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Review Article

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Alzheimer's Disease: Perspective on Therapeutic Options and Recent Hallmarks in Clinical Research

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative, a primarily concerned and leading cause of mortality worldwide which has no cure so far, of the world. The disease progresses from memory loss to cognitive decline gradually. The severity of Alzheimer's grows up from mild, moderate to severe. Hallmarks of the research of AD reported, are the identification of amyloid-beta (Aβ) plaques and tau protein tangles between and within the neuronal cells, oxidative stress, low acetylcholine, and most importantly the genetic connection. Diagnosis of this condition is not so simple since there is no single test that identifies Alzheimer's as early as possible. The therapies for the disease just provide symptomatic relief but not cure. The present review emphasizes the disease burden in the world, neurobiological aspects, and its management through conventional drug therapies along with novel research on therapeutic strategies, new drugs which showed excellent results that are to be approved and were approved, including investigations on plant medicine.

Key words: *Alzheimer's, Cognitive function, Amyloid-beta, Tau protein, Therapeutic strategies, Plant medicine*

INTRODUCTION

Alzheimer's disease (AD), a kind of dementia that differs from age-associated memory impairment [1]. AD is common in elderly people of the age of 65 and above. It is an irreversible, neurodegenerative, progressive brain disorder [1]. The early symptoms include the difficulty of remembering recent conversations or events, apathy, and depression which may proceed further to impaired communication, disorientation, confusion, poor judgment, behavioural changes, and, ultimately difficulty in speaking, swallowing, and walking too. Neurodegeneration is associated with various factors like genetic mutations (less than 5%), incorrect protein folding, and damage in membrane neurons, mitochondrial dysfunction, oxidative stress, toxic molecule formation, and neuroinflammatory processes. The greatest challenge in treating Alzheimer's would be the lack of efficient biomarkers for early diagnosis, prevention, and treatment methods [2].

Clinical outcomes in the patients like mild cognitive impairment (MCI) will later develop into dementia. AD or non-AD, AD accounts for 60–80% of cases [3, 4] and 1.9% relative risk and prevalence. Nearly 1 in 3 adults suffer from multiple chronic conditions globally [5]. In the year 2008 as a part of the "Mental health Gap Action Programme" [6] (mhGAP), the world health Organisation (WHO) declared dementia as a priority condition. The theme for mhGAP Forum 2018 is Accelerating Countries' Action on Mental Health [7]. According to a report,

there could be an increase of 35% of new AD cases in the next 20yrs [8] That approximates the total number of new dementia cases annually worldwide is nearly 7.7 million that is defining a fresh case for every 4 sec. In 2015 the prevalence is 4.4 million, which estimates to be doubled by 2050 [9]. The incidence of AD is in increasing order as, Asia, Europe, and North America [10]. 1-6% of recorded cases are of the age 30-60 which is termed as an early-onset disease. The mortality increases as the disease progress [11]. In India, the order of prevalence of AD is West India, South India, North India, and East India in order. Neurons are the primary targets in AD. When nerve cells die brain shrinks. Plaques are clusters of protein fragments, formed between neurons and tangles are twisted strands of the other protein responsible for the disturbed neurotransmitter function [12].

Treatment

Treating Alzheimer's is a challenge because there is no cure for this condition, a lot of efforts were kept into finding preventive strategies, ways to improve the condition, and ultimately a solution for AD. The primary treatment aims to improve symptoms. US-FDA has approved two categories of drugs **(Table 1)** in the treatment of AD. 'Acetylcholinesterase inhibitors' and 'NMDA (N-methyl D-aspartate) receptor antagonists,' [13] to treat AD for cognitive improvement but neither of them targets the formed plaques or the tangles to halt the disease progression [13].

Table 1. US-FDA-approved drug list [14, 15]

Drug name	Drug type	Mechanism	Approved for	Side effects
Donepezil (Aricept)	Cholinesterase inhibitor.	Acetylcholine(ACh) breakdown in the brain is prevented.	Mild to severe	Nausea, Increased frequency of bowel moments, and loss of appetite
Galantamine (Razadyne)	Cholinesterase inhibitor	ACh breakdown is prevented and nicotinic receptors are stimulated to release ACh.	Mild to moderate	Nausea, Increased frequency of bowel moments, and loss of appetite
Rivastigmine (Exelon)	Cholinesterase inhibitor	ACh and Butyryl choline break down is prevented	Mild to moderate	Nausea, Increased frequency of bowel moments, and loss of appetite
Memantine (Namenda)	NMDA antagonist	Regulate the excess glutamate activation and associated toxic effects.	Moderate to severe	Confusion, dizziness, headache, and constipation.
Memantine + donepezil (Namzaric)	NMDA antagonist and cholinesterase inhibitor	ACh breakdown is prevented and glutamate toxicity is blocked.	Moderate to severe	Confusion, dizziness, headache, Nausea, Increased frequency of bowel moments, loss of appetite

Cholinergic hypothesis

Initially, it was believed that the cause of this disease might be related to Acetylcholine (Ach) a neurotransmitter, functions in learning and memory. Ach produced from choline and acetyl coenzyme-A reaches the synapse through microtubules. Acetylcholinesterase (AchE) hydrolyses Ach [16], anti-AchE increases the cholinergic-synaptic transmission by inhibiting AchE at synaptic-cleft thus hydrolysis of Ach is decreased [17]. Henceforth, AD patients were treated with AchE inhibitors to improve memory since the primary symptom is memory loss. Donepezil, Rivastigmine are selective AchE inhibitors whereas Tacrine and Physostigmine inhibit both acetyl and butyrylcholinesterase.

'Tacrine' (9-amino-1,2,3,4-tetrahydroacride hydrochloride hydrate) [18]. Tacrine, the first drug approved by the US-FDA for the treatment [16] of Alzheimer's disease in 1993 [19] is a nonselective reversible AchE inhibitor. T ½ is 2-4 hrs. and the drug intended to be taken four times daily. Tacrine use has been limited because it causes asymptomatic elevation of serum aminotransferase concentrations and causes hepatotoxicity. Physostigmine is a tertiary amine, nonselective reversible inhibitor of AchE and Butyryl-cholinesterase. Its t1/2 is 30 min and hence it was administered every 2 hrs initially, later a controlled release formulation made it possible to take twice daily. Donepezil is approved by the FDA in the year 1996 is a reversible, selective AchE inhibitor. A longer t1/2 enables the dose as once daily and is the most widely used drug for AD.

Metrifonate also is known to be Trichlorfon, is an anthelmintic drug that has anticholinesterase activity. To inhibit anti cholinesterase [20] it undergoes non-enzymatic hydrolysis to dichlorvos (a pseudo-irreversible inhibitor). It can rapidly enter the brain and has a half-life better than physostigmine and donepezil. The most common side effects observed to be diarrhea, leg cramps, and muscle weakness. Eptastigmine is a carbamate

derivative of physostigmine, a reversible inhibitor of AchE. Sinus bradycardia, granulocytopenia, and hepatotoxicity are common side effects of the drug [21]. Rivastigmine is a relatively pseudo irreversible inhibitor of acetylcholinesterase with a duration of action of 10hrs.

NMDA-receptor partial antagonist

'NMDA (N -methyl -D-aspartate) receptor antagonist' drugs treat brain damage, memory loss, and AD [22]. Glutamate a neurotransmitter processes signaling by attaching itself to a new cell by using NMDA receptor [23]. Glutamate at the NMDA receptor site enables calcium to pass into the cell carrying chemical or electric signals which is important for learning n memory functions. L-Glutamate in abnormal conditions acts as neurotoxins also called endogenous amino acids (EAA). These toxins open membrane cation channels to an excessive influx of sodium and a passive influx of Calcium and water which results in acute neuronal swelling [23, 24].

Memantine (Ebixa®, Axura®, Namenda®, Akatinol®), a partial antagonist of NMDA receptors was approved (2003) for treating moderate to severe AD. In normal neurological conditions, memantine is ineffective but becomes effective at higher concentrations of glutamate associated with over activation of NMDARs. Besides, NMDARs blockage mitigates amyloid beta induce degeneration of cholinergic neurons [25]. Research suggests the prodrug of memantine called "memit" is an agent to treat Alzheimer's. Hydrogen sulphide is found to have anti-inflammatory and neuroprotective activity. Replacing the free amine with isothiocyanate functions as a putative hydrogen sulphide donor. Memit changes to memantine through cystine mediated mechanism by releasing hydrogen sulphide. The study reveals the reduction of Aβ (1-42) self-aggregation and has cytoprotective action [26].

Anti-amyloid approach

Amyloid beta-peptide (Aβ) was first sequenced and recognized as a potential marker by Glenner& Wong, 1984 [27]. Later 39- 43 amino acid peptides were identified as the major content of extracellular plaques. Aβ is a cleavage product of a large, transmembrane protein APP (amyloid precursor protein). The evidence that Aβ plaques have a major deteriorating role in the progress of AD, can be considered as a therapeutic target and deal with several aspects of APP metabolism. APP is cleaved in two pathways (amyloidogenic and non-amyloidogenic) by α, β and γ-secretase enzymes [28]. First, if the APP is cleavaged by α-secretases which prevent the formation of the Aβ instead forms sAPPα fragments (neuroprotective) is formed. However, if β and γ- secretases predominate then Aβ is formed, which aggregates forming senile plaques which produce neurotoxins [29].

The Aβ1-40 isoform, the most prevalent peptide, followed by the Aβ1-42 peptide (hydrophobic) generates aggregates at a faster rate [30]. Aβ42 causes oxidative damage to promote hyperproliferation of tau gives a toxic effect on synapses and mitochondria [31]. Microglial cells were induced by Aβ42 results in the release of proinflammatory cytokines including IL-1β, TNF-α, and IFN-γ [32]. These cytokines stimulate the closest astrocytes producing further amounts of Aβ42 oligomers [33]. Secretase enzyme receptors play a key role in amyloid synthesis. α secretase is regulated at Muscarinic and GABA agonist. Another approach is to regulate β-secretase. Inhibition of β-secretase approach to regulating Aβ plaques.

Drugs like Tramiprosate (Alzhemed), Colostrinin (CLN), Epigallocatechin (EGCG), NIC5- 15, Nasal insulin are anti-Aβ agents that act by inhibiting the Aβ peptides or dissolves their formed fibrils. Anti-amyloid beta monoclonal antibodies like Solanezumab, Gantenerumab and Crenezumab, and BAN 2401 were tested to act against Aβ. Of the four Gantenerumab is in clinical trial phase III at present(NCT03444870) [34]. Gantenerumab human IgG1 antibody has an affinity to bind with a conformational epitope on Aβ fibrils. At the beginning of 2019, Roche announced the halt of clinical trials (CREAD 1 and CREAD 2) of the anti-amyloid antibody Crenezumab [35]. Solanezumab, trial phaseIII is a miss, as it cannot slow cognitive decline in AD. BAN2401 failed to meet the primary endpoint in phase II trials but this yet may have benefited so the company announced phase III of the trial. Elenbecestat a molecule blocks amyloid production is still in testing. So far, Aducanumab is found to be successful to act against Aβ [36].

Tau protein targeting

Tau proteins are associated with microtubule stabilization which aids axons and dendrites for neuronal transmission. In the 1980s researchers discovered that the main protein that binds neurofibrillary tangles (NFTs) was 'tau'. Tau is a phosphoprotein, found in neurons in the peripheral and central nervous systems [37]. Tau has

6 isoforms in the human brain. Increased tau phosphorylation decreases the amount of microtubule-bound protein. Thus, Phosphorylation in the microtubule-binding domain of tau is regulating microtubule stabilization. Critically phosphorylation of the orthologous residues in adjacent microtubule-binding repeats at S262 and S356 is observed [38]. Therapy aims to prevent the aggregation of paired, helically twisted filaments of hyper-phosphorylated tau, a key component of neurofibrillary tangles [39].

Inhibition of tau phosphorylation can be a great therapeutic target. Glycogen synthase kinase 3 (GSK3), a primary enzyme in tau phosphorylation is targeted [29]. 'Tideglusib' (NP031112) is an irreversible GSK3β inhibitor. The stabilization of microtubules can be a therapeutic target as well which improved axonal transport, microtubule density, and motor function (eg. Paclitaxel, Epothilone, D-NAP(NAPVSIPQ), and D-SAL(SALLRSIPA). Drugs (Astemizole, Lansoprazole, and methylthioninechloride) have a strong affinity for tau protein indirectly to reduce tau-tau interaction by blocking the tau oligomerization [40]. Heat shock protein 90 (Hsp 90), folds denatured-proteins aids in preventing tau degradation. Curcumin a natural plant extract is also known to inhibit Hsp 90 [41].

Intracellular signaling cascades

Modulation of intracellular signaling cascades can also be a therapeutic intervention in AD. Inhibitors of phosphodiesterase (PDE) provide significant benefits ie the region-specific alterations in the expression of PDE7 and PDE8 mRNA levels in the hippocampal region of the brain. Reduced PDE7A transcripts and increased PDE8B are observed in the later stages of AD [42, 43]. Rolipram, Sildenafilortadalafil, Cilostazol is PDE selective inhibitors that effectively alter memory, cognitive functions, decrease Aβ accumulation, and tau phosphorylation. Cilostazol is a PDE3 inhibitor and an antiplatelet agent that treats subcortical vascular disease by increasing the cAMP level by promoting phosphorylation of CREB. It improves cerebral blood flow aids in antioxidative effect and is proved to prevent Aβ aggregation [41, 44]. Rolipram shows a better synaptic function and improves cognitive function [43]. Sildenafil is a PDE5 inhibitor that shows a reversal of cognitive impairment [45].

Modulated levels of neurotransmitters

In AD the cholinergic neurons and glutamatergic neurons of the hippocampal region are affected first. Etazolate and SGS742, GABA antagonist showed promising results in preclinical and phase-I studies. Etazolate is a selective GABA(A) receptor modulator, stimulates sAPPalpha production in cortical neurons [46].

Oxidative stress

Accumulated Aβ blocks mitochondrial import channels and increases ROS production, thereby increased mitochondrial ROS production will further cause mitochondrial dysfunction, affects membrane lipids, enzymes, DNA, and lastly to cell death [47]. Antioxidants like vitamins E, C, and carotenoids, phytochemicals, and synthetic compounds reduce oxidative stress in the brain. Alpha-tocopherol (vitamin E) limits free radical formation, lipid peroxidation, and oxidative stress promoting the survival of neurons exposed to plaques. Selegiline is a mono-amino oxidase inhibitor, increases brain catecholamines. Idebenone is a benzoquinone derivative with the anti-oxidative property [48].

Immunotherapy

Much research is done to clearAβ through Aβ antigens (active vaccination) or anti-Aβ antibodies (passive vaccination). Inactive immunization uses an active vaccine with multiple doses of Aβ42, Antibodies were developed reported adverse events [49]. Passive immunization with human recombinant Aβ monoclonal antibodies administered (Intravenously) acts against the N terminus of Aβ [50] **Table 2** lists the immunotherapeutic agents that are in various stages of clinical trials. According to Jeffrey Cummings, on a whole of 112 agents in the current AD treatment, many immunotherapeutic agents are in various phases of clinical trials [50].

Table 2. List of the biological or immunological agents of AD under research (clinical trials), both active and passive [51-55]

Chemical Compound	Status	Trial Organizer/ sponcer	Category/Target	Immuno-therapy
AAB-003	Discontinued	Janssen, Pfizer	Amyloid beta	Passive
AADvac-1	Phase-2,	Axon Neuroscience SE	Tau	Active

AB vac 40	Phase 2	Araclon Biotech	Amyloid beta	Active
ACI-24	Phase 1/2,	AC Immune SA	Amyloid beta	Active
ACI-35	Phase 1	AC Immune SA, Janssen	Tau	Active
AN-1792	Discontinued	Janssen, Pfizer	Amyloid beta	Active
Aducanumab	Phase 3	Biogen, Neurimmune	Amyloid beta	Passive
Affitope AD02	Phase 2	AFFiRiS AG	Amyloid beta	Active
BAN2401	Phase 2	Biogen, Eisai Co., Ltd.	Amyloid beta	Passive
BIIB076	Phase 1	Biogen, Neurimmune	Tau	Passive
BIIB092	Phase 2	Biogen, Bristol-Myers Squibb	Tau	Passive
Bapineuzumab	Discontinued	Janssen, Pfizer	Amyloid beta	Passive
C2N 8E12	Phase 2	AbbVie, C2N Diagnostics, LLC	Tau	Passive
CAD106	Phase 2/3	Novartis Pharmaceuticals Corporation	Amyloid beta	Active
Crenezumab	Phase 3	AC Immune SA, Genentech, Hoffmann-La Roche	Amyloid beta	Passive
Etanercept	Phase 2	Amgen, Inc., Pfizer	Inflammation	Passive
GSK933776	Inactive	GlaxoSmithKline (GSK)	Amyloid beta	Passive
Gammagard®	Discontinued	Baxter Healthcare	Amyloid beta and inflamation	Passive
Gamunex	Phase 2/3	Grifols Biologicals Inc.	Aβ target Inflammation	Passive
Gantenerumab	Phase 3	Chugai Pharmaceutical Co., Ltd., Hoffmann-La Roche	Amyloid beta	Passive
JNJ-63733657	Mild AD Phase 1	Janssen	Tau	Passive
LY2599666	Discontinued	Eli Lilly & Co.	Amyloid beta	Passive
LY3002813	Phase 2	Eli Lilly & Co.	Amyloid beta	Passive
LY3303560	Phase 2	Eli Lilly & Co.	Tau	Passive
LY3372993	Phase 1	Eli Lilly & Co.	Amyloid-beta	Passive
Lu AF20513	Phase 1	H. Lundbeck, Otsuka Pharmaceutical Co., Ltd.	Amyloid-beta	Active
MEDI1814	Phase 1	Eli Lilly & Co.	Amyloid beta	Passive
Octagam®10%	Inactive	Octapharma	Aβ target Inflammation	Passive
Ponezumab	Discontinued.	Pfizer	Amyloid beta	Passive
RG7345	Discontinued	Roche	Tau	Passive
RO 7105705	Phase 2	AC Immune SA, Genentech, Hoffmann-La Roche	Tau	Passive
SAR228810	Phase 1	Sanofi	Amyloid beta	Passive
Solanezumab	Phase 3	Eli Lilly & Co.	Amyloid beta	Passive
UB 311	Phase 2	United Neuroscience	Amyloid beta	Active
Vanutidecridificar	Discontinued	Janssen	Amyloid beta	Active

Herbal therapy for Alzheimer's

Extensive research on different plants is underway worldwide as plant extracts have a rather more therapeutic advantage, with fewer untoward effects, and are more economical. Using herbal medicine is in practice. Moreover, people tend to be interested in traditional medicine in recent times. Herbal medicine offers several options for altering the progress and symptoms of AD. Memory ailments are treated by herbal medicine indigenously in several cultures. In India, Ashwagandha, Turmeric, Brahmi Shankhpushpi, Gotu Kola, Jyotishmati, and Jatamansitreat AD [56]. Other plants which are reported to treat AD are listed in **Table 3**. Also, studies have concluded, the inclusion of herbal medicine in conventional therapy brings in promising changes in the cognitive function of the patient.

Table 3. List of the Plants, extracts, and chemical constituents that were studied to have therapeutic action against AD [57, 58]

Plant	Family	Extract/Constituents	Mechanism	Ref
Panax ginseng	Araliaceae	Ginsenosides	Decrease Aβ protein formation, inhibits β- and γ-secretase activity, Promote Aβ peptide degradation.	[58, 59]
		Gintonin	Attenuates brain amyloid plaque deposits	
Ginkgo Biloba	Ginkgoaceae	Ginkgolide A,	Aβ-induced caspase-3 reduced and platelet	[60, 61]

		Ginkgolide B	activating factor inhibition	
Curcuma longa	Zingiberaceae	Curcumin	Protect neuronal cells from Aβ Aβ-induced tau phosphorylation.	[62]
Coptischinensis	Ranunculaceae	Berberine	Suppress Aβ induced inflammation and the phosphorylation of tau	[63]
Melissa officinalis	Lamiaceae	4-O-methylhonokiol	Inhibition of Aβ1-42-induced ROS generation neuron death.	[64]
Polygala tenuifolia	Polygalaceae	Tenuifolin	Decrease Aβ secretion with no alteration in the ratio of Aβ1-40 and Aβ-42, Possess neuroprotective effect. Improve the cognitive deficits	[65]
Crocus sativus	Iridaceae	Crocin	Significantly improve memory impairment, Significantly prevent cognitive impairments.	[66]
Saliva militiorrhiza	Lamiaceae	Tanshinone IIA	Protection from Aβ25-35-induced toxicity.	[67]
		Salvianolic acid A	Inhibit Aβ self-aggregation and blocks the	
		Salvianolic acid B	Neuroprotective, anti-inflammatory and anti-oxidative effects	
		Cryptotanshinone	Cholinesterase inhibitor improves learning, Improve the cognitive ability to	
Withaniasomnifera	Solanaceae	Withanolide A and withanoside IV	Behavioural deficits were reversed and plaque load decreased significantly.	[57, 67]
HuperziaSerrata	Lycopodiaceae	Huperzine A	Inhibition of Aβ-induced APP secretion.	[68]
Moringaoleifera	Moringaceae	Myricetin	Regulating levels of α-secretase	[69]
Bacopamonnieri	Plantaginaceae	95% ethanolic extract.	Inhibition of amyloid peptide-activated intracellular acetyl-cholinesterase activity	[70]
Cinnamomumzeylanicum	Lauraceae	Aqueous extract	Inhibits fibril formation and destabilization of formed fibrils.	[71]
Ganodermalucidum	Ganodermataceae	Aqueous extract	Aβ-induced synaptotoxicity, inhibition of Aβ-induced	[57]

Recent hallmarks in the alzheimer's research

Almost by the end of 2019 two drugs, Biogen's (USA) 'Aducanumab (BIIB03) and Shanghai Green valley Pharmaceuticals' (China), GV-971 (Oligomannate) emerged out with glory and proved to be treating Alzheimer's disease.

Aducanumab: An antibody, a protein designed to target Aβ. It preferentially binds to aggregates of Aβ and reduces the amyloid plaques. Biogen sponsored seven clinical trials [72]. Phase-1 was with healthy people (NCT02782975) and patients in the US(NCT01397539) and Japan (NCT02434718). Phase-1 trial (NCT01677572), double-blind randomization, a placebo-controlled trial, 'PRIME' with 192 pre-dementia and mild Alzheimer's patients concludes significant reduction is observed at higher doses and slow rate of cognitive decline. Later another two trials were initiated by biogen, double-blind randomization (1:1) phase-3 clinical trial, named ENGAGE (NCT02477800) and EMERGE (NCT02484547) treatment dose once a month by infusions. The primary aim of these two trials is to assess the efficacy of BIIB037 [73]. As the trials were unlikely to meet the primary objective, the trials were halted with a decision based on safety concerns [74]. Later another phase 2 trial (NCT 03639987) start to evaluate the safety of the continued dosing of the drug. In patients with mild AD, it was also halted in march 2019. Then analysis was conducted with more data from participants who did not complete the trial. EMERGE met the primary and secondary endpoint on the other hand ENGAGE is a failure. Based on the results of the new analysis biogen declared they would file for regulatory approval in early 2020 [75].

GV-971: A start-up firm (Shanghai Green Valley Pharmaceuticals) from China has surprised the neuroscientist and drug developers of the world with conditional approval for their seaweed-derived molecule GV-971 in November 2019. The drug grew out of research by a 'GengMeiyu' of 'The Chinese Academy of Science's Shanghai Institute of MateriaMedica', a centre for research into traditional Chinese medicine [76]. The active ingredient in GV-971 is sodium oligo-mannurate is derived from Brown algae, a seaweed. This molecule got the praises and attention of the world's neuroscientists as it was the first drug to get approval in the past two decades

and it has presented a new therapeutic approach aiming at inflammation and improving cognition in patients [77].

Various therapeutic strategies targeting amyloid-beta and tau phosphorylation have shown constant disappointment in the clinical trials, which gave rise to considering a new therapeutic strategy for the disease. This compound interacts with the Intestinal microflora and host immune system [78]. As a part of the host immune response, many inflammatory diseases (including inflammation during AD) may arise in connection to disturbances in intestinal microflora [79]. Using 5XFAD transgenic (Tg) mouse models, as the disease progress changes in gut microflora lead to an increase of phenylalanine and isoleucine stimulates pro-inflammatory T helper cells (Th1). Th1 cells along with M1 microglia activation cause neuroinflammation. This component suppresses phenylalanine/isoleucine accumulation reducing neuroinflammation [80] also crosses Blood-brain - barrier (BBB) through glucose transporter (GLUT1) and stops Aβ fibril formation and destabilizes formed fibrils to non-toxic monomers [81].

Phase-1 trial with 112 normal individuals, Phase-2 with 255 patients from different sites of China received a dose of 600-900mg per day with placebo for 6 months. Phase-1 and 2 trials showed a safe and well-tolerated profile. Phase 3 trial (NCT02293915) conducted at 34 sites, 818 [80] patients were treated with 900mg/ day or placebo for 9 months with no other AD drugs [82]. The trial met the primary endpoint with a statistical significance of $P<0.001$ and no serious adverse events occurred with a similar rate between drug and placebo.

CONCLUSION

Alzheimer's disease is one of the top listed causes of death in the world. The mortality rate of AD over a period has increased, and so as the concerns for treating the infected population too. The cure for AD is still in finding since the first report of the Disease. The strategy of Alzheimer's research is finding better biomarkers that could reasonably identify the risk of the disease and finding therapeutic agents that control the disease or the symptoms. There were only a few drugs that were approved to treat the disease which targets the symptoms.

Decades of research concluded multiple causes of the disease. With no dubiety, certainly, there is a demand for superior therapy to treat the patients. Several drug molecules are in different stages of clinical trials that target other causes of the disease apart from improving memory. Another therapeutic concern of the disease is to identify the early stage AD and treat it. In support of Alzheimer's research and understanding the criticality, US-FDA lowers the bar for clinical trial success (Feb- 2018) of drugs that treat the early stages of Alzheimer's. This states the necessity for the new molecules or new plant constituents to control the estimated statistics of AD deaths in the future. Furthermore, the success of components extracted from natural sources like curcumin and the very recent GV-971 obtained from a seaweed brown alga gives a scope and hope for the emerging researchers, to consider natural components to elicit certain pharmacological action and could be proved as potential drugs for the future.

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