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Minireview

A review on phyto-nanotechnology for therapy of alzheimer's disease

Gayathri Rajamanickam & Manju SL*
School of advanced sciences, VIT, Vellore-632 014, Tamil Nadu, India

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Alzheimer's disease (AD) is a common chronic neurodegenerative disease (ND) that is mainly investigated nowadays because of its increased incidence and burden on the elderly population. It leads to atrophy of the brain. Clinical features of AD include loss of memory with impaired cognition and behaviour, which leads to mood instability and death. Aggregation of beta-amyloid protein(Aβ) and neurofibrillary tangles within the neuronal cells are the accepted pathophysiological process of AD. Studies have demonstrated that medicinal plants and herbs could improve memory and cognitive function affected by AD. The bioavailability of active herbal components is affected by rapid metabolism, less permeability, and decreased stability within the CNS. Many studies have reported that the application of nanotechnology to plant extracts enhances the efficacy of extracts. Adding herbal extracts into the nanoparticle system could improve the action of extracts, promote the sustained release of bioactive components, decrease the required dose, and lower the side effects. Using published articles from trustworthy resources like PubMed, Google Scholar, Research Gate, Web of Science, and Wiley Online Library, with keywords like "natural products," "Alzheimer's disease," and "nanotechnology," herein we reviewed and summarized recent nano-drug delivery treatment strategies for AD using natural products.

Keywords: Amyloid plaque, Blood-brain barrier, CNS, Nanotechnology, Natural products

Introduction

Alzheimer's disease (AD) is a condition that causes memory loss and cognitive decline in the elderly due to the degeneration of neurons in the brain. It is described by progressive memory loss, cognition, and behavioral impairment (dementia) and is associated with mood instability and death. The pathophysiological mechanisms involved in AD are an accumulation of extracellular Aβ plaques and intracellular neurofibrillary tangles in the cerebral cortex[1]. As per recent data, 35.6 million people are affected by dementia in the world. The global dementia caseload is projected to double by 2030 and more than triple by 2050 and developing countries will be affected more by dementia[2].

"The existing literature review concludes that neurobiological mechanisms involved in AD are Aβ-induced neurotoxicity, leading to Ca^{2+} dyshomeostasis, mitochondrial dysfunction, increased oxidative stress, cholinergic dysfunction, and neuroinflammation"[3]. The before-mentioned processes lead to neuronal/synaptic dysfunction and neuronal loss, dysregulation of protein degradation pathway, malfunction of the immune system, and imbalance in lipid and cholesterol metabolism. Alterations in cortical and subcortical glutamatergic structures in AD were also demonstrated by other studies[4]. The nine biological hallmarks of ageing are genomic instability, telomere attrition, epigenetic changes, proteostasis loss, mitochondrial dysfunction, cellular senescence, sensing of deregulated nutrition, stem cell exhaustion, and alterations in intercellular communication that are accountable for AD[5]. Excessive production of reactive oxygen species (ROS) damages lipids, proteins, and DNA, resulting in aging and degenerative illnesses in humans[6]. Earlier studies have shown that loss of cholinergic neurons, absence of acetylcholine transferasemarkers, decreased choline uptake, and reduced acetylcholine are the events that result in AD. So, cholinesterase inhibitors (*e.g.*, rivastigmine, donepezil, galantamine) are used as a first line of drugs in AD to reduce cholinergic neurotransmission. Cholinesterase inhibitors and NMDA receptor blockers are the available options for symptomatic treatment[7].

"Nerve growth factor stimulation, gamma-aminobutyric acid receptor modulators, serotonin reuptake, somatostatin secretion stimulants, astrocyte modulating agents, phosphodiesterase four inhibitors

*Correspondence:
E-mail: slmanju@vit.ac.in

Abbreviations: AChE, Acetylcholinesterase; AD, Alzheimer's disease; ASH, *Ashwagandha*; Aβ, beta-amyloid protein; BM, *Bacopa monnieri*; CA, *Centella asiatica*; GB, *Ginkgo biloba*; ND, Neurodegenerative diseases; NLC, nanostructured lipid carriers (NLC); SLN, solid lipid nanoparticles; WS, *Withania somnifera*

and cannabinoid agonists are some of the treatment trails that are currently undergoing AD treatment"[8]. However, currently available medications have serious adverse effects such as insomnia, nausea, lack of appetite, diarrhoea, muscular cramps, muscle weakness, Low blood pressure, trouble breathing, and bradycardia[9]. Some studies targeted the amyloid-centric approach to developing the drug for the prevention of disease in the early stages. Extensive first-pass metabolism, the blood-brain barrier, reduced half-life, and probable adverse effects in non-target peripheral tissues are significant concerns in CNS-targeted drug delivery. Medications presently in use to treat AD, galantamine and physostigmine are natural products; the former is an alkaloid found in the bulbs of the *Galanthus woronowii* and bulbs of numerous Amaryllidaceae family plants, while the latter is derived from the deadly seeds of *Physostigma venosum*[10]. A standardized extract called EGb 761 is prescribed in many countries outside of the US[11]. Bacognize® extract is a clinically validated natural standardized extract from *Bacopa monnieri* that improves cognitive function in elderly Alzheimer's patients and is presently available on the market[12].

The role of natural products in AD therapy

As people become more worried about the adverse effects of synthetic pharmaceuticals, natural remedies are becoming more popular. The therapeutic impact of herbs is being examined worldwide, even though the popularity of traditional remedies varies by nation. Herbal plant varieties can offer a wide variety of medicinal properties that might be beneficial in the treatment of ND. The medicinal plants should aid memory and cognition, which often worsen with Alzheimer's disease. Neuroprotective qualities connected to antioxidant activities have been proven in a range of herbal extracts and phytocomponents. The mechanism of action of natural compounds is either by directly activating antioxidant response genes or by increasing the body's inherent antioxidant defence system and anti-inflammatory action. Bioavailability is hampered by rapid metabolism, low permeability, and decreased stability in the central nervous system[13].

Natural products

Studies have reported the beneficial effects of *Ginseng, Ashwagandha (ASH)*, *Bacopa monnieri (BM)*, *Ginkgo biloba (GB)*, *Centella asiatica (CA)*, and phytoconstituents,for example, flavonoids, celastrol, trehalose, lycopene, sesamol, resveratrol, and curcumin against the neurodegenerative diseases"[13].

Ginsenoside and gintonin extracted from Panax ginseng extracts work by reducing Aβ production, inhibiting beta and gamma-secretase activity, acetylcholinesterase (AChE) activity, and Aβ-induced neurotoxicity and neuroinflammatory reactions in AD. Gintonin increases acetylcholine and choline acetyltransferase activity in the brain via activating lysophosphatidic acid receptors[14].

Withania somnifera (WS) has been utilized for neurological problems since ancient times. In the PC-12 rat neuronal cells, withanamides A and C of WS showed a good affinity with Aβ and hampered the synthesis of fibril[15]. Withaferin A (WA) brings down the Aβ levels in the cell cultures without any cytotoxic effects. "WA exhibited a protective role in the human neuroblastoma cells with healthy growth and decreased dendritic beading and cytoplasmic vacuoles in the SH-APP cells"[16]. *In vitro* studies of ASH from WS roots demonstrated Aβ diminution in treated groups as compared to non-treated groups[17]. The major drawbacks of these molecules are the lack of efficient delivery of the drug into the CNS and lower bioavailability. These facts are putting pressure on scientists to find a potent smaller molecule with similar properties.

BM and its bioactive components bacosides enhanced cognition and learning behaviour by lowering ROS, inhibiting Aβ, neuroinflammation, and aggregation. The findings showed that BM has an inhibitory effect on Tau-mediated toxicity and could be used as a lead drug in the treatment of AD and other neuropathological disorders[18].

GB exhibits beneficial effects by regulating homeostasis, altering tau protein phosphorylation, and enhancing growth factor synthesis[19]. By showing the protective role in various parts of the CNS, GB is used to treat cerebrovascular disease and AD. Administration of GB extracts about 22-24 weeks in 1,628 dementia patients showed the improvement of behavioural and psychological symptoms of dementia and stress felt by the caregiver. GB extracts induced the differentiation of stem cells into nerve cells, bringing hope to patients suffering from neurological disorders[20]. Flavonoids, bilobalide, and specific ginkgolides (B and J) have potent neuroprotective properties.

CA acts as an AChE inhibitor and lowers the phospholipase A2 activity. It shows the considerable impact on Aβ toxicity and AD prevention. An earlier study with Gotu kola extracts conducted with 28 healthy elderly individuals showed a decrease in

mood disorders and age-related cognitive decline. Though Gotu kola is safe to use, the greater doses can lead to drowsiness[21]. The investigators studied that CA treatment improved memory by increasing ARE gene expression in the hippocampus and reducing oxidative stress[22]. In MC65 and SH-SY5Y cell lines, mono- and dicaffeoylquinic acids (CQAs) in CA act as neuroprotective agents by Aβ-induced alterations in tau expression and phosphorylation[23].

Curcumin from *Curcuma longa* protects against AD via multiple mechanisms, including anti-amyloid and antioxidant properties. Curcumin enhanced the synaptic performance in human and animal models of AD by crossing the BBB and shielding neurons against various toxic insults associated with aging. Curcumin's limited bioavailability is related to its low intestine absorption, quick metabolism, and hydrophobic nature. As a result, new technology is required to improve curcumin bioavailability for the treatment of AD[24]. The dual cholinesterase inhibitory action of isocorilagin A (*Phyllanthus niruri*) can serve as an encouraging herb for AD[25]. Ethanolic extracts of *Phyllanthus emblica* fruit enhance cognition, which has more significant implications in treating AD[26]. In scopolamine-induced dementia and oxidative stress rats, methanolic extract of *Phyllanthus acidus (PA) L.* improves cognitive functions and reduces oxidative stress by increasing brain antioxidant enzymes and lowering lipid peroxidation and AChE activity[27]. Ethanolic extract of *Pseudarthria viscida* (EEPV) has anti-amnesiac and cognitive-enhancing properties in beta-amyloid-induced amnesia in mice model. It resulted in an increased level of antioxidant enzymes and reduced the acetylcholine level[28].

Huperzine, sesquiterpene alkaloids derived from the herbs of *Huperzia serrata* of the *Huperziceae* family, has significant neuroprotective properties via anti-cholinesterase activity, which was beneficial for cognitive development[29].

The role of flavonoids in AD

High flavonoid contents in this plant may give benefits as a dietary complement in AD patients. Flavonoids such asapigenin, epicatechin, quercetin, pinocembrin, and rutinreduce AD progress by inhibiting APP processing, Aβ deposition, Aβ and tau pathology, neuroinflammation, oxidative stress, and neurogenesis. The flavonoids, according to various studies, might be interesting candidates for neurological diseases[30].

Marine products

Bryostatin-1 from the extract of Bugulaneritina decreases neurotoxic Aβ accumulation, directs anti-apoptotic ability, and synaptogenic effects[31]. Chitosan, a bioactive substance generated from fish waste, inhibits BACE-1 expression and activity. Both *in vitro* and *in vivo* trials have a considerable impact on medicine delivery in AD[32]. Spongionella-derived gracilins show multi-target activities associated with inhibition of Aβ precursor protein cleaving enzyme-1, BACE1 and extracellular-signal-regulated kinase (ERK) and reducing tau hyperphosphorylation[33].

Fucoidan and *Symphyocladia latiuscula Yamada* have been shown to be beneficial in the treatment of AD[34]. Fucosterol (brown seaweed) was shown to protect against cognitive dysfunction in ND by quilling age-induced ER stress[35]. Manzamine Y revealed the inhibitory activity of glycogen synthase kinase 3, an enzyme associated with AD pathology. Marine sponges act as exceptional neuroprotection agents. They can inhibit the β-amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) and modulate the production or activity of AChE and glutamate, increase serotonin, reduce oxidative stress, inhibit kinases and proteases, and promote neurite growth[36].

Nanotechnology

Nanotechnology is a ground-breaking approach to technological progress that deals with material management at the nanoscale scale. The use of nanoparticles for disease diagnosis, monitoring, control, prevention, and therapy is the goal of nanotechnology applications. Nanoparticle-based treatments have the potential to circumvent biological barriers, distribute hydrophobic medicines and biologics efficiently, and target disease areas selectively[37].

Need for nanotechnology for AD

The traditional drug delivery mechanism utilized to distribute the natural product has become outdated, resulting in decreased therapeutic efficacy. The difficulties in employing natural products include molecular complexity, limited solubility, functional group reactivity, and general instability. The critical limiting constraints in utilizing CNS-targeted medications include the BBB, the blood-cerebrospinal fluid barrier, drug outflow by P-glycoprotein, and the action of plasma proteins in the circulatory system[38].

The delivery of drugs using nanoparticles is a promising technique for increasing the CNS penetration of numerous therapeutic agents. To address the challenges of traditional natural product drug delivery, nano carrier-based natural product delivery has piqued interest, potentially improving the therapeutic action of phytoconstituents, improving the sustained release extract, reducing dose requirements, and causing fewer side effects. Different types of nanoparticles can be prepared to deliver the drug to the target cells in the organ. Nanoparticles are available in many forms like emulsions, liquid crystals, nanorods and solid lipid nanoparticles (SLN), *etc*. So, linking the bioactive natural compounds with nanoparticles will be a promising approach in neurotherapeutics[39].

Advances in utilizing phyto nanotechnology in ad therapy

In vitro AChE inhibitory activity of green-synthesized ZnONPs utilizing methanolic extracts of *Sabal black Burniana* was shown to be more promising than donepezil in AD. Molecular docking investigations validated it even more. These plant flavonoids with the highest scores exhibit a similar binding mechanism to galantamine (co-crystallized ligand) inside the human AChE active site[40].

By inhibiting the cholinergic receptor, an aqueous extract of the whole plant of *Convolvulus pluricaulis* impregnated with synthetic iron oxide nanoparticles (CPIO) enhanced cognition in exteroceptive and interoceptive models. As a result, CPIO may play a beneficial role in AD[41].

The research study using silver nanoparticles (SNP) with *L. coccineus* and *M. lutea* showed greater anti-AChE and antioxidant activity than both plants' aqueous extracts. In the *in vivo* trial, the extracts with nanoparticles enhanced the AChE level and decreased the amount of oxidative stress. The existence of macromolecules such as an epicatechin5-O-beta-D-glucopyranoside-3-benzoate inhibitor of butyrylcholinesterase, catechin, can inhibit AChE, and -Sitosterol 3-O-D-glucoside, which is the inhibitor of glutathione transferase, was discovered by the molecular docking study. By inhibiting the enzymes mentioned above, the extract compounds can prevent the progress of AD[42].

Quercetin has been shown to suppress the aggregation of the amyloid-beta peptide A, suggesting its considerable potential as a neuroprotective agent. However, because of quercetin's limited solubility and substantial metabolism, reaping its advantages is exceptionally challenging. The nanoparticles encapsulating the quercetin with solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are functionalized with transferrin, leading the nanoparticles to cross the BBB through transferrin receptors. Those receptors are expressed more in the endothelial cells of the brain blood vessels. They also demonstrated the inhibition of Aβ by the NLC-transferrin complex through their amyloid-beta studies. The study by R.G.R. Pinheiro et al successfully evidenced the usage of quercetin encapsulated nanoparticles for AD treatment[43].

Both quercetin and QT-SPION are antioxidants that demonstrated an improvement in learning and memory in rats undergoing the Morris water maze test. But QT-SPION showed better results in comparison with free quercetin models. QT will improve learning and memory by binding with proteins that are responsible for neural cell apoptosis. QT bioavailability could be increased by conjugating QT with SPIONs[44]. The SeNPs-loaded Curcumin/poly (lactic-co-glycolic acid) (PLGA) complex was created. The study in brain samples of 5XFAD mice determined that curcumin-loaded Se-PLGA nanoformulation has been used to treat AD that acts by decreasing the Aβ deposition[45].

Conclusion

The medical fraternity is trying to eradicate many chronic diseases that are causing social and economic burdens. AD remains a leading problem due to its multifactorial causes and reaching target cells by drugs. Recent trials are exploring approaches for brain-targeted drug delivery for better drug efficacy. The BBB is the most significant impediment to therapeutic medications accessing damaged brain tissues. Natural phytochemicals are abundant and might be used as neuroprotective. Nanotechnology is widely acknowledged as a potential future option for many diseases, including AD. In recent years, researchers have witnessed promising brain-targeted drug delivery using nanoparticles. The use of phytochemicals in conjunction with nanotechnology enhances the therapeutic impact and offers a new solution to address severe economic and environmental issues. The efficacy and potency of nanomedicine will depend on the sensible approach and properties of the chosen nanoparticle. Comprehensive information and correct biological investigations may be used to design and formulate

acceptable natural product-based nanomaterials. This research summarizes the most current advances in phyto nanomedicine for AD therapy. Still, more effective, non-toxic nanomedicine inventions are required to effectively address AD.

Conflicts of interest

All authors declare no conflicts of interest.

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