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REVIEW

Nanoparticle-conjugated nutraceuticals exert prospectively palliative of amyloid aggregation

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Abstract: Alzheimer's disease (AD), an age-related neurodegenerative disease, the most common causes of dementia is a multifactorial pathology categorized by a complex etiology. Numerous nutraceuticals have been clinically evaluated, but some of the trials failed. However, natural compounds have some limitations due to their poor bioavailability, ineffective capability to cross the blood–brain barrier, or less therapeutic effects on AD. To overcome these disadvantages, nanoparticle-conjugated natural products could promote the bioavailability and enhance the therapeutic efficacy of AD when compared with a naked drug. This application generates and implements new prospect for drug discovery in neurodegenerative diseases. In this article, we confer AD pathology, review natural products in clinical trials, and ascertain the importance of nanomedicine coupled with natural compounds for AD.

Keywords: Alzheimer's disease, amyloid beta, bioavailability, natural products, nutraceuticals

Introduction

Alzheimer's disease (AD), a progression and age-related neurodegeneration disease, is a multifactorial pathology categorized by a complex etiology. AD is increasingly documented as one of the most vital medical problems affecting the elderly and is the most common type of dementia. The symptoms of AD include progressive memory loss, cognitive impairment such as difficulty solving problems, and disorientation in time and space, among others in an aging population that causes a severe damage of cholinergic neurons in a particular area of the brain, that is, hippocampus. Remarkably, AD is a prominent cause of death in the USA since 2013; mortality of advanced stage AD increase by 11% per year. 2016 statistics of Medicaid for the AD predicted to be 19 times more for recipients >65 years, who do not have the following symptom.[1] Apart from the disease itself, it is the burden of care cost that seriously jeopardizes the health and financial security of the patient's family. Of note, three hallmarks of AD pathology are beta-amyloid (Aβ) accumulations, tau phosphorylation, and inflammation that have been postulated.[2] The molecular pathology of AD illustrates the abnormal shearing of β- and γ-secretase resulting in Aβ accumulation (Figure 1). 1) The accumulation of Aβ: Aβ accumulation is caused by inaccurate cleavage of the amyloid precursor protein (APP) with β- and γ-secretase;[2] and subsequently, the massive accumulation of Aβ mainly formed the plaques. Recently, the hallmarks of molecular features in senile plaque are the unfolding/misfolding of specific proteins/peptides. Aβ peptide consequently becomes susceptible to aggregate into toxic assemblies and deposits that are a crucial histopathological feature, neurofibrillary (tau) tangles, synapse loss, ROS production, and extensive oxidative stress.[3] This Aβ-induced oxidative stress is demonstrated via several clues such as protein oxidation, lipid peroxidation, free

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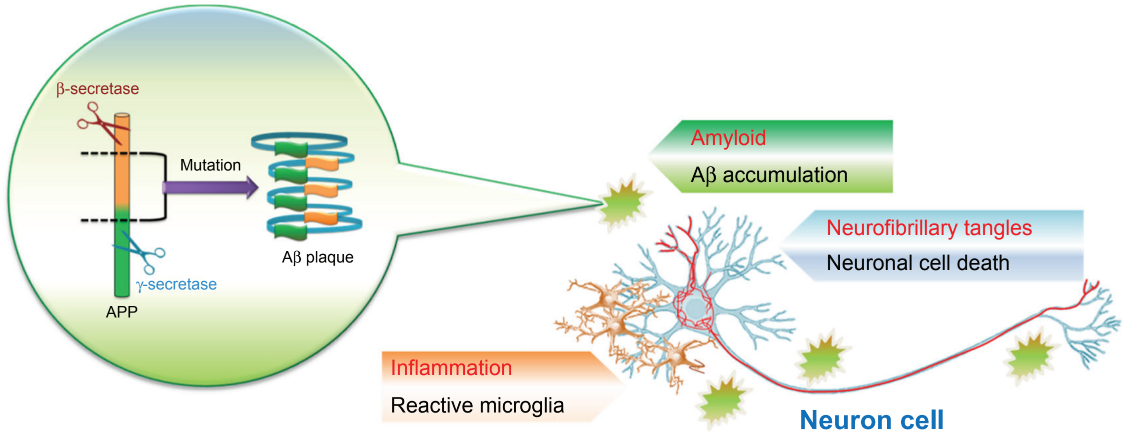

Figure 1 Alzheimer's disease pathology includes the abnormal shearing of β- and γ-secretase resulting in Aβ accumulation.
Notes: Phosphorylation of tau protein causes nerve entanglement. Inflammation and phagocytosis are induced by microglia.
Abbreviations: Aβ, beta amyloid; APP, amyloid precursor protein.

radical formation, DNA oxidation, and neuronal cell death.[4] Novel metabolic processing events such as δ-secretase and β-secretase have revealed that they generate previously uncharacterized APP metabolic fragments with the impending to be involved in AD pathogenesis.[5] The accumulation of amyloid plaque in the brain due to the accumulation caused by Aβ1-40 and Aβ1-42 peptides, Aβ 1-40 and Aβ 1-42 inhibit endocytosis, and Aβ 1-40 can inhibit lysosomes. The uptake led to increased accumulations of Aβ 1-42, Aβ 1-40, and Aβ 1-42, which also perturbs neuronal trafficking and vesicular dynamics.[6] 2) Hyperphosphorylation of tau protein: tau protein is a microtubule-associated protein expressed in the axons and soma of nerve cells.[7] Phosphorylation of tau protein is due to phosphorylation of serine and threonine sites for the tau protein.[8] The tau protein hyperphosphorylation led to neurofibrillary tangles because cognitive impairment may be a more direct effect than Aβ accumulations.[9] And 3) microglia communication driving for AD-related functional impairments. In AD, microglia aging is owing to cytokines that complement extracellular vesicles. The consequence of these changes includes augmented inflammation, reduced phagocytosis, and declined motility.[10] Furthermore, aged microglia would augment the levels of IL-1β, tumor necrosis factor-α, and IL-6.[11] Microglia enhances inflammatory responses and inhibits phagocytosis that presumably might be increased by age and led to decreased synaptic plasticity.[12]

Clinically, the early stages of AD have been treated by using acetylcholinesterase inhibitors.[13] As we know, there are five Food and Drug Administration-approved treatment medicines for the management of AD, which all offer symptomatic benefits. Tacrine, donepezil, galantamine, and rivastigmine are acetylcholinesterase inhibitors and are N-methyl-D-aspartate receptor antagonists.[14] Unfortunately, none of these drugs could cure or delay the commencement of AD due to various causes of dementia and neuropathology in many patients.[15] This failure could be owing to the unclear underlying pathways of AD. For example, the accumulation of neurotoxic Aβ peptides in the brain exemplifies a pathogenic hallmark of AD, which is the most general form of dementia in an aging population.[16] It was found that the decreased clearance rather than the production of Aβ is the primary formation of the deleterious Aβ plaques in the brain.[17] The lessened removal of Aβ from the brain into the blood can be moderately attributed to the dysfunction of P-gp function, leading to the progression of AD.[18–20] Furthermore, it has been shown that Aβ can downregulate the P-gp expression along with other transporters, which consequently results in further accelerated neurodegeneration.[21] Hence, it has been suggested that the increased Aβ clearance from the brain by restoring blood–brain barrier (BBB) P-gp function to diminish Aβ brain accumulation is a new strategy for medical treatment in the early stage of AD.[22,23] Unexpectedly, as of 2017, Alzheimer's treatment drugs, verubecestat and solanezumab, have been discontinued in phase III clinical trials of Aβ protein, but they have also led to the worldwide pathogenesis of AD, and new candidates require more attention to accelerate drug discovery for clinical use.[24–26] Therefore, the devotion of discovering agents against amyloidosis has turned to the search from natural compounds for meeting this demand.

Natural compounds act as nutraceuticals

The alternative approach instead of standard medical treatments in clinic for treating the patients is broadly recognized by using chemical derivatives,[27–30] natural sources including herb, and traditional medicine even natural compounds. In this article, we mainly focus on the benefits of natural compounds as an alternative use for neurodegenerative disease to confer this theme. Natural compounds are found abundantly in nature, particularly in daily foods, such as edible vegetable and fruit juices, green tea, wine, turmeric, and even cigarettes.[31] All of which contain antioxidative substances, especially polyphenols that act as both ROS scavengers and transition metal chelators.[32] Their antioxidant effects are naturally linked to anti-AD potential. In addition, their evolutional structure has made them become beneficial enzyme activators, channel openers, and receptor agonists.[33] Owing to the antioxidant activity in higher plants, consideration has improved about the defending activity of its natural antioxidants against chronic disorders caused by the oxidative process.[34] Antioxidants and nutrition have long been deliberated as an approach to alleviate AD progression. Numerous investigations have exposed that folic acid, vitamin B12, choline, vitamin C, vitamin K3, vitamin D3, vitamin E, zinc, selenium, s-ethyl cysteine, s-propyl cysteine, citicoline, rivastigmine, memantine, tea polyphenol, curcumin, caffeine, α-lipoic acid, N-acetylcysteine, and dietary polyphenols are able to interact with gene expressions and epigenetic mechanisms.[35–39] A growing evidence also suggests that epigenetic alterations are elicited by dietary nutrients that possess an imperative role in health and the preventative occurrence of some diseases, particularly neurodegenerative disorders. Assured natural dietary polyphenolic phytochemicals have paid extensively recent attention as alternative candidates for AD therapy. In particular, curcumin, resveratrol, piperine and spices, extra virgin olive oil, red wine, red berries, and green tea catechins contained antiamyloidogenic, antioxidative, and anti-inflammatory properties that have been postulated to have the preventative potential for AD.[40,41] Therefore, the attention of discovering agents against amyloidosis has turned to the search of natural compounds. Prominently, natural compounds have often been demonstrated to have better pharmacological properties than synthetic small molecules, especially with regard to less toxicity and good absorption.[33] Emergent studies revealed that some natural compounds isolated from Chinese herbs could be administered for disease or cancer therapy.[42,43] Based on these successes, we have listed the natural substances of the most studied on neuroprotective and reviewed the following natural compounds: 1) scyllo-inositol, 2) curcumin, 3) *Ginkgo biloba* extract, 4) resveratrol, and 5) epigallocatechin gallate along with their current clinical trials on AD treatment (Table 1). And the chemical structures of four discussed compounds are also exhibited underneath.

Scyllo-inositol

Scyllo-inositol, an inositol stereoisomer, is abundant in the coconut palm. Numerous studies have shown that scyllo-inositol can bind and inhibit Aβ aggregation and the formation of Aβ fibrils in vitro.[44] In the TgCRND8 mice model, the amyloid pathology has delayed in a dose-dependent fashion.[45] The phenomenon of neuronal autophagy in TgCRND8 model has also been explored.[46] The clinical trial assessing the safety and efficacy of multiple oral dosages of scyllo-inositol has applied to the treatment of AD, which started in 2007. However, serious adverse events occurred, including the death of nine patients, and have forced the company to stop the highest two doses and retain 250 mg scyllo-inositol twice a day until 2017. The differences between the 250 mg

Table 1 Summary of natural products in clinical trial

Compounds	Source	Pathway	Trial status	Reference/ ClinicalTrials.gov ID
Acetyl-L-carnitine	Meat	Antioxidative stress	Phase II (failed)	136, 137
Bryostatin 1	*Bugula neritina*	Reduce Aβ formation	Phase II (ongoing)	NCT02431468
Curcumin	*Curcuma longa*	Reduce Aβ formation	Phase II (failed)	78/CT00099710
Docosahexaenoic acid	Fish oil	Reduce Aβ formation	Phase II (failed)	79/NCT00440050
n-Butylphthalide	Ligusticum	Reduce Aβ formation	Phase II (ongoing)	138/NCT02711683
Pinitol	Sutherlandia frutescens	Inhibit γ-secretase	Phase II (completed, result not published)	139/NCT01928420
Scyllo-inositol	Coconut palm	Reduce Aβ formation	Phase II (evidence insufficient)	80/NCT00568776, NCT00934050
Epigallocatechin gallate	Green tea	Antioxidative stress	Phase II (completed, result not published)	140/NCT00951834
Ginkgo biloba extract	*G. biloba*	Antioxidative stress	Phase III (failed)	81, 82/NCT00010803
Resveratrol	Grape	Reduce Aβ formation	Phase II (evidence insufficient)	141/NCT01504854
Huperzine A	*Huperzia serrata*	Reduce Aβ formation	Phase II (unknown)	142

scyllo-inositol and placebo groups were not significant for the coprimary or secondary endpoints.

Curcumin

Curcumin (diferuloylmethane), one component of turmeric, is isolated from the rhizome of *Curcuma longa* and abounds in ginger family (Zingiberaceae). Numerous studies have focused on the various facets of curcumin due to its antioxidant and anti-inflammatory properties; curcumin also plays a significant advantageous and pleiotropic regulatory role in various pathological conditions which including hyperglycemia, oxidative stress, and cancer,[47] cardiovascular disease, AD, anti-inflammation,[48] neurological disorders,[49] and various malignant diseases.[50] Apart from these well-known suppressing activities, this natural polyphenolic compound also exerts its profitable effects by mediating different signaling molecules such as transcription factors, chemokines, cytokines, tumor suppressor genes, adhesion molecules, and microRNAs.[51] Notably, oxidative stress (free radicals) and inflammation are responsible for many human health problems including aging, arthritis, cancer, cardiovascular disease, diabetes, neurological disorders, AD, Parkinson's disease, mild cognitive impairment, alcohol-induced liver disease, ulcerative colitis, and atherosclerosis.[52] The neuroprotective effects of curcumin and curcuma oil exert its significant action in the decline of NO-induced peroxynitrite formations and cell apoptosis in the transient middle cerebral artery occlusion (MCAo) model and focal embolic stroke model rat.[53,54] Furthermore, curcuminoids have been used to perform as latent therapeutic implications for various neurodegenerative diseases.[55] The mechanism of curcumin for protecting the rat hippocampus combating with the neurotoxicity of homocysteine oxidative stress could be possible by increasing the endogenous defenses against oxidative stress via inhibiting the ROS generation of brain.[56] In cellular studies, curcumin inhibits cyclooxygenase-2, tumor necrosis factor-α, and IL-1 expression.[57] It downregulates IL-6 signaling via suppressing phosphorylation of STAT3[58] and inhibits Aβ-induced microglial inflammation through modulating ERK1/2 and p38 signaling pathways.[59] Curcumin can serve as a neuroprotective reagent through various signal pathways: acting against endothelin-1-mediated cell death (decreasing proapoptotic signaling) via blocking an increase in c-Jun levels in primary hippocampal neurons[60] and inhibiting Aβ generation through induction of autophagy by downregulating PI3K/Akt/mTOR signaling pathway.[61] Furthermore, chronic application of curcumin might ameliorate AD-related cognitive deficits and upregulate brain-derived neurotrophic factor-ERK signaling in the hippocampus.[62] There was a marked reduction in the production of Aβ when human neuroblastoma cells were treated with curcumin.[63] The aggregation of Aβ in a rat model of AD was also reduced after oral curcumin administration, as well as with the improvement of cognitive impairment in a spatial learning and memory test, suggesting that curcumin could be a candidate for treating AD. Currently, there are three clinical trials investigating the effect of anti-Aβ formation, but all of them failed to exhibit clinical or biochemical evidence of efficacy for AD. Even the underlying mechanisms of curcumin will be hampering the formation and promoting the disaggregation of Aβ plaques, mitigating the hyperphosphorylation of tau and augmenting its clearance, binding copper, lowering cholesterol, amending microglial activity, inhibiting acetylcholinesterase, regulating the insulin signaling pathway, and is an antioxidant as well.[64]

EGb-761

EGb-761 is made of ginkgo leaves, one dry extract that is adjusted to contain ginkgo flavonoids and terpene lactones.[65] In the cellular study, EGb-761 decreases free cholesterol levels and neuronal Aβ production, and the level of Alzheimer's amyloid precursor in the brain is also decreased.[66] It has been found in rescuing impaired mitochondrial function and improving neuronal energy supply.[67] The protective and rescuing abilities of EGb-761 are attributable to the antioxidant properties and the ability to inhibit NO-stimulated protein kinase C activity.[68] The increased production of toxic mediators such as hydrogen peroxide and platelet-activating factor in the brain may be critical in the pathological mechanism of neurodegenerative diseases particularly AD and is blocked by EGb-761.[69] In the current study, the dopamine level increased in the rat prefrontal cortex after EGb-761 administration, which implied a benefit for memory function.[70] Although the active ingredients of EGb-761 have not been explored, it still has the potential to treat or prevent AD. Nevertheless, the clinical trial for evaluating *G. biloba's* ability to abrogate memory loss or delay dementia still leads to negative outcomes.

Resveratrol

Resveratrol (Res), a phytochemical, has been found in many plant species such as herbs, berries, grapes, and peanuts. Res exhibits diverse biochemical properties, such as antiplatelet[71] and anti-inflammatory properties.[72] It has been shown to reduce oxidative stress and stabilize mitochondria through regulating Sirt1 pathway. Res is reported as a potential nutraceutical agent for AD; evidence indicates that Res alleviated Tau hyperphosphorylation at Ser396 site and oxidative damage in rat hippocampal slices exposed to vanadate via ERK1/2 and glycogen synthase kinase-3β signaling cascades.[73]

Res retreating Aβ-induced learning and memory disorder may involve the regulation of neuronal inflammation and apoptosis via phosphodiesterase-4-related Cyclic adenosine monophosphate (cAMP)-CREB-brain-derived neurotrophic factor signaling[74] and inhibit Aβ-induced neuronal apoptosis through reversion of silent information regulator 1 activity and subsequently the downregulation of Rho-associated kinase 1 signaling pathway.[75] Recently, one study showed that resveratrol changed three Aβ conformers into nontoxic alternations, suggesting that Res could mediate Aβ toxicity.[76] It also lowered Aβ levels in Tg2576 mice by stimulating nonamyloidogenic processing of APP.[77] According to its amyloidogenic-delaying and antioxidant effects, Res could be helpful in fighting AD. In recent years, four clinical trials assessing the effects on AD were established. However, none of them succeeded in different phases due to insufficient evidence and nonsignificant outcomes. Among these natural compounds with high neuroprotective effects that have broadly studied, have extensively used as an antioxidant for free radical scavenger. Nevertheless, the antioxidant and anti-Aβ formation activity of these natural compounds in vitro/in vivo failed to be well translated into therapeutic effects for patients with AD in clinical trial.[78–82] In fact, the therapeutic success of many pharmaceutical remain moderate because of their low penetration across BBB, which limits their targeting. Therefore, carrying sufficient drugs through BBB becomes a long-term issue. Despite such phenomenal advances in medicinal applications, the clinical implication of native curcumin is hindered due to poor aqueous solubility, physicochemical instability, low compatibility, rapid metabolism, and poor pharmacokinetics.[83] Therefore, low compatibility and low bioavailability may hinder its usefulness as a therapeutic agent. Once the defy of low bioavailability is overcome, curcumin-based medications for AD might be in the prospect.

In view of nanoparticles posture that is extensively researched in many fields, that provides this new approach for facilitating the efficiency of disease therapy particular in neurodegenerative diseases including AD. According to the abovementioned five natural compounds for AD treatment in clinical trial, however, no extensive studies on the potential pharmaceutical applications of combinations of Epigallocatechin gallate, *EGb-761*, and *Scyllo-inositol* with nanoparticles and their synergistic effects have been performed. Furthermore, conventional strategies failed to treat AD in clinical trials, partly due to the poor solubility, low bioavailability, and ineffectiveness of the tested natural compounds to cross BBB. We will plausibly deliberate the beneficial effect or potency of nanocarriers conjugated with two natural compounds (resveratrol and curcumin) and feasibly postulate a potential natural candidate quercetin to complement a new expectation for AD treatment.

Nanoparticles conjugated natural products for AD

The nanocarrier formulations, which are featured in its particle size, adjustable component, and surface charges, have demonstrated to encapsulate commercial drugs or molecules.[84,85] The technique may provide an alternative way to augment drug transport through the BBB in neurodegenerative disorders.[86] In addition, by conjugating specific antibodies, nanoparticle may target specific regions.[87] Therefore, to address natural compounds for the brain via nanocarriers becomes a popular topic. Next, we describe nanoparticle as a successful delivery carrier in the development of AD therapeutics and diagnostics.

Nanoparticle-conjugated curcumin

Gold

Gold nanoparticles (AuNPs) are one of the major components of bionanotechnology applications.[88] Special properties of AuNPs are low toxicity, highly biocompatible,[89] well functionalization, and plasmon-based strong optical characters that are used for detection/imaging.[90–92] In addition, curcumin is hydrophobic in nature that shows less solubility limited to therapeutic applications;[93] however, some results show that curcumin is conjugated with hyaluronic acid and polymers on the surface of AuNPs to improve bioavailability.[94,95] In one previous study, curcumin was modified by monocarboxylic acid conjugated with primary amine-terminated silica-coated AuNPs that was applied to evaluate water solubility of conjugated complex (Figure 2A). In nanoparticle conjugated curcumin becomes more water-soluble and can efficiently interact with amyloid protein/peptide, offering enhanced performance in inhibiting amyloid fibrillation and dissolving amyloid fibrils. Curcumin monocarboxylic acid derivative was measured using hen egg white lysozymes compared with naked curcumin and Au-curcumin modification in which Au-curcumin derivatives show high inhibits of Aβ fibrillation and dissolve/disintegrate Aβ fibrils.[96] After this conjugation, the data confirmed to improve the water solubility of curcumin for a promising therapeutic approach. However, unmodified curcumin has poor sensitivity, specifically it is difficult to penetrate the blood–brain barrier, researchers choosing

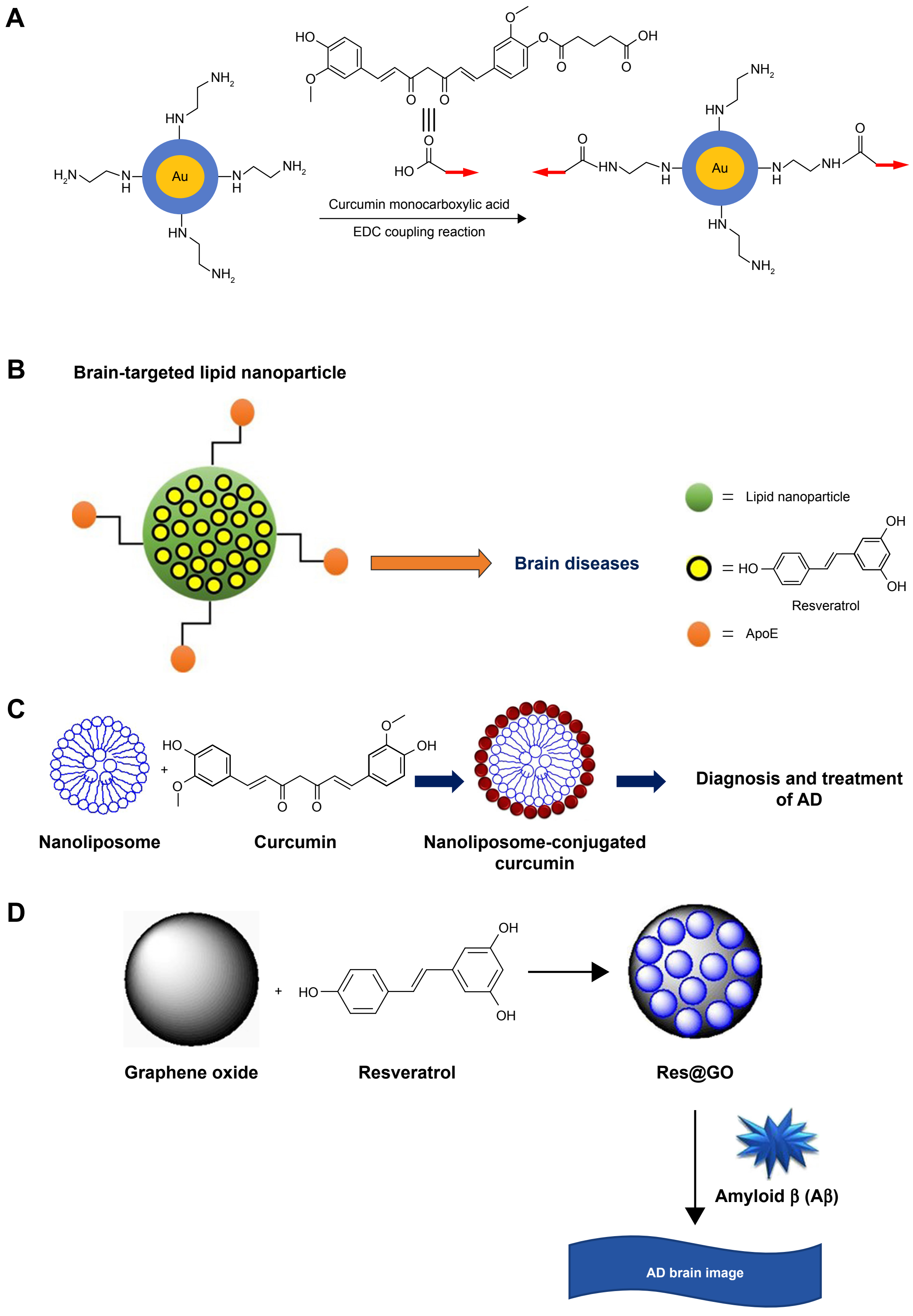

Figure 2 The applications of natural compounds conjugated with nanoparticles.

Notes: (**A**) Synthesis of curcumin-functionalized gold nanoparticles by using EDC coupling. © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. reproduced from Palmal S, Maity AR, Singh BK, Basu S, Jana NR. Inhibition of amyloid fibril growth and dissolution of amyloid fibrils by curcumin-gold nanoparticles. *Chemistry*. 2014;20(20):6184–6191.[96] (**B**) Resveratrol-conjugated solid lipid nanoparticles. Copyright ©2016 Neves et al. Reproduced from Neves AR, Queiroz JF, Reis S. Brain-targeted delivery of resveratrol using solid lipid nanoparticles functionalized with apolipoprotein E. *J Nanobiotechnology*. 2016;14(1):27.[131] (**C**) Nanoliposomes conjugated with a curcumin derivative. (**D**) Simple construction of Res@GO for the rapid fluorogenic probing of Aβ. Adapted with permission from He XP, Deng Q, Cai L, et al. Fluorogenic resveratrol-confined graphene oxide for economic and rapid detection of Alzheimer's disease. *ACS Appl Mater Interfaces*. 2014;6(8):5379–5382. Copyright 2014 American Chemical Society.[132]

Abbreviations: Aβ, beta amyloid; AD, Alzheimer's disease; APP, amyloid precursor protein; APoE, apolipoprotein E; EDC, N-(3-dimethyl amino propyl)-N-ethyl carbodiimide; GO, graphene oxide.

alternatively, the polyhydroxyl substituted squaraine dyes 1–3 under investigation act as effective protein-labeling and destabilizing agents of the protein amyloidogenesis as well.[97] Undeniably, AuNPs were more expensive than silver (Ag). Recently, fluorescence quenching by lipid encased Ag nanoparticle is performed to discover that membrane-inserted Aβ oligomers have a preferred molecular orientation.[98] These new approaches might be useful for accelerating the investigation of molecular mechanism in AD treatment to discover new drug for therapy.

Nanogels

Hydrogels are hydrophilic three-dimensional polymers[99] that are manipulated into nano dimensions called nanogels.[100] The diameter of nanogels varies from 10 to 300 nm and depends on component ratio.[101,102] This nanogel has special features such as high loading capacity and stability and variable environment factors (ionic strength, pH, temperature) that provide a novel platform for drug delivery. Additionally, it has a microheterogeneous structure, small size, and high surface to volume ratio.[103,104] Furthermore, nanogels create hydrophobic interactions that can increase oral and brain delivery of low-molecular-weight drugs and biomacromolecules.[104] Nanogel-conjugated poor water-soluble drugs such as curcumin could improve their bioavailability.[105,106] Another drawback of curcumin was unstable and it is easy to be degraded in alkaline aqueous solutions.[107,108] To overcome this limitation, multifunctional nanogels conjugated with curcumin giving the improvement of stability and the protection of curcumin degradation as well, making curcumin more potentially bioavailable for therapeutic applications in AD that could more efficiently inhibit Aβ fibrillogenesis and amyloid cytotoxicity than those of nonconjugation curcumin.[106]

Polymers

Polymer nanoparticles are characterized as solid and colloidal whose particles size ranges from 10 to 1,000 nm.[109,110] They show excellent properties such as biocompatibility and biodegradability for therapeutic applications.[111,112] Furthermore, hydrophobic drugs such as curcumin conjugated or encapsulated with polymers could enhance the curcumin bioavailability.[113–115] In addition, curcumin encapsulation with poly(butyl)cyanoacrylate nanoparticles was conjugated on outer surface with apolipoprotein E3 to promote therapeutic efficacy against Aβ-induced cytotoxicity in SH-SY5Y neuroblastoma cells; interestingly, poly(butyl)cyanoacrylate-loaded curcumin shows high therapeutic efficacy compared with nonencapsulation curcumin.[116] Water-soluble poly(lactide-co-glycolide) (PLGA) nanoparticle loaded curcumin covalently conjugated with the Tet-1 peptide is able to destroy amyloid aggregation and enhance antioxidative and noncytotoxic properties of this complex are examined by in vitro studies.[117] Another interesting fact is that PLGA nanoparticles encapsulated with curcumin in the ratio of 50:50 (w/w) are able to suppress or cease phosphorylation of protein kinase B (Akt) and tau proteins in human neuroblastoma SK-N-SH cells. The formulations have immense applications in pharmacology and have also been applied to treat neurodegenerative diseases such as AD.[118] The encapsulation of curcumin with PLGA nanoparticles in a diameter that varies from 80 to 120 nm is nontoxic to the SK-N-SH cells and protects neurons from oxidative damage in AD.[119] In recent studies, the functionalization of PLGA nanoparticles with glutathione (GSH) was loaded with curcumin using click reaction innovative strategy for neuronal cell delivery.[120]

Nanoliposomes

Liposome is originally derived from two Greek words: "Lipos" meaning fat and "Soma" meaning body. Liposomes were first described in 1960s by Bangham et al[121] and implicated as a potential drug delivery system in early 1970s.[122,123] Liposomes are made up of phospholipids and are self-enclosed to form spheres of lipid bilayers and with an aqueous core in its bilayers. Owing to the side of the hydrophobic and hydrophilic character (in addition to biocompatibility), liposomes are accomplished systems for drug delivery.[124]

Curcumin shows high affinity for Aβ peptide with the fluorescence character, however, extremely low aqueous solubility limits its clinical use. Thereby, curcumin-conjugated nanoliposomes were designed for monitoring the amyloid peptide deposits as they were more stable and appeared as monodisperse. They had nontoxic in vitro properties, down-regulated the secretion of Aβ peptide, and partially prevented Aβ-induced toxicity. Additionally, this conjugation firmly marked Aβ deposits in postmortem brain tissues of AD patients and APP/PS1 mice. Moreover, curcumin-conjugated nanoliposomes were injected into the hippocampus and the neocortex of APP/PS1 mice; the data showed that curcumin nanoliposomes were specifically stained in the Aβ deposits in vivo. Therefore, curcumin-conjugated nanoliposomes could discover the application of diagnosis and targeted drug delivery in AD patients (Figure 2C).[125]

Nanoliposomes conjugated with a curcumin derivative formed a planar structure for interaction with Aβ that could be detected by using surface plasmon resonance experiments. The second type of liposomes was conjugated with phospholipid in which the planar structure of curcumin does not show the planner structure. Both types of curcumin-decorated vesicles with diameters between (131–207 nm) and marginally negative ζ-potential values based on their lipid composition. Also, they were highly stable lasting up to 20 days. They likewise showed high integrity during incubation in the presence of plasma protein delivery in AD. In surface plasmon resonance experiments, the measurements of the binding of flowing liposomes to immobilized Aβ 1-42 revealed that the liposomes exposing to the curcumin derivative (maintaining the planarity) have an extremely high affinity for Aβ 1-42 fibrils (1–5 nM), owing to the occurrences of multivalent interactions; whereas nonplanar curcumin did not bind to Aβ 1-42. However, curcumin derivative demonstrated that planar with a high affinity for Aβ 1-42 fibrils is taken into considerations as vectors in the targeted delivery of new diagnostic and therapeutic molecules for AD.[126]

Nanoparticle-conjugated resveratrol

Resveratrol (Res), a polyphenol compound, has shown great significance in therapeutic effects, including anticancer, antioxidation, and anti-inflammation. However, there are some limitations in pharmacokinetic characters such as low aqueous solubility and poor bioavailability. Recently, nanoformulations are viewed as a novel technique for enhancing the pharmacokinetic features as well as enhancing target ability and bioavailability of Res.[127] Also, Res is able to inhibit the formation and aggregation of Aβ peptides, which are liable for neuronal dysfunction and death associated with AD due to its ROS-generating action.[128] When rats received a single intracerebroventricular injection of Aβ 1-42 (2 nmol), and 1 day after Aβ infusion, they were intraperitoneally administered either free Res or (Res)-loaded lipid-core nanocapsules (5 mg/kg, each 12 hours) for 14 days. Aβ 1-42-infused animals were proved to be a significant impairment of learning memory capacity, which was associated with a significant decrease in hippocampal synaptophysin levels. Furthermore, astrocytes and microglial cells of animals are activated as well as the disturbance in c-Jun N-terminal kinase and glycogen synthase kinase-3β (GSK-3β) activated, beyond destabilization of β-catenin levels. These results remarkably reveal that by utilizing lipid-core nanocapsules, Res could protect the deleterious effects of Aβ 1-42 while treatments with Res alone present only partial beneficial effects. The increase of Res concentrations might explain these findings in the brain tissues achieved by lipid-core nanocapsules.[129] It is noteworthy that AD treated with grape skin and grape seed extracts increases the inhibitory effect on Aβ aggregation. However, after intravenous injection, Res is rapidly metabolized into both glucuronic acid and sulfate conjugated with the phenolic groups in the liver and intestinal epithelial cells (within $<$2 hours), which are then eliminated. A recent report has demonstrated that solid lipid nanoparticles (SLNs) functionalized with the antitransferrin receptor monoclonal antibody (OX26 mAb) can work as a possible carrier for transporting this extract to target the brain. In human brain-like endothelial cells, experiments illustrate that the cellular uptake of the OX26 SLNs is considerably more efficient than that of normal SLNs and SLNs functionalized with an nonspecific antibody. Consequently, the transcytosis ability of these different SLNs is higher when functionalized with OX26.[130] On the contrary, Res encapsulation SLNs were functionalized with apolipoprotein E, which can be perceived by the overexpressed BBB of low-density lipoprotein receptors (Figure 2B). In vitro cytotoxicity of hCMEC/D3 cell line assessed by MTT and LDH assays, the results revealed no toxicity up to 50 μM over 4 hours of incubation. The permeability through hCMEC/D3 monolayers showed a significant increase (1.8-fold higher) in Res encapsulation of SLNs functionalized with apolipoprotein E compared with nonfunctionalized ones.[131]

Additionally, Res is performed to detect AD for increasing an advantageous potential of the real-time probing concerning Aβ that is closely implicated in AD or ought to assist higher understanding or monitoring the disease. Res combined with graphene oxide (GO) for the rapid, fluorogenic recognition of Aβ. This Res@GO composite could capture both Aβ monomers and fibers in a physiological buffer solution within 3 minutes that have been proved in this study. And Res@GO composite can be used to detect the fluorescent image of Aβ deposits in a mouse brain within 30 mins. This instant protocol is much cheaper and faster than conventional immunofluorescence staining technique clinically employed and provides an economic approach for detection of AD (Figure 2D).[132]

The potential candidates for AD treatment

Nanoparticle-conjugated quercetin

Quercetin, a flavonoid existing in various foodstuffs, has antioxidative properties and increases GSH levels and antioxidant enzyme function. Extensive consideration has focused on increasing the intracellular GSH levels in many diseases, including AD. Aβ 1-42 peptide when elevated in the brain of AD is associated with oxidative stress and neurotoxicity.[133] In this study, nanoparticle-conjugated quercetin plays an important role in AD as the results demonstrated that neuronal cell death is attributable to metal-induced oxidative stress. Prominent among redox active metals initiating oxidative stress is Cu(II). Bioactive hybrid nanoparticles are developed for overcoming oxidative stress, and they are capable of working as host carriers for potent antioxidants such as the quercetin is detected in the release profiles of the loaded nanoparticle under oxidative stress in neuronal cultures. The bioactivity profile of quercetin nanoparticles in a neurodegenerative environment brought on by Cu(II) denotes the improved specificity of antioxidant reactivity counteracting oxidative stress and sets the stage for the development of molecular protection and preventive medical nanotechnology of relevance to neurodegenerative AD.[134]

PLGA nanoparticles conjugated quercetin

In vitro cytotoxicity studies of PLGA-conjugated quercetin (PLGA@QT)NPs inhibited and disassembled Aβ_{42} fibrils neuroblastoma in SH-SY5Y cells; PLGA@QTNPs led to a concentration behavior with low cytotoxicity, illustrating that PLGA@QTNPs can inhibit the neurotoxicity of Zn^{2+}-Aβ_{42} system and improve the viability of neuron cells. Additionally, PLGA@QTNPs are injected into APP/PS1 mice that led to partially abrogate memory impairments and also ameliorate cognition. Most interestingly, in vivo systemic toxicity of PLGA@QTNPs did not show any deterioration according to the histological analysis of significant organs in mice. Thereby, quercetin-based nanocarrier can augment therapeutic effects and subsequently reduce side effects, suggesting that the PLGA@QTNPs may be a potential candidate for AD treatment.[135]

Conclusion

Searching natural sources to be exploited as a complementary and alternative medicine such as nutraceuticals to meet urgent demand for the treatment of neurodegenerative disease has become a critical issue. Evidence base shows some natural compounds that contained the potential for AD treatment. However, the characters of natural compounds hindered the divergence including low water solubility, physicochemical instability, low aqueous stability, low bioavailability, low biocompatibility, rapid metabolism, and poor pharmacokinetics. This discrepancy leads to low efficacy of compounds in medical use. Nanoparticles possessing the unique properties become a new approach to improve this weakness. The nanocarrier formulations are featured in its particle size, adjustable component, and surface charges, which have been demonstrated to encapsulate commercial drugs or molecules. Hereby, nanoparticles conjugated with natural products could enhance the bioavailability and promote the efficacy of AD therapy when compared with naked drugs. Achievably, new delivery strategy creates and implements a new hope for drug discovery and is more effective for the application in the treatment of neurodegenerative diseases including AD. We warrant further studies in human subjects using nanocarriers conjugated with these potential natural compounds.

Author contributions

KRK, S-HY, and L-WW contributed to this review article writing. Both C-HL and C-FW executed as a supervisor to discuss and modify this manuscript. All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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