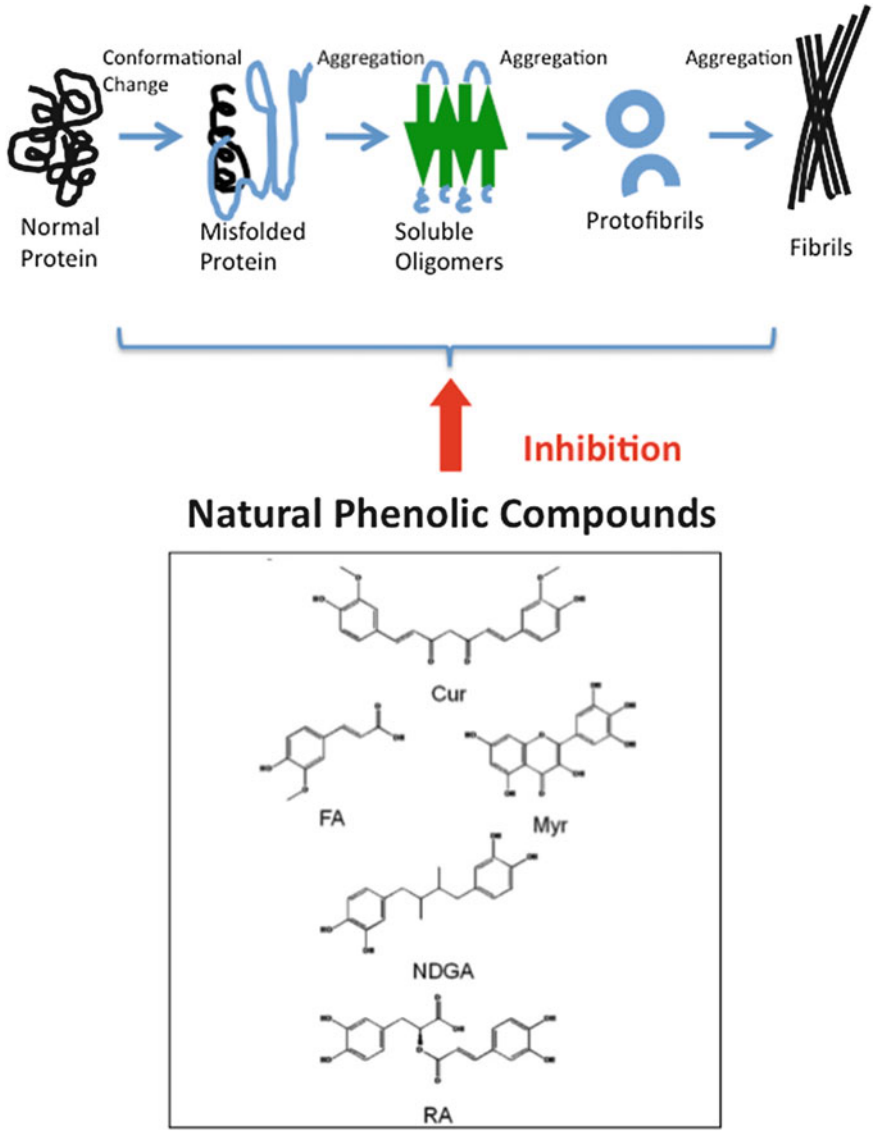

Fig. 4.3 A pathway of protein aggregation for the amyloid-β peptide (Aβ) and α-synuclein protein. The same five phenolic compounds with inhibitory effects on Aβ aggregation in our *in vitro* studies were used for our *in vivo* studies with an animal model. *Cur* curcumin, *FA* ferulic acid, *Myr* myricetin, *NDGA* nordihydroguaiaretic acid, *RA* rosmarinic acid

of αS aggregates (Bieschke et al. 2010; Grelle et al. 2011; Caruana et al. 2012; Marchiani et al. 2013; Lorenzen et al. 2014), and inhibition of tau phosphorylation and aggregation (Taniguchi et al. 2005; Ho et al. 2009b; Ksiezak-Reding et al. 2012; Patil et al. 2013; Yao et al. 2013). Such effects have been reported in various phenolic compounds: flavones such as baicalein (Caruana et al. 2012), flavonols such as Myr, quercetin, and morin (Ono et al. 2003, 2006a, 2012; Masuda et al. 2006; Chakraborty et al. 2011; Caruana et al. 2012; Ho et al. 2013), isoflavones such as glycitein and genistein (Hirohata et al. 2012), flavanols such as EGCG and theaflavins (Ono et al. 2003, 2006a; Levites et al. 2003; Rezai-Zadeh et al. 2005; Obregon et al. 2006;

Bastianetto et al. 2006; Ehrnhoefer et al. 2008; Bieschke et al. 2010; He et al. 2011; Grelle et al. 2011; Cheng et al. 2013; Sinha et al. 2012; Rushworth et al. 2013; Palhano et al. 2013; Zhang et al. 2013; Lorenzen et al. 2014), stilbenes such as resveratrol, nordihydroguaiaretic acid (NDGA), piceid, and viniferin (Ono et al. 2002, 2003, 2006a, 2012; Savaskan et al. 2003; Marambaud et al. 2005; Rivière et al. 2007, 2009; Gauci et al. 2011; Capiralla et al. 2012; Ge et al. 2012; Feng et al. 2013; Vingtdeux et al. 2010; Caruana et al. 2012; Rushworth et al. 2013; Richard et al. 2013), phenolic acids such as rosmarinic acid (RA), tannic acids (TA), ferulic acid (FA), ellagic acid, and gallic acid (Ono et al. 2003, 2004b, 2005, 2006a, 2012; Sultana et al. 2005; Joshi et al. 2006; Feng et al. 2009; Cui et al. 2013; Zhang et al. 2013; Yao et al. 2013; Yoshida et al. 2014), curcuminoids such as curcumin (Cur) (Ono et al. 2004b, 2006a, 2012; Yang et al. 2005; Shoval et al. 2008; Marchiani et al. 2013; Patil et al. 2013), secoiridoids such as oleuropein (Rigacci et al. 2011; Kostomoiri et al. 2013), and others (Thapa et al. 2011). In addition, extracts of phenolic compounds of natural products have been used for studies, including extracts of grape seeds, wine, berries, tea, cocoa, guarana, and *Pueraria lobata* (Ono et al. 2008; Wang et al. 2008, 2014; Ho et al. 2009a; Choi et al. 2010; Fuentealba et al. 2011, 2012; Gauci et al. 2011; Caruana et al. 2012; Ksiezak-Reding et al. 2012; Wong et al. 2013; Cimini et al. 2013; da Silva Bittencourt et al. 2014).

To develop therapeutics and preventives for cerebral Aβ amyloidosis (AD and CAA), we investigated whether such natural phenolic compounds with possible anti-dementia/AD effects suggested in the epidemiological studies have anti-aggregation effects on Aβ. We first examined the effects of Myr, morin, quercetin, kaempferol (+)-catechin, (−)-epicatechin, NDGA, Cur, RA, and FA on the formation, extension, and destabilization of Aβ fibrils (fAβ) *in vitro*, using fluorescence spectroscopy with thioflavin T and electron microscopy (Ono et al. 2003, 2004b, 2006b). All examined phenolic compounds dose-dependentlyinhibited formation of fAβ from fresh Aβ(1–40) (Aβ40) and Aβ(1–42) (Aβ42), as well as their extension (Fig. 4.4a–c). Moreover, these polyphenols dose-dependently destabilized preformed fAβ40 and fAβ42. The effective concentrations (EC50) of Myr, morin, quercetin, NDGA, Cur, and RA for the formation, extension and destabilization of fAβ40 and fAβ42 were in the order of 0.1–1 μM. In cell culture experiments, Myr-treated fAβ were less toxic than intact fAβ, as demonstrated by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assays.

We further investigated the effects of Myr, NDGA, FA, Cur, and RA on Aβ oligomerization and a mechanistic basis of the anti-aggregation effects of these compounds (Ono et al. 2012). We revealed that, using the method of photo-induced cross-linking of unmodified proteins (PICUP), these five phenolic compounds dose-dependently inhibited oligomerization of Aβ40 and Aβ42 (Fig. 4.4d). The circular dichroism (CD) spectroscopy studies showed that both Myr and RA stabilized Aβ populations comprising mostly random coil and inhibited statistical coils to β-sheet conversion. However, at the atomic level, a study with nuclear magnetic resonance (NMR) spectroscopy showed that Myr and RA behave differently, in that Myr shows significant binding to monomeric Aβ42 (Fig. 4.5), whereas RA does not bind to the monomer. It is possible that RA could prevent aggregation by binding to non-NMR detectable early-formed oligomers or distinct monomer conformers/structures causing the inhibition of oligomerization (Fig. 4.5).

There has been mounting evidence that Aβ oligomers rather than mature fibrils are toxic and considered to induce the deleterious cascade(s) involved in the pathophysiology of AD [see review (Larson and Lesne 2012)]. We investigated whether these phenolic compounds with anti-oligmerization effects could attenuate toxicity (Ono et al. 2012). Long-term potentiation (LTP) and depression (LTD) are neurophysiological models of neuronal plasticity for memory and learning; using electrophysiological assays for LTP and LTD in hippocampal slices, we found that Myr and RA decreased Aβ oligomer-induced synaptic toxicities. We evaluated the effects of these phenolic compounds on Aβ-oligomer in-

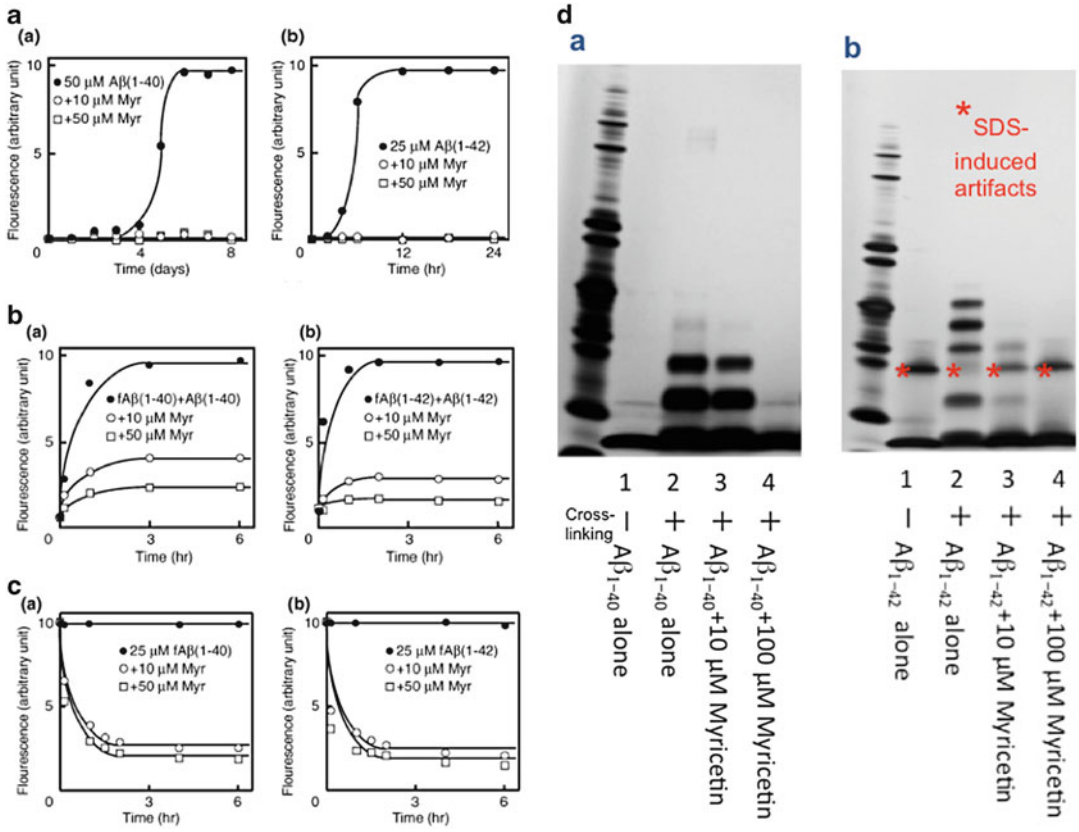

Fig. 4.4 Myricetin inhibits formation of Aβ fibrils (fAβ) from fresh Aβ(1–40) (Aβ40) and Aβ(1–42) (Aβ42) (**A**), extension of fAβ (**B**), destabilized preformed fAβ (**C**), and inhibit oligomerization of Aβ40 and Aβ42 (**D**). The inhibitory and destabilizing effects are also demonstrated with other methods such as electron microscopy and atomic force microscopy (not shown). Details of the experiments were described in the references (Ono et al. 2003, 2012) [**A**, **B**, **C**: thioflavin T; **D**: Photo-induced Cross-linking of Unmodified Proteins (PICUP)]

duced cytotoxicity using MTT assays. Aβ40 and Aβ42 oligomers exhibited cellular toxicity, however, Myr and RA reduced the Aβ oligomer-induced cytotoxicity.

4.2.2 Studies with *In Vivo* Models of Cerebral Amyloidosis

The natural phenolic compounds with *in vitro* anti-amyloidogenic effects have been tested for the effects in *in vivo* models of cerebral amyloidosis. Reductions of amyloid deposition, Aβ oligomer levels, inflammation, or oxidative stress in the brain with attenuation of cognitive deterioration have been reported in transgenic mouse models treated with: Cur (Lim et al. 2001; Yang et al. 2005; Hamaguchi et al. 2009; Ray et al. 2011), EGCG (Rezai-Zadeh et al. 2005, 2008), Myr (Hamaguchi et al. 2009), RA (Hamaguchi et al. 2009), resveratrol (Karuppagounder et al. 2009; Capiralla et al. 2012; Solberg et al. 2014; Porquet et al. 2014), tannic acid (Mori et al. 2012), FA (Mori et al. 2013), rutin (a glycone of quercetin) (Xu et al. 2014), oleuropein (Grossi et al. 2013), hopeahainol A (Zhu et al. 2013), grape seed polyphenolic extract (GSPE) (Wang et al. 2008; Liu et al. 2011), proanthocyanidins of GSPE (Wang et al. 2012), red wine/its polyphenolic contents (Wang et al. 2006; Ho et al. 2009a), anthocyanin-enriched blueberry and blackcurrant

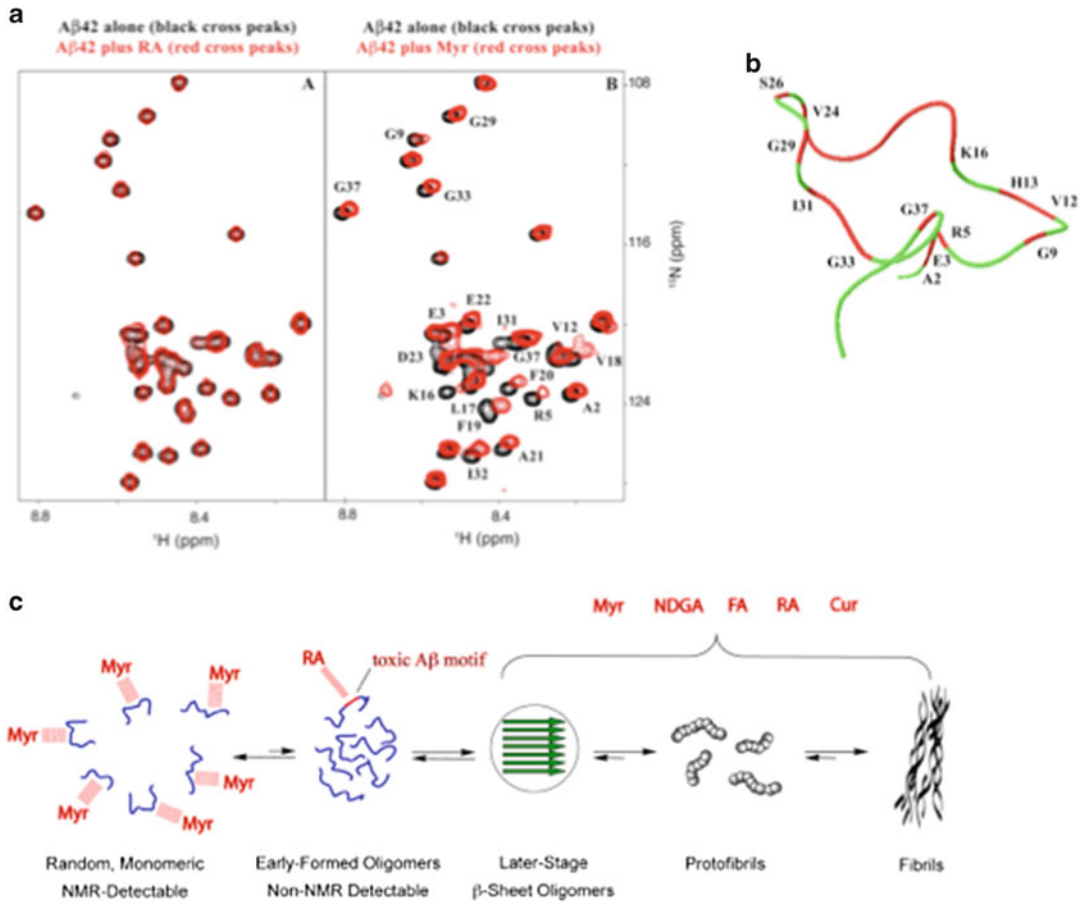

Fig. 4.5 Binding of phenolic compounds to Aβ (**a**). In nuclear magnetic resonance (NMR) spectroscopy studies, myricetin (Myr) shows NH chemical shift movements indicative of binding (*right*), but rosmarinic acid (RA) does not (*left*) (**b**). A representative structural model of Aβ42 that shows binding locations with Myr (indicated by *red* color) (**c**). The summary of our studies for mechanism of polyphenolic inhibition of Aβ aggregation. The phenolic compounds [Myr, RA, nordihydroguaiaretic acid (NDGA), ferulic acid (FA), and curcumin (Cur) (see Fig. 4.3)] exert inhibitory effects through different binding to Aβ. Details of the studies were described in the reference (Ono et al. 2012)

extracts (Vepsäläinen et al. 2013), pomegranate juice containing high levels of polyphenols (Hartman et al. 2006), and a natural diet rich in polyphenols and polyunsaturated fatty acids (LMN diet) (Fernández-Fernández et al. 2012). Other models include an Aβ-infused rat AD model treated with Cur (Hoppe et al. 2013), and a transgenic *Caenohabditis elegans* model of Aβ amyloidosis treated with quercetin (Regitz et al. 2014) and oleuropein (Diomede et al. 2013; Grossi et al. 2014). Furthermore, attenuation of neuropathology was reported in a tau transgenic mouse model of tauopathy treated with GSPE (Wang et al. 2010; Santa-Maria et al. 2012). In addition, EGCG prevented the accumulation of αS in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice, a model of α-synucleinopathy (Mandel et al. 2004).

We focused on the natural phenolic compounds that exerted anti-Aβ aggregation effects in our *in vitro* studies as described above, and systematically investigated whether these five phenolic compounds (Cur, FA, Myr, NDGA, and RA) (Fig. 4.3) also have *in vivo* effects in APP transgenic mice (Tg2576) that show

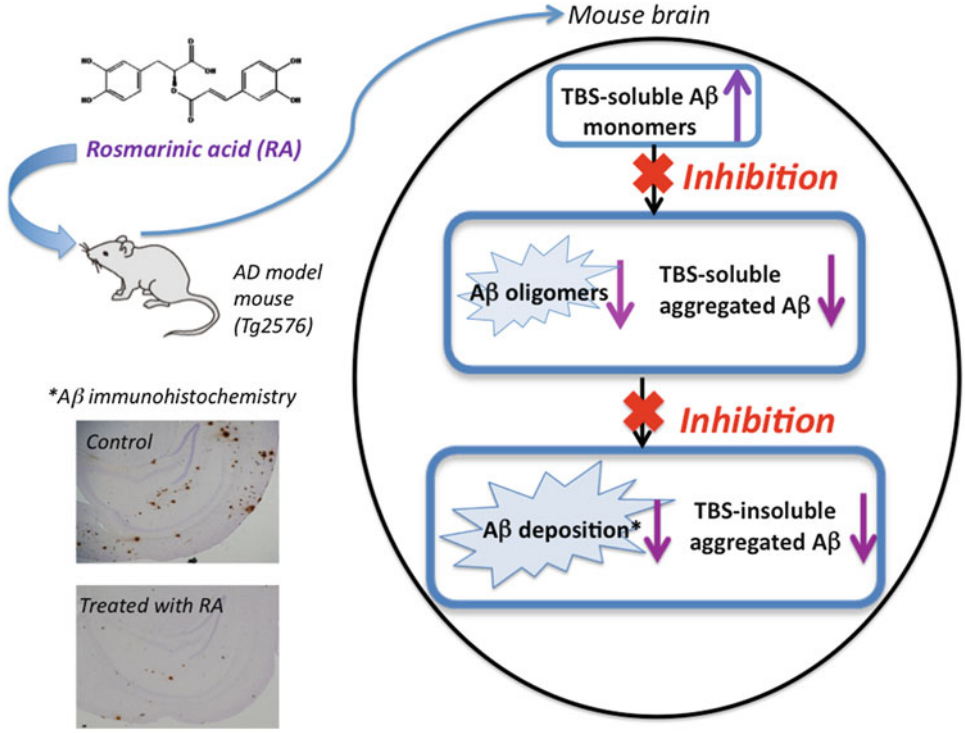

Fig. 4.6 Treatment of Alzheimer's disease (AD) model mice (Tg2576) with rosmarinic acid (RA) showed reductions of both soluble aggregated Aβ, such as Aβ oligomers, and insoluble aggregated Aβ, and an increase of Aβ monomers in the brain. These findings indicate that RA inhibits both the steps from Aβ monomers to oligomers and from oligomers to fibrils. Details of the *in vivo* study on the effects of treatment with diets of the natural phenolic compounds were described in the reference (Hamaguchi et al. 2009)

cerebral Aβ amyloidosis including parenchymal and vascular amyloid deposition (Hamaguchi et al. 2009). Mice were fed Cur, FA, Myr, NDGA, or RA for 10 months from the age of 5 months. Immunohistochemical analysis, in both the NDGA- and RA-treated groups, revealed that Aβ deposition was significantly decreased in the brain ($p < 0.05$). In the RA-treated group, the level of soluble Aβ monomers was increased ($p < 0.01$), while that of oligomers, as probed with the A11 antibody (A11-positive oligomers), was decreased ($p < 0.001$) (Fig. 4.6). However, in the NDGA-treated group, the abundance of A11-positive oligomers was increased ($p < 0.05$) without any change in the levels of soluble or insoluble Aβ. In the Cur- and Myr-treated groups, changes in the Aβ profile were similar to those in the RA-treated group, but Aβ plaque deposition was not significantly decreased. In the FA-treated group, there was no significant difference in the Aβ profile. These results showed that oral administration of the natural phenolic compounds influenced AD pathology and Aβ monomer/oligomer/fibril deposition levels in the brain by differentially modulating Aβ aggregation pathways *in vivo*. From our results, RA appeared to be the best compound, because it was found to inhibit both steps from monomers to soluble oligomers, and from soluble oligomers to insoluble aggregated Aβ deposition (Fig. 4.6). Cur and Myr also seemed effective because they significantly decreased soluble oligomer levels, although the reduction of Aβ deposition did not reach significant levels. FA showed no significant effect. NDGA would be inappropriate, because it significantly increased soluble Aβ oligomer levels, which would suggest that it inhibited only the step from soluble oligomers to

insoluble aggregated Aβ deposition, resulting in an increase of potentially toxic soluble oligomers.

4.3 Clinical Trials with Natural Phenolic Compounds for Alzheimer's Disease

For clinical use, several phenolic compounds have been investigated or are under current investigation in clinical trials. Concerning Cur, two clinical trials in AD have been published. In a double-blind, placebo-controlled, randomized, 6-month trial of Cur with 34 AD patients in Hong Kong, 4 g, 1 g (plus 3 g placebo), or 0 g (plus 4 g placebo) of Cur in addition to 120 mg ginkgo leaf extract were orally administered once daily, and showed no significant difference in changes in MMSE or plasma Aβ40 levels between 0 and 6 months (Baum et al. 2008). Cur showed no significant side effects in this pilot study (Baum et al. 2008). In another double blind, placebo-controlled, randomized, 24-week trial of Cur in California, 34 patients with AD daily received placebo, 2 g, or 4 g of Curcumin C3 Complex® (Ringman et al. 2012). There were no differences between treatment groups in clinical or biomarker efficiency measures including the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), levels of Aβ40 and Aβ42 in plasma, levels of Aβ42 and total and phosphorylated tau in cerebrospinal fluid (CSF) (Ringman et al. 2012). For adverse effects, Cur was largely well–tolerated, however, three subjects in the Cur group withdrew due to gastrointestinal symptoms (Ringman et al. 2012). Pharmacokinetic results for Cur and its metabolites suggested limited bioavailability of this compound; levels of native Cur were undetectable in the CSF (Ringman et al. 2012). These published data failed to demonstrate clinical or biomarker evidence of efficacy of a half-year oral Cur intake. Further studies are necessary with a larger number of patients, a longer duration of treatment, and better Cur preparations with higher bioavailability and penetration to the brain.

The website of the U.S. National Institute of Health (NIH) (ClinicalTrials.gov) reports that clinical studies with Cur for subjects at the stage of MCI are ongoing. In a double blind, randomized interventional study at UCLA, subjects with MCI or age-associated cognitive impairment are recruited and receive Cur (Theracurmin® 180 mg/day) or placebo; outcome measures include cognitive testing, amyloid PET, and inflammatory markers. Effects of Cur (800 mg) and yoga in subjects with MCI are investigated in a double blind, randomized trial using interventions by Cur or placebo, and aerobic or non-aerobic yoga.

Regarding resveratrol, to our knowledge, there have been no publications of clinical trials for AD or dementia. The NIH website reports that three clinical trials of resveratrol for AD or MCI are active or completed (ClinicalTrials.gov). A double blind, placebo-controlled, randomized, multicenter study operated by the Alzheimer's Disease Cooperative Study in the U.S. is ongoing; it is scheduled that 120 subjects with AD will be enrolled and receive resveratrol (500 mg to 2 g/day by mouth) or placebo for 52 weeks, and CSF markers and MRI as well as safety and tolerability are primary outcome measures. A single-center, multi-site, randomized, double blind, placebo-controlled 12-month trial of liquid resveratrol with glucose and malate to slow the progression of AD in New York has been completed with enrollment of 27 AD subjects, but no results are posted. To test enhancement of memory functions in subjects with MCI by dietary interventions and in combination with exercise and cognitive training, a double blind, placebo-controlled, randomized trial in Germany is ongoing with multiple arms that include a group of resveratrol supplementation.

Clinical trials with EGCG for AD or Down syndrome are also posted on the NIH website (ClinicalTrials.gov). A double-blind, placebo-controlled, randomized, 18-month trial of EGCG in early or mild AD is ongoing in Germany; it is planned that 50 patients will be recruited and receive EGCG (200–800 mg) or placebo added to donepezil with evaluation of cognitive functions. Older subjects with Down syndrome show progression of AD-like lesions in the brain. To test improvement of cognitive performance and deceleration of AD-like progression in

Down syndrome by EGCG, a double-blind, placebo-controlled, randomized study is ongoing in Spain; the participants receive a daily oral dose containing 9 mg/kg of EGCG or placebo, and changes in cognitive functions and amyloid markers are primary outcome measures.

In addition, two clinical trials of isoflavones (including genistein) in AD and two interventional trials of pomegranate polyphenol extract or juice in non-demented subjects are ongoing (ClinicalTrials.gov).

Our group started clinical studies with RA, based on the results of our *in vitro* and *in vivo* studies with models of Aβ amyloidosis (Ono et al. 2004b, 2012; Hamaguchi et al. 2009). First, we completed a double-blind, placebo-controlled, randomized trial in healthy individuals to reveal pharmacokinetics, safety, and tolerability of RA. Next, we are conducting a double-blind, placebo-controlled, randomized trial of RA for mild AD with investigations of cognitive functions and biomarkers including amyloid PET and CSF markers.

Targets of future clinical trials with natural phenolic compounds will extend to other cerebral amyloidoses or protein aggregation disorders than AD, including CAA, PD, DLB, and non-AD tauopathies.

4.4 Conclusions

Epidemiological studies suggest an association of diets rich in phenolic compounds or polyphenols (Mediterranean diet, red wine, green tea, etc.) with reduction of risk of dementia or AD. In addition to the general beneficial effects of these compounds such as anti-oxidant and anti-inflammatory properties, experimental studies indicate that natural polyphenols have specific effects on pathways involved in the pathophysiology of cerebral amyloidosis; the effects include modulation of APP processing, inhibition of Aβ aggregation and destabilization of aggregates, promotion of Aβ degradation/clearance, alleviation of Aβ-induced oxidative stress, leading to reductions of amyloid deposition, Aβ oligomer levels and inflammation in the brain, with attenuation of cognitive deterioration in treated animal models. For clinical use, several phenolic compounds are under investigation by clinical trials for AD or MCI, although no compounds have been yet proved to have certain therapeutic or preventive effects so far. Further clinical trials and preventive interventions of these phenolic compounds with efforts to improve oral bioavailability and brain penetration are necessary to establish their efficacy in AD and other human cerebral amyloidoses.

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