Published online: September 30, 2019

Review

Current anti-Alzheimer's disease effect of natural products and their principal targets

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DOI:10.31083/j.jin.2019.03.1105

Various bioactive substances isolated from natural products play a pivotal role in the prevention and cure of neurodegenerative diseases, such as Alzheimer's disease. Currently, there are many theories about the pathogenesis of this disease. In this review we discuss among them, the cholinergic hypotheses, the Aβ toxicity hypothesis, and the tau dysfunction hypothesis. Multiple potential targets are a focus for the development of anti-AD drugs. There is an urgent need to develop more effective therapies to treat and delay the onset of the disease and to find safe and effective drugs. In this review, the recent progress of anti-AD effects and their principal targets are updated.

Keywords

Alzheimer's disease; natural products; cholinergic hypotheses; Aβ toxicity; tau hyperphosphorylation; neurochemistry; acetylcholinesterase activity

1. Introduction

Alzheimer's disease (AD) is a chronic progressive neurodegenerative disease associated with memory loss and cognitive impairment (Colligris et al., 2018). This disorder has reached worrying epidemic proportions related to the aging of the global population. Many studies have shown mechanisms for the pathogenesis of AD, including among others, the cholinergic hypothesis (Leblhuber et al., 2018; Mesulam and Geula, 1991), Aβ amyloid toxicity hypothesis (Verdile et al., 2007), tau dysfunction hypothesis (Bagyinszky et al., 2018), vascular hypothesis (Snyder et al., 2015), insulin hypothesis (Chornenkyy et al., 2018) and gene mutation hypothesis (Ringman and Coppola, 2013). Among them, the most studied have been the cholinergic, Aβ toxicity, and tau dysfunction hypotheses.

The cholinergic hypothesis proposes that increased AChE activity in AD patients with brain lesions may lead to the loss of the acetylcholine of cholinergic synapses, affect the conduction of nerve impulses and result in cognitive and memory impairment (Leblhuber et al., 2018; Mesulam and Geula, 1991). Thus, increased AChE activity is one of the main causes of AD, and inhibition of AChE activity may alleviate these symptoms in patients. AChE inhibitors increase cholinergic transmission by blocking the degradation of ACh and are therefore considered to be a promising approach for the treatment of AD. Currently, the main therapies available for AD treatment are based on the cholinergic hypothesis (Lleo et al., 2006; Reitz et al., 2011). As described by Barage and Sonawane (Barage and Sonawane, 2015), the biochemical studies of biopsy tissue and post-mortem brain tissues from AD patients showing a reduction in relation to the choline acetyltransferase activity, ACh synthesis, choline uptake and ACh release. These notable data indicated the clinical importance referred to degeneration of cholinergic neurons and related loss of cholinergic neurotransmission, considering the cerebral cortex as well as other areas that brought about a significant contribution to impairment of cognitive functions in AD.

According to the so called Aβ toxicity hypotheses, the accumulation of Aβ in the brain of AD patients is the principal pathological event in AD, which eventually leads to a number of secondary neuropathological changes such as accumulation of the hyperphosphorylated tau protein forming neurofibrillary tangles (NFTs), synaptic degeneration, neuronal cell death and dementia (Kuperstein et al., 2010). Among these, the extracellular deposition of Aβ forming toxic plaques along with the intracellular accumulation of the hyperphosphorylated tau protein forming NFTs in the brain, have been considered as the major pathological hallmarks of AD (Takahashi et al., 2017). The tau deposition in brain NFTs, has been suggested to be the consequence of the accumulation of Aβ plaques (Hutton et al., 1998; Lewis et al., 2001). Furthermore, the pathogenic role of genetic variations at the apolipoprotein E (apoE) locus has also been reported to involve Aβ metabolism. Thus, knockout mutant mice for apoE (apoE-deficient mice) exhibited strikingly reduced Aβ deposition (Bales et al., 1997). A number of genetic variations, involving breakdown and clearance of Aβ have been correlated/linked to the risk of AD development (Awasthi et al., 2016). Thus, ACH shows that cerebral deposits of Aβ are the main pathological trigger in AD development, while the remaining changes, such as tau tangle formation, result from an imbalance in the equilibrium between Aβ production and clearance.

The tau dysfunction hypothesis proposes that helically twisted filaments of hyperphosphorylated tau are crucial pathogenetic features in AD. Based on the β-amyloid hypothesis, which was proposed in 1991, NFT generation is preceded by deposits of Aβ (Hardy and Allsop, 1991). The lack of balance between the for-

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mation and removal of Aβ from brain tissue results in a situation that leads to toxic aggregation and production of senile plaques. This process promotes hyperphosphorylation of tau protein, thus resulting in destabilization of the cytoskeleton and degeneration of nerve cells (de Castro et al., 2019). It is noteworthy that not only plaque formation promotes hyperphosphorylation of tau, and this finding is supported by the fact that the neurofibrillary degeneration starts in the allocortex of the medial temporal lobe (entorhinal cortex and hippocampus), thus spreading to the associative isocortex. However, the entorhinal cortex is not susceptible to plaques formation (Serrano-Pozo et al., 2011). Tau protein is characterized by its implications in the stabilization of cytoskeletal microtubules (Garcia and Cleveland, 2001). In AD, hyperphosphorylated tau is displaced to the somatodendritic portion. Tau phosphorylation is critical to its function, but hyperphosphorylated tau no longer binds to microtubules, instead aggregating into paired helical filaments (Lee and Trojanowski, 1992). The result is a general instability of microtubules and disruption of axonal transport that leads to neuronal injury and cell death. Increased levels of phosphorylated or total tau in the CSF are strong indicators of neurodegenerative diseases or injury (Clark et al., 2003).

Acetylcholinesterase (AChE) inhibitors have been reported to inhibit Aβ deposition and tau hyperphosphorylation. Some inhibitors are synthetic while others are natural. Although some synthetic drugs have been clinically employed, their wider use is limited due to side effects and inefficiencies (Bastianetto et al., 2000). Alternatively, natural products exert anti-AD effects through multi-targeting, which provides advantages and the possibility of wide application (McKenna et al., 2001; Morasch et al., 2015; Zanforlin et al., 2017).

2. Inhibition of AChE activity

2.1 AChE in the pathogenesis of AD

The cholinergic hypothesis proposes that increased AChE activity in AD patients with brain lesions may lead to the loss of the acetylcholine of cholinergic synapses, affect the conduction of nerve impulses and result in cognitive and memory impairment (Leblhuber et al., 2018; Mesulam and Geula, 1991). Thus, increased AChE activity is one of the main causes of AD, and inhibition of AChE activity may alleviate these symptoms in patients. AChE inhibitors increase cholinergic transmission by blocking the degradation of ACh and are therefore considered to be a promising approach for the treatment of AD. Recently, AChE inhibitors such as donepezil, huperzine A and galantamine have been used for the treatment of AD. However, they only relieved the symptoms of AD rather than prevent, terminate and reverse development of the disease. These current drugs exhibit some side effects such as nausea, vomiting, and insomnia (Bastianetto et al., 2000). It is therefore urgent to find novel drugs that can effectively prevent and treat AD. Recently, with the rapid development of technologies in separation, purification and analysis natural products have been sought for the prevention and treatment of AD. Natural products might have advantages such as less toxicity in the prevention and treatment of AD. Researchers have found many natural AChE inhibitors (see Table 1). In this section known natural AChE inhibitors are summarized, and their chemical structures are given by ChemDraw software. Most of them are alkaloids, including isoquinolines, indoles, and quinolizines. There are also some non-alkaloids, including terpenoids, flavonoids and phenolic compounds (Orhan et al., 2009). Some of these natural products show much lower IC50s than that of the agents currently employed (Ingkaninan et al., 2006; Rollinger et al., 2006; Wang et al., 2016; Yang et al., 2012). Ellman's method is currently the most widely used for the evaluation of AChE inhibitors, and it can be used to quantitatively determine the inhibitory activity of the tested drugs (Pohanka et al., 2011).

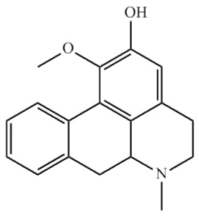
Table 1. IC50 of natural products as AChE inhibitors

AChE inhibitors	Compound	IC50 (μM)
Alkaloids	N-methylasimilobine	1.5
	Taspine	0.33
	Serpentine	0.775
	Stylopine	15.8
	Epiberberine	6.5
	Pseudo-ocorydaline	8.4
	Pseudo-berberine	4.3
	Pseudo-copsitine	4.5
	Berberine	0.44-0.8
	Columbamine	0.44-0.8
	Jatrorrhizine	0.44-0.8
	Coptisine	0.44-0.8
	Tetradehydrocheilanthifoline	0.44-0.8
	Coronaridine	8.6
	Yoacangine	4.4
	10-hydroxycoronaridine	29
	19,20-dihydrotabernamine	0.227
	19,20-dihydroervahanine A	0.071
	Geissoschizine methyl ether	3.7
	N-demethylpuqietinone	6.4
	Ebeiedinone	5.7
	Hupeheninoside	16.9
	Chuanbeinone A	7.7
	Yibeinoside	6.5
	Sophoflavescenol	8.37
	Icariine	6.47
	Demethylanhydro-icaritin	6.67
Non-Alkaloids	8-C-lavandurylkaempferol	5.16
	Kaempferol	3.31
	(4R,4aS)-4-vinyl-4,4a,5,6,6-tetrahydro-3H-pyrano [3,4-cpyran]-1-one	1
	Secostrychnosin	0.5
	Biatractylolide	6.54

2.2 Natural products that inhibit AChE activity

2.2.1 Alkaloids

A large number of alkaloids isolated from nature inhibit AChE activity. N-methylasimilobine (C1) is a noncompetitive AChE inhibitor isolated from lotus and has strong AChE inhibitory activity with an IC50 of 1.5 μg/mL (Yang et al., 2012). Taspine (C2), an alkaloid isolated from magnolia grandiflorum is a long-acting AChE inhibitor (IC50 = 0.33 μM) in a dose-dependent manner with better inhibitory activity than galantamine (IC50 = 3.2 μM). Molecular docking studies have shown that taspine inhibits AChE



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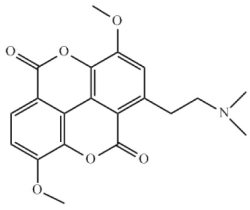

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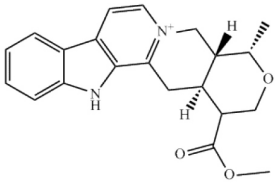

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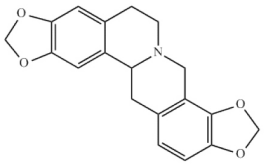

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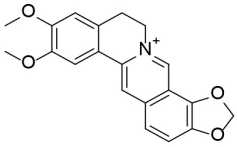

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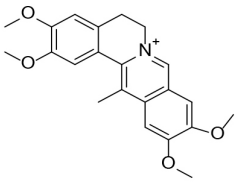

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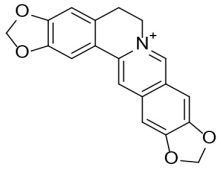

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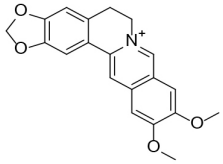

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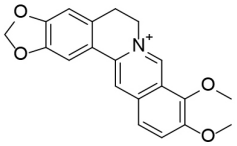

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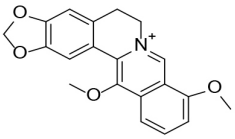

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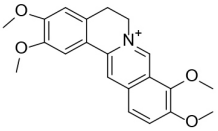

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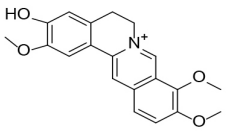

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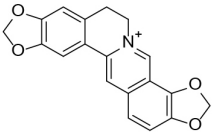

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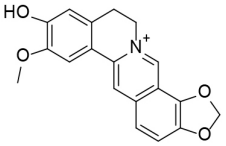

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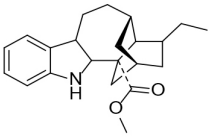

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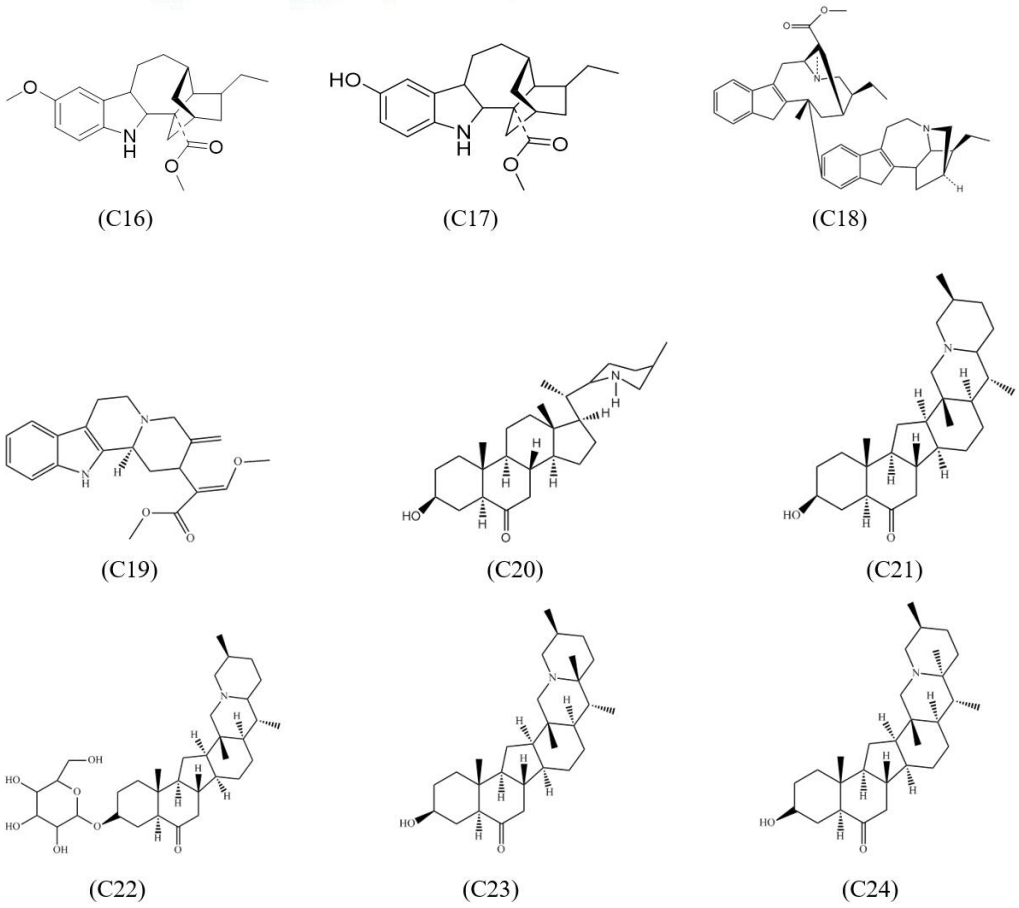
activity through three pathways: (1) The planar aromatic ligand forms a π - π stacking interaction with the Trp84 and Phe330 amino acid residues in AChE (Rollinger et al., 2006); (2) The esterification site connects with an amino side chain; (3) Hydrogen bonds are interconnected. Serpentine (C3) isolated from Catharanthus roseus inhibits AChE (IC50 = 0.775 μM) which is better than that of physostigmine *in vitro,* and it might be developed as an anti-AD drug (Wang et al., 2016). It has been shown that corydalis plants are used to treat memory impairment (Pereira et al., 2010) and demonstrated that several isoquinoline alkaloids extracted from dentate corydalis root have AChE inhibitory activities (Hung et al., 2008). These alkaloids include stylopine (C4), epiberberine (C5), Pseudo-corydaline (C6), pseudo-berberine (C7) and pseudocopsitine (C8). Their IC50 values for inhibition of AChE are 15.8, 6.5, 8.4, 4.3 and 4.5 μM, respectively. Among them, pseudoberberine and pseudo-copsitine have better activity, and pseudoberberine improves the memory damage induced by scopolamine. It has been suggested that the benzylisoquinoline skeleton alkaloids isolated from the genus Corydalis with aromatic methylenedioxy and quaternary nitrogen atoms show stronger AChE inhibitory activities. Neuroprotective alkaloids such as berberine (C9), columbamine (C10), jatrorrhizine (C11), coptisine (C12) and tetradehydrocheilanthifoline (C13) have been isolated from the Coptis Chinensis root. They inhibit the activity of AChE with IC50 values between 0.44 μM and 0.80 μM and all exhibit aromatic methylenedioxy groups (Ingkaninan et al., 2006).

Several monoterpene indole alkaloids such as coronaridine (C14) and voacangine (C15), isolated from the traditional Chinese medicine Cynodon dactylon, potentially inhibit AChE activity. The structural difference between them is that their methoxy



groups are on different positions of the aromatic rings. Their IC50 values for inhibiting AChE are 8.6 μM and 4.4 μM, respectively, which are similar to those of galantamine (3.3 μM). However, the IC50 value of 10-hydroxycoronaridine (C16) was 29 μM, mainly due to the introduction of hydroxyl groups on the aromatic ring (Rai et al., 2011). The previous study has identified several bisindole alkaloids in the roots of Ervatamia divaricata. Among them, 19,20-dihydrotabernamine (C17) and 19,20-dihydroervahanine A (C18) showed strong AChE inhibitory activities with respective IC50s of 0.227 μM and 0.071 μM (Zhang et al., 2007).

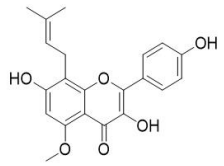
The traditional Chinese medicine Uncaria rhynchophylla is commonly used in the treatment of epilepsy and other neurological disorders. It has been shown that extracted alkaloids have neuroprotective effects (Atta Ur et al., 2002). Geissoschizine methyl ether (C19), a reversible non-competitive inhibitor, effectively inhibits AChE with an IC50 of 3.7 μM. The traditional Chinese medicine Fritillaria is mainly used for relieving cough, asthma, and as an expectorant. Several new terpenoid alkaloids have been extracted from it and show a mild inhibitory effect on AChE activity (Atta Ur et al., 2002). Lin et al. (2006) conducted a cholinesterase activity assay on 18 alkaloids from five Fritillaria plants. Results showed N-demethylpuqietione (C20), ebeiedinone (C21), hupeheninoside (C22), chuanbeinone A (C23) and yibeinoside (C24), isolated from Fritillaria cirrhosa, Fritillaria ussuriensis, Hubei Fritillaria, Fritillaria delavayi and Fritillaria pallidiflora Schrenk, respectively, had strong inhibitory activity against AChE with IC50s of 6.4, 5.7, 16.9, 7.7, and 6.5 μM, respectively. Following structural analysis of these AChE inhibitors, it was found that these compounds typically contain five or six heterocycles or carbocyclic C-27 cholestane carbon skeletons. The study of structure-activity relationships showed that the C-3 position and the C-6 ketone group enhanced inhibitory effects on AChE. The introduction of hydroxyl at C-20 and the introduction of N-methyl reduced the effect of AChE inhibition.

2.2.2 *Non-alkaloids*

Although most potential AChE inhibitors are alkaloids, there are many potential non-alkaloid AChE inhibitors in traditional Chinese medicine, including terpenoids, sterols, flavonoids, phenols compounds and some other small molecules (Boonyaketgoson et al., 2018; Huang et al., 2013; Jung et al., 2011; Orhan et al., 2009).

Flavonoids isolated from Leguminosa flavescens have strong anti-AD activity. Sophoflavescenol (C25), icaritin (C26), demethylanhydro-icaritin (C27), 8-C-lavandurylkaempferol (C28) and kaempferol (C29) show strong inhibition of AChE activity with IC50 values of 8.37, 6.47, 6.67, 5.16 and 3.31 μM, respectively (Jung et al., 2011).

Biatractylolide is an active component existing in Atractylodis Macrocephalae Rhizome. This small molecule has a symmetrical structure containing a novel double sesquiterpene ester. Xie et al. (2016) showed that biatractylolide (C30) had a significant effect on inhibiting the activity of AChE in the brain and improved the memory ability of dementia mouse induced by aluminum trichlo-



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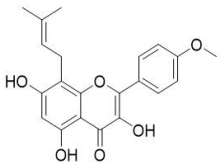

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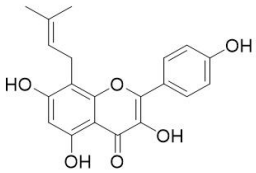

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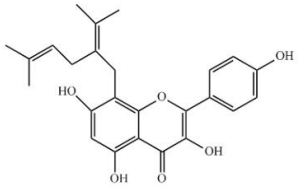

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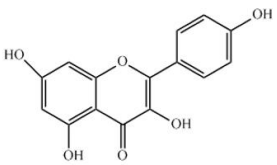

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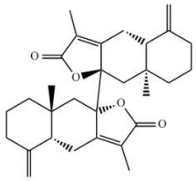

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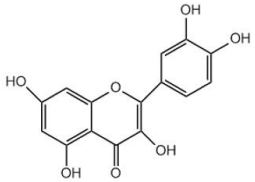

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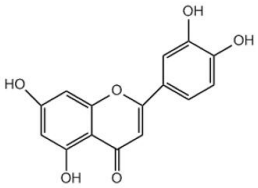

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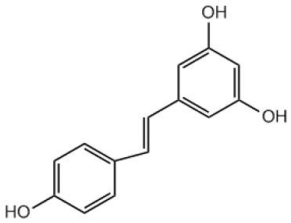

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ride. The IC50 values of inhibiting AChE activity is 6.55 μM and its molecular mechanisms includes not only binding to AChE but also reducing AChE expression by inhibiting the activity of glycogen synthase kinase (GSK) 3.

Lee et al. (2007) isolated two compounds from Gentiana macrophylla: (4R, 4aS)-4-vinyl-4, 4a, 5, 6, 6-tetrahydro-3H-pyrano [3, 4-cpyran]-1-one and secostrychnosin. Their minimum inhibitory doses against AChE were respectively 1.0 μg/mL and 0.5 μg/mL (Lee et al., 2007).

The classical function of AChE is to hydrolyze ACh and terminate nerve conduction. AChE inhibitors can relieve excessive hydrolysis of ACh in the brain of AD patients and enhance cognitive function. AChE inhibitors ameliorate the symptoms of AD but do not significantly alleviate disease progression (Zimmermann, 2013).

3. Inhibition of Aβ deposition

3.1 Aβ in AD pathogenesis

Senile plaque is one of the pathological signs of AD (Hardy and Selkoe, 2002). An imbalance of Aβ production and clearance leads to Aβ accumulation in the central nervous system (CNS). As a cause of AD, this production and clearance is a key target for the development of therapeutic agents (Verdile et al., 2007). The amyloid precursor protein (APP) produces Aβ protein through two pathways, either by α-secretase shearing or shearing by β-secretase in the extracellular domain and γ-secretase in the transmembrane domain of APP to produce soluble Aβ protein (Gotz and Scharnagl, 2018; Klein et al., 2001; Resende et al., 2008; Zetterberg et al., 2010). Aβ production and clearance dysfunction lead to plaque generation (Hefti et al., 2013; Walter et al., 2001). Thus, inhibiting the accumulation of Aβ precipitation and accelerating the clearance of Aβ have become a focus for the development of anti-AD drugs (see Table 2). In this section the natural products known to target Aβ production or clearance dysfunction are summarized, and their chemical structures are given by ChemDraw software.

3.2 Natural products that inhibit Aβ aggregation

The marginal effects observed in recent clinical studies of both solanezumab, which targets monomeric Aβ, and bapineuzumab, which targets amyloid plaques, support the opinion that AD drug discovery should focus on soluble Aβ rather than fibrillar Aβ deposits (Hefti et al., 2013; Walter et al., 2001). Accumulating data suggests that soluble Aβ oligomers represent the optimal intervention target within the amyloid domain. Investigators have determined that some compounds inhibit Aβ aggregation, including flavonoids, polyphenols, alkaloids, and terpenoids.

3.2.1 Flavonoids

Quercetin (C31), a polyphenolic flavonoid, is widely distributed in natural food. Dhawan et al. (2011) found that the administration of quercetin through intravenous injection provided an obvious protective effect for AD rats. A high dose of quercetin significantly inhibited Aβ aggregation and reduced H_2O_2-induced oxidative stress. Low doses (5-20 μM) of quercetin reduced Aβ-induced neuronal apoptosis in hippocampus (Manca et al., 2014). Luteolin (C32), a crystal flavonoid, is widely distributed in food. Liu et al. (2011) reported that luteolin down-regulates the expression of AβPP decreases the production of Aβ1-42 and exerts a neuroprotective effect in copper-induced SH-SY5Y cytotoxicity.

3.2.2 *Polyphenols*

Resveratrol (C33) is one polyphenol widely distributed in fruits and nuts (Mullin, 2011). Pharmacological studies show that this polyphenol has antitumor, anti-inflammatory, cardiovascular protective, hypoglycemic, and neuroprotective effects (Li et al., 2012b). Li et al. (2012a) found that resveratrol provides a neuroprotective role by reducing Aβ production and increasing Aβ clearance. Ge et al. (2012) reported that it inhibits Aβ aggregation by binding to different Aβ sites Curcumin (C34) is a polyphenolic compound with anti-AD biological activity found recently. It (5-10 μM) exerts a neuroprotective effect by inhibiting oxidative stress injury, inhibiting calcium influx and inhibiting tau hyperphosphorylation (Park et al., 2008). Xiong et al. (2011) reported that curcumin could both significantly reduce Aβ production in a dose-dependent manner in SH-SY5Y neuroblastoma cells transfected with APP and reduce Aβ production by inhibiting GSK3β-mediated PS1 activation. Therefore, curcumin exerts its anti-AD effect through multiple targets.

3.2.3 *Alkaloids*

Huperzine A (C35) is an anti-AD drug in the clinic. Studies focus on clarifying its mechanisms of action, and it improves cognitive impairment in transgenic AD mice by activating the PKC/MAPK signaling pathway and increasing phosphorylation of GSK3β (Ratia et al., 2013). Wang et al. (2011) found that huperzine A reduces the level of Aβ in transgenic APP overexpressing mice and enhances cleavage of non-beta-like forms of amylin by inhibiting the activity of GSK3α/β and activating the Wnt/β-catenin signaling pathway to exert its neuroprotective effect. Berberine (9) is an isonicotinoid alkaloid with many biological activities including antioxidant, inhibition of AChE, BChE and monoamine oxidase activity and reduction cholesterol activity (Vuddanda et al., 2010). It has been shown that berberine has a neuroprotective effect on TgCRND8 transgenic AD model mice, reduces the levels of soluble and insoluble Aβ and activates the Akt/GSK3 signaling pathway in mice (Durairajan et al., 2012). Zhu et al. (2011) found that in HEK293 cells transfected with the APP695 gene of a Swedish mutation, berberine inhibits the expression of β-secretase by activating the ERK1/2 signaling pathway and ultimately reduced the production of Aβ41/42 (Zhu et al., 2011). Kim et al. (2017) found that the alkaloid manzamine A (C36) isolated from Halicrona sp. is a strong cell GSK inhibitor that non-competitively inhibits GSK3β and CDK-5 during Tau protein phosphorylation. Hymenaldisine (C37) is a class of marine alkaloids containing bromopyrrole and sulfhydryl groups which were isolated from Agelacsidae. Meijer et al. (2000) found that Hymenaldisine is a GSK-3β competitive ATP inhibitor and a CDK-5/p35 inhibitor.

3.2.4 *Terpenoids*

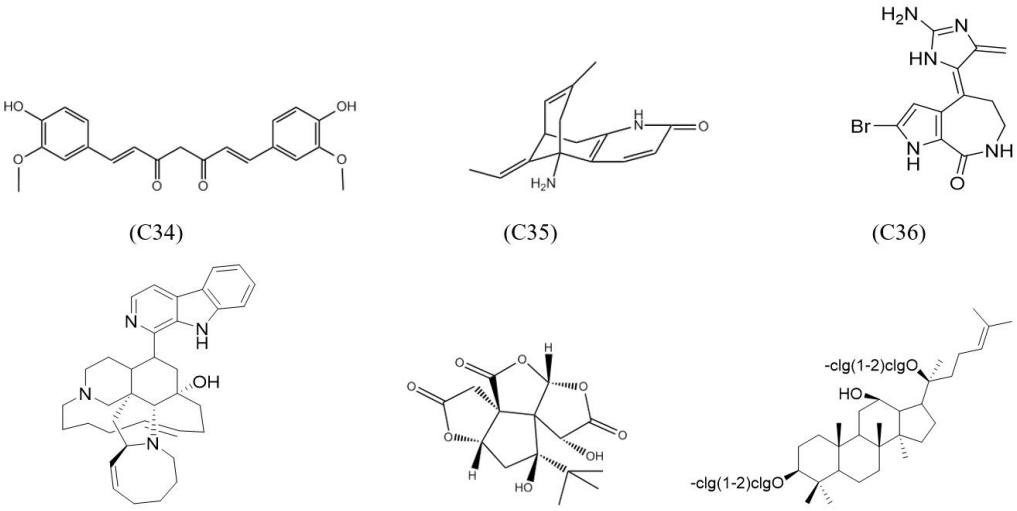
Ginkgolide (C38) is a terpene compound that is isolated from the traditional Chinese medicine Ginkgo biloba. Ginkgolide blocks early apoptosis and decreases the levels of p53, Bax, and caspase-3 in ROS-induced PC12 cell apoptosis (Zhou and Zhu, 2000). Shi et al. (2011) revealed that ginkgolide inhibits β-secretase activity through the PI3K signaling pathway and reduces the production of both Aβ and soluble AβPP.

Biatractylolide (C30) significantly reduces cholinesterase activity in AD model rats and improves the behavior and memory of these rats when induced by $A\beta_{1-40}$. It has also been confirmed that biatractylolide has a neuroprotective effect on glutamate-induced injury in PC12 and SH-SY5Y cells through a mechanism of the PI3K-Akt-GSK3β-dependent pathways (Zhu et al., 2017).

4. Inhibition of tau hyperphosphorylation

4.1 Tau hyperphosphorylation in AD pathogenesis

Intracellular tau aggregations form in several neurodegenerative diseases in a condition termed tauopathy. Tauopathies include AD, progressive supranulear palsy, corticobasal degeneration, and front temporal dementia (Liu et al., 2006). An abnormally high level of phosphorylated tau aggregation resulting in nerve entanglement (NFT) is one of the pathological signs of AD. Normal tau protein promotes microtubule stability, participates in the cell skeleton and maintains the normal physiological function of cells. It regulates physiological functions through phosphorylation and dephosphorylation which are respectively catalyzed by protein ki-



(C34) (C35) (C36)

(C37) (C38) (C39)

Table 2. Current anti-Alzheimer's disease effect of natural products and their principal targets

Principle targets	Inhibition of AChE activity	Inhibition of Aβ deposition	Inhibition of tau hyperphosphorylation	Regulators
Alkaloids	N-methylasimilobine	Huperzine A	Berberine	Galantamine
	Taspine	Ginkgolide	Dehydroevodiamine	Hydroxamic acid
	Serpentine	Biatractylolide	Isorhynchophylline	Casealen B
	Stylopine		Manzamine A	Lovastatin
	Epiberberine		Hymenaldisine	
	Pseudo-ocorydaline		Manzamine A	
	Pseudo-berberine		Hymenaldisine	
	Pseudo-copsitine			
	Berberine			
	Columbamine			
	Jatrorrhizine			
	Coptisine			
	Tetradehydrocheilanthifoline			
	Coronaridine			
	Yoacangine			
	10-hydroxycoronaridine			
	19,20-dihydrotabernamine			
	19,20-dihydroervahanine A			
	Geissoschizine methyl ether			
	N-demethylpuqietinone			
	Ebeiedinone			
	Hupeheninoside			
	Chuanbeinone A			
	Yibeinoside			
Non-Alkaloids	Sophoflavescenol	Quercetin	Ginsenoside Rb1	
	Icariine	Luteolin	Ginsenoside Rd	
	Demethylanhydro-icaritin	Resveratrol	Cornel iridoid glycoside	
	8-C-lavandurylkaempferol	Curcumin	Geniposide	
	Kaempferol	Ginkgolide	Xanthoceraside	
	(4R,4aS)-4-vinyl-4,4a,5,6,6-tetrahydro-3H-pyrano [3,4-cpyran]-1-one	Biatractylolide	Biatractylolide	
	Secostrychnosin			
	Biatractylolide			

nase and phosphorylase. When unbalanced, excessively phosphorylated tau leads to NFT (Baskaran and Velmurugan, 2018). The main protein phosphorylases are PP1, PP2A and PP2B. Both the abnormal activation of protein kinases and the down-regulation of phosphorylase activity leads to hyperphosphorylation of tau (Gu et al., 2010; Nisbet et al., 2015). Hyperphosphorylation of tau undermines the structural and physiological functions of cells and exacerbates Aβ neurotoxicity, which leads to accelerated AD progression. In clinical trials for severe AD patients the treatment effect of drugs on tau protein may be better than that of anti-Aβ agents (Zhao et al., 2013). Therefore, an increasing number of investigations are focused on the anti-AD drugs that inhibit the hyperphosphorylation of tau protein (see Table 2). Inhibition of phosphorylation of the Tau microtubule-binding region (pthr251 and pser396) is significant for preventing aggregation and hyperphosphorylation. Natural anti-tau compounds include saponins, terpenoids, and alkaloids. In this section these natural products summarized and their chemical structures are given by ChemDraw software.

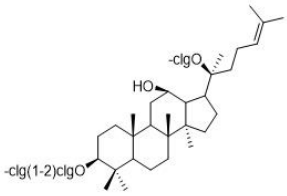
4.2 Natural products that inhibit tau hyperphosphorylation

4.2.1 Saponins

The active ingredients of ginseng express anti-AD activity. Evidence shows that ginsenoside Rb1 (C39) inhibits hyperphosphorylation of tau in aluminum-induced AD mice by reversing the expression of p-GSK3 and PP2A (Wei et al., 2016). Ginsenoside Rb1 also reduces the level of p25 and Aβ-induced hyperphosphorylation of tau through the CDK5 signaling pathway (Xie et al., 2007). Zhang et al. (2014) reported that ginsenoside Rd (C40) reduced phosphorylation of tau in cerebral ischemia-induced AD mouse models via the PI3K/AKT/GSK3β signaling pathway.

4.2.2 Terpenoids

Iridoid glycosides isolate from the Cornus Officinalis exhibited anti-aging effects. In an ADSK-N-SH cell model induced by wortmannin and GF-109203X, cornel iridoid glycoside (C41) upregulates the activity of PP2A by demethylating PP2Ac. This leads to the inhibition of hyperphosphorylation of tau protein (Jung et al., 2009). Geniposide (C42), an iridoid from gardenia, improves the learning ability of STZ-induced AD rats by upregulating the



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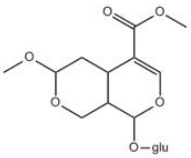

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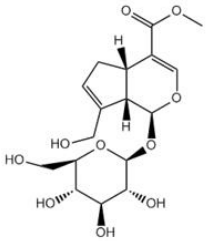

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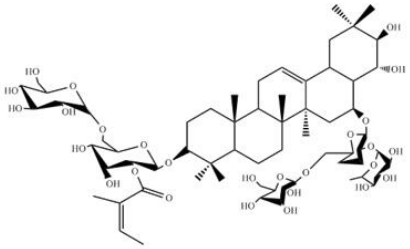

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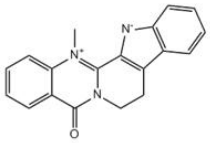

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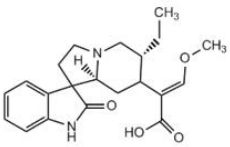

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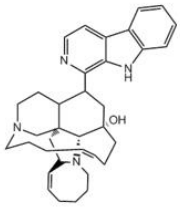

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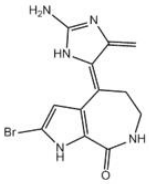

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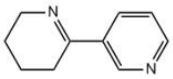


(C48)

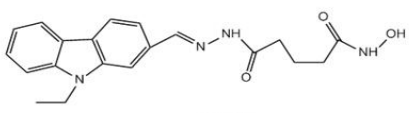
expression of GSK3β (pS-9, pY-216) and reducing the level of tau phosphorylation (Gao et al., 2014). Xanthoceraside (C43) is a member of the triterpenoid saponins, which improves the cognitive ability of STZ-induced brain injury in rats. The underlying mechanism is an increased expression of PP1 and PP2A, increased phosphorylation of PI3K (p85) and Akt (Ser473) and decreased phosphorylation of GSK3β (tyr216), leading to a reduced level of tau phosphorylation (Liu et al., 2014).

Xie et al. (2016) demonstrated that biatractylolide (C30) could strongly inhibit AChE activity with an IC50 value of 6.5458 μM. The underlying molecular mechanisms are not only binding to AChE but also reduced AChE expression by inhibition of GSK3 activity. Biatractylolide also has a neuroprotective effect on glutamate-induced injury in PC12 and SH-SY5Y cells through a mechanism of the PI3K-Akt-GSK3β-dependent pathways (Zhu et al., 2017).

4.2.3 Alkaloids

Berberine (C9) both increases the survival rate and reduces the cytotoxicity of HEK293 cells induced by the protein phosphatase inhibitor calyculin A and down-regulates the phosphorylation of Tau by restoring the activity of PP2A and decreasing the level of GSK3β (Yu et al., 2011). Dehydroevodiamine (C44) activates a PP2A Tyr307 site and inhibits phosphorylation of tau in rat brain (Fang et al., 2007). Isorhynchophylline (C45) restores Aβ-induced cognitive impairment, inhibits neuronal apoptosis, and reduces phosphorylation of tau by inhibiting GSK3β activity and activating the PI3K/Akt signaling pathway (Xian et al., 2014).

Manzamine A (C46) is a strong cell GSK inhibitor that noncompetitively inhibits GSK3β and CDK-5 in the phosphorylation of tau protein It thus provides a new type of backbone for the synthesis of GSK3β inhibitors (Peng et al., 2003). Hymenaldisine (C47) is a marine alkaloid containing bromopyrrole and sulfhydryl groups in agelasidae, axinellidae and halichondri-idae. Meijer et al. (2000) identified that hymenaldisine is a GSK3β competitive ATP inhibitor and a CDK-5/p35 inhibitor.



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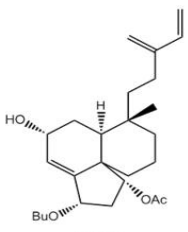

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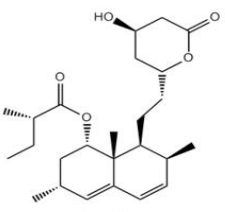

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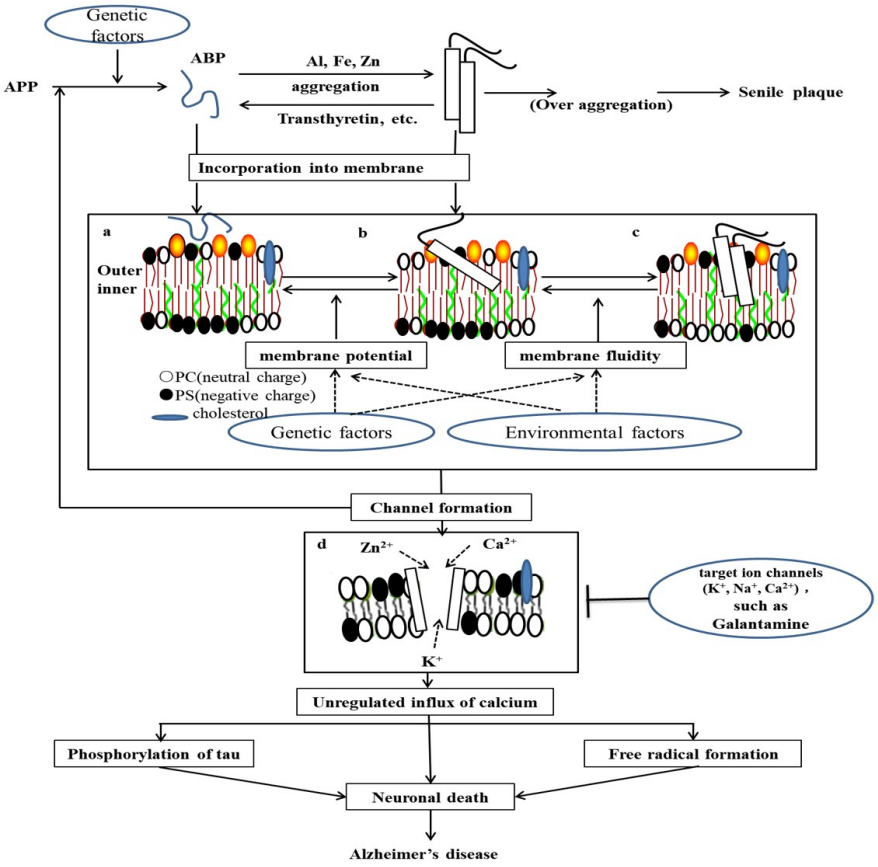

Figure 1. Aß-amyloid protein channel hypothesis and natural products action site. (a) Aß produced by hydrolysis of ßAPP first acts on the cell membrane, the net charge on the surface of the membrane plays a key role in this step. The distribution of phospholipids on the cell membrane is not uniform. Neutral lipids are usually distributed on the outer membrane surface, and negatively charged phospholipids are usually distributed on the inner surface. (b) Once the Aß aggregated by Zn^{2+} and Cu^{2+} is inserted into the membrane, the normal membrane structure is disturbed, and the structure of ion channels related to the membrane changes slightly. This affects the function of the original membrane ion channels. (c) The inserted Aß can further aggregate in the membrane, gradually forming channels. The formation of ion channels on the membrane is quite lethal to nerve cells. The formation of channels enhances the permeability of the cell membrane, triggers the abnormal flow of ions inside and outside the membrane, destroys the regional distribution of ions, and ultimately leads to cell dysfunction. (d) Ion channel blockers such as Galantamine could specifically target ion channels (K^+, Na^+ and Ca^{2+}) or inhibit their formation, thus help maintain normal central nervous system function.

5. Regulators based on other potential targets

5.1 Ion channels, synaptic regeneration and cholesterol synthesis in AD pathogenesis

Studies have increasingly demonstrated that ion channels, synaptic regeneration, and cholesterol synthesis play an important role in AD pathology. Among them, ion channels act as a key component in maintaining normal CNS function. Synaptic regeneration is an important mechanism of synapse formation between neurons and is an important contributor to learning, memory and cognitive function. Dietary cholesterol can accelerate the production of Aβ and the appearance of pathological AD symptoms.

5.2 Ion channel regulator

Ion channels have a key role in maintaining normal CNS function. The channel hypothesis supports that ion channels constructed by Aβ on the nerve cell membrane allow abnormal flows of intracellular and extracellular ions, destroy the dynamic balance of ions and leads to nerve cell death (Thapa et al., 2017). Kem et al. (1997) found that alkaloids in marine-derived larvae regulated ion channels. Galantamine (C48), an alkaloid derived from Aconitum heterophyllum, specifically targets ion channels (K^+, Na^+, Ca^{2+}) in rat hippocampus neurons (Song et al., 2008) (see Fig. 1).

5.3 Enhancer acting on synaptic regeneration

Synaptic regeneration has an immense influence on learning, memory, and cognitive work (Sun and Alkon, 2019). The type I histone deacetylase (HDAC) inhibitors, such as hydroxamic acid (C49), promote synapse production (Xu et al., 2011). Xu et al. (2015) obtained10 new diterpenoids from the ethyl acetate extract of Casearia graveolens Dalzell root and found that Casealen B (C50) had a strong nerve growth factor-mediated synapse formation activity.

5.4 Cholesterol synthesis inhibitor

Dietary cholesterol accelerates the production of Aβ and the appearance of pathological symptoms of AD. Statins inhibit hydroxymethylglutaryl coenzyme A reductase and decrease choles-

terol biosynthesis. It has been reported that the lipid-lowering drug lovastatin (C51) isolated from Monascus could be used for the treatment of AD (Won et al., 2008).

6. Conclusions

Natural products have been used in many regions of the world for thousands of years to treat cancer, cardiovascular and neurodegenerative diseases (Howes et al., 2017; Jernigan et al., 2017; Tewari et al., 2019). Increasing research demonstrates that natural products have great neurogenic potential and represent promising therapeutic agents for AD treatment (Hashiguchi et al., 2015). Not surprisingly, there are many natural products that bring about significant results in the control of AD and have important outcomes in AD therapy (Shakeri et al., 2016).

With an increased understanding of pathogenesis, the treatment strategy for AD has gradually changed from single target to multi-target and multi-function drugs. Drugs derived from natural products have a valuable characteristic of multi-targeting and limited adverse reactions. The long-term practice has shown that natural drugs have certain advantages in the treatment of AD and multiple targeting have significant potential in the development of anti-AD drugs. Natural products provide a powerful armamentarium for human intervention in AD (Ballatore et al., 2007).

Acknowledgment

Thanks to all the peer reviewers and editors for their opinions and suggestions.

Conflicts of interest

The authors declare no conflict of interest.

Submitted: July 08, 2019
Accepted: September 03, 2019
Published: September 30, 2019

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