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REVIEW ARTICLE

Natural Product-based Nanomedicine: Recent Advances and Issues for the Treatment of Alzheimer's Disease

Choy Ker Woon[1], Wong Kah Hui[2], Razif Abas[3], Muhammad Huzaimi Haron[4], Srijit Das[5] and Teoh Seong Lin[6,*]

[1]Department of Anatomy, Faculty of Medicine, Universiti Teknologi MARA, 47000 Selangor, Malaysia; [2]Department of Anatomy, Faculty of Medicine, Universiti Malaya, 50603 Kuala Lumpur, Malaysia; [3]Department of Human Anatomy, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Selangor, Malaysia; [4]Department of Pharmacology, Faculty of Medicine, Universiti Teknologi MARA, 47000 Selangor, Malaysia; [5]Department of Human and Clinical Anatomy, College of Medicine and Health Sciences, Sultan Qaboos University, Al-Khoud, Muscat 123, Sultanate of Oman; [6]Department of Anatomy, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Kuala Lumpur, Malaysia

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Abstract: Alzheimer's disease (AD) affects the elderly and is characterized by progressive neurodegeneration caused by different pathologies. The most significant challenges in treating AD include the inability of medications to reach the brain because of its poor solubility, low bioavailability, and the presence of the blood-brain barrier (BBB). Additionally, current evidence suggests the disruption of BBB plays an important role in the pathogenesis of AD. One of the critical challenges in treating AD is the ineffective treatments and their severe adverse effects. Nanotechnology offers an alternative approach to facilitate the treatment of AD by overcoming the challenges in drug transport across the BBB. Various nanoparticles (NP) loaded with natural products were reported to aid in drug delivery for the treatment of AD. The nano-sized entities of NP are great platforms for incorporating active materials from natural products into formulations that can be delivered effectively to the intended action site without compromising the material's bioactivity. The review highlights the applications of medicinal plants, their derived components, and various nanomedicine-based approaches for the treatment of AD. The combination of medicinal plants and nanotechnology may lead to new theragnostic solutions for the treatment of AD in the future.

Keywords: Alzheimer's disease, amyloid-β, nanoparticles, blood-brain barrier, phytochemicals, drug delivery.

1. INTRODUCTION

Alzheimer's disease (AD) is the most frequent cause of dementia in the world, and its prevalence is on an increasing trend due to the world's aging population [1]. AD is an irreversible, progressive and degenerative brain disease that causes moderate memory loss in its early stage [2]. The disease gradually erodes memory and thinking abilities, eventually rendering patients unable to carry on a conversation or respond to their surroundings in the later stage [2]. According to the 2016 World Alzheimer Report, there are approximately 46.8 million individuals worldwide, who suffer from AD. The number of AD patients is anticipated to nearly quadruple every 20 years, bringing the total population of AD to 74.7 million in 2030 and 131.5 million by the year 2050 [3]. After cardiovascular and cerebrovascular disorders and malignant tumors, AD is considered as the third leading cause of disability and mortality among aged individuals. Till date, the pathophysiology of AD is still not fully understood because of the complexity of human brains, lack of acceptable animal models, and research tools.

AD can be classified by the onset of symptoms: early (between a person 30's and mid-60s) or late onset (first appearing in their mid-60s). In patients with early-onset AD, a non-memory phenotype is typical and patients present with common symptoms of apraxia or visuospatial impairment [4]. Dementia is the most frequent form of late-onset AD. Unlike early-onset autosomal dominant AD, which is connected to amyloid-β (Aβ) abnormalities, the pathophysiology of late-onset AD is yet unknown [5]. According to the current research, late-onset AD is a polygenic illness involving abnormal interactions among numerous molecular pathways. Age is the most significant risk factor for AD, followed by the ε4 allele of apolipoprotein E gene (*APOE***ε4*), cardiovascular and lifestyle risk factors [5]. The clinical manifestation of age-related neurodegenerative illness includes a progressive loss of memory and other cognitive skills. The clinical presentation that meets numerous criteria, as well as fluid and imaging indicators, are used to make a diagnosis in AD [1].

*Address correspondence to this author at the Department of Anatomy, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Kuala Lumpur, Malaysia; Tel: +603-91458635;
E-mail: teohseonglin@ppukm.ukm.edu.my

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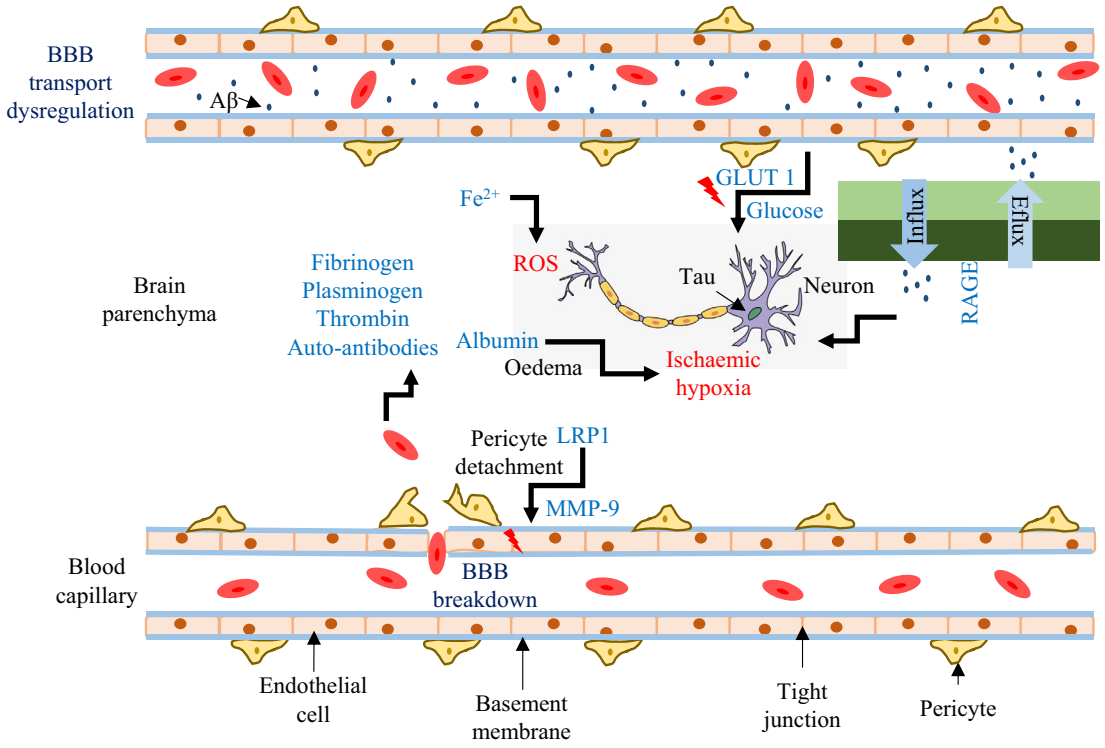


Fig. (1). The disruption of the BBB and dysregulated transport networks contribute to the development of neurodegenerative alterations, the accumulation of Aβ and tau pathology, and neuronal death, as shown in this graphical abstract of AD animal model. Breakdown of the BBB causes perivascular buildup of blood-derived neurotoxic chemicals which lead to oxidant stress in neurons (1) and eventually contributing to hypoperfusion, edema and tissue hypoxia (2). BBB disintegration is caused by degradation of BBB tight connection and basement membrane molecules (3). A loss of equilibrium between Aβ efflux and influx over the BBB occurs when BBB transport is disrupted (4). The downregulation of BBB GLUT1 transporter hastens the breakdown of the BBB and the development of Aβ pathology, as well as tau pathology and neuronal death (5). The elevated RAGE expression at the BBB also contributes to Aβ buildup in the brain (6). *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

2. ROLE OF BBB IN THE PATHOGENESIS OF AD

An important neuropathological feature of AD is the accumulation of toxic oligomers, such as hyperphosphorylated-tau in neurofibrillary tangles, and Aβ in plaques [6]. The pathogenesis of AD was suggested to be initiated by the formation of Aβ oligomers in cortical neurons, which would catalyze the formation of tau oligomers. Both Aβ oligomers and the toxic tau oligomers lead to synaptic and neuronal dysfunction, and eventually neuronal loss [7].

Currently, there is also increasing evidence demonstrating numerous alterations in cerebral vasculature and the blood-brain barrier (BBB) occur in AD. Recent neuroimaging investigations in individuals with mild cognitive impairment and early AD revealed a disruption of the BBB in the hippocampus and various grey and white matter regions before brain atrophy or dementia [8]. Additionally, cerebrospinal fluid analysis of pericyte damage and BBB integrity breakdown were related to the severity of AD pathology [9]. The BBB is a dynamic interface made up of capillary endothelial cells that are intimately connected by tight intercellular junctions and have a high trans-endothelial electrical resistance [10]. The BBB regulates the composition of the internal milieu of neurons, which is necessary for appropriate neuronal and synaptic function. The breakdown of the BBB causes perivascular build-up of blood-derived neurotoxic chemicals in the brain, such as free iron (Fe^{2+}), which produces reactive oxygen species (ROS) and causes oxidant stress; plasma proteins such as fibrinogen, plasminogen, thrombin, and autoantibodies, which may lead to neuronal injury, and inflammatory response; and albumin, which may contribute to the development of oedema, hypoperfusion, and tissue hypoxia [11]. The detachment of pericytes inhibits the proinflammatory cyclophilin A (CypA)-matrix metallopeptidase-9 (MMP-9) pathway on MMP-9 *via* low-density lipoprotein receptor-related protein-1 (LRP1), resulting in BBB tight junction and basement membrane protein degradation [12]. On the other hand, the balance between Aβ efflux (decreased LRP1 receptor expression) and influx (increased receptor for advanced glycation end products (RAGE) expression) via the BBB was shown to be dysregulated in AD [13]. Glucose uptake in the brain across the BBB is also decreased in AD due to the downregulation of GLUT1 transporter at the BBB, which exacerbates AD cerebrovascular degeneration and cognitive function [14]. The disruption of the BBB contributed to the development of neurodegenerative alterations in AD are shown in the Fig. (**1**).

3. TREATMENT MODALITIES OF AD

Several hypotheses have been used to produce anti-AD medications, including a cascade hypothesis, tau theory, inflammation theory, cholinergic and oxidative stress theory,

and glucose hypometabolism theory [15]. Since the first AD patient was identified a century ago, the Food and Drug Administration (FDA) has approved six medications to treat the disease. However, these approved medications provide only transient and ineffective symptomatic relief, as well as severe adverse effects. The marginal benefits were insufficient to delay the progression of AD. Furthermore, some of these drugs are unable to pass through the BBB. This emphasizes the need for tailored combination therapy for discovering medications that are more effective in treating AD.

3.1. Current Approved Drug Therapy for AD

Although Aβ plaques and neurofibrillary tangles remain to be the hallmark of AD, numerous drugs targeting the production, aggregation, and clearance of Aβ and tau oligomers have failed in clinical trials [16]. The first five drugs approved by the FDA are classified either as cholinesterase inhibitors (CIs) or N-Methyl-D-aspartate (NMDA) antagonists [17]. Drugs categorized under CIs include tacrine (Cognex, First Horizon), donepezil (Aricept, Eisai/Pfizer), rivastigmine (Exelon, Novartis), and galantamine (Razadyne, formerly Reminyl, Ortho-McNeil) [18]. The fifth drug is known as memantine (Namenda, Forest) and categorized under NMDA antagonists that block the NMDA receptors by opposing glutamate activity [17]. FDA has recently granted approval for aducanumab, a human IgG1 anti-Aβ monoclonal antibody (Aduhelm, Biogen), the first disease-modifying therapy for AD as per notification on June 7, 2021 [19]. However, the approval of this drug has been debated since it was based on the reduction of Aβ and not on clinical efficacy of the drug [19, 20].

These approved drugs improved the clinical signs of AD. The average effects of CIs on cognition and function are moderate, and response rates are diverse, with about a third of patients showing no benefits and a smaller proportion (about one-fifth) exhibiting a greater benefit [21]. Additionally, many studies have reported numerous adverse effects of AD drug therapies such as liver damage, gastrointestinal based adverse reactions, sleep disorders, dizziness, headache, somnolence, constipation, and hypertension [17, 22-25].

Approximately 8% of hospital admissions in the United States of America are caused by adverse effects of synthetic drugs [26]. It was also reported that approximately 100,000 individuals die each year due to drug toxicity [27]. In comparison, the cases of toxicity and death are rare with consumption of herbal product. This has prompt researchers to search for alternative to synthetic drugs therapies from natural resources. Clinical drug treatment merely relieves the symptoms of any disease rather than preventing its progression [28]. In contrast, the active components present in natural product are hypothesized to act in an additive or synergistic manner on several molecular targets [29]. Hence, there is an urgent need to look for alternative to the existing synthetic drugs.

3.2. Complementary and Alternative Therapies for AD

Other therapies for AD include non-cholinergic therapeutic approaches such as vitamin therapy [30], antioxidants [31], antihypertensive or lipid-lowering medications [32], stem cell therapy [33], hormonal therapy [34], selective phosphodiesterase inhibitors [35] and nonsteroidal anti-inflammatory drugs (NSAIDs) [36]. Other neurotransmitter-based therapies such as GABAergic modulators, serotonin receptor modulators, histaminergic modulators, and adenosine receptor modulators have also been researched [37]. Stimulatory therapies such as physical workouts, psychotherapy, socialization and music have been explored as well [38].

Selective phosphodiesterase inhibitors have been proposed as another potential new therapy for preventing the course of AD and related dementia caused by pharmaceutical drugs, aging, and mutations in human amyloid precursor proteins (APP) [35]. In transgenic mouse models, inhibitors of β-secretase (BACE)-1 were shown to reduce brain Aβ and improve cognition [39]. Although γ-secretase enzyme inhibitors were also proposed as anti-AD therapy, they showed substantial side effects in experimental animals [40]. Furthermore, primary and secondary natural antioxidants have been shown to reduce neuronal cell death in AD, and thus can be exploited in the development of antioxidative drugs to combat the disease [41]. Antihypertensive medicines were found to lessen the risk of AD and dementia in a clinical trial [42]. Another study found no conclusive evidence for the use of lipid lowering medications in the treatment of cognitive decline and memory impairment [43].

AD patients presented significantly lower blood levels of vitamins B2, C and A compared to the healthy controls [44]. Additionally, AD was reported to be associated with low serum vitamin E level in older individuals [45]. Although nutrition supplements such as antioxidants, inositol, medium-chain triglyceride, omega-3 and vitamins were reported to lower AD risk variables; however, meta-analysis demonstrated that these isolated nutrient supplementations showed no evidence of providing significant benefits related to the clinical manifestations of AD [46-48].

Aromatherapy using various essential oil as complementary therapies is an effective non-pharmacological treatment for neurodegenerative diseases [49]. AD mice exposed to a mixture of rosemary and lemon oil at night-time, and a mixture of lavender and orange oil in the day-time showed improved cognitive function, and reduced Aβ and phosphorylated tau levels in the brain [50]. Similarly, aromatherapy diffused by rosemary and lemon essential oils in the morning or lavender and orange essential oils in the evening was found to improve symptoms and cognition in people with dementia and AD [51]. Hand massage aromatherapy using a mixture of lemongrass essential oil and eucalyptus oil, or aromatherapy inhalation with lavender essential oil was able to improve agitation and neuropsychiatric symptoms significantly in patients with dementia [52]. On the other hand, aromatherapy did not reduce belligerent and resistive behaviors in dementia patients in another trial study [49]. To further assess the efficacy of aromatherapy against dementia and AD, a larger sample size as well as the inclusion of several types of aromatherapy and dementia, are required in clinical trials [49].

3.3. BBB as the Limiting Barriers in Drug Delivery in AD

The brain is the most important organ in the body, with the BBB as its protective barrier [10]. The BBB separates the brain from the systemic circulation and serves as the major

route for medications to reach the central nervous system (CNS). The BBB's major function is to provide nutrients to the brain, maintain ionic homeostasis for neuronal activities, and protect the brain from dangerous or toxic chemicals through selective transport systems [53]. The BBB is also the major obstacle to effective therapeutic medication transport to the CNS [10].

Furthermore, the CNS has other functional barriers, such as influx and efflux transporters, that allow xenobiotics to enter and exit the CNS [54]. Enzymes in the brain such as peptidase and cholinesterase also act as a barrier to drug delivery, degrading them and reducing their concentration in the brain. The general consideration for any neurotherapeutics should be lipid soluble have a relatively small molecular weight of less than 500 Da, have a partition coefficient (pKa) between 0.5 and 6.0, and be either neutral or generally neutral (*i.e.* uncharged) at physiological pH in order to easily cross the BBB by passive diffusion [55]. However, a recent study found numerous outliers to this generalised pattern. Large molecules such as CINC-1 can penetrate the BBB via transmembrane diffusion, but very lipophilic compounds may not be able to do so at sufficient concentrations [56]. Molecules with a polar surface area more than 80, high H-bonding affinity, and a chemical structure that is heavily branched are poor candidates for crossing the BBB [57]. As a result, it is critical to consider these factors while developing possible new drugs for the treatment of AD.

Numerous new approaches for therapeutic drug groups and drug delivery systems are being developed to overcome the BBB restriction to provide a more effective delivery of medications into the CNS [58]. One of the approaches is the use of nano-drug delivering systems. In the case of nano particles (NPs)-based pharmacotherapy for AD, certain attempts have been made to encapsulate various types of neurotherapeutics into NPs for targeted delivery to the CNS [59]. Other studies focused on developing NPs to help amyloid clusters avoid toxicity by boosting systemic clearance or altering their aggregation dynamics in the brain and blood [59]. In fact, the "sink effect", or peripheral treatment with neurotherapeutics that have a substantial affinity for Aβ, can diminish the level of Aβ in the brain. Sequestered plasma Aβ is then guided to hepatic and splenic macrophages for destruction by surface engineered/targeted NPs with a considerably high affinity for Aβ [59].

4. NATURAL PRODUCT-DERIVED NANOPARTICLES AND THEIR THERAPEUTIC EFFECTS ON AD

Traditional medicines have been used as complementary therapeutic agents for the treatment of various neurodegenerative diseases [60-63]. Holistic practitioners commonly use traditional medicines as they are well accepted and relatively safer compared to synthetic drugs. One of the key distinguishing attributes of traditional medicines is their affinity for the target protein or specific biomolecule in humans. Moreover, 88% of World Health Organization (WHO) Member States have acknowledged the use of traditional medicine corresponding to 170 Member States. Over the past decade, approximately 80% of the world population has been using herbal medicines to complement their basic health needs [64].

Research has been redirected to focus on the studies of bioactive compounds, chemical composition and therapeutic potentials in the anticipation of discovering active ingredients with minimal adverse effects arising from natural sources [65]. In contrast to synthetic compounds, the biological compounds possess more chiral centers (more carbon, hydrogen and oxygen but less nitrogen); higher molecular weight as well as higher polarities [62]. Biological compounds also contain more sp^3-hybrid carbon atoms allowing the tetrahedron carbons to form flexible chains or cyclic structures, whereas the multi-functional groups make them bind strongly to the biological targets and increase the additional interactions with biological molecules [66]. The intrinsic complexity of natural products can become the substrate for one or more of the transporter systems for the targeted intracellular delivery [67].

Nevertheless, the discovery of natural products has been associated with several issues. The variability in the composition of natural products is owing to factors, such as environmental variations, which remain a major challenge for the development of botanical drugs. For instance, stress and defense responses stimulate metabolic changes that may result in a composition disparity in the biosynthesis of bioactive compounds having pharmaceutical or nutritional value [68]. In addition, high molecular weight of plant derived-phytochemical compounds, namely phenols, flavonoids, alkaloids, cardiac glycosides, saponins, terpenoids, steroids and tannins have been a great concern in assessing therapeutic efficacy due to their poor permeation through lipid bilayers, resulting in reduced bioavailability in humans [69].

Considering the emerging trends in nanotechnology, it has become possible to address the issues and revolutionize the development of formulations of natural products, allowing the application of these compounds on a large scale [70]. Nanotechnology offers multiple advantages in treating chronic diseases by improving plasma bioavailability, targeting sites and controlled release. Accumulating evidence has demonstrated that nanomaterials derived from natural products could delay the development of drug resistance, which might potentially improve poor response to approaches in modern medicine [71]. In the present review, we highlight some of the phytochemicals and natural products incorporated into nanomaterials, and their potential use in the treatment of AD (Fig. **2**, Table **1**).

4.1. Curcumin

Curcumin is a polyphenol that is present as the main constituent of the rhizomes of turmeric *Curcuma longa*. In general, curcumin was reported to possess antibacterial, anti-inflammatory, antiseptic, antioxidant, antimalarial, hypolipidemic and hepatoprotective effects [72]. Curcumin treatment was shown to ameliorate cognitive impairment, improve neurogenesis and reduce amyloid plaque burden in AD models [73, 74]. However, curcumin's structural-pharmacokinetic properties, *e.g*., low water solubility, high lipophilicity, metabolic instability, and hardly being dissolved in the gastrointestinal aqueous fluid, have limited its application in the pharmaceutical field [75]. Additionally, curcumin has poor permeability across the BBB [76].

Loading curcumin into NPs is one of the strategies to enhance the delivery of curcumin to the brain. Curcumin

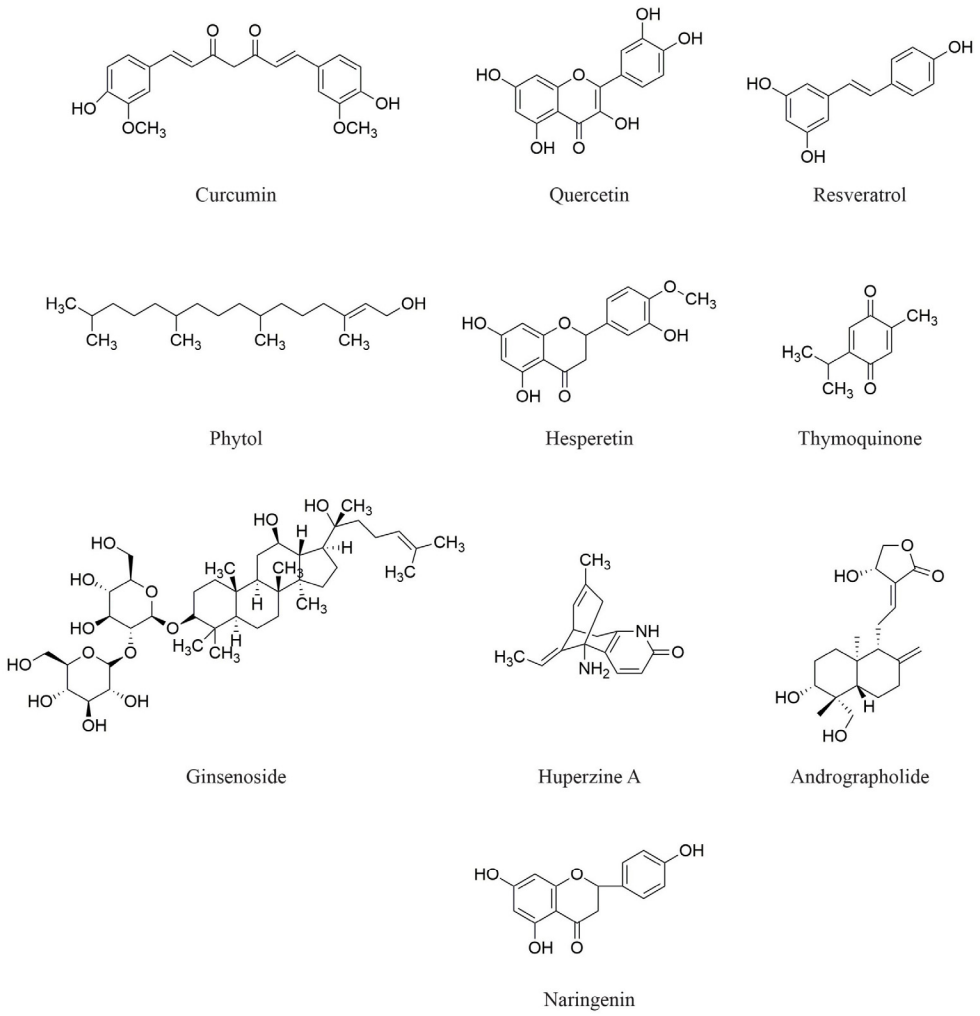


Fig. (2). Phytochemical for the natural product involved in AD.

loaded to polylactide-co-glycolic-acid (PLGA) NPs and chitosan-bovine serum albumin NPs was shown to improve the penetration of curcumin across the BBB, compared to free curcumin [77, 78]. Furthermore, curcumin-loaded NPs treatment significant decreased Aβ aggregates, and improved spatial learning and memory capability in *in vitro* and *in vivo* AD models [79-81]. Gao *et al.* [82] developed a curcumin-loaded red blood cell membrane-coated PLGA NPs to stabilize and promote sustained curcumin release, thus providing improved biocompatibility to treat AD. The concentration of curcumin in the brain was six-fold higher in the intravenously administered NPs group, compared to that of the free curcumin treated group [82]. More importantly, no toxicity effects were observed in the NPs-treated mice [82, 83].

In addition to the widely used intravenous and intraperitoneal administration of curcumin-loaded NPs, the intranasal route may be an alternative for the delivery of curcumin to the brain. While using 2% crosslinked starch curcumin-loaded amylolipid nanovesicles, curcumin was detected in an average of 140 ng/g brain levels and 12 ng/mL plasma concentrations following one hour after intranasal administration of 160 μg/kg of curcumin [84]. Similarly, curcumin-encapsulated chitosan-coated PLGA NPs administered intranasally also showed a much higher concentration of curcumin in the brain compared to the plasma [85]. These studies suggested that intranasal administration would allow the majority of the curcumin to be transported to the brain via olfactory and trigeminal pathways, compared to the systemic circulation [85].

4.2. Quercetin

Quercetin is a common flavonoid present ubiquitously in fruits and vegetables. It has been shown to exhibit cardioprotective, neuroprotective, gastroprotective, anticarcinogenic, antimicrobial, anti-malarial, anti-inflammatory, antioxidative, immunomodulatory and bone-conserving properties [86, 87]. Quercetin treatment was shown to inhibit Aβ aggregation, tau hyperphosphorylation, and ameliorate neurogenesis through the modulation of multiple signaling pathways, such as PI3 kinase, AKT/PKB tyrosine kinase and protein kinase C in AD [88]. Similar to curcumin, quercetin's instability, low aqueous solubility and poor permeability has limited the application of developing quercetin as a clinical drug [89].

NPs can protect unstable phytochemicals against degradation. Quercetin loaded into lipid NPs (solid lipid NPs and

nanostructured lipid carriers) were shown to be protected against UV-induced photodegradation, where 55% of free quercetin was photodegraded, compared to only 10% of quercetin loaded lipid NPs degraded [90]. Additionally, the quercetin loaded lipid NPs showed no cytotoxicity effects and good permeability through human cerebral microvascular endothelial hCMEC/D3 cells, a widely used BBB *in vitro* model [90, 91].

Free quercetin has low bioavailability in the brain [92]. Animals treated with quercetin loaded to zein NPs showed a significant increase in brain concentration of this flavonoid, compared to free quercetin-treated mice [92]. The increase in bioavailability of quercetin was also shown in other types of NPs, *e.g*., superparamagnetic iron oxide NPs [93] and plasma exosomes [94].

In vivo experiments showed that quercetin-loaded NPs exhibited potent anti-amyloid and antioxidant activity as evident *via* inhibition of Aβ aggregation, decreased Aβ-induced oxidative stress and protected cells from Aβ-mediated cytotoxicity [89, 95-97]. Similarly, intravenous and oral administration of quercetin-loaded sulphur NPs improved the learning and memory deficits and inhibited neuronal loss in animal AD models [94, 98, 99]. Furthermore, oral supplementation of superparamagnetic iron oxide NPs, increased the antioxidant enzymes (SOD1, GPX1 and CAT) and anti-apoptotic genes (BCL2 and BAX) genes expression in aluminium chloride ($AlCl_3$)-induced AD rats [100].

4.3. Resveratrol

Resveratrol is a polyphenol present in red wine, grapes, berries, pomegranates and peanuts, that has been reported to possess pharmacological activities such as antioxidant, anti-inflammatory, anti-aging and anti-cancer effects [101, 102]. Numerous studies have demonstrated consistent neuroprotective effects of resveratrol in AD models due to mechanisms such as inhibition of Aβ plaque accumulation and hyperphosphorylation of tau protein [103].

Resveratrol coated onto solid lipid NPs and selenium NPs showed no cytotoxicity on the cells and was able to permeate well through BBB *in vitro* models [104-106]. Additionally, the antioxidative effect of resveratrol coated selenium NPs protect cells from Aβ-induced cell apoptosis and prevents ROS generation [105].

Free resveratrol is rapidly metabolized in the liver and intestine, which is then eliminated within 2 hours following intravenous injection, greatly limiting its pharmacological benefits [107]. With the advantage of physicochemical properties of NPs and red blood cell (RBC) membrane, resveratrol loaded onto RBC membrane-coated nanostructured lipid carriers (NPs@RBCm) improved resveratrol biocompatibility and long-term circulation. High accumulation of NPs@RBCm was detected in the brain, after 30 mins of its intravenous administration [108]. Furthermore, treatment with 2 mg/kg body weight of RSV NPs@RBCm every two days for a total of 30 days improved memory impairments, reduced the lipid peroxidation damage and restored antioxidant enzyme levels in transgenic APP/PS1 mice [108]. Intranasal administration of resveratrol-coated NPs showed a higher resveratrol concentration in the brain, compared to oral administration where the highest resveratrol concentration was observed in the liver [109]. Additionally, nanostructured hydrogel gel showed fivefold higher permeation of resveratrol across the nasal mucosa compared to resveratrol suspension-based *in situ* gel [110]. Most importantly, intranasal administration of resveratrol-coated gold NPs demonstrated no toxicity in the olfactory epithelium and improvement in learning in the rats [111].

4.4. Phytol

Phytol is a diterpene constituent of chlorophyl and is known for its anti-inflammatory and anticarcinogenic properties [112, 113]. Phytol-loaded PLGA NPs was shown to exhibit anti-cholinesterase activity, inhibit Aβ aggregation and protect Neuro2a cells from Aβ toxicity [114]. Transgenic *Caenorhabditis elegans* AD model received phytol-loaded PLGA NPs treatment, which was shown to increase lifespan, suppress defect in chemotaxis behavior and attenuate intracellular ROS production level [115]. Similarly, oral administration of phytol-loaded PLGA NPs (100 and 200 mg/kg) for 14 days was able to ameliorate the cognitive deficits caused by scopolamine, a muscarinic acetylcholine receptor antagonist, on spatial and short-term memory in Wistar rats [116]. The study also demonstrated that phytol-loaded PLGA NPs possess a strong penetration capacity to cross the BBB *in vivo* [116].

4.5. Thymoquinone

Seeds of *Nigella sativa,* commonly known as 'black seed' have been used to treat various diseases for centuries. The main constituent in *N. sativa* seeds is thymoquinone, a monoterpene molecule which is known to exhibit anti-inflammatory, antioxidant, antimicrobial, anti-cancer, antidiabetic, antihistaminic, anticonvulsant and wound healing effects [117, 118]. Preclinical studies demonstrated *N. sativa* and thymoquinone to exhibit neuroprotective effects via their antioxidant properties, which ameliorate neuro-inflammation and neurodegeneration changes in the AD models [119].

The bioavailability of thymoquinone is limited in the brain due to its high lipophilicity. Intraperitoneal administration of thymoquinone-loaded mesoporous silica NPs was able to enhance thymoquinone delivery to brain regions such as the cortex, thalamus, hypothalamus and midbrain, and shown to reduce oxidative stress in these regions, compared to free thymoquinone [120]. Similarly, treatment with polysorbate-80 coated PLGA thymoquinone NPs passed through the BBB successfully and ameliorated protein aggregates in the brains of streptozotocin-induced AD mice [121]. Nanoemulsion of thymoquinone showed neuroprotective effects against high fat/cholesterol diet-rats by reducing Aβ production and by increasing the APP processing, Aβ degradation and insulin degrading enzyme [122].

4.6. Ginsenoside

Ginseng derived from the roots of *Panax ginseng* Meyer has long been used as a traditional medicine and food supplement. Ginseng and its active ingredients, ginsenosides, have been reported to exhibit various pharmacological effects such as immune-modulatory, anti-inflammatory, antioxidative, anti-diabetic, anticarcinogenic, anti-aging, antidepression, delaying of neurodegenerative process and improvement of memory [123]. Treatment with red ginseng

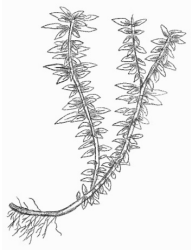
Table 1. Natural product-derived nanoparticles and their therapeutic effects on AD.

Variety	Nanoparticle (Size)	Model	Route	Finding	Refs.
Phytochemicals Loaded Nanoparticles					
Curcumin (*Curcuma longa*) 	PLGA NPs modified with g7 ligand (200 - 250 nm)	Primary hippocampal cell cultures treated with Aβ	-	Partially increased cell viability in cells treated with Aβ Inhibited Aβ aggregation	[79]
	PLGA NPs conjugated with cyclic CRTIGPSVC peptide (< 150 nm)	APP/PS1dE9 mice	Intraperitoneal	Effectively transported across BBB Improved spatial memory and recognition Decreased Aβ, reactive oxygen species (ROS), TNF-α and IL-6 levels Enhanced super oxide dismutase (SOD) activities and synapse numbers	[77]
	PLGA-PEG NPs conjugated with B6 peptide (< 150 nm)	APP/PS1 mice	Intraperitoneal	Improved spatial learning and memory capability Reduced hippocampal Aβ production Decreased tau phosphorylation	[80]
	Chitosan-bovine serum albumin NPs (≈ 140 nm)	Mouse leukemic monocyte macrophage RAW 264.7 cells	-	Effectively permeate through BBB *in vitro* model Improved cellular uptake of curcumin in macrophage Induced $A\beta_{42}$ phagocytosis in macrophage Inhibited M1 macrophage polarization Reduced expression of TNF-α and IL-6.	[78]
	Selenium doped PLGA NPs (≈ 160 nm)	5XFAD mice	Intravenous	Inhibited Aβ aggregation	[81]
	Red blood cell membrane (RBCm)-coated PLGA NPs bearing T807 molecule (< 200 nm)	Okadaic acid (OA)-induced AD mice	Intravenous	Effectively transported across BBB Decreased tau phosphorylation Reduced cell death in the hippocampus Inhibited microglia and astrocytes activations	[82]
	RBCm-coated PLGA NPs bearing T807 and triphenylphosphine molecules (< 120 nm)	OA-induced AD mice	Intravenous	Mitigated mitochondrial oxidative stress Suppressed cell death	[83]
Quercetin	Zein NPs (≈ 260 nm)	Transgenic SAMP8 mice	Oral	Improved cognition and memory impairments Decreased hippocampal GFAP expression	[92]
	Polysorbate 80-coated gold-palladium NPs (< 100 nm)	Human neuroblastoma SH-SY5Y cells treated with Aβ	-	Effectively permeate through BBB *in vitro* model Promote fusion of autophagosomes and lysosomes Accelerated Aβ clearance Protect cells from Aβ-induced cytotoxicity damage	[95]
	Solid lipid NPs and nanostructured lipid carriers (NLC) functionalized with transferrin (≈ 200 nm)	Human cerebral microvascular endothelial hCMEC/D3 cells	-	Effectively permeate through BBB *in vitro* model Inhibited Aβ aggregation	[90]
	Solid lipid NPs and NLC functionalized with RVG29 peptide (< 250 nm)	hCMEC/D3 cells	-	Effectively permeate through BBB *in vitro* model Inhibited Aβ aggregation	[91]

(Table 1) contd….

Variety	Nanoparticle (Size)	Model	Route	Finding	Refs.
-	Sulphur NPs in microbubbles (≈ 50 nm)	APP/PS1 mice	Intravenous	Effectively transported across BBB. Reduced neuronal apoptosis, inflammatory response, calcium homeostasis imbalance and oxidative stress Improved learning and memory impairments Reduced Aβ aggregation Inhibited neuronal loss	[98]
	Modified magnetic core-shell mesoporous silica nano-formulation (200 - 250 nm)	Primary hippocampal cell culture treated with Aβ	-	Inhibit Aβ aggregation Protect cells from Aβ toxicity Reduced Aβ-induced ROS generation	[96]
	Plasma exosomes (≈ 150 nm)	OA-induced AD mice	Intravenous	Increase bioavailability and accumulation of quercetin in the brain Attenuated OA-induced learning and memory deficits Reduced neuronal apoptosis in hippocampus Inhibited tau phosphorylation Reduced formation of neurofibrillary tangles	[94]
	Selenium NPs (≈ 90 nm)	Adrenal pheochromocytoma PC12 cells treated with H_2O_2	-	Inhibit Aβ fibrillation Protected cells from H_2O_2-induced cell death	[97]
	Superparamagnetic iron oxide NPs (30 - 50 nm)	Aluminium chloride ($AlCl_3$) induced AD rats	Oral	Attenuated $AlCl_3$-induced learning and memory impairment Reduced APP gene expression Increase miR-101, antioxidant enzymes (SOD1, GPX1 and CAT) and anti-apoptotic genes (BCL2 and BAX) expression levels	[100]
Resveratrol	Solid lipid NPs functionalized with anti-transferrin receptor monoclonal antibody (≈ 180 nm)	Endothelial cells derived from hematopoietic stem cells isolated from umbilical cord blood	-	Effectively permeate through BBB *in vitro* model Inhibit Aβ aggregation	[104]
	NLC (≈ 155 nm)	*Caenorhabditis elegans*	-	Increased acetylcholine concentration Decrease AChE gene expression Improved memory	[106]
	Selenium NPs (≈ 100 nm)	PC12 cells treated with Aβ	-	Inhibit Aβ aggregation Protected cells from $Aβ_{42}$-Cu^{2+} complexes-induced cell apoptosis Prevented $Aβ_{42}$-Cu^{2+} complexes-induced ROS generation	[105]
	In situ nanostructured hydrogel (≈ 150 nm)	Scopolamine-induced amnesia Wistar rats	Intranasal	Improved memory impairments	[110]
	Gold NPs (≈ 100 nm)	Scopolamine-induced amnesia Wistar rats	Intranasal	Improved learning and memory impairments	[111]
	RBCm-coated NLC bearing rabies virus glycoprotein (RVG29) and triphenylphosphine cation (TPP) molecules (< 160 nm)	APP/PS1 mice	Intravenous	Improved memory impairments Decreased soluble and insoluble $Aβ_{1–42}$ Restored decreased MnSOD level Reduced the lipid peroxidation Decreased GFAP and Iba-1 protein levels	[108]

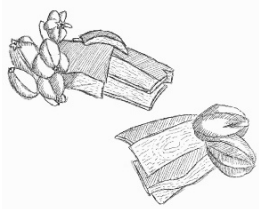
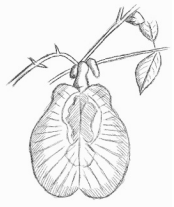
(Table 1) contd….

Variety	Nanoparticle (Size)	Model	Route	Finding	Refs.
Phytol	PLGA NPs (< 200 nm)	Neuro2a cells treated with Aβ	-	Inhibited AChE Inhibited Aβ aggregation Protected cells from Aβ toxicity	[114]
	PLGA NPs (< 200 nm)	Transgenic *C. elegans* AD model	-	Increased lifespan Suppressed neuronal Aβ expression and ROS production Downregulated AD associated genes (Aβ, *ace-1* and *hsp-4*) expressions Upregulated gene involved in the longevity to nematodes (*dnj-14*) Reduced Aβ protein level	[115]
	PLGA NPs (< 200 nm)	Scopolamine-induced amnesia Wistar rats	Oral	Enhanced biodistribution and release profile of phytol in the brain and plasma Ameliorated spatial and short term memory impairment Inhibited AChE, BChE and BACE1 activities Reduced ROS and RNS level	[116]
Thymoquinone (*Nigella sativa*) 	Polysorbate-80 coated PLGA NPs (≈ 200 nm)	Streptozotocin (STZ)-induced AD mice	Intraperitoneal	Increased SOD Ameliorated proteins aggregates	[121]
Ginsenoside (*Panax ginseng*) 	PLGA NPs (≈ 100 nm)	Rat glial C6 cells, human monocytic THP-1 cells	-	Effectively permeate through BBB *in vitro* model Decreased amyloid fibril formation Decreased ROS and RNS activity Reduced AβPP, TNF-α and IL-1β genes expression	[127]
Huperzine A (*Huperzia serrata)* 	PLGA NPs with surface modification by lactoferrin-conjugated N-trimethylated chitosan (≈ 150 nm)	Kunming (KM) mice	Intranasal	Facilitated huperzine A distribution in the brain	[131]
Andrographolide (*Andrographis paniculata*) 	Human albumin NPs (≈ 210 nm)	TgCRND8 mice	Intraperitoneal	Crossed BBB effectively and penetrated undamaged and damaged brain tissues Ameliorated cognitive impairment Reduced astrocyte activation	[133]

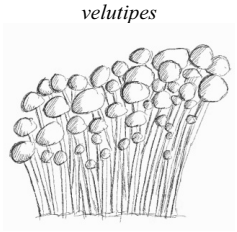
(Table 1) contd….

Variety	Nanoparticle (Size)	Model	Route	Finding	Refs.
Nanoparticles of Phytochemical/Extract					
Hesperetin	Evaporative precipitation of nanosuspension (ND)	STZ-induced AD rats	Oral	Improved memory retrieval and recognition memory consolidation. Increased antioxidant enzymes (SOD, glutathione GPx, GRx and CAT) activity and GSH levels Decreased lipid peroxidation in the hippocampus	[137]
	Evaporative precipitation of nanosuspension (ND)	STZ-induced AD rats	Oral	Reversed anxiogenic-like behavior Reversed STZ-induced lipid peroxidation Elevated antioxidant enzymes (CAT, SOD and GRx) activities and gene expressions	[136]
	Nanocrystal by small-scale milling (< 200 nm)	SH-SY5Y cells harbouring neuronal amyloid precursor protein (APP_{695})	-	Increased mitochondrial ATP levels and respiratory chain complex activity Reduced cytochrome C activity	[138]
Quercetin	Pulsed laser ablation (≈ 50 nm)	SH-SY5Y cells treated with Aβ	-	Inhibited Aβ aggregation Decreased Aβ-induced oxidative stress and Aβ-mediated cytotoxicity	[89]
	Antisolvent precipitation under sonication (520 - 750 nm)	$AlCl_3$ induced AD rats	Oral	Reduced neuronal degenerative changes, amyloid plaques and neurofibrillary tangles formation Upregulated tyrosine hydroxylase	[99]
Thymoquinone (*Nigella sativa*) 	Nanoemulsion (ND)	High fat/cholesterol diet-induced rats	Oral	Reduced brain $A\beta_{40}$ and $A\beta_{42}$ levels Modulated APP and PSEN2 gene Reduced BACE1 and RAGE protein levels Increased IDE and LRP-1 protein levels	[122]
Naringenin	Nanoemulsion (≈ 50 nm)	SH-SY5Y cells treated with Aβ	-	Alleviated Aβ-mediated cytotoxicity Reduced ROS production Downregulated APP and BACE protein level Decreased tau phosphorylation	[142]
Green Synthesized Nanoparticles					
Aqueous extract of aerial part of *Lampranthus coccineus* 	Silver NPs (≈ 30 nm)	$AlCl_3$ induced AD rats	Intraperitoneal	Protection against oxidative damage Inhibition of AChE	[145]
Aqueous extract of aerial part of *Malephora lutea* 	Silver NPs (≈ 30 nm)	$AlCl_3$ induced AD rats	Intraperitoneal	Protection against oxidative damage Inhibition of AChE	[145]

(Table 1) contd….

Variety	Nanoparticle (Size)	Model	Route	Finding	Refs.
Aqueous extract of *Millettia pinnata* flower 	Silver NPs (≈ 50 nm)	-	-	Inhibition of AChE and BChE Exhibited antibacterial and cytotoxicity activities	[147]
Aqueous extract of *Nepenthes khasiana* leaf 	Silver NPs (≈ 15 nm)	STZ-induced AD rats	Intraperito-neal	Ameliorated recognition and spatial memory impairment	[152]
Ethanolic extract of *Terminalia arjuna* bark 	Gold NPs (20 - 50 nm)	-	-	Inhibition of AChE and BChE Exhibited antioxidant property Inhibit Aβ aggregation	[146]
Aqueous extract of *Clitoria ternatea* flower 	Graphene quantum dots (≈ 10 nm)	Scopolamine-induced amnesia Wistar rats	ND	Improved learning and memory capacity Inhibition of AChE Increased glutathione level Decreased lipid peroxide and nitric oxide levels	[153]
Aqueous extract of *Cladospori-um* sp. 	Silver NPs (≈ 24 nm)	-	-	Inhibition of AChE and BChE	[149]

(Table 1) contd….

Variety	Nanoparticle (Size)	Model	Route	Finding	Refs.
Aqueous extract of *Flammulina velutipes* 	Silver NPs (≈ 20 nm)	-	-	Inhibition of AChE and BChE	[148]
Methanolic extracts of *Sabal blackburniana* leaves, fruits, and pollen grains 	Zinc oxide NPs (< 50 nm)	-	-	Inhibition of AChE	[151]
Aqueous extracts of *Sageretia thea* leaves 	Zinc oxide, nickel oxide, iron oxide, lead oxide and cobalt oxide NPs (≈ 20 nm)	-	-	Inhibition of AChE	[150]

extract was shown to improve Aβ accumulation, neuroinflammation, neurodegeneration, and adult hippocampal neurogenesis in transgenic AD mice [124]. Furthermore, treatment with ginsenoside Rb1 and Rg3 was shown to improve cognitive and memory functions by improving the mitochondrial dysfunction and inhibiting the levels of pro-apoptosis mediators in the rat brain [125, 126].

Despite numerous studies demonstrating the potential of ginsenoside in the treatment of AD, there are limited studies using adaptations of nanoformulation of ginsenoside to treat AD. PLGA NPs encapsulated ginsenoside Rg3 was shown to be safe and permeate well through BBB *in vitro* model [127]. Furthermore, the study found that administration of Rg3-encapsulated NPs significantly decreased Aβ fibril formation compared to free Rg3, and was able to decrease ROS activity and reduce AβPP, TNF-α and IL-1β genes expression [127].

4.7. Huperzine A

Huperzine A, a potent AChE inhibitor*,* is an alkaloid isolated from the club moss *Huperzia serrata* [128]. An oral dose of 0.2 mg twice a day for 8 weeks showed significant improvement in cognition and task switching abilities compared with baseline performance [129]. Sheng *et al.* [130] and Meng *et al.* [131] reported an intranasally administered huperzine A complex in the brain. The complex was known as huperzine A -loaded muco-adhesive and PLGA-NPs with external adjustment by lactoferrin-conjugated *N*-trimethylated chitosan (Lf-TMC NPs). The remarkable findings indicate a possible nose-to-brain NP delivery route for the treatment of AD by facilitating the distribution of huperzine A in the brain. The drug targeting index for the olfactory bulb, cerebrum (with hippocampus removal), cerebellum and hippocampus were in the range of 1.6-2.0 [131]. Conversely, *ex vivo* drug release and cell viability assays using 16HBE and SH-SY5Y cells supported the controlled drug release and safety of the developed NPs for intranasal administration [131].

4.8. Andrographolide

Andrographolide is a major diterpenoid of *Andrographis paniculata* and possesses pharmacological activities such as antiretroviral, antibacterial, antimalaria, anti-inflammatory and antioxidant [132]. Andrographolide loaded to human albumin NPs was shown to be able to cross the BBB and penetrate the brain parenchyma of the TgCRND8 AD mouse model following intravenous administration [133]. Furthermore, Bilia *et al.* [133] demonstrated that intraperitoneal injection of andrographolide loaded NPs to AD mice for 4 weeks ameliorated cognitive dysfunctions and reduced astrocyte reaction, indicating the anti-inflammatory property of andrographolide.

4.9. Hesperetin

Hesperetin, a citrus flavonoid, found abundantly in orange and grape juice, was shown to elevate oxidative stress, neuroinflammation, apoptosis and memory impairment in the CNS [134, 135]. Similar to other phytochemicals discussed early, hesperetin's low bioavailability due to its water insolubility, and rapid clearance from the body has limited its clinical applications [136]. Treatment with nanosuspension of hesperetin produced *via* evaporative precipitation exhibit-

ed superior neuroprotective effect in AD model, compared to free hesperetin. Kheradmand *et al.* [137] and Hajizadeh Moghaddam *et al.* [136] showed improvement in memory retrieval and recognition memory consolidation, increased antioxidant enzymes (SOD, glutathione GPx, GRx and CAT) activity and decreased lipid peroxidation in the hippocampus of streptozotocin-induced AD rats following treatment of nano-hesperetin with a dose of 10 and 20 mg/kg for three weeks by oral gavage. Similarly, hesperetin nanocrystals produced by small-scale milling treated SH-SY5Y-APP$_{695}$ cells improved mitochondrial function as shown by increased ATP levels and respiratory chain complex activity [138].

4.10. Naringenin

Naringenin is a flavonoid present abundantly in citrus fruits. It was reported to possess antioxidant, antithrombotic, anti-atherosclerosis, antidiabetic, antihypertension, anti-inflammatory and anticancer properties [139]. Naringenin was shown to reduce Aβ levels and protect cells against Aβ$_{1-42}$-induced neurotoxicity [140]. Additionally, naringenin treatment was able to alleviate lipopolysaccharide-induced cognitive impairment and neuroinflammation [141]. Naringenin nanoemulsion significantly alleviated the Aβ neurotoxic effects on SH-SY5Y cells by reduced cellular ROS production, and decreased APP, BACE and tau phosphorylation [142].

4.11. Green synthesized NPs with Extracts of Natural Products

The synthesis of NPs usually requires the use of highly toxic chemicals [143]. In order to reduce the impact of NPs synthesis on the environment, numerous plant extracts have been used as chelating and stabilizing agents in NPs synthesis, which has promoted the use of green synthesized NPs [143]. Additionally, green synthesized NPs were shown to exhibit better biocompatibility and less toxicity compared to conventional NPs synthesized via chemical methods [144].

Aqueous extracts of *Lampranthus coccineus* and *Malephora lutea* have been used for the synthesis of silver NPs with a size less than 30 nm [145]. The nanosilver aqueous extracts of both *L. coccineus* and *M. lutea* showed high AChE-inhibiting and antioxidant activity, suggesting a potential target for the treatment of AD [145]. Similarly, other plant mediated synthesis of NPs, such as *Sageretia thea* leaves, *Millettia pinnata* flower, *Terminalia arjuna* bark, endophytic fungi *Cladosporium* species, edible mushroom *Flammulina velutipes* and *Sabal blackburniana* leaves, fruits and pollen grains exhibited excellent inhibitory efficacy against AChE and butyrylcholinesterase (BChE) [146-151]. Furthermore, treatment of *Nepenthes khasiana* leaf extract-mediated silver NPs and *Clitoria ternatea* flower extract mediated graphene quantum dots have been shown to improve learning and memory capacity in AD models [152, 153].

5. MECHANISTIC BASIS OF NANOPARTICLE-BASED TREATMENT IN AD

Literature has revealed various sources of natural products or phytochemicals used in NP that are beneficial for the treatment of AD. The types of NPs or nanopreparation used as the delivery agents also varied, from the most basic nanoemulsion (used to deliver osthole) [154], to complex lipid-based NPs (such as lipid core NP used to deliver curcumin) [155] and polymeric NPs (such as the PLGA NP used to deliver triptolide) [156].

Due to the heterogeneity of preparations available, multiple mechanisms of action leading to neuroprotective effects were reported. These can be broadly categorised according to their effect(s) on (i) Aβ and related molecules, (ii) neurotransmitter levels, (iii) general pathological states like oxidative stress, inflammation and apoptosis, and (iv) other miscellaneous parameters.

5.1. Reducing Aß and its Related Molecules

Irrespective of whether Aß is the cause or consequence of the pathophysiology of AD, targeting this protein has been the focus of countless researchers in the pursuit of new AD therapies. Because of their limitation in delivery over the BBB, Aβ subfragments were employed in combination with NPs for active immunotherapy [157]. This method was used to create intramembranous Aβ fragment-loaded chitosan NPs for improved brain delivery. The study's ELISA results revealed that the formulation had a high potential for immunogenicity [157]. For example, quercetin-loaded PLGA NPs (PLGA@QT) managed to disrupt Aß$_{1-42}$ aggregation using the ThT assay [158], thus implying their potential to reduce the downstream processes leading to neurodegeneration. Aside from this, they also reported that PLGA@QT was better than free quercetin at reducing aggregation, preventing fibril formation, and dissolving formed Aß aggregates. The use of phytochemicals in the green synthesis of gold and silver NPs observed this direct effect on Aß aggregation [159, 160], but this was due to the innate property of the NPs themselves, rather than that of the phytochemicals. Moreover, quercetin-loaded superparamagnetic iron oxide NP (QT-SPION) also managed to reduce the expression of APP in the brain of AD rats [161]. APP overexpression is one of the causes of increased Aß production by neurons, leading to neurodegeneration [162]. Thus, the ability of QT-SPION to reduce APP expression will be beneficial in AD. This effect was also reported by Amin *et al.* [163] to be one of the mechanisms of anthocyanin-loaded PLGA NP (An-NP) in reducing Aß$_{1-42}$-induced SH-SY5y toxicity. In this study, An-NP also reduced the expression of BACE-1, which encodes for the APP-cleaving BACE responsible for the formation of Aß fragments. Additionally, both these effects were reported to be more prominent in An-NP when compared to free anthocyanin.

5.2. Increasing ACh Concentration in the Brain

Low ACh levels are another hallmark of AD, which is due to increased expression and/or activity of AChE [164], hence making the latter as a target for inhibition in AD therapy. Several phytochemicals described in this review also possess this AChE inhibition activity, like curcumin, quercetin, resveratrol, phytol, extract of *L. Coccineus, M. lutea, M. pinnata*, *T. arjuna*, *C. ternatea*, *Cladosporium* sp., *F. velutipes*, *S. blackburniana*, and *S. thea*. Kakkar, Kaur [165] were one of the earliest researchers who demonstrated the AChE inhibition property of curcumin-loaded solid lipid NP (C-SLN) in $AlCl_3$-induced AD in rats. The inhibition by C-SLN was better than free curcumin, but they also reported a similar effect of empty SLN on the AChE.

Aside from curcumin-loaded NPs, quercetin-loaded SPIONs (QT-SPION) produced by Jajin *et al.* also displayed AChE inhibition in $AlCl_3$-induced AD in rats [161]. As a result, treated rats performed significantly better in the Morris water maze and passive avoidance tests; QT-SPION treatment proved superior to free QT in attenuating AD-induced worsening of the test parameters.

5.3. Attenuation of General AD Pathophysiological Processes

Various agents and phytochemicals have been shown to reduce oxidative stress, inflammation and eventually apoptosis in combating the neurodegeneration observed in AD.

5.3.1. Oxidative Stress

The ability to attenuate oxidative stress is the most assessed parameter when phytochemical-loaded NPs are investigated as potential agents for AD therapy. C-SLN was shown to reduce oxidative stress in $AlCl_3$-induced AD in rats by reducing lipid peroxidation and increasing the expression of endogenous antioxidants (GSH, SOD and CAT)[165]. These effects were comparable to the positive control rivastigmine (AChE inhibitor used in AD treatment) and were superior to free curcumin. Other oxidative stress parameters ameliorated by phytochemical-loaded NPs include increased DPPH free radical scavenging activity by *Centella asiatia* nanoemulsion [166], increased total antioxidant status by thymoquinone nanoemulsion [167], reduced ROS generation by anthocyanin-PLGA [163], and reduced MMP production by *Saussurea lappa* essential oil-polymethyl methacrylate (PMMA)-based NPs [168]. In all these reports, the NP formulation of the phytochemicals was found to be superior to the free formulation.

5.3.2. Inflammation

A recent association study reported a possible link between the anti-inflammatory NSAID use and cognitive improvement in patients with AD [169], thus providing more evidence that inflammation plays a key role in AD pathophysiology.

Anthocyanin-loaded PLGA (An-NP) used by Ul Amin *et al.* on $Aß_{1-42}$-treated SH-Sy5y cells showed reduced expression of phosphorylated NFkB, TNF-α and iNOS [163]. An-NP treatment resulted in better viability of the $Aß_{1-42}$-treated SH-SY5Y cells, thus implying better neuroprotective effect. Quercetin-loaded NP was also shown to have an anti-inflammatory effect. Quercetin-SPION treatment of $AlCl_3$-induced AD rats restored elevated iNOS levels in their brains back to comparatively normal levels, which was not produced by free quercetin [161]. Other inflammatory parameters were reported to be ameliorated in other studies and these included reduction in IL-6 by baicalein-loaded PEG-PLA micelles [170]. These reports stated the superior effects of the NP formulations.

5.3.3. Apoptosis

Neuronal death commonly occurs by apoptosis and is usually the culmination of the multiple insults described in the preceding paragraphs. Cucurmin RBCm-coated PLGA NPs bearing T807 and triphenylphosphine molecules showed suppressed primary brain microvascular endothelial cell and astrocyte death [83]. Quercetin loaded selenium NPs demonstrated low cytotoxicity in the presence of PC12 cells and also protected PC12 cells from damage by H_2O_2 [97].

6. TOXICITY CONCERNS WITH NPS THERAPY IN AD

Over the years, a major limiting factor in the effort to translate promising experimental results observed with phytochemical-loaded NPs into clinically applicable products is the lack of data on cytotoxicity. In general, NPs formulation of phytochemicals improve their dispersibility in aqueous environments, which contributes to their improved bioavailability. However, at higher concentrations, increased dispersibility will increase tissue delivery to a level that would tip the balance towards toxicity as it increases tissue penetration [171, 172]. Few studies uncovered the potential danger of the NPs formulation when compared to the free formulation. For instance, Gutierrez *et al.* [155] reported that curcumin-loaded lipid core NP (LCN-C) treatment of AD mice could not reduce COX-2 expression; thus LCN containing both curcumin and meloxicam is needed to reduce it. Furthermore, free curcumin treatment was observed to be better at reducing COX-2 expression than LCN-C, with the latter observed to increase COX-2 expression to a higher level than non-treated AD mice. More work is needed, especially looking at the tissue level and long-term toxicities of the phytochemical-loaded NPs, in order for them to be serious contenders for the various clinical applications that their experimental data suggest.

7. LIMITATIONS AND FUTURE APPLICATION OF NATURAL PRODUCT-BASED NANOMEDICINE IN AD

Advances in nanotechnology have led to a rise in potential therapeutic strategies against AD progression. For AD nanotherapeutics, a biocompatible nano-carrier with adequate size, shape, charge, and surface characteristics corresponding to the intended site/mechanism of action is required [173].

However, there are still certain obstacles to overcome in the realm of AD nanotherapeutics. For example, at the site of the Aβ fibrillar event, for example, a larger pool of small NPs functions as a monomer to trigger fibrillation, whereas a larger pool of big surface NPs would efficiently absorb free fibrils and suppress fibrillation [173]. Other investigations have found that NPs with a smaller size and a negative charge are more effective at crossing the BBB and exerting inhibitory effects [174]. A few additional polymeric NPs were shown to have improved targeting and efficacy, but only under certain pH and temperature conditions [175]. In another study, it was discovered that some metallic nanocarriers aided Aβ fibrillation-mediated AD development and were also implicated in bio-accumulation-mediated neurotoxicity [176]. Thus, an appropriate biocompatible nanocarrier fabricated with suitable size, shape and charge, and surface modification corresponding to the targeted site/mechanism of action is essential for AD nanotherapeutics [177]. In addition, AD is a multi-faceted clinical complication, so fabricating a single NP entity with several drug molecules or multi-potential drug candidates can possibly

curb the AD progression more effectively, perhaps due to s ynergistic effects [178].

This review summarized numerous *in vitro* studies which have demonstrated the potential usefulness of NPs in modulating the AD pathology. However, this must be further supported by *in vivo* experiments before proceeding to clinical trials. The *in vivo* studies need to be able to indicate long-term systemic effects and, pharmacokinetic and pharmacodynamic profiles of these NPs, and to identify potential toxicity in the body systems [179]. Furthermore, the evaluation of these natural product-derived NPs compounds in clinical trials is important to validate their application in the treatment of AD.

CONCLUSION

The current review focused on the in-depth roles of NPs in the delivery of natural products, specifically in the treatment of AD. Even though conventional medicinal properties were established to treat this disease, challenges were discovered, especially due to its poor solubility and low bioavailability upon crossing the BBB. Hence, numerous natural products using NPs were identified to promote a therapeutic effect on AD. Nanotechnology advancements may aid in achieving the larger concentrations of natural compounds required for efficacy against AD. Though there remain some concerns about general safety and environmental consequences, that need to be resolved with more extensive studies. To summarize, nanotechnology containing one or more natural chemicals has the potential to be within reach for treating AD soon.

LIST OF ABBREVIATIONS

Aβ	=	Amyloid-β
AChE	=	Acetylcholinesterase
AD	=	Alzheimer's disease
APP	=	Amyloid precursor proteins
BACE	=	β-secretase
BBB	=	Blood-brain barrier
BChE	=	Butyrylcholinesterase
Cis	=	Cholinesterase inhibitors
CNS	=	Central nervous system
FDA	=	Food and Drug Administration
LRP1	=	Low-density lipoprotein receptor-related protein-1
MMP-9	=	Matrix metallopeptidase-9
NMDA	=	N-Methyl-D-aspartate
NPs	=	Nanoparticles
NSAIDS	=	Nonsteroidal anti-inflammatory drugs
PLGA	=	Polylactide-co-glycolic-acid
RAGE	=	Receptor for advanced glycation end products
ROS	=	Reactive oxygen species
WHO	=	World Health Organization

AUTHORS' CONTRIBUTIONS

CKW and SD designed the conceptual framework. TSL, WKH, RA, MHH and CKW contributed to the write-up of the manuscript. TSL, CKW and SD performed the critical revision of the article. RA revised the format of the manuscript. All authors read and approved the final version of the manuscript.

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