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Multi-targetable chalcone analogs to treat deadly Alzheimer's disease: Current view and upcoming advice

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ABSTRACT

The complications of Alzheimer's disease AD were deadly dangerous cause of neurodegenerative disorders connected with the decline of the cognitive functions and loss of memory. The common form of dementia is accounted as the sixth leading cause of the death affecting any stage of people in a lifetime. Synthetic natural chalcone analogs were currently a hot research topic for the treatment of (AD) which has affected millions of peoples throughout the world. The present aim was set to understand the important problems of the AD and its treatment based on natural derivatives of novel chalcones. One interesting strategy currently of searching for the treatment of AD is to find inhibitors for acetylcholinesterase (AChE) and using metal chelators to target amyloid-β (Aβ) peptides, and then metal-Aβ complexes for the AD pathogenesis. The present compressed review focuses and highlights the design and synthesis of new approaches for the construction of important chalcones playing multiple beneficiary roles in the AD treatments. These hallmarks of concurred research represent the immediate needs of development of novel therapeutic drugs for effective treatment of ADs by understanding the specific pharmacology targets.

1. Introduction

Alzheimer's disease (AD) is one of the neurodegenerative disorders featured with cognitive dysfunction and memory lapse which accounts for the major dementia cases. The progressiveness AD in live people today was estimated to be 45 million and the improper treatment leading to increase of dementia worldwide has raised to 131 million by 2050 as documented [1,2]. Even though the actual etiologic for the AD progression is not fully explored, many pathophysiology factors such as deficits of acetylcholine (ACh), oxidative stress, inflammation,β-amyloid (Aβ) deposits, tau-protein aggregation, and dyshomeostasis of biometals are considered as important key hidden players for the progression of the disease (Fig. 1) [3–5]. To date, there is no medication available to cure the AD or stop its progression in the world. Fortunately, a few medications have been approved or suggested for AD patients to act as temporary systematic relief [6–8].

1.1. Drug targets-candidates: current opinions of Alzheimer's disease (AD) ??

The human nervous system is well organized for inter and intra mutual communication in the brain, which is connected with neurons to communicate at synapses where the information is exchanged between the cell to another by neurotransmitters. The AD actually involved in the disruption of this network communication in the brain by destroying the synapses and neurons which in turn cause the main AD symptom such as impaired conidia and intense loss of memory due to many etiology of AD. Various mechanisms about what leads to neuronal death thereby are getting more attention for the development of a promising treatment for this frontline health problem [9]. The two main hallmarks involving in the AD initiation are specified by the deficit of acetylcholine (cholinergic) hydrolysis and by acetylcholinesterase (AChE) when deposition of the senile plaques occurred around the neurons and twisted neurofibrillary tangles inside the neurons [10]. The deposition of plaques was linked with miss folding of the proteins, which in turn leads to pooling of amyloid-β (Aβ) peptides and tau-proteins for extra and intracellular aggregation respectively [11]. On the other hand, some of the other major AD pathophysiology features are related to the disruption of enzyme metal homeostasis [12] and oxidative stress etc. [13].

1.2. Multi-target drug approaches

Many researchers participated in the field of understanding the

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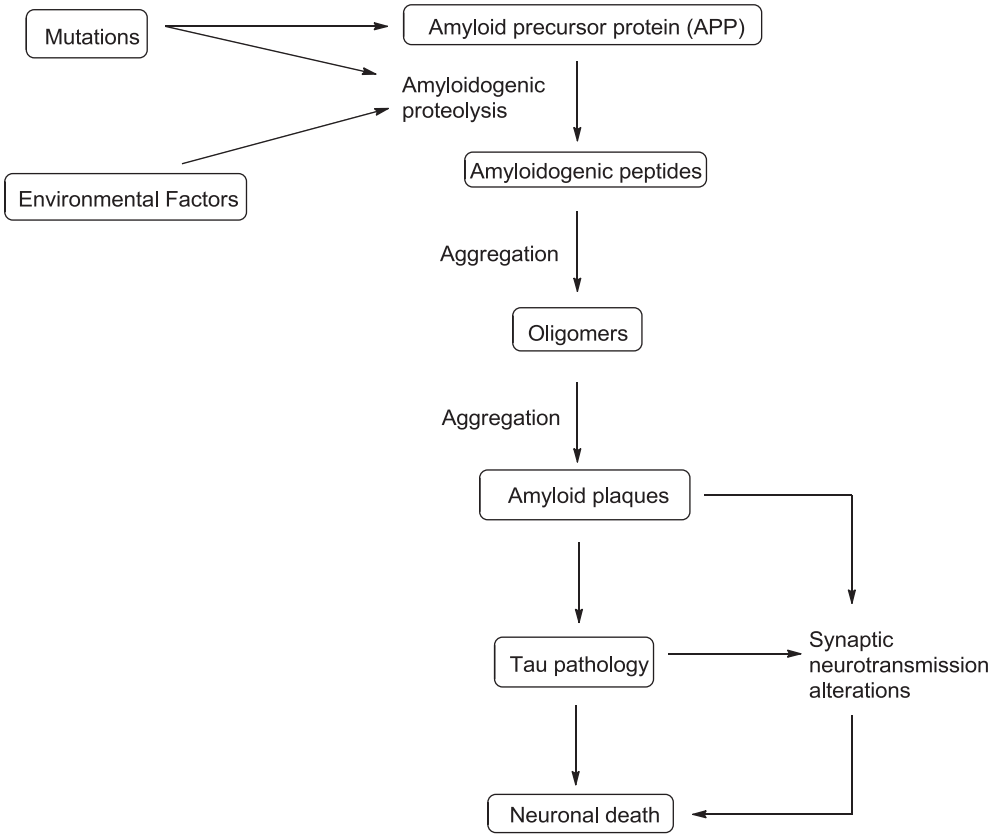

Fig. 1. The multiple mechanisms of pathogenesis condition involved progression of Alzheimer's disease (AD).

pathogenesis and etiology of the AD, but so far, no effective drug has emerged for the treatment of the AD. To treat AD, the AchE is the most successive target investigated for inhibition available so far in the literature [14–18]. Currently, several inhibitors used for the treatment of AD patients were approved by the US Food and Drug Administration (FDA) as AChE inhibitors (AChEIs). They include tacrine (TAC), donepezil, rivastigmine, galanthamine and onememantine functioning, a receptor antagonist for *N*-methyl-D-aspartate (NMDA) (Table 1 and Fig. 2). These developed targeted drugs, can only modulate a few neurotransmitters and improve the memory of the patient (ameliorate symptoms) in a limited period of the window (1–2 years), but they cannot be used as a solution in the course of the AD [19].

The literatures reported that the accumulation of the Aβ in the cerebral cortex is the first in the early event of the AD pathogenesis. This important factor used to prevent the oligomerization of the Aβ or its disruption has been attractive for the development of new paradigms for the treatments of the suppression of AD progression [20–24]. Other interesting factors are the accumulation of Cu^{2+} and Zn^{2+} metal ions concentrations involved in the senile plaques [25,26] and their interactions with the Aβ peptides to promote the assembly of toxic Aβ oligomers [27,28] to generate the reactive oxygen species (ROS) [11,29] (Fig. 3). Remarkable progress has been made to understand that small metal chelators are promising candidates to target Aβ species in inhibition of the cholinesterases AChE or butyrylcholinesterase (BChE) to become potential therapeutics in future. In addition, the chelators are specifically recognized very important solution with their chelating property in disruption of the metals of iron, copper, and zinc ect., in dyshomeostasis of the brains of AD patients as chemotherapy agents to cure disease. Furthermore, the limited toxic nature of the specific metal chelators appears to be one of the promising lead for AD medicine development [26,30,31].

Even though an important milieu in biological research has been developed, there is still an urgent need in searching for and designing of novel health beneficiary candidates from the natural sources. In this regard, a vast number of chemical diversity in nature should not be underestimated. Many natural sources with different biological activities of anti-inflammatory, anticancer, anti-diabetic, anti-bacterial, anti-fungal, and other many have been investigated [26,32–34].

Table 1
Medications approved by the US Food and Drug Administration (FDA) for treating the symptoms of Alzheimer's disease.

Drug name	Brand name	Approved for	Approved in
Tacrine	Cognex	All stages/ discontinued	1993
Donepezil	Aricept	All stages	1996
Rivastigmine	Exelon	All stages	2000
Galanthamine	Razadyne	Mild to moderate	2001
Memantine	Namenda	Moderate to severe	2003
Donepezil with memantine	Namzaric	Moderate to severe	2014

1.3. Chalcones as potential targets for AD

Chalcones, a class of natural compounds commonly existing in fruits, tea, spices and vegetables, belong to the flavonoid family which consist of two aromatic rings connected by α,β-unsaturated carbonyl group. Probably due to the flexible structures, chalcones can effectively bind to many kinds of enzymes or receptors exhibit diverse biological applications and their structural representation was depicted (Fig. 4) [35–44]. In nature, chalcone (1,3-diphenyl-2-propen-1-one) is one of the open chain flavonoids containing 15-carbon arranged in a C_6C_3-C_6 configuration, which are generally found in the form of chalcone aglycones and chalcone *O*-glycosides. In present, many mono, dicotyledonous plants, gymnosperms, and pteridophytes of main components in families of *Asteraceae*, *Moraceae*, *Fabaceae* and *Aristolochiaceae* were