Molecular Neurobiology (2019) 56:5556–5567
https://doi.org/10.1007/s12035-019-1469-6

Procyanidins and Alzheimer's Disease

Siqi Zhao[1,2,3] · Li Zhang[4] · Chenlu Yang[1,2,3] · Zhenghua Li[5] · Shuang Rong[1,2,3]

Received: 13 August 2018 / Accepted: 7 January 2019 / Published online: 16 January 2019

Abstract

Procyanidins, the oligomeric compounds formed from catechin and epicatechin molecules, are potentially effective targets as nutraceuticals or pharmaceuticals in the prevention and treatment of Alzheimer's disease (AD). Natural procyanidins can attenuate AD pathological features, extracellular amyloid deposits, and neurofibrillary tangles via reducing Aβ accumulation and tau pathology. The enhancement of cognition as well as modulation of synaptic plasticity by these compounds also participated in the alleviation of AD. Notably, procyanidins and some of their metabolites have been observed to upregulate SIRT1 (silent information regulator 1) which is essential for normal cognitive and synaptic plasticity, and stimulate CREB (cAMP response element binding) which acts as a molecular switch from short- to long-term memory. Based on the interplay of CREB-SIRT1 axis, it is therefore conceivable that the regulation of procyanidins by the means of CREB-SIRT1 could promote the cognitive function and is thus conducive for AD pathogenesis. This review focuses on the role of procyanidins, the main group of flavonoids, on AD and the potential mechanism involved CREB-SIRT1 axis.

Keywords Procyanidins · SIRT1 · CREB · Alzheimer's disease · Synaptic plasticity

Introduction

Alzheimer's disease (AD), the most common form of dementia, is a neurodegenerative disease which clinically characterizes progressive memory impairment, cognitive dysfunction, personality change, and speech problem [1, 2]. Current estimates present that till now, there are approximately 5.7 million people diagnosed with AD in America. Moreover, the costs of care for these individuals in 2018 were about $277 billion [3]. Unfortunately, none of the pharmacologic treatments available for AD delay or reverse the course of neurodegenerative dysfunction [4–6], so preventions become more practical to solve the public health concern.

Over the last decade, a variety of potential preventive or therapeutic phytochemicals which can relieve clinical symptoms of AD including impairment of cognitive function have been under investigated [7]. Among them, more and more attentions have been put into the study of procyanidins for health promotion especially neuroprotection during aging [8–11]. Procyanidins, composed of flavan-3-ols monomeric subunits [e.g., (−)-epicatechin or (+)-catechin] [12], are among the most abundant polyphenol present in human diets. In the USA, the dietary intake of procyanidins was estimated to be about 100 mg/day [13], and procyanidins can be found in a variety of foods such as fruits, vegetables, and beverages.

Many studies have reported that procyanidins could amerliorate brain neuropathology of AD through blocking the generation of toxic peptides [14] which include amyloid precursor protein (APP) processing, amyloid-β protein (Aβ) accumulation [15], and tauopathy [16, 17]. Furthermore, procyanidins can attenuate oxidative stress and prevent lipid peroxidation to exert beneficial effects in brain cells. Additionally, the activation of protein kinases and regulation of gene transcription also contribute to the amelioration effect of procyanidins on AD. Notably, some investigations have

Siqi Zhao and Li Zhang contributed equally to this study and should be co-first authors.

✉ Shuang Rong
rongshuang@wust.edu.cn

1 Department of Nutrition and Food Hygiene, School of Public Health, Medical College, Wuhan University of Science and Technology, Wuhan 430065, China

2 Institute of Nutrition and Chronic Diseases, Wuhan University of Science and Technology, Wuhan 430065, China

3 Hubei Province Key Laboratory of Occupational Hazard Identification and Control, Wuhan University of Science and Technology, Wuhan 430065, China

4 Department of Neurology, Hubei Provincial Hospital of Integrated Chinese & Western Medicine, Wuhan 430015, China

5 Wuhan Puren Guanghui Hospital, Wuhan 430084, China

illustrated that procyanidins metabolites such as 3'-O-methyl-epicatechin-5-O-β-glucuronide (3'-O-Me-EC-Gluc) can cross the blood-brain barrier and regulate signal transduction pathways, thereby affecting memory and cognition [18]. Evidence has increasingly shown that procyanidins may play a useful role in the prevention and treatment of AD. However, the underlying molecular mechanism by which procyanidins improve cognitive function reducing the risk of AD has not been adequate attention. The review aims to discuss the molecular mechanisms regarding the preventive and therapeutic role of procyanidins on AD and multiple studies suggest that it would be necessary to better understand how procyanidins influences brain functions.

Procyanidins and AD

AD is a progressive neurodegenerative disorder characterized by memory decline and cognitive impairment. The pathological hallmarks of AD are the aggregation of Aβ and accumulation of hyperphosphorylated tau proteins known as neurofibrillary tangles. Furthermore, these phenomena are associated with oxidative stress since the brain is particularly vulnerable to reactive oxygen species (ROS) [19]. Procyanidins which possess remarkable free radical eliminating capability have received considerable attention in recent years. Studies have shown that procyanidins can enforce antioxidant capacity and antagonize OS-mediated damage by scavenging ROS, preventing lipid peroxidation and mediating multiple signaling pathways in OS-related diseases such as AD [20]. Procyanidins can disrupt lipid peroxidation chain reactions to protect neurons by activating Akt phosphorylation [21]. Procianidins, meanwhile, can ameliorate OS through the activation of Nrf2, NF-κB, and MAPK signaling cascades to prevent and treat various OS-related diseases [9, 22, 23].

It should be noted, however, that increasing evidence suggests that some other mechanisms may involve the modulation of brain functions such as the alteration of several specific brain proteins expression or modification, not just antioxidant enzyme system. Especially in the nervous system, procyanidins and their brain-targeted metabolite are more likely to play a protective role by regulating multiple signaling pathways which involve in synaptic plasticity, cell proliferation, inflammation, and energy metabolism, eventually attenuating cognitive decline, preventing neurodegeneration, and maintaining mitochondrial homeostasis. Therefore, as effective antioxidants, the regulatory effect of procyanidins on antioxidant enzyme system may play a major role in the antioxidant properties. Simultaneously, the role of procyanidins, as a modifier, in learning and memory involving in the regulation of several important brain protein in memory-related brain regions also requires attentions.

Accordingly, considerable epidemiological, preclinical, and clinical studies have been conducted to explore the beneficial effects of procyanidins on AD-related pathology. For instance, in a randomized control trial with procyanidins-rich grape juice consumption for 12 weeks, Krikorian et al. found a significant enhancement of cognitive function relative to placebo-controlled elderly [24]. Likewise, Lamport et al. reported improved spatial memory and driving performance following 12 weeks of concord grape juice supplementation in healthy, middle-aged working mothers [25]. It is worth mentioning that a somewhat similar observation by Haskell-Ramsayl et al. reported the benefits after purple grape juice on improvement of cognition and mood in healthy young adults [26]. Combined with another current research on the impact of grape consumption in elderly participants with mild cognitive impairment (MCI) on brain metabolism and cognition [27], these findings suggested that cognitive improvement following procyanidins-rich diet supplemention exists in diverse populations. Thus, although procyanidins may not revers or cure AD, their neuroproctive capabilities could reduce the risk of AD and ameliorate relevant clinical symptom as well as pathological features, consequently preventing and slowing down its progress.

In addition to those human intervention trials with procyanidins-rich foods, animal and cell experiments have also been performed in order to provide further mechanism information about the neuroprotective potential of procyanidins. In this regard, previous studies demonstrated that procyanidins could effectively improve cognitive function in AD mice [18], suppress Aβ aggregation [15], and inhibit tau protein excessive phosphorylation and accumulation [16, 28]. Moreover, our previous studies have confirmed that procyanidins can exert neuroprotective effects in cognitively impaired aged rats by attenuating oxidative stress [29], inhibiting the lipid peroxidation and accumulation of age-related oxidative DNA damage in brain [29], enhancing the cholinergic neuron function [30] and changing the nitric oxide system [31]. In agreement with these results, several studies also reported that after receiving the procyanidins extracts, there was an increase in activity of antioxidant enzymes in animal brain [32], reduction of amyloid protein content, and attenuation of cognitive deterioration [33, 34]. Furthermore, a supplement study in conjunction with exercise by Satpati Abhijit and coworkers confirmed that grape seed proanthocyanidin extract (GSPE) can improve learning and memory [35]. Supplementation with a mixed blueberry and grape extracts in aged beagle dogs has been suggested to provide protection against memory decline and cognitive impairment [36]. Some works have been published reporting that procyanidins can improve memory and cognition, causing neuroprotection in different animals and humans experimental models. In spite of this, there is a lack of information about the exact mechanism by which procyanidins improve cognitive function reducing the risk of AD.

Role of CREB-SIRT1 Axis in the Onset and Progression of AD

AD is a devastating neurodegenerative disease featured by progressive neuronal damage leading to impairments of memory and cognitive function. The essential pathological events in AD are the extracellular accumulation of amyloid-β (Aβ)-containing neuritic plaques and the intraneuronal aggregation of tau-containing neurofibrillary tangles (NFTs) [37]. It is widely assumed that toxic effects of Aβ and tau in synaptic function are important factors for AD, and ultimately leading to cognitive deficits and memory impairments in patients [38]. On the other hand, tau is believed to disturb spatial cognition by involving in grid cell dysfunction and neuronal loss [39]. Relatedly, abundant studies indicated that the burden of NFTs is associated with the severity of cognitive impairments [40]. Additionally, other brain alterations such as inflammation, oxidative stress, and mitochondria disorder may occur in the process of AD [1, 41, 42]. Sirtuin 1 (SIRT1) protein is localized both in the cytoplasm and nucleus of mammalian as a kind of anti-aging protein. At present, SIRT1 exhibits its scientific value in the field of life science. CREB protein is a cAMP response element-binding protein, which is an important transcription regulator in nerve cells. More importantly, recent numerous mechanism studies indicate that the activation of CREB and SIRT1 may play focal role in the progression of AD because of their regulation action on multiple aspects including cortical and hippocampal neuron function and survival, energy metabolism, stress response, and apoptosis. Nevertheless, whether a SIRT1-CREB signaling axis is involved in AD-associated pathology and, by extension, in the memory and cognition impairments is still unknown. In the section below, we will review the relevant evidence and discuss the role of SIRT1 and CREB in the progression of AD.

Role of CREB Signaling in AD

The clinical manifestation of AD is a progressive memory loss progressing to severe cognitive impairment. Generally, compared with NFTs and Aβ, synaptic deficits are most closely correlated with the cognitive impairments in AD brains [43]. Importantly, in the field of memory study, scientists found that conversion of short-term memory (STM) to long-term memory (LTM) which is a process known as memory consolidation requires new gene transcription and protein synthesis in order to stimulate structural alteration of the synapses [44–46]. This alteration is indispensable for synaptic plasticity, including long-term potentiation (LTP), which has been considered to be a molecular correlate of memory [47]. In AD animal models, synaptic deficits such as LTP impairment and gradual cognitive decline can be obviously observed [18, 48]. Therefore, to shed light on the molecular mechanism contributing to synaptic deficits as well as the transcriptional mechanism needed for synaptic plasticity and memory will provide new ideas to treat cognitive and memory decline in the prevention and control of AD.

As a cellular transcription factor, the importance of CREB in the modulation of gene expression in response to synaptic plasticity, memory consolidation, and neurogenesis have been widely reported [49–52]. Activation of CREB, in other words, remains important in the "molecular switch" from STM to LTM. Moreover, the trigger of CREB-dependent transcription of various genes including brain-derived neurotrophic factor (BDNF), c-fos, and Nr4a2 requires CREB phosphorylation at Ser 133 [50, 51]. There are multiple intracellular signals (Ca^{2+} and cAMP) leading to CREB phosphorylation, such as cAMP-dependent pathway (e.g., protein kinase A, PKA) and cAMP pathway and Ca^{2+}/CaM-dependent protein kinase (e.g., CaMKII and CaMKIV) [53, 54]. In fact, it has been discovered that CREB may be involved in synaptic dysfunction caused by Aβ and tau pathologies. A recent study has demonstrated that tau accumulation disrupts synaptic function and memory via calcineurin-mediated inactivation of nuclear CaMKIV/CREB signaling [55]. Simultaneously, the impact of Aβ on synapse loss, synaptic plasticity, and memory also involve in the CREB signaling pathway [56, 57]. Previous study in human neuroblastoma cells showed that the regulation of Beta-site APP-cleaving enzyme 1 (BACE1) expression and Aβ production depend on PKA/CREB pathway [58]. Direct in vivo evidence supported that CREB overexpression can ameliorate age-related cognitive impairments [52]. Therefore, CREB has been identified to be essential in memory formation and consolidation.

Additionally, another mechanism of memory deficits associated with the CREB-regulated transcriptional coactivators (CRTCs) has attracted a lot of attentions. CRTCs, also called transducers of regulated CREB activity (TORCs) can mediate CREB transcription in response to cAMP and Ca^{2+} signals [59–61]. In mammals, there are three forms of the CRTC family (CRTC1, CRTC2, and CRTC3). Intriguingly, while CRTC2 and CRTC3 are found in most tissues, CRTC1 is mainly expressed in neurons [62]. Emerging evidence suggests that involvement of CRTC1 is also essential for synaptic plasticity. More specifically, alterations in CRTC1 activity or expression will be accompanied with alterations in memory and cognition [61, 63]. On the other hand, Aβ can disrupt the CREB-dependent gene transcription required for memory through the CRTC1 in brain [59]. Thus, altered CRTC1 activity may participate in synaptic dysfunction and memory impairments during AD. In fact, besides CRTC, other CREB transcriptional cofactors such as CBP and p300 may be more informative since these factors also participate in various physiological events particularly in memory formation and consolidation. Severe deficits in memory caused by the reduction in CBP activity are related with CREB-mediated gene expression in CBP+/− mice [45]. In some circumstances,

CBP/p300 is considered to recruit RNA polymerase II complexes and acetylate nucleosomal histones, subsequently promoting CREB target gene expression [64, 65]. To sum up, these results reveal the key role of CREB signaling in learning and memory. Besides its role in the modulation of memory, CREB target genes expression also plays critical roles in various biological effects, including neuroprotection, neuronal plasticity, proliferation, and neuronal survival [66, 67]. However, it is not surprising that CREB involves in the mechanism underlying AD memory dysfunction and may serve as a potential target for preventing AD.

Role of SIRT1 Signaling in AD

Sirtuin 1 (SIRT1), a ubiquitous and prominent histone decaetylase, has attracted a lot of attention because of its functions in metabolism, genomic stability, stress resistance, and neurogenesis [68–70]. SIRT1 is indispensable for normal cognitive function (learning and memory) and synaptic plasticity [71–73]. In the SIRT1 KO mice, impairment of cognitive function and defect in LTP can be observed clearly [71, 74]. Nevertheless, upregulating SIRT1 expression presents the neuroprotective effects and the cognitive enhancement in the mouse hippocampus [75]. Similarly, Carl et al. [76] found that in the parietal cortex of AD patients, the concentration of SIRT1 was decreased significantly compared with controls, and the levels of SIRT1 including mRNA and its translated protein correlated inversely with the accumulation of tau and the duration of AD symptoms. It is proposed that SIRT1 may evolve as a predictive biomarker of AD in early stages because a decline in serum concentration of SIRT1 in healthy people with time and a further decline in MCI and AD patients have been detected [77]. Moreover, accumulating evidence supports the mechanisms whereby SIRT1 has an impact on AD-related pathologies, developing from the direct effects on Aβ and tau to the indirect effects. The data obtained with the AD mice and human has demonstrated that SIRT1 loss is closely correlated with Aβ deposition and tau accumulation [76, 78]. On one hand, SIRT1 can decrease Aβ levels via activating α-secretase ADAM10 [79, 80] which can facilitate APP cleavage [81–83], and reduce tau-induced memory deficits by deacetylating tau and thereby enhancing tau turnover and decreasing tau levels [84, 85]. On the other hand, the role of SIRT1 as a deacetylase is related to a variety of signaling and metabolic proteins participated in modulating neuroinflammation, neuronal apoptosis, or mitochondria metabolism in AD-related celluar models and aged mice [70, 86–89]. Collectively, SIRT1 could potentially modify the initiation and progression of AD by affecting multiple aspects of cortical and hippocampal neuron functions, thus becoming a potent therapeutic target for the prevention and treatment of AD [90, 91].

Recently, the direct or indirect connection between CREB and SIRT1 during age-related cognitive dysfunction such as AD has started to be focused on and gradually become a hotspot of research. A study on goldfish (*Carassius auratus*) reported that in telencephalon, suppression of SIRT1 can inhibit the activation of ERK1/2 and CREB signaling pathway, and reduce downstream BDNF expression, further repressing synaptic transmission and memory formations [92]. The observation suggests the effect of SIRT1 on CREB phosphorylation. However, Jeong et al. [93] confirmed that SIRT1 could also deacetylate CRTC1 (TORC1) to promote its interaction with CREB, modulating BDNF gene transcription in mice with Huntington's disease. Furthermore, in the model rats of subchronic aluminum (Al) exposure, investigators observed that Al may reduce the concentrations of intracellular Ca^{+} and cAMP, weaken CRTC1/TORC1 nuclear translocation, decline the levels of TORC1, SIRT1, and pCREB, and finally, suppress the transcription of the BDNF gene, ultimately leading to LTM impairment [94]. Therefore, it is likely that SIRT1 is involved in CREB-regulated transcription required for synaptic plasticity and memory in AD. Surprisingly, recent studies have reported that SIRT1 can inhibit the expression of miR-134, consequently regulating CREB expression, which inevitably affects neurodevelopmental process and synaptic plasticity [74, 95]. Nevertheless, Fusco and his coworkers found that the expression of CREB is not effected by SIRT1, while CREB-dependent genes are markedly downregulated in the SIRT1 KO mouse brain [96]. The discrepancy in regulation of CREB expression could be due to different experimental model mice. In brains of mutant mice lacking SIRT1 catalytic activity (SIRT1Δ), unlike SIRT1 KO mice, an inactive form of SIRT1 may be expressed potentially acting against other molecules capable of regulating CREB expression in a possible dominant-negative manner [96]. The above results indicate that impact of SIRT1 on activity and content of CREB may exist simultaneously in the brains.

Interestingly, since CREB also serves as a substrate of SIRT1, the activation of CREB is likely to modify the beneficial effect of SIRT1 on AD. For instance, the detrimental effect of SIRT1 knockdown on cell proliferation and survival are associated with altered CREB phosphorylation in a SH-SY5Y cell culture model [97]. Nevertheless, in neural stem cells (NSCs) and the mouse hippocampus, a glucose-sensing circuitry is involved in a CREB-SIRT1 signaling axis that modulates Hes-1 (hairy and enhancer of split 1) expression and neurogenesis. Most importantly, phosphorylated and acetylated CREB could displace SIRT1 at the Hes-1 CRE region, and stimulate transcription, thus enhancing Hes-1 expression and cell proliferation [98]. Additionally, several studies performed in non-neuron cells or tissue such as liver [99, 100], adipose tissue [101], and anterior pituitary cells [102] also reveal that SIRT1 can suppress the phosphorylation of CREB through deacetylation, causing inactivation of CREB

and thus altering the pathways downstream of related target gene. Hence, it is suggested that SIRT1 may regulate CREB activity via deacetylation in different tissues or organs.

Conversely, it has been demonstrated that CREB, as a transcription factor, participates in SIRT1 transcription. A recent study reports that NAM exerts protective actions against plamilate-induced endoplasmic reticulum stress in hepatocytes by enhancing SIRT1 [103, 104]. Further mechanism research discovered that when the cAMP/PKA/CREB pathway was blocked, NAM-induced SIRT1 upregulation disappeared in HepG2 cell and primary mouse hepatocytes [103]. These results in vitro and in vivo demonstrated that activation of the cAMP/PKA/CREB signaling cascade plays a critical role in NAM-induced SIRT1 upregulation. Chalkiadaki et al. [105] found in the liver the transcriptional complex CREB-CRTC2 can stimulate the transcription of SIRT1 gene contributing to the procedure of energy homeostasis. Consistently, Fusco and colleagues reported the important evidence about transcriptional regulation of SIRT1 by CREB in BCKO (Brain CREB KO) mice brains and neuronal cells, suggesting the transcription of SIRT1 is mediated by CREB directly which subsequently affect neuronal plasticity and memory [96]. SIRT1, therefore, as a direct transcriptional target of CREB may partly explain the related pathogenesis of AD including energy metabolism and cognition dysfunction.

To date, increasing evidence indicates that the dysregulation of miRNA may contribute to synaptic defects, then further affecting memory and cognition in AD [106]. Of these, miR-132, as a potential therapeutic target for AD, is closely associated with the regulation of CREB and SIRT1 [107–109]. A recent study on triple transgenic AD (3xTg-AD) mice indicated that the deficiency of miR-132 can affect its target genes, such as SIRT1, leading to abnormal Aβ deposition and downstream signaling events misregulation [108]. On the contrary, the expression of miR-132 can be prompted by the activation of CREB, which regulates the downstream signaling pathway of CREB involving synaptic function in AD [110]. Together, there may be a tight relationship between CREB and SIRT1 in the light of miR-132-regulated molecular network.

Taken together, CREB and SIRT1 play an essential role in the regulation of wide range neurophysiological processes such as synaptic plasticity, energy metabolism, and memory formation in the nervous system. Indeed, as previously mentioned, a class of functional interplay demonstrated that SIRT1 modulates transcriptional ability of CREB; in turn, CREB modulates the transcription of SIRT1. At least to some extent, CREB and SIRT1 are reciprocally dependent, and work together in various signaling pathways. Although molecular details on the interaction between CREB and SIRT1 require further investigation, there is compelling evidence for an implication of the unique molecular network, CREB-SIRT1 axis in the onset, and progression of AD.

SIRT1-CREB Axis-Mediated Protective Effect of Procyanidins against AD

Previous studies warrant consideration of procyanidins as a promising strategy for the treatment of AD. Several works have been published showing that procyanidins can attenuate related pathophysiologic states such as oxidative stress, inflammation, neuron apoptosis, and even the aggregation of Aβ peptide and tau proteins, but less is known about the molecular mechanism by which procyanidins affects these biological processes. Moreover, it is important to note that several procyanidins metabolites can reach and accumulate in the brain and should be concerned equally during exploring effective and safe preventive methods for AD. For example, 3'-O-Me-EC-Gluc (3'-O-methyl-epicatchin-5-O-glucuronide), a bioactive procyanidins metabolite, can be identified in the AD mice brain and regulate signal transduction pathways [18]. Such results of various dietary intervention experiments in human, rodents, and mammal models are pertinent with respect to neuroprotective effects due to the strong relationship between procyanidins and cognitive function (Table 1). The modification of SIRT1 and CREB are suggested to play a pivotal role in AD and procyanidins can exert widely biological effects in SIRT1/CREB-dependent manner, thus these results provide impetus to discuss the underlying mechanisms of action responsible for the beneficial effects against AD-related pathology.

Regulation of CREB by Procyanidins

Nowadays, the role of procyanidins and their metabolites in the AD has become the region of interest when identifying the protective mechanisms. Procyanidins, which are flavonoids with an oligomeric structure, their metabolites can cross the blood-brain barrier and be uptaken and detected in brain. In one significant study for example, 3'-O-Me-EC-Gluc, one of the procyanidins metabolites detected in brain, modulates CREB activation through mediation of the ERK 42/44 pathway, which means it has some beneficial impact on the synaptic function and LTP [18]. (−)-Epicatechin, a component of procyanidins, and one of its metabolites (3′-O-methyl-(−)-epicatechin) have been indicated to regulate ERK phosphorylation and increase CREB-mediated gene expression, and thus exert potential effects on brain functions [111]. Our previous study has also demonstrated that procyanidns reverses the declines of ERK 42/44 and CaMKIV phosphorylation levels and consequently leads to enhancement of CREB-dependent transcription in aged impaired animals [112]. Based on these findings, it is evident that procyanidins might act as neuroprotective agent against cognitive and memory impairment via phosphorylation of CREB, then resulting in enhanced transcription of various genes which are strongly implicated in learning and memory.

Table 1 Main studies examining the association between procyanidins and AD-related pathology

Products	Subject description	Intervention	Results	References
Apple procyanidins	PC-12 cells	24 h	To suppress Aβ aggregation, dissociate aggregated Aβ42, and prevent Aβ42-induced cytotoxicity	[15]
Lotus seedpod procyanidins	Male ICR mice exposed to ELF-EMF	15 days	To scavenge oxygen-free radicals, improve learning and memory deficits, and reverse ELF-EMF-induced reduction of CREB phosphorylation	[9]
Grape seed polyphenolic extract	Hemizygous male transgenic JNPL3 mice	6 months	To attenuate the neuromuscular deficiency and reduce tau neuropathpology by inhibiting tau hyperphorsphorylation and conformational modification	[16]
Procyanidins extracted from the lotus seedpod	4 and 18 months Sprague–Dawley rats	8 weeks	To ameliorate memory impairment, reverse the age-related anti-oxidant deficit, reduce lipid peroxidation, and restore acetyl-choline (ACh) contents and acetylcholinesterase (AChE) ac-tivities	[29, 30]
Procyanidins extracted from the lotus seedpod	4 and 18 months Sprague–Dawley rats	7 weeks	To improve cognitive function, decrease inducible nitric oxide synthase (iNOS) activities, and improve neuronal nitric oxide synthase (nNOS) phosphorylation status	[31]
Grape-derived polyphenolics	6 and 10 months Tg2576 AD model mice	5 months	To attenuate cognitive deterioration and inhibit amyloid-β protein aggregation	[33]
Lotus seedpod proanthocyanidins	Aging mice induced by D-galactose	6 weeks	To attenuate cognitive damage, reduce the Aβ1–42 level, and improve nitrosative-oxidative stress	[34]
Grape seed proanthocyanidin	4 and 18 months Wistar rats	14 weeks	To promote spatial learning and working memory, to balance the redox state of the brain, modulate the activation of CREB, and increase BDNF expression	[35]
Polyphenol-rich extract from grape and blueberry	Aged beagle dogs	75 days	To improve cognitive function, ameliorate memory impairments, and elevate the active of antioxidant enzymes	[36]
Grape seed-derived polyphenols	PHF material isolated from autopsy AD brains		To alter the sedimentation properties and facilitate ultrastructural disintegration of filaments	[17]
Concord grape juice	12 subjects with MCI (8 males; mean age 78.2 y)	12 weeks	Significantly effect for word recall item acquisition (CVLT), non-significant trends towards improved delayed recall and spatial memory	[24]
Concord grape juice	25 health mothers; 40–50 y	12 weeks	Significant improvements in immediate spatial memory and driving performance	[25]
Purple grape juice	20 health young adults (7 males; mean age 21.05 y)	Baseline and following a 20-min absorption period	Significantly improved reaction time and increased calm ratings, no significant effects on memory measures	[26]
Freeze-dried grape powder	10 subjects with MCI (5 males; mean age 72.2 y)	6 months	No significant differences in scores on the neuropsychological battery, stable brain metabolism	[27]

ELF-EMF, extremely low frequency electromagnetic field; *MCI*, mild cognitive impairment; *y*, year old; *CVLT*, the California Verbal Learning Test

Regulation of SIRT1 by Procyanidins

Importantly, as well as effects on the activation of CREB, procyanidins can also regulate SIRT1 participating in diverse physiological processes. Meanwhile, mounting evidence supports that the activation of SIRT1 by procyanidins is a promising therapeutic approach to alleviate oxidative and inflammatory stress, apoptosis [113, 114], hypertension [115], obesity [116], and nonalcoholic fatty liver disease [117]. In work by Ibars and coworkers, procyanindins could reduce hyperphagia and improve leptin resistance partially via preventing inflammation and increasing SIRT1 expression [118]. Also, procyanidins remarkably inhibited apotosis and ameliorated mitochondrial dysfunction via restoring the activation of the AMPK-SIRT1-PGC1α axis in rat mesangial cells or podocytes cells [113, 114]. It has been also demonstrated that flavanols, which are a subunits of procyanidins, present anti-hypertensive properties by decreasing blood pressure in a SIRT1-dependent manner [119]. A relevant review has identified that dietary strawberry improves metabolism and mitochondrial function at least in part by upregulating SIRT1-mediating signaling pathway [120]. However, to the best of our knowledge, whether the neuroprotective effects of procyanidins on AD pathology are related with the regulation of SIRT1 may not been well illustrated. Of note, flavonoids such as apigenin, catechin, and eipcatechin were considered to inhibit NAD^+ consuming enzymes such as cyclic ADP-ribose (cADP) synthases (CD38), and poly (ADP-ribose) polymerases (PARPs) [121, 122], reduce the NAD^+ consumption and upregulate the activity or expression of NAD^+-dependent

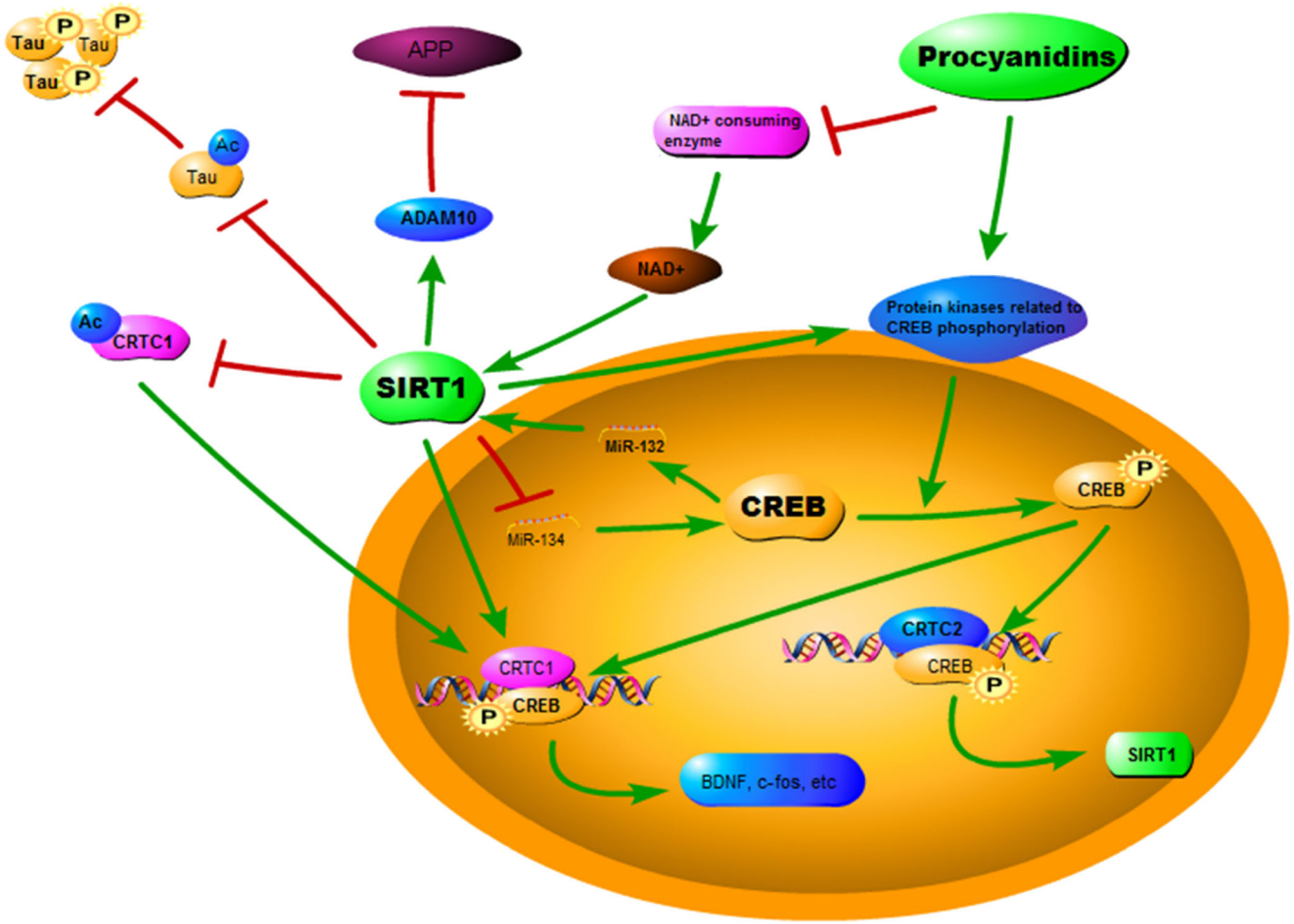

Fig. 1 The possible mechanism of procyanidins improving cognition by interfering with CREB-SIRT1 axis. Treated to procyanidins might inhibit NAD+ consuming enzyme to reduce the NAD^+ consumption and enhance SIRT1 activity. The enhancement of SIRT1 can activate α-secretase ADAM10 to facilitate APP cleavage, leading to Aβ levels decline. Meantime, SIRT1 might inhibit tau acetylation to reduce tauopathies. Moreover, SIRT1 can deacetylate and activate CRTC1 by promoting its nuclear translocation and interaction with CREB, regulating BDNF gene transcription. In addition, SIRT1 can prevent miR-134-induced downregulation, thereby regulating the expression of CREB and BDNF. On the contrary, the expression of miR-132 can be prompted by the activation of CREB, then affecting its target genes, such as SIRT1. Procyanidins can increase CREB phosphorylation via elevating the phosphorylation states of PKA, CaMKIV, or MAPK, and then pCREB and CRTC2 might finally affect the transcription of SIRT1 gene. CREB phosphorylation also participates in the initiation of BDNF gene expression. CREB, cAMP response element-binding protein; SIRT1, NAD^+-dependent histone deacetylase; ADAM10, a disintegrin and metalloproteinase 10; PARP-1, poly (ADP-ribose) polymerase; CD38, and cyclic ADP-ribose (cADP) synthases; CRTCs/TORCs, cAMP response element-binding protein (CREB)-regulated transcription coactivator; PKA, cAMP-dependent protein kinase A; CaMKIV, Ca^{2+}/calmodulin (CaM)-dependent protein kinases

sirtuins including particularly SIRT1 and SIRT3 which are related to aging and neurodegeneration by deacetylation [123], ultimately ameliorating the hallmarks of AD [124, 125]. These results suggest that procyanidins may be able to impact several enzymes and stimulate SIRT1-mediated signaling pathway, then enhancing neural plasticity, improving cognitive function and attenuating neurotoxicity caused by Aβ and tau during AD.

Taken together, evidence from animal and human studies indicated that procianidins regulate SIRT1 to exhibit multiple biological effects in various aspects. Nonetheless, it is not clarified whether procyanidins can evolve complex systemic roles in AD prevention and treatment, and whether the exact mechanism about this effect may rely on SIRT1 mediation. Based on the interplay of CREB-SIRT1 axis, it is therefore conceivable that the regulation of procyanidins by the means of CREB-SIRT1 could promote the cognitive function and is thus conducive for AD pathogenesis (Fig. 1).

Conclusion

The role of SIRT1 in longevity, metabolic homeostasis, gluconeogenesis, mitochondrial biogenesis, inflammation, and amyloidosis provides an opportunity to explore the molecular mechanism in the pathogenesis of AD. As well, CREB has been verified to be a molecular switch from STM to LTM. Procyanidins are nutritional bioactive compounds that have

neuroprotective property that exert moderate SIRT1 and/or CREB enhancement and lead to the recovery of downstream genes expression, which are related with memory and cognition. Based on the interplay of CREB-SIRT1 axis, it is therefore conceivable that the regulation of procyanidins by the means of CREB-SIRT1 could promote the cognitive function and is thus conducive for AD pathogenesis. Additionally, better understanding relevant aspects such as the maintenance of bioavailability after dietary supplementation, the impact on the blood-brain barrier, especially the interaction of SIRT1 and CREB, will propel procyanidins to be efficacious candidates as nutraceuticals or medicines in the prevention and treatment of AD. Therefore, it is expected that the number of further investigations on the protective effect of procyanidins on AD will be increased, and the potential mechanisms involved CREB-SIRT1 axis also need to be confirmed and complemented.

Compliance with Ethical Standards

Conflict of Interest The authors declare that there is no conflict of interest.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Kerr JS, Adriaanse BA, Greig NH, Mattson MP, Cader MZ, Bohr VA, Fang EF (2017) Mitophagy and Alzheimer's disease: cellular and molecular mechanisms. Trends Neurosci 40(3):151–166. https://doi.org/10.1016/j.tins.2017.01.002
2. Wilson RS, Segawa E, Boyle PA, Anagnos SE, Hizel LP, Bennett DA (2012) The natural history of cognitive decline in Alzheimer's disease. Psychol Aging 27(4):1008–1017. https://doi.org/10.1037/a0029857
3. 2018 Alzheimer's disease facts and figures (2018) Alzheimers Dement 14(3):367–429. https://doi.org/10.1016/j.jalz.2018.02.001
4. Honig LS, Vellas B, Woodward M, Boada M, Bullock R, Borrie M, Hager K, Andreasen N et al (2018) Trial of Solanezumab for mild dementia due to Alzheimer's disease. N Engl J Med 378(4):321–330. https://doi.org/10.1056/NEJMoa1705971
5. Relkin NR, Thomas RG, Rissman RA, Brewer JB, Rafii MS, CHv D, Jack CR, Sano M et al (2017) A phase 3 trial of IV immunoglobulin for Alzheimer disease. Neurology 88(18):1768–1775
6. Ostrowitzki S, Lasser RA, Dorflinger E, Scheltens P, Barkhof F, Nikolcheva T, Ashford E, Retout S et al (2017) A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. Alzheimers Res Ther 9(1):95. https://doi.org/10.1186/s13195-017-0318-y
7. Russo P, Frustaci A, Del Bufalo A, Fini M, Cesario A (2013) Multitarget drugs of plants origin acting on Alzheimer's disease. Curr Med Chem 20(13):1686–1693. https://doi.org/10.2174/0929867311320130008
8. Xu Z, Du P, Meiser P, Jacob C (2012) Proanthocyanidins_ oligomeric structures with unique biochemical properties and great therapeutic promise. Nat Prod Commun 7(3):381–388
9. Duan Y, Wang Z, Zhang H, He Y, Fan R, Cheng Y, Sunb G, Sun X (2014) Extremely low frequency electromagnetic field exposure causes cognitive impairment associated with alteration of the glutamate level, MAPK pathway activation and decreased CREB phosphorylation in mice hippocampus: reversal by procyanidins extracted from the lotus seedpod. Food Funct 5:2289–2297. https://doi.org/10.1039/C4FO00250D
10. Kent K, Charlton KE, Netzel M, Fanning K (2017) Food-based anthocyanin intake and cognitive outcomes in human intervention trials: a systematic review. J Hum Nutr Diet 30(3):260–274. https://doi.org/10.1111/jhn.12431
11. Devore EE, Kang JH, Breteler MM, Grodstein F (2012) Dietary intakes of berries and flavonoids in relation to cognitive decline. Ann Neurol 72(1):135–143. https://doi.org/10.1002/ana.23594
12. Ou K, Gu L (2014) Absorption and metabolism of proanthocyanidins. J Funct Foods 7:43–53. https://doi.org/10.1016/j.jff.2013.08.004
13. Wang Y, Chung SJ, Song WO, Chun OK (2011) Estimation of daily proanthocyanidin intake and major food sources in the U.S. diet. J Nutr 141(3):447–452. https://doi.org/10.3945/jn.110.133900
14. Nehlig A (2013) The neuroprotective effects of cocoa flavanol and its influence on cognitive performance. Br J Clin Pharmacol 75(3):716–727. https://doi.org/10.1111/j.1365-2125.2012.04378.x
15. Toda T, Sunagawa T, Kanda T, Tagashira M, Shirasawa T, Shimizu T (2011) Apple procyanidins suppress amyloid beta-protein aggregation. Biochem Res Int 2011:784698. https://doi.org/10.1155/2011/784698
16. Santa-Maria I, Diaz-Ruiz C, Ksiezak-Reding H, Chen A, Ho L, Wang J, Pasinetti GM (2012) GSPE interferes with tau aggregation in vivo: implication for treating tauopathy. Neurobiol Aging 33(9):2072–2081. https://doi.org/10.1016/j.neurobiolaging.2011.09.027
17. Ksiezak-Reding H, Ho L, Santa-Maria I, Diaz-Ruiz C, Wang J, Pasinetti GM (2012) Ultrastructural alterations of Alzheimer's disease paired helical filaments by grape seed-derived polyphenols. Neurobiol Aging 33(7):1427–1439. https://doi.org/10.1016/j.neurobiolaging.2010.11.006
18. Wang J, Ferruzzi MG, Ho L, Blount J, Janle EM, Gong B, Pan Y, Nagana Gowda GA et al (2012) Brain-targeted proanthocyanidin metabolites for Alzheimer's disease treatment. J Neurosci 32(15):5144–5150. https://doi.org/10.1523/JNEUROSCI.6437-11.2012
19. Singh SK (2017) Oxidative stress and Alzheimer's disease. J Clin Exp Neuroimmunol 2(2):100E102
20. Yang L, Xian D, Xiong X, Lai R, Song J, Zhong J (2018) Proanthocyanidins against oxidative stress: from molecular mechanisms to clinical applications. Biomed Res Int 2018:8584136–8584111. https://doi.org/10.1155/2018/8584136
21. Dong C (2015) Protective effect of proanthocyanidins in cadmium induced neurotoxicity in mice. Drug Res (Stuttg) 65(10):555–560. https://doi.org/10.1055/s-0034-1395544
22. Nazima B, Manoharan V, Miltonprabu S (2015) Grape seed proanthocyanidins ameliorates cadmium-induced renal injury and oxidative stress in experimental rats through the up-regulation of nuclear related factor 2 and antioxidant responsive elements. Biochem Cell Biol 93(3):210–226. https://doi.org/10.1139/bcb-2014-0114
23. Mantena SK, Katiyar SK (2006) Grape seed proanthocyanidins inhibit UV-radiation-induced oxidative stress and activation of MAPK and NF-kappaB signaling in human epidermal keratinocytes. Free Radic Biol Med 40(9):1603–1614. https://doi.org/10.1016/j.freeradbiomed.2005.12.032
24. Krikorian R, Nash TA, Shidler MD, Shukitt-Hale B, Joseph JA (2010) Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment. Br J

Nutr 103(5):730–734. https://doi.org/10.1017/S0007114509992364
25. Lamport DJ, Lawton CL, Merat N, Jamson H, Myrissa K, Hofman D, Chadwick HK, Quadt F et al (2016) Concord grape juice, cognitive function, and driving performance: a 12-wk, placebo-controlled, randomized crossover trial in mothers of preteen children. Am J Clin Nutr 103(3):775–783. https://doi.org/10.3945/ajcn.115.114553
26. Haskell-Ramsay CF, Stuart RC, Okello EJ, Watson AW (2017) Cognitive and mood improvements following acute supplementation with purple grape juice in healthy young adults. Eur J Nutr 56(8):2621–2631. https://doi.org/10.1007/s00394-017-1454-7
27. Lee J, Torosyan N, Silverman DH (2017) Examining the impact of grape consumption on brain metabolism and cognitive function in patients with mild decline in cognition: A double-blinded placebo controlled pilot study. Exp Gerontol 87(Pt A):121–128. https://doi.org/10.1016/j.exger.2016.10.004
28. Wang J, Santa-Maria I, Ho L, Ksiezak-Reding H, Ono K, Teplow DB, GM P (2010) Grape derived polyphenols attenuate tau neuropathology in a mouse model of Alzheimer's disease. J Alzheimers Dis 22(2):653
29. Xu J, Rong S, Xie B, Sun Z, Zhang L, Wu H, Yao P, Hao L et al (2010) Procyanidins extracted from the lotus seedpod ameliorate age-related antioxidant deficit in aged rats. J Gerontol A Biol Sci Med Sci 65(3):236–241. https://doi.org/10.1093/gerona/glp211
30. Xu J, Rong S, Xie B, Sun Z, Zhang L, Wu H, Yao P, Zhang X et al (2009) Rejuvenation of antioxidant and cholinergic systems contributes to the effect of procyanidins extracted from the lotus seedpod ameliorating memory impairment in cognitively impaired aged rats. Eur Neuropsychopharmacol 19(12):851–860. https://doi.org/10.1016/j.euroneuro.2009.07.006
31. Xu J, Rong S, Xie B, Sun Z, Deng Q, Bao W, Wang D, Yao P et al (2011) Changes in the nitric oxide system contribute to effect of procyanidins extracted from the lotus seedpod ameliorating memory impairment in cognitively impaired aged rats. Rejuvenation Res 14(1):33–43. https://doi.org/10.1089/rej.2010.1076
32. Devi SA, Jolitha AB, Ishii N (2006) Grape Seed Proanthocyanidin Extract (GSPE) and antioxidant defense in the brain of adult rats. Med Sci Monit 12(4):BR124–BR129
33. Wang J, Ho L, Zhao W, Ono K, Rosensweig C, Chen L, Humala N, Teplow DB et al (2008) Grape-derived polyphenolics prevent Abeta oligomerization and attenuate cognitive deterioration in a mouse model of Alzheimer's disease. J Neurosci 28(25):6388–6392. https://doi.org/10.1523/JNEUROSCI.0364-08.2008
34. Gong YS, Guo J, Hu K, Gao YQ, Xie BJ, Sun ZD, Yang EN, Hou FL (2016) Ameliorative effect of lotus seedpod proanthocyanidins on cognitive impairment and brain aging induced by D-galactose. Exp Gerontol 74:21–28. https://doi.org/10.1016/j.exger.2015.11.020
35. Abhijit S, Subramanyam MVV, Devi SA (2017) Grape seed proanthocyanidin and swimming exercise protects against cognitive decline: a study on M1 acetylcholine receptors in aging male rat brain. Neurochem Res 42(12):3573–3586. https://doi.org/10.1007/s11064-017-2406-6
36. Fragua V, Lepoudere A, Leray V, Baron C, Araujo JA, Nguyen P, Milgram NW (2017) Effects of dietary supplementation with a mixed blueberry and grape extract on working memory in aged beagle dogs. J Nutr Sci 6:e35. https://doi.org/10.1017/jns.2017.33
37. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E (2011) Alzheimer's disease. Lancet 377(9770):1019–1031. https://doi.org/10.1016/s0140-6736(10)61349-9
38. Forner S, Baglietto-Vargas D, Martini AC, Trujillo-Estrada L, LaFerla FM (2017) Synaptic impairment in Alzheimer's disease: a dysregulated symphony. Trends Neurosci 40(6):347–357. https://doi.org/10.1016/j.tins.2017.04.002
39. Fu H, Rodriguez GA, Herman M, Emrani S, Nahmani E, Barrett G, Figueroa HY, Goldberg E et al (2017) Tau pathology induces excitatory neuron loss, grid cell dysfunction, and spatial memory deficits reminiscent of early Alzheimer's disease. Neuron 93(3):533–541 e535. https://doi.org/10.1016/j.neuron.2016.12.023
40. Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, Castellani RJ, Crain BJ et al (2012) Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J Neuropathol Exp Neurol 71(5):362–381. https://doi.org/10.1097/NEN.0b013e31825018f7
41. Tramutola A, Lanzillotta C, Perluigi M, Butterfield DA (2017) Oxidative stress, protein modification and Alzheimer disease. Brain Res Bull 133:88–96. https://doi.org/10.1016/j.brainresbull.2016.06.005
42. Laurent C, Buée L, Blum D (2018) Tau and neuroinflammation: what impact for Alzheimer's disease and Tauopathies? Biom J 41:21–33. https://doi.org/10.1016/j.bj.2018.01.003
43. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT (2011) Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 1(1):a006189. https://doi.org/10.1101/cshperspect.a006189
44. Wood MA, Kaplan MP, Park A, Blanchard EJ, Oliveira AMM, Lombardi TL, Abel T (2005) Transgenic mice expressing a truncated form of CREB-binding protein (CBP) exhibit deficits in hippocampal synaptic plasticity and memory storage. Learn Mem 12(2):111–119
45. Alarcon JM, Malleret G, Touzani K, Vronskaya S, Ishii S, Kandel ER, Barco A (2004) Chromatin acetylation, memory, and LTP are impaired in CBP+/- mice: a model for the cognitive deficit in Rubinstein-Taybi syndrome and its amelioration. Neuron 42(6):947–959. https://doi.org/10.1016/j.neuron.2004.05.021
46. Kida S, Josselyn SA, Pena de Ortiz S, Kogan JH, Chevere I, Masushige S, Silva AJ (2002) CREB required for the stability of new and reactivated fear memories. Nat Neurosci 5(4):348–355. https://doi.org/10.1038/nn819
47. Clark JK, Furgerson M, Crystal JD, Fechheimer M, Furukawa R, Wagner JJ (2015) Alterations in synaptic plasticity coincide with deficits in spatial working memory in presymptomatic 3xTg-AD mice. Neurobiol Learn Mem 125:152–162. https://doi.org/10.1016/j.nlm.2015.09.003
48. Tan L, Yang H, Pang W, Li H, Liu W, Sun S, Song N, Zhang W et al (2017) Investigation on the role of BDNF in the benefits of blueberry extracts for the improvement of learning and memory in Alzheimer's disease mouse model. J Alzheimers Dis 56(2):629–640. https://doi.org/10.3233/JAD-151108
49. Kandel ER (2012) The molecular biology of memory: cAMP, PKA, CRE, CREB-1, CREB-2, and CPEB. Mol Brain 5:14. https://doi.org/10.1186/1756-6606-5-14
50. Ortega-Martinez S (2015) A new perspective on the role of the CREB family of transcription factors in memory consolidation via adult hippocampal neurogenesis. Front Mol Neurosci 8:46. https://doi.org/10.3389/fnmol.2015.00046
51. Kida S, Serita T (2014) Functional roles of CREB as a positive regulator in the formation and enhancement of memory. Brain Res Bull 105:17–24. https://doi.org/10.1016/j.brainresbull.2014.04.011
52. Yu XW, Curlik DM, Oh MM, Yin JC, Disterhoft JF (2017) CREB overexpression in dorsal CA1 ameliorates long-term memory deficits in aged rats. Elife 6. https://doi.org/10.7554/eLife.19358
53. Kelly MP (2018) Cyclic nucleotide signaling changes associated with normal aging and age-related diseases of the brain. Cell Signal 42:281–291. https://doi.org/10.1016/j.cellsig.2017.11.004
54. Ma H, Groth RD, Cohen SM, Emery JF, Li B, Hoedt E, Zhang G, Neubert TA et al (2014) gammaCaMKII shuttles Ca(2)(+)/CaM to the nucleus to trigger CREB phosphorylation and gene

expression. Cell 159(2):281–294. https://doi.org/10.1016/j.cell.2014.09.019
55. Yin Y, Gao D, Wang Y, Wang ZH, Wang X, Ye J, Wu D, Fang L et al (2016) Tau accumulation induces synaptic impairment and memory deficit by calcineurin-mediated inactivation of nuclear CaMKIV/CREB signaling. Proc Natl Acad Sci U S A 113(26): E3773–E3781. https://doi.org/10.1073/pnas.1604519113
56. Vitolo OV, Sant'Angelo A, Costanzo V, Battaglia F, Arancio O, Shelanski M (2002) Amyloid -peptide inhibition of the PKA/CREB pathway and long-term potentiation: Reversibility by drugs that enhance cAMP signaling. Proc Natl Acad Sci 99(20):13217–13221. https://doi.org/10.1073/pnas.172504199
57. Taglialatela G, Zhang W, Reese LC (2010) Beta-amyloid-dependent alteration of calcineurin and pCREB in the Alzheimer and MCI brain. Alzheimers Dement 6(4):S406–S407. https://doi.org/10.1016/j.jalz.2010.05.1369
58. Gabr AA, Lee HJ, Onphachanh X, Jung YH, Kim JS, Chae CW, Han HJ (2017) Ethanol-induced PGE2 up-regulates Abeta production through PKA/CREB signaling pathway. Biochim Biophys Acta 1863(11):2942–2953. https://doi.org/10.1016/j.bbadis.2017.06.020
59. Espana J, Valero J, Minano-Molina AJ, Masgrau R, Martin E, Guardia-Laguarta C, Lleo A, Gimenez-Llort L et al (2010) Beta-amyloid disrupts activity-dependent gene transcription required for memory through the CREB coactivator CRTC1. J Neurosci 30(28):9402–9410. https://doi.org/10.1523/JNEUROSCI.2154-10.2010
60. Saura CA, Cardinaux JR (2017) Emerging roles of CREB-regulated transcription coactivators in brain physiology and pathology. Trends Neurosci 40(12):720–733. https://doi.org/10.1016/j.tins.2017.10.002
61. Parra-Damas A, Chen M, Enriquez-Barreto L, Ortega L, Acosta S, Perna JC, Fullana MN, Aguilera J et al (2017) CRTC1 function during memory encoding is disrupted in neurodegeneration. Biol Psychiatry 81(2):111–123. https://doi.org/10.1016/j.biopsych.2016.06.025
62. Watts AG, Sanchez-Watts G, Liu Y, Aguilera G (2011) The distribution of messenger RNAs encoding the three isoforms of the transducer of regulated cAMP responsive element binding protein activity in the rat forebrain. J Neuroendocrinol 23(8):754–766. https://doi.org/10.1111/j.1365-2826.2011.02178.x
63. Parra-Damas A, Valero J, Chen M, Espana J, Martin E, Ferrer I, Rodriguez-Alvarez J, Saura CA (2014) Crtc1 activates a transcriptional program deregulated at early Alzheimer's disease-related stages. J Neurosci 34(17):5776–5787. https://doi.org/10.1523/JNEUROSCI.5288-13.2014
64. Asahara H, Santoso B, Guzman E, Du K, Cole PA, Davidson I, Montminy M (2001) Chromatin-dependent cooperativity between constitutive and inducible activation domains in CREB. Mol Cell Biol 21(23):7892–7900. https://doi.org/10.1128/MCB.21.23.7892-7900.2001
65. Kim TK, Kim TH, Maniatis T (1998) Efficient recruitment of TFIIB and CBP-RNA polymerase II holoenzyme by an interferon-β Enhanceosome in vitro. Proc Natl Acad Sci U S A 95(21):12191–12196
66. V P KTM (2013) Role of CREB signaling in aging brain. Arch Ital Biol 151(1):33–42
67. Haus-Seuffert P, Meisterernst M (2000) Mechanisms of transcriptional activation of cAMP-responsive element-binding protein CREB. Mol Cell Biochem 212(1–2):5–9
68. Watroba M, Szukiewicz D (2016) The role of sirtuins in aging and age-related diseases. Adv Med Sci 61(1):52–62. https://doi.org/10.1016/j.advms.2015.09.003
69. Heo J, Lim J, Lee S, Jeong J, Kang H, Kim Y, Kang JW, Yu HY et al (2017) Sirt1 regulates DNA methylation and differentiation potential of embryonic stem cells by antagonizing Dnmt3l. Cell Rep 18(8):1930–1945. https://doi.org/10.1016/j.celrep.2017.01.074
70. Ma CY, Yao MJ, Zhai QW, Jiao JW, Yuan XB, Poo MM (2014) SIRT1 suppresses self-renewal of adult hippocampal neural stem cells. Development 141(24):4697–4709. https://doi.org/10.1242/dev.117937
71. Michan S, Li Y, Chou MM, Parrella E, Ge H, Long JM, Allard JS, Lewis K et al (2010) SIRT1 is essential for normal cognitive function and synaptic plasticity. J Neurosci 30(29):9695–9707. https://doi.org/10.1523/JNEUROSCI.0027-10.2010
72. Donmez G (2012) The effects of SIRT1 on Alzheimer's disease models. Int J Alzheimers Dis 2012:509529. https://doi.org/10.1155/2012/509529
73. Zhang L, Tu R, Wang Y, Hu Y, Li X, Cheng X, Yin Y, Li W et al (2017) Early-life exposure to lead induces cognitive impairment in elder mice targeting SIRT1 phosphorylation and oxidative alterations. Front Physiol 8:446. https://doi.org/10.3389/fphys.2017.00446
74. Gao J, Wang W-Y, Mao Y-W, Gräff J, Guan J-S, Pan L, Mak G, Kim D et al (2010) A novel pathway regulates memory and plas. Nature 7310(466):1105–1109
75. Corpas R, Revilla S, Ursulet S, Castro-Freire M, Kaliman P, Petegnief V, Gimenez-Llort L, Sarkis C et al (2017) SIRT1 overexpression in mouse hippocampus induces cognitive enhancement through proteostatic and neurotrophic mechanisms. Mol Neurobiol 54(7):5604–5619. https://doi.org/10.1007/s12035-016-0087-9
76. Julien C, Tremblay C, mond VE, Lebbadi M, Norman Salem J, Bennett DA, Calon F'd'r (2009) Sirtuin 1 reduction parallels the accumulation of tau in Alzheimer disease. J Neuropathol Exp Neurol 68(1):48–58
77. Kumar R, Chaterjee P, Sharma PK, Singh AK, Gupta A, Gill K, Tripathi M, Dey AB et al (2013) Sirtuin1: a promising serum protein marker for early detection of Alzheimer's disease. PLoS One 8(4):e61560. https://doi.org/10.1371/journal.pone.0061560
78. Karuppagounder SS, Pinto JT, Xu H, Chen H-L, Beal MF, Gibson GE (2009) Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of Alzheimer's disease. Neurochem Int 54(2):111–118. https://doi.org/10.1016/j.neuint.2008.10.008
79. Donmez G, Wang D, Cohen DE, Guarente L (2010) SIRT1 suppresses β-amyloid production by activating the α-secretase gene ADAM10. Cell 142(3):494–495. https://doi.org/10.1016/j.cell.2010.07.034
80. Endres K, Fahrenholz F (2010) Upregulation of the alpha-secretase ADAM10–risk or reason for hope? FEBS J 7(227): 1585–1596
81. Lee HR, Shin HK, Park SY, Kim HY, Bae SS, Lee WS, Rhim BY, Hong KW et al (2015) Cilostazol upregulates autophagy via SIRT1 activation: reducing amyloid-beta peptide and APP-CTFbeta levels in neuronal cells. PLoS One 10(8):e0134486. https://doi.org/10.1371/journal.pone.0134486
82. HR L, HK S, SY P, HY K, WS L, BY R, KW H, CD K (2014) Cilostazol suppresses β-amyloid production by activating a disintegrin and metalloproteinase 10 via the upregulation of SIRT1-coupled retinoic acid receptor-β. J Neurosci Res 11(92): 1581–1590
83. Wang XF, Liu DX, Liang Y, Xing LL, Zhao WH, Qin XX, Shang DS, Li B et al (2016) Cystatin C shifts APP processing from amyloid-beta production towards non-amyloidgenic pathway in brain endothelial cells. PLoS One 11(8):e0161093. https://doi.org/10.1371/journal.pone.0161093
84. Min SW, Cho SH, Zhou Y, Schroeder S, Haroutunian V, Seeley WW, Huang EJ, Shen Y et al (2010) Acetylation of tau inhibits its degradation and contributes to tauopathy. Neuron 67(6):953–966. https://doi.org/10.1016/j.neuron.2010.08.044

85. Min SW, Chen X, Tracy TE, Li Y, Zhou Y, Wang C, Shirakawa K, Minami SS et al (2015) Critical role of acetylation in tau-mediated neurodegeneration and cognitive deficits. Nat Med 21(10):1154–1162. https://doi.org/10.1038/nm.3951
86. Kumar R, Nigam L, Singh AP, Singh K, Subbarao N, Dey S (2017) Design, synthesis of allosteric peptide activator for human SIRT1 and its biological evaluation in cellular model of Alzheimer's disease. Eur J Med Chem 127:909–916. https://doi.org/10.1016/j.ejmech.2016.11.001
87. Palomera-Ávalos V, Griñán-Ferré C, Izquierdo V, Camins A, Sanfeliu C, Pallàs M (2017) Metabolic stress induces cognitive disturbances and inflammation in aged mice_ protective role of resveratrol. Rejuvenation Res 20:202–217. https://doi.org/10.1089/rej.2016.1885
88. Sasaki T, Kikuchi O, Shimpuku M, Susanti VY, Yokota-Hashimoto H, Taguchi R, Shibusawa N, Sato T et al (2014) Hypothalamic SIRT1 prevents age-associated weight gain by improving leptin sensitivity in mice. Diabetologia 57(4):819–831. https://doi.org/10.1007/s00125-013-3140-5
89. Chang HC, Guarente L (2014) SIRT1 and other sirtuins in metabolism. Trends Endocrinol Metab 25(3):138–145. https://doi.org/10.1016/j.tem.2013.12.001
90. Wong SY, Tang BL (2016) SIRT1 as a therapeutic target for Alzheimer's disease. Rev Neurosci 27(8):813–825. https://doi.org/10.1515/revneuro-2016-0023
91. Fujitsuka N, Asakawa A, Morinaga A, Amitani MS, Amitani H, Katsuura G, Sawada Y, Sudo Y et al (2016) Increased ghrelin signaling prolongs survival in mouse models of human aging through activation of sirtuin1. Mol Psychiatry 21(11):1613–1623. https://doi.org/10.1038/mp.2015.220
92. Rajan KE, Thangaleela S, Balasundaram C (2015) Spatial learning associated with stimulus response in goldfish Carassius auratus: relationship to activation of CREB signalling. Fish Physiol Biochem 41(3):685–694. https://doi.org/10.1007/s10695-015-0038-9
93. Jeong H, Cohen DE, Cui L, Supinski A, Savas JN, Mazzulli JR, Yates JR, Bordone L et al (2011) Sirt1 mediates neuroprotection from mutant huntingtin by activation of the TORC1 and CREB transcriptional pathway. Nat Med 18(1):159–165. https://doi.org/10.1038/nm.2559
94. Yan D, Jin C, Cao Y, Wang L, Lu X, Yang J, Wu S, Cai Y (2017) Effects of aluminium on long-term memory in rats and on SIRT1 mediating the transcription of CREB-dependent gene in hippocampus. Basic Clin Pharmacol Toxicol 121(4):342–352. https://doi.org/10.1111/bcpt.12798
95. Chen T, Yang YJ, Li YK, Liu J, Wu PF, Wang F, Chen JG, Long LH (2016) Chronic administration tetrahydroxystilbene glucoside promotes hippocampal memory and synaptic plasticity and activates ERKs, CaMKII and SIRT1/miR-134 in vivo. J Ethnopharmacol 190:74–82. https://doi.org/10.1016/j.jep.2016.06.012
96. Fusco S, Ripoli C, Podda MV, Ranieri SC, Leone L, Toietta G, McBurney MW, Schutz G et al (2012) A role for neuronal cAMP responsive-element binding (CREB)-1 in brain responses to calorie restriction. Proc Natl Acad Sci U S A 109(2):621–626. https://doi.org/10.1073/pnas.1109237109
97. Li H, Wang R (2017) Blocking SIRT1 inhibits cell proliferation and promotes aging through the PI3K/AKT pathway. Life Sci 190:84–90. https://doi.org/10.1016/j.lfs.2017.09.037
98. Fusco S, Leone L, Barbati SA, Samengo D, Piacentini R, Maulucci G, Toietta G, Spinelli M et al (2016) A CREB-Sirt1-Hes1 circuitry mediates neural stem cell response to glucose availability. Cell Rep 14(5):1195–1205. https://doi.org/10.1016/j.celrep.2015.12.092
99. Qiang L, Lin HV, Kim-Muller JY, Welch CL, Gu W, Accili D (2011) Proatherogenic abnormalities of lipid metabolism in SirT1 transgenic mice are mediated through Creb deacetylation. Cell Metab 14(6):758–767. https://doi.org/10.1016/j.cmet.2011.10.007
100. Shen Z-l, Wang B, K-w J, C-x Y, Cheng C, Y-c Y, J-z Z, Yang Y et al (2016) Downregulation of miR-199b is associated with distant metastasis in colorectal cancer via activation of SIRT1 and inhibition of CREBKISS1 signaling. Oncotarget 7(23):35092–35105
101. Paz JC, Park S, Phillips N, Matsumura S, Tsai W-W, Kasper L, Brindle PK, Zhang G et al (2014) Combinatorial regulation of a signal-dependent activator by phosphorylation and acetylation. Proc Natl Acad Sci U S A 48(111):17116–17121
102. Monteserin-Garcia J, Al-Massadi O, Seoane LM, Alvarez CV, Shan B, Stalla J, Paez-Pereda M, Casanueva FF et al (2013) Sirt1 inhibits the transcription factor CREB to regulate pituitary growth hormone synthesis. FASEB J 27(4):1561–1571. https://doi.org/10.1096/fj.12-220129
103. Li J, Dou X, Li S, Zhang X, Zeng Y, Song Z (2015) Nicotinamide ameliorates palmitate-induced ER stress in hepatocytes via cAMP/PKA/CREB pathway-dependent Sirt1 upregulation. Biochim Biophys Acta 1853(11 Pt A):2929–2936. https://doi.org/10.1016/j.bbamcr.2015.09.003
104. Shen C, Dou X, Ma Y, Ma W, Li S, Song Z (2017) Nicotinamide protects hepatocytes against palmitate-induced lipotoxicity via SIRT1-dependent autophagy induction. Nutr Res 40:40–47. https://doi.org/10.1016/j.nutres.2017.03.005
105. Chalkiadaki A, Guarente L (2011) Metabolic signals regulate SIRT1 expression. EMBO Rep 12(10):985–986. https://doi.org/10.1038/embor.2011.179
106. Hebert SS, De Strooper B (2009) Alterations of the microRNA network cause neurodegenerative disease. Trends Neurosci 32(4):199–206. https://doi.org/10.1016/j.tins.2008.12.003
107. Nudelman AS, DiRocco DP, Lambert TJ, Garelick MG, Le J, Nathanson NM, Storm DR (2010) Neuronal activity rapidly induces transcription of the CREB-regulated microRNA-132, in vivo. Hippocampus 20(4):492–498. https://doi.org/10.1002/hipo.20646
108. Hernandez-Rapp J, Rainone S, Goupil C, Dorval V, Smith PY, Saint-Pierre M, Vallee M, Planel E et al (2016) microRNA-132/212 deficiency enhances Abeta production and senile plaque deposition in Alzheimer's disease triple transgenic mice. Sci Rep 6:30953. https://doi.org/10.1038/srep30953
109. Salta E, De Strooper B (2017) microRNA-132: a key noncoding RNA operating in the cellular phase of Alzheimer's disease. FASEB J 31(2):424–433. https://doi.org/10.1096/fj.201601308
110. Wayman GA, Davare M, Ando H, Fortin D, Varlamova O, Cheng HY, Marks D, Obrietan K et al (2008) An activity-regulated microRNA controls dendritic plasticity by down-regulating p250GAP. Proc Natl Acad Sci U S A 105(26):9093–9098. https://doi.org/10.1073/pnas.0803072105
111. Schroeter H, Bahia P, Spencer JP, Sheppard O, Rattray M, Cadenas E, Rice-Evans C, Williams RJ (2007) (-)Epicatechin stimulates ERK-dependent cyclic AMP response element activity and up-regulates GluR2 in cortical neurons. J Neurochem 101(6):1596–1606. https://doi.org/10.1111/j.1471-4159.2006.04434.x
112. Xu J, Rong S, Xie B, Sun Z, Deng Q, Wu H, Bao W, Wang D et al (2010) Memory impairment in cognitively impaired aged rats associated with decreased hippocampal CREB phosphorylation: reversal by procyanidins extracted from the lotus seedpod. J Gerontol Ser A Biol Med Sci 65A(9):933–940. https://doi.org/10.1093/gerona/glq094
113. Cai X, Bao L, Ren J, Li Y, Zhang Z (2016) Grape seed procyanidin B2 protects podocytes from high glucose-induced mitochondrial dysfunction and apoptosis via the AMPK-SIRT1-PGC-1alpha axis in vitro. Food Funct 7(2):805–815. https://doi.org/10.1039/c5fo01062d

114. Bao L, Cai X, Zhang Z, Li Y (2014) Grape seed procyanidin B2 ameliorates mitochondrial dysfunction and inhibits apoptosis via the AMP-activated protein kinase–silent mating type information regulation 2 homologue 1–PPARγ co-activator-1α axis in rat mesangial cells under high-dose glucosamine. Br J Nutr 113(01): 35–44. https://doi.org/10.1017/S000711451400347X
115. Cui X, Liu X, Feng H, Zhao S, Gao H (2012) Grape seed proanthocyanidin extracts enhance endothelial nitric oxide synthase expression through 5'-AMP activated protein kinase/ Surtuin 1-Krupple like factor 2 pathway and modulate blood pressure in ouabain induced hypertensive rats. Biol Pharm Bull 35(12):2192–2197
116. Rabadan-Chávez G, Quevedo-Corona L, Garcia AM, Reyes-Maldonado E, Jaramillo-Flores ME (2016) Cocoa powder, cocoa extract and epicatechin attenuate hypercaloric diet-induced obesity through enhanced β-oxidation and energy expenditure in white adipose tissue. J Funct Foods 20:54–67. https://doi.org/10.1016/j.jff.2015.10.016
117. Ren T, Huang C, Cheng M (2014) Dietary blueberry and bifidobacteria attenuate nonalcoholic fatty liver disease in rats by affecting SITR1-mediated signaling pathway. Oxidative Med Cell Longev 2014:469059. https://doi.org/10.1155/2014/469059
118. Ibars M, Ardid-Ruiz A, Suarez M, Muguerza B, Blade C, Aragones G (2017) Proanthocyanidins potentiate hypothalamic leptin/STAT3 signalling and Pomc gene expression in rats with diet-induced obesity. Int J Obes 41(1):129–136. https://doi.org/10.1038/ijo.2016.169
119. Pons Z, Margalef M, Bravo FI, Arola-Arnal A, Muguerza B (2016) Grape seed flavanols decrease blood pressure via Sirt-1 and confer a vasoprotective pattern in rats. J Funct Foods 24: 164–172. https://doi.org/10.1016/j.jff.2016.03.030
120. Giampieri F, Alvarez-Suarez JM, Battino M (2014) Strawberry and human health: effects beyond antioxidant activity. J Agric Food Chem 62(18):3867–3876. https://doi.org/10.1021/jf405455n
121. Geraets L, Moonen HJJ, Brauers K, Wouters EM, Bast A, Hageman GJ (2007) Dietary flavones and flavonoles are inhibitors of poly (ADP-ribose)polymerase-1 in pulmonary epithelial cells. J Nutr 10(137):2190
122. Escande C, Nin V, Price NL, Capellini V, Gomes AP, Barbosa MT, O'Neil L, White TA et al (2013) Flavonoid apigenin is an inhibitor of the NAD+ase CD38. Diabetes 62:1084–1093. https://doi.org/10.2337/db12-1139/-/DC1
123. Verdin E (2015) NAD^+ in aging, metabolism, and neurodegeneration. Science 6265(350):1208–1213
124. Ruan Q, Ruan J, Zhang W, Qian F, Yu Z (2017) Targeting NAD(+) degradation: the therapeutic potential of flavonoids for Alzheimer's disease and cognitive frailty. Pharmacol Res 128: 345–358. https://doi.org/10.1016/j.phrs.2017.08.010
125. Ajami M, Pazoki-Toroudi H, Amani H, Nabavi SF, Braidy N, Vacca RA, Atanasov AG, Mocan A et al (2017) Therapeutic role of sirtuins in neurodegenerative disease and their modulation by polyphenols. Neurosci Biobehav Rev 73:39–47. https://doi.org/10.1016/j.neubiorev.2016.11.022