

Dietary phytochemicals: As a potential natural source for treatment of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a common neurodegenerative disease, which seriously impairs human health and life. At present, scientists have proposed more than a dozen hypotheses about the pathogenesis of AD, including the tau propagation hypothesis. However, the exact ultimate pathogenic factor of AD remains unknown. Based on the current hypotheses, some anti-AD drugs (e.g., donepezil and Ketamine) have been developed and used in clinical treatment, which fall into two main categories, acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists, the former representative drug is donepezil, and the latter representative drug is memantine. Since these drugs have undesirable side effects, it is necessary to find safer alternatives for AD treatment. Interestingly, dietary phytochemicals have the advantages of wide source, safety, and high biological activity, which is the natural route for screening anti-AD drugs. In this study, several representatives' dietary phytochemicals with anti-AD effect, including resveratrol, lycopene, gallic acid, berberine, ginsenoside Rg1, pseudoginsenoside-F11, ginsenoside Rh2, artemisinin, and torularhodin were selected from the published data over the last 10 years and their potential molecular mechanisms and clinical applications reviewed in the treatment of AD.

Citation: Ren Z, Yang H, Zhu C, Fan D, Deng J. 2023. Dietary phytochemicals: As a potential natural source for treatment of Alzheimer's Disease. *Food Innovation and Advances* 2(1):36–43 <https://doi.org/10.48130/FIA-2023-0007>

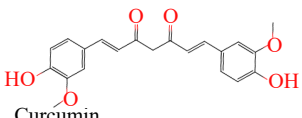
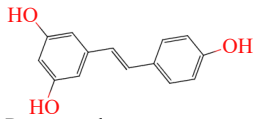
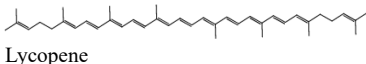
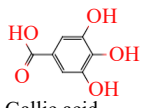
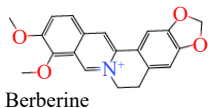
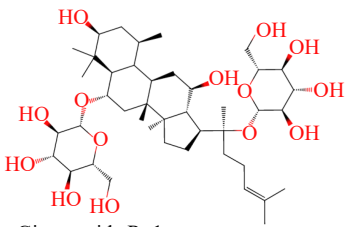
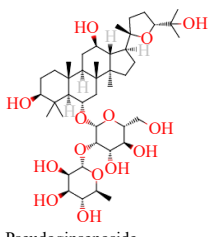
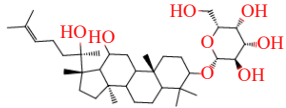
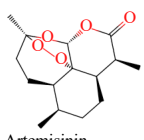
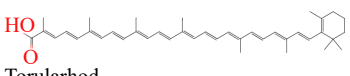
Introduction

Alzheimer's disease (AD) is a common neurodegenerative disease that seriously affects memory and thinking. More than 60% of dementia cases are attributed to AD. Statistics from the World Alzheimer Report 2022 showed that more than 55 million patients worldwide suffered from AD, and this number is expected to exceed 139 million by 2050^[1]. Based on incomplete statistics, the cost of treatment and care for AD exceeded USD\$ 1 trillion in 2018 and is expected to double to USD\$ 2 trillion by 2030^[2]. Various AD remission drugs (e.g., donepezil and Ketamine) are used in clinical treatment. These drugs fall into two main categories, acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists, the former representative drug is donepezil, and the latter representative drug is memantine^[3]. Without exception, all these drugs are neurotransmitter regulators with undesirable side effects. In addition, they only temporarily improve cognitive capability, therefore, safer and more effective drugs are needed for the treatment of AD. Coincidentally, dietary phytochemicals have shown excellent performance in treating AD. Curcumin mimic C1 provides a good biological environment for autophagy and lysosomes, rapidly decomposes amyloid precursor protein (APP) and tau congeries, decreases amyloid β ($A\beta$) levels, restores and reverses synaptic dysfunction, and effectively increases the cognitive level^[4]. Furthermore, pterostilbene reduced neuronal damage and inhibited oxidative stress^[5]. It also alleviated cognitive dysfunction. Taking lycopene regularly can reduce neuroinflammation and enhance the ability of learning and memory^[6]. Moreover,

regular intake of gallic acid can relieve oxidative stress in the brain (Table 1)^[7].

A daily dose of berberine also significantly improved learning and memory (Table 1)^[8]. Previous studies have shown that berberine can play a neuroprotective role in AD caused by heavy metals^[9]. In recent years, studies have demonstrated that ginsenosides have protective effects on AD, including ginsenoside Rb1 and ginsenoside Rg1^[10]. Moreover, the number of publications on 'Alzheimer's disease and phytochemicals' (Indexed by Web of Science) has improved significantly since 2012 and has seen the most rapid growth over the past four years (2018–2021) (Fig. 1). Together, these data indicate that dietary phytochemicals have potential in treating AD. In this review, we have collected representative literature from the last 10 years from the Web of Science. 'AD and dietary phytochemicals' was used as keywords to search highly cited literature, we found that curcumin, resveratrol, lycopene, gallic acid, berberine and ginsenoside are the most frequently studied. Then, we searched the literature using 'xx and AD' as keywords like curcumin and AD. For each phytochemical, we selected 3–5 reports with high citation rate or the latest research (in the last two years). In the 'others' section, we found dietary phytochemicals related to those we identified in the first step, such as torularhodin, and recent substances of interest, such as artemisinin, and more cited articles, not highly cited articles, such as sesamin. Based on this, we discussed the molecular mechanisms of several representative dietary phytochemicals in the treatment of AD. This review will contribute to the development of potentially effective AD treatment strategies.

Table 1. Structures of dietary phytochemicals and their potential anti-AD mechanisms.

Dietary phytochemicals	Model	Dosage	Molecular mechanism	Ref.
 Curcumin	Wistar rats	Cur-PLGA-NPs (5–20 mg/kg body weight, 3 weeks)	Cur-PLGA-NPs causes enhances the nuclear translocation of β -catenin, decreases GSK-3 β levels, and increases promoter activity of the TCF/LEF and cyclin-D1.	[18]
	Transgenic APP/PS1 mice	Curcumin (160 ppm, 6 months)	Curcumin reduces the level of neuropro-inflammatory miR-146a, up-regulates the expression of CFH protein, and inhibits the phenotype of M1 microglia.	[20]
 Resveratrol	ICR mice	TGN-Res@SeNPs (50 mg/kg body weight, 16 weeks)	kappa B \downarrow / protein kinase \downarrow / Akt \downarrow NF- κ B/ mitogen-activated protein kinase/Akt signal pathway.	[26]
	Wistar rats	RSV-SeNPs (200 mg/kg body weight, 8 weeks)	RSV-SeNPs up-regulates the expression of GSK3 β and SIRT1, and down-regulates the expression of microRNA-134, consequently increasing neurite outgrowth.	[25]
 Lycopene	Transgenic APP/PS1 mice	Lycopene (4 mg/kg body weight, 5 days)	LXR \uparrow / PI3K \uparrow / AKT \uparrow Lycopene alleviates neurovascular changes in APP/PS1 mice by activating the LXR-PI3K-AKT signaling pathway.	[6]
	Wistar rats	Lycopene (1–4 mg/kg body weight, 2 weeks)	Lycopene decreases NF- κ B expression and downregulates IL-1 β and TNF- α production.	[28]
 Gallic acid	Transgenic APP/PS1 mice	Gallic acid (20 mg/kg body weight, 6 months)	Gallic acid increases the ADAM10 proprotein convertase furin, activates ADAM10 and directly inhibits BACE1 activity, does not alter ADAM10 or BACE1 transcription.	[7]
 Berberine	Transgenic APP/tau/PS1 mice	Berberine (100 mg/kg body weight, 4 months)	Berberine ameliorates cognitive deficits, reduces the A β accumulation, inhibits the apoptosis of neurons, and promotes the formation of microvessels in the mouse brain by enhancing brain CD31, VEGF, N-cadherin, and Ang-1.	[8]
 Ginsenoside Rg1	Sprague dawley rat hippocampal neurons	Ginsenoside Rg1 (60 μ M, 24 h)	CDK5 \downarrow / IDE \uparrow / BACE1 \uparrow Ginsenoside Rg1 significantly decreases CDK5 expression, inhibits PPAR γ phosphorylation at serine 273, elevates IDE expression, downregulates BACE1 and APP expression.	[44]
	Tree shrews	Ginsenoside Rg1 (30 mg/kg body weight, 8 weeks)	Bcl-2/Bax \uparrow / Wnt \uparrow / GSK-3 β \downarrow / β -cateni \uparrow Rg1 increases the ratio of Bcl-2 to Bax and the expression of neuronal markers MAP2 and NeuN Rg1 regulates oxidative stress, cell apoptosis, and neuroinflammation by the Wnt/GSK-3 β / β -catenin signaling pathway.	[45]
 Pseudoginsenoside	Wistar rats	Pseudoginsenoside-F11 (2–8 mg/kg body weight, 4 weeks)	Calpain I \downarrow / CDK5 \downarrow / GSK-3 β \downarrow Pseudoginsenoside-F11's decreased GSK-3 β (Ser9) phosphorylation and CDK5 activity.	[46]
 Ginsenoside Rh2	ICR mice	Ginsenoside Rh2 (12.5 and 25 mg/kg, 14 days)	ERK \uparrow / CREB \uparrow / BDNF \uparrow Rh2 upregulates the phosphorylation of the ERK-CREB-BDNF pathway in the hippocampus.	[47]
 Artemisinin	PC12 cells	Artemisinin (0–50 μ M, 0–80 min)	ERK1/2 \uparrow Artemisinin suppresses LDH release; Artemisinin restrains the production of intracellular ROS; Artemisinin modulating $\Delta\psi_m$ and caspase 3/7 dependent pathway; Artemisinin activates ERK1/2 signaling.	[48]
 Torularhod	ICR mice	Torularhodin (0.5 and 1.5 mg/kg body weight, 4 weeks)	Nrf2 \uparrow / NF- κ B \downarrow Torularhodin ameliorates neuronal oxidative damage via the activation of Nrf2 translocation, upregulation of HO-1, and inactivation of NF- κ B.	[49]

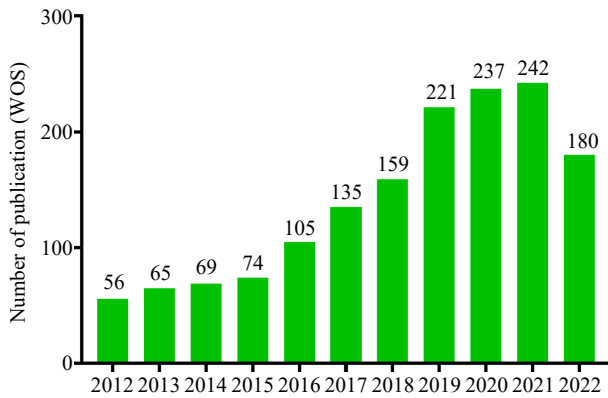


Fig. 1 The number of publications on 'Alzheimer's disease and dietary phytochemicals' (indexed by Web of Science) significantly increased since 2012 and the breakout increase occurred in the last four years (2018–2021).

Pathogenesis of Alzheimer's disease

The pathological features, pathogenesis, and drug treatment of AD have been studied for more than half a century since 1963 by Robert Terry and Michael Kidley, who observed neurofibrillary tangles (NFTs) using electron microscopy^[11,12]. At present, more than a dozen hypotheses about the pathogenesis of AD, including the tau propagation hypothesis. Among these hypotheses of AD, the tau propagation hypothesis is the most influential (Fig. 2)^[13]. However, this is just a hypothesis, and causes of AD are still being explored. Fortunately, the three major pathological features of AD are known, including amyloid plaques ($A\beta$), tau protein tangle, and neurofibrillary tangle in AD's brains^[14]. Unfortunately, the accumulation of neurofibrillary tangle leads to neuron loss and degeneration, a form of cell death. Furthermore, the continued neuron loss and degeneration activated microglia and reactive astrocytes further contribute to Blood Brain Barrier (BBB) leakage and neuroinflammation (Fig. 3)^[15].

Dietary phytochemicals

Curcumin

Curcumin (Cur) (Table 1), a natural dietary polyphenol isolated from turmeric, has various biological activities and has been shown to be beneficial for many brain diseases^[16]. Various

studies show that Cur is not only well documented for its anti-carcinogenic, antioxidant and anti-inflammatory properties, but also possessing neuroprotective and cognitive-enhancing properties that may help delay or prevent neurodegenerative diseases, including AD^[17]. New material carriers and Cur derivatives activate transcription factor EB, promote lysosomal and autophagy activity, attenuate $A\beta$ and tau pathology, are also effective in preventing memory impairment in AD^[4]. Cur nanoparticles show neuroprotective effects by increasing neuronal differentiation through activation of the Wnt/ β -catenin pathway (Fig. 4), which enhances the brain's self-repairing mechanism and has great potential in alleviating AD (Table 1)^[18]. Interestingly, Curcumin-primed exosomes potentially ameliorate cognitive function in AD mice by inhibiting hyperphosphorylation of the tau protein through the AKT/GSK-3 beta pathway^[19]. In addition, Gong & Sun confirmed that Cur can significantly reduce the level of neuropro-inflammatory miR-146A, and play a role in treating AD (Table 1)^[20]. These studies laid a foundation for the development of Cur as a novel drug for AD.

Resveratrol

Resveratrol (Res) (Table 1), a natural dietary polyphenol, has been shown to have pleiotropic activity in numerous clinical trials^[21]. Moussa et al. found that Res may slow cognitive decline by improving the coordination of the peripheral and central immune systems^[22]. In previous studies, it has shown that Res offer neuroprotection *via* modulation of proteolytic mechanisms^[23]. Although the application of Res is supported by a wealth of clinical data, the development of Res is limited by its poor stability and bioavailability^[24]. With this new development, new composite material is at a breakthrough point. Res-selenium nanoparticles, a new material, not only reduce neuroinflammation and neurotoxicity, but also maximize the therapeutic potential of Res for AD (Fig. 4 and Table 1)^[25]. Moreover, Res-selenium-peptide nanocomposites, a novel composite material decorated with a TGN peptide (blood-brain barrier transport peptide), significantly alleviated neuroinflammation by improving delivery efficiency (Table 1)^[26].

Lycopene

Lycopene (Lyc) (Table 1) is a fat-soluble carotenoid. As a potent antioxidant, its antioxidant far exceeds vitamin E and carotene^[27]. Regular Lyc intake can reduce memory damage in the brain (Table 1)^[28]. Fang et al. have confirmed that Lyc

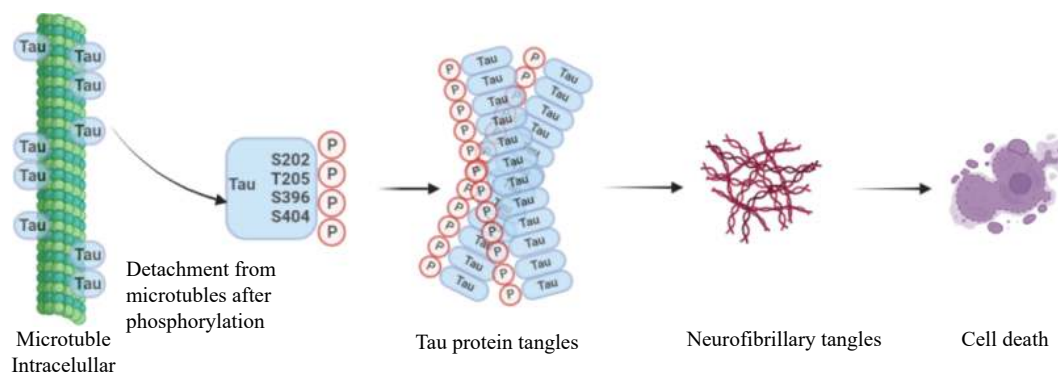


Fig. 2 Hypothesis of tau propagation. The tau proteins are usually hyperphosphorylated by binding to amino residues, typically Ser202, Thr205, Ser396, and Ser404. Then these monomers aggregate to form tau protein tangles, a complex oligomer, that eventually form neurofibrillary tangles, resulting in cell death. Drawing on <https://app.biorender.com/>.

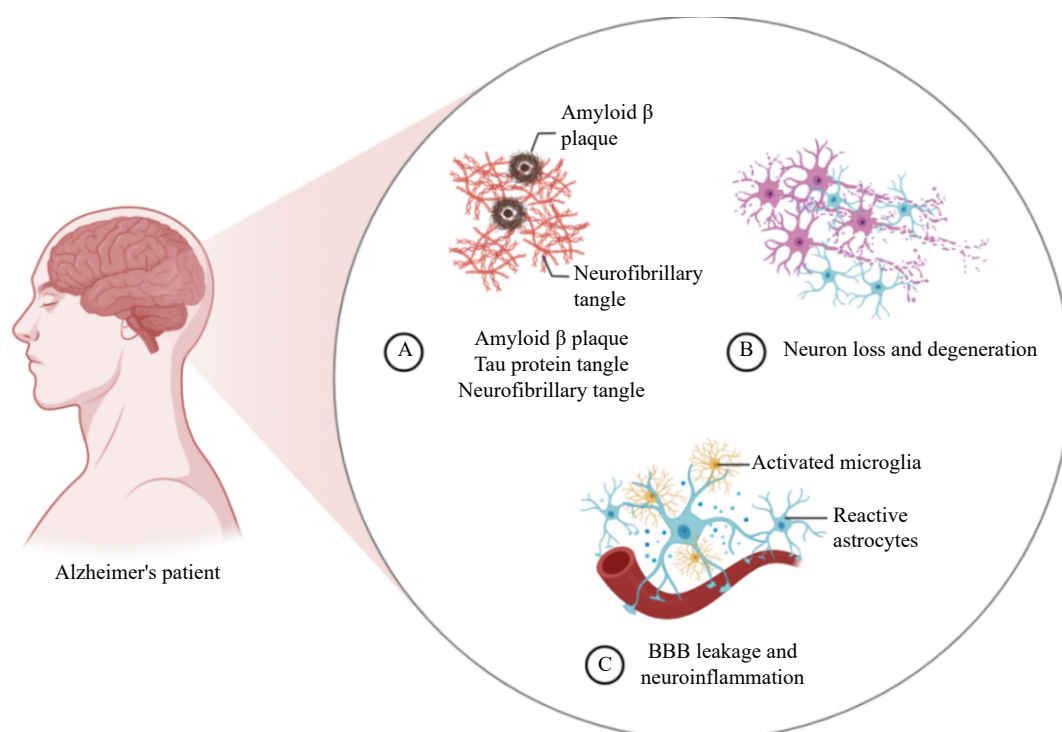


Fig. 3 (A) Three main pathological features of Alzheimer's disease (AD), amyloid beta plaques ($A\beta$), tau protein tangle and neurofibrillary tangle in the brains of AD patients. (B) The accumulation of neurofibrillary tangle leads to neuronal loss and degeneration, a form of cell death. (C) The continued neuronal loss and degeneration activates microglia and reactive astrocytes, which further contributes to blood brain barrier (BBB) leakage and neuroinflammation. Drawing on <https://app.biorender.com/>.

prevents $A\beta$ -induced damage by reducing the expression of β -secretase. Moreover, *in vitro* experiments have shown that Lyc can alleviate oxidative stress by inhibiting the expression of BACE^[29]. Lyc is effective in reducing neuroinflammation (Fig. 5 and Table 1)^[6,30], and also significantly reduces oxidative stress^[31]. In addition, Lyc can improve cognitive and motor impairments by increasing dopamine levels^[32].

Gallic acid

Gallic acid (GA) (Table 1), also known as benzoic acid, is a dual α/β -secretase modulator^[33]. Mori et al. have demonstrated that GA alleviates neuro-inflammation and stabilizes oxidative stress^[6]. We can see that dietary GA supplementation can effectively alleviate oxidative stress induced AD, preserve the healthy state of the hippocampus to against environmental neurotoxins^[34]. Furthermore, GA reacts with gallic catechins to get Epigallocatechin-3-Gallate (EGCG). Payne et al. have shown that EGCG treats AD by inhibiting neuroinflammation, aging, protein aggregation, and autophagy^[35]. In addition, Araújo et al. have designed a new drug-carrying molecules, a dendritic macromolecule based on GA-terminated. The special structure further enhancing the ability of GA to destroy $A\beta$ fibers to protect the nervous system in AD^[36].

Berberine

Berberine (BBR) (Table 1), an alkaloid, has neuroprotective effects^[37]. Zhang et al. have shown that BBR has a neuroprotective effect in AD^[38]. Živančević et al. have confirmed that BBR antagonizes genes affected by mutual for AD and metal toxicity^[39]. In addition, it has been shown that BBR improved cognitive deficits, inhibited neuronal apoptosis, and further promoted micro-vessel formation (Table 1)^[7]. *In vitro* studies confirmed the efficacy of BBR against AD by showing reduced

proinflammatory cytokine production^[40]. Inevitably, the bioavailability of BBR is also not high. El-Enin et al. have designed a new material, BER-CTS-NLCs (BBR-laden nanostructured lipid carriers overlaid with chitosan). It effectively transmits to the brain *via* intranasal pathways^[41]. In the same vein, lactoferrin-modified berberine nanoliposomes is also a breakthrough, it inhibits hippocampus apoptosis and enhances the neuroprotective effects of berberine nanoliposomes in AD^[42].

Ginsenoside

Ginsenoside, a tetracyclic triterpenoid compound, have many different monomers, have been certified to relieve AD through antioxidant and anti-inflammatory effects^[43]. Ginsenoside Rg1 (Rg1), one of the monomers, has shown neuroprotective effects in *in vitro* studies (Table 1)^[44]. In addition, *in vivo* studies have confirmed the antioxidant and anti-inflammatory effects of Rg1 (Fig. 3 & Table 1)^[45]. Rg1 has neuroprotective effects against AD. Pseudoginsenoside-F11 (PF11) and Ginsenoside Rh2 (Rh2) have the same efficacy (Table 1). *In vivo* studies have confirmed that PF-11 improves learning and memory deficits in AD (Table 1)^[46]. Thus, the therapeutic potential of PF11 in managing AD is excellent. Rh2 has also shown excellent antioxidant action *in vivo* (Table 1)^[47].

Others

Other dietary phytochemicals also have excellent therapeutic potential in managing AD, including artemisinin and torularhodin. *In vitro* studies have shown that artemisinin alleviated AD by its antioxidant action (Table 1)^[48]. Moreover, *in vivo* studies have shown that torularhodin can effectively improve neuroinflammation and cognitive dysfunction by inhibiting oxidative stress, thereby preventing AD (Table 1)^[49]. Sesamin protects the nervous system through antioxidant

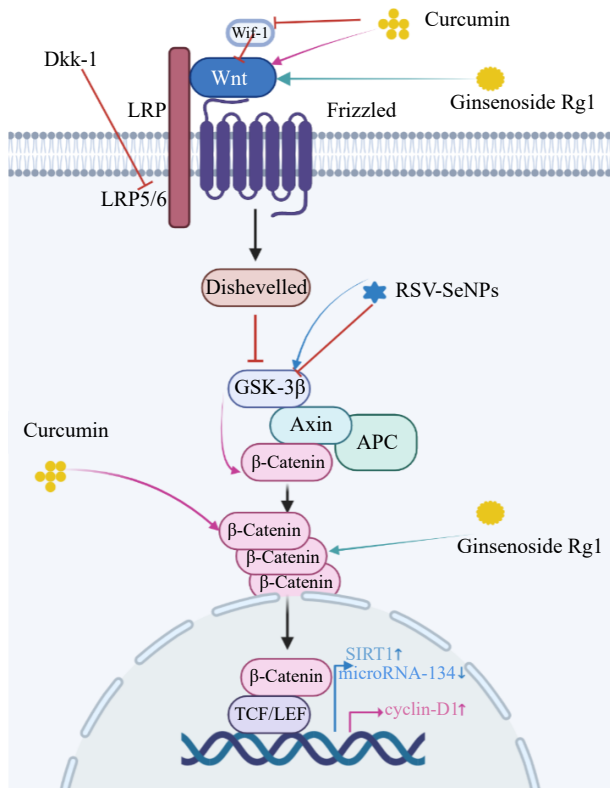


Fig. 4 Schematic model of the role of dietary phytochemicals in neurogenesis through activation of the Wnt/ β -catenin signaling pathway. Pink arrows: Curcumin interacts with Wif-1 and Dkk-1 to increase Wnt levels and activate the Wnt pathway. Wnt interacts with frizzled receptors to down-regulate low-density lipoprotein (LRP-5/6) expression and trigger cytoplasmic disheveled (Dvl). Then it breaks the Axin/APC/GSK-3 β homeostasis and down-regulates the expression of GSK-3 β . This sequence of reactions ultimately up-regulates cytoplasmic β -catenin expression and transfers it from the cytoplasm to the nucleus. After cellular internalization curcumin directly upregulates cytoplasmic β -catenin levels. In the nucleus, TCF/LEF and cyclin d1 promoter activity were enhanced. Green arrows: Rg1 activates Wnt/GSK-3 β / β -Catenin signaling pathway by inhibiting the activation of GSK-3 β and phosphorylation of β -Catenin. Wnt signaling pathways are critical in the pathogenesis of the AD. Blue arrows: RSV-SeNPs upregulate the expression of GSK3 β , Sirtuin-1 (SIRT1) and decrease that of microRNA-134, consequently increasing neurite outgrowth. Drawing on <https://app.biorender.com/>.

action, is a potential dietary phytochemical in treating AD^[50]. Many dietary phytochemicals have been reported to have significant effects on the prevention and treatment of AD. However, additional research is needed to turn these natural compounds into novel drugs.

Clinical application

Research into dietary phytochemicals will eventually have to revert to clinical applications. Cur has been subject to numerous patents and clinical trials, but none of them have yielded conclusive results^[51]. The instability and low bioavailability of Cur limit its clinical application. Nanocarriers have the potential to solve both challenges^[52]. Res has two major disadvantages: low bioavailability and low solubility *in vivo*, which prevents

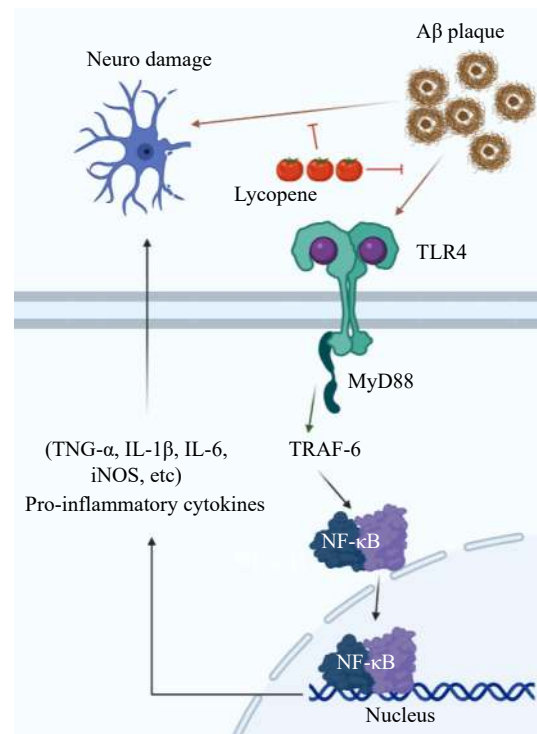


Fig. 5 Lycopene inhibits the down-regulation of TLR4 (Toll-like receptors 4) by A β , which further affects MyD88 (Myeloid differentiation primary response gene 88) and TRAF6, thereby activating the NF- κ B pathway. On the other hand, lycopene directly inhibits A β induced neuronal damage, as shown by decreased levels of serum inflammatory cytokines and increased expression of the p65 subunit and TLR4. Drawing on <https://app.biorender.com/>.

patent treatment^[23,53,54]. For Lyc and GA, research on AD is still in its infancy, thus, currently most clinical studies focus on other diseases, such as chronic periodontitis^[55], prostate cancer^[56], osteoporosis^[57], Type 2 diabetes^[58], and acne vulgaris^[59]. Although clinical research on BBR for AD is also in its infancy, schizophrenia^[60] and cardiovascular disease^[61] are still closely related to AD. For ginsenoside, ginsenoside H dripping pill (GH), a novel Rh2 product, is in a phase 2 clinical study^[62]. However, the trial is focused on its anticancer effect, not its anti-AD effect. For artemisinin, it is a miracle cure for malaria, and triple artemisinin-based combination therapies are enrolled in a new randomized clinical trial^[63]. Similarly, artemisinin is known for its antimalarial effect, not its anti-AD effect. Furthermore, research for torularhodin is still experimental. Thus, the commercial potential of torularhodin is still unexplored^[64].

Conclusion and perspectives

AD is a common disease, and scientists all over the world are trying to find ways to prevent and treat AD. Dietary phytochemicals are safe and have low toxicity, which have been reported to exhibit preventive and therapeutic effects on AD, such as curcumin, resveratrol, lycopene, gallic acid, berberine, ginsenoside Rg1, pseudoginsenoside-F11, ginsenoside Rh2, artemisinin, and torularhodin. Many underlying mechanisms have been identified, including reducing A β deposition and

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inhibiting tau hyperphosphorylation to rescue synaptic dysfunction, thereby improving mitochondrial activity, anti-apoptosis, anti-oxidation and anti-inflammatory. In future studies, we should focus on evaluating the alleviating effects of natural compounds in human AD, and come up with better ways develop these natural compounds into new drugs faster, to treat the increasing number of AD patients. Therefore, to develop new drugs from dietary phytochemicals as quickly as possible, clinical trials are essential. Unignorably, safety is still of key importance, although natural compounds are usually safe, research must be performed to find the safest pharmaceutical and intake concentration. Finally, dietary phytochemicals can be developed into novel drugs for the prevention and treatment of AD, and into food health products.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (21978236 and 21978229, Natural Science Basic Research Program of Shaanxi (2023-JC-JQ-17), and Qin Chuangyuan cited the High-level Innovation and Entrepreneurship Talent Program (QCYRCXM-2022-129).

Conflict of interest

The authors declare that they have no conflict of interest.

Dates

Received 10 January 2023; Accepted 8 February 2023; Published online 6 March 2023

REFERENCES

- Gauthier S, Webster C, Servaes S, Morais JA, Rosa-Neto P. 2022. *World Alzheimer Report 2022: Life after diagnosis: Navigating treatment, care and support. Executive summary*. London, England: Alzheimer's Disease International. pp. 25–26. www.alzint.org/u/World-Alzheimer-Report-2022.pdf
- Siva N. 2021. New global initiative to tackle Alzheimer's disease. *Lancet* 397:568–69
- Qian X, Hamad B, Dias-Lalcaca G. 2015. The Alzheimer disease market. *Nature Reviews Drug Discovery* 14:675–76
- Song J, Malampati S, Zeng Y, Durairajan S, Yang C, et al. 2020. A small molecule transcription factor EB activator ameliorates beta-amyloid precursor protein and Tau pathology in Alzheimer's disease models. *Aging cell* 19:e13069
- Xu J, Liu J, Li Q, Mi Y, Zhou D, et al. 2021. Pterostilbene alleviates A β ₁₋₄₂-induced cognitive dysfunction via inhibition of oxidative stress by activating Nrf2 signaling pathway. *Molecular Nutrition & Food Research* 65:2000711
- Xu X, Teng Y, Zou J, Ye Y, Song H, et al. 2020. Effects of lycopene on vascular remodeling through the LXR-PI3K-AKT signaling pathway in APP/PS1 mice. *Biochemical and Biophysical Research Communications* 526:699–705
- Mori T, Koyama N, Yokoo T, Segawa T, Maeda M, et al. 2020. Gallic acid is a dual α/β -secretase modulator that reverses cognitive impairment and remediates pathology in Alzheimer mice. *The Journal of Biological Chemistry* 295:16251–66
- Ye C, Liang Y, Chen Y, Xiong Y, She Y, et al. 2021. Berberine improves cognitive impairment by simultaneously impacting cerebral blood flow and β -amyloid accumulation in an APP/tau/PS1 mouse model of Alzheimer's disease. *Cells* 10:1161
- Hussien HM, Abd-Elmegied A, Ghareeb DA, Hafez HS, Ahmed HEA, et al. 2018. Neuroprotective effect of berberine against environmental heavy metals-induced neurotoxicity and Alzheimer's-like disease in rats. *Food and Chemical Toxicology* 111:432–44
- Yang Y, Li S, Huang H, Lv J, Chen S, et al. 2020. Comparison of the protective effects of ginsenosides Rb1 and Rg1 on improving cognitive deficits in SAMP8 mice based on anti-neuroinflammation mechanism. *Frontiers in Pharmacology* 11:834
- Kidd M. 1963. Paired helical filaments in electron microscopy of Alzheimer's disease. *Nature* 197:192–93
- Terry RD. 1963. The fine structure of neurofibrillary tangles in Alzheimer's disease. *Journal of Neuropathology & Experimental Neurology* 22:629–42
- Liu P, Xie Y, Meng X, Kang J. 2019. History and progress of hypotheses and clinical trials for Alzheimer's disease. *Signal Transduction and Targeted Therapy* 4:29
- Lee JH, Yang D, Goulbourne CN, Im E, Stavrides P, et al. 2022. Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of A β in neurons, yielding senile plaques. *Nature Neuroscience* 25:688–701
- Castillo E, Leon J, Mazzei G, Abolhassani N, Haruyama N, et al. 2017. Comparative profiling of cortical gene expression in Alzheimer's disease patients and mouse models demonstrates a link between amyloidosis and neuroinflammation. *Scientific Reports* 7:17762
- Lee WH, Loo CY, Bebawy M, Luk F, Mason RS, et al. 2013. Curcumin and its Derivatives: Their Application in Neuropharmacology and Neuroscience in the 21st Century. *Current Neuropharmacology* 11:338–78
- Goozee KG, Shah TM, Sohrabi HR, Rainey-Smith SR, Brown B, et al. 2016. Examining the potential clinical value of curcumin in the prevention and diagnosis of Alzheimer's disease. *The British Journal of Nutrition* 115:449–65
- Tiwari SK, Agarwal S, Seth B, Yadav A, Nair S, et al. 2014. Curcumin-loaded nanoparticles potently induce adult neurogenesis and reverse cognitive deficits in Alzheimer's disease model via canonical Wnt/ β -catenin pathway. *ACS Nano* 8:76–103
- Wang H, Sui H, Zheng Y, Jiang Y, Shi Y, et al. 2019. Curcumin-primed exosomes potently ameliorate cognitive function in AD mice by inhibiting hyperphosphorylation of the Tau protein through the AKT/GSK-3 β pathway. *Nanoscale* 11:7481–96
- Gong J, Sun D. 2022. Study on the mechanism of curcumin to reduce the inflammatory response of temporal lobe in Alzheimer's disease by regulating miR-146a. *Minerva Medica* 133:109–18
- Singh AP, Singh R, Verma SS, Rai V, Kaschula CH, et al. 2019. Health benefits of resveratrol: Evidence from clinical studies. *Medicinal Research Reviews* 39:1851–91
- Moussa C, Hebron M, Huang X, Ahn J, Rissman RA, et al. 2017. Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease. *Journal of Neuroinflammation* 14:1
- Sarroca S, Gatius A, Rodríguez-Farré E, Vilchez D, Pallàs M, et al. 2021. Resveratrol confers neuroprotection against high-fat diet in a mouse model of Alzheimer's disease via modulation of proteolytic mechanisms. *The Journal of Nutritional Biochemistry* 89:108569
- Drygalski K, Ferencik E, Koryciński K, Chomentowski A, Kielczewska A, et al. 2018. Resveratrol and Alzheimer's disease. From molecular pathophysiology to clinical trials. *Experimental Gerontology* 113:36–47
- Abozaid OAR, Sallam MW, El-Sonbaty S, Aziza S, Emad B, et al. 2022. Resveratrol-selenium nanoparticles alleviate neuroinflammation and neurotoxicity in a rat model of Alzheimer's disease by regulating Sirt1/miRNA-134/GSK3 β expression. *Biological Trace Element Research* 200:5104–14
- Li C, Wang N, Zheng G, Yang L. 2021. Oral administration of resveratrol-selenium-peptide nanocomposites alleviates Alzheimer's disease-like pathogenesis by inhibiting A β aggregation and regulating gut microbiota. *ACS Applied Materials & Interfaces* 13:46406–20

27. Przybylska, S. 2020. Lycopene – a bioactive carotenoid offering multiple health benefits: a review. *International Journal of Food Science & Technology* 94:11–32
28. Sachdeva AK, Chopra K. 2015. Lycopene abrogates $A\beta(1-42)$ -mediated neuroinflammatory cascade in an experimental model of Alzheimer's disease. *The Journal of Nutritional Biochemistry* 26:736–44
29. Fang Y, Ou S, Wu T, Zhou L, Tang H, et al. 2020. Lycopene alleviates oxidative stress via the PI3K/Akt/Nrf2 pathway in a cell model of Alzheimer's disease. *PeerJ* 8:e9308
30. Xu ZG, Liu C, Wang R, Gao XR, Hao C, et al. 2021. A combination of lycopene and human amniotic epithelial cells can ameliorate cognitive deficits and suppress neuroinflammatory signaling by choroid plexus in Alzheimer's disease rat. *The Journal of Nutritional Biochemistry* 88:108558
31. Wang R, Xu ZG, Li YF, Li WJ, Gao XR, et al. 2021. Lycopene can modulate the LRP1 and RAGE transporters expression at the choroid plexus in Alzheimer's disease rat. *Journal of Functional Foods* 85:104644
32. Ratto F, Franchini F, Musicco M, Caruso G, di Santo SG. 2022. A narrative review on the potential of tomato and lycopene for the prevention of Alzheimer's disease and other dementias. *Critical Reviews in Food Science and Nutrition* 62:4970–81
33. Bai J, Zhang Y, Tang C, Hou Y, Ai X, et al. 2021. Gallic acid: Pharmacological activities and molecular mechanisms involved in inflammation-related diseases. *Biomedicine & Pharmacotherapy* 133:110985
34. Ogunlade B, Adelakun SA, Agie JA. 2022. Nutritional supplementation of gallic acid ameliorates Alzheimer-type hippocampal neurodegeneration and cognitive impairment induced by aluminum chloride exposure in adult wistar rats. *Drug and Chemical Toxicology* 45:651–62
35. Payne A, Nahashon S, Taka E, Adinew GM, Soliman KFA. 2022. Epigallocatechin-3-Gallate (EGCG): New Therapeutic Perspectives for Neuroprotection, Aging, and Neuroinflammation for the Modern Age. *Biomolecules*. 12:371
36. Araújo AR, Correa J, Dominguez-Arca V, Reis RL, Fernandez-Megia E, et al. 2021. Functional gallic acid-based dendrimers as synthetic nanotools to remodel amyloid- β -42 into noncytotoxic forms. *ACS Applied Materials & Interfaces* 13:59673–82
37. Wang Y, Tong Q, Ma S, Zhao Z, Pan L, et al. 2021. Oral berberine improves brain dopa/dopamine levels to ameliorate Parkinson's disease by regulating gut microbiota. *Signal Transduction and Targeted Therapy* 6:77
38. Zhang C, Li C, Chen S, Li Z, Jia X, et al. 2017. Berberine protects against 6-OHDA-induced neurotoxicity in PC12 cells and zebrafish through hormetic mechanisms involving PI3K/AKT/Bcl-2 and Nrf2/HO-1 pathways. *Redox Biology* 11:1–11
39. Živančević K, Baralić K, Bozic D, Miljaković EA, Djordjević AB, et al. 2022. Involvement of environmentally relevant toxic metal mixture in Alzheimer's disease pathway alteration and protective role of berberine: Bioinformatics analysis and toxicogenomic screening. *Food and Chemical Toxicology* 161:112839
40. Wong LR, Tan EA, Lim MEJ, Shen W, Lian X, et al. 2021. Functional effects of berberine in modulating mitochondrial dysfunction and inflammatory response in the respective amyloidogenic cells and activated microglial cells-*In vitro* models simulating Alzheimer's disease pathology. *Life Sciences* 282:119824
41. Abo El-Enin HA, Elkomy MH, Naguib IA, Ahmed MF, Alsaidan OA, et al. 2022. Lipid Nanocarriers Overlaid with Chitosan for Brain Delivery of Berberine via the Nasal Route. *Pharmaceuticals*. 15:281
42. Wang L, Zhou B, Li Y, Jiang Q, Cong W, et al. 2022. Lactoferrin modification of berberine nanoliposomes enhances the neuroprotective effects in a mouse model of Alzheimer's disease. *Neural Regeneration Research* 18:226–32
43. Chen YY, Liu QP, An P, Jia M, Luan X, et al. 2022. Ginsenoside Rd: A promising natural neuroprotective agent. *Phytomedicine* 95:153883
44. Quan Q, Li X, Feng J, Hou J, Li M, et al. 2020. Ginsenoside Rg1 reduces β -amyloid levels by inhibiting CDK5-induced PPAR γ phosphorylation in a neuron model of Alzheimer's disease. *Molecular Medicine Reports* 22:3277–88
45. Yang Y, Wang L, Zhang C, Guo Y, Li J, et al. 2022. Ginsenoside Rg1 improves Alzheimer's disease by regulating oxidative stress, apoptosis, and neuroinflammation through Wnt/GSK-3 β / β -catenin signaling pathway. *Chemical Biology & Drug Design* 99:884–96
46. Zhu L, Hou X, Che X, Zhou T, Liu X, et al. 2021. Pseudoginsenoside-F11 attenuates cognitive dysfunction and tau phosphorylation in sporadic Alzheimer's disease rat model. *Acta Pharmacologica Sinica* 42:1401–8
47. Lv J, Lu C, Jiang N, Wang H, Huang H, et al. 2021. Protective effect of ginsenoside Rh2 on scopolamine-induced memory deficits through regulation of cholinergic transmission, oxidative stress and the ERK-CREB-BDNF signaling pathway. *Phytotherapy Research* 35:337–45
48. Zeng Z, Xu J, Zheng W. 2017. Artemisinin protects PC12 cells against β -amyloid-induced apoptosis through activation of the ERK1/2 signaling pathway. *Redox Biology* 12:625–33
49. Zhang W, Hua H, Guo Y, Cheng Y, Pi F, et al. 2020. Torularhodin from *Sporidiobolus pararoseus* attenuates D-galactose/AICl $_3$ -induced cognitive impairment, oxidative stress, and neuroinflammation via the Nrf2/NF- κ B pathway. *Journal of Agricultural and Food Chemistry* 68:6604–14
50. Ruankham W, Suwanjang W, Wongchitrat P, Prachayasittikul V, Prachayasittikul S, et al. 2021. Sesamin and sesamol attenuate H $_2$ O $_2$ -induced oxidative stress on human neuronal cells via the SIRT1-SIRT3-FOXO3a signaling pathway. *Nutritional Neuroscience* 24:90–101
51. Gagliardi S, Morassa C, Stivaktakis P, Pandini C, Tinelli V, et al. 2020. Curcumin formulations and trials: what's new in neurological diseases. *Molecules* 25:5389
52. Lv H, Wang Y, Yang X, Ling G, Zhang P. 2022. Application of curcumin nanoformulations in Alzheimer's disease: prevention, diagnosis and treatment. *Nutritional Neuroscience*
53. Anton SD, Ebner N, Dzierzewski JM, Zlatar ZZ, Gurka MJ, et al. 2018. Effects of 90 days of resveratrol supplementation on cognitive function in elders: A pilot study. *Journal of Alternative and Complementary Medicine* 24:725–32
54. Turner RS, Thomas RG, Craft S, van Dyck CH, Mintzer J, et al. 2015. A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. *Neurology* 85:1381–91
55. Tawfik MS, Abdel-Ghaffar KA, Gamal AY, El-Demerdash FH, Gad HA. 2019. Lycopene solid lipid microparticles with enhanced effect on gingival crevicular fluid protein carbonyl as a biomarker of oxidative stress in patients with chronic periodontitis. *Journal of Liposome Research* 29:375–82
56. Lane JA, Er V, Avery KNL, Horwood J, Cantwell M, et al. 2018. ProDiet: A phase II randomized placebo-controlled trial of green tea catechins and lycopene in men at increased risk of prostate cancer. *Cancer Prevention Research* 11:687–96
57. Russo C, Ferro Y, Maurotti S, Salvati MA, Mazza E, et al. 2020. Lycopene and bone: an in vitro investigation and a pilot prospective clinical study. *Journal of Translational Medicine* 18:43
58. Ferk F, Kundi M, Brath H, Szekeres T, Al-Serori H, et al. 2018. Gallic acid improves health-associated biochemical parameters and prevents oxidative damage of DNA in type 2 diabetes patients: results of a placebo-controlled pilot study. *Molecular Nutrition & Food Research* 62:1700482
59. Kozan A, Guner R, Akyol M. 2020. A retrospective assessment and comparison of the effectiveness of benzoyl peroxide; the combination of topical niacinamide, gallic acid, and lauric acid; and the combination of benzoyl peroxide and erythromycin in acne vulgaris. *Dermatologic Therapy* 33:e13534

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60. Li M, Liu Y, Qiu Y, Zhang J, Zhang Y, et al. 2021. The effect of berberine adjunctive treatment on glycolipid metabolism in patients with schizophrenia: A randomized, double-blind, placebo-controlled clinical trial. *Psychiatry Research* 300:113899
61. Zhao JV, Yeung WF, Chan YH, Vackova D, Leung JYY, et al. 2021. Effect of berberine on cardiovascular disease risk factors: a mechanistic randomized controlled trial. *Nutrients* 13:2550
62. Wang Z, Liu R, Chen L, Wang H, Zhou M, et al. 2021. Pharmacokinetics of ginsenoside Rh2, the major anticancer ingredient of ginsenoside H dripping pills, in healthy subjects. *Clinical Pharmacology in Drug Development* 10:669–74
63. van der Pluijm RW, Tripura R, Høglund RM, Phyto AP, Lek D, et al. 2020. Triple artemisinin-based combination therapies versus artemisinin-based combination therapies for uncomplicated Plasmodium falciparum malaria: a multicentre, open-label, randomised clinical trial. *Lancet* 395:1345–60
64. Mussagy CU, Gonzalez-Miquel M, Santos-Ebinuma VC, Pereira JFB. 2021. Microbial torularhodin – a comprehensive review. *Critical Reviews in Biotechnology*



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