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Plant alkaloids as drug leads for Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative illness associated with dementia and is most prevalent among the elderly population. Current medications can only treat symptoms. Alkaloids are structurally diverse and have been an important source of therapeutics for various brain disorders. Two US Food and Drug Administration (FDA)-approved acetylcholinesterase inhibitors for AD, galantamine and rivastigmine, are in fact alkaloids. In addition, clinical trials of four other extensively studied alkaloids—huperzine A, caffeine, nicotine, and indomethacin—have been conducted but do not convincingly demonstrate their clinical efficacy for AD. Interestingly, rhynchophylline, a known neuroprotective alkaloid, was recently discovered by *in silico* screening as an inhibitor of EphA4, a novel target for AD. Here, we review the pathophysiological mechanisms underlying AD, current treatment strategies, and therapeutic potential of several selected plant alkaloids in AD, highlighting their various drug targets and the key supportive preclinical and clinical studies. Future research should include more rigorous clinical studies of the most promising alkaloids, the further development of recently discovered candidate alkaloids, and the continual search for new alkaloids for relevant drug targets. It remains promising that an alkaloid drug candidate could significantly affect the progression of AD in addition to providing symptomatic relief.

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1. Alzheimer's disease and its underlying pathophysiological mechanisms

Alzheimer's disease (AD) is a neurodegenerative disease and the most common form of dementia and cause of disability in the elderly worldwide (Blennow et al., 2006; De-Paula et al., 2012; Kumar et al., 2015). Besides dementia, AD is characterized by impaired speech comprehension, poor coordination, and diminished executive functions. AD can be classified as familial or sporadic (Shinohara et al., 2014). Familial AD is inherited, rare, and characterized by early onset; it presents mainly as mutations of the amyloid precursor protein (APP), presenilin-1 (PS-1), and presenilin-2 genes (Krstic and Knuesel, 2013; Karch et al., 2014; Mitsui and Tsuji, 2014; Soldano and Hassan, 2014). Most AD cases are the sporadic (or late-onset) form and usually develop after 65 years of age. Although late-onset AD shows no obvious genetic inheritance, apolipoprotein E4 is the major known risk factor (Michaelson, 2014; Mitsui and Tsuji, 2014).

Numerous studies have elucidated some of the molecular mechanisms underlying the pathogenesis of AD. The major pathological characteristics of AD include amyloid beta (Aβ) plaques, neurofibrillary tangles comprising hyperphosphorylated and aggregated tau protein, neuroinflammation, and neurodegeneration (Farías et al., 2011; Guzmán-Martinez et al., 2013; Meraz-Ríos et al., 2013; Millington et al., 2014; Sperling et al., 2014; Heneka et al., 2015). Extracellular deposition of Aβ peptides as senile plaques is the classic neuropathological sign of AD. Diseased forms of Aβ are derived from the sequential cleavage of APP by β-secretase and γ-secretase complexes (Soldano and Hassan, 2014). Mutations of APP, PS1, and PS2 cause abnormal APP processing in familial AD (Krstic and Knuesel, 2013; Karch et al., 2014; Mitsui and Tsuji, 2014; Soldano and Hassan, 2014). Although the original amyloid hypothesis focuses on deposited Aβ as the major cause of pathogenesis, mounting evidence suggests that the soluble oligomeric species of Aβ actually mediates the synaptic dysfunctions in AD (Paula-Lima et al., 2013; Fu et al., 2014; Tu et al., 2014; Xia et al., 2014). Oligomeric Aβ can bind to its potential receptors, which are expressed on astrocytes, microglia, and neurons, to induce synaptic toxicity; these receptors include *N*-methyl-D-aspartate receptor (NMDAR), cellular prion protein, α7 nicotinic acetylcholine receptor (nAChR), p75 neurotrophin receptor, β-adrenergic receptors, erythropoietin-producing hepatocellular (Eph) receptors, paired immunoglobulin-like receptor B, PirB's human ortholog receptor, and Fcγ receptor II-b (Tu et al., 2014; Xia et al., 2014). Thus, extensive efforts have targeted the Aβ cascade through inhibition and modulation of secretase activities, with the aim of counteracting the formation of Aβ aggregates or removing various Aβ forms.

In normal cells, tau protein is a neuronal microtubule-associated protein that stabilizes axonal microtubules and is responsible for intracellular trafficking. Tau is dissociated from microtubules when phosphorylated. In AD, tau becomes abnormally hyperphosphorylated by kinases such as cyclin-dependent kinase-5 (Cdk5), glycogen synthase kinase-3β (GSK-3β), Ca^{2+}/calmodulin-activated protein kinase II, casein kinase I, and dual-specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A) kinase (Ryoo et al., 2007; Farías et al., 2011; Guzmán-Martinez et al., 2013). Hyperphosphorylated tau destabilizes the microtubule network, leading to cytoskeletal collapse, loss of viability, and neuronal death. The Aβ and tau pathologies are not unrelated pathways. Indeed, Aβ may accelerate tau aggregation, and reduced tau expression can block Aβ-induced neuronal dysfunction in the AD mouse model (Stancu et al., 2014; Lloret et al., 2015). The tau-centered approach for AD drug development targets kinases responsible for tau hyperphosphorylation. Moreover, tau aggregation inhibitors and microtubule stabilizers are also under development (West and Bhugra, 2015).

Chronic neuroinflammation is a critical feature related to AD, and associated with increased populations of activated microglia and astrocytes (Meraz-Ríos et al., 2013; Millington et al., 2014; Morales et al., 2014; Heneka et al., 2015). Accordingly, multiple inflammatory stimuli can trigger the activation of microglia and astrocytes; these stimuli can be peripheral (e.g., systemic infections and peripheral chronic inflammation) or local (e.g., brain injury and the presence of various forms of Aβ and tau proteins). Activated microglia and astrocytes release neurotoxic proinflammatory cytokines such as interleukin-1β, interferon-γ, tumor necrosis factor-α (TNF-α), and interleukin-6 as well as reactive oxygen, nitrogen, and carbonyl species, which damage surrounding neurons. Damaged or dying neurons subsequently release immune mediators and modulators, exacerbating the inflammatory neurotoxicity and consequently leading to chronically unresolved brain inflammation. Moreover, proinflammatory cytokines and reactive oxygen species can stimulate γ-secretase activity, and enhance APP expression and amyloidogenic APP processing (Blasko et al., 2004; Liao et al., 2004; Agostinho et al., 2010; Morales et al., 2014). Thus, anti-inflammatory approaches have been considered for the treatment and prevention of AD (Trepanier and Milgram, 2010; Morales et al., 2014). Clinical studies show delayed onset of AD in patients with long-term nonsteroidal anti-inflammatory drug (NSAID) administration, but randomized controlled trials have not demonstrated these beneficial effects of NSAIDs in AD patients (Heneka et al., 2015; ADAPT-FS Research Group, 2015). Moreover, the NSAID naproxen does not exhibit any significant preventive effect against dementia development in asymptomatic individuals (ADAPT-FS Research Group, 2015).

As mentioned above, Aβ oligomers, hyperphosphorylated tau, and neuroinflammation all lead to synaptic loss, neuronal damage, and ultimately cell death. Thus, brain atrophy is rapidly accelerated in AD compared to that in normal aging. Substantial neurodegeneration occurs in the cerebral cortex and parts of the subcortical areas in AD brains when memory deficits become clinically detectable (Blennow et al., 2006; De-Paula et al., 2012). In particular, the loss of cognitive function in AD patients is strongly correlated with the depletion of cholinergic neurotransmission in the basal forebrain; parietal, prefrontal, and entorhinal cortices; and hippocampus (Kása et al., 1997). Dying neuronal cells release glutamate in the vicinity of degenerating regions; this surge in extracellular glutamate leads to excitotoxicity, which is primarily mediated via NMDAR. As neurodegeneration is prominent in AD, neuroprotection, especially against excitotoxicity, is an accepted therapeutic strategy in addition to targeting the individual mechanisms underlying the pathogenesis of AD as mentioned above.

In summary, accumulating neuropathological, epidemiological, and genetic evidence provides critical insights into the design of therapeutic strategies against AD. Despite such progress, however, an effective therapy to halt the progression of neuronal cell damage in AD patients is still lacking.

2. Current treatment strategies for AD

Existing pharmacological treatments for AD act by relieving symptoms rather than targeting the etiological mechanisms. The US FDA-approved medications for AD include acetylcholinesterase (AChE) inhibitors and NMDAR antagonist (Allgaier and Allgaier, 2014; Schneider et al., 2014; National Institute on Aging, 2015). As the loss of cognitive function in AD patients is strongly correlated with the reduction of cholinergic neurotransmission in the brain, rebalancing cholinergic input should theoretically increase memory and cognition in AD patients (Craig et al., 2011).