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Review article

Alzheimer's disease: An overview of amyloid beta dependent pathogenesis and its therapeutic implications along with *in silico* approaches emphasizing the role of natural products

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ABSTRACT

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder characterized by amyloid beta (Aβ) deposition in brain with subsequent formation of neuritic plaques leading to dementia. A number of therapeutic strategies targeted against Aβ depositions have been rigorously explored which provided successful results corresponding to the existing symptomatic treatments. However, at the same time, several failures corresponding to the disease altering therapies and drugs have also been observed due to potential drawbacks in understanding of the pathogenesis of the disease, development of drug candidates and subsequent designing of clinical trials. Preclinical research, along with experimental and clinical studies, is continuously providing novel information which may reveal multi-target directed ligands and combination therapies for targeting Aβ. Thus, in view of the estimated increase in the number of AD patients globally, the present review attempts to summarize the available evidence dealing with various therapeutic approaches targeting Aβ, focusing specifically on pharmaceutical compounds under various stages of clinical trials. Furthermore, in view of a number of computational advances having significant impact in the field of computer aided drug design, we have also presented results of analysis of natural compounds as potential therapeutic molecules in preventing Aβ plaque formation using *in silico* approaches.

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1. Introduction

Alzheimer's disease (AD), named after its discoverer Alois Alzheimer, is characterized by progressive deterioration of memory, cognition and behavior [105]. It is the leading cause of dementia worldwide, affecting around 24 million demented individuals across all nations [10]. As a consequence of the steady growth of the aging population, the prevalence of dementia is expected to further increase in future in both developed and developing countries. The estimates of dementia prevalence are higher in Asia and Latin America, while lower in India and sub-Saharan Africa. Epidemiological studies have revealed that AD is the most common cause of dementia in India, affecting 2.7% of the population [71]. Environmental and biological factors such as lifestyle, social, cultural, dietary habits, cardiovascular and genetic factors might be related to lower rates of dementia in India [148]. AD has been considered as the sixth leading cause of death in the United States and fifth leading cause of death for the older population (those over age 65). In addition to being a leading cause of death, AD is also a leading cause of disability and morbidity [5].

Three main stages of pathological progression of AD have been defined, namely preclinical AD [141], mild cognitive impairment (MCI) [3] and dementia [100]. A diagnosis of preclinical AD requires the presence of a biomarker (*e.g.*, the presence of a genetic risk factor like the ApoE4 gene, an imaging marker such as an amyloid scan or volumetric hippocampal analysis, CSF tau/amyloid levels, *etc.*) and is itself a spectrum, which ranges from those who are completely asymptomatic but are at risk of developing AD, to those with subtle cognitive symptoms not severe enough to warrant an MCI diagnosis. MCI is diagnosed once cognitive impairments become noticeable and demonstrable on cognitive testing, but not severe enough to significantly interfere with activities of daily living, and can be classified as "prodromal AD" if a biomarker is present, whereas dementia diagnosis requires significant functional impairment to be present in addition to cognitive impairment [17,58,89]. Accordingly, the strategies applied for the treatment of dementia will vary depending upon these three stages of AD. The drugs currently available in the market for the treatment of AD such as donepezil, rivastigmine and galantamine have limited efficiency as well as various side effects [32,54]. These drugs provide mild improvements in cognition and delay the progression of AD only up to a few months. Therefore, in order to lessen the burden of this neurodegenerative disorder and its associated adverse effects, it is desirable to understand the pathology of this disease along with the causes of drug failures for prevention in the preclinical and clinical stages, respectively. The identification of novel therapeutic approaches has gained considerable interest to reduce the incidence and prevalence of dementia. The present review summarizes the results of amyloid-beta (Aβ) mediated progression of AD and development of drugs along with their different stages of clinical trials. Furthermore, *in silico* approaches for development of potential therapeutic molecules for treatment of Aβ-dependent AD, with special reference to plant derived natural products, have also been presented.

2. The amyloid (Aβ) pathway

Aβ are small peptides whose aggregates, once deposited in cell membranes and dendrites of the neurons, progressively lead to development of dementia in AD. Two types of Aβ peptides, namely Aβ42 and Aβ40, are produced by cleavage of the amyloid precursor protein (APP) by the action of β-secretase and γ-secretase (Fig. 1). Aβ42 consists of 42 amino acids while that of Aβ40 is shorter by two amino acids at the C-terminus [56]. Both types of peptides (monomers) can exist inside as well as outside the nerve cells and can make various types of oligomeric structures, namely protofibrils, fibrils and plaques depending upon the extent of oligomerization. Thus, several Aβ peptides, linked together through hydrogen bonds, lead to formation of protofibrils (25–30 Å), comprised of short beta sheets along its width with aligned strands along the length. Aggregation of several protofibrils generates the structures called fibrils (60–80 Å) and further aggregation of these fibrils generates plaques which are highly neurotoxic [97,131]. The cross-beta sheet structure of amyloid fibrils has been validated by the X-ray diffraction studies of microcrystals which reveal short amyloidogenic regions running perpendicular to the filament axis [144]. Aβ42 has been reported to oligomerize and aggregate easily as it is more hydrophobic than Aβ40 [132].

A wide variety of neuronal and non-neuronal cells, like skin fibroblasts and glioma cells, along with blood platelets are major sources of Aβ synthesis [25,30]. After the release of Aβ42 and Aβ40 peptides from these cells, they are adsorbed to the cell surface of vulnerable cells [23]. After adsorption of the Aβ molecules, they are internalized within vesicles like lysosomes inside the cell [23,104] with the help of various uptake processes assisted by several factors such as lipid clusters and various lipid-associated proteins [76]. The neurons and glial cells have been reported to possess receptors for Aβ. One of these receptors is a Receptor for Advanced Glycation End products (RAGE) present on the cell membranes of neurons, glia and endothelial cells [39]. Other possible receptor-like targets are membrane-associated channels, receptors for aspartic acid, glutamate and glycine, which require high concentrations (1–10 mM) of Aβ to become activated [34,40,113]. Moreover, the prion protein is also suggested as a receptor for Aβ [28].

Concentrations of Aβ42 in the CSF as well as in the plasma vary widely in patients of AD though its concentration in the CSF is about 100 times higher than that in the plasma. Thus, the concentration of Aβ42 in CSF of AD patients varies in the range of 500–900 ng/mL (corresponding to approximately 100–200 nM), while that in the plasma varies in the range of 7–9 ng/mL (corresponding to approximately 1.6–2.0 nM) [102]. Furthermore, it has been suggested that concentrations between 1 and 100 nM of Aβ42 oligomers are sufficient to cause significant neuron damage in a tissue specific manner for example, 1 nM Aβ42 concentration in plasma and 100 nM in case of CSF.

The oligomerization of Aβ monomers has been reported to occur at Aβ concentrations of more than 3000 nM in the neurons [108,154]. It has been reported that the concentration of both Aβ monomers and oligomers are related to the severity of dementia in human patients [36], though correlation between the extent of amyloid plaques and severity of dementia is still ambiguous [145].

The changes in fluorescence intensity of specific dyes such as Thioflavin T (ThT) and Congo red (CR) help to determine the presence of the amyloid fibrils by intercalating into the cross beta sheet structure of the fibril allowing them to be used as analytical tools for detection of fibrils [144]. A radioactive ligand with high affinity towards the Aβ plaques has been used to visualize the amyloid plaques in human brains through positron emission tomography (PET) and brain scans of AD patients.