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Therapeutic Interventions in Alzheimer's Disease: an Update

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ABSTRACT: Alzheimer's disease is progressive neurodegenerative disease causing memory deficit and cognitive decline. The aggregation and accumulation of amyloid-β plaques and tau proteins in the brain have been central characteristics in the pathophysiology of Alzheimer's disease (AD), making them the distinct focal point of most of the pharmacological research exploring potential therapeutics for this neurodegenerative disease. This review of literature provides an update on the clinical and preclinical arguments and aspects supporting anti-Alzheimer's disease (AD) properties of anti-hypertensive drugs, anti-oxidants, HMG CoA inhibitors, gamma secretase modulators, caspase inhibitors, P- gp, gamma and beta secretase inhibitors, Neuroprotective and Neurorestorative approaches, vaccination and immunization therapies etc. on various components of Alzheimer's disease pathophysiology.

KEYWORDS: Alzheimer's disease, pathophysiology, neuroprotection, cognitive enhancement, anti-hypertensive agents, anti-oxidants, anti-inflammatory agents, vaccination and immunization therapies.

I. BACKGROUND

The total number of people with dementia worldwide in 2018 was estimated to be about 50 million and will increase to nearly triple, reaching 150 million in 2050. Around 70% of these cases are attributed to Alzheimer's disease (AD), a devastating condition leading to dependence to caregivers. AD thus represents an enormous strain on the health-care system, underlining the need for medicines that would slow progression, halt or prevent AD(1). Findings from observational studies have linked several vascular risk factors with increased risk of late-life cognitive impairment and Alzheimer's disease. According to recent meta-analysis, a one third of AD cases worldwide could be attributed to seven modifiable factors (low education, midlife hypertension, midlife obesity, diabetes, physical inactivity, smoking, and depression)(1). In an extended 20 year-long study gathering 1,409 middle-aged individuals, future dementia was significantly predicted by high age, low education, hypertension, hypercholesterolemia, and obesity. This survey aims to provide an update on the clinical and preclinical arguments supporting anti-AD properties of various therapeutic agents. The aims of this review is to provide a comprehensive outcome of a timely debate, and to inspire future therapeutic guidelines and trials(1).

II. INTRODUCTION

Alzheimer disease (AD) is a neurodegenerative disorder featuring gradually progressive cognitive and functional deficits as well as behavioral changes and is is characterized by an accumulation of abnormal neurotic plaques (amyloid beta protein deposition) and neurofibrillary tangles (tau proteins deposition) Cognitive symptoms of AD most commonly include deficits in short-term memory, executive and visuospatial dysfunction, and praxis. Alzheimer's disease are often inherited as an autosomal dominant disorder with nearly complete penetrance.

Mutations in AAP gene on chromosome 21, Presenilin1 (PSEN1) on chromosome 14, and Presenilin 2 (PSEN2) on chromosome 1 accounts for about 5 % to 10 % of all the cases and about the majority of early-onset Alzheimer's disease. Several rarer variants of AD with relative preservation of memory have been recognized(2).Three cholinesterase inhibitors (CIs) are currently available and have been approved for the treatment of mild to moderate AD. A further therapeutic option is available for moderate to severe alzheimer's disease is memantine, an N-methyl-D-aspartate receptor non-competitive antagonist. Treatments capable of stopping or a minimum of effectively modifying the course of

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AD, mentioned as 'disease-modifying' drugs, are still under extensive research(3).

β-SECRETASE INHIBITORS

β-Secretase, is a membrane-anchored aspartyl protease from the pepsin family. Amyloid beta protein is generated from amyloid precursor protein by β and γ-secretase-mediated cleavage. The therapeutic potential of β-secretase inhibition in alzheimer disease, with limited mechanism-based toxicity, has been suggested by preclinical studies conducted in β-site APP cleaving enzyme 1 (BACE-1) knockout mice, which were shown to produce much less beta amyloid level from APP. Injection of the β- secretase inhibitor KMI-429 into the hippocampus of APP transgenic mice significantly reduced the amount of Aβ production in vivo(5). The development of β-secretase inhibitors is challenging because of constraints of the active site; however, there are several small molecules under active investigation(6).Figure(1) shows the docking of BACE 1, a beta secretase inhibitor with beta secretase human target.

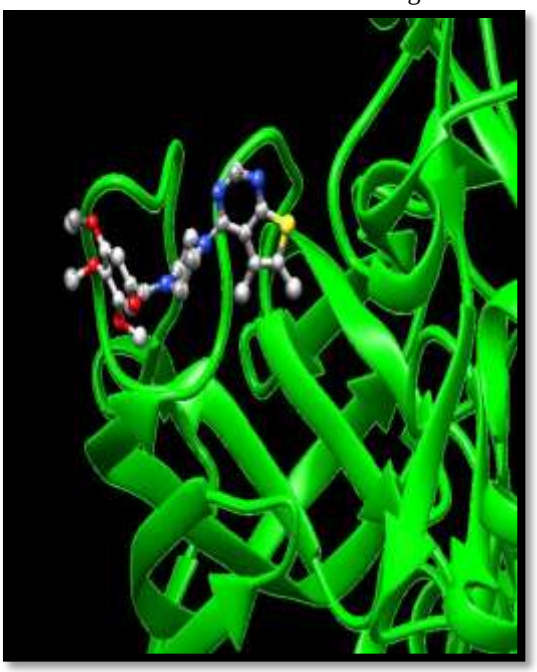

Figure (1) BACE 1(beta secretase inhibitor) undergone docking with beta secretase (human target)

γ-SECRETASE INHIBITORS

The reductions in amyloid beta levels in the brain, plasma and the cerebrospinal fluid have been reported in rodents which were treated with DAPT, a γ-secretase inhibitor(7).Acute treatment with DAPT at a certain dose that reduced beta amyloid concentrations in the brain attenuated cognitive impairment in a transgenic mouse model of Alzheimer's disease, with no effect on performance in controls. This study suggested that cognitive decline in AD might be associated abnormal level of amyloid beta concentration in the brain, potentially in advance of plaque formation, and might be reversible with an acute pharmacologic treatment with gamma secretase inhibitors. In a randomized, controlled clinical trial conducted in 70 patients with mild to moderate AD, plasma Aβ 1-40 was decreased by 38% with administration of LY450139 di-hydrate for 6 weeks, whereas CSF Aβ1-40 levels showed no significant change. Treatment with the γ-secretase inhibitorswere well-tolerated. Further studiesarerequired to determine whether the higher doses will yield more beneficial changes in the beta amyloidconcentrations without an increase in toxicity(8).

γ-SECRETASE MODULATORS

Chronic treatment with CHF5074 reducedthe brain amyloid beta implication, associated microglia inflammation and attenuated spatial memory deficit in hAPP mice. This novel γ-secretase modulator is a favourable therapeutic agent for Alzheimer's disease(9). In epidemiologic investigations, traditional non-steroidal anti-inflammatory drugshave been associated with a significant reduction in the risk of Alzheimer's disease. Negative findings from the recent controlled clinical trials of individual NSAIDs suggest that protection against Alzheimer's disease is not a benefit provided by the entire class of this drugs.

Tarenflurbil modulates γ-secretase to produce less of the toxic form of Aβ (Aβ42) and more of the non-toxic shorter length peptide and it reduces beta production by human cells and reduces the plaque burdens in transgenic mouse modules of AD. A phase II trial of Tarenflurbilconducted in patients with mild or moderate AD displayed no overall benefit after 12 months of treatment. In the sub-groupanalyses, the patients with mild AD who had received the highest dose and had the highest blood levels of the drug exhibited a significant benefit in activities of daily living and global function(9-10). An additional analysis of adverse events showed that a delay of almost ayear in the onset of behavioral symptoms in the patients receiving tarenflurbil when compared with the placebo-treated group. An

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ongoing phase III study is further testing the potential utility of this agent(10).

CASPASE INHIBITORS

Caspase enzymes might represent an important link between amyloid plaques and neurofibrillary tangles in Alzheimer's disease as well as being critical to cell death pathways. Neurons treated with amyloid β peptide activate caspases, which in turn triggers the cleavage of tau proteins and produce truncated forms of the proteins that rapidly and extensively assemble into abnormal filaments characteristic of the tangles found in AD(11).Caspase activation is also required for apoptosis in forebrain neurons and is increased in the brains of patients with AD. A cortical cell cultureexposure to a caspase-3 inhibitors blocked the caspase-induced cleavage of tau. In addition, caspase inhibitors have prevented neuronal damage or loss in animal models of head injury and stroke suggesting this approach might have an utility in the treatment of Alzheimer's disease(11).

NMDA-RECEPTOR ANTAGONISTS

Memantine, a NMDA receptor antagonist in treatment of moderate to severe AD, might reduce the glutaminergic excitotoxicity and provide symptomatic improvement by affecting the neuronal function in the hippocampus.The cognitive impairment inAD has been associated with neuronal toxicity caused by the persistent over activation of NMDA receptors by glutamate. Abnormalconcentration of amyloid beta and tau proteins in the brain, appears to be the trigger for excessive activation of NMDA (N-methyl-D-aspartate) receptors and thus resulting in excitotoxicity pathway that leads to cell death. A double-blind, randomised, placebo controlled phase III study conducted in the U.S. in patients with moderate to severe Alzheimer's disease showed a significant improvement with memantine (20 mg/day) versus placebo in daily activities andpsychological outcomes. There were no clinically relevant differences observed in the safety profiles of memantine and placebo treatments(12). Neramexane, another NMDA receptor antagonist have demonstrated the neuroprotective capacity in preclinical investigations and are proceeding to clinical development. In a double-blind, placebo, randomised controlled phase II clinical trial conducted in patients with moderate to severe Alzheimer's disease, patients receiving neramexane therapy for 24 weeks had showed a significant improvement in daily activities compared with the patients receiving placebo. There was no significant difference demonstrated in measures of cognitive function(13).

P- GLYCOPROTEIN

P- gp, a 140- kDA membrane protein encoded by the multidrug resistance 1 gene, actively utilizes ATP to export substances across the membranes of tissues with excretory or barrier functions, including kidneys, liver and intestines. In the brain, P- gp is predominantly expressed on the luminal (blood- facing) surface of the blood brain barrier endothelium, serves a protective role regulating the passage of a wide variety of endo- and xenobiotic -compounds out of the central nervous system (14). P- gp has also been identified in rat and human neuronal cells, astrocytes, microglia and on the abluminal membrane of the BBB. Human, animal and in vitro studies investigate the relationship between P- gp and Aβ in the context of AD pathogenesis, and the potential of P- gp modulation as a new therapeutic strategy for AD have been discussed. Amplifying the expression and function of P- gp in the brain could present as an effective therapeutic strategy to reduce the levels of neurotoxic Aβ species in AD(14).

In a randomized triple- blind controlled trial involving 101 mild- to- moderate AD subjects, combined daily administration of these antibiotics for 3 months resulted in significantly lower dysfunctional behavior and cognitive decline compared to placebo treatments. This effect continued for 9 months after the treatment period. Unfortunately, these results could not be replicated in a larger 12- month randomized controlled trial conducted in 406 patients with mild- to- moderate AD(15). This may be due to the inductive effects of both antibiotics being more pronounced for systemic rather than BBB P- gp expression. Another interesting observation is that OS and neuroinflammatory response, observed in several neurodegenerative diseases including AD, can modulate P- gp expression. Moreover, not only amyloid β oligomers can generate inflammation and OS, but inversely, inflammation and oxidative stress can cause Aβ accumulation. Consequently promoting P- gp activity could have the dual advantage of increasing Aβ clearance and attenuating neuroinflammation in the AD brain. A number of P- gp inducers have been identified ,

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which could be exploited for in vivo studies in AD(16).

ACE INHIBITORS

Angiotensin-Converting Enzyme (ACE) inhibitors are the oldest class of drugs targeting the renin-aldosterone angiotensin system and also one of the most prescribed anti-hypertensive agents. The case for ACE inhibitors in AD became certainly weaker after a demonstration that ACE was an Aβ peptide-cleaving enzyme, it was first shown in cellular models and later demonstrated at a molecular level(17).ACE converts Aβ43 and Aβ42 to the less aggregable Aβ41 and Aβ40 protein species, respectively, and its inhibition seems to enhance amyloid β deposition in the brain of amyloid-beta precursor transgenic mice. Conversely, mice with excess expression of ACE in monocytes and macrophages display a reduction inamyloid β deposits and a retention of cognitive abilities. This apparent protection from AD pathology supports an important role for ACE in amyloid β clearance, at least in the context of a transgene abnormal over expression and claimed against the use of centrally active ACE inhibitors in AD(18).

ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin receptor blockers are non-peptide compounds that specifically block the binding of angiotensin II to the angiotensin I receptor. ARBs act downstream of ACE inhibitors within the RAAS. Most preclinical studies generally support the utilization of ARBs in AD, with only rare exceptions. About 55 commonly prescribed anti-hypertensive drugs were undergone screening to look for anti-Alzheimer's disease properties in-vitro, the previous studies determined that only valsartan and losartan were capable of both lowering Aβ and decreasing oligomerization of Aβ peptides in primary neuronal cell cultures, but candesartan acted only on oligomerization. Investigations on animal models showed that preventive treatment of Tg2576 mice with valsartan have significantly reduced brain amyloid β deposits and Aβ-mediated cognitive deterioration(19).

CALCIUM CHANNEL BLOCKERS

Calcium ions are critical mediators of cell signaling process, and the calcium channels are omni presently expressed. Far from being specific to vascular smooth muscle cells, the L-type calcium channels, the primary target of calcium channel blockers (CCBs), are expressed by brain neurons (20) and may be reached by CCBs depending on brain penetration capacity of that drug. Therefore, the calcium channel blockers are good candidates as pleiotropic drugs that could positively influence both neural conduction and cerebral blood flow to circumvent AD.

Action of CCBs on amyloid-beta proteins are well supported by most published works. In rats, impairment of spatial memory following intracerebroventricular injection of Aβ was prevented both by nilvadipine and nimodipine treatments (20). In a thorough study, Paris et al. showed that chronic oral therapy with nilvadipine decreased Aβ burden in the brains of transgenic PS1/APPsw mice, and improved learning capacity and spatial memory [21]. The presumed mechanisms of action of CCBs on amyloid are three-fold. The initial hypothesis was that CCBs suppress Aβ- induced calcium release. In fact, the in vitro studies suggest that the neurotoxicity of Aβ species is mediated by an increase in cytosolic calcium concentration, resulting from direct or indirect stimulation of L-type calcium channels [21].

Nimodipine hasrecurrently shown to attenuate amyloid β-induced neurotoxicity [22] Amyloidogenesis inhibition is the second putative effect of CCBs. In a primary neuronal cultures expressing human amyloid precursor protein, a sustained high concentration of the cytosolic calcium inhibited the alpha-secretase cleavage of APP (non-amyloidogenic pathway) and resulted in intraneuronal induction of Aβ42 production (amyloidogenic pathway), anevent that was prevented by nimodipine [22]. The result is controversial since nimodipine was shown to increase Aβ42 production and secretion in a different culture setting [22-23]. Figure(2) illustrates the molecular docking of nimodipine with L-type voltage gated calcium channel.

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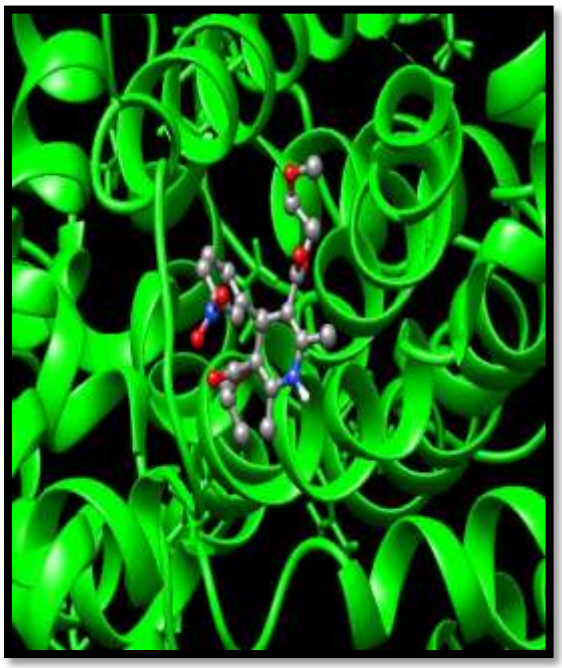

Figure (2) Nimodipine undergone docking with L-type voltage gated calcium channel (human and animal target)

Paris et al. showed that among several L-type calcium channel blockers, nilvadipine and to a lesser extent nitrendipine were able to reduceamyloid β production, independent of their action on L-type voltage gated calcium channels. The effect might be due to inhibition of the spleen tyrosine kinase, which caused the indirect inhibition the β-cleavage of APP [23].Other than the additional possible mechanisms of neuroprotection. CCBs resulted in the inhibition of Tau hyperphosphorylation and also the inhibition of Aβ-induced release of proinflammatory cytokines by microgliacondition and prevention of iron entry and neurotoxicity (23).

ANTI-FIBRILLIZATION AGENTS

The fibrillary aggregates targeting strategies of Aβ protein are being explored. In neuronal cell cultures, the sulfated glycosaminoglycan mimetic tramiprosate (NC-531) was found to maintain Aβ in a non-fibrillar form and reduce Aβ42-induced cell death.Treatment with tramiprosate significantly reduced amyloid plaque load and soluble and insoluble Aβ40 and Aβ42 levels in brain of transgenic mice. In a 3-month, double-blind stage of a phase II trial conducted in 58 patients with mild to moderate AD, tramiprosate-treated patients exhibited dose-dependent reductions in CSF Aβ42 levels(24). Treatment appeared to be well-tolerated, with no reports of serious adverse events(24).

HMG-CoA INHIBITORS

Alzheimer's disease (AD) include extracellular deposition of amyloid-β peptide, a product of amyloid precursor protein (APP) cleavage, as well as, the presence of intracellular hyperphosphorylated tau-protein deposits. Aβ deposits stimulates the uptake of apolipoprotein E (ApoE), cholesterol transporter complex, into brain astrocytes and presence of apolipoprotein E4 allele makes a greater risk of occurrence of neurotoxicity and neurodegeneration, and development of AD. (25).High level of cholesterol is linked with increased amyloid-beta synthesis, statins may cholesterol-dependently play a vital role in restriction of Aβ formation and eventual deposition. Treatment with Lovastatin can delay the onset and lower the progression rate of Alzheimer's disease through reduction of Aβ levels. In vitro investigations have proposed statins to decrease Aβ synthesis through depletion of isoprenoids. Recent investigations have demonstrated that AD mice were on a statin simvastatin-supplemented diet experienced an improvement of learning and memory(25-26).

NEUROPROTECTIVE AND RESTORATIVE THERAPY IN ALZHEIMER'S DISEASE

Nerve growth factor (NGF) is a member of the neurotrophin family of polypeptides. Neurotrophin- 3, neurotrophin-4, and brain-derived neurotrophic factorexhibit similarities in structure and function (27). Each of these growth factors plays an important role in normal neural development and maintenance of the mature central and peripheral nervous systems, including arbitration of neuronal proliferation, differentiation, and neuronal survival of nerve growth factor, like other neurotrophins, promotes cell survival by signaling through specific tyrosine kinase receptors, thus engaging internal cellular machinery to effectively block apoptosis from occurring in either a developing or damaged neurons. Given their survival-promoting properties, neurotrophins (NT) are considered potential therapeutic agents for neurodegenerative disease mainly for AD,Evidence from studies in mice suggests that NGF might play a significant role in sustaining neuronal integrity, also survival in response to injury of the basal cholinergic forebrain neurons. A lack of endogenous nerve growth factor can lead to memory deficits, whereas NGF administration

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rescues the neurons from injury-induced cell damage and result in associated memory improvements. Therefore, NGF and NGF-related agents might have neurorestorative as well as neuroprotective properties. The impermeability of the blood-brain barrier to exogenous NGF and other neurotrophins presents a significant challenge for evaluation of potential therapeutic benefits in Alzheimer's disease. The strategies to bypass this transport challenge are the surgical implantation of NGF-expressing cells (eg, gene therapy) or administration of agents that or potentiate the endogenous production of NGF and other neurotrophins.

The non-peptidic agent xaliproden, a neurotrophic factor enhancer, demonstrates neurotrophic effects in several preclinical neurodegenerative in vivo and in vitro models. Xaliproden activates endogenoussynthesis ofneurotrophins, including the NGF and BDNF, in rat cortical astrocytes. Forebrain cholinergic neuron and memory deficits of Alzheimer's disease in a rat model, xaliproden have reversed hippocampal choline acetyltransferase reduction (a measure of cellular activity and viability) and decreased behavioral disturbances. Magnetic resonance imaging have demonstrated the neuroprotective effects of Xaliproden in this model. The ongoingcontrolled, randomized, phase III trials are currently assessing effects of this agent on cognitive and global functions in patients with mild to moderate AD Cerebrolysin, a peptide mixture with neurotrophic activity, which enhances synaptic regeneration, reduces amyloid β deposition, and ameliorates the performance deficits in APP transgenic mice. Double-blind, randomised, placebo controlled studies show that cerebrolysin infusions significantly improve activities of daily living and cognitive function(27).

ANTI-OXIDANTS

Oxidative injury is one of the underlying cause of Alzheimer's disease. The studies in transgenic model of AD suggested that oxidative stress might be an important early event in the pathogenesis of disease. Conflicting results have been reported in longitudinal studies of the putative free-radical scavenger α- tocopherol (vitamin E) in dementia-free elderly populations. In a cross-sectional, prospectivestudy of dementia in elderly individuals use of vitamin E and vitamin C supplements in combination was associated with reduced prevalence and incidence of AD(28). In research conducted by the Alzheimer Disease co-operative Study, the effects of vitamin E, selegiline (amonoamine oxidase Binhibitor), these two agents in combination and placebo were compared on time to nursing home placement and to death,progression to severe case of dementia, or a severityin impairment of daily activities ofpatients with moderate AD. After adjusting for the severity of baseline cognitive impairment, significant delays in the onset of at least oneof these four outcomes were observed with vitamin E and selegiline, or combination therapy versus placebo after 2 years. In a recent randomised, double-blind study in patientswith MCI, there was no significant differences between the groups receiving vitamin E or placebo in theprobability of progression to AD(29).

Resveratrol: Resveratrol is another well- known antioxidant having neuroprotective effect on alzheimer's disease by promoting intracellular degradation of amyloid beta through ubiquitin proteasome system. In a in-vitro study conducted on rat glioma cell culture showed activity against amyloid toxicity by reducing the COX-2 and iNOS expression, preventing uncontrolled release of NO and prostaglandin E(30).

Apigenin: Apigenin is a powerful antioxidant thatexerts neuroprotection against amyloid β-mediated toxicity mainly through the mechanisms of regulating redox imbalance, maintaining mitochondrial function, inhibiting various pathways like p38 MAPK-MAPKAP kinase-2 (MK2)-heat shock protein 27 (HSP27) and stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK)-c-Jun pathways, and depressing apoptosis. The neuroprotective potential of apigenin in a double transgenic mouse model of AD (APP/PS1) indicated that Apigenin could ameliorate alzheimer's disease-associated memory impairment, thus reducing the Aβ plaque burden and inhibition of oxidative stress(31). Pharmacokinetics studies of Apigenin crosses the brain-blood-barrier, and concentrations in rats reached optimum after daily intraperitoneal administration of 20 mg/kg of apigenin potassium salt (which was solubilized in water and stored frozen until use) for 1 week(31).

Curcumin: Curcumin is another powerful antioxidant that has the potential to treat AD. In vitro studies have shown that curcumin protects neuron cells from β -amyloid toxicity andthe polyphenol displayed a neuro protective effect greater than a well-known antioxidant α -tocopherol. Curcumin suppressed inflammation

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and oxidative damage in the brain of transgenic mice model(32) Curcumin given intravenously for 7 days to transgenic APPswe mice, crosses the blood–brain barrier and binds to β -amyloid deposits in the brain, thus accelerates their rate of clearance. Curcumin disaggregates and inhibits β -amyloid aggregation(32).

Melatonin: Melatonin is a mammalian hormone synthesized mainly in the pineal gland and its function is toscavenge oxygen and nitrogen-based reactants generated in mitochondriaby stimulating the expression and activity of glutathioneperoxidase, nitric oxide synthetase and superoxide dismutase and it also contributes to the reduction of oxidative damage in cells. Currently conduced studies have shown thatantioxidant melatonin could inhibit Aβ-induced toxicityand mitigate tau hyperphosphorylation (33). In vivo, melatonin have improved learning and memory deficits inan APP695 transgenic mouse model and in vitro, the melatonin attenuated Aβ-induced apoptosis in AD cell models suchas mouse microglial BV2 cells, PC12 cells andrat astroglioma C6 cells. Besides, the studies performed in transgenic AD miceand cultured cells have suggested that administration ofmelatonin inhibited the Aβ-induced mitochondria-related bax increase and it may also initiate the survival signalpathways. Further experiment demonstrated that melatonininhibited the phosphorylation of NADPH oxidase via aPI3K/Akt-dependent signaling pathway in microglia exposedto Aβ1–42. Some studies also pointed that in APPTg2576 mice models, melatonin have decreased the Aβ burden inyoung mice but showed no effects on F2-IsoPs or Aβ burden in older plaque-bearing mice. Taken together, theabove evidence suggests that melatonin serves as a potential antioxidant therapeutic strategy for Alzheimer's disease but further clinical trials are still needed to determine the clinicalvalue and efficacy of melatonin in the future (34).

Herbal Antioxidants:There are some traditional herbal antioxidants that exhibits potential for AD treatment. Jung et al. reported that the three major alkaloids in Coptidis Rhizoma-groenlandicine, palmatine andberberine can potentially exhibit anti-AD effects throughboth ChEs and Aβ pathways and antioxidant capacities to inhibit ROS and RNS. In addition, silibinin, a flavonoid derived from the herb milk thistle (Silybummarianum), has also shown to have antioxidativeproperties. Silibinin also prevents memory impairment andoxidative damage induced by Aβ in mice and may be apotential therapeutic agent for Alzheimer's disease (35). Ginkgo biloba is a natural plant that contains a variety of compounds such as flavonoids and terpenoids which have free radical scavenging ability. Previous investigations have shown that Ginkgo biloba can reduce amyloid precursor protein and inhibit Aβ aggregation in vitro. Stackman et al. have reported that Tg2576 mice treated with Ginkgo biloba showed cognitive improvement without any effects on Aβ levels or senile plaque. In 2010, Garcia-Alloza et al.report deported that there was no significant effect on senile plaque size after treatment with Ginkgo biloba, and did not show any effects on Aβ levels measured postmortem by ELISAIn addition, there have been several reports of serious side effects associated with commercially available ginkgo, including bleeding seizures and coma. At present, there is still little evidence to support the use of Ginkgobiloba for the treatment of AD (35).

ANTI- CANCER DRUGS

Imatinib, is an anti- cancer drug approved by the FDA for the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors, targets the Bcr-Abl complex and binds to the ATP-binding site of c-ABL and other thyrosine kinases. Several in vitro and in vivo studies have demonstrated reduced β-amyloid (Aβ) production in AD models treated with imatinib [36]. In addition to reducing the amount of Aβ deposits, imatinib also demonstrates neuroprotective effects. Though mild cardiotoxicity has been described, there have been no major adverse effects reported with imatinib's use in humans. Paclitaxel is a microtubule-stabilizing agent that is FDA approved for the treatment of ovarian carcinoma, breast cancer, non-small-cell lung cancer, and AIDS-related Kaposi's sarcoma. Studies have demonstrated its treatment potential in AD and tauopathies. tau (p-tau) reduces tau's ability to bind microtubules and enhances fibrillization. Similar to imatinib, paclitaxel is a glycoprotein-p substrate and achieves poor central nervous system penetration. Paclitaxel's putative effect in neurodegenerative illnesses is related to microtubule stabilization, reduction of tau phosphorylation, improvement of tau function, and inhibition of Aβ-induced activation of the cystolic cdk5-p25 complex and calpain [37].

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VACCINATION AND IMMUNIZATION THERAPIES

The passive transfer of Aβ monoclonal antibodies from vaccinated mice to AD model mice reduced cerebral amyloidosis. The first efficacy analysis conducted in a small subset of AN1792-treated patients showed antibodies generated against Aβ and significantly slower rates of decline in cognitive function and activities of daily living(38).

Recent studies of using combinations in 3X TG AD mouse model reported amelioration of behavioral deficits clearance of cerebral amyloidosis and reduction of soluble hyper phosphorylated tau proteins. The Aβ vaccine with a full length 1-40 administered by a different route (intranasal route) produced significant Aβ antibodies tities and have effectively reduced cerebral Aβ /plaque levels in the PDAAP mouse model. The antibodies, thus, produced were largely of IgG1 and IgG2b isotypes widely recognized as the B- cells epitopes(39). Studies in which transcutaneous Aβ vaccination with a full length of Aβ along with cholera-toxin to PSAPP mouse model where brain to blood efflux was noted and reduction of cerebral Aβ levels by 50% have been reported. Furthermore, no induction of micro hemorrhage and nil aseptic inflammation which were earlier reported after passive Aβ immunization in AD mice were observed(39). Several trials with passive immunization or vaccination with selective Aβ monoclonal antibodies are underway. Immunoglobulin G (IgG) contains anti-Aβ antibodies, and passive immunization of AD patients(40).

NANOTECHNOLOGY IN ALZHEIMER'S DISEASE THERAPY

In order to overcome the limitation/hurdle faced by CNS drugs to cross the blood brain barrier, innovative approaches in drug development have become the need of the hour(41). Various nanotechnology-based approaches meet this demand by improving the efficacy as well as sustained releasing of the entrapped drug. Some of the nanotechnology-based approaches include polymers, lipocarriers, solid-lipid carriers, lipoprotein-based nanoparticles, curcumin-based nanoparticles, optical imagingtechniques metal-based carriers, nanoparticle conjugates etc. (42)

POLYMERIC NANOPARTICLES

Polymeric nanoparticles are designed with the aim of protecting hydrophobic drugs from degradation and environmental deactivation and to increase the bioavailability of the drug. Kulkarni et al. (2010) developed an n-butyl-2-cyanoacrylate (PBCA)-based, brain-targeting nanopolymeric system encapsulating the radio-labelled amyloid affinity drug 125I-(CQ)clioquinol (CQ, 5-chloro-7-iodo-8-hydroxyquinoline) for the early diagnosis of AD. Loaded nanoparticles (NPs) effectively crossed the BBB in a mouse model and significantly increased the brain retention of 125I-CQ-PBCA NPs(43).

Jaruszewski et al. (2012) considered Ab aggregation in AD and utilized chitosan for drug delivery across the BBB. Immunovehicles were designed based on chitosan coated PLGA nanoparticles (NPs) conjugated with a novel anti-Ab antibody(44). The study is valued by those seeking to develop nanocarriers that can cross the BBB with a drug payload, and the results showed an enhanced BBB uptake and better targeting of the Ab proteins in vitro and additionally chitosan enhanced the aqueous dispersibility and the stabilities of immuno-nanovehicles during lyophilization. This characteristics suggests the further possibility of transforming them into vehicles suitable for delivering therapeutic and diagnostic agents in neurodiseases, especially AD and Parkinson's disease.(45).

Zhang et al. (2013) developed a dual-function, nanoparticle drug delivery system constructed by conjugating PEGylated polylactic acid (PLA) polymer with TGN and QSH (two targeting peptides), which specifically targets blood brain ligands and Ab1-42, respectively(44). Optimization favoured a molar ratio of 1:3 for QSH and TGN respectively, with drug maleimide which showed a good result. Nanoparticles(NPs) are capable of efficiently and precisely targeting AD lesions in the brains of AD-affected mice without inducing meaningful cytotoxicity(46).

LIPOSOMES

Liposomes were discovered in the 1960s and are important due their characteristic properties such as no immunogenicity, biodegradability, lower toxicity, flexibility and biocompatibility(47). Mourtas et al. (2014) designed multifunctional liposomes containing a curcumin derivative and a BBB transport mediator (anti-transferrin antibody (TrF)(48).Analysis of post-mortem brain samples from AD patients showed that liposomes containing the curcumin derivatives or the curcumin derivative and anti-TrF had high affinities for amyloid deposits. The authors also

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reported that curcumin-derivative-containing liposomes did not block Ab deposit staining or prevent Ab aggregation. On the other hand, the presence of a curcumin–PEG–lipid conjugate did not reduce the brain-targeting capability, which suggests that the multifunctional NLs have potential as efficient AD theranostics.(49)

SOLID LIPID CARRIERS

Lipid nanoparticles (LNPs) such as nano-structured lipid carriers and solid lipid nanoparticles (SLNs) have been developed with the aim of overcoming limitations observed in various colloidal carriers including polymeric NPs, liposomes, emulsions whicharerapidly excreted via reticuloendothelial system, intermembrane transferand cell interactions, reduced the encapsulation efficacy, poor stability and shorter shelf life. Development of LNPs has resulted in targeted drug delivery, a good release efficiency of the drug andincreased physical stability(50). Bernardi et al. (2012) prepared indomethacin-loaded lipid-core nanocapsules (IndOH-LNCs) and investigated their protective effects against Ab1-42-induced cell damage and neuroinflammation (51) They found IndOH-LNCs attenuated Ab-induced cell death and blocked the neuroinflammation triggered by Ab1-42 in organotypic hippocampal cultures. Additionally, they reported IndOH-LNC treatment increased interleukin-10 release and reduced glial activation and c-Jun N-terminal kinase phosphorylation.(51).

LIPID/LIPOPROTEIN-BASED NANOPARTICLES

Lipoprotein-based nanoparticles are used for both diagnostic and therapeutic purposes and are known to exhibit high affinity to amyloid beta, thereby facilitating its degradation.(50) Song et al. (2014) devised an apolipoprotein E3–reconstituted high-density lipoprotein (ApoE3–rHDL) nanoparticle system to remove Ab. It was observed around 0.4% ID/g of ApoE3–rHDL accessed mouse brain 1 h after IV administration, after 4 weeks of daily treatment, amyloid beta deposits, neurological changes and memory deficits, microgliosiswere diminished, thus suggesting the possible therapeutic use of ApoE3–rHDL in AD. But its toxicology has yet to be determined (52). Loureiro et al. (2017) reported that grape skin and grape seed extracts inhibited Ab aggregation in AD patients. Grapeswere selected for the study because it contains resveratrol, which iswidely known for its neuroprotective effects.(53). They observed that solid lipid NPs (SLNs) functionalized with anti-transferrin receptor monoclonal antibody (OX26 mAb) acted as carriers to transport the bioactive extract to in-vitro model of the human BBB. Experiments on human brain-like endothelial cells showed that the cellular uptake of OX26 SLNs was substantially greater than that of non-functionalized SLNs and SLNs functionalized with an unspecific antibody (53).

CURCUMIN-LOADED NANOPARTICLES

Brambilla et al. (2012) developed a class of high molecular weight glycolated polyethylene nanocarriers that bind to Ab1-42 and have the ability to alter their serum conformations, which was demonstrated in-silico studies and by modelling. The authors proposed these particles behave as ‘nanosinks’ by binding to toxic forms of Ab (54)Mathew et al. (2012) described the synthesis of water-soluble polylactic-co-glycolic acid (PLGA)-coated curcumin nanoparticles conjugated with Tet-1 peptide. This work was highly significant because of the components used.(55) Curcumin is one of the most exploited natural molecules because it has wide-ranging bioactivity, which include anti-AD activity.It has also been reported to act as an MRI contrast agent for the detection of Ab plaque. Despite these activity, the hydrophobic nature of curcumin hampers its in-vivo applications. They attempted to overcome this obstacle by coating curcumin with water-soluble PLGA Tet-1 peptide, which has been reported to have affinity for neurons and retrograde transportation properties. It was found that curcumin-encapsulated PLGA nanoparticles destroyed Ab aggregates and had antioxidative effects with no observable cytotoxicity.(56).

OPTICAL IMAGING

Optical imaging emerged recently and was used in molecular biomarker imaging for diagnosis of AD. Optical imaging studies used for treatment purpose have also been recorded.[57] Li et al. (2012) have demonstrated that graphene oxide (GO), a unique material that can be viewed as a single monomolecular layer of graphite with various oxygen-containing functionalities such as carboxyl, carbonyl, hydroxyl and epoxidegroups might be useful for the photothermal treatment of AD.[57] They are linked covalently that is GO to ThS (thioflavin-S), which can selectively attach itself to amyloid beta aggregates, to form a conjugated structure of GO–ThS–Ab. Consequently, they used a near-IR laser to locally

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and remotely target GO–ThS and effectively dissociate Ab fibrils.[58]

NANOPARTICLE CONJUGATES

DNA–nanoparticle complexes can detect even a very low concentration of protein biomarkers, about 10–18 moles per litre. This detection technique, also known as the bio barcode technique, utilizes specific protein-targeted anti-body tagged with gold nanoparticles.(59) Zhang et al. (2014) designed a dual-function, spherical, drug delivery system loaded with b-sheet breaker peptide H102 (TQNP/H102).[58]Two targeting peptides, that is QSH and TGN were conjugated to the surfaces of nanoparticles to enable BBB transit and Ab42 targeting, respectively. Zhang and co-workers introduced a novel dual-functional material which was found to be a promising nanocarrier for peptides and proteins and for targeted drug delivery into the CNS, and , later to brain AD lesions. This novel system offers the possibility of a highly specific type of AD therapy.(60).

ANTIBODY-TETHERED NANOPARTICLES

Antibodies are neutralizers of antigens and complement system activators. Being nanosized biological products, the antibody conjugation to nanoparticles was developed to eliminate possible immune responses and is used rapidly in diagnosis as well as research in AD.[61]Carradori et al. (2018) reported Ab1-42 monoclonal antibody-tethered nanoparticles induced memory recovery in a mouse model of AD. This study was the first attempt to investigate the use of Ab1-42 monoclonal antibody-decorated nanoparticles against Alzheimer's diseaseand demonstrated a complete correction in an experimental mouse model. Advanced studies are required to develop a more potent antibody-functionalized nanoparticle formulation with enhanced performance and reduced toxicity(62). Tamba et al. (2018) developed surface-modified fluorescent silica NP derivatives (Ru@SNPs) coated with glucose (Glu) and glucose–poly(ethylene glycol) methyl ether amine (Glu-PEG) and analyzed their abilities to penetrate the mouse BBB.(63) Interestingly, it was observed that silica NP derivatives efficiently traversed the BBB and acted as excellent drug delivery vehicles that reached the brain through specific and non-specific mechanisms.(63)

CUBOSOMES

Cubosomes are liquid crystalline nanostructured particles composed of biocompatible carriers. It comprises a three-dimensionally organized bicontinuous curved lipid bilayer separated by two aqueous channels within which the bioactive ingredients and proteins come into contact. The characteristic features of cubosomes are capable of encapsulating substances that arehydrophilic, hydrophobic and amphiphilic which can maintain controlled release of the drug and bioadhesion. Theyare thermodynamically stable and are promising vehicles for various drug administration routes(64).

Elnaggar et al. (2015) synthesized a Tween-integrated monoolein cubosomes (T-cubs) loaded with piperine (a naturally occurring alkaloid that has been reported to improve memory) and examined their abilities to target the AD brain(65). The in-vivo studies on wistar rats showed that treatment resulted in cognitive enhancement and halted AD progression, which were attributed to its anti-inflammatory and anti-apoptotic activity. Additionally, the formulation used was not found to have any observable toxicity on kidneys and livers in rats.(65).

III. CONCLUSION

An extensive research is being conducted targeting the Alzheimer's disease pathophysiology to find effective strategies to prevent and cure AD. Diverse agents explained above have significant therapeutic action on AD targets. Current research on AD is being focused on oxytocin and Nanotechnology. Nanotherapeutics has emerged as a stand-alone option for the treatment of AD, because unlike conventional therapeutic methods, it enables the targeted delivery of drugs to brain lesions. Developmental successes have been achieved in the nanosensor and nanocontrast fields with respect to the early detection of AD. Evidence from animal model and human shows effectiveness of Aβ immunotherapy in AD patients. Recent findings on Aβ-protein targeted AD drugs, including β-secretase inhibitors, γ-secretase inhibitors and modulators, α-secretase activators, direct inhibitors of Aβ aggregation focusing mainly on those currently under clinical trials. Reducingtau protein hyper phosphorylation, limiting oxidation, excitotoxicity, and controlling inflammation might be beneficial disease modifying strategies. Anti cancer drugs also demonstrated potential therapeutic effect on AD. Potentially neuroprotective and restorative treatments such as neurotrophins, neurotrophic factor enhancers, and

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stem cell-related approaches are also under investigation.

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