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REVIEW ON MECHANISM OF ACTION OF ALZHEIMER'S DRUG

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ABSTRACT

Alzheimer's disease (AD) represents a global health crisis. Treatments are needed to prevent, delay the onset, slow the progression, improve cognition, and reduce behavioral disturbances of AD. We review the current clinical trials and drugs in development for the treatment of AD. Treatment for Alzheimer's disease is entering a new and exciting phase, with several new drugs beginning clinical trials. Many of these new therapies are based on our best current understanding of the pathogenesis of Alzheimer's disease, and are designed to try to either slow or halt the progression of the disease. There are several different theories underlying the current efforts, and these are briefly reviewed. Therapies directed against some aspect of β-amyloid formation, against neurofibrillary tangle formation and against the inflammatory response are all considered, as are the problems associated with each area. It is as yet unclear which, if any, of these approaches will be successful, but the high level of activity in each of these three fields provides some hope that an effective treatment for Alzheimer's disease is on the horizon. Alzheimer's disease (AD) is a disorder that causes degeneration of the cells in the brain and it is the main cause of dementia, which is characterized by a decline in thinking and independence in personal daily activities. AD is considered a multifactorial disease: two main hypotheses were proposed as a cause for AD, cholinergic and amyloid hypotheses. Additionally, several risk factors such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors play a role in the disease. Nowadays, the research is focusing on understanding AD pathology by targeting several mechanisms, such as abnormal tau protein metabolism, β-amyloid, inflammatory response, and cholinergic and free radical damage, aiming to develop successful treatments that are capable of stopping or modifying the course of AD.

KEYWORDS: Aducanumab, Alzheimer's disease, Amyloid, Biomarker, Donanemab, Inflammation, Lecanemab, Rivastigmine.

INTRODUCTION

Alzheimer's disease (AD) (named after the German psychiatric Alois Alzheimer) is the most common type of dementia and can be defined as a slowly progressive neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles as a result of amyloid-beta peptide's (Aβ) accumulation in the most affected area of the brain, the medial temporal lobe and neocortical structures.[1] Alois Alzheimer noticed a presence of amyloid plaques and a massive loss of neurons while examining the brain of his first patient that suffered from memory loss and change of personality before dying and described the condition as a serious disease of the cerebral cortex. Emil Kraepelin named this medical condition Alzheimer's disease for the first time in his 8th edition psychiatry handbook. Progressive loss of cognitive functions can be caused by cerebral disorder like Alzheimer's disease (AD) or other factors such as intoxications, infections, abnormality in the pulmonary and circulatory systems, which causes a reduction in the oxygen supply to the brain, nutritional deficiency, vitamin B12 deficiency, tumors, and others.

Alzheimer's disease diagnostic criteria

A patient suspected to have AD should undergo several tests, including neurological examination, magnetic resonance imaging (MRI) for neurons, laboratory examinations such as vitamin B12, and other tests besides the medical and family history of the patients. Vitamin (vit.) B12 deficiency has been long known for its association with neurologic problems and increasing risks of AD, according to some studies. A special marker of vit. B12 deficiency is elevated homocysteine levels, which can cause brain damage by oxidative stress, increasing calcium influx and apoptosis. Diagnoses of vit. B12 deficiency can be done by measuring serum vit. B12 level alongside complete blood count and serum homocysteine levels tests.[2] In 1984, The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's disease and

Related Disorders Association (ADRDA) formed a work group (NINCDS-ADRDA) to establish a clinical diagnostic's criteria for Alzheimer's disease. This criteria includes: (1) probable Alzheimer's disease, which can be diagnosed by dementia that is confirmed by neuropsychological tests, progressive memory loss, impaired daily-life activity, and other symptoms like aphasia (impairment of a language), apraxia (a motor skills disorder), and agnosia (a loss of perception).[3] All of these symptoms can start from age 40–90, with the absence of any systemic or brain diseases, (2) possible Alzheimer's disease can be applied in the absence of neurologic, psychiatric disorders, and the presence of another illness like systemic or brain disorder, but they are not the primary cause of dementia, and (3) definite Alzheimer's disease, that is confirmed by histopathologic confirmation obtained from a biopsy or autopsy.

Alzheimer's disease's neuropathology

There are two types of neuropath logical changes in AD which provide evidence about disease progress and symptoms and include: (1) positive lesions (due to accumulation), which are characterized by the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads, and other deposits found in the brains of AD patients. In addition to (2) negative lesions (due to losses), that are characterized by large atrophy due to a neural, neuropil, and synaptic loss. Besides, other factors can cause neurodegeneration such as neuroinflammation, oxidative stress, and injury of cholinergic neurons.[4]

Senile plaques (SP)

The senile plaques are extracellular deposits of beta-amyloid protein (Aβ) with different morphological forms, including neuritic, diffuse, dense-cored, or classic and compact type plaques. Proteolytic cleavage enzymes such as β-secretase and γ-secretase are responsible for the biosynthesis of Aβ deposits from the transmembrane amyloid precursor protein (APP) These enzymes cleave APP into several amino acid fragments: 43, 45, 46, 48, 49, and 51 amino acids, which reach the final forms Aβ40 and Aβ42. There are several types of Aβ monomers, including large and insoluble amyloid fibrils which can accumulate to form amyloid plaques and soluble oligomers that can spread throughout the brain. Aβ plays a major role in neurotoxicity and neural function, therefore, accumulation of denser plaques in the hippocampus, amygdala, and cerebral cortex can cause stimulation of astrocytes and microglia, damage to axons, dendrites, and loss of synapses, in addition to cognitive impairments.

Neurofibrillary tangles (NFTs)

NFT are abnormal filaments of the hyperphosphorylated tau protein that in some stages can be twisted around each other to form paired helical filament (PHF) and accumulate in neuralperikaryal cytoplasm, axons, and dendrites, which cause a loss of cytoskeletal microtubules and tubulin-associated proteins.[5] The hyperphosphorylated tau protein is the major constituent of NFTs in the brains of AD patients, and its evolution can reflect NFTs morphological stages, which include: (1) pre-tangle phase, one type of NFT, where phosphorylated tau proteins are accumulated in the somatodendritic compartment without the formation of PHF, (2) mature NFTs, which are characterized by filament aggregation of tau protein with the displacement of the nucleus to the periphery part of the soma, and (3) the extracellular tangles, or the ghost NFTs stage, that results from a neuronal loss due to large amounts of filamentous tau protein with partial resistance to proteolysis.

Synaptic loss

A synaptic damage in the neocortex and limbic system causes memory impairment and generally is observed at the early stages of AD. Synaptic loss mechanisms involve defects in axonal transport, mitochondrial damage, oxidative stress, and other processes that can contribute to small fractions, like the accumulation of Aβ and tau at the synaptic sites. These processes eventually lead to a loss of dendritic spines, pre-synaptic terminals, and axonal dystrophy. Synaptic proteins serve as biomarkers for the detection of synapses loss, and severity, such as neurogranin, a postsynaptic neuronal protein, visinin-like protein-1 (VILIP-1), and synaptotagmin-1.[6]

The stages of alzheimer's disease

The clinical phases of Alzheimer's disease can be classified into (1) pre-clinical or the pre-symptomatic stage, which can last for several years or more. This stage is characterized by mild memory loss and early pathological changes in cortex and hippocampus, with no functional impairment in the daily activities and absence of clinical signs and symptoms of AD. (2) The mild or early stage of AD, where several symptoms start to appear in patients, such as a trouble in the daily life of the patient with a loss of concentration and memory, disorientation of place and time, a change in the mood, and a development of depression. (3) Moderate AD stage, in which the disease spreads to cerebral cortex areas that results in an increased memory loss with trouble recognizing family and friends, a loss of impulse control, and difficulty in reading, writing, and speaking. (4) Severe AD or late-stage, which involves the spread of the disease to the entire cortex area with a severe accumulation of neuritic plaques and neurofibrillary tangles, resulting in a progressive functional and cognitive impairment where the patients cannot recognize their family at all and may become bedridden with difficulties in swallowing and urination, and eventually leading to the patient's death due to these complications.[7]

Causes and risk factors of alzheimer's disease

AD has been considered a multifactorial disease associated with several risk factors such as increasing age, genetic factors, head injuries, vascular diseases,

infections, and environmental factors (heavy metals, trace metals, and others). The underlying cause of pathological changes in Alzheimer's disease (Aβ, NFTs, and synaptic loss) is still unknown. Several hypotheses were proposed as a cause for AD but two of them are believed to be the main cause: some believe that impairment in the cholinergic function is a critical risk factor for AD, while others suggest that alteration in amyloid β-protein production and processing is the main initiating factor. However, at present, there is no accepted theory for explaining the AD pathogenesis.[8]

Drug and its mechanism of action

Currently, Alzheimer's disease cases worldwide are reported to be around 24 million, and in 2050, the total number of people with dementia is estimated to increase 4 times. Even though AD is a public health issue, as of now, there is only two classes of drugs approved to treat AD, including inhibitors to cholinesterase enzyme (naturally derived, synthetic and hybrid analogues) and antagonists to N-methyl D-aspartate (NMDA). Several physiological processes in AD destroy Ach-producing cells which reduce cholinergic transmission through the brain. Acetyl cholinesterase inhibitors (AChEIs), which are classified as reversible, irreversible, and pseudo-reversible, act by blocking cholinesterase enzymes (AChE and butyrylcholinesterase (BChE)) from breaking down ACh, which results in increasing ACh levels in the synaptic cleft . On the other hand, over activation of NMDAR leads to increasing levels of influxed Ca^{2+}, which promotes cell death and synaptic dysfunction. NMDAR antagonist prevents over activation of NMDAR glutamate receptor and hence, Ca^{2+} influx, and restores its normal activity.[9] Despite the therapeutic effect of these two classes, they are effective only in treating the symptoms of AD, but do not cure or prevent the disease . Unfortunately, only a few clinical trials on AD have been launched in the last decade and their outcome was a big failure. Several mechanisms have been proposed to understand AD pathology in order to modify its pathway and develop successful treatments, which include abnormal tau protein metabolism, β-amyloid, inflammatory response, and cholinergic and free radical damage. On the other hand, most AD modifiable risk factors such as cardiovascular or lifestyle habits can be prevented without medical intervention. Studies showed that physical activity can improve the brain health and reduce AD by activating the brain vascularization, plasticity, neurogenesis, and reducing inflammation by decreasing Aβ production, which all result in improving cognitive function in older people. Moreover, the Mediterranean diet (MD), intellectual activity, and higher education all may reduce the progression of AD and memory loss and increase the brain capacity and cognitive functions. Several studies revealed that multi-domain intervention which includes lifestyle (diet, exercise, and cognitive training), depression of AD symptoms, and controlling cardiovascular risk factors, can increase or maintain cognitive function and prevent new cases of AD in older people.

Cholinesterase inhibitors

According to the cholinergic hypothesis, AD is due to the reduction in acetylcholine (ACh) biosynthesis.[10] Increasing cholinergic levels by inhibiting acetyl cholinesterase (AChE) is considered one of the therapeutic strategies that increases cognitive and neural cell function. AChEIs are used to inhibit acetylcholine degradation in the synapses, which results in continuous accumulation of ACh and activation of cholinergic receptors. Tacrine (tetrahydroaminoacridine) was the first FDA (Food and Drug Administration)-approved cholinesterase inhibitor drug for the treatment of AD, which acts by increasing ACh in muscarinic neurons, but it exited the market immediately after its introduction due to a high incidence of side effects like hepatotoxicity and a lack of benefits, which was observed in several trials. Later on, several AChEIs were introduced, such as donepezil, rivastigmine, and galantamine, and are currently in use for the symptomatic treatment of AD .Another strategy that may help in the treatment of AD is increasing choline reuptake and as a result, increasing acetylcholine synthesis at the presynaptic terminals. This can be achieved by targeting choline transporter (CHT1) which is responsible for supplying choline for the synthesis of ACh. Developing drugs that are capable of increasing CHT1 at the plasma membrane may become the future therapy of AD.

Donepezil

Donepezil is an indanonebenzylpiperidine derivative and a second generation of AChEIs and is considered the leading drug for AD treatment. Donepezil binds to acetyl cholinesterase reversibly and inhibits acetylcholine hydrolysis, which leads to a higher concentration of ACh at the synapses.[11] The drug is well-tolerated with mild and transient cholinergic side effects which are related to the gastrointestinal and nervous systems. It should be noted that donepezil is used to treat symptoms of AD such as improving cognition and behavior without altering the AD progression.

Rivastigmine

Rivastigmine is a pseudo irreversible inhibitor of AChE and butyrylcholinesterase (BuChE) that acts by binding to the two active sites of AChE (anionic and estearic sites), which results in preventing ACh metabolism. BuChE is found mostly in glial cells with only 10% of AChE activity in the normal brain, whereas in the AD brain, its activity is increased to 40–90%, while ACh activity is reduced simultaneously, which suggests that BuChE action may indicate a moderate to severe dementia.[12] Rivastigmine dissociates more slowly than AChE, which is why it is called a pseudo-irreversible, and it undergoes metabolism at the synapse by AChE and BuChE.[13] The drug is used in mild to moderate AD cases. It improves cognitive functions and daily life activities. Oral administration of the drug is associated with adverse effects such as nausea, vomiting, dyspepsia, asthenia, anorexia, and weight loss. In many cases, these side effects are the main reason behind stopping taking

the medicine, however, they can be settled down in time and consequently, the drug becomes more tolerated. Rivastigmine can be delivered by transdermal patches for controlled and continuous delivery of the drug through the skin, with enhanced tolerability and caregiver satisfaction. Also, the patches can deliver a lower dosage compared to pills, which results in reduced side effects. Most AD patients suffer from memory loss and swallowing problems which affect their compliance in administering oral drugs at regular intervals. Therefore, the use of transdermal patches is the most appropriate method for delivering the drug in AD patients.[13,14]

Galantamine (GAL)

Galantamine is considered a standard first-line drug for mild to moderate AD cases. GAL is a selective tertiary isoquinoline alkaloid with a dual mechanism of action in which it acts as a competitive inhibitor of AChE and can bind allosterically to the α-subunit of nicotinic acetylcholine receptors and activates them. GAL can improve behavioral symptoms, daily life activities, and cognitive performance with good efficacy and tolerability, similar to other AChE inhibitors. Several delivery systems were developed to improve the drug delivery to the brain: Wahba et al. attached GAL to ceria-containing hydroxyapatite particles for selective delivery of the drug to the affected regions in the brain. Misra et al. and Fornaguera et al. used solid-lipid nanoparticles and nano-emulsification approaches respectively, to carry GAL hydrobromide. The results of these studies demonstrated a promising strategy for safe delivery of the drug. Hanafy et al. developed nasal GAL hydrobromide/chitosan complex nanoparticles which showed good pharmacological efficacy, while Woo et al. utilized the patch system as a carrier for a controlled release dosage form of the drug.[14]

N-methyl D-aspartate (NMDA) antagonists

NMDAR is believed to have a dominant role in the pathophysiology of AD. NMDAR stimulation results in Ca^{2+} influx which activates signal transduction and as a consequence, it triggers gene transcription essential for the formation of a long-term potentiation (LTP), which is important for synaptic neurotransmission, plasticity, and memory formation. Over-activation of NMDARs causes an abnormal level of Ca^{2+} signaling and overstimulation of glutamate, which is the primary excitatory amino acid in the CNS, which results in excitotoxicity, synaptic dysfunction, neuronal cell death, and a decline in cognitive functions. Several NMDAR uncompetitive antagonists have been developed and entered clinical trials, however, most of them failed due to low efficacy and side effects. Memantine is the only approved drug in this category to treat moderate to severe AD; in addition, other NMDAR uncompetitive antagonist compounds are being developed, such as RL-208 (3,4,8,9-tetramethyltetracyclo [$4.4.0.0^{3,9}.0^{4,8}$] dec-1-yl) methylamine hydrochloride), a polycyclic amine compound that may possess a promising therapeutic effect in age-related cognitive problems and AD.[15]

Memantine

Memantine is a low-affinity uncompetitive antagonist of the NMDAR, a subtype of glutamate receptor that prevents over-activation of the glutaminergic system involved in the neurotoxicity in AD cases. Memantine is used for the treatment of moderate to severe AD alone or in combination with AChEI. The drug is safe and well-tolerated; it blocks the excitatory receptor without interfering with the normal synaptic transmission due to memantine's low affinity, where it is displaced rapidly from NMDAR by high concentrations of glutamate, thus avoiding a prolonged blockage. The latter is associated with high side effects, especially on learning and memory.[16]

Disease-modifying therapeutics (DMT)

Disease-modifying treatment or therapy (DMT) alters the progression of AD by working on several pathophysiological mechanisms. This is in contrast to symptomatic therapy which works on improving the cognitive functions and decreasing symptoms such as depression or delusions without affecting or modifying the disease. DMTs, either immunotherapies or small molecules, are administrated orally and are being developed to prevent AD or decrease its progression. Several DMTs have been developed and entered the clinical trials, such as AN-1792, a synthetic Aβ peptide (human $A\beta_{1-42}$ peptide of 42-amino acids with the immune adjuvant QS-21) and the first active immunotherapy for AD which entered phase II clinical trials and discontinued due to a meningoencephalitis side effect in 6% of the patients. Other drugs were also developed and failed in the clinical trials, including the anti-Aβ antibody (solanezumab and bapineuzumab), γ-Secretase inhibitors (semagacestat 6, avagacestat 7, and tarenflurbil 8) and β-secretase inhibitors (BACE) (Lanabecestat 9, verubecestat 10, and atabecestat 11). DMTs failures are due to several factors, such as starting therapy too late, giving treatment for the wrong main target, use of inappropriate drug doses, and misunderstanding of the pathophysiology of AD.[17] Several immunotherapies have been developed over decades, including: CAD106, an active Aβ immunotherapy that induces Aβ antibodies in animal models and consists of multiple copies of Aβ1–6 peptide coupled to Qβ coat protein, a virus-like particle, and is still in clinical trials, and CNP520 (umibecestat, 12) a small molecule that inhibits beta-scretase-1 (BACE-1) and therefore inhibits Aβ production. CNP520 was found to reduce Aβ plaque deposition and Aβ levels in the brain and CSF in rats, dogs, and healthy adults ≥ 60 years old, and is still under clinical trials. Furthermore, aducanumab, gantenerumab, and crenezumab are all human Aβ monoclonal antibody that bind with high affinity to aggregated Aβ, and they are still under study in the clinical phases with other DMTs.[18] Another class targeting the α-secretase enzyme was developed and has been considered as therapeutic agents. α-secretase modulators or activators stimulate the cleavage of APP. There is little knowledge about the activation pathway,

but research assumes that it is promoted by the phosphatidylinositol 3-kinase (PI3K)/Akt pathway or by γ-aminobutyric acid (GABA) receptor signaling. Targeting these pathways may give potential therapeutic agents for AD.

Chaperones

Protein misfolding caused by mutations or environmental factors results in aggregations that are toxic, and their accumulation causes neurodegenerative disorders like AD. Naturally, cells develop protein quality control (PQC) systems that inhibit protein misfolding before exerting their toxic effects. With age, this balance is altered and the misfolded shapes overwhelm the PQC system, which in turn activates the unfolded protein response (UPR) that stops the protein synthesis and increases chaperone production. Generally, the cells in humans have proteins that are responsible for other proteins to function and arrive to their destination in the cell. These proteins are called "chaperones". Chaperones are involved in protein folding and improvement of the PQC system efficiency.[19] Therefore, it is considered a promising candidate for treating neurodegenerative diseases. It can be classified into three groups: (1) molecular chaperones, which are proteins that assist other nonnative proteins in their folding or unfolding, like over expression of heat shock proteins (Hsps) that serve as neuroprotective agents, (2) pharmacological chaperones, which are low molecular weight compounds (enzymes or receptor-ligand or selective binding molecules) that induce refolding of proteins, stabilize their structure, and restore their function, and (3) chemical chaperones, also low molecular weight compounds, which are divided into two groups, osmolytes and hydrophobic compounds. The members in these two groups have no specific mechanism of action and need high concentrations to exert their therapeutic effect.

Heat shock proteins (Hsps)

The causes for most neurodegenerative diseases are protein misfolding and aggregation, which lead to cell death. The molecular chaperone can be intracellular, such as in the case of heat shock proteins (e.g., Hsp40, Hsp60, Hsp70, Hsp90, Hsp100, and Hsp110), and extracellular, such as clustering and alpha-macroglobulin.[20] HSPs play an essential role in the protein folding process and protect cells from harmful stress-related events. There are two families of Hsps: (a) classic Hsps that possess an ATP-binding site with a molecular weight of 60 kD or more. This family includes Hsp100, Hsp90, Hsp70, and Hsp60, and (b) the small Hsps such as αB-crystalline, Hsp27, Hsp20, HspB8, and HspB2/B3 that lack ATP-binding site, with a molecular weight of 40 kD or less. These proteins can assist other Hsps in their refolding function. Failure of these mechanisms can lead to oxidative stress, mitochondrial dysfunction, and many other conditions that cause damage, a loss of neurons, and a progression of neurodegenerative diseases. Different HSPs can block the aggregation process of misfolded proteins, like amyloidogenic proteins (Aβ and tau), and promote their degradation.[21]

Vacuolar sorting protein 35 (VPS35)

An accumulation of proteins in neurons and glial cells leads to disturbance of cellular protein homeostasis. The endosomal-lysosomal system is responsible for transporting proteins for recycling and degradation. Any malfunction in the system can lead to several diseases, such as Alzheimer's disease. Retromer is a complex of regulator proteins composed of sorting nexin (SNX1, 2, 5, 6) and vacuolar sorting proteins (VPS 26, 29, 35), which are responsible for transporting cargo molecules from the endosome to the trans-Golgi network. A loss of retromer's function results in the downregulation of VPS35, which can increase Aβ formation, induce cognitive impairments, and cause synaptic dysfunction, which is reported in AD patients. A study on 3xTg mice brains was conducted to evaluate the effect of VPS35 overexpression on memory function.[22] The study showed that a significant reduction of the Aβ peptide and tau neuropathology (soluble, insoluble, and phosphorylated tau) was associated with overexpression of VPS35, in addition to a reduction in neuroinflammation and ameliorating synaptic dysfunction. Therefore, VPS35 is an important promising therapeutic target for AD treatment. A small pharmacological chaperones molecule called R55 (thiophene-2,5-diylbis (methylene) dicarbamimid othioatedihydrochloride), a thiophenethiourea derivative, can enhance retromer stability and function by increasing retromer proteins, shifting AOO from the endosome, and reducing pathogenic processing of APP, which may serve as a promising therapeutic molecule for neurodegenerative diseases.

OT1001

Studies demonstrated that the accumulation of gangliosides has been associated with misfolding and aggregation of proteins in neurodegenerative diseases.[23] Abnormal levels of mono-sialoganglioside (GM1, GM2, and GM3) have been reported in AD brains. Mutant forms of Aβ, like Dutch mutant APPE693Q, showed susceptibility to pro-aggregation properties of GM2 and GM3, resulting in the formation of Aβ peptides complexes with gangliosides (ganglioside-bound Aβ (GAβ) peptide) and subsequently leading to an acceleration of aggregation and accumulation of Aβ peptides. β-hexosaminidase (β-hex) is a lysosomal enzyme that acts by catabolizing GM2 ganglioside, and increasing its activity can lead to a reduction of GM2 levels and Aβ aggregation and accumulation. Small molecules like pharmacological chaperones (PC) can selectively bind and stabilize wild-type proteins and restore their normal folding. OT1001 is an iminosugar PC that targets β-hex and increases its level in the brain and reduces GAβ pathology.[24,25] Studies on Dutch APPE693Q transgenic mice showed that OT1001 has good pharmacokinetics, brain penetration ability, and

tolerability, with lower side effects. These make the compound a good drug candidate for increasing the β-hex activity.

Natural extract

For a long time, natural compounds have been used as therapeutic agents for several pathological diseases, and recent studies showed that they possess a neuroprotective effect. In vitro and in vivo studies have proven that natural compounds possess a therapeutic potential for AD, which allowed some of them to enter the clinical trials stages. Nicotine was the first natural compound entered in the clinical trials for AD, and then other compounds like vitamins C, E, and D gained more attention and interest due to their protective role against neuroinflammation and oxidative damage. Recently, bryostatin, a macrolide lactone extract from bryozoan Bugula neritina, has been evaluated and showed the ability to induce α-secretase activity, reduce Aβ production, and enhance the learning and memory in an AD mice model. Other natural compounds used in folk medicine (traditional Chinese medicine (TCM)) demonstrated a great potential in treating AD by acting on several mechanism.[26]

CONCLUSIONS

Alzheimer's disease is now considered a world health concern; as a consequence, the National Institute on Aging Alzheimer's Association reclassified and updated the 1984 NINCDS-ADRDA criteria for higher specificity, sensitivity, and early identification of patients at risk of developing AD. Several criteria have been proposed for a more accurate diagnosis of AD, including clinical biomarkers, bodily fluids, and imaging studies. Despite that, the treatment of AD remains symptomatic, without alteration in the disease's prognosis. Inhibitors to cholinesterase enzyme such as galantamine, donepezil, and rivastigmine, and NMDA antagonists such as memantine, improve memory and alertness but do not prevent progression. Several studies have shown that modification in lifestyle habits like diet and exercise can improve brain health and reduce AD without medical intervention and is considered as a first-line intervention for all AD patients. Recently, the research is focusing on targeting the pathological features of AD such as Aβ and p-tau. Future therapies such as disease-modifying treatment can alter the progression of AD by targeting the Aβ pathway, and many drugs have entered the clinical trials, like AN-1792, solanezumab, bapineuzumab, semagacestat, avagacestat, and tarenflurbil, but failed in demonstrating efficacy in the final clinical stages. Other DMTs are still under investigation, such as those targeting Aβ and tau pathologies, such as aducanumab, gantenerumab, crenezumab, tideglusib, lithium, and others. Other promising compounds called chaperones like heat shock proteins and vacuolar sorting protein 35 (VPS35) function by assisting other proteins to function normally and to arrive at their destination in the cell safely, and therefore can be used as a treatment for neurodegenerative diseases. Moreover, the natural extracts used in folk Chinese medicine showed great potential in treating AD by acting on several mechanisms' pathways. In conclusion, the success of AD treatment depends on its early administration and patient monitoring for disease progression using biomarkers diagnosis. Future therapies that target tau pathology and the use of combination therapy may have a potential to slow the progression of AD pathology. Designing a potent, selective, and effective drug is urgently needed to treat patients with AD and those at risk for developing the disease.

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