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# Nanodelivery systems for Alzheimer's disease: Prospects of natural therapeutic agents

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**ABSTRACT**

Diseases that cause deterioration of the neurons are many and Alzheimer's disease (AD) is a typical example. The prevalence of AD is increasing with a huge impact on the family, society, and the economy of nations. The central nervous system and its periphery have barriers which are crucial interfaces preventing the entrance of awkward materials. Among these barriers, the blood–brain barrier (BBB) is the most selective and comprises cells coupled with fitted intersections. Nanosized carriers have the prospect for administering drugs to the brain and examples include nanoemulsions, those based on solid lipids and those based on solid and liquid lipids. These formulations can encapsulate active molecules and target necessary transport systems in the brain, thus enabling drug uptake through the BBB. Nanoparticles are of different types and are obtained using diverse techniques and materials. What is common to all nanocarriers is the small sizes and specificity in site targeting. Conventional drugs used in the treatment of AD and bioactive agents can be designed as nanocarriers for improved efficacy. This paper elucidates the use of nanoparticles in managing AD while touching on the prospects of natural therapeutic agents and highlighting future perspectives.

## INTRODUCTION

Neurodegenerative diseases affect over 10 million people with an estimated increase of 20% in 10 years to come; this is not surprising since the aging populace is increasing, and in some countries, life expectancy is growing (Spuch and Navarro, 2011). Neurodegenerative diseases have been reported to rank fourth among death-causing ailments, such as cardiovascular problems, and cancers of various types in the Western world (OECD, 2010). The diseases have many similarities on a subcellular level, can begin at any age, but are much common among the elderly (Forlenza *et al*., 2010). The most common neurodegenerative diseases are amyotrophic lateral sclerosis, Huntington's disease, frontotemporal dementia, prion diseases, and Alzheimer's disease (AD) (Bertram and Tanzi, 2005). Among these diseases, Parkinson's syndrome and AD are the most common, producing outstanding debilitating conditions of significant public health concern (Spuch and Navarro, 2011). Health statistics have shown that among millions of people suffering from dementia, a majority have AD and are elderly (Morgan, 2011). The disease (AD) is a neurodegenerative disorder, first observed as senile dementia and described over a century ago by Alois Alzheimer (Ferri *et al*., 2005; Nazem and Mansori, 2008). Learning and memory impairment are typical clinical manifestations of AD, while the pathology can be described by gross cerebral atrophy indicative of neuronal loss (Mucke, 2009). It is a multifactorial disease with several contrivances and conduits having somehow permanent pathology, and current treatments are for lowering related signs (Nasem and Mansori, 2011). Some of the causes of AD have been shown to include deficiency of acetylcholine, imbalance in the glutamatergic system, deposition of phosphorylated tau proteins, and amyloid plaques (Ayaz *et al*., 2017; Khalil *et al*., 2018).

The occurrence and frequency of AD increases with age, but degeneration of nervous tissues generally commence after several years, up to a decade or more, before the symptoms of AD manifests in the patient (Mortimer *et al*., 2005; Nestor *et al*., 2004; Sloane *et al*., 2002). AD is a disease of major public health concern because the elderly population is increasing globally. AD progresses slowly, the signs are somewhat silent in the early

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stages, and its effect deteriorates as time goes on; the indicators could be the inability to remember recent events, inability to obtain new information, poor judgment and missing the way home are also very common among patients (Rocha, 2013). Patients with AD experience behavioral instability, cerebral dysfunction, and deficiency in normal life activities. After a couple of years, AD patients begin to suffer from three-dimensional awkwardness which oftentimes makes them unaware of their surroundings. The situation leads them to an overall indifference to happenings in their surroundings and they may become a great burden to their loved ones due to poor emotional regulation. Inability to write and walk properly also occurs with time because the patients also lose motor handling abilities (Rocha, 2013). All these lead to a huge socio-economic burden on the family and the overall healthcare delivery system (Ali *et al*., 2017). An estimate by the United States National Institute of Health reported that the annual cost of managing AD is $100 annually (Roney *et al*., 2005). This shows the extent of the economic burden for families and society at large. There is also the silent but heavy cost of loss of man-hours and funds because AD patients require to be looked after by relatives or hired caregivers. It is worrisome, therefore, that conventional medical approaches seem incapable of terminating the disease or reversing the progression irrespective of early diagnosis when possible. Furthermore, the fundamental mechanisms of AD are not completely understood, although there are diverse methodologies geared toward impeding the disease progression (Citron, 2010).

**Active Pharmaceutical Agents in the Pursuit of a Cure for AD**

Some orally administered pharmaceutical agents that are clinically approved to treat AD include memantine, galantamine, donepezil, tacrine, and rivastigmine (Pasic *et al*., 2011). Memantine is a glutamatergic system modulator, while the remaining four drugs are cholinesterase inhibitors (Ayaz *et al*., 2015; Kamal *et al*., 2015). These medications have narrow activity in addition to untoward side effects; for example, tacrine is hepatotoxic (Watkins *et al*., 1994). Unfortunately, the majority of the drugs administered to the patients never enter the brain in effective concentrations due to partial or total hepatic breakdown and inability to pass through the biological barrier of the brain. Higher drug concentrations, which can produce toxicity in vital organs of the body, may be thus required due to the inefficient drug utilization. In addition, some of the therapeutic agents have poor solubility while others have outright insolubility in aqueous solutions, making their oral or parenteral delivery quite tasking. Recent outcomes from clinical evaluations carried out in patients having mild to moderate dementia have established the need to search natural sources for more effective but safe substitutes (Cummings *et al*., 2014; Yiannopoulou and Papageorgiou, 2013).

Therapies found useful for AD have different mechanisms for tackling the problem of neurodegeneration. For example, therapies called cholinesterase inhibitors impede acetylcholinesterase, thus increasing the concentration of acetylcholine in the connection point and upgrading transmission enabled in the neurons by choline. Examples are donepezil, galantamine, tacrine, and rivastigmine (Zarotsky *et al*., 2003). Non-steroidal anti-inflammatory drugs are also helpful as they inhibit pro-inflammatory mediators such as cyclooxygenase which is neurotoxic (Ho *et al*., 2001). The excessive generation of reactive oxygen or nitrogen species has been proposed as one of the causes of neurodegeneration (Emerit *et al*., 2004). These free radicals are released during inflammatory reactions or normal oxidative metabolism, auto-oxidation of certain neurotransmitters. Antioxidants are useful in handling dementia by scavenging reactive oxygen and nitrogen species which are causative agents for oxidative injury in neurons. Some compounds are capable of inhibiting monoamine oxidase which is an enzyme responsible for the collapse of dopamine at the neuronal junction. Dopamine inhibitors cause it to increase, thus helping in the improvement of dementia (Stafford *et al*., 2007).

Harmane and harmaline are alkaloids that excite dopamine release from striatal cells (Schwarz *et al*., 2003), thus improving dementia. Compounds that also prevent the aggregation of Aβ fragment, a precursor in the formation of β amyloid plaque, are also useful. For example, previous studies have shown that curcumin helps in plaque disorder and restoration of inflamed nerves *in vivo* (Taniguchi *et al*., 2005). Metal chelators are indirect antioxidants that chelate divalent ions like copper and zinc which have roles in the clumping of alpha–beta portions (Craig *et al*., 2005).

**Natural Products as Sources of Drugs for AD**

In addition to synthetic drugs approved by various regulatory establishments, studies on herbal extracts containing single or multiple herbs or a blend of herbs and minerals have been conducted for their activity in protecting the neurons which slow down the advancement of AD symptoms. Examples of such plants which have been evaluated and found possessing anti-Alzheimer's properties include *Abies koreana*, whose essential oil was extracted, evaluated, and found to improve memory *in vivo* using the scopolamine-induced amnesia mice model (Kim *et al*., 2006). *Bacopa monnieri* also enhanced intellectual capacity and memory by helping to reduce the loss of neurons using an AD animal model in past studies (Saini *et al*., 2012; Uabundit *et al*., 2010).

Furthermore, different plant extracts have demonstrated activities through diverse mechanisms. Examples include *Salvia officinalis*, *Cassia obtusifolia*, and *Desmodium gangeticum*, which all act through cholinesterase inhibition; *Moringa oleifera*, a common plant in West Africa, acts through the modification of monoamines and antioxidant effect, while *Ginkgo biloba* acts through anti-amyloid aggregation and antioxidant action (DeKosky *et al*., 2008). Dried ginger (*Zingiber officinale*) has demonstrated butyrylcholinesterase inhibitory properties and antagonistic activity against calcium ions, all leading to AD treatment (Ghayur *et al*., 2008). *Salvia officinalis* and *D. gangeticum* also demonstrate an antioxidant effect. The seeds of *Cassia obtisufolia* have also shown the capacity to protect neurons from degeneration when tested on animals; the mechanism was found to be a reduction of ancillary deregulation of calcium ions and organelle contaminant (Obulesu and Rao, 2011). The following are natural bioactive substances with proven activity toward the treatment of AD.

**Colostrinin™**

Colostrinin™ is a product of ReGen Therapeutics; it consists of varied polypeptides extracted from the colostrum of sheep (Williams *et al*., 2011). Colostrum is a form of milk produced by the mammary glands of mammals. Mammals usually produce milk in the third trimester of pregnancy and this milk is called colostrum. Oral tablets of colostrinin have shown improved mental

state with the development of new memories in 15 Alzheimer's patients better than controls (Leszek *et al*., 1999). Additionally, in an extensive double-blind study, Bilikiewicz and Gaus (2004) reported that low-dose colostrinin was effective in upholding reasoning and attending to routine tasks in 105 Alzheimer's patients over a period of 15 weeks. The drug was also well tolerated by the patients; it is now officially available in Australia and US as a nutraceutical.

**Resveratrol (trans-3,4′,5-trihydroxystilbene)**

Resveratrol is commonly referred to as a wine polyphenol and is present in grapes (Vitis vinifera L.; family Vitaceae). The wine polyphenol is a phenylpropanoid ester and a stilbenoid with various activities, which have been investigated for preventive, antioxidant, and relevance in AD treatment. Resveratrol rummages reactive oxygen species; it also causes an increase in the number of receptors on the surface of target cells, and has *in vitro* and *in vivo* neuroprotective properties against oxidative stress (Kim *et al*., 2010; Rossignol *et al*., 2008). Resveratrol is reported to promote the removal of alpha–beta within the cells by enabling the breakdown of proteasomes (Marambaud *et al*., 2005). Feng *et al*. (2009) also suggested the disruption of Aβ42 hydrogen bonding, thus preventing fibril formation with a ranking of resveratrol > catechin > curcumin > piceid > ginkgolides; it can destabilize preformed fAβ42 *in vitro* (Lee *et al*., 2007).

Resveratrol has been subjected to various clinical trials for obesity, diabetes, cancer, cardiovascular diseases, and neurological disorders. The outcome of these trials has also varied due to diverse investigational surroundings and dissimilar doses (Berman *et al*., 2017; Pezzuto, 2019). One item of challenge in all the trials is the poor bioavailability of resveratrol which points to the need for more evaluations (Ramírez-Garza *et al*. 2018).

**Curcumin (diferuloylmethane)**

Curcumin obtained from turmeric *Curcuma longa* L. (Zingiberaceae) is a polyphenolic ingredient, and is quite popular in traditional Indian cuisine. Curcumin possesses higher absorptivity to the blood–brain barrier and minimal toxicity (Yang *et al*., 2005). Curcumin efficiently impedes the formation of alpha–beta oligomers, reduces amyloid *in vivo*, and binds prevailing abnormal patches (Yang *et al*., 2005). The neuroprotective effect of curcumin has been attributed to the inhibition of microglial activation (Lee *et al*., 2007). Past reports have shown that curcumin possesses anti-inflammatory and free radical scavenging properties (Aggarwal *et al*., 2003).

The effect of curcumin on human cognitive control was conducted by randomization within 8 years and only two yielded positive outcome on memory improvement (Baum *et al*., 2008; Kuszewski *et al*., 2018; Lee *et al*., 2014). Hishikawa *et al*. (2012) conducted another study that concentrated on the properties of curcumin to improve social and psychosomatic indicators of dementia in three AD patients (Hishikawa *et al*., 2012).

**Alkaloids**

These are varied and typical examples are physostigmine, nicotine, melatonin, and memantine. Generally, alkaloids are AChe inhibitors and have been reported to assist *in vivo* intellectual roles in both patients having dementia and normal people (Howes and Houghton, 2009). A few of them are discussed below.

*Physostigmine*

Eserine or physostigmine is a naturally occurring organic compound containing nitrogen, generally called alkaloid. It was isolated from *Physostigma venenosum* Balf seeds (family: Leguminosae). Eserine has a pyrrole–indole skeleton which is a potent, short-acting reversible inhibitor of AChe (Kamal *et al*., 2000). To improve the efficacy and pharmacokinetic outlook of physostigmine, numerous equivalents of it have been investigated. For example, rivastigmine, which is the carbamate type, has been the most therapeutically effective and is currently certified for use in AD patients who show signs of mild to moderate dementia (Onor *et al*., 2007).

*Nicotine*

Nicotine is an alkaloid from the family Solanaceae that possesses *in vitro* effects on multiple stages of amyloidogenesis attributed to the presence of N-methyl pyrrolidine moieties (Nordberg *et al*., 2002). Nicotine successfully inhibits the development and propagation, in addition to disrupting preformed fAβ40 and fAβ42 but could not break down the aggregates to their respective forms (Ono *et al*., 2002). However, Nordberg *et al*. (2002) reported that the concentration of Aβ plaque was considerably lowered in mice into which foreign genes have been inserted and compared with controls after treatment for 5.5 months. Nicotine also showed undesired side effects *in vivo* studies where its presence increased the accumulation of tau proteins and the addition of phosphoryl groups to them (Oddo *et al*., 2005).

*Melatonin*

Melatonin is an anti-aggregation phytoconstituent available in numerous organisms and possesses the ability to effectively cross the blood–brain barrier (BBB). Melatonin promotes random coil conformations of Aβ peptides by unsettling the salt connections existing among the histidine and asparagine residues, thus expediting clearance (Pappolla *et al*., 1998). Its anti-aggregation properties make it invaluable in the management of AD.

*Homotaurine*

Tramiprosate®, whose active ingredient is homotaurine, is one of the foremost natural products to demonstrate an anti-clumping pathway (Gervais *et al*., 2007). Homotaurine or 3-aminopropanesulfonic acid can be found in seaweed (Ito *et al*., 1977). Bellus Health, formerly known as Neurochem, markets homotaurine as a memory protective nutraceutical called Vivimind™ in some countries (Neurochem, 2010).

*Huperzine A*

One of the metabolites isolated from *Huperzia serrata* (Thunb.) Trevis, from the family Lycopodiaceae, is Huperzine A. The isolate has been extensively investigated as a reversible inhibitor of acetylcholinesterase. Huperzine A improves perceptive purposes in animal and elderly patients of AD with narrow adverse reactions (Howes and Houghton, 2009). Huperzine A is also neurotrophic (Tang *et al*., 2005) and neuroprotective and has found usefulness in handling symptoms of AD in China (Wang *et al*., 2006). In addition, the powder of *H. serrata* has been commercialized the US for alleviating retention deficiency (Ma *et al*., 2007). A usefulness and

safety evaluation of Huperzine A showed it to be well tolerated and to meaningfully mend cerebral performance and events of daily life in AD patients (Wang *et al*., 2009).

**The Peculiarities of Central Nervous System in Offering Answers to AD**

Drug delivery for tackling any disease of the central nervous system requires targeting the brain if there would be a success in therapy. However, it is not easy to transport drugs to the central nervous system because of the BBB which hinders access (Patel *et al*., 2012). The BBB majorly protects the brain from harm by controlling the selective carriage of supplies to the brain. The selective barrier to the brain consists of microglial chambers, pericytes, astrocytes, and endothelial cells that have tight junctions in between them (Gao *et al*., 2013; Rubin and Staddon, 1999). The existence of closely packed intersections between adjacent cells embedded in larger ones, thus causing the passage of materials through the BBB to occur by the transcellular route. In addition, the combination of tight junctions and the two membranes (abluminal and luminal), which covers the inward part of the receptacle, typifies the BBB with low absorptivity to large, lipophilic, and ionic materials. Macromolecules like proteins and smaller molecules are restricted from passing through the BBB except by interaction with specific receptors and carriers resident in the lumen of cells located within larger ones (Rubin and Staddon, 1999). Receptor-mediated transcytosis is a means of transport using ligand-specific receptor systems and is useful for larger molecules like insulin and certain hormones to enter the brain (Gao *et al*., 2013; De Rosa *et al*., 2012).

To dodge the selective barrier and transport medicines to the brain, three approaches that have been employed in the past include pharmacological, invasive, and physiological.

*Pharmacological slant*

In the pharmacological slant, drugs are modified to shrink the comparative amount of water-loving segments, thus improving the prospect of giving passage to the drug through the BBB (Pardridge, 2005). For example, creatine is a polar compound that cannot cross the BBB, yet it possesses neuroprotective properties. To apply the pharmacological method of slighting the BBB for creatine, a derivative of the drug with hydrophobic nature was produced to combat neurodegenerative conditions. The disadvantage of this procedure is a reduction in the desired therapeutic activity of the modified drug compared to the original drug, even though alteration enabled their crossing of the BBB.

*Invasive method*

The invasive method was used to boost drug transfer to the brain by mechanically breaching the BBB using intracerebroventricular infusion and convection. The drawbacks include higher costs due to patient hospitalization, extended opening periods of the BBB, infections, damage to neurons, and possible damage to the BBB (Pardridge, 2005).

*Physiological approach*

The physiological approach leverages the intrinsic recognition of the BBB for essential substances, like glucose, growth hormones, insulin, and low-density lipoproteins, which helps the brain in metabolism and optimal subsistence. The drug to be transported is altered to bear a resemblance to the nutrient vehicle of the blood–brain barrier or joined to a ligand, thus gain recognition as receptors at the BBB (Pehlivan, 2013). The problem with this method is that the drug could dissociate from the ligand and hurt other body structures.

**Nanotechnology as a Solution to Effective Drug Delivery in AD Management**

Nanotechnology is a broad term referring to a field of applied science and technology-centered on the regulation of substance at the molecular level ranging from 1 to 1000 nanometers, and the designing of equipment within that scope (Guar and Batia, 2008). Nanotechnology draws from many disciplines such as physics, chemistry, geography, biology, engineering agriculture, biotechnology, pharmacy, and medicine. In the previous decade, nanoparticulate materials were quite attractive for commercial development due to their diverse usefulness. Nanoparticles have been useful in the manufacturing of cosmetics and personal care products; electrical and electronic supplies and consumables; pharmaceuticals and medical devices; in addition to diagnostic tools in debilitating conditions, discovery of new active pharmaceutical ingredients, and solving bioavailability (Joshi *et al*., 2012).

Nanotechnology is also a promising method of early diagnosis and management of AD. In diagnosis, nanoparticles can identify minute quantities of biological markers for AD and other numerous biological indicators in the brain, before significant damage occurs (Nazem and Mansoori, 2012). Interestingly also, nanoparticles can be used to detect the pathology of AD, autonomous of the brain standby. Most of the methods for early detection using nanoparticles are centered around the presence of amyloid patches using magnetic resonance imaging (Brambilla *et al*., 2011). When AD onset begins, amyloid peptides begin to accrue and as the disease matures, they can be easily observed (Brambilla *et al*., 2011). Magnetic iron oxide nanoparticles, which are medically useful in the liver have also been noted for prospective use in the brain. Furthermore, iron oxide contrast agents have been reportedly used to identify sections of the brain having a high attraction for amyloid-β peptides by using mice brains when they were deployed across the selective barrier of the brain (Brambilla *et al*., 2011). The nanoparticles could detect and possibly remove peptides associated with the inception of AD. The deadlock for progress in this direction can only be removed until human testing can be adjudged safe, especially with the handling of the BBB for an efficient crossing of the nanoparticles. The growing interest in the use of nanodrug delivery for AD as seen in the scientific literature from two search engines, PubMed and Science Direct, is shown in Figure 1. Figure 1 shows that the number of scientific publications in PubMed increased from 55 in 2010 to almost 653 in the year 2020, indicating a 12-fold increase in publications.

Since the different approaches employed to tackle AD had been limited by the BBB which hinders the penetration of many drugs, yet some other methods which circumvent the BBB have significant drawbacks, the use of novel carriers for drugs becomes imperative. The progress of nanoparticle-based drug transport methods that could cross the BBB is novel and can benefit the treatment and management of AD. For example, the drug rivastigmine inhibits the enzyme in the brain which destroys acetylcholine, thus improving cognitive behavior and function in AD patients. The low concentration of rivastigmine reaching the brain however limits its clinical use. A study in an animal model has shown a significant increase in the

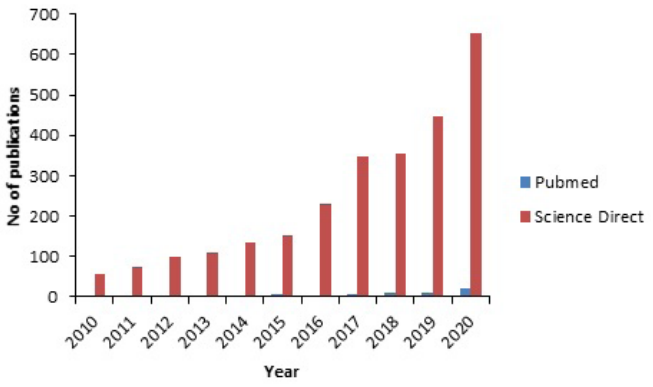


**Figure 1.** Scientific literature published on nanodelivery drug systems for AD per year.

concentration of rivastigmine reaching the brain when it was loaded into nanocarriers (Brambilla *et al*., 2011).

## Unique Studies on the Use of Nanodelivered Drugs for AD

The bioavailability and brain delivery of active pharmaceutical ingredients have been reported to have great improvement using peptide–polymer conjugates (Antunes *et al*., 2013). These conjugates achieve such by promoting the pharmacokinetic profiles of the drugs through an increase in their molecular mass, thus offering protection from proteolytic enzymes (Antunes *et al*., 2013). For example, peptides have low bioavailability and metabolic firmness in a normal physiological environment, and the conjugation of peptides to polymers in nanoparticle drug carrier schemes has prospects in handling neurodegenerative diseases by improving the stability and bioavailability (Gentilucci *et al*., 2010).

Nanoparticles of functional siRNA were prepared using peptide-tagged polyethylene glycol (PEG)-related chitosan polymer and used against the Ataxin-1 gene in an *in vitro* model of neurodegenerative disorder. The outcome showed the suppression of SCA1 protein within two days, which is of great influence on the therapy of AD, Parkinson's disease, and others (Malhotra *et al*., 2013). The beneficial influence of using nanoparticulate formulations in the management of neurodegenerative diseases has been expanded with the use of cerium oxide nanoparticles. Their unique characteristics include the average nanosize which enables its crossing of the BBB in addition to its antioxidant properties (Naz *et al*., 2017).

## Typical Examples of Nanoparticles that have Shown Promise

Typical examples of nanoparticles that have shown promise include liposomes (Mourtas *et al*., 2014), niosomes, polymeric nanoparticles, micelles (Hagl *et al*., 2015), solid lipid nanoparticles (SLN; Dang *et al*., 2014), nanostructured lipid carriers (NLC; Puglia *et al*., 2012), and nanoemulsions (Sood *et al*., 2014). Methods that have been used in the preparation of nanodelivery drugs are presented in Table 1. Nanoparticulate drug delivery systems have diverse benefits such as the incorporation of oily and aqueous drugs, high drug loading, improved stability, scaling up, avoidance of organic solvent, and drug targeting (Muller *et al*., 2000).

The conveyance of nanoparticles to the brain in the amelioration of neurodegenerative diseases is influenced by diverse factors. They include particle size, diffusion of molecules to the brain parenchyma, modification of BBB in neurological disorders, and formation of corona biomolecules on nanoparticle surfaces (Masserini, 2013). Particle sizes that have been reported to cross the BBB vary depending on the drug, route of administration, and formulation type. For example, intravenous dendrimer of about 12 nm crossed, while larger particles could not (Sarin *et al*., 2008). In another study, orally administered gold nanoparticles with a size lower than 58 nm were reported to have crossed the BBB (Schleh *et al*., 2012). The SLNs and NLCs contain solid lipid matrices obtained from triglycerides, waxes, and complex mixtures of glycerides; the lipophilic structures of these preparations enable the crossing of the BBB by endocytic mechanism (Kreuter, 2001; Wang *et al*., 2002; Wissing *et al*., 2004).

*Ginkgo biloba* extract (GbE) prepared as phytosomes was orally administered to rats and compared to sodium nitrite treatment; the results showed that GbE-phytosomes increased the action of enzymes involved in scavenging free radicals in all parts of the brain (Naik *et al*., 2006). Furthermore, two formulations (niosome and tablets) containing G. biloba extract were prepared and the in vivo distribution in rats was studied. The content of flavonoid glycoside biomarker in the blood, lung, and brain of the rats was considerably higher for the GbE-niosome-treated rats when compared to the tablets (Jin *et al*., 2013). The rats which received the tablets had no flavonoid glycosides in the brain tissue, but they were observed in those that received niosomes. The study reported a higher accumulation of GbE in the brain, and the

**Table 1.** Methods that have been used in the preparation of nano delivery drugs.

| S.No | Method | References |
|---|---|---|
| 1. | High-Pressure Homogenization | Lee *et al*., 2014a; 2014b |
| 2. | Microfluidization | Jo and Kwon, 2014 |
| 3. | Particle replication in non-wetting templates | Gratton *et al*., 2007; Chu *et al*., 2013; Galloway *et al*., 2013 |
| 4. | Spray drying | Ali and Lamprecht, 2014 |
| 5. | Spontaneous emulsification or solvent diffusion | Calvo *et al*., 1997; Murakami *et al*., 1999 |
| 6. | Nanoprecipitation | Bilati *et al*., 2005; Mazzarino *et al*., 2014 |
| 7. | Polymer polymerization | Boudad *et al*., 2001; Souto *et al*., 2012 |
| 8. | Supercritical fluid technology | Hu *et al*., 2011 |
| 9. | Emulsion solvent evaporation | Mainardes *et al*., 2005; Mainardes and Gremião, 2012 |
| 10. | Coacervation | Dong *et al*., 2013; Arora *et al*., 2011 |
| 11. | Sonication | da Silva *et al*., 2014 |

pharmacokinetic profiles and *in vivo* drug distribution indicate the superior properties of niosomes in conditions affecting the brain such as ADs compared to tablets (Fonseca-Santos *et al*., 2015).

Liposomes have been used as nanocarriers to overcome the BBB using the intranasal pathway (Mainardes *et al*., 2006). Studies on liposomes loaded with rivastigmine prepared by lipid hydration for intranasal delivery to the brain showed that intranasally delivered liposome was 10-fold higher in plasma compared to the intranasally or orally delivered free drug (Arumugam *et al*., 2008). In addition, rivastigmine-loaded liposome administered intraperitoneally to AD animal model indicated that the liposome formulations demonstrated the highest inhibition of AChE showing its potential in alleviating AD (Mutlu *et al*., 2011).

Nanoparticles of poly(D, L-lactide-co-glycolide) and poly(butyl cyanoacrylate) loaded with rivastigmine were produced by emulsion polymerization and adapted method of nanoprecipitation; the rivastigmine-loaded nanoparticles were administered to mice with scopolamine-induced amnesia. The results showed that mice given rivastigmine-loaded nanoparticles showed a considerable reduction in amnesia, while the control group which received rivastigmine dissolved in saline did not reveal any improvement in memory or learning capacities (Joshi *et al*., 2010).

To improve the uptake of rivastigmine to the brain through intranasal delivery, chitosan nanoparticles were produced by ionic gelation and the concentration of the drug *in vivo* was studied using confocal laser scanning. The results indicated that the amount of rivastigmine in the brain was found to be profoundly higher when matched to rivastigmine solution using the same intranasal or intravenous routes (Fazil *et al*., 2012).

Curcumin-conjugated nanoliposomes prepared and administered by injection *in vivo* in mice showed that the Aβ deposits of the hippocampus and neocortex of the animals were specifically stained (Lazar *et al*., 2013). This is considered a strong reflection that the nano-liposomes can find application in diagnosis and directed drug transfer for AD.

Studies have shown that microemulsions for transdermal delivery can be used in the management of AD with improved outcomes. Patel *et al*. (2013) compared the results of microemulsions loaded with huperzine A for transdermal usage and huperzine A suspension given orally to mice. The group for huperzine A microemulsions exhibited enhanced perceptive roles when related to mice to which Huperzine A suspension was administered peroral. Curcumin-loaded nanoemulsions administered through the intranasal route have also led to significant improvement in learning and memory in animals compared with animals treated with pure curcumin (Sood *et al*., 2013). Some patented nanoparticulate delivery systems for neurodegenerative diseases are shown in Table 2.

## Challenges of Nanoparticle Drug Delivery in the Management of AD

The application of nanodelivery drugs in the management of AD has some challenges despite the advantages. A search in the scientific literature showed that clinical activities of nanodelivered solutions for AD are scarce in comparison to cancer and other diseases (Wen *et al*., 2017). The industrial perspectives, processing, cost, and comparable benefits of using nanodelivery systems for AD treatment are also down-played (Wen *et al*., 2017). This can limit the production of nano-based drug delivery systems for AD. Many studies have been carried out on animals; however, there is the need to step up research from lower animals to higher ones and then to human trials. This is crucial because no current evidence has been documented showing the effectiveness and safety boundary of nanoparticles in patients having AD (Kassem *et al*., 2020). The physicochemical properties of nanoparticles are also important aspects requiring consideration in utilizing the delivery system for AD management. For example, sizes lower than 100 nm are preferable for use in neurodegenerative ailments like AD; higher sizes affect the biodistribution and bioavailability of embedded drugs (Hoshyar *et al*., 2016).

The stability of nanoparticulate formulations is also of importance as the aggregation of dispersed particles in the blood must be prevented, otherwise toxicity can occur (Gnach *et al*., 2015). Where gene-targeting brain delivery is to be used, the invasive method must be avoided in delivering the drug into the brain tissues, otherwise the blood–brain barrier may become injured; an example is the PEGylated immune-liposomes via receptor-mediated transcytosis (Kabanov and Batrakova, 2017). Furthermore, whenever there is elongated blood circulation time, some nanoparticles, e.g., PEGylated nanoparticles, will offer lower uptake and prolonged time (Ou *et al*., 2018). The safety of nanodelivery systems in AD management and other vital areas are challenging for the uptake of nanodelivery systems in brain infirmities. Cost-effectiveness is another major challenge in the application of nanodelivered solutions for AD. Clinical trials are expensive studies that will ultimately add to the cost on the patient thus reducing the number of patients who can benefit from the nanodelivered medications (Wen *et al*., 2017).

## Future Perspectives on the Management of AD

The FDA has not approved a new drug for AD in the last 17 years, but the organization plans to decide on Aducanumab, a new drug produced by Biogen Inc. for the treatment of AD in

**Table 2.** Patents of nanoparticulate delivery systems for neurodegenerative diseases.

| Product | Institution | Patent No | Properties | Inventor |
|---|---|---|---|---|
| Nanoparticle-based technology | Medinova Medical Consulting GmbH, Germany | US6117454 | Enables BBB crossing with improved drug distribution and efficacy | Kreuter J, Alyautdin R, Karkevich D, Sabel B. |
| Patents on brain permeable nanoparticles | | US6607708 | Promotes penetration of drugs or diagnostic agents across the BBB | Saluja V, Chopra D |
| Nanogels with polyion polymer | University of Nebraska. | US6696089 | Site-specific delivery | Kabanov A, Vinogradov S |
| Differential delivery of therapeutic agents across BBB | National Institute of Health (NIH), Department of Health and Human Services | US5124146 | Utilizes drug neutralization technology, and the selective permeability | Neuwelt EA |
| An improved method for diagnosing and characterizing brain lesion | Oregon State Board of Higher Education | US5059415 | Diagnosis of Alzheimer's disease | Neuwelt EA |

March 2021 (Newton, 2020). The drug is a human monoclonal antibody engineered in a laboratory, and there are speculations that if approved, its coverage may be limited. This is probably due to debatable efficacy, high cost, and safety concerns (Budson, 2020).

For the future, magnetic nanoparticles, dendrimers, and nanoemulsions are fertile areas to explore for their potential technological applications (Harilal *et al*., 2019). Biocompatible nanoparticles will make a significant impact in the next 10 years and douse the safety concerns of nanodelivered medications in AD.

In the future, healthcare providers will need to do more on preventive measures for AD than treatment. According to the National Health Service, the risk of AD is lesser in people who sustain social and mental activities in addition to living healthy (NHS, 2018). Examples of mental and social activities which can prevent AD and other neurodegenerative ailments include reading, learning foreign languages, playing musical instruments, volunteering in local communities, participating in sports, picking up new hobbies, and playing games. Healthy lifestyle measures that will be helpful include not smoking, reducing alcohol intake, exercise, keep blood pressure under control, and maintaining specified diets for diabetics.

## CONCLUSION

AD is of significant public health importance, especially with increased life expectancy with the attendant increase in the number of the elderly. The management of AD has been negatively influenced due to the failure of most active moieties to permeate the BBB in sufficient concentration. The treatment of AD can be boosted with nanosized formulations containing conventional drugs or bioactive agents, and present opportunities for different methods of preparations to suit the active agents and varied routes of administration to achieve desirable therapeutic patient outcomes. Herbal extracts containing single or multiple herbs or a blend of herbs and minerals have neuroprotective potentials in slowing down the advancement of AD symptoms. These natural products are potential sources of bioactive agents that could be valuable in the management of AD. However, more medical evaluations are essential to further authenticate the usefulness of bioactive agents and novel drug delivery systems in the management AD.

## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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