Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Alzheimer's disease and its therapeutic treatment: A Review

Priyanka Singh*, Vinay Sharma, Sadhana Tripathi, Dakshi Verma, Bhawana Kharayat

Department of Bioscience and Biotechnology, Banasthali University, Rajasthan, India.

ARTICLE HISTORY

Received: 18.10.2017

Accepted: 30.01.2018

Available online: 30.03.2018

Keywords:

Alzheimer, chemotherapeutic treatment, Nanotechnology

***Corresponding author:**

Email : priyay20@gmail.com
Tel.: 01438-228313

ABSTRACT

Alzheimer's disease (AD) is developing gradually with various types of neurodegenerative disorder, which causes chronic disease in the late adult life. Pathologically it is characterized by intracellular neurofibrillary tangles and extracellular amyloidal protein deposits contributing to senile plaques. The chemotherapeutic treatment based on acetylcholinesterase inhibitors (donepezil ,rivastigmine, galantamine,) and N-methyl D-aspartate receptor antagonist (memantine) have led to promising investigational therapies. These drugs reduce the development of the disease, provide temporary relief but fail to achieve a definite cure. In the last couple of years, nanotechnology offers a novel strategy to treat AD disease by increasing the bioavailability of drug across the blood brain barrier in neuronal system of brain.

This review article will highlight extensive discussion on the possible therapeutic treatment of alzheimers disease based on chemodrugs and ongoing efforts of nanotechnology to develop novel therapies.

INTRODUCTION

Alois Alzeihmer has first coined the term "Alzheimer's disease (AD)" for neurodegenerative disorder among late adulthood. Classic clinical features of Alzheimer's disease are an amnesic type of memory impairment [1,2,3], deterioration of language[4], and visuospatial deficits [5]. This is caused by the formation of amyloid rich senile plaques [6] and neurofibrillary tangles [7], which cause death of neuronal cell and results impairment of cognitive skills, linguistic ability, poor understanding and poor judgment [8].

This disease is rapidly growing in whole world and currently the number of people with dementia is expected to grow from 35 million to 65 million by the year 2030 [9,10,11]. This disease affects 10% of people over the age of 65% and 50% of people over the age of 85. This disease is about 1.5 times more likely to develop in women than in men [12]. This disease is categorized in three classes of mild, moderate and severe according to symptoms as listed in Table1. Magnetic resonance imaging and positron emission tomography contrast techniques have been applied to detect amyloid plaques and neurofibrillary tangles in AD patients (Fig.1). Food and Drug Administration (FDA) has approved the drug "Rivastigmine tartrate" for the treatment of AD, but it has many drawbacks like cholinergic side effects, necessitating frequent dosing and restricted entry into brain due to its hydrophilicity [13,14]. In pharmaceutical research, targeting of drugs to the brain is one of the most challenging issues, as many hydrophilic drugs and neuropeptides are unable to cross the bloodbrain barrier (BBB). The insufficient absorptibility of drug within brain system might be due to high lipophilic nature of the Blood Brain Barrier.

Many strategies have been developed to overcome this problem which includes chemical delivery systems, magnetic drug targeting and nanoparticle based drug delivery system. The major neuroprotecting factor approaching nanotechnology includes polymeric nanocarriers and metal-chelator nanocarriers (including iron, gold and copper chelators). Recently polymeric nanoparticles have attracted great attention as potential drug delivery systems due to their small size. Nanoparticles penetrate into small capillaries and results an efficient drug accumulation at the targeted sites in the body. For nanoparticle preparation, biodegradable materials are used that allows sustained drug to release at the target site over a period of days or even weeks after injection. Drugs like loperamide, tubocurarine, hexapeptide-dalargin, and dipeptide-kyotorphin, doxorubicin have been successfully delivered into the brain using the carrier poly (butyl cyanoacrylate). The higher degree of bioabsorptibility and bioavailability of nano encapsulated drug into the brain cells open a new era for treating diseases such as brain tumors, multiple sclerosis and Alzheimer [13,14].

Biocompatible nanoparticle of range 1-100nm has been used to target delivery system for Rivastigmine drugs to overcome blood brain barrier (BBB) and minimize the side effects caused by over-dose. Biocompatible materials with enhanced optical and magnetic properties are excellent alternative agents for early

Table 1 : Symptoms of all stages of Alzheimer's disease

Stages of Alzheimer	Physiological change in cerebral cortex	Symptoms
Mild (Duration:2years)	Disease spreads to the lateral temporal and parietal lobes	Memory loss, reading problem, mood swings, poor object recognition, poor direction sense,
Moderate: (Duration:2years)	Disease spreads to frontal lobe	Poor judgment, short attention, personality changes, , long term memory affected, wandering, aggression, confusion,
Severe: (Duration:3years)	Disease spread to Occipital lobe	Visual problem, Gait, bed ridden, long term care is needed

stage diagnosis in Alzheimer's patient.Nanoparticles (NPs) with high affinity for the circulating amyloid-beta (Aβ) firms may induce “sink effect” and improve the Alzheimer disease (AD) condition. Ultrasensitive nanoparticle based bio-barcodes; immunosensors as well as scanning tunneling microscopy were used as in vitro diagnostic techniques to detect Aβ plaques in alzheimers patients

This review will highlight the progress in treatment of alzheimer's disease by comparative analyzing the role of various chemotherapeutic treatment and nanoencapsulated drugs.

1.1 Chemotherapeutic Treatment

Treatment of Alzheimer's disease is a major challenge, since drug delivery to the brain depends on their ability of formulation to pass through numerous protective barriers surrounding the central nervous system. In this disease, glutamate and acetylcholine secreting from neurons and their associated synapses are generally damaged. Some chemodrugs have been designed by targeting following specific neurotransmitter of

Table 2 : List of FDA-approved drugs for treatment of Alzheimers disease

Chemodrug	Year of FDA Approval	Stages of AD patient	Mechanism of action
TACRINE (Brand name-cognex®)	1993	Mild to Moderate	It is a cholinesterase inhibitor which increases the availability of acetylcholine in muscarinic neurons. It has a mean bioavailability of about 17 percent after oral administration[44,45].
DONEPZIL(Brand name-Aricept)	1996	All stages	It is an indanone benzylpiperidine derivative having selective reversible acetylcholine esterase inhibitor activity. It is approximately 10 times more potent than tacrine as an inhibitor of acetylcholinesterase , and 500–1000-fold more selective for acetylcholine esterase over butylcholinesterase [46].
RIVASTIGAMINE (Brand name-Exelon,	2000	All stages	It is a slowly reversible inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) and effectively inhibit the formation of Aβ-plaques [47].
GALANTMINE (Brand name-Razadyne)	2001	mild stage	It is specific, competitive and reversible acetylcholinesterase inhibitor [48].
MEMANTINE	2003	Moderate stage	It is voltage-dependent and uncompetitive binds to NMDA-receptor antagonist which results inhibition of excessive calcium influx induced by chronic overstimulation of the NMDA receptor[49]

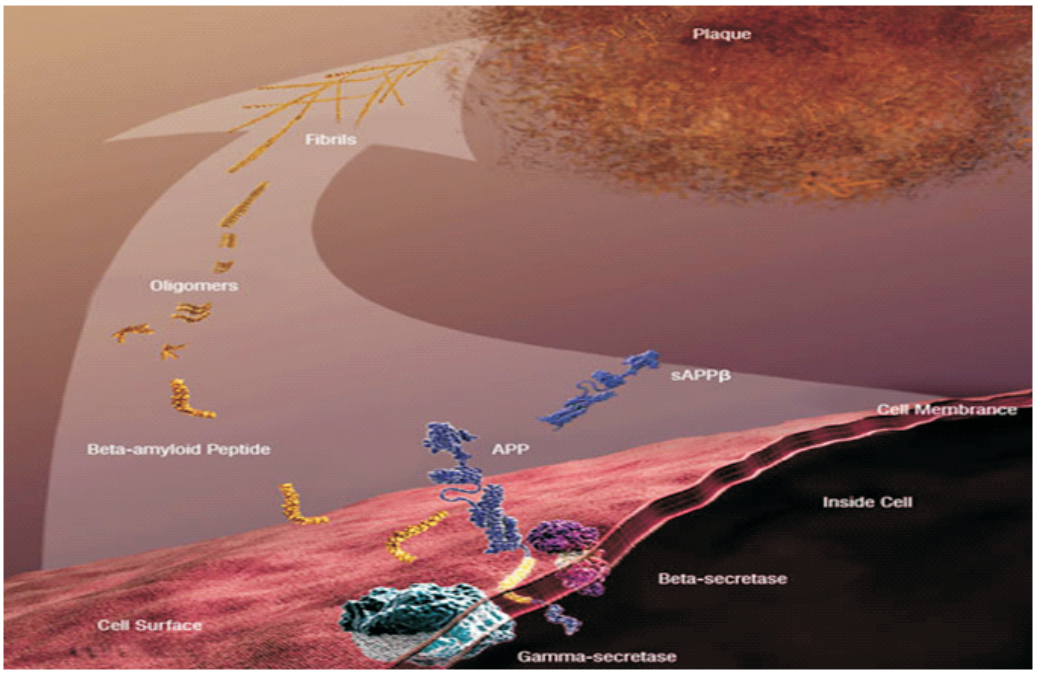

Fig. 1 : Neural degradation in cerebral cortex of Alzheimer's patient due to formation of extracellular fibrillar amyloid-beta (Aβ) plaques [13] (https://www.thealzheimerssolution.com/plaques-and-tangles-in-the-alzheimers-brain-which-one-is-most-to-blame-for-alzheimers-disease/)

brain:

1.1.1 Drug based on Acetylcholinesterase inhibitors (AChEIs)

These drugs improve memory function and attention in AD patients by interfering with the breakdown of acetylcholine, thereby increasing the levels of the neurotransmitter at the synapse. These inhibitors play crucial role in signal neurotransmission and also considered for the anti-inflammatory action to establish neural protection in the brain. Some AChEIs drugs commonly used for treatment of this disease are listed in Table2. Recent researches have also approved the direct link between the cholinergic and inflammation through 'cholinergic anti-inflammatory pathway'. Subsequently, AChEIs suppress the secretion of cytokines from monocytes and microglia as well as they also prevents the cell from free radical toxicity [15]. They have been claimed for indirect effects on cerebrovascular function improving brain perfusion and for the promotion of non-amyloidogenic pathways for amyloid precursor protein processing. The intake of these drugs results side effects like nausea, vomiting, loss of appetite and increased frequency of bowel movements, headache, constipation, confusion and dizziness.

1.1.2 Drug based on NMDA- receptor antagonist

Glutamate neurotransmitter binds to N-methyl D-aspartate receptor (NMDA) and regulate cell signaling process by permitting exposure of the cell to calcium ions (Ca^{2+}). In alzhiemer's patient, elevation of glutamate level leads to excess flow of Ca^{2+} ion at the post synaptic nerve cells and cause damage to nerve cells. Memantine as another FDA-approved drug for AD patients bind efficiently to NMDA (glutamate) receptor. Under the condition of strong transient glutamate signal, this binding will be collapsed due to voltage dependent nature of memantine [16]. These drugs also showed some side effects like gastrointestinal upset, dizziness, and headache. Memantine (1-amino-3, 5-dimethyladamantane) with Namenda as its commercial name is FDA-approved drug for treatment of moderate to severe Alzheimer's disease. Memantine acts as a neuroprotective agent against excitotoxicity, an excessive exposure to the excitatory neurotransmitter, glutamate, or overstimulation of its membrane receptors, leading to neuronal injury or death. Excitotoxic neuronal cell death is mediated, in part, by overactivation of N-Methyl-D-Aspartate (NMDA)-type glutamate receptors. Nevertheless, NMDA receptor activity is also essential for normal neuronal function. This means that potential neuroprotective agents that block virtually all NMDA receptor activity will very likely have unacceptable clinical side effects. Memantine preferentially blocks excessive NMDA receptor activity without disrupting normal activity**[17]**. Although memantine is already approved by FDA for Alzheimer's disease treatment, studies are underway for other diamondoid derivatives which could have stronger neuroprotective and possibly regenerative capability as well as their application for the treatment of diseases related to glutamatergic dysfunction. In recent year, Memantine encapsulated with Diamondoids are in commercial use to slow down the progression of the Alzheimer's disease.

Fullerenols is a water soluble hydroxyl functionalized derivative of fullerene which showed neuroprotective properties against amyloid plaques (Aβ) on NMDA receptor site. These may neutralize the effect of oxidative stress in the brain due to their antioxidant property. Some functionalized fullerene derivatives including carboxyfullerene and hydroxyfullerene (*fullerenols*), are being used as effective drugs for treatment of alzheimers patients [18,19,20].

1.2 Other supplementation therapy

L-methionine, the principal sulfur-containing amino acid in proteins, plays critical roles in cell physiology as an antioxidant and in the breakdown of fats and heavy metals [21,22,23,24,25). Methionine is also used to produce creatine, which is an essential

compound for energy production and muscle building [26]. In addition, it may be useful in the treatment of depression [27,28]; and also improve memory recall. Methionine deficiencies can trigger several alterations, such as fatty liver, slow growth, weakness, edema and skin lesions [29,30]. Conversely, severe methionine deficiency might cause dementia [31]. The effect of methionine on the brain of mice was studied by supplying methionine enriched [32,33] and results showed that the brains of mice with a methionine-rich diet presented increased levels of phosphorylated *tau* protein, amyloid-β (Aβ) peptides and Aβ oligomers, neuroinflammation, nitro-tyrosinated protein (marker of oxidative stress), decreased levels of pre- and post-synaptic proteins, and memory impairment accompanied by the loss of function of the *Wnt* signaling pathway. These results suggest that a methionine-enriched diet triggers neurotoxic effects *in vivo* and might contribute to the appearance of Alzheimer's-like neurodegeneration [34]. L-methoininase isolated from microbial strains can be used as enzyme supplemention therapy to reduce level of L-methioinine in diet and hence improve the condition in Alzheimers patients.

Resveratrol is a polyphenolic phytochemical component (3,4',5-trihydroxystilbene) which are widely present in grapes, berries, and peanuts. This component is preferred for the treatment of cancers, tissue injury, cardiovascular disease and also used in reducing the risk of neurodegenerative disorders, especially Alzheimer's disease (AD). This component acts as neuroprotective agent in AD patients by promoting non-amyloidogenic cleavage of the amyloid precursor protein and enhancing clearance of amyloid beta-peptides [35].

Nattokinase enzyme isolated from a specific fermented soup of Japan called as" Natto" prevent neuronal damage in AD patients by dissolving amyloid fibrils responsible for formation of plaque in the brain cells. It has also tendency to dissolve blood clots and hence minimized the risk of thrombosis and heart attacks [36].

Lipoic acid acts as cofactor for pyruvate dehydrogenases and α-ketoglutarate dehydrogenase present in mitochondria. This component chelates redox-active transition metals and thus inhibits the formation of hydroxyl radicals. It also scavenges reactive oxygen species (ROS), thereby increasing the levels of reduced glutathione. It also regulates the expression of redox-sensitive pro-inflammatory proteins including tumor necrosis factor and inducible nitic oxide synthase. It can scavenge lipid peroxidation products such as hydroxynonenal and acrolein. In human plasma, this component exists in an equilibrium of free and plasma protein bound form. Alzheimer's patients show high level of improvement on admistration of lepoic acid with drugs based on ACHEIs. Some study also showed that the intake of lipoic acid along with nutraceuticals such as curcumin, epigallocatechin gallate and docohexaenoic acid synergistically decreases oxidative stress, inflammation, Aβ plaque and thus provide a combined benefit for the treatment of AD[37].

1.3 Nanotechnology solution

Recently nanotechnology has improved therapeutic effectiveness of these AD drugs by overcome the limitation of chemodrugs of penetrating the protective blood-brain barrier. Nanotechnology makes use of the engineered polymeric materials to design devices with the small functional organization on the nanometer scale (1-100 nm) that are able to interact with biological systems at a molecular level. They induce desired physiological responses while simultaneously minimizing undesirable side effects by stimulating, responding and interacting with target cells and tissues. This provides many ways to manipulate complex biological systems with greater selectivity [8]. This technology can be used to develop diagnostic tools as well as nano-enabled delivery systems that can bypass the Blood Brain Barrier in order to facilitate conventional and novel neurotherapeutic interventions such as tissue regeneration, drug therapy and gene therapy. This is used to process the discovery of drug target, drug delivery, biomarkers and molecular diagnostics, which could be relevant to the management of Alzheimer Disease and Parkinsons Disease [8].

Pharmaceutical scientist got attracted by nanoparticles in the drug delivery system due to versatility in targeting tissues, accessing deep molecular targets and controlling drug release. Nanoparticles are composed of synthetic, natural or semi-synthetic polymers encapsulating the drug molecule and are solid colloidal drug carriers ranging from 10-100 nm in diameter. Due to its biodegradability, biocompatibility, easier formulation techniques and versatility in application aided with low toxicity chitosan offers certain advantages over others amongst the polymeric carriers for nanoparticulate drug delivery [38]. Nanomedicines in the form of drug carriers (e.g., particles, liposomes, dendrimers) play an important role to warrant safe and efficient delivery of active compounds to their intended site of action. The advantages of nanoparticles over microparticles include the ability to improve drug encapsulation, bioavailability as well as therapeutic efficacy and pharmacokinetics. Nanotechnology has opened up a new span in the field of drug delivery. The polymeric carriers should be easy to synthesize and characterize inexpensive, biocompatible, biodegradable, non-immunogenic, non-toxic and water soluble for delivery of nanodrugs [38].

Nanomedicine formulation depends on the choice of suitable polymeric system having maximum encapsulation efficiency, improvement of bioavailability and retention time. Desired nanomedicines are generally achieved by hit and trial method. The encapsulation process with polymeric nanoparticles is in more advance condition in comparison to other nanoparticle systems. The formulations of nanodrugs are superior to traditional medicine with respect to control release, targeted delivery and therapeutic impact. These targeting capabilities of nanomedicines are influenced by hydrophobicity, particle size, surface charge, and surface modification. Size distributions of nanoparticles are important to determine their interaction with the cell membrane and their penetration across the physiological drug barriers. Size of nanoparticles for different biological barriers is dependent on the tissue, target site and circulation. For the cellular internalization of the nanoparticles, surface charge is important in determining whether the nanoparticles would cluster in blood flow or would adhere to, or interact with oppositely charged cells membrane. Cationic surface charge is desirable as it promotes interaction of the nanoparticles with the cells and hence increases the rate and extent of internalization. For targeted delivery, persistence of nanoparticles is required in systemic circulation of the body [39]. The major neuroprotecting agents approaching nanotechnology include metallic nanoparticles and biodegradable nanoparticles.

1.3.1. Metallic nanoparticle

Silver nanoparticles for these drugs improved their bioavailability and biosorptibility in targeted sites in brain. These nanodrugs showed the possible ways for penetration into the

brain cell cytoplasm and the possibility of inducing effective cellular changes which are required for the specific treatment of AD patient [40].

Gold nanoparticles have specific binding affinity for anti-amyloid (Aβ) components present in cytoplasm of brain because of their high surface-to-volume ratio along with its specific mobility. These fibrillar amyloids plaques complexed with gold nanoparticles are being solubilized by weak-microwave fields and by implementing thermal energy at molecular level [17]. Although, this approach has a possible disadvantage of the formation of small neurotoxic oligomeric species associated with the breakdown of amyloid plaques. Therefore, some specific improvement is necessary for the advancement of this approach to make them more defined, non-toxic and even more effective.

Metal ions such as Fe^{2+}, Cu^{2+} are normally present with significant concentration in the brain. Any deviations in the homeostatic regulating mechanisms of these metal ions may lead to the presence of their higher concentration than in the normal conditions [41]. Due to the presence of some specific metal binding sites on Amyloid-β peptide (Aβ), these excess metal ions (Fe^{2+} and Cu^{2+}) lead to Aβ aggregation. This interaction result into the production of neurotoxic hydrogen peroxides which causes the oxidative injury in the AD patients. Recently, the chelator nanoparticle systems (CNPS) have been used to reverse the amyloid aggregations and also to decrease the extracellular oxidative stress. CNPS was produced by the bond formation between amino group of FDA approved metal chelator known as Desferrioxamine and the carboxyl group present on the surface of nanoparticles. Successful traverse of the iron chelator across the BBB was reported with the use of CNPS. Moreover, the successful traverse of CNPS in the reverse direction was also observed across the BBB. Undoubtfully the neurotoxic effect associated with use of metal chelators was also decreased with the use of conjugated Desferrioxamine. Nowadays, nanoparticle-chelator conjugates (Nano-N2PY) were introduced for the inhibition of neurotoxic effects on the human brain cortical neurons to result successful transmission of metal chelators across the Blood Brain Barrier.

The conjugation of D-penicillamine drug with the nanoparticles containing, 1,2-Dioleoyl-snglycero-3-phosphoethanolamine-N-[4-(p-maleimidophenyl)butyramide] and pyridyldithio-propionyl phosphoethanolamine was demonstrated for the AD treatment. Success transportation of D-penicillamine through the BBB in spite of its highly hydrophilic properties was observed with its Aβ42 solubilizing capability as well [42]. These conjugation methods showed some disadvantages like hindrances in passing across the blood brain barrier (BBB), possibility of non-defined metal chelation from other tissues and pooling of metal ions into fibrillar amyloid plaques. Association of metal chelation therapy with nanotechnology approaches has provided some recent modification in this strategy to overcome these obstacles in AD treatment.

1.3.2. Role of Biodegradable Nanoparticle for improved solubility of drugs

Biodegradable nanoparticles are mostly used for improving the therapeutic value of various water soluble/insoluble medicinal drugs and bioactive molecules by improving bioavailability, solubility and retention time. These nanodrugs formulation reduces the risks of toxicity and patient expenses. Drug efficacy, specificity, tolerability and therapeutic index of corresponding drugs are increased by drug efficacy of medicinal drugs. These nanomedicines have many advantages in respect to the protection of premature degradation and interaction with the biological environment, enhancement of absorption into a selected tissue, bioavailability, retention time and improvement of intracellular penetration. Many disease related drugs/bioactive molecules are successfully encapsulated to improve bioavailability, bioactivity and control delivery [38]. Biodegradable polymeric nanoparticles are mostly preferred because of slow controlled/sustained release property, subcellular size and biocompatibility with tissue and cells. Apart from this, these nanomedicines are non- inflammatory, biodegradable, non-toxic, nonthrombogenic, non immunogenic, avoid reticulo-endothelial system, do not activate neutrophils, stable in blood, and are applicable to various molecules such as drugs, proteins, peptides, or nucleic acids. The drug molecules can be bound to surface as nanosphere or can be encapsulated inside as nanocapsules [39]. Biodegradable nanoparticles can be used for modulating the drug release profile by controlling the polymer degradation [13].

Biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA), poly(glycolic acid) (PGA) and poly(lactic acid) (PLA) have been approved by FDA for certain medical applications, because their products of degradation are eliminated from the body in the form of carbon dioxide and water [43]. Biodegradable polymers can be obtained from natural origin or “biopolymers” produced by living organisms during the cell growth cycle. They can also be manufactured, which is a great advantage for these materials because they show great synthesizing flexibility. Biodegradable polymers have the possibility to become a part of new medical devices with specific and unique physical, chemical, and mechanical properties, such as mechanical strength, electrical conductivity, chemical reactivity and optical properties. The development of matrices to control the release of drugs into specific sites in the body is the goal of biodegradable polymeric materials [43]. Therefore, there are nanodrugs specifically designed to carry therapeutic molecules that are directly coupled, functionalized, coated, or entrapped in devices produced by controlled manipulations of size and shape at the nanometer scale. Nanoparticles composed of biodegradable polymers have been used for the treatment of neurodegenerative diseases, because of their efficient ability to cross the blood-brain barrier and their high drug-loading capacity. They are also used in the diagnosis and treatment of cardiovascular disease, because of their size, shape, and an available surface area for biomolecule conjugation. Biodegradable polymeric nanoparticles influence the pharmacokinetic behavior of drugs by sustained release of nerve growth factor encapsulated in poly phosphoesters [43]. The degradation of biodegradable polymers may lead to complete elimination of degradation products from the organism. The mechanisms of degradation for different polymers depend on the chemistry, molecular weight, and morphology of each type of polymer, and environmental factors such as pH or temperature. Degradation occurs mainly by hydrolysis, oxidation, or enzymatic reactions.

Chitosan (mucopolysaccharide) exhibits greater solubility and faster degradation due to its low molecular weight. Chitosan nanoparticles have applications in nonviral gene delivery, vaccine delivery, ocular drug delivery, electrodeposition, brain targeting drug delivery, parentral drug delivery, per-oral administration of drugs, mucosal drug delivery in controlled drug delivery of drugs, in tissue engineering and in the effective

delivery of insulin [38]. Chitosan nanoparticles loaded with Poly ethylene glycol (PEG) are also used for treating Parkinson's disease because of high permeability for the blood-brain barrier and property of nonimmunogenic. The relative bioavailability of dopamine drug has been modified by incorporating into a smart nanocrystal conjugated with PEG and covered by a carbohydrate shell allowing recognition of glucose transporter [43].

1. Concluding remarks and perspectives

From last few decades, tremendous efforts have resulted in numerous inventions to improve drug delivery in Alzheimer's patients. Nanotechnology has been used as an effective approach to improve the drug delivery system by encapsulating AD drugs onto metallic and polymeric nanoparticle carrier system. This review article has laid possible therapeutic treatment of Alzheimer patients by discussing the comparative analysis of chemotherapeutic treatment versus treatment based on nanotechnology.

ACKNOWLEDGEMENT

We are thankful to Banasthali University for providing resources for analysis of literature in this manuscript.

REFERENCES

1. Greene JD, Baddeley AD, Hodges JR. Analysis of the episodic memory deficit in early Alzheimer's disease: evidence from the doors and people test. Neuropsychologia. 1996; 34(6):537-551.
2. Standaert DG, Young AB. Treatment of central nervous system disorders. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics. 2001; pp 549568, McGraw-Hill: New York.
3. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimers Res Ther 2014; 6(4), 37.
4. Price DL, Borchelt DR, SisodiaSS. Alzheimer disease and the prion disorders amyloid beta-protein and prion protein amyloidoses. Proc Natl Acad Sci USA. 1993; 90: 6381-6384.
5. Kirk A, Kertesz A. On drawing impairment in Alzheimer's disease. Arch Neurol1991; 48(1), 73-77.
6. Selkoe DJ. The origins of Alzheimer disease: α is for amyloid. JAMA. 2000; 283(12):1615-1617.
7. Spillantini MG, Goedert M. Tau protein pathology in neurodegenerative diseases. Trends Neurosci. 1998; 21(10):428-433.
8. Modi G, Pillay V, Choonara YEAdvances in the treatment of neurodegenerative disorders employing nanotechnology. Ann NY Acad Sci 2010; 1184:154-172.
9. Brookmeyer R., Gray S., Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health. 1998; 88(9):1337-1342.
10. Wimo A, Winblad B. Health Economical Aspects of Alzheimer Disease and its treatment. Psychogeriatrics. 2001; 1:189-193.
11. Huang Y, Mucke L.).Alzheimer Mechanisms and Therapeutic Strategies. Cell. 2012; 148(6): 1204-1222.
12. Gao S, Hendrie HC, Hall KS, Hui S. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. Arch Gen Psychiatry1998; 55(9), 809-815.
13. Joshi SA, Chavhan SS, Sawant KK. Rivastigmine-loaded PLGA and PBCA nanoparticles: Preparation, optimization, characterization,in vitro and pharmacodynamic studies. Eur J Pharm Biopharm 2010; 76:189-199.
14. Cirrito JR, Holtzman DM. Amyloid β and Alzheimer disease therapeutics: the devil may be in the details. *J Clin Invest* 2003; 112(3):321-323.
15. Tabet N. Acetylcholinesterase inhibitors for Alzheimer's disease: anti-inflammatories in acetylcholine clothing. *Age and Ageing*.2006; 35 (4):336-338.
16. Thomas SJ, Grossberg GT. Memantine: A Review of Studies into Its Safety and Efficacy in Treating Alzheimer's Disease and Other Dementias.*Clin Interv Aging*. 2009; 4: 367377.
17. Nazem A, Mansoori GA. Nanotechnology for Alzheimer's disease detection and treatment. Insciences J 2011; 1(4):169-193.
18. Vorobyov V, Kaptsov V, Gordon R, Makarova E, Podolski I, Sengpiel F. Neuroprotective effects of hydrated fullerene c60: cortical and hippocampal EEG interplay in an amyloid-infused rat model of Alzheimer's disease. J Alzheimers Dis. 2015; 45 : 217233.
19. Xie L, Luo Y, Lin D, Xi W, Yang X, WeiG. The Molecular Mechanism of Fullerene-Inhibited Aggregation of Alzheimer's β-Amyloid Peptide Fragment. Nanoscale. (2014); 6 (16): 9752-9762.
20. Dugan LL, Turetsky DM, Du C, Lobner D, Wheeler M, Almli CR, Shen CK, Luh TY, Choi DW, Lin TS. Carboxyfullerenes as neuroprotective agents. Proc Natl Acad Sci USA1997; 94(17):9434-9439.
21. Irwin MI, Hegsted DM. A conspectus of research on amino acid requirements of man. J Nutr 1971; 101(4):539566.
22. Millward J. Amino acid requirements in adult man. Am J Clin Nutr. 1990; 51(3): 492496.
23. Levine RL, Mosoni L, Berlett BS, Stadtman ER. Methionine residues as endogenous antioxidants in proteins. Proc Natl Acad Sci USA1996; 93:1503615040.
24. Levine RL, Berlett BS, Moskovitz J, Mosoni L, Stadtman ER. Methionine residues may protect proteins from critical oxidative damage. Mech Ageing Dev 1999; 107:323332.
25. Stadtman ER, Moskovitz J, Levine RL. Oxidation of methionine residues of proteins: biological consequences. Antioxid Redox Signal. 2003; 5(5):577582.
26. Caso G, Garlick PJ. Control of muscle protein kinetics by acid-base balance. Curr Opin Clin Nutr Metab Care 2005;8(1):7376.
27. Mischoulon D, Fava M. Role of S-adenosyl-L-methionine in the treatment of depression: A review of the evidence. Am J Clin Nutr. 2002; 76(5):1158S1161S.
28. Hardy ML, Coulter I, Morton SC, Favreau J, Venuturupalli S, Chiappelli F, Rossi F, Orshansky G, Jungvig LK, Roth EA, Suttorp MJ, Shekelle P. S-adenosyl-L-methionine for

treatment of depression, osteoarthritis, and liver disease. Evid. Rep Technol Assess (Summ). 2003; 64:1-3.

29. Garlick PJ. Toxicity of methionine in humans. J Nutr 2006;136:1722S1725S.
30. Toue S, Kodama R, Amao M, Kawamata Y, Kimura T, Sakai R. Screening of toxicity biomarkers for methionine excess in rats. J Nutr. 2006; 136:1716S1721S.
31. Koladiya RU, Jaggi AS, Singh N, Sharma BK. Ameliorative role of Atorvastatin and Pitavastatin in L-Methionine induced vascular dementia in rats. BMC Pharmacol 2008; 8:14.
32. Hrncic D, Rasic-Markovic A, Stojkovic T, Velimirovic M, Puskas N, Obrenovic R, Macut D, Susic V, Jakovljevic V, Djuric D, Petronijevic N, Stanojlovic O. Hyperhomocysteinemia induced by methionine dietary nutritional overload modulates acetylcholinesterase activity in the rat brain. Mol Cell Biochem 2014; 396 (1-2):99105.
33. Velez-Carrasco W, Merkel M, Twiss CO, Smith JD. Dietary methionine effects on plasma homocysteine and HDL metabolism in mice. J Nutr Biochem. 2008; 19:362370.
34. Tapia-Rojas C, Lindsay CB, Montecinos-Oliva C, Arrzola MS, Retamales RM, Daniel Bunout D, Hirsch S, Inestrosa NC. Is L- Methionine a trigger factor for Alzheimer's loke neurodegeneration? Changes in A-β oligomers tau phosphorylation, synaptic proteins, wnt signalling and behavioral impairement in wild type mice. Mol Neurodegener. 2015; 10:62.
35. Li F, Gong Q, Dong H, Shi J. Resveratrol, a neuroprotective supplement for Alzheimer's disease. Curr Pharm Des2012; 18(1):27-33.
36. Barron J. Nattokinase enzyme reduces Alzheimer's risk, Baseline of Health Foundation. 2009; https://jonbarron.org/article/nattokinase-enzyme-reduces-alzheimers-risk.
37. Maczurek A, Hager K, Kenklies M, Sharman M, Martins R, Engle J, Carlson DA, Munch G. Lipoic acid as an anti-inflammatory and neuroprotective treatment for Alzheimer's disease. Adv Drug Deliv Rev.2008; 60(13-14): 1463-1470.
38. Nagpal K, Singh SK, Mishra DN. Chitosan nanoparticles: a promising system in novel drug delivery. Chem. Pharm. Bull. (Tokyo). 2010; 58(11):1423-1430.
39. Kumari A, Yadav SK, Yadav SC. Biodegradable polymeric nanoparticles based drug delivery systems. Colloids Surf. B Biointerfaces2009; 75(1):1-18.
40. Aliev G, Daza J, Herrera AS, Del Carmen Arias Esparza M, Morales L, Echeverria V, Bachurin SO, Barreto GE. Nanoparticles as Alternative Strategies for Drug Delivery to the Alzheimer Brain: Electron Microscopy Ultrastructural Analysis. CNS Neurol Disord Drug Targets. 2015;14(9):1235-1242.
41. Bush AI. Drug development based on the metals hypothesis of Alzheimer's disease. J Alzheimers Dis 2008; 15:223-240.
42. Liu G, Men P, Perry G, Smith MA. Nanoparticle and Iron Chelators as a Potential Novel Alzheimer Therapy. *Methods Mol Biol*. 2010; *610:*123 144.
43. Martin P, Giardiello M, McDonald TO, Rannard, SP, Owen A. Mediation of in vitro cytochrome P450 activity by common pharmaceutical excipients.Mol Pharm. 2013; 10(7):27392748.
44. Freeman SE, Dawson RM. Tacrine: a pharmacological review. Prog Neurobiol1991; 36(4):257-277.
45 Crismon ML. Tacrine: first drug approved for Alzheimer's disease. Ann Pharmacother 1994; 28(6):744-751.
46. Cacabelos R. Donepezil in Alzheimer's disease: From conventional trials to pharmacogenetics. Neuropsychiatr Dis Treat2007; 3(3):303333.
47. Onor ML, Trevisiol M, Aguglia E. Rivastigmine in the treatment of Alzheimer's disease: an update. Clin Interv Aging2007; 2(1):1732.
48. Olin J, Schneider L. Galantamine for Alzheimer's disease, Cochrane Database Syst Rev. 2002; 3,CD001747, DOI: 10.1002/14651858.CD001747.
49. Robinson DM, Keating GM. Memantine: a review of its use in Alzheimer's disease. Drugs. 2006; 66(11),1515-34.
50. Mahajan G. Fighting Alzheimer's Disease with