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Plant alkaloids as drug leads for Alzheimer's disease

Yu Pong Ng, Terry Cho Tsun Or, Nancy Y. Ip*

Division of Life Science, Molecular Neuroscience Center, State Key Laboratory of Molecular Neuroscience, The Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong, China

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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.

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

* Corresponding author.
E-mail address: boip@ust.hk (N.Y. Ip).

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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). Cholinergic transmission is mediated by the neurotransmitter acetylcholine (ACh) through the activation of ionotropic nicotinic and metabotropic muscarinic acetylcholine receptors. AChE inhibitors can enhance cholinergic transmission by limiting degradation of ACh. In fact, the first FDA-approved medication for AD was an AChE inhibitor; tacrine (Cognex™) was approved in 1993, but withdrawn from the market in 2012 because of its hepatotoxicity (National Institute on Aging, 2015). The three most commonly prescribed AChE inhibitors are donepezil (Aricept™), rivastigmine (Exelon™), and galantamine (Reminyl™), which were approved in 1996, 2000, and 2001, respectively (Allgaier and Allgaier, 2014; Schneider et al., 2014). Donepezil is the only AChE inhibitor approved for the treatment of all stages of AD (Allgaier and Allgaier, 2014; Schneider et al., 2014; National Institute on Aging, 2015).

The second class of FDA-approved medications acts by blocking NMDAR. In AD, excess glutamate released from damaged cells causes a massive influx of calcium into neurons via NMDAR activation; this results in excitotoxicity, ultimately leading to neuronal death. Memantine (Namenda™), a neuroprotective agent that blocks NMDAR, was approved for the treatment of moderate to severe AD in 2003 (Allgaier and Allgaier, 2014; Schneider et al., 2014; National Institute on Aging, 2015). Memantine can be used alone or in combination with other AChE inhibitors such as donepezil (National Institute on Aging, 2015).

3. Use of plant alkaloids for AD

Alkaloids are a class of naturally occurring organic nitrogen-containing compounds (IUPAC, 1997; Meyers, 2002) that are found primarily in plants, especially in certain families of flowering plants. The Dictionary of Natural Products (http://dnp.chemnetbase.com/intro/) identifies more than 27,000 alkaloids. A single plant species usually contains only a few kinds of alkaloids, but certain plant families such as *Papaveraceae* (poppies family), *Ranunculaceae* (buttercups), *Solanaceae* (nightshades), and *Amaryllidaceae* (amaryllis) are particularly rich in alkaloids. A few alkaloids can also be found in animal species, such as latrunculin A isolated from *Negombata magnifica* (Red Sea sponge) and batrachotoxin from *Phyllobates* spp. (poison dart frogs).

Alkaloid-containing extracts have been used as therapeutics for

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over 3000 years, e.g., for treating snakebites, fever, and insanity. Extracts from plants containing toxic alkaloids such as curare, aconitine, and tubocurarine are used to poison arrows (Cushnie et al., 2014). Morphine was the first alkaloid discovered by modern chemistry in the 19th century (Laux-Biehlmann et al., 2013). Several other alkaloids such as caffeine, coniine, and nicotine have been discovered since then. In modern medicine, alkaloids have a wide range of pharmacological applications because of their effects. These include analgesic (e.g., morphine), antiasthmatic (e.g., ephedrine), antiarrhythmic (e.g., quinidine), anticancer (e.g., berberine), antihypertensive (e.g., reserpine), antipyretics (e.g., quinine), antibacterial (e.g., ciprofloxacin), and antihyperglycemic (e.g., piperine) effects. Other alkaloids possess psychotropic (e.g., psilocin) and stimulant effects (e.g., cocaine, caffeine, and nicotine) and have been used in rituals or as recreational drugs. Despite the long history and many uses of alkaloid applications, only a few alkaloids are actually marketed as drugs (Amirkia and Heinrich, 2014). Coincidentally, two of the FDA-approved cholinesterase inhibitors for the treatment AD, galantamine and rivastigmine (a synthetic derivative of physostigmine), are alkaloids (Konrath et al., 2013), highlighting the importance of this group of compounds as a source for AD drugs. Below, we will discuss the current and potential applications of plant alkaloids for AD treatment, including conventional approaches, the latest breakthroughs, and new research strategies.

3.1. Galantamine

Galantamine (also called galanthamine) belongs to the isoquinoline alkaloid family. It was first discovered and isolated from *Galanthus nivalis* (common snowdrop) and *Galanthus woronowii* (*Amaryllidaceae*) in the 1950s. Today, it is isolated from *Narcissus* spp. (daffodil), *Leucojum* spp. (snowflake), and *Lycoris* including *Lycoris radiata* (red spider Lily) in industrial production. *Galanthus caucasicus* extract (wild Caucasian snowdrop) was first applied by a Russian pharmacologist to treat poliomyelitis. Galantamine has been used in humans for decades as an anesthetic and to treat neuropathic pain. Synthetic galantamine was first approved for the treatment of AD in Sweden in 2000 and was subsequently approved in the European Union and the United States (Heinrich and Lee Teoh, 2004).

Galantamine has a dual action mechanism on the cholinergic system: it inhibits AChE and allosterically modulates nAChR activity (Parys, 1998; Scott and Goa, 2000). The AChE-inhibiting properties of galantamine were first demonstrated in *ex vivo* experiments using striated and smooth muscles (Mashkovsky and Kruglikova-Lvova, 1951). The binding of galantamine to brain AChE reduces ACh catabolism, which increases ACh levels in the synaptic cleft. Galantamine has 53-fold greater selectivity for human AChE than butyrylcholinesterase (BChE, another type of cholinesterase abundantly expressed in other non-neuronal tissues); this contrasts with nonselective agents such as tacrine and physostigmine, which block both AChE and BChE activities (Thomsen et al., 1990; Bickel et al., 1991; Harvey, 1995). The half maximal inhibitory concentrations (IC_{50}) of galantamine for AChE and BChE are 0.35 and 18.6 μM, respectively (Harvey, 1995). A structure–activity relationship study revealed that the hydroxyl group at C-3 on galantamine contributes to its effective binding to AChE (Bores et al., 1996).

In addition to AChE inhibition, galantamine modulates nicotinic neurotransmission via allosteric potentiation of pre- and postsynaptic nAChR (Schrattenholz et al., 1996; Woodruff-Pak et al., 2001). As presynaptic nAChRs can mediate ACh release, allosteric modulation of these receptors can increase the release of ACh and other neurotransmitters such as glutamate and dopamine, which play important roles in normal brain function (Lawrence and Sahakian, 1998; Amenta and Tayebati, 2008). Therefore, galantamine exhibits important clinical benefits in AD by potentiating the effects of agonists on nAChR.

Many studies have aimed to elucidate the neuroprotective effects of galantamine (Kihara et al., 2004; Takada-Takatori et al., 2006; Egea et al., 2012). Galantamine inhibits Aβ aggregation and cytotoxicity (Matharu et al., 2009; Melo et al., 2009). It can scavenge reactive oxygen species, which protects neurons against oxidative damage (Tsvetkova et al., 2013). Galantamine also promotes adult neurogenesis in the mouse hippocampus via M1 muscarinic and α7 nicotinic ACh receptors (Kita et al., 2014). Therefore, galantamine may alleviate neurodegeneration in AD through neuroprotection and neurogenesis.

Furthermore, clinical studies on galantamine initiated in the 1990s demonstrate that administration at 8–32 mg/day results in consistent symptomatic improvement of cognitive functions and activities of daily living in patients with mild to moderate AD over 3–6 months (Heinrich and Lee Teoh, 2004; Schneider et al., 2014). Moreover, galantamine (24 mg/day) exerts a sustained effect for 12 months (Richarz et al., 2014; Miranda et al., 2015). However, galantamine is associated with side effects, the most common being nausea, vomiting, diarrhea, and anorexia (Schneider, 2000; Wilcock et al., 2003). A study directly comparing galantamine and donepezil treatment over a one-year period shows that both drugs have a similar side-effect profile (Schneider, 2000; Wilcock et al., 2003). Galantamine is now prescribed in sustained-release capsules to treat mild to moderate AD. As both cholinergic and glutamatergic dysfunction are believed to underlie the symptomatology of AD, it is hypothesized that galantamine and memantine can be used together to address impairments in both systems. Epidemiological studies support the use of adjunct therapy with memantine in patients with moderate to severe AD currently treated with an established galantamine regimen (Matsuzono et al., 2015).

3.2. Huperzine A

Huperzine A is an alkaloid isolated from *Huperzia serrata* (Thunb.) Trev. (also known as *Lycopodium serratum* Thunb.). *H. serrata* (*qian ceng ta* in Chinese) has been used for centuries to treat fever, inflammation, contusions, strains, swelling, and schizophrenia (Skolnick, 1997; Wang et al., 2006a; Ma et al., 2007). It occurs naturally in very rare and slow-growing members of *Huperziaceae*. Therefore, there is strong interest in developing alternative sources of huperzine A. Attempted strategies include *in vitro* tissue culture of *Phlegmariurus squarrosus*, a member of *Huperziaceae* that produces higher concentrations of huperzine A (Ma and Gang, 2008); extraction of huperzine A from endophytic fungi isolated from huperzine A-producing herbs (Su and Yang, 2015; Yan et al., 2014); and the total synthesis of naturally occurring stereoisomer (−)huperzine A from commercially abundant (R)-pulegone (Ding et al., 2012).

Huperzine A spurred great excitement in the Chinese pharmaceutical community in the 1980s as it demonstrated the potential of treating AD with a naturally occurring molecule. Huperzine A is a potent specific mixed competitive inhibitor of AChE (Liu et al., 1986; Wang et al., 1986, 2006a). It inhibits AChE with an IC_{50} of 0.1 μM, which is ~1000-fold more potent than its inhibition of BChE (Wang et al., 2006a). It was subsequently found that (−)huperzine A is 70 times more potent in inhibiting AChE than (+)huperzine A (Tang et al., 1994). The crystal structures of AChE/huperzine A complex reveal critical interactions between huperzine A and the anionic subsite of the catalytic domain, paving the way for the development of more versatile huperzine A-derived cholinesterase inhibitors (Raves et al., 1997). For instance, novel heterodimers comprising dimethoxyindanone (from donepezil) and hupyridone (from

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huperzine A) connected by a multimethylene linker have been proposed as next-generation AChE inhibitors for the treatment of AD (Hu et al., 2013); these compounds exhibit higher potency towards AChE with an IC_{50} of 9 nM and an undetectable inhibitory effect on BChE at 1 mM.

The effect of huperzine A on the central cholinergic system of rats *in vivo* was demonstrated shortly after its discovery. Huperzine A administered by intraperitoneal injection reaches different brain regions and inhibits AChE activity in a dose-dependent manner (Tang et al., 1989; Wang and Tang, 1998). Importantly, *in vivo* experiments also demonstrate that compared to tacrine and donepezil, huperzine A exerts a more prolonged inhibitory effect on AChE in the brain, has higher bioavailability, and probably has higher penetration through the blood–brain barrier (Wang and Tang, 1998; Wang et al., 2006a). Subsequent studies reported that huperzine A improves learning and memory in adult and aged rodents, monkeys, and various experimental cognitive impairment models (Wang et al., 2006a). Huperzine A was also found to alleviate cognitive dysfunction induced by intracerebroventricular infusion of Aβ in rats as assessed by a water maze task (Wang et al., 2001b).

Huperzine A targets the pathogenesis of AD via its neuroprotective effect. It protects mitochondrial functions from the toxic effects of Aβ both *in vitro* and *in vivo* (Gao and Tang, 2006; Gao et al., 2009; Yang et al., 2012). Huperzine A also exerts neuroprotective effects via nerve growth factor secretion and signaling (Tang et al., 2005a, b; Wang et al., 2006b). It reduces glutamate excitotoxicity by acting as an NMDAR antagonist (Wang et al., 1999; Gordon et al., 2001; Zhang and Hu, 2001; Zhang et al., 2002). The neuroprotective effect of huperzine against neuronal apoptosis in AD can also be achieved by regulating the expression of pro-apoptotic genes/proteins and increasing the expression of anti-apoptotic genes/proteins (Wang et al., 2001a, 2001b; Zhou et al., 2001; Xiao et al., 2002).

Furthermore, patients with AD or mild cognitive impairment have elevated brain iron levels (Bartzokis et al., 1994; Smith et al., 2010). In addition, current evidence implies that Aβ production, aggregation, and toxicity in AD are caused by abnormal interactions with neocortical iron (Bush, 2003). These findings strongly support the idea that iron dyshomeostasis plays an initial and central role in the pathogenesis of AD. Long-term treatment with huperzine A can significantly reduce iron content and transferrin receptor 1 expression in the brains of transgenic AD mice (Huang et al., 2014). However, the beneficial effects of long-term treatment with huperzine A, such as reduced insoluble and soluble Aβ levels, ameliorated amyloid plaque formation, and hyperphosphorylated tau in the cortex and hippocampus of transgenic AD mice, are abolished in transgenic AD mice fed with a high iron diet.

The role of huperzine A in adult hippocampal neurogenesis was recently revealed (Ma et al., 2013); treatment with huperzine A promoted the proliferation of cultured mouse embryonic hippocampal neural stem cells and increased newly generated cells in the subgranular zone of the hippocampus in adult mice. Thus, these findings provide new insights into the therapeutic effects of huperzine A in neurological disorders via a neurogenesis-related mechanism.

Huperzine A is approved in China for the treatment of AD and vascular dementia. Its clinical efficacy is corroborated by several clinical trials conducted in China (Wang et al., 2006a). However, in a phase II clinical trial conducted and completed in 2007 in the US, huperzine A (200 μg twice daily) had no demonstrable cognitive effect on patients with mild to moderate AD (Rafii et al., 2011), while huperzine A (400 μg twice daily) showed some evidence of cognitive enhancement. A systematic review and meta-analysis of randomized clinical trials on huperzine A indicates that huperzine A improves cognitive function, daily living activities, and global clinical assessment in patients with AD (Li et al., 2008; Yang et al., 2013). Thus, huperzine A may produce short-term symptomatic improvement. Another epidemiological study on memantine and huperzine A combination therapy for AD shows that patients with mild to moderate symptoms treated with the combination therapy exhibit better clinical scores than those treated with memantine monotherapy (Shao, 2015). This result provides further evidence of the efficacy of huperzine A with memantine in patients with mild to moderate AD. However, additional studies are required to confirm the specific clinical efficacy of huperzine A in AD. Although the US FDA has not approved the therapeutic use of huperzine A in AD because of its aforementioned failure in clinical trials, it is widely available as an over-the-counter nutraceutical in the US (Orhan et al., 2011).

3.3. Berberine

Berberine is a plant isoquinoline alkaloid commonly found in traditional Indian and Chinese medicines. It has been used as a natural yellow dye for decades because of its characteristic yellow fluorescence upon ultraviolet activation. Berberine is mainly distributed in the roots, bark, and stems of several medicinal plants including *Berberis* spp., *Hydrastis canadensis*, and *Coptidis* rhizome (Ye et al., 2009). Recent studies show that berberine has diverse pharmacological functions including anti-inflammatory, cardioprotective, neuroprotective, antitumor, and antimalarial effects (Ma et al., 1999; Küpeli et al., 2002; Tran et al., 2003; Zheng et al., 2003; Kettmann et al., 2004; Racková et al., 2004; Letasiová et al., 2006). In addition, berberine exhibits beneficial effects in AD through different mechanisms.

Several studies demonstrate that berberine inhibits both AChE and BChE (Abd El-Wahab et al., 2013; Bonesi et al., 2013; Su et al., 2013) with IC_{50} of 0.37 and 18.21 μM, respectively. Therefore, it has higher selectivity for AChE than BChE (Su et al., 2013). These results suggest that berberine enhances cholinergic stimulation and can therefore be used to improve cognitive impairment in AD.

Berberine inhibits the formation of pathogenic Aβ and Aβ aggregation in neuronal cells stably expressing human Swedish mutant APP (Asai et al., 2007; Su et al., 2013; Durairajan et al., 2012, 2014). Moreover, berberine reduces learning deficits and increases the long-term spatial memory retention of TgCRND8 transgenic AD mice compared to controls. Mice treated with berberine at 25 mg kg^{-1} day^{-1} for 4 months exhibit decreased plaque load, and soluble and insoluble Aβ levels in the brain via the reduction of GSK-3β activity (Durairajan et al., 2012). In a rabbit AD model, berberine increases survival rate and reduces hippocampal damage by attenuating β-secretase activity (Panahi et al., 2013).

Recent research indicates that berberine inhibits the production of proinflammatory cytokines such as interleukin-6 and C–C motif chemokine 2 (CCL2) in Aβ-stimulated primary microglia and in a murine microglial cell line (BV-2) (Jia et al., 2012). In addition, berberine reduces the expressions of cyclooxygenase-2 and inducible nitric oxide synthase. Although the underlying mechanisms require further investigation, current evidence suggests that berberine may exert its anti-inflammatory effects via the inhibition of the nuclear factor-κB, phosphoinositide 3-kinase, and mitogen-activated protein kinase signaling pathways (Jia et al., 2012).

The anti-oxidative effects of berberine have been widely studied. Berberine scavenges nitric oxide, peronitrite ($ONOO^-$), hydrogen peroxide, and 1, 2-diphenyl-2-picryl hydrazyl radicals (Racková et al., 2004; Jung et al., 2009; Abd El-Wahab et al., 2013). It can also reduce lipid peroxidation (Racková et al., 2004; Abd El-Wahab et al., 2013). Besides scavenging free radicals, berberine enhances the activities of anti-oxidative enzymes such as

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superoxide dismutase and glutathione peroxidase to combat oxidative stress (Abd El-Wahab et al., 2013). Berberine also rescues homocysteic acid-induced neurotoxicity in HT-22 hippocampal neuronal cells and significantly decreases homocysteic acid-induced levels of reactive oxygen species, lactate dehydrogenase release, and subsequent cell death; this protective effect involves the Akt signaling pathways (Chen et al., 2015). Another study found that berberine rescues calyculin-induced cell death in neuroblastoma-2a cells by reducing oxidative stress (Liu et al., 2014). These findings collectively indicate that berberine is a promising anti-oxidant against oxidative stress involved in AD.

Moreover, berberine can reduce tau hyperphosphorylation in several *in vitro* systems including HEK293 cells, calyculin-A–treated neuroblastoma-2a cells, and neuroblastoma-2a cells stably expressing human Swedish mutant APP by modulating phosphatase 2A activity (Yu et al., 2011; Durairajan et al., 2012; Liu et al., 2014). In HEK293 cells, berberine decreases tau hyperphosphorylation upon calyculin-A treatment by restoring protein phospatase-2A activity and inhibiting GSK-3β activation (Yu et al., 2011).

Although berberine has various beneficial effects on AD and is generally considered safe for human use, the results of several experimental studies have raised concerns regarding its neurotoxicity, induction of bradycardia, and exacerbation of neurodegeneration, especially as a consequence of increasing the bioavailability of berberine with increasing dose and its tendency to accumulate in the central nervous system (Wang et al., 2005; Shin et al., 2013; Kysenius et al., 2014). Therefore, additional studies are required to evaluate the potential neurotoxicity of berberine for the treatment of AD.

3.4. Caffeine

Caffeine is present in many dietary sources including coffee (71–220 mg caffeine/150 mL), tea (32–42 mg/150 mL), cola (32–70 mg/330 mL), and cocoa (4 mg/150 mL) (Nehlig, 1999). Caffeine is well known for its short-term stimulating effects on the central nervous system via its ability to antagonize adenosine A2A receptors. It can promote behavioral functions including vigilance, attention, mood, and arousal as well as improve cognition (Fredholm et al., 1999; Smith, 2002). Low to moderate doses of caffeine (50–300 mg) cause the most notable stimulating effect while higher doses result in anxiety, restlessness, insomnia, and tachycardia (Nehlig, 1999). However, the long-term impacts of caffeine remain unclear.

Caffeine reduces levels of Aβ and Aβ-induced neurotoxicity both *in vitro* and *in vivo* as well as improves cognitive performance in Aβ-induced AD mouse models. Caffeine reduces levels of Aβ in neuroblastoma-2a cells stably expressing human Swedish mutant APP (Arendash et al., 2009) and protects cerebellar granule neurons and basal forebrain neurons from neurotoxicity caused by Aβ (Dall'Igna et al., 2007; Chu et al., 2012). Caffeine exerts this protective effect partly by reducing caspase-3 expression. Different *in vivo* models have further demonstrated the protective effects of caffeine in AD. For instance, sub-chronic administration of caffeine prevents Aβ-induced amnesic effects in both inhibitory avoidance and spontaneous alternation tasks in mice (Dall'Igna et al., 2007). Caffeine prevents and reverses cognitive impairment in young and aged Swedish mutant APP transgenic mice, respectively (Arendash et al., 2006, 2009). Caffeine decreases the levels of PS1, β-secretase, and soluble Aβ in the hippocampus, and reduces Aβ deposition in the hippocampus and entorhinal cortex. The caffeine-induced reduction of β-secretase in the brains of AD transgenic mice is mediated by the downregulation of the cRaf-1/NF-κB pathway (Arendash et al., 2009). In addition, caffeine can stimulate the survival pathway by increasing PKA activity and phospho-CREB levels while suppressing phospho-JNK and phospho-ERK expressions in the striatum of the Swedish mutant APP transgenic mouse model. These results suggest that caffeine promotes neuronal survival in AD pathogenesis, which may contribute to its beneficial effects in AD (Zeitlin et al., 2011).

Caffeine also exhibits anti-inflammatory and anti-oxidative properties. In THY-Tau22 transgenic mice, whose markers of innate immunity (e.g., CD68, CD45, and toll-like receptor 2), several proinflammatory cytokines (e.g., CCL4, CCL5, and TNF-α), and the astrocytic marker GFAP are significantly higher in the hippocampus than those in wild-type animals, caffeine treatment significantly decreases the mRNA levels of CD45, toll-like receptor 2, CCL4, and TNF-α (Laurent et al., 2014). As evidence of its potent anti-oxidative effects, caffeine can scavenge OH and OCH3 free radicals (Leon-Carmona and Galano, 2011) as well as suppress the mRNA levels of several oxidative stress markers in THY-Tau22 mice (Laurent et al., 2014). In addition, caffeine treatment significantly reduces hippocampal tau phosphorylation and the respective proteolytic tau fragments in THY-Tau22 mice (Laurent et al., 2014). Caffeine-treated THY-Tau22 mice also exhibit improved spatial memory performance in the Morris Water Maze test (Laurent et al., 2014). The anti-oxidative effect of caffeine has also been demonstrated to be associated with the decrease of Aβ and phosphorylated tau in the cholesterol-induced sporadic AD model in rabbits (Prasanthi et al., 2010). These studies collectively demonstrate that caffeine intake is beneficial in models of AD-like tau pathology and that its anti-inflammatory and anti-oxidative effects may underlie this beneficial effect.

Furthermore, the beneficial effects of caffeine in AD have been evaluated in clinical trials. One trial investigated the association between caffeine intake and AD risk (Maia and de Mendonça, 2002). Patients with AD had an average daily caffeine intake of 74 mg during the 20 years that preceded the diagnosis of AD, whereas the controls had an average daily caffeine intake of 199 mg during the corresponding 20 years. Logistic regression analysis indicated that caffeine intake during this period was inversely associated with AD (Maia and de Mendonça, 2002). A recent “Cardiovascular Risk Factors, Aging and Dementia” (CAIDE) study reports that drinking three to five cups of coffee daily at midlife is associated with a 65% lower risk of dementia (Vartiainen et al., 1994; Eskelinen and Kivipelto, 2010). These studies corroborate the beneficial effects of caffeine in AD progression and prevention. However, the latest meta-analysis of observational epidemiological studies on the association between caffeine intake from coffee or tea and the risk of cognitive disorders found no association between caffeine intake and the risk of cognitive disorders (Kim et al., 2015). Therefore, additional studies with longer follow-up periods are required to clarify the relationship between caffeine and AD.

3.5. Rhynchophylline and isorhynchophylline

Rhynchophylline and isorhynchophylline are tetracyclic oxindole alkaloids isolated from the herb *Uncaria rhynchophylla*, accounting for 28–50% and 15% of its total alkaloid content, respectively. Investigation of the pharmacological effects of rhynchophylline and isorhynchophylline reveal that they exert beneficial effects on cardiovascular diseases including hypertension, bradycardia, and arrhythmia. They act as calcium channel antagonists, anticoagulants, and vascular smooth muscle cell proliferation inhibitors (Chen et al., 1992; Shi et al., 2003; Zhang et al., 2004; Zhou and Zhou, 2012; Li et al., 2013). Moreover, they exert beneficial effects on central nervous system diseases such as dementia, ischemia, amnesia, and epilepsy (Mohamed et al., 2000; Hsieh et al., 2009; Zhou and Zhou, 2010, 2012).

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The therapeutic roles of rhynchophylline and isorhynchophylline in AD have recently been investigated. Both are found to have neuroprotective effects and rescue PC12 neuronal cells from cell death after Aβ challenge (Xian et al., 2012a, 2012b, 2013, 2014). Their neuroprotective effects are at least partly mediated via the reduction of Ca^{2+} overload and tau protein hyperphosphorylation (Xian et al., 2012a). Another study demonstrates that isorhynchophylline exhibits anti-oxidative properties and inhibits caspase-3, increases the ratio of Bcl-2/Bax protein expression, and stabilizes mitochondrial membrane potential, all of which may underlie its neuroprotective effect (Xian et al., 2012b). The signaling cascades mediating the neuroprotective effect of isorhynchophylline have also been studied. Isorhynchophylline can reverse the Aβ-attenuated phosphorylation of Akt, cAMP response element-binding protein, and GSK-3β signaling proteins (Xian et al., 2013). *In vivo*, the neuroprotective effect of isorhynchophylline against Aβ is observed by the reversal of the cognitive and behavioral impairments in AD rats.

Our recent study has revealed the molecular target of rhynchophylline. Rhynchophylline has been identified as an inhibitor of the receptor tyrosine kinase EphA4, and is implicated in rescuing hippocampal synaptic dysfunctions in AD (Fu et al., 2014). Soluble Aβ oligomers can activate EphA4 in cultured hippocampal neurons, and EphA4 signaling is enhanced in the hippocampus of APP/PS1 transgenic mouse model of AD. Furthermore, blockade of EphA4 activation in cultured hippocampal neurons and acute hippocampal slices ameliorates Aβ-induced defects including the concomitant reduction in spine density and impaired neurotransmission, and decreases long-term potentiation, respectively. Finally, reduced EphA4 function in the hippocampal CA1 region reverses the suppression of hippocampal long-term potentiation in APP/PS1 mice. These findings indicate that EphA4 activation by Aβ contributes to the synaptic dysfunction observed in AD.

Our group performed *in silico* screening to search for small molecules that bind to the extracellular ligand-binding domain of EphA4 with high affinity. Rhynchophylline was identified as a top candidate. The binding of rhynchophylline to the extracellular domain of EphA4 and the inhibitory effect of rhynchophylline on EphA4 activation were further demonstrated in *in vitro* assays. Moreover, oral administration of rhynchophylline restores impaired long-term potentiation in the hippocampus of APP/PS1 transgenic mice by reducing EphA4 activity. Thus, our findings demonstrate that rhynchophylline has beneficial effects on synaptic dysfunctions in AD.

3.6. Indometacin

Indometacin (also called indomethacin) belongs to the pyrrolizidine class. It is an NSAID that selectively inhibits cyclooxygenase in the production of prostaglandins. Indometacin (Indicin®) is currently prescribed to reduce fever as well as relieve moderate to severe pain, tenderness, swelling, and stiffness caused by osteoarthritis, rheumatoid arthritis, and acute gouty arthritis. Because of its anti-inflammatory properties, the effect of indometacin in AD has been studied in various cell culture and animal models, with promising results (Heneka et al., 2011; Bernardi et al., 2012). Preliminary clinical drug trials of indometacin further demonstrate its ability to slow cognitive decline in AD. However, appropriate follow-up trials have yet to be conducted.

3.7. Indirubin

The *bis*-indole alkaloid indirubin and its analogues are mainly recognized as kinase inhibitors, but several other properties make them possible therapeutic candidates for AD (Leclerc et al., 2001). For example, indirubin-3′-monoxime is a potent inhibitor of GSK-3β both *in vitro* and *in vivo*; it prevents abnormal tau phosphorylation and rescues spatial memory deficits in AD mouse models (Leclerc et al., 2001; Selenica et al., 2007; Ding et al., 2010). Indirubin-3′-monoxime also inhibits the phosphorylation of CDK5/p25 activity *in vivo*, which is also related to neuropathological events associated with AD (Leclerc et al., 2001).

3.8. Capsaicin

Capsaicin is the primary capsaicinoid found in chili peppers and is responsible for their spiciness. It exhibits a wide range of biological properties and acts as a hypolipidemic, antioxidant, and anti-inflammatory agent. Capsaicin ameliorates synaptic damage and tau hyperphosphorylation in stressed mouse models (Jiang et al., 2013). However, Pákáski et al. (2009) demonstrate that capsaicin increases the level of membrane-bound APP in rat brains, which facilities the production of pathogenic Aβ.

3.9. Harmine

Harmine belongs to the β-carboline alkaloid family and is characterized by a core indole structure and a pyridine ring. It was recently identified to potently inhibit DYRK1A activity (Göckler et al., 2009). Harmine also potently reduces tau protein phosphorylation and inhibits the DYRK1A-catalyzed direct phosphorylation of tau. These results suggest that harmine may have promising therapeutic benefits in the treatment of AD (Frost et al., 2011).

3.10. Morphine

Opioids such as morphine and codeine have been used extensively for centuries. They are potent and reliable analgesics that are still widely used for pain management today. Opioids are defined by their actions at one of four opioid G protein-coupled receptors: μ, δ, κ, and the nociceptin orphanin peptide receptor. Only agonists that target the μ-opioid receptor, such as heroin, morphine and oxycodone, consistently possess analgesic effects; these are also the most commonly abused (Le Moal and Koob, 2007; Pasternak and Pan, 2011). Several studies investigating morphine as a therapeutic agent for treatment of AD demonstrate that morphine protects neurons against microglia-mediated neuroinflammation and oxidative stress (Rambhia et al., 2005; Qian et al., 2007). Morphine protects against intracellular amyloid toxicity by inducing estradiol release and the upregulation of heat shock protein-70. Activation of μ-opioid receptor also attenuates Aβ oligomer-induced neurotoxicity via mTOR signaling. These studies decisively identify opioid receptors as potential therapeutic targets for AD. However, because of their highly addictive properties, the use of opioids as therapeutics is severely restricted and limited.

3.11. Nicotine

Aβ is suggested to have high affinity for nAChR (Wang et al., 2000). Given that the tobacco alkaloid nicotine can enhance cholinergic function, its therapeutic potential has been investigated extensively. Nicotine binds to Aβ and blocks its aggregation, therefore exerting a neuroprotective effect (Salomon et al., 1996). Nicotine also diminishes AD pathology in animal models (Shim et al., 2008). However, clinical studies investigating the efficacy of nicotine against AD pathology have not demonstrated significant improvements in memory (White and Levin, 1999; Howe and Price, 2001), although they demonstrate a clear positive effect on attention in AD patients (White and Levin, 1999). Nicotine's failure to

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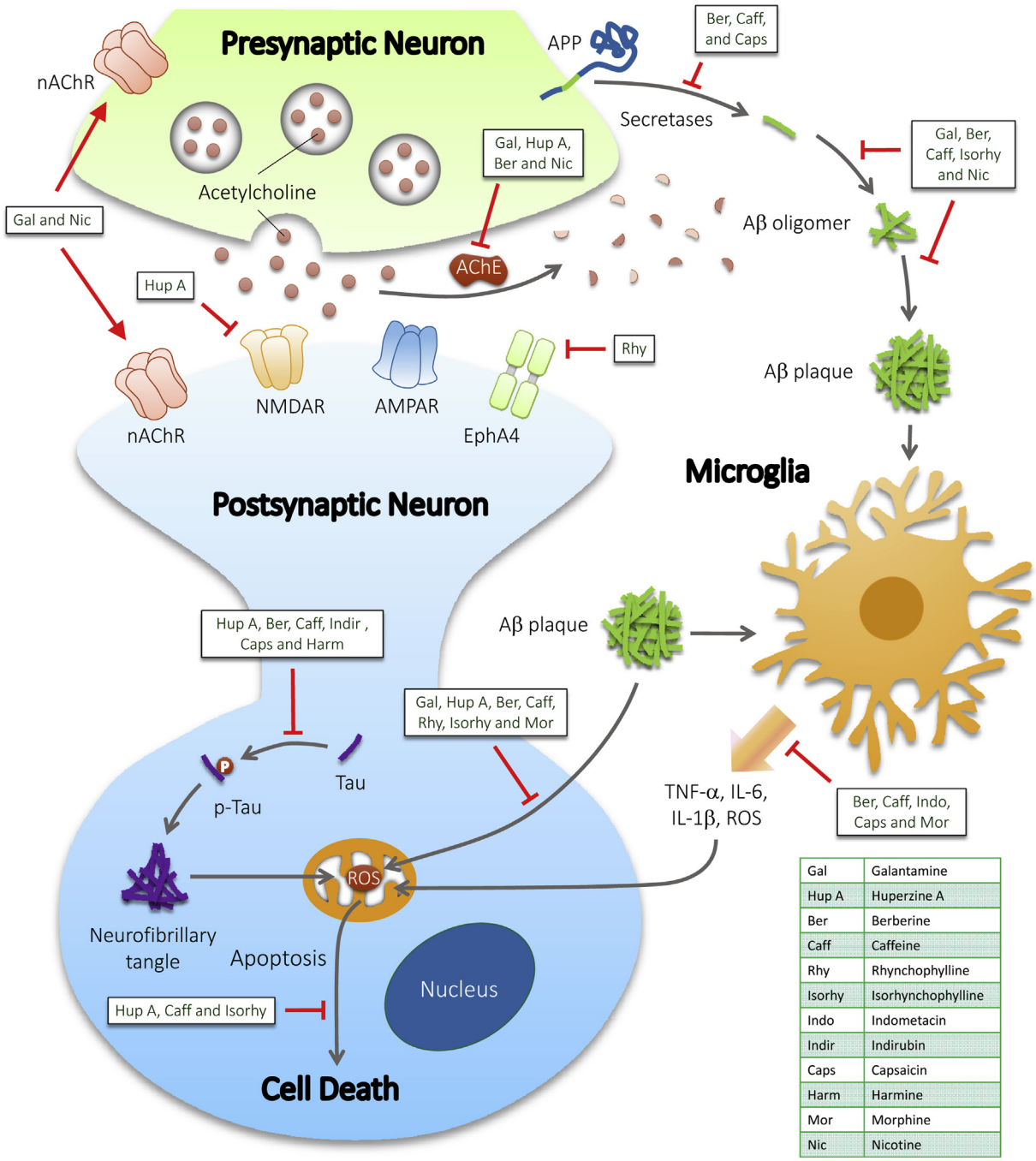

Gal	Galantamine
Hup A	Huperzine A
Ber	Berberine
Caff	Caffeine
Rhy	Rhynchophylline
Isorhy	Isorhynchophylline
Indo	Indometacin
Indir	Indirubin
Caps	Capsaicin
Harm	Harmine
Mor	Morphine
Nic	Nicotine

Fig. 1. Targeted mechanisms of alkaloid candidates against Alzheimer's disease. The major pathological characteristics of Alzheimer's disease include the amyloid-beta (Aβ) and tau pathologies, neuroinflammation and neurodegeneration. The plant alkaloids with potential therapeutic value are grouped according to various pathophysiological mechanisms. It is interesting to note that most of the selected candidates affect more than one pathway.

improve memory in AD patients, and its short half-life, inherent toxicity, induction of tachyphylaxis, and addictiveness has dampened enthusiasm for its clinical use.

As an alternative to nicotine, cotinine, the main metabolite of nicotine, has been examined for the treatment of AD. Cotinine has similar beneficial properties against AD pathology but lacks the adverse side-effects. Cotinine prevents working and reference memory loss in an AD mouse model, prevents the aggregation of Aβ peptides both *in vitro* and *in vivo*, inhibits GSK-3β activity, and activates the pro-survival enzyme Akt (Echeverria et al., 2011). Thus, cotinine may represent a new molecular entity for AD treatment.

4. Conclusion

Over the past 20 years, drug development for AD has been mainly driven by the amyloid hypothesis. The breakthrough discoveries of the two US FDA-approved AChE inhibitors, galantamine and rivastigmine, spurred interest in identifying alkaloids for managing AD, in particularly via AChE inhibition. However, recent biological studies as well as preclinical and clinical outcomes have led to the discovery of additional novel and well-defined therapeutic targets for AD treatment. Furthermore, the recent research suggests that additional alkaloids, either novel compounds or new

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uses for existing drugs, could be used in conventional as well as novel approaches. Selected potential candidate alkaloids and their targeted action mechanisms are summarized in Fig. 1. It is interesting to note that most of the compounds were initially identified to affect one pathway in AD pathogenesis, but subsequent studies have demonstrated other possible action mechanisms. Moreover, the promising clinical results of galantamine and memantine combination therapy support multitarget-directed ligands as a new treatment strategy for etiologically complex diseases such as AD (Matsuzono et al., 2015). As most natural compounds including alkaloids have multiple targets, strategies such as combined treatments, and the development of synthetic heterodimers by linking different functional motifs with different targets (Lu et al., 2012; Hu et al., 2013), may help improve the potency of existing drugs and aid the development of new classes of drugs.

In alkaloid drug research, data are usually generated from acute administration in cells-based and animal models. However, further research in animal models, in particularly studies on chronic administration and detailed safety investigations of potential drug leads, is required, because their beneficial effect in AD may require long-term administration. More rigorous clinical trials aiming to demonstrate the therapeutic effects of alkaloids such as huperzine A and indometacin in AD patients are also essential to secure FDA approval. With a number of promising compounds currently under investigation, more effective therapeutic candidates for the treatment of AD are eagerly anticipated in the near future.

Conflicts of interest

All authors and the study sponsors have no financial or commercial conflicts of interest related to the study.

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List of abbreviations

Aβ	amyloid beta
ACh	acetylcholine
AChE	acetylcholinesterase
AD	Alzheimer's disease
APP	amyloid precursor protein
BChE	butyrylcholinesterase
CAIDE	cardiovascular Risk Factors, Aging and Dementia
Cdk5	cyclin-dependent kinase-5
DYRK1A	dual-specificity tyrosine phosphorylation regulated kinase 1A
EphA4	erythropoietin-producing hepatocellular A4
FDA	food and drug administration
GSK-3β	glycogen synthase kinase-3β
IC_{50}	half maximal inhibitory concentration
mTOR	mammalian target of rapamycin
nAChR	nicotinic acetylcholine receptor
NMDAR	*N*-methyl-D-aspartate receptor
NSAID	nonsteroidal anti-inflammatory drug
PS	presenilin
TrkA	tropomyosin receptor kinase A
TNF-α	tumor necrosis factor-α

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